Analytical Characteristics of High-Sensitivity Cardiac Troponin Assays
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BACKGROUND: Cardiac troponins I (cTnI) and T (cTnT) have received international endorsement as the standard biomarkers for detection of myocardial injury, for risk stratification in patients suspected of acute coronary syndrome, and for the diagnosis of myocardial infarction. An evidence-based clinical database is growing rapidly for high-sensitivity (hs) troponin assays. Thus, clarifications of the analytical principles for the immunoassays used in clinical practice are important.

CONTENT: The purpose of this mini-review is (a) to provide a background for the biochemistry of cTnT and cTnI and (b) to address the following analytical questions for both hs cTnI and cTnT assays: (i) How does an assay become designated hs? (ii) How does one realistically define healthy (normal) reference populations for determining the 99th percentile? (iii) What is the usual biological variation of these analytes? (iv) What assay imprecision characteristics are acceptable? (v) Will standardization of cardiac troponin assays be attainable?

SUMMARY: This review raises important points regarding cTnI and cTnT assays and their reference limits and specifically addresses hs assays used to measure low concentrations (nanograms per liter or picograms per milliliter). Recommendations are made to help clarify the nomenclature. The review also identifies further challenges for the evolving science of cardiac troponin measurement. It is hoped that with the introduction of these concepts, both laboratorians and clinicians can develop a more unified view of how these assays are used worldwide in clinical practice.

Cardiac troponins I (cTnI)4 and T (cTnT) have been endorsed internationally as the standard biomarkers for the detection of myocardial injury, risk stratification in patients suspected of acute coronary syndrome, and for the diagnosis of myocardial infarction (1, 2). Thus, clarification of the analytical principles of the immunoassays used in clinical practice is important (3). Furthermore, an evidence-based clinical database is growing rapidly for high-sensitivity (hs) troponin assays (4–8). This database includes risk–outcomes data involving measurements of concentrations within healthy reference populations (6, 7), which heretofore have not been measurable owing to the limited analytical sensitivity (detection limits) of current assays (9). This rapid accumulation of information supports an accompanying need for a better general understanding of the analytical characteristics of cardiac troponin assays. This review does not intend to break new ground or supplant present guidelines, but to help clarify them.

Troponin Biochemistry
CARDIAC TROPONIN T
Three different isoforms of TnT encoded by individual genes have been identified in cardiac muscle, fast-twitch skeletal muscle, and slow-twitch skeletal muscle (10). There is sequence homology between cTnT and skeletal muscle troponin T (sTnT), with a difference of 125 amino acid residues between adult sTnT from fast-twitch skeletal muscle (fast sTnT) and cTnT (56.6% homology) and a 120-residue difference between adult sTnT from slow-twitch skeletal muscle (slow sTnT) and cTnT (58.3% homology). The potential impact of the regeneration of skeletal muscle and of the develop-

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4 Nonstandard abbreviations: cTnI, cardiac troponin I; cTnT, cardiac troponin T; hs, high-sensitivity; sTnT, skeletal muscle TnT; fast sTnT, sTnT from fast-twitch skeletal muscle; slow sTnT, sTnT from slow-twitch skeletal muscle; MAb, monoclonal antibody; TnC, troponin C; FAB, fragment antigen binding.
ing heart and skeletal muscle on the reexpression of the genes encoding the cross-reacting cTnT isoforms has been reviewed (10). The use of an antibody pair specific to adult cTnT found no evidence of cTnT isoforms corresponding to adult cTnT in skeletal muscle from patients with renal disease (11). The presence of a human fetal exon with complete sequence homology to an exon in fast sTnT and in cTnT may account for previous reports of apparent cross-reactivity in immunohistochemical studies that used anti-cTnT antibodies. The fourth-generation cTnT assay uses monoclonal antibodies (MAbs) that recognize epitopes 5 residues apart in the central part of the molecule: M7 (which recognizes an epitope at residues 125–131) and M11.7 (which recognizes an epitope at residues 136–147). This antibody selection corresponds to the cardiospecific sequences that have no sequence homology to fetal TnT. A recent analysis has reported, however, that a protein found in skeletal muscle of patients with primary skeletal muscle disease is captured by all of these antibodies, again raising the possibility that the specificity of cTnT for cardiac muscle may not be absolute (12).

