Cardiac troponins are heavily relied on in the laboratory evaluation of patients with suspected myocardial infarction (MI) because of their putative high sensitivity and specificity for detection of myocardial necrosis. According to the National Academy of Clinical Biochemistry guidelines, "In the presence of a clinical history suggestive of acute coronary syndrome, maximal concentration of cardiac troponin exceeding the 99th percentile of values ... for a reference control group on at least 1 occasion during the first 24 hour after the clinical event is considered indicative of myocardial necrosis consistent with myocardial infarction."2

How Would the Reverend Bayes Interpret High-Sensitivity Troponin?

George A. Diamond, MD; Sanjay Kaul, MD

Deep down, we’re all Bayesians, except sometimes when making mistakes.
—I.J. Good, Good Thinking: The Foundations of Probability and its Applications.1

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Until recently, the commercially available troponin assays used in clinical practice lacked the stringent precision (10% coefficient of variation for levels below the 99th percentile cut-off) required by the guidelines.3 Over the past few years, however, so-called high-sensitivity, or ultrasensitive, assays have been developed that meet these requirements. Several recent studies have reported enhanced diagnostic and prognostic accuracy of these high-sensitivity troponin assays across a spectrum of patients with cardiovascular disease, including acute coronary syndromes (ACS),4,5 heart failure,6 and chronic stable coronary artery disease (CAD) without left ventricular systolic dysfunction.7

In this issue of Circulation, Januzzi et al8 compare the diagnostic performance of a new high-sensitivity troponin T (hsTnT) assay with that of the conventional cardiac troponin T (cTnT) assay in a single-center cross-sectional study of 377 emergency room patients with chest pain and low-to-intermediate likelihood of ACS (MI or unstable angina). The reference diagnosis was based on the judgment of 2 physicians with access to all clinical and laboratory data, including the results of conventional serial troponin measurements and stress tests, through 6 months of follow-up. Comparisons were also made with anatomic findings from cardiac computed tomography with use of a 64-slice scanner. A key feature of the study was that the hsTnT assays, sampled once at a median of 4 hours from presentation at the time computed tomography was performed, were done solely for research purposes, and the results were not provided to the clinicians to guide patient treatment.

Of the 377 patients enrolled (from a total of 1869 screened), 37 (9.8%) had an adjudicated final diagnosis of ACS—8 (2.1%) with acute MI and 29 (7.7%) with unstable angina. The remaining 340 patients (90.2%) had no evidence of active myocardial ischemia at the time of hospital discharge.

The authors conclude that hsTnT provides superior overall diagnostic performance in comparison with cTnT. The greater accuracy of hsTnT for diagnosis of ACS was driven by its enhanced diagnostic sensitivity (from 35% to 62%) at the cost of a significant reduction in specificity (from 99% to 89%). As a result of this trade-off, hsTnT >13 pg/mL correctly detected 11 more cases than did cTnT >0.03 ng/mL among the 37 ACS patients, but it falsely detected 35 more cases among the 340 non-ACS patients. Elevations in hsTnT, nevertheless, “identified patients with significant structural heart disease irrespective of the diagnosis of ACS.”

Two noteworthy aspects of the current study deserve emphasis. First, in addition to conventional measures of diagnostic accuracy (sensitivity, specificity, and predictive accuracy) and strength of association (odds ratio), the authors also assessed the incremental discriminant accuracy of the new assay by comparing the C statistic (area under the receiver operating characteristic curve) for a prediction model using hsTnT with that for a prediction model using cTnT. The 0.05 gain in C statistic observed with hsTnT (from 0.74 to 0.79) failed to achieve statistical significance (P=0.28) but might yet be clinically important given the relative insensitivity of the C statistic for detecting moderately sized effects. For example, widely established cardiovascular risk factors such as systolic blood pressure and cholesterol are associated with small incremental gains in the C statistic (0.03 to 0.04) for the prediction of cardiovascular events.9 In performing these analyses, Januzzi et al used a diagnostic standard for the presence or absence of MI relative to hsTnT that considered all relevant clinical observations, including the results of cTnT.8 It is not clear how this choice affected the C statistic and other metrics of diagnostic accuracy reported by them.

