Critical Review Form
Diagnostic Test

Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays, *NEJM* 2009; 361: 858-867

Objectives: **To examine the diagnostic performance of new sensitive cardiac troponin assays, performed on blood samples obtained at the time of patients presentation to the emergency department, for the early diagnosis of acute myocardial infarction". (p. 859)**

Methods: **Prospective observational international multicenter study coordinated by the University Hospital Basil. The manuscript does not detail how many or which countries/hospitals are participating in this project. From April 2006-April 2008, 786 consecutive ED patients with symptoms suggesting acute myocardial infarction (AMI) with the onset or peak of symptoms in the preceding 12 hours before presentation were enrolled. The only exclusion criterion was chronic renal failure patients on dialysis. All patients had history and physical exam, ECG, chest x-ray and standard labs as well as standard cardiac biomarkers at presentation and 6-9 hours later.**

Two independent cardiologists examined all available medical records except experimental troponin levels from ED arrival until 60 days later to adjudicate the outcomes of AMI, unstable angina (USA) or non-coronary chest pain. AMI was defined as myocardial necrosis (rising/falling cardiac standard troponin with ≥ 1 value above the 99th percentile and <10% imprecision) in association with clinical signs of ischemia. USA was defined as normal troponin levels and at least one of the following: resting angina, deterioration of previously stable angina, positive cardiac stress test, cardiac cath with >70% stenosis, or 60-day MI/unexpected cardiac death.

Blood specimens were collected upon arrival and at 1, 2, 3 and 6 hours after presentation. After centrifugation, samples were frozen at -80º C until they were assayed in a blinded fashion in two batches in a dedicated core laboratory. The following ultra-sensitive troponin tests (with limit of detection and coefficient of variation) were evaluated:

- **Abbott-Architect Troponin I Architect System (0.01*ug*/L, <10%)**
- **Roche High-Sensitive Troponin T Elecsys 2010 (0.01 *ug*/L, <10%)**
- **Roche Troponin I Elecsys 2010 (0.10 *ug*/L, <10%)**

- **Siemens Troponin I Ultra ADVIA Centaur (0.006 *ug*/L, <10%)**

Sensitivity and specificities were computed at 99th percentile cutoff points and ROC AUC were reported.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Yes, treating clinicians were evaluating ED chest pain patients within 12 hours of symptom onset without any knowledge of criterion standard test results (cardiac catheterization, 60-day outcome) or sensitive troponin assay levels.
B.	**Was there a blind comparison with an independent gold standard applied similarly to the treatment group and to the control group?** **(Confirmation Bias)**	Yes. "To determine the final diagnosis for each patient, two independent cardiologists reviewed all available medical records – the clinical history, findings on physical examination, and results of laboratory tests (including cardiac troponin values obtained at the participating hospitals, but not those being assessed as part of this study), radiological studies, ECG, echocardiography, cardiac exercise testing, and coronary angiography – from the time of the patient's arrival in the emergency department to the end of the 60-day follow-up period". (p. 860)
C.	**Did the results of the test being evaluated influence the decision to perform the gold standard?** **(Ascertainment Bias)**	No. The final discharge diagnosis was the gold standard and every patient had their diagnosis adjudicated as described above.
II.	**What are the results?**	

A.

What likelihood ratios were associated with the range of possible test results?

Test	Sensitivity 95% CI	Specificity 95% CI
Abbott-Architect Trop I*	**86 (79-92)**	**92 (90-94)**
Roche High Sensitive Trop T**	**95 (90-98)**	**80 (77-83)**
Roche Trop I***	**84 (76-90)**	**94 (91-95)**
Siemens Trop I Ultra†	**89 (82-94)**	**92 (89-94)**
Roche Trop T 4th generation‡	**83 (76-90)**	**93 (91-95)**

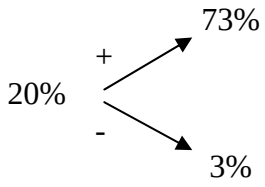
Test	LR^+	LR^-	AUC
Abbott-Architect Trop I*	**10.7 (9-13)**	**0.15(0.1-0.2)**	**0.96**
Roche High Sensitive Trop T**	**4.8 (4-5)**	**0.06 (0.03-0.1)**	**0.96**
Roche Trop I***	**13.8(11-17)**	**0.17(0.12-0.24)**	**0.94**
Siemens Trop I Ultra†	**11.1(9-13)**	**0.12(0.07-0.18)**	**0.96**
Roche Trop T 4th generation‡	**11.7(9-14)**	**0.19(0.13-0.26)**	**0.90**

***** **≥ 0.028 *ug*/L**
****** **≥ 0.002 *ug*/L**
******* **≥ 0.160 *ug*/L**
† **≥ 0.040 *ug*/L**
‡ **Limit of detection 0.010 *ug*/L**

- 718/786 (91%) had all 5 troponin assays.
- Amongst the 718, the median age was 64, 66% were male, median BMI 26 kg/m^2, 16% were diabetic, 61% had HTN, 43% with hyperlipidemia, and 24% were smokers. Prior MI had occurred in 25% and 35% had previously established CAD.
- The final diagnoses were AMI 17%, USA 16%, cardiac ST with CAD in 13% and non-cardiac etiology in 46% (8% unknown causes).
- The diagnostic accuracy at initial patient presentation for each troponin assay is reported to the left

- The diagnostic properties for all troponin assays were similar for STEMI and NSTEMI, in men and women, in renal dysfunction and in those ≥ 70 years old.
- The AUC was not most pronounced for chest pain ≤ 3 hours.

- **The diagnostic accuracy to distinguish USA from other non-cardiac causes of CP was low and variable**:
  - Abbott Trop I AUC = 0.65
  - Roche High Sen Trop T AUC = 0.76
  - Roche Trop I AUC = 0.56
  - Siemens Trop I AUC = 0.68

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?**	Probably – would just need the central lab to pick one troponin assay. Siemens Trop I probably optimizes LR^+ and LR^-
B.	**Are the results applicable to the patients in my practice?**	Yes, ED patients with acute chest pain. AMI prevalence 17% higher than BJH angina MI rate but similar.
C.	**Will the results change my management strategy?**	Not unless one of these assays becomes available at BJH.
D.	**Will patients be better off as a result of the test?**	Yes by diagnosing AMI (STEMI and NSTEMI) earlier. If one were to use the Siemens Trop I Ultra for example with a pre-test probability of AMI 20%  However, "since this was a prospective, observational study, we cannot quantify the clinical effect associated with the increase in early diagnostic accuracy". (p. 866) The ultra-sensitive troponin assays are probably not sufficient to differentiate USA from non-cardiac chest pain.

Limitations

1) **Undefined HTN, DM, hyperlipidemia, etc (diagnostic and prognostic risk factors).**

2) **No description of number or location of ED's involved.**

3) **No description of acute or sub-acute MI management.**

4) **No 2x2 tables or LR's were reported.**

5) **No description of costs for various assays.**

Bottom Line

Multiple sensitive troponin assays can increase the diagnostic accuracy for acute MI in ED chest pain patients, particularly within the first 3º of symptom onset. However, these rapid troponin assays do not increase post-test probability to 100% or decrease it to 0% and they cannot be used to distinguish USA from other forms of non-cardiac chest pain. Furthermore, other conditions like myocarditis and heart failure also increase troponin levels so clinical evaluations will still be required.