The majority of cTnT is found in the contractile apparatus (approximately 10 ng/g tissue) and is released via proteolytic degradation. Although 6%–8% of cTnT has been reported to occur as a free cytosolic component (13), the precise amount is not certain, because studies have used tissues from variable sources, such as organ donor tissue, postmortem tissue, or atrial tissue. Release from a cytosolic pool has been suggested to occur with ischemia; however, the current accepted evidence supports the concept that the release of cTnT (and cTnI) is due to cell death and is irreversible. Cardiac troponin release has also been suggested to be due to reversible ischemic injury. The proposed mechanisms of cardiac troponin release include apoptosis, normal myocyte turnover, cellular release of proteolytic degradation products, increased cell wall permeability, and formation and release of membranous blebs (14). The half-life of cTnT in the circulation is thought to be 120 min (15), with the prolonged window of detection being due to continuous release of cTnT from the myofibrillar pool as the contractile apparatus within the cell undergoes degradation during necrosis. The clearance and degradation of cTnT remains undefined, however. Studies have suggested that intact cTnT is present as a complex with tropinin C (TnC) and cTnI, and as free cTnT (16) although these conclusions have been questioned (17). Further studies are required.

The effect of EDTA in the cTnT assay seems to be minimal, whereas differences between serum and plasma values have been reported for a number of cTnI methods. Initial reports showed a variable difference between cTnT and cTnI values for serum and heparin-treated plasma; however, this variability has been corrected with the current formulation of the cTnT assay. In patient samples, cTnT appears to be very stable, not only at room temperature and at 4 °C, but also when repeatedly frozen and thawed (samples do not exhibit significant changes after 5 freeze–thaw cycles). Assay imprecision varies modestly, depending on the specific instrument used in a given laboratory (18).

The hs-cTnT assay uses fragment antigen binding (FAB) portions of 2 cTnT-specific mouse MAbs directed against epitopes in the central region of human cTnT. The capture antibody (M7) is biotinylated and directed against an epitope at amino acid residues 125–131 and is identical to that in the fourth-generation assay. The detection antibody is directed against an epitope at amino acid residues 136–147. The original antibody (M11.7) has been reengineered, with the constant C1 region of the FAB being replaced by a human IgG C1 region to produce a mouse–human chimeric detection antibody. Assay sensitivity has been increased by increasing the sample volume from 15 to 50 µL, increasing the ruthenium concentration of the detection antibody, and lowering the background signal by buffer optimization. The assay is calibrated against recombinant human cTnT produced in Escherichia coli cell culture (19). Assay calibration is not identical to that of the fourth-generation assay, so identical samples measured with the fourth-generation and hs-cTnT assays will give different results independently of the influences of imprecision. The 30-ng/L cutoff in the fourth-generation assay corresponds to 50 ng/L in the new hs assay.

**CARDIAC TROPONIN I**

Human cTnI occurs in cardiac muscle tissue as a single isoform of 209 amino acid residues, with a molecular weight of approximately 23–24 kDa. Three human cTnI isoforms have been described: one is produced in cardiac muscle (cTnI), and 1 isoform each is produced in slow-twitch and fast-twitch skeletal muscles (slow sTnI and fast sTnI, respectively) (10). The overlap in sequence between cTnI and slow sTnI is approximately 40% and somewhat less for fast sTnI. Therefore, antibodies selected for cTnI assays should be tested to ensure that there is no cross-reaction with skeletal isoforms of the protein. The cTnI molecule contains 2 serine residues that can be phosphorylated in vivo by protein kinase A. Thus, 4 forms of the protein can coexist in the cell: 1 dephosphorylated, 2 monophosphorylated, and 1 bisphosphorylated. Phosphorylation of cTnI changes the conformation of the protein and modifies its interaction with other troponins, in addi-
tion to its interaction with anti-TnI antibodies. A substantial part of cTnI released into a patient’s bloodstream appears to be phosphorylated (20), although other posttranslationally modified TnI isoforms, including those that have been oxidized, reduced, or partially digested by proteases, have been found in the circulation (15). The majority of cTnI is found in the contractile apparatus (approximately 4–6 mg/g tissue) and is released by proteolytic degradation, with 2% to 8% of cTnI reported to occur as a free cytosolic component (21).

