Critical Review Form
Diagnostic Test

PGY-4

Reichlin T, Twerenbold R, Wildi K, et al. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. CMAJ. 2015 May 19;187(8):E243-52.

Objectives: **"to prospectively validate the high-sensitivity cardiac troponin T 1-hour algorithm in a large independent cohort." (p. E244)**

Methods: **This prospective, multicenter study was conducted at 6 hospitals in Switzerland, Spain, and Italy. Consecutive patients aged 18 or older presenting to the ED with nontraumatic chest pain or other symptoms 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 hs-cTnT (high sensitivity cardiac troponin T) drawn at presentation to the ED and 1, 2, 3, and 6 hours later. Clinicians were not aware of the results of the hs-cTnT assay.**

Follow-up beyond hospital stay was conducted at 3, 12, and 24 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.

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.**

A total of 1714 subjects were initially enrolled in the database. Patients with ST-elevation MI (n = 58) and those without a 1-hour hs-cTnT (n = 336) were excluded, leaving 1320 patients in the final analysis. Among these patients, the final diagnosis was acute MI in 229 (17.3%), unstable angina in 109 (8.3%), cardiac chest pain not due to coronary artery disease in 194 (14.7%), noncardiac in 732 (55.5%), and of unknown origin in 56 (4.2%).

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). The results of hs-cTnT, the assay being studied, were used in the adjudication process (incorporation bias).
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 algorithm, 786 patients (59.5%) cohort could be considered **ruled out**, with a sensitivity of 99.6% (95% CI 97.6-99.9), negative predictive value of 99.9% (95% CI 99.3-100). There was one missed MI. • There were 216 patients (16.4%) that were considered **ruled-in**, with a specificity of 95.7% (95% CI 94.3-96.8) and positive predictive value of 78.2% (95% CI 72.1-83.6). • There were 318 patients (24.1%) classified to the **observational zone**. The prevalence of acute MI in this group was 18.6%.
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-cTnT.

Limitations:

1. **Nearly one fourth of enrolled patients were excluded from the study due to lack of 1-hour troponin levels.**
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, 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 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.**
6. **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. 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.