What Criteria Should Be Used to Assess Troponin Assays?

To the Editor:

Since the introduction of cardiac troponin testing in the 1990s, troponin measurement has become the main diagnostic criterion for the diagnosis of myocardial infarction. In 2000, a joint working party of the European Society of Cardiology and the American College of Cardiology redefined myocardial infarction, giving major importance to the rise and fall of troponin concentrations in the diagnosis (1). This importance was confirmed in a more recent universal definition of myocardial infarction (2). The laboratory community was involved in these definitions, and published guidelines of the National Academy of Clinical Chemistry concur with them (3). Since troponin assays became routinely available, there have been several improvements in the available commercial assays, including lower detection limits for assays, better precision at low concentrations, and improvements in standardization. Because the troponin concentration has been shown to be a powerful predictor of death and a requirement for revascularization in patients presenting with acute coronary syndrome, the analytical performance of troponin assays is very important. Frequently, clinical decisions, such as anticoagulation therapy, hospital admission, and referral to a cardiologist, will be based on increased values in troponin assays. The performance of the different assays can be difficult to assess objectively, however.

In an effort to allow better evaluation for the clinical and laboratory community, Apple has suggested a scorecard for cardiac troponin assays (4) that uses 2 criteria to assess the value of a troponin assay. The main criterion is the precision of the assay at the 99th percentile of a reference population. A good assay is one with a 10% CV at the population’s 99th percentile, and a “clinically usable” assay is one with a CV between 10% and 20% at the 99th percentile for a population. On the other hand, any assay with a CV >20% at this cutpoint would be deemed unacceptable. Apple further differentiates assays on their ability to detect troponin in healthy control individuals. Although we believe it is timely to think about the performance of troponin assays and to give clinicians and laboratorians guidance about evaluating the quality of troponin assays, we have concerns about some of the elements he has proposed and about some elements he has not included.

Our major point of disagreement with Apple is that he uses the 99th percentile of a reference population and the precision of the assay for assessing assay quality but gives no consideration to the clinical value of that assay. This latter point is of great importance. For example, Venge et al. used samples from the FRISC (Fast Revascularisation during Instability in Coronary Artery Disease) study to compare the performance of the Liaison cardiac troponin I assay (DiaSorin) in unstable coronary artery disease (5). The Liaison assay showed high precision, with a 10% CV at 0.027 μg/L and a 20% CV at 0.015 μg/L, and the 99th percentile of the upper reference limit of a reference population was 0.041 μg/L. This assay would have qualified as acceptable; however, a comparison with another troponin assay (Access AccuTnI; Beckman Coulter) showed that the Liaison assay missed about 10% of patients with unstable angina and at an increased risk of death or acute myocardial infarction within 6 months. This result was independent of whether the 99th percentile or a 20% CV was chosen as the cutoff.

More recently, large prospective cohort studies of patients presenting with chest pain to the emergency department showed similar results (6, 7). In these studies, more-sensitive assays for troponin I showed a performance for diagnosing acute myocardial infarction that was improved over that for so-called standard assays (the troponin II fourth-generation assays and the Siemens Dimension RxL troponin I assay). Assays with superior diagnostic performance in these recent studies of 2 cohorts were the Abbot Architect, the Siemens Centaur Ultra, and the Roche Elecsys highly sensitive troponin T assays. Assays that were less sensitive included the fourth-generation troponin T assay in particular. According to Apple’s scorecard, however, the Abbott Architect assay is ranked as “clinically usable” at level 1, similar to that of the fourth-generation Roche Elecsys troponin T assay (clinically usable level 1) and the Siemens Dimension RxL assay. The Siemens Centaur Ultra is labeled as “guideline acceptable” level 1, whereas the Roche Elecsys highly sensitive troponin T assay is labeled guideline acceptable level 4. We therefore feel that the use of an assay imprecision defined as a 10% CV and the 99th percentile of control individuals falls short in the judgment of assay performance.

A better way to compare assay performance might be to use pools of patient sera with different concentrations of cardiac troponins. An important study that used serum pools was published in 2004 (8). Although the study did not allow the comparison of troponin I and troponin T values because patient pools were selected, it could clarify which assays have less sensitivity for troponin. For example, in this study the Abbott AxSYM analyzer was unable to measure the pool with the lowest concentration, as was the Immuno 1 analyzer.
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Clinical Chemistry published this year associated with differences. In a study Centaur TnI-Ultra might be associated with the Access AccuTnI and the sensitive second-generation assays currently not recognized in the national patients at risk and is translates into the recognition of additional patients at risk and is currently not recognized in the scorecard. Even the use of highly sensitive second-generation assays such as the Access AccuTnI and the Centaur TnI-Ultra might be associated with differences. In a study published this year (9), 1251 patients of the GUSTO 4 cohort (Global Use of Strategies to Open Occluded Coronary Arteries) were investigated with 2 cardiac troponin I assays that both claimed to have a 10% CV below the 99th percentile of a reference population. The AccuTnI assay identified more patients at risk than the Centaur TnI assay. Furthermore, these additional patients had increased cardiac mortality; however, to obtain the optimal sensitivity necessitated that the specificity of the assay for this high-risk population be very poor.

Apple uses the 10% CV criterion in his scorecard as an important point of assay differentiation. This 10% CV criterion has been widely accepted and is used in the recommendations of both the Cardiac Society of Australia and New Zealand and the National Academy of Clinical Biochemistry. There is no evidence base to support the use of the 10% CV criterion, however, and in fact the opposite is true. In an elegant study reported in 2005, Apple et al. (10) used mathematical modeling to show that use of an assay with a CV of 25% at the 99th percentile will not lead to large numbers of additional patients classified as false positives, compared with an assay that has a CV of 10% at the 99th percentile. In fact, because serial measurements of cardiac troponin are typical, only about 3 to 5 of 1000 patients in clinical practice are likely to be misclassified as false positives in an assay with a 25% CV at the 99th percentile. Furthermore, a wealth of evidence now shows that in the setting of acute coronary syndrome, troponin concentrations corresponding to assay CVs well above the 10% CV cutoff are informative of a worse prognosis (5, 10, 11).

What is the way forward? Although we agree that assays can and should be scored objectively on their technical characteristics, we also believe that assays can and should be compared with respect to their clinical performance. Information that is useful for comparing troponin assays includes clinical cohort studies that use chest pain patients in the emergency department, patients with a high pretest probability for unstable angina, and patient populations from the glycoprotein IIB/IIIa inhibitor trials. Additional clinically relevant information can be obtained from the exchange of patient pools and their measurements with different analyzers and assays. The reliance on the 99th percentiles of healthy reference populations and the value of the 10% CV of the assay are helpful in the overall specification of the assay and might contribute to the judgment of the quality of an assay, but they should not be the final criteria for scoring a troponin assay. This matter needs further debate.

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 of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.
Consultant or Advisory Role: H.G. Schneider, Amgen advisory board.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: None declared.
Expert Testimony: None declared.
Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References

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Previously published online at  
DOI: 10.1373/clinchem.2009.137422