The first cTnI immunoassay was described by Cummins et al. in 1987 (22), with the first commercial cTnI assay for the Stratus I analyzer (Dade Behring) appearing in 1996. More than 20 years later, the cTnI immunoassay has been transformed considerably. Current generations of commercially available assays have an analytical sensitivity almost 100-fold higher (1 vs 100 ng/L) than that of the experimental and commercial assays that were initially described (9). MAbs specific to several selected epitopes of cTnI are able to recognize all known modifications circulating in the blood. Different forms of the antigen used as standards or calibrators have helped to improve the correlations between the different commercial assays by more than 10-fold, but standardization has not yet been achieved (23). A working group of the IFCC is cooperating with manufacturers to address the question of whether cTnI standardization or harmonization can be achieved (24). The most common reason for the discrepancy in cTnI measurements is the difference in epitope specificity of the antibodies used in different assays. We now know that cTnI measurements are influenced by multiple factors, among which are the aforementioned posttranslational modifications [proteolytic degradation (25), phosphorylation (20)] and complexing with other molecules [e.g., TnC (26), heparin (20), heterophile or human antimouse antibodies, and cTnI-specific autoantibodies circulating in patients’ blood (27)]. Different mono- and polyclonal antibodies used in assays are sensitive to these factors to varying degrees. Therefore, it becomes increasingly important that hs-cTnI assays use antibodies specific to epitopes in the central part of the troponin molecule that are not affected by the numerous modifications found in human blood noted above.

HyTest Ltd. has assessed several hundred different 2-site MAb combinations to find the best one for accurately measuring cTnI by immunoassay (28). This firm has concluded that it is currently not possible to have a single antibody pair (i.e., 1 capture antibody and 1 detection antibody) that would be totally insensitive to all known cTnI modifications and interferences. Given these data, it seems wise to consider the recommendation of this group to use combinations of >2 MAbs for the development of precise cTnI immunoassays. One could use 2 MAbs for capture and 2 MAbs for detection (conjugated with the specific label)—a “2 + 2” concept (28). In these assays, MAbs should be selected in such a way that if one of the MAbs (capture or detection) is sensitive to the presence of an antigen in the sample, then the other MAb should be insensitive to the same antigen. Thus, the effect of negative or positive interference would be minimized. In addition, the antibodies used in the assay should be specific to the cardiac isoform of troponin and should not show cross-reaction with the 2 skeletal muscle troponin isoforms.

Factors that influence cTnI measurements are presented schematically in Fig. 1. Antibodies specific to different parts of the molecule are sensitive to these factors to different degrees. For example, purified cTnI is well known to be highly susceptible to proteolytic degradation; however, the central part of cTnI closely interacts with TnC in the troponin complex, and TnC protects cTnI from proteolytic degradation. Consequently, the epitopes located in the central part of the cTnI molecule are substantially more stable than the epitopes located in the terminal parts of the molecule. Concurrently, TnC competes with antibodies for binding to cTnI, and only a few antibodies specific to the central part of cTnI can recognize the cTnI–TnC complexed form. cTnI was recently demonstrated to be cleaved by endogenous proteases during incubation of necrotic myocardial muscle after an acute myocardial infarction (25, 26). Consequently, a mixture of the intact cTnI molecule and its proteolytic fragments can be detected in the bloodstream several hours after the onset of the chest pain, although the ratio of fragment molecules to intact molecules, the sizes of fragments, the relationship of the fragmentation with the infarct size, and many other questions need to be addressed. Given that the vast majority (>95%) of cTnI in human blood occurs as a binary cTnI–TnC complex, the antibodies used in the assay should recognize cTnI in complex with TnC. Ideally, antibodies used in assays should recognize all circulating cardiac troponin forms on an equimolar basis.

How Does an Assay Become Designated “High Sensitivity”?

