Critical Review Form
Diagnostic Test

PGY-3

Neumann T, Sorensen N, Schemer T, et al. Diagnosis of Myocardial Infarction Using a High-Sensitivity Troponin I 1-Hour Algorithm. JAMA Cardiol. 2016 June.

Objectives: "to develop an algorithm for accurate and rapid exclusion and diagnosis of AMI [acute myocardial infarction] after 1 hour using a cutoff below the 99th percentile and compare it with the recommended 3-hour approach." (p. E2)

Methods: This study sought to prospectively derive an algorithm using a cohort of patients aged 18 years or older presenting to the emergency department of the University Medical Center Hamburg-Eppendorf between July 19, 2013 and December 31, 2014 with acute chest pain (the BACC cohort). Patients with ST-elevation MI were excluded. All patients had blood drawn at admission, after 1 hour, and after 3 hours, and blood was tested using high-sensitivity troponin I immunoassay

Final diagnosis was determined by two cardiologists who were blinded to study troponin I results. Diagnosis was based on high-sensitivity troponin T as well as all other clinical, laboratory, and imaging findings during the hospital stay. In cases of disagreement, a third cardiologist "refereed."

The optimal cut-off point in the BACC cohort was found to be an initial troponin I level of 6 ng/L. NSTEMI was considered ruled out if the level was < 6 ng/L at admission and after either 1 or 3 hours. To rule in NSTEMI, the following algorithms were evaluated:

1. A value > 6 ng/L at 1 hour OR an increase or decrease of at least 12 ng/L from the admission level.

2. A value > 6 ng/L at 3 hours OR an increase or decrease of at least 12 ng/L from the admission level.

Patients in whom NSTEMI was neither ruled in nor ruled out were considered to be in the "grey-zone" group.

This BACC cohort consisted of 1040 patients with a median age of 65, of whom 64.7% were male. Of these, 184 were classified as having NSTEMI and 799 as not having NSTEMI. 57 patients with STEMI were excluded.

The algorithm derived in this BACC cohort was then retrospectively validated in two additional cohorts (ADAPT, APACE) that were previously evaluated in a prospective fashion. In the ADAPT cohort, which consisted of 1748 patients, troponin I levels were measured on presentation and after 2 hours. On the APACE cohort, which

consisted of 2261 patients, troponin I levels were measured at admission and after 1 hour.

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 17.7% 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.
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?**	BACC cohort: • 39% of patients were considered **ruled-out** by the algorithm, with a false-negative rate of 1.0% and a NPV of 99.0% (95% CI 97.5-99.7). • For **ruling-in** acute MI, the PPV was 87.1% (95% CI 79.6-92.6) at 1 hour, and 84.6% (95% CI 78.0-89.9) at 3 hours. • The 12-month mortality in the rule-out group was 1.0%; in the "gray-zone" group it was 8.2%, and in the rule-in group it was 6.7%). ADAPT cohort: • For **ruling-out** acute MI, the algorithm had a NPV of 99.7% (95% CI 99.2-99.4) at 2 hours. • For **ruling-in** acute MI, the PPV was 81.5% (95% CI 75.3-86.3) at 2 hours. APACE: • For **ruling-out** acute MI, the algorithm had a NPV of 99.2% (95% CI 98.4-99.2) at 1 hour and 99.1% (95% CI 97.1-99.8) at 3 hours.

		• For **ruling-in** acute MI, the PPV was 80.4% (95% CI 75.1-84.9) at 1 hour and 68.8% (59.2-77.3) at 3 hours.
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 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-cTnT levels, which has been shown to correlate well with hs-cTnI 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-cTnI interpretation on clinical management or outcomes.**
4. **The authors note that informed consent was required for study inclusion, and report that recruitement 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).**
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 retrospective diagnostic study evaluating the accuracy of a 0/1, 0/2, and 0/3 hour algorithms using a hs-cTnI assay, the authors demonstrate a very high negative predictive value in both the derivation cohort (BACC) and two previously reported validation cohorts (ADAPT and APACE). 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, and by the strong likelihood of incorporation bias.