EDITORIAL

Clinical Application of Sensitive Troponin Assays

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Despite the pervasive measurement of cardiac troponin for the diagnosis of myocardial infarction, the continued evolution of assays and guidelines for their application has created uncertainty among many practitioners regarding the use of cutoff values for clinical interpretation. As such, many clinicians may not welcome more sensitive assays for troponin. Nevertheless, professional societies have advocated for improved analytic performance of commercial assays, resulting in a current generation of widely used troponin assays that are more sensitive than their predecessors. In this issue of the *Journal*, important studies by Keller et al.[1] and Reichlin et al.[2] reveal the advantages and limitations of diagnostic testing with the latest generation of sensitive assays for troponin.

Preclinical and clinical evidence conclusively show that troponin offers levels of sensitivity and specificity for cardiomyocyte injury that are superior to those for the creatine kinase MB fraction (CK-MB), which exists in tissues other than myocardium. Since 1999, professional societies have recommended the use of troponin as the preferred biomarker for evaluation of patients with suspected myocardial infarction.[3-5] Testing for troponin is now widespread and has replaced testing for CK-MB in some countries. However, this transition has occurred with growing pains.

At the time of the initial approval of troponin testing for clinical use, manufacturer-recommended cutoff values for troponin were developed from comparative studies of results of CK-MB testing. However, this approach was flawed because the derived thresholds were based on comparisons with a less sensitive test. For this reason, laboratory guidelines recommended a reduced cutoff value on the basis of the distribution of troponin in healthy reference populations.[3] This approach of defining an upper limit of normal at the 97.5th or 99th percentile of a reference population is the method used to establish cutoff values for many clinical laboratory tests. For troponin, professional societies recommended the 99th percentile (i.e., a positive test for 1 in 100 persons in the reference group) as more conservative than the 97.5th percentile.[6] Since 2000, cardiology and laboratory guidelines have endorsed a single cutoff value for the diagnosis of myocardial infarction at the 99th percentile for each assay.[4-6] Nevertheless, on the basis of the outdated laboratory guidelines,[3] many laboratories continue to report an "inconclusive" or "suggestive" range using two cutoff values.

Concurrent with changes in guidelines, manufacturers have progressively enhanced the analytic performance of troponin assays. This effort has reduced the incidence of analytic false positives (i.e., an elevated value despite an absence of circulating troponin). Also, as a result of better precision, the new assays are analytically more sensitive and can detect substantially lower concentrations of troponin than previous generations of assays. This trend has led to two critical questions: What is the diagnostic sensitivity and specificity of the more sensitive assays? And is the low concentration of detectable troponin clinically meaningful?

Keller et al. and Reichlin et al. report large, multicenter evaluations of the diagnostic performance of several sensitive assays for troponin. Their principal findings are highly consistent. In the two studies, the accuracy of troponin for the diagnosis of myocardial infarction was improved with the sensitive assays (94 to 96%), as compared with the older assays (85 to 90%). The im-

proved accuracy was most pronounced soon after the onset of chest-pain symptoms. In the study by Reichlin et al., the accuracy of the sensitive assays within 3 hours after the onset of chest pain was 92 to 94%, as compared with 76% for the standard assay.

Not surprisingly, this enhanced accuracy arose from a substantial increase in clinical sensitivity with the analytically more sensitive assays.[7] In the study by Keller et al., the clinical sensitivity at the 99th percentile cutoff value increased from 63.7% to 90.7% with the newer assay. However, the improved sensitivity was accompanied by a reduced specificity for myocardial infarction, as compared with the standard assay (90.2% vs. 97.2%). Consequently, for every 100 patients with an elevated troponin level detected with the sensitive assay, 77 had a final diagnosis of myocardial infarction. This positive predictive value was as low as 50% with one of the assays that were studied by Reichlin et al.