It is important to understand that the term “high sensitivity” reflects the assay’s characteristics and does not refer to a difference in the form of cardiac troponin being measured. There is a need for a consensus on defining what nomenclature should be used for an hs assay. Several names have been used in the literature for these assays, including “high-performance,” “highly
sensitive,” “high-sensitive,” “ultrasensitive,” “novel highly sensitive,” “sensitive,” and “high sensitivity.” We propose that the term “high-sensitivity” be uniformly used for publication in Clinical Chemistry and throughout the scientific literature. This term, however, begs the question: How does one define an hs assay? In a scorecard concept, an assay was proposed to be hs if it met 2 basic criteria (9). First, the total imprecision (CV) at the 99th percentile value should be \( \leq 10\% \). Second, measurable concentrations below the 99th percentile should be attainable with an assay at a concentration value above the assay’s limit of detection for at least 50% (and ideally \( > 95\% \)) of healthy individuals to attain the highest level of scorecard designation. It is unclear which data in the literature should be used for such an analysis, as study findings are variable. For hs-cTnT, the initial validation study showed measurable concentrations above the limit of detection for a large number of healthy individuals (29). A later study, however, showed much lower rates of measurable concentrations (18), as did a study of a large population that included patients with cardiovascular disease, for whom one would expect higher percentages of samples with measurable cTnT (6). As Table 1 shows, none of the currently marketed assays for both central laboratory and point-of-care testing met the 2-fold criteria for an hs-designated level 4 assay. Table 2 shows that the reformulated and newer hs assays (5 hs-cTnI assays and 1 hs-cTnT assay) potentially meet these criteria. The one hs assay that is commercially available worldwide (except in the US, because it has not yet obtained US Food and Drug Administration clearance) is the Roche hs-cTnT assay. Concentrations for hs assays are expressed in nanograms per liter (picograms per milliliter) instead of the commonly published units of micrograms per liter. We propose that all journals, manufacturers, and laboratories universally adopt the former unit of measure to avoid confusion and decimal points followed by unnecessary zeros. For example, a concentration of 0.0015 \( \mu \)g/L would need to be reported as 1.5 ng/L. Adoption of this convention would also help avoid clinical errors in data reporting for both electronic medical records and electronic data transfer, for which the rounding of decimals to zero is a real risk. It should be appreciated that using nanograms per liter as the standard unit will produce very high cardiac troponin values (\( > 1000 \)ng/L) after large cardiac insults.

**Defining Healthy Reference Populations for Determining the 99th Percentile**

Tables 1 and 2 present 99th percentile reference values for each assay, as designated by the manufacturer of each assay. A close examination of the package inserts, however, will reveal very little consistency in the types or numbers of individuals enrolled for determining the 99th percentile. No clear standard has been set for the statistical analysis used to calculate the 99th percentile. Defining what constitutes a healthy reference individual is currently a topic of debate. Should these individuals be apparently healthy individuals younger than 30...
years, or should they be age-matched patients hospitalized without known cardiovascular disease, similar to the demographics of patients who rule in for an acute myocardial infarction, likely between the ages of 30 and 90 years? How does one determine who is apparently healthy, i.e., normal? Should these individuals be selected: (a) via personal interview with questions addressing known medications, such as the use of statins for hyperlipidemia; (b) after obtaining information about known diseases associated with cardiovascular disease, such as renal disease or diabetes; or (c) via definitive evaluation of an individual by a physician taking a history and conducting a physical examination, including an electrocardiogram and an echocardiogram? The third option, in our opinion, would be ideal but is likely cost-prohibitive. Sequential selection of a reference population on this basis can be shown to shift the derived 99th percentile (30). For deriving reference intervals for each assay, we recommend a 2-fold approach in which both younger (<30 years) and older (>30 years, with a median age of 60 to 65 years to be representative of the ages of cardiac patients) apparently healthy reference groups are recruited. Inclusion criteria should be based on data obtained from an interview for a history of medications and known underlying disease, as well as a blood measurement of a natriuretic peptide (N-terminal pro-B-type natriuretic peptide or B-type natriuretic peptide) interpreted via a cutoff value for the exclusion of ventricular dysfunction (31) to serve as a surrogate biomarker for underlying myocardial dysfunction. In addition, the groups should be split equally by sex and include a

