Critical Review Form
Diagnostic Test

PGY-1

Jaeger C, Wildi K, Twerenbold R, et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. Am Heart J. 2016 Jan;171(1):92-102.e1-5.

Objectives: **"to address 4 questions: First, is it possible to derive and validate a similar 0-/1-hour algorithm for hs-cTnI [high sensitivity cardiac troponin I] to possibly extend the former finding to cardiac troponin I (cTnI) and specifically to the novel precommercial hs-cTnI Siemens Vista assays. Second, what are the specific cutoff values for hs-cTnI that allow safe rule-out and accurate rule-in within 1 hour? Third, how many patients can be reliably assigned rule-out and rule-in within 1 hour? Fourth, how does the hs-cTnI 0-/1-hour algorithm compare versus the current standard of care combining the 12-lead ECG with hs-cTn?" (p.93)**

Methods: **This prospective, multicenter study was conducted at 9 hospitals in Switzerland, Spain, and Italy. Consecutive patients aged 18 or older presenting to the ED with chest discomfort concerning for acute MI, with an onset or peak within 12 hours of presentation, were eligible for inclusion. Patients on dialysis and those with an ST-elevation MI were excluded. All patients underwent a standard clinical assessment, and all patients had blood samples for determination of hs-cTnI and hs-cTnT (high sensitivity cardiac troponin T) drawn at presentation to the ED and 1, 2, and 3 hours later.**

Follow-up beyond hospital stay was conducted at 3 and 12 months 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 results of serial hs-cTnT measurements were also made available. In cases of disagreement between the two cardiologists, a third cardiologist adjudicated the final diagnosis.

A total of 1500 subjects were included in the analysis. The first 750 were used to derive an algorithm for use of hs-cTnI to rule-in and rule-out MI and to determine the appropriate cut-off threshold for the test. A classification and regression tree (CART) analysis was used to calculate the cut-off threshold by incorporating the baseline hs-cTnI, absolute change in hs-cTnI in the first hour, gender, and ECG features. The algorithm was then tested in the remaining 750 subjects.

For the 1500 patients, the final diagnosis was acute MI in 233 (16%), unstable angina in 172 (12%), cardiac chest pain not due to coronary artery disease in 246 (16%), noncardiac in 768 (51%), and of unknown origin in 81 (5%).

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 16% 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-cTnI testing. "Adjudication included, in addition to the cTn blood concentrations as obtained as part of local clinical care, also serial measurements of hs-cTnT from study blood samples to take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by hs-cTn assays." (p. 93)
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-cTnI 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?**	• The optimal threshold for **ruling out** acute MI was defined in the derivation cohort as a baseline hs-cTnI < 5 ng/L and an absolute change within 1 hour of < 2 ng/L. • The optimal threshold for **ruling in** acute MI was an absolute change in in hs-cTnI of 19 ng/L at one hour and a baseline value of 107 ng/L.

		• Using this cut-off, 48% of the derivation cohort could be considered "ruled out," with a sensitivity of 97.1% (95% CI 92.6-99.2), negative predictive value of 98.9% (95% CI 97.2-99.7). Four males with acute MI were missed. • 19% of the derivation cohort was considered "ruled-in", with a specificity of 94.6% (95% CI 92.5-96.3) and positive predictive value of 76.6% (95% CI 68.7-83.3). • Using the cut-off values defined in the derivation cohort, 57% of patients in the validation cohort could be considered **ruled out** by the algorithm at one hour. The sensitivity and NPV in this cohort were 100% (95% CI 96.3-100) and 100% (95% CI 95-100). No patients with MI were missed. • In the validation cohort, 13% of patients were considered **ruled-in**, with a specificity of 95.6% (95% CI 93.7-97) and positive predictive value of 70.4% (95% CI 60.3-79.2). • The negative predictive value of the algorithm was similar in women (100%, 95% CI 98.6-100) and men (99.2%, 95% CI 98-99.8).
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-cTnI 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 do not report likelihood ratios, and do not report enough information to calculate these (specifically for ruling out MI, they do not provide the specificity, which would be needed to make this calculation).**
2. **The authors apply the results universally to all patients, without considering pre-test probabilities of disease.**
3. **Adjudication of myocardial infarction was largely made based on hs-cTnT levels, which, as the authors point out, correlate well with hs-cTnI levels, the assay being studied. This method of adjudication lends itself to incorporation bias.**
4. **This was an observational study and did not address the impact of hs-cTnI interpretation on clinical management or outcomes.**
5. **The authors note that informed consent was required for study inclusion, and report that recruitment was low compared to registries. They do not provide a flowchart indication numbers of patients eligible but not enrolled, not do they compare enrolled patients with those why opted out (Gorkin 1996, Bahit 2003).**
6. **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.**
7. **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 retrospective, observational diagnostic study evaluating the accuracy of a 0/1 hour algorithm using a hs-cTnI assay, the authors demonstrate a very high negative predictive value in both derivation and validation cohorts. While the positive predictive value was much lower, the authors fairly point out that most of the patients who "ruled-in" but were ultimately determined not to have AMI had other disease processes that would require cardiac catheterization anyway. 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.