In these studies, the two groups of investigators showed that a new generation of sensitive assays for troponin improved overall diagnostic accuracy and thus functioned as a better test. The findings support current professional guidelines for the use of troponin[4,5] and a rationale for the use of more sensitive assays. However, their results also confirm a trade-off of superior clinical sensitivity for diminished clinical specificity for the diagnosis of myocardial infarction.

It is essential to differentiate between the tissue specificity of troponin for cardiomyocyte injury and the clinical specificity for myocardial infarction, which is defined by ischemia as the mechanism of injury.[5] The adoption of troponin has revealed the occurrence of myocardial injury in many conditions in which it was not previously detected with the use of CK-MB. Such detection has given the impression of an increased number of false positive results. However, this occurrence does not impugn the tissue specificity of troponin but rather underscores that myocardial injury may result from a variety of mechanisms. It also shows that a clinical diagnosis of myocardial infarction depends both on elevated levels of troponin and on clinical data (e.g., the presence of typical symptoms) that support ischemia as the cause.[4,5] On the basis of this pathophysiology, it is not possible to reliably discriminate ischemic from nonischemic causes (e.g., myocarditis) by simply raising the cutoff value. However, a rising or falling pattern of troponin values is helpful in discriminating acute injury from chronic causes, such as end-stage renal disease.[4,5] Also, imaging techniques, such as cardiac magnetic resonance imaging, are likely to play an increasing role in distinguishing patterns of myocardial injury.

In addition to these diagnostic considerations, the prognostic implications of low-level increases in troponin that are detected with sensitive assays must be addressed. At least six studies, including clinical trials and community-based investigations, have firmly established the prognostic relevance of a small elevation in troponin (>99th percentile with the use of the previous generation of assays) in patients with an acute coronary syndrome.[5] Collectively, these data indicate a more than doubling of the adjusted risk of death or recurrent ischemia in patients with a small troponin elevation.[5] Among patients with a high probability of an acute coronary syndrome, the approximately 20% of patients who were missed with the use of outdated cutoff values for troponin were at high risk for recurrent events. These patients derived significant benefit from an early invasive evaluation, which shows the cost of using higher cutoff values in an attempt to increase clinical specificity.[8] Similar investigations of outcomes and therapeutic implications have yet to be performed for the majority of sensitive assays studied by Reichlin et al. A single-center evaluation of the assay studied by Keller et al. suggested that the prognostic implications of low-level troponin are maintained,[9] but results from larger studies are needed.

The studies by Keller et al. and Reichlin et al. indicate that sensitive assays for troponin are a step forward with respect to overall diagnostic accuracy for myocardial infarction. Additional studies are warranted to clarify the association between changes in troponin levels measured with sensitive assays and short-term and long-term outcomes of patients.

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1. Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med 2009;361:868-77.

2. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858-67.
3. Wu AH, Apple FS, Gibler WB, Jesse RL, Warshaw MM, Valdes R Jr. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. Clin Chem 1999;45:1104-21.
4. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Eur Heart J 2007;28:2525-38.
5. Morrow DA, Cannon CP, Jesse RL, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Clin Chem 2007;53:552-74.
6. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined — a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959-69. [Erratum, J Am Coll Cardiol 2001; 37:973.]
7. Melanson SE, Morrow DA, Jarolim P. Earlier detection of myocardial injury in a preliminary evaluation using a new troponin I assay with improved sensitivity. Am J Clin Pathol 2007;128: 282-6.
8. Morrow DA, Cannon CP, Rifai N, et al. Ability of minor elevations of troponin I and T to identify patients with unstable angina and non-ST elevation myocardial infarction who benefit from an early invasive strategy: results from a prospective, randomized trial. JAMA 2001;286:2405-12.
9. Apple FS, Smith SW, Pearce LA, Ler R, Murakami MM. Use of the Centaur TnI-Ultra assay for detection of myocardial infarction and adverse events in patients presenting with symptoms suggestive of acute coronary syndrome. Clin Chem 2008; 54:723-8.