

EDITORIAL COMMENT

Will High-Sensitivity Troponin Improve the Evaluation of Patients With Chest Pain in the Emergency Department?*

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Approximately 8 million people in the United States are evaluated for chest pain in the emergency department (ED) each year at an estimated cost of over \$10 billion (1,2). Most of these individuals do not have an acute coronary syndrome (ACS). However, atypical symptoms of myocardial ischemia are common in certain patient subsets, and the initial electrocardiogram (ECG) is often normal or non-specific. In patients with a missed diagnosis of ACS, the mortality rate is increased (3), and malpractice expenses are high (4). Therefore the traditional approach has been to admit most of these patients. In an attempt to develop more efficient and less costly practice models, many institutions

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have implemented the chest pain unit. The standard protocol consists of serial measurements over several hours of the ECG and biomarkers, usually troponin (Tn) I or T, followed by stress testing with or without echocardiographic or nuclear imaging (1). Computed tomographic angiography (CTA) is also being investigated for its potential role in this setting (2,5). Although the chest pain unit approach can reduce unnecessary hospital admissions, patient evaluation is time-consuming and labor-intensive, contributing to overcrowding and lengthy stays in the ED.

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Given these issues, there is tremendous appeal in identifying a biomarker that could be easily measured early in the ED evaluation that would provide accurate diagnosis and risk stratification. Troponin is the preferred biomarker for diagnosing acute myocardial infarction (6). Current Tn assays have high clinical sensitivity but nonetheless can only detect Tn values in the nanogram/milliliter range (normal <0.01 ng/ml). A new generation of “high-sensitivity” Tn (hsTn) assays are more sensitive by an order of magnitude, with values reported in the picogram/milliliter range (7–9).

In this issue of *JACC*, Ahmed et al. (10) evaluated the association between hsTnT and both abnormal myocardial perfusion measured by single photon emission computed tomography (SPECT) and the extent of coronary artery disease (CAD) measured by CTA in a subset of 138 patients enrolled in the ROMICAT I (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial (5). The hsTnT levels were significantly different between patients with normal versus abnormal SPECT: median values 4.89 pg/ml versus 9.41 pg/ml ($p = 0.001$). At hsTnT levels in the range of 4 to 6 pg/ml, sensitivity to detect abnormal SPECT was 80% to 90%, and negative predictive value was 96%. The discriminatory ability of hsTnT to predict abnormal SPECT assessed by receiver-operating characteristic curve analysis reported area under the curve of 0.739. The hsTnT levels were significantly correlated with the SPECT ischemia score ($r^2 = 0.15$, $p < 0.0001$) and CTA plaque burden ($r^2 = 0.08$, $p = 0.0004$).

These findings are intriguing, but the reader should be aware of several limitations when interpreting the results of this study. First, the study group was small and highly selected. Exclusion criteria for the ROMICAT I trial included new diagnostic ECG changes, elevated cardiac bio-

marker, serum creatinine >1.3 mg/dl, or history of CAD revascularization (5). These criteria contributed to recruiting a low-risk population for the current study with mean age of 54 years, 54% female, and 82% Thrombolysis In Myocardial Infarction score 0 to 1. The results of this study might not be generalizable to other ED populations, which characteristically include older patients with more comorbidities, many of whom have established CAD. Second, hsTnT was measured at a single time point. The authors provide only the median time (4.2 h) but not the time range. The hsTnT measured at 4 h after presentation might not provide the same information as a measurement at 2 h or 6 h, even in the same patient. Serial measurements likely reflect optimal performance of the assay (7,9). Third, 19 patients (14%) had abnormal SPECT, but only 10 of these patients had ischemia. The distinction between ischemic and fixed SPECT defects is clinically important, but the authors did not test for differences in hsTnT between these patient subsets. Only 7 of the 19 patients (37%) with abnormal SPECT had a significant stenosis ($>50\%$ diameter narrowing) by CTA or invasive angiography. What is the etiology of the “perfusion defect” in the other 12 patients? The authors suggest that these defects could be caused by plaque rupture in an insignificant stenosis with downstream embolization (Fig. 5 in Ahmed et al. [10]) but offer no proof for this concept. Of note, mean body mass index of the population was 30 ± 6 kg/m², and attenuation correction was not applied for processing the SPECT images. Some of the perfusion defects might have represented attenuation artifacts, posing a challenge to explain a statistically significant association between hsTnT levels and the SPECT findings. Fourth, Ahmed et al. (10) analyzed the utility of hsTnT cut-points between 4.26 to 8.62 pg/ml for targeted sensitivities between 60% and 90% (Table 2). Inspection of Figure 1 in Ahmed et al. (10) reveals that these substantial differences in sensitivity thresholds are based on only a handful of data points crossing a narrow range of hsTnT cut-points. The findings would be more robust if based upon more data points. Fifth, the receiver-operating characteristic curve (Fig. 2 in Ahmed et al. [10]) reveals only fair operating characteristics for hsTnT, which might not result in dismissal of enough patients without

performance of additional testing to be cost-effective. Sixth, Figure 3 in Ahmed et al. demonstrates statistically significant associations between log-transformed hsTnT and SPECT summed difference score and CTA coronary segments with plaque, but the correlation coefficients are weak ($r^2 = 0.15$ and 0.08 , respectively). Most of the data points line up along the $y = 0$ axis. The slope of the curve for the SPECT ischemia analysis is heavily influenced by 2 extreme data points in the northeast quadrant of the graph. Seventh, potentially interesting and useful information is not included in the manuscript. The authors allude to the performance of invasive angiography in some patients, but the number of these patients is not provided. The agreement between stenosis number and severity detected by CTA and invasive angiography is not stated. For discrepant results, the authors do not specify which result they selected for their statistical analyses. The original ROMICAT trial (5) reported outcome endpoints. Comparing the prognostic accuracy of hsTnT, SPECT, and CTA could provide insight substantiating the clinical value of these measurements.

Despite these limitations Ahmed et al. (10) have provided an important first step in evaluating hsTnT against conventional imaging modalities commonly applied in the ED. High-sensitivity TnT will detect more CAD than conventional Tn assays. Although Tn assays have high analytic specificity, an elevated Tn does not have high clinical specificity for the clinical scenario of plaque rupture (type I) myocardial infarction (6). A negative hsTnT will be highly reassuring for ruling out myocardial necrosis and might eliminate the need for subsequent testing in some patients, but a potential concern is that hsTnT will be commonly elevated in clinical scenarios not associated with ACS and lead to additional and possibly unnecessary testing in other patients. More robust data are needed to support the statement of the authors that hsTnT might serve as a “powerful triage tool.” The correct application and interpretation of hsTn in the ED will require obtaining greater clinical experience using these assays in larger and broader patient populations.

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