Increased Concentrations of Cardiac Troponin I Are Equivalent to Increased Cardiac Troponin T in Identifying Chest Pain Patients at Short-Term Risk of Myocardial Infarction

To the Editor:

A recent paper by Christenson et al. (1) presented a comparative analysis of cardiac troponin I (cTnI) and T (cTnT). Their objective was to stratify patients for short-term risk of an acute coronary event on the basis of initial marker concentration as determined within 3.5 h of ischemic symptoms. The authors suggest that cTnT is a better predictor than cTnI on the basis of comparisons of the area under the curve (AUC) of ROC curves for cTnT (AUC = 0.68) and cTnI (AUC = 0.64). However, although weakly significant (P = 0.0375), the 95% confidence interval (CI) for the two areas overlap almost completely (95% CI for cTnI, 0.56–0.72; 95% CI for cTnT, 0.6–0.75). The fact that the samples were not tested for the two analytes simultaneously, but >1 year apart, could easily account for this small difference.

Using cutoffs of >0.1 ng/mL (0.1 μg/L) for cTnT and >1.5 ng/mL (1.5 μg/L) for cTnI, the authors found 90.4% concordance between the two assays. After correction for samples falling within the 95% CI around the cutoffs, the overall concordance rose to 93%. Of the 66 cTnT-positive/ cTnI-negative patients, 7.5% died and 70% suffered from an acute myocardial infarction (AMI). The authors use this as evidence that cTnT is more sensitive than cTnI for risk stratification but neglect to present data recalculating the cTnI sensitivity/specificity profile using a cutoff of 0.4 ng/mL (0.4 μg/L), which has been demonstrated to be the more appropriate concentration for cTnI in risk stratification of chest pain patients (2). The authors cite that the cutoffs used are in accordance with the manufacturer’s specifications; however, the Dade Stratus® Cardiac Troponin-I package insert (3) describes in detail the multicenter, outcomes-based study of Antman et al. (2), where 0.4 ng/mL (0.4 μg/L) was used as a cutoff. The insert also states that in two separate studies, the 97.5 percentile distribution of ostensibly healthy individuals (n = 156) and patients with chest pain but confirmed not to have AMI (n = 149) was 0.4–0.6 ng/mL (0.4–0.6 μg/L).

Both the Christenson et al. study (1) and a previous report describing the use of cTnT in risk assessment of patients with myocardial ischemia (4) used a high-risk population in whom >72% of the patients were diagnosed as having an AMI. The patient population upon which both studies were based came from the GUSTO IIa thrombolytic trial (5), which studied the efficacy of thrombolytic therapy (streptokinase or tissue plasminogen activator–alteplase) for those who had ST-segment elevation in randomization with administration of either the anticoagulant heparin or hirudin (4, 5). An analysis of the electrocardiographic (ECG) classification reveals that 435 of 755 (58%) of that population had ST-segment elevations sufficient to qualify them for thrombolytic therapy. On the basis of WHO criteria, these patients were diagnosed with AMIs based on chest pain and ECG ST-segment elevation and did not require any biochemical marker for initial AMI diagnosis. Regardless of cTnI or cTnT values at presentation, 83% of the patients had a cardiac event, defined as death, AMI, or revascularization therapy (1). In their study, the single best predictor of 30-day mortality was not cTnT, but the ECG categorization (P = 0.045 for cTnT and 0.019 for ECG).

In clinical studies using the recently developed Chiron Diagnostics ACS:180 cTn assay, which is calibrated to the Dade Stratus cTn assay, the cTn concentrations in 158 ostensibly healthy patients were <0.1 ng/mL (0.1 μg/L), and the median values in 73 unstable angina patients were 0.8 μg/L and 7.6 μg/L in 130 confirmed AMI patients (data on file, Chiron Diagnostics Corp.). These findings corroborate the use of lower cutoffs for cTnI in risk stratification. Why the authors did not simply recalculate the comparative data using this lower cutoff for cTnI is questionable, because they clearly were aware of the Thrombolitics in Myocardial Infarction (TIMI IIIb) trial and the subsequent cTnI substudy (2, 6).

