Evidence-Based Algorithms Using High-Sensitivity Cardiac Troponin in the Emergency Department

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For nearly 2 decades, experts and professional society bodies had pressed manufacturers to improve the analytical performance of assays for cardiac troponin (cTn). This effort generated a steady increase in analytical and clinical sensitivity and has led to the current generation of high-sensitivity assays for cTn (hsTn) that are used routinely in many regions of the world, but are not available in the United States. The increased sensitivity of current assays for cTn, inclusive of contemporary sensitive assays used in the United States and hsTn assays used elsewhere, has presented the practitioner with both advantages and disadvantages. A marked increase in the proportion of patients with elevated cTn results has frustrated physicians; many such patients ultimately receive a diagnosis for a cause of myocardial injury other than myocardial infarction (MI). At the same time, hsTn assays have opened the door to emerging applications, such as for risk stratification in atrial fibrillation, stable ischemic heart disease, and heart failure as well as screening for structural heart disease. In addition, use of hsTn for rapid triage of patients presenting to the emergency department (ED) with chest pain is an application likely to be embraced by practitioners. In this issue of JAMA Cardiology, Neumann et al and Carlton et al report 2 separate prospective studies that move the field forward toward evidence-based strategies incorporating hsTn for this purpose.

Current State of Troponin Testing in the ED

Of more than 8 million ED visits related to chest pain that occur annually in the United States, well less than a third will result in a final diagnosis of an acute coronary syndrome. Despite this low pretest probability, physicians are obligated to exclude myocardial ischemia with a high degree of probability and engage in time-consuming and costly testing strategies to do so. To manage costs and the adverse effects of overcrowding in the ED, it is a high priority to rapidly and safely identify patients with a sufficiently low probability for acute coronary syndrome (<0.5%-1%) so that they can be discharged efficiently and avoid unnecessary testing.

Cardiac biomarkers have proven useful for this purpose. Accelerated diagnostic protocols that incorporate the clinical history, electrocardiogram, and cTn concentrations provide a framework to rapidly evaluate and triage patients with chest pain suspicious for ischemia. Introduction of cTn has truncated the historical 3 serial blood samples 6 to 8 hours apart necessary when using creatine kinase. With the use of contemporary sensitive cTn assays and a diagnostic cutoff for MI at the 99th percentile upper reference limit, a strategy of measurement at presentation and 3 to 6 hours later provides a negative predictive value (NPV) greater than 99% in low-risk patients without ischemic electrocardiographic abnormalities or other higher risk features. Therefore, present US practice guidelines recommend (class I) testing at presentation (0 hours) and 3 to 6 hours after symptom onset in low-risk patients, with additional testing beyond 6 hours in patients who have electrocardiographic changes or intermediate/high-risk clinical features.

In parallel, accumulating data support the proposal that when using hsTn assays, the interval between serial sampling for cTn can be further reduced to 1 to 2 hours while maintaining an NPV of approximately 99% among otherwise low-risk patients. In light of such data, the 2015 European Society
of Cardiology\textsuperscript{10} practice guidelines for management of non-ST-segment elevation acute coronary syndrome recommend (class I) that, if an hsTn assay with a validated 0-hour and 1-hour algorithm is available, testing at presentation and 1 hour, together with the absence of high-risk clinical features, is an alternative to testing at 0 hours and 3 hours. This recommendation establishes a need for well-validated algorithms, tested in robustly sized, geographically diverse, clinically relevant populations to guide hospitals using hsTn now and forecasts the same need for health systems that may adopt hsTn in the future.

**Leveraging the Sensitivity in hsTn Assays**

As a foundation for this evolution in guidelines,\textsuperscript{10} the superior analytical performance of hsTn assays has been leveraged as a strength in the ED to detect myocardial injury earlier after onset and in concentrations lower than those determined with previous cTn assays.\textsuperscript{11} For example, in a multicenter European study of patients presenting to the ED within 12 hours of symptom onset (1439 patients [18.6% with MI]), an initial hsTnT less than the 99th percentile upper reference limit (14 ng/L or 0.014 ng/mL [conversion to micrograms per liter is 1:1]) achieved an NPV of 97.1%. Repeating hsTnT at 1 hour improved the NPV to 99.6%. Therefore, a strategy using baseline and 1-hour hsTnT testing and the 99th percentile upper reference limit missed only 3 patients with acute MI (1.1% of all MI).\textsuperscript{12} In that study, among the 25% of patients with an hsTnT value below the limit of detection (<5 ng/L) at presentation, the NPV for MI was already 99.7%, suggesting that serial testing may be unnecessary in such patients. Similarly, Shah and colleagues\textsuperscript{13} reported that, among 4870 patients presenting with chest symptoms, the optimal threshold for ruling out MI with a single hsTnI concentration determined at presentation was less than 5 ng/L (approximately 50% of the population) with an NPV of 99.6%. In both of these populations, application of a very low cutoff (<99th percentile upper reference limits for these assays) provided an excellent NPV based on a single sample at presentation.

The reports from Neumann et al\textsuperscript{14} and Carlton et al\textsuperscript{15} build on these data. Neumann and colleagues conducted a single-center study in Germany enrolling 1040 patients with suspected acute coronary syndrome without ST-elevation (17.7% with MI). In this population, 12.3% of patients had baseline and 1-hour hsTnI values below the limit of detection (2 ng/L), with an NPV of 100% for MI. Using a cutoff level of 6 ng/L, offered as optimal by the authors, the proportion meeting the criterion increased to 39% and the NPV was 99.0% (CI, 97.5%-99.7%). The sensitivity was 97.8%, missing 2.2% of non-ST-segment elevation MIs. The investigators validated the NPV in 2 separate populations with resultant values of 99.7% and 99.2%. Not surprisingly, use of a higher cutoff at the 99th percentile upper reference limit (27 ng/L) at 1 hour had a higher rate of false-negative results (NPV, 94.8%). Moreover, considering only a first hsTn result less than 6 ng/L, the NPV was 97.1%. Data using a single sample with a cutoff at 2 ng/L were not reported.