Nevertheless, the thoughtful clinician is more likely interested in the extent to which a biomarker correctly reclassifies individuals to a higher or lower risk of a specific outcome, especially if that reclassification has potentially important therapeutic implications. Such reclassification metrics depend heavily on the correlation matrix between hsTnT and cTnT.

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and on the frequency and pattern of discordant observations. Unfortunately, these data are not presented in the current report. Thus, it remains to be established whether treatment of patients by the use of hsTnT is associated with an overall improvement in clinical outcome.

The second noteworthy aspect of this study is the association of elevated hsTnT with prevalent cardiovascular disease as assessed by cardiac computed tomography. Nearly 11% (38 of 340) of patients without ACS also had elevations of hsTnT >13 pg/mL. These patients were more likely to have risk factors or a previous history of CAD, a greater burden of CAD, larger cardiac chamber sizes, and greater left ventricular mass than were those without elevated hsTnT. This observation indicates that troponin, in addition to being a marker of ACS, might also be a marker of underlying structural heart disease, thereby supporting the use of hsTnT for cardiovascular screening. The mechanisms responsible for this association are unknown but might include silent myocardial ischemia, vascular inflammation, cardiomyocyte apoptosis, pressure and volume overload, and impairment of renal clearance.

Whether elevations in hsTnT also identify a greater burden of cardiovascular disease in patients with ACS (as they do in those without ACS) is not directly apparent from this study. Furthermore, the investigators recently reported (in the same patients evaluated in this study) that both coronary artery plaque and stenosis detected by computed tomographic angiography predict ACS independently of cardiovascular risk factors or Thrombolysis in Myocardial Infarction risk score. Whether the predictive accuracy of hsTnT is improved when combined with cardiac computed tomography findings merits careful consideration.

Although not directly tested by the investigators, an important advantage of the newer assays is in reliably ruling out MI early in the diagnostic process. For patients with suspected low likelihood of ACS, a single negative troponin level determined within 4 hours of presentation (having a negative predictive value in excess of 95%) would probably be sufficient to exclude ACS. On one hand, this holds promise of expediting the triage of patients with suspected ACS, thereby facilitating the process of appropriate healthcare delivery. On the other hand, the trade-off in clinical specificity for the diagnosis of ischemic myocardial injury might result in a substantially higher number of false-positive findings, especially when the pretest probability of ACS is low. This might be the case when sensitive assays are widely used in general clinical practice, not only in preselected patients in chest pain units or emergency rooms, as in the present study.

Serial high-sensitivity troponin determinations (3 to 6 hours apart) might better define the kinetics of the release process and thereby improve discrimination of patients with acute myocardial injury (secondary to ischemia) from those with chronic injury (secondary to structural heart disease and other confounding conditions, such as myocarditis, acute heart failure, pulmonary embolism, and septic shock). Given the imperfect sensitivities and specificities resulting from these confounding conditions, therefore, even high-sensitivity troponin is best interpreted in conjunction with clinical and laboratory assessment by use of the Bayes’ theorem.

### Bayesian Analysis of Troponins

Determining whether or not a particular troponin elevation is due to ischemic myocardial injury is dependent on its pretest probability. Pretest probability for obstructive CAD has been formally quantified in reference to coronary angiography on the basis of observable clinical characteristics such as age, sex, risk factors, and the quality of presenting symptoms. Similarly, factors associated with a high pretest probability of ACS include a history of CAD or its risk factors, typical ischemic symptoms (rest or crescendo angina), ECG changes (ST depression of ≥1.0 mm or T wave inversion) and wall-motion abnormalities detected by noninvasive imaging.

An ideal strategy for interpretation of troponin would define the patient-specific posttest probability of disease given the patient-specific pretest probability and the patient-specific observed troponin level. One such algorithm (based on clinical presentation, ECG changes, age, renal function, and cTnT) was recently shown to provide more accurate diagnosis of ACS but has not yet been prospectively validated.

