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EDITORIAL

Increasingly Sensitive Troponin Assays: Is Perfect the Enemy of Good?

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For over 20 years, cardiac troponin has been the gold standard biomarker for the diagnostic evaluation of patients with acute chest pain.[1] Refinement in assay technology led to the development of high-sensitivity cardiac troponin (hs-cTn) assays able to measure troponin concentrations in a least 50% of healthy individuals with high precision (coefficient of variation of ≤10%) at the 99th percentile.[2] When compared with conventional troponin assays, hs-cTn assays improve the speed and accuracy of myocardial infarction (MI) diagnosis,[3] rule out MI more efficiently, reduce costs,[3,4] and identify a greater number of patients at high risk for future cardiovascular events.[5] hs-cTn assays are now used globally, frequently embedded within several validated algorithms for ruling in or out non–ST-segment–elevation MI (NSTEMI).[6] These algorithms have attempted to find the perfect balance of sensitivity and specificity for diagnosing NSTEMI while maintaining efficiency.

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Notably, there are important distinctions among hs-cTn assays. Although all hs-cTn assays are expected to measure troponin in at least 50% of healthy adults, substantial differences in sensitivity and precision may exist between assays at low troponin concentrations. With this in mind, several preclinical assays have been developed that have remarkable low-end sensitivity able to measure troponin concentrations in >99% of healthy individuals with 10% analytical variation at concentrations <1 ng/L.[7] Whether hs-cTn assays with this degree of sensitivity and precision could improve clinical outcomes when compared with other less sensitive hs-cTn assays has been relatively unexplored; in theory, greater sensitivity might improve negative predictive value, but at the expense of specificity. Thus, clinical data evaluating hs-cTn assays with such sensitivity are crucial.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Tjora and colleagues derived an admission and a 0/1-hour algorithm using the preclinical high-sensitivity cardiac troponin I (hs-cTnI) assay (Singulex; no longer commercially available) with a limit of detection of 0.08 ng/L and 99th percentile of 8.67 ng/L.[8] The investigators compared the performance of this hs-cTnI algorithm with the 2015 European Society of Cardiology algorithms using commercially available high-sensitivity cardiac troponin T (Roche Diagnostics)[9] or hs-cTnI (Abbott),[9] and compared it with 2 previously derived Singulex hs-cTnI algorithms by Neumann[10] and Body.[11]

To derive their algorithm, data from the WESTCOR derivation cohort (which enrolled 985 patients admitted to Haukeland University Hospital in Norway between September 2015 and February 2017) were used; 1-hour samples were available in 465 patients.[8] The investigators found that Singulex hs-cTnI cutoffs of 2 ng/L for a single troponin admission rule out and 10 ng/L with a Δ of <3 ng/L for the 0/1-hour algorithm had the optimal sensitivity and specificity. Their single rule-out value of 2 ng/L (a value notably higher than the limit of detection of the assay of 0.08 ng/L but well below the range that some other troponin assays can

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accurately measure) had a similar sensitivity (99.2%), negative predictive value (99.7%), and long-term major adverse events prediction to the previously established algorithms but had a higher specificity of 42.5% for NSTEMI (≤35.1% for other algorithms) and ruled out 37% of patients (rule out ranged from 9% to 31% for the other algorithms).[8] The newly derived Singulex 0/1-hour algorithm had similar sensitivity (100%) and negative predictive value (100%) for its rule-out cutoffs and a similar specificity (97%) for its rule-in cutoffs (70 ng/L or a 0–1 hour Δ of ≥5 ng/L) when compared with other algorithms.[8] However, the Singulex 0/1-hour algorithm ruled in or out more patients (92%) compared with the other algorithms (56%–78%).[8] Notably, although more patients were ruled out with the new 0/1-hour Singulex algorithm, their event rate (5.3%) over a median follow-up period of 723 days was higher than patients ruled out by other algorithms (1.6%–3.4%).[8]

This study has several noteworthy findings. First, the investigators demonstrate that the highly sensitive and precise Singulex assay could safely rule out in-hospital NSTEMI with a single blood draw with similar sensitivity to other algorithms but with greater specify and allowed for rule out of a larger portion of patients (over one third) in a cohort inclusive of early presenters. This speaks to the ability to resolve low concentrations of troponin below the measuring range of other high-sensitivity assays, and theoretically could facilitate earlier discharge of a larger proportion of patients from the emergency department with a single blood draw. Second, the newly derived Singulex 0/1-hour algorithm using 0-hour troponin cutoff of >99th percentile maintained a similarly high sensitivity and negative predictive value to other algorithms but had a higher specificity and could rule out or in a higher proportion of patients (>90%). This algorithm could potentially reduce emergency department stay times by reducing the number of patients who need further observation. Notably, however, patients ruled out by this algorithm had higher rates of all-cause mortality or nonfatal MI over the medium-term follow-up period when compared with patients ruled out by other algorithms. This is likely because of the rule out of patients with mild myocardial injury (ie, troponin concentrations of >99th percentile). It adds to the growing evidence that even mild elevations in cardiac troponin are associated with increased risk of major adverse cardiovascular events.[5,12–15] Notably, the adverse events appeared to accumulate slowly over time in this rule-out group. Therefore, if this algorithm were to be used in clinical practice, early outpatient follow-up would be critical to identify and address modifiable cardiovascular risk factors in the hope of preventing adverse events.

Although informative, there are several limitations to this study. First, the cohort to derive this algorithm is from a single center in Norway and thus may not be generalizable to other populations with differing demographics. Second, the cohort used to derive 0/1-hour algorithm is relatively small (<500 patients), and there was no validation cohort used in this study. Third, although the investigators report the median estimated glomerular filtration rate in their baseline characteristic tables, they do not report the number of patients with chronic kidney disease included in this study. This information is important as using a rule-out cutoff of >99th percentile may miss events if examined in a healthier population with lower prevalence of comorbidities associated with increased troponin concentrations. Fourth, the investigators provide data for long-term events but they do specifically examine 30-day major adverse cardiovascular events. Future studies will be needed to examine the safety of their 0/1-hour Singulex hs-cTnI algorithm with respect to these short-term events. Last, the investigators did not use sex-specific cutoffs and thus further studies are also needed to examine the safety of these algorithms in women.

In summary, using even more sensitive hs-cTn assays, algorithms optimized for sensitivity and specificity have the potential to rule out a larger proportion of patients with chest pain without compromising safety in terms of missed in-hospital NSTEMI. However, this is offset by ruling out patients at higher risk of subsequent cardiovascular events over a medium-term period of 2 years. As has been widely said in the biomarker community, when troponin was a lousy assay, it was a great test, because patients with an abnormal value were more likely to have an acute MI than not. In the current era of increasing sensitivity, hs-cTn assays that can measure down to the femtomolar level are on the near horizon; these assays will eventually be used clinically, so it is critically important to understand their strengths and potential weaknesses. As the old adage goes, perfect may be the enemy of good; when implementing assays with higher and higher sensitivity, one should be mindful of the potential down sides in what may result.

ARTICLE NFORMATION

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