Critical Review Form
Diagnostic Test

PGY-2

Mueller C, Giannitsis E, Christ M, et al; TRAPID-AMI Investigators. Multicenter Evaluation of a 0-Hour/1-Hour Algorithm in the Diagnosis of Myocardial Infarction With High-Sensitivity Cardiac Troponin T. Ann Emerg Med. 2016 Jul 68(1):76-87.e4.

Objectives: **"to externally validate the diagnostic accuracy of the hs-cTnT [high sensitivity cardiac troponin T] 0-hour/1-hour algorithm for rapid rule-out and rule-in of acute myocardial infarction and thereby evaluate its suitability for routine clinical care." (p. 77)**

Methods: **This prospective, multicenter study was conducted at 12 hospitals in 3 continents. Consecutive patients aged 18 or older presenting to the ED with chest discomfort concerning for acute MI, with an onset or maximum discomfort within 6 hours of presentation, were eligible for inclusion. Exclusion criteria included renal failure requiring dialysis; trauma, cardioversion, defibrillation, or thrombolytic therapy prior to enrollment; coronary artery bypass grafting within the previous month; admission for acute MI within the previous 3 weeks; and pregnancy or breastfeeding. All patients underwent a standard clinical assessment, and treatment was at the discretion of the attending physician. All patients had blood samples for determination of hs-cTnT and sensitive cardiac troponin I ultra (s-cTnI-ultra) drawn within 45 minutes of ED presentation and 1, 2, and 4 to 14 hours later.**

Follow-up beyond hospital stay was conducted at 1 week, 30 days, and 1 year by telephone call or in written form. Additionally, the national registry on mortality, the hospital's diagnosis registry, and the family physician's records were reviewed for further information regarding death.

Final diagnosis was adjudicated by two independent cardiologists who reviewed all available medical records from the initial ED presentation out to 90 days of follow-up. The cardiologists were blinded to the results of serial hs-cTnT measurements, although they did have access to s-cTnI-ultra results. In cases of disagreement between the two cardiologists, a third cardiologist adjudicated the final diagnosis.

For the purposes of diagnostic classification, 0 and 1 hour hs-cTnT results were classified as follows:

- **Patients with initial hs-cTnT < 12 ng/L and Δ1 hour < 3 ng/L were assigned to rule out status.**
- **Patients with initial hs-cTnT ≥ 52 ng/L and Δ1 hour ≥ 5 ng/L were assigned to rule in status.**

- **Remaining patients were assigned to observational status.**

Between August 2011 and June 2013, 1458 patients were enrolled, of whom 1282 were eligible for analysis. The median time from chest pain onset or maximum intensity to ED presentation was 1.8 hours, and median time until first study blood draw was 3.4 hours.

For the 1282 patients, the final diagnosis was acute MI in 213 (17%), unstable angina in 167 (13%), cardiac chest pain not due to coronary artery disease in 113 (9%), noncardiac in 288 (22%), and of unknown origin in 501 (39%).

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Yes. The study enrolled all patients presenting to the ED with chest pain concerning for acute MI. Of these, only 17% were found to have had an MI, and more than half had noncardiac chest pain.
B.	**Was there a blind comparison with an independent gold standard applied similarly to the treatment group and to the control group? (Confirmation Bias)**	No. There is no true gold standard for the diagnosis of acute MI, although review of all relevant records is most likely a good surrogate. While not specifically stated, it seems unlikely that all patients underwent stress testing or cardiac catheterization (which some may consider to be the gold standard). Also, the cardiologists who determined final diagnosis were specifically blinded to the results of hs-cTnT testing. They were, however, made aware of the results of s-cTnI-ultra testing.
C.	**Did the results of the test being evaluated influence the decision to perform the gold standard? (Ascertainment Bias)**	No. The same method was used to make the final diagnosis in all patients, regardless of the results of hs-cTnT testing, and the cardiologists who determined final outcome were blinded to these results. On the other hand, additional testing (such as stress testing and cardiac catheterization) may have been influenced by the standard cardiac troponin results.
II.	**What are the results?**	
A.	**What likelihood ratios were associated with the range of possible test results?**	Using the predefined algorithm: • 813 (63.4%) of patient could be classified to "rule-out" status. 30-day mortality in this group was 0.1%. • 184 (14.4%) were classified to rule-in status. 30-day mortality in this group was 2.7%. • 285 (22.2%) were classified to observational zone status. 30-day mortality in this group was 0.7%. • The negative predictive value to rule-out patients was 99.1% (95% CI 98.2-99.7) and the sensitivity

		was 96.7% (95% CI 93.4-98.7). The miss rate was 0.9%. • The positive predictive value to rule-in patients was 77.2% (95% CI 70.4-83.0) and the specificity was 96.1% (95% CI 94.7-97.2).
III.	**How can I apply the results to patient care?**	
A.	**Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?**	Yes. Although we currently do not have access to this ultra high sensitivity hs-cTnT assay, we should be able to obtain similar results to those in the study if the assay were made available.
B.	**Are the results applicable to the patients in my practice?**	Likely yes. Assuming a similar negative predictive value in our institution (which would assume a similar prevalence of disease) the results would allow for the more rapid discharge of patients being rule out for MI.
C.	**Will the results change my management strategy?**	Uncertain. It remains to be seen is the clinical impact of this algorithm compared to current standard of care, and the final disposition of those who do not "rule out" for MI; it is unclear if such patients should undergo additional testing at later time-frames, and if such testing would allow discharge in a significant portion of these patients.
D.	**Will patients be better off as a result of the test?**	Again, uncertain. This study did not assess the clinical impact of the proposed algorithm, and does not address the disposition and additional testing of patients with a positive hs-cTnI.

Limitations:

1. **The authors apply the results universally to all patients, without considering pre-test probabilities of disease.**
2. **Adjudication of myocardial infarction was largely made based on hs-cTnI levels, which, as the authors point out, correlate well with hs-cTnT levels, the assay being studied. This method of adjudication lends itself to incorporation bias.**
3. **This was an observational study and did not address the impact of hs-cTnT interpretation on clinical management or outcomes.**
4. **The calculations for sensitivity and specificity included patients assigned to the observation zone, and counted these patients as true positives and true negative. This caused a mild inflation of the reported sensitivity, but a large inflation of the reported specificity.**
5. **The study was largely industry-funded by the maker of the troponin assay, suggesting a possible conflict of interest (Ioannidis 2016).**

Bottom Line:

In this prospective, observational diagnostic study evaluating the accuracy of a 0/1 hour algorithm using a hs-cTnT assay, the authors demonstrate a very high negative predictive value for ruling-out acute MI, with a modest positive predictive value for ruling-in acute MI. The study was limited primarily by failure to incorporate patients' pre-test risk, by the strong likelihood of incorporation bias, and by the lack of an impact analysis comparing this algorithm to current standard of care.