<table>
<thead>
<tr>
<th>Company/platform/assay</th>
<th>Cardiac troponin concentration at:</th>
<th>99th Percentile, g/L (CV)%</th>
<th>10% CV concentration, g/L</th>
<th>Amino acid residues of epitopes recognized by capture (C) and detection (D) MAbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott AxSYM ADV</td>
<td>0.02</td>
<td>0.04 (14%)</td>
<td>0.16</td>
<td>C: 87–91, D: 41–49</td>
</tr>
<tr>
<td>Abbott ARCHITECT</td>
<td>0.009</td>
<td>0.028 (14%)</td>
<td>0.032</td>
<td>C: 87–91, D: 41–49</td>
</tr>
<tr>
<td>Abbott i-STAT</td>
<td>0.02</td>
<td>0.08 (16.5%)</td>
<td>0.10</td>
<td>C: 41–49, D: 28–39, 62–78</td>
</tr>
<tr>
<td>Alere Triage</td>
<td>0.05</td>
<td>&lt;0.05 (NA)</td>
<td>NA</td>
<td>C: 27–40</td>
</tr>
<tr>
<td>Alere Triage Cardio3</td>
<td>0.01</td>
<td>0.02 (17%)</td>
<td>0.06</td>
<td>C: 41–49, D: 24–40</td>
</tr>
<tr>
<td>Beckman Access AccuTnI</td>
<td>0.01</td>
<td>0.04 (14%)</td>
<td>0.06</td>
<td>C: 41–49, D: 24–40</td>
</tr>
<tr>
<td>bioMérieux Vidas Ultra</td>
<td>0.01</td>
<td>0.01 (27.7%)</td>
<td>0.11</td>
<td>C: 41–49, 22–29, D: 87–91, Mab 789</td>
</tr>
<tr>
<td>Mitsubishi Pathfast</td>
<td>0.008</td>
<td>0.029 (5.0%)</td>
<td>0.014</td>
<td>C: 41–49, D: 71–116, 163–209</td>
</tr>
<tr>
<td>Ortho Vitros Eci ES</td>
<td>0.012</td>
<td>0.034 (10%)</td>
<td>0.034</td>
<td>C: 24–40, 41–49, D: 87–91</td>
</tr>
<tr>
<td>Radiometer AQ T90 cTnI</td>
<td>0.009</td>
<td>0.023 (17.7%)</td>
<td>0.039</td>
<td>C: 41–49, 190–196, D: 137–149</td>
</tr>
<tr>
<td>Radiometer AQ T90 cTnT</td>
<td>0.008</td>
<td>0.017 (15.2%)</td>
<td>0.026</td>
<td>C: 125–131, D: 136–147</td>
</tr>
<tr>
<td>Response RAMP</td>
<td>0.03</td>
<td>&lt;0.01 (18.5% at 0.05)</td>
<td>0.21</td>
<td>C: 85–92, D: 26–38</td>
</tr>
<tr>
<td>Roche cobas h232 Cardiac Tr&lt;sup&gt;c&lt;/sup&gt;d</td>
<td>0.05</td>
<td>NA</td>
<td>0.30</td>
<td>C: 125–131, D: 136–147</td>
</tr>
<tr>
<td>Roche Elecsys TnT Gen 4</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>0.030</td>
<td>C: 136–147, D: 125–131</td>
</tr>
<tr>
<td>Roche Elecsys Tnl</td>
<td>0.16</td>
<td>0.16 (10%)</td>
<td>0.30</td>
<td>C: 87–91, 190–196, D: 23–29, 27–43</td>
</tr>
<tr>
<td>Roche Cardiac Reader cTnT&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.03</td>
<td>NA</td>
<td>0.30</td>
<td>C: 125–131, D: 136–147</td>
</tr>
<tr>
<td>Siemens Centaur Ultra</td>
<td>0.006</td>
<td>0.04 (8.8%)</td>
<td>0.03</td>
<td>C: 41–49, 87–91, D: 27–40</td>
</tr>
<tr>
<td>Siemens Dimension RxL</td>
<td>0.04</td>
<td>0.07 (20%)</td>
<td>0.14</td>
<td>C: 27–32, D: 41–56</td>
</tr>
<tr>
<td>Siemens Immulite 2500</td>
<td>0.1</td>
<td>0.2 (NA)</td>
<td>0.42</td>
<td>C: 87–91, D: 27–40</td>
</tr>
<tr>
<td>Siemens Stratus CS</td>
<td>0.03</td>
<td>0.07 (10%)</td>
<td>0.06</td>
<td>C: 27–32, D: 41–56</td>
</tr>
<tr>
<td>Siemens Vista</td>
<td>0.015</td>
<td>0.045 (10%)</td>
<td>0.04</td>
<td>C: 27–32, D: 41–56</td>
</tr>
<tr>
<td>Toosh AIa</td>
<td>0.06</td>
<td>&lt;0.06 (NA)</td>
<td>0.09</td>
<td>C: 41–49, D: 87–91</td>
</tr>
</tbody>
</table>

