Edging Closer to Early Optimal Patient Management With High-Sensitivity Cardiac Troponin Assay

Fred S. Apple, PhD

These are exciting times in the evolution of cardiac biomarkers. In the past 12 years, we have witnessed the transition from creatine kinase-MB to cardiac troponin I (cTnI) and T (cTnT) as the standard biomarkers to aid in the diagnosis of acute myocardial infarction (MI). This is evidenced by the overwhelming endorsement through recommendations from laboratory medicine, cardiology, and emergency medicine. At present, the biomarker field is moving forward with an analytic advancement of technologies to be able to measure both cTnT and cTnI for the precise measurement at concentrations within normal reference subjects. High-sensitivity cardiac troponin assays show great promise for earlier diagnostic accuracy for detection of MI, improved triage of patients to allow for better outcomes assessment of low-risk acute coronary syndrome patients, and to address a role in primary prevention as a necessary tool to assist clinicians in all cardiovascular evaluations. What distinguishes these new high-sensitivity assays from their predecessors is the ability to measure very low cTnT and cTnI concentrations (1 to 20 pg/mL, which equals 0.001 to 0.020 μg/L, well below the limit of detection of the sensitive and contemporary assays used in clinical practice today), with an excellent imprecision (coefficient of variation ≤10%) at and below the assay’s 99th percentile value. This added sensitivity allows high-sensitivity cardiac troponin assays to reliably measure concentrations in almost 100% of healthy individuals. Contemporary assays can typically measure cardiac troponin values in only 10% to 20% of individuals from the general, apparently healthy population.

The role that the biomarker cardiac troponin occupies in assisting in the diagnosis of MI is further solidified in the findings presented by Reichlin and coworkers in the present issue of Circulation of their study examining absolute and relative changes in patients presenting to rule out MI. Unique to their study is their observation that an absolute concentration change significantly improves the ability to define an MI at 2 hours after presentation compared with a relative present change. In an adjudicated subgroup of the APACE study, these patients are not without (acute) and long-term (more chronic) events, which often may be due to more chronic pathologies. However, as pointed out by Reichlin et al, these patients are not without risk and need to be evaluated for risk of both short-term (acute) and long-term (more chronic) events, which often occur because of lack of cardiology attention.

Third, Reichlin et al discuss the importance of the role of short-term biological variation as a tool to differentiate changes in cardiac troponins over time versus same-day patient variation, which for high-sensitivity assays varies between 46% and 85%, which shows that these absolute concentrations indicate real changes outside normal biological variation. However, an important tool that was not rigorously addressed was the ascertainment of an optimal

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(Advantageous Predictors of Acute Coronary Syndromes Evaluation), they demonstrate clinical sensitivities for MI between 89% and 93% at 2 hours after presentation using both cTnT as measured by the Roche high-sensitivity assay (hs-cTnT) and cTnI as measured by the Siemens sensitive assay. This finding appears to confirm previous observations by this group that the diagnostic accuracy of the hs-cTnT assay and the Siemens sensitive cTnI assay does not differ. This raises my first question: How does one define an assay as “high-sensitivity”? Neither of the assays studied in the present report are novel, as implied through the report. Previously, I proposed a scorecard approach to designate the level of analytic sensitivity of an assay that would define the assay’s ability to measure normal (healthy) subjects, as well as whether the assay’s imprecision meets the Global Task Force’s recommended 10% coefficient of variation at the 99th percentile reference value. Although the Roche hs-cTnT assay met this level 4 high-sensitivity criteria designation, the Siemens cTnI assay only qualified as a level 1 clinically usable, sensitive assay. Yet these assays appear to have similar clinical performance. Keeping in mind that the high-sensitivity level 4 designation is only about the assay and not about measuring a different cTnT protein, there exists a need to perform similar studies using the prototype/research of hs-cTnI assays in direct comparison with the hs-cTnT assay to validate the designation of high-sensitivity assays in the clinical setting.

My second observation is the improvement of the positive predictive value and specificity using the absolute 2-hour change criteria. Typically, with improved analytic sensitivity, cardiac troponin assays detect non–acute coronary syndrome pathologies that cause myocardial cell death, giving rise to increased cTnT and cTnI concentrations that are not the result of MIs, a major concern of clinicians confronted with many positive troponins without a clinical explanation. Some such increases may be due to other acute cardiovascular events, such as pulmonary embolism, myocarditis, or sepsis, but many may be due to more chronic pathologies. However, as pointed out by Reichlin et al, these patients are not without risk and need to be evaluated for risk of both short-term (acute) and long-term (more chronic) events, which often occur because of lack of cardiology attention.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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receiver operating characteristic curve–determined clinical delta (change) value based on each assay studied, which previously was shown to be 30% for another sensitive assay.\textsuperscript{16} Reichlin et al\textsuperscript{9} studied only the relative change percent between 0 and 2 hours. It would be informative to determine assay-dependent clinical delta values for comparison with the absolute change values. This analysis may be important to determine whether an optimal clinical delta value may or may not improve clinical specificity, as previously shown over a 6-hour time period (but without improvement in clinical sensitivity).\textsuperscript{16}

Fourth, closer examination of the MI patients in the 0±0.002 μg/L concentration MI group and the unstable angina group in whom optimal care is clinically very important is needed, so therapeutic interventions are not missed to benefit short-term patient outcomes. Studies will need to be performed to compare absolute concentration changes and clinical delta percent changes or a combination thereof. This approach will need to be addressed in the next revision of the Global Task Force’s universal definition of MI.

Fifth, the findings of the present study need to be confirmed by (high-sensitivity) cTnI assays, which hold a worldwide market share of >70% compared with cTnT assays, as well as extended to include risk outcomes assessment based on absolute change and delta percent changes, with assessment for major adverse cardiac events for short-term outcomes.

Sixth, the observation that the absolute changes are greater for cTnT using a sensitive assay compared with the hs-cTnT assay underscore the need for clinicians and laboratorians to understand that there is no harmonization between cTnT and cTnI assays. When hs-cTnI assays begin to be studied, the reader must understand that not all cTnI assays are created equal. There is no harmonization of concentrations between cTnT assays because of a lack of standardization across all cTnI assays, even within the same manufacturers of multiple assays under the same brand.\textsuperscript{11} Thus, absolute concentrations should never be assumed to be generalized in any recommendations, because this will only cause clinical confusion for interpretation.

Finally, a limitation in the data set presented by Reichlin et al\textsuperscript{9} concerns Table 3, in which the authors attempt to demonstrate that independent of the baseline cardiac troponin concentration, either above or below the 99th percentile value, an absolute change over 2 hours improves diagnostic accuracy. However, it does not appear that this claim can be made as strongly as suggested, because the patients described in each group above and below the 99th percentile for each assay are not well described for number or diagnosis. Furthermore, percentage changes versus the baseline were variable; for example, a change from 7 to 14 pg/mL, which is 7 pg/mL, represented a 100% change, which differs from the 50% change that resulted from the change from 14 to 21 pg/mL, also a 7-pg/mL change. This will help clinicians understand the likely advantage of absolute change. Further studies are needed to substantiate this important but preliminary observation.

In summary, we don’t need new biomarkers, we need a better understanding of how high-sensitivity cardiac troponin assays improve patient care through earlier and more accurate diagnosis. Reichlin and coworkers\textsuperscript{9} describe important information that may be applied toward addressing this goal.

**Disclosures**

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**References**


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