The use of cTnI as a predictor of short-term acute coronary events in chest pain patients based on marker values on presentation has now been demonstrated in a number of studies (1, 2, 7, 8). The TIMI IIIb substudy specifically analyzed cTnI concentrations on the most difficult to diagnose chest pain population, patients with no or transient ST-segment elevation or depression who are not candidates for acute thrombolytic therapy (2). By using the lower 0.4 μg/L cutoff, this study on 1404 patients showed that patients presenting between 0 and 24 h after chest pain onset with a cTnI concentration above the cutoff were 3.8-fold more likely to die within 42 days of presentation compared with patients with concentrations <0.4 μg/L. When the initial measurement was taken after at least 6 h after onset of chest pain, consistent with the temporal profile of increased cTnI in the majority of AMI patients, the risk ratio of mortality at 42 days was 9.5-fold higher in patients with cTnI concentrations >0.4 μg/L. In terms of overall risk of a short-term acute cardiac event, this population was at much lower risk compared with the population described in the GUSTO IIa studies (1, 4, 5). Comparisons show that the death rate was 2.7-fold...
lower (2.4% vs 6.4% of the study population) and that the rate of AMI was ~13-fold lower (5.4% vs 72%) compared with the population studied by Christenson et al. (1). This was expected, because 58% had severe ST-segment elevation in the GUSTO IIa study, compared with <10% with only transient elevations in the TIMI IIIB study. Given the lower overall risk of the TIMI IIIB population, the ability to identify candidates at high risk of an acute coronary event is important because, typically, patients with unstable angina are not monitored as rigorously as patients who have a confirmed AMI. The ability to stratify and closely monitor such a subpopulation during this interval of heightened risk will likely have impact on the morbidity and mortality of unstable angina patients who progress to AMI.

Finally, a recent paired study used both point-of-care qualitative and laboratory-based quantitative tests for cTnT and cTnI to assess the efficacy of initial diagnosis and short-term risk stratification based on marker concentrations at presentation (7). Of 773 patients presenting to an emergency department, 171 were positive for cTnI and 123 were positive for cTnT. Among 47 patients with AMI that evolved while at the hospital, 94% were positive for cTnT and 100% were positive for cTnI. Among 315 patients with unstable angina, 70 patients were positive for cTnT (22%) and 114 were positive for cTnI (36%). During 30 days of follow-up, 34 cardiac events were reported, 20 fatal and 14 nonfatal AMIs. Of these, 20% of the deaths (4 of 20) had a negative cTnT result and only 5% (1 of 20) had a negative cTnI result. Of the nonfatal AMI patients, 21% (3 of 14) had negative cTnT values and 7% (1 of 14) had negative cTnI values. As predictors of a cardiac event at 30 days, both assays were highly significant predictors regardless of the ECG value; however, the odds ratio for cTnI was >2.4-fold that of cTnT. The authors’ conclusions were exactly the opposite of Christenson et al. (1), i.e., cTnI is slightly more sensitive than cTnT.

At this stage in the evolution of understanding of how to best utilize cTnT and cTnI results, on balance, careful analysis of the literature suggests that both proteins are about comparable in terms of initial diagnosis of AMI and prediction of short-term cardiac events. Selection of one assay vs the other may therefore be made more on the basis of convenience, system availability, and analytical rather than clinical performance. Additional well-controlled studies with a primary objective of direct cardiac marker comparisons similar to that of Hamm et al. (7) are required to determine if cTnI or cTnT is truly the better marker. Any assessment of the utility of troponins in assigning predictive value must clarify the status of the unstable angina/non-Q wave myocardial infarction population because they are the most problematic to diagnose and manage. In that regard, cTnI data from the TIMI IIIB study (2, 6) provide convincing evidence of the utility of cTnI in risk stratification. Similar comprehensive studies on unstable angina/non-Q wave myocardial infarction are required of cTnT to assure comparability.

References


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To the Editor:
I commend Christenson et al. (1) for performing analysis of both cardiac troponin T (cTnT) and I (cTnI) in a large population of patients with acute coronary syndromes to compare the abilities of these cardiac markers to stratify risk. I’d like to comment on three points regarding findings from this paper. First, one issue that should be addressed more rigorously by the authors involves the 1.5 µg/L cTnI (Stratus) cutoff concentration used for predicting clinical outcomes. Although it is true that the Dade Stratus® package insert states an upper reference limit for acute myocardial infarction as 1.5 µg/L, the 97.5% percentile of the distribution of 150 individuals presenting with chest pain but subsequently diagnosed as non-acute myocardial infarction was 0.6 µg/L. Thus, 0.6 µg/L should be the cutoff value used for comparison with the cTnT cutoff value of 0.1 µg/L, which is the upper reference limit established in clinical trial studies for cTnT ((2); Christenson et al. reference 24). If the authors were to establish for themselves appropriate cutoff concentrations using ROC curve analyses using the same population of patients, they would find that the Stratus cTnI cutoff of 1.5 µg/L corresponds to a cTnT cutoff of 0.2 µg/L and that a cTnI cutoff of 0.6 µg/L corresponds to a cTnT value of 0.1 µg/L (unpublished results from our laboratory). Thus, it would be of value to report the cTnI concentrations of the 66 patients who were