Consider a specific application of this approach. Suppose our patient has an hsTnT of 15 pg/mL. We can use the data in Table 2 of the article by Januzzi and colleagues to interpret this observation relative to a diagnosis of ACS by use of the Bayes’ theorem. According to the data of Januzzi et al, the sensitivity for hsTnT >13 pg/mL is 62% and the specificity is 89% for ACS. Thus, if our patient has a pretest probability for ACS of 10% (based on clinical judgment or a formal algorithmic tool), Figure 1 shows the posttest probability of ACS given hsTnT >13 pg/mL to be 39% (consistent with the positive predictive value reported in Table 2 for an ACS prevalence of 9.4%). The figure also shows the corresponding posttest probabilities for positive cTnT levels by use of the >0.01 and >0.03 ng/mL cut-offs to be 64% and 80%, respectively—values that are higher...
Bayesian analysis of acute myocardial infarction

Based on the sensitivity and specificity for high-sensitivity troponin T (hsTnT) data provided by Januzzi et al (top curve) and Reichlin et al (bottom curve) for the 99th percentile hsTnT cutoff, the post-test probabilities for a given pretest probability of 2.1% and 17% (prevalence of myocardial infarction in the 2 studies, respectively) are 11% and 50%.

than those for hsTnT. The difference in posttest probabilities becomes more pronounced at low pretest probabilities, highlighting the impact of low specificity of hsTnT in patients presenting with low pretest probability of ACS. By contrast, hsTnT delivers a posttest probability of ≥85% in patients with a pretest probability for ACS of ≥50%, illustrating that reduced specificity is of minor relevance in patients with intermediate to high pretest probability of ACS. Similar observations are apparent when the Bayes’ theorem is applied to the diagnosis of MI or unstable angina.

Thus, even very high values of troponin do not establish a diagnosis of ACS with confidence if the pretest probability is low. Conversely, very low values do not reliably exclude the diagnosis of ACS if pretest probability is high. From a Bayesian perspective, therefore, troponins are no different from any other imperfect diagnostic test, and even putative “high-sensitivity” assays must obey the mathematical laws of probability.

Figure 2 illustrates the comparable analysis of hsTnT for diagnosis of acute MI in the current study by Januzzi et al and a previously reported study by Reichlin et al. Despite a higher-risk population enrolled in the study by Reichlin et al (prevalence of MI and ACS being 17% and 33%, respectively, versus 2.1% and 9.8% in the study by Januzzi et al), the posttest probability curves are virtually superimposed. The difference in posttest probabilities for MI in the 2 studies (11% versus 50%) despite comparable diagnostic accuracy highlights the impact of pretest probability on diagnostic interpretation.

Just as a tool is only as good as its operator, a diagnostic test can be only as good as its interpretation. Expecting the test to provide all the answers without including the proper clinical context can lead to erroneous diagnoses. As our tests become more sophisticated so must our diagnostic interpretations. If we can appropriately control the process of diagnosis, we can appropriately control the quality and cost of health care. The Bayes’ theorem provides us with the appropriate language to exert this control.

Future troponin research, therefore, should be directed (1) at developing and validating clinically relevant algorithms for estimating the pretest probability of various components of the composite diagnosis of ACS, (2) at characterizing the sensitivity and specificity of particular levels of troponin (in contrast to the open-ended cutpoints assessed by Januzzi et al) across the entire clinical spectrum of levels, and (3) at determining the optimal posttest probability thresholds for initiating appropriate therapeutic management strategies.

In summary, although high-sensitivity troponin assays offer potential advantages over the conventional assays, the major problem with them, as with any other laboratory test, is often an inappropriate request and improper interpretation of the results, not the marker itself. Troponin evaluation should be performed only if clinically indicated, and elevated troponin should always be interpreted in the context of the clinical presentation. Only in this way can high-sensitivity troponin assays encourage optimal diagnosis, risk stratification, and patient treatment.

Disclosures

None.

References


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