<sup>a</sup> LoD, limit of detection; NA, not available; Gen 4, fourth-generation assay.
<sup>b</sup> CV at 99th percentile.
<sup>c</sup> Not cleared by the US Food and Drug Administration.
<sup>d</sup> Standardized against hs-cTnT assay.
<sup>e</sup> Standardized against Gen 4 cTnT assay.
diverse racial and ethnic mix. The CLSI recommends a minimum of 120 individuals per group of healthy individuals for an appropriate statistical determination of a normal reference limit cutoff. This number was suggested as the minimum number of individuals necessary for estimating the limits of a central 95% reference interval (with limits at the 2.5th and 97.5th percentiles) by use of the nonparametric estimation method. This number of individuals is not adequate for determining a 99th percentile value, for which 300–500 individuals have been recommended to allow an appropriately powered analysis. To date, no study has compared all contemporary sensitive assays and/or hs assays within the same reference or disease population. For the hs assays, data indicate a higher 99th percentile value for males than for females, for hs-cTnI [Singulex assay (32)] and hs-cTnT (18), but not for hs-cTnI measured with the Beckman Coulter assay (8). Unpublished data for the Abbott ARCHITECT prototype STAT hs-TnI assay showed that concentrations were significantly sex and age dependent (F.S. Apple, personal communication). In addition, the percentage of individuals within each reference study with a measurable value above the limit of detection has been shown to vary from study to study. This variation is likely dependent on sample type, sample handling and storage, and whether samples were analyzed fresh or after a freeze–thaw cycle.

**Biological Variability**

Determining the biological variation is not possible for both cTnI and cTnT with the contemporary sensitive assays in clinical practice today, because these assays cannot reliably measure concentrations in healthy individuals. Most of these assays detect measurable values in <15% of healthy individuals (33, 34). In contrast, Table 3 demonstrates the biological-variation characteristics of 5 hs assays (35–38), with the same samples used for measuring short-term variation as initially collected by Wu et al. (35) for all but 1 study (36). Within-individual mean cardiac troponin concentrations ranged between 2.2 ng/L and 4.9 ng/L for both cTnI and cTnT, and reference change values ranged from 32% to 69.3%. In a comparison of 2 independently published studies of hs-cTnT, characterization of the biological variation yielded positive reference change values of 84.5% (35) and 47% (36). These data, along with imprecision data at the 99th percentile (discussed below), will need appropriate statistical evaluation to establish guidelines to assist in the clinical interpretation of cardiac troponin results, both for single test results and for evaluating what changes in cardiac troponin in serial testing represent actual abnormality and change over time, and what changes are merely noise.

**Imprecision at the 99th Percentile**

The 2007 universal definition of myocardial infarction guidelines published by the Joint Task Force (1) recommended preferential use of assays that demonstrated a total CV of ≤10% at the 99th percentile, on the assumption that better precision will improve the ability to detect a significant serial change. Evidence-based data, however, now support the use of assays
with a CV of ≤20% at the 99th percentile (39, 40), because a 20% CV does not lead to misclassification of patients in diagnostic or risk-assessment management. This information is promising for the contemporary sensitive cTnI assays used in current practice, because the large majority of assays used worldwide fall into this category.

Table 2 shows both the CVs at the 99th percentile concentration for the 6 hs cardiac troponin assays and the lowest concentrations reported for which a 10% CV was obtained. All hs assays demonstrated a CV ≤10% at the 99th reference percentile, and several assays demonstrated a 10% CV at a concentration an order of magnitude lower. Such information is useful to laboratorians and clinicians because it allows them to confidently report hs cardiac troponin values and changing results over time that are unaffected by analytical noise. The true test of how well the total imprecision of cardiac troponin assays (as reported in Tables 1 and 2) from manufacturer studies will hold up is when assays are used daily in clinical practice and QC materials are evaluated over weeks, after numerous calibrations and reagent lot changes. For now, only the Roche hs-cTnT assay has been used in clinical practice, and it appears to have maintained the 10% total CV quality characteristic at the 99th percentile concentration (18, 19). Comparison of the new hs-cTnT assay with the previous fourth-generation cTnT assay has shown good agreement for values >100 ng/L in 2 studies (slope, 0.962–1.087) (18) but higher discordance in another study (slope, 0.77) (29).

Conclusion

This review has attempted to clarify the important analytical and reference-limit issues pertaining to cTnl and cTnT assays and has specifically addressed hs assays used to measure low concentrations (i.e., nanograms per liter or picograms per milliliter). Recommendations have been made to help clarify the nomenclature. The review also has identified additional challenges for the evolving science of cardiac troponin measurement. It is hoped that by the introduction of these concepts, both laboratorians and clinicians can develop a more unified view of how these assays are used worldwide in clinical practice.

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High-Sensitivity Cardiac Troponin Assays

References