Carlton et al\textsuperscript{15} report a pooled analysis of 5 prospective ED cohort studies in Australia, New Zealand, and England (3155 patients [9.2% with MI], 33.5% presenting <2 hours from symptom onset). Among patients with a nonischemic electrocardiogram and using the same assay as Neumann et al,\textsuperscript{14} Carlton et al found that a single hsTn result less than 1.2 ng/L (18.8% of patients) delivered an NPV of 99.5% (95% CI, 98.4%-99.9%) and sensitivity of 99.0% (95% CI, 96.8%-99.7%). For comparison with other studies of the same assay, their analysis revealed NPVs at 2 ng/L, 5 ng/L, and 6 ng/L that were 99.3%, 99.2%, and 99.1% with corresponding sensitivities of 98%, 94.5%, and 93%, respectively. Carlton et al emphasize that the clinical sensitivity of cutoffs suggested by prior studies\textsuperscript{11} and that are higher than the limit of detection did not meet a criterion of 99% or greater sensitivity (ie, missing ≤1% of all MIs). Only a cutoff at 1.2 ng/L met this aim based on the first sample alone. Moreover, in early presenters (ie, time from symptom onset to ED presentation ≤2 hours), the sensitivity, even at 1.2 ng/L, was slightly diminished at 98.6%.

**Summary and Lessons Learned**

Taken together with prior studies,\textsuperscript{10,13} the findings from the studies of Neumann et al\textsuperscript{14} and Carlton et al\textsuperscript{15} lend strong support to the notion that accelerated diagnostic protocols that incorporate hsTn can facilitate earlier triage while maintaining an acceptable NPV. These studies illustrate key concepts that will continue to shape emerging accelerated diagnostic protocols. Better-performing assays enable a shift to more rapid exclusion strategies. To maintain an acceptable sensitivity using a 1- to 2-hour algorithm to exclude MI, it is necessary to use an hsTn assay with cutoffs lower than the 99th percentile upper reference limit. Assessing for a change in cTn between 2 time points (“Δ value”) improves both the negative (flat Δ) and positive (meaningful Δ) predictive performance.\textsuperscript{6,14} A single very low hsTn result at presentation may be sufficient to exclude MI with a greater than 99% NPV in otherwise low-risk patients. Present data suggest that the limit of detection is preferable as a cutoff to deliver an acceptable NPV at presentation. This criterion may be met in approximately 20% of patients with chest pain and a nonischemic electrocardiogram. Predictably, higher cutoff levels will include more patients at the cost of more false negatives. Considering the timing of symptom onset is critical. Shorter times to sampling diminish the NPV. It seems prudent to obtain a sample at 3 hours or later in early presenters (or ambiguous timing) and in patients with clinical high-risk features. The proportion of patients with hsTn in the very low range will vary with demographics in the local ED, and the NPV will depend on the prevalence of MI in the local population. The NPVs reported in these studies\textsuperscript{6,7} will be misleading if the accelerated diagnostic protocol is applied in high-risk patients. It is important to know the performance both of your cTn assay and in your population. Assays for cTn are only tests and must be integrated with other clinical assessments. Finally, it is necessary and possible to use evidence-based algorithms for rapid rule-out protocols specific to individual hsTn assays.

Despite many strengths of the available evidence, there are some reasons that these data may overstate the diagnostic performance of rapid strategies to exclude acute coronary syndromes.\textsuperscript{15} There is a need for additional studies per-
formed in diverse health care settings, including in the United States, to add to the robustness of the estimated NPV across a variety of populations. At present, because hsTn assays are not available in the United States, serial testing at presentation and 3 to 6 hours with a contemporary sensitive assay remains the US standard of care.

**REFERENCES**


Understanding the Adverse Effects of Ticagrelor in Practice

Christopher B. Granger, MD; Peter B. Berger, MD

**Whether and when** to prolong dual antiplatelet therapy beyond 1 year after an acute coronary syndrome remains controversial.1 Continuation of dual antiplatelet therapy beyond 1 year reduces the risk of myocardial infarction and stent thrombosis, with the tradeoff of increased bleeding.2 Like all effective therapies, however, the potential benefits depend on the ability to adhere to the therapy.

Patients discontinue treatment for a variety of reasons. These include the perception that the treatment is not working, the expense, adverse effects, and simply forgetting to take the medication. Some adverse effects are intolerable (such as persistent coughing while receiving angiotensin-converting enzyme inhibitors) or are so dangerous (such as angioedema) that the risk of continuing treatment outweighs the potential benefit. Other side effects are self-limited, minor, or even favorable (eg, treating patients with hypertension with phosphodiesterase inhibitors and discovering that this type of treatment improves erectile dysfunction, or discovering that treatment with minoxidil has the side effect of hair growth, which is useful to treat male pattern baldness). But for unpleasant or even mildly harmful adverse effects, balancing the potential benefits of therapy against these adverse effects is a clinical challenge that is strongly influenced by patient perceptions and preferences. Further complicating the situation is that adverse effects are commonly ascribed to treatments even if symptoms are actually likely not due to the treatment, as is the case with muscle symptoms with statins.3,4

Observational cohort studies show that a complex set of medical, psychosocial, economic, and behavioral issues result in only about half of patients continuing to take their evidence-based medications a year after starting them.4 Even for a serious disease such as diabetes, it has been shown that 15% of patients never even fill their first prescription.6

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