Critical Review Form
Diagnostic Test

Sensitive Troponin I Assay in Early Diagnosis of Acute Myocardial Infarction, *NEJM* 2009; 361: 868-71

Objectives: **To evaluate "the diagnostic accuracy, discrimination, and clinical usefulness of a sensitive troponin I assay for the early diagnosis and risk stratification of myocardial infarction in a large prospective, multicenter study involving patients with chest pain who had a high pretest probability of acute myocardial infarction". (p. 869)**

Methods: **Between June 2007-December 2008 all patients ages 18-85 years presenting with angina or angina equivalent symptoms to Johannes Gutenberg University Medical Center (Mainz Germany), Federal Armed Forces Hospital (Koblenz), or University Hospital Hamburg-Eppendorf chest pain units were eligible. Exclusion criteria included trauma or surgery within the previous four weeks, pregnancy, obvious intravenous drug abuse, or hemoglobin <10 g/dL.**

Risk factor definitions were operationalized as follows:

Hypertension- present if previously diagnosed or treated with anti-HTN medications.

Smoking – if currently smoking, formerly smoking if quit sometime within the previous 4-40 years prior to enrollment, or never smoked.

Diabetes- Diagnosed or treated, even if only by diet.

Hyperlipidemia – total cholesterol >200 mg/dL at admission.

Blood was drawn at admission, 3 hours and 6 hours. All patients were followed for 30 days after hospitalization. The primary outcome was the composite of death, MI, stroke, hospital admission for cardiovascular reasons or unplanned percutaneous intervention (PCI).

The sensitive Troponin I assay was obtained with the TnI ultra assay on an ADVIA Centaur XP system with an assay range 0.006-50 ng/mL and a coefficient of variation

at 0.3 ng/mL of 10%. For a healthy population the reference range is 0.04 ng/mL (99th percentile). Two hospitals measured Troponin T (using the Elecsys Troponin T with a detection limit and reference range 0.01 ng/mL) and the other used Troponin I (using the Dimension RxL TnI with a detection limit of 0.04 ng/mL and reference limit of 0.14 ng/mL).

Two-by-two tables were constructed contrasting AMI against non-coronary chest pain. Sensitivity & specificity were assessed using cut-offs for ultra-sensitive Troponin-I of 0.04 ng/mL, Troponin-T of 0.01 ng/mL, and standard Troponin-I of 0.04 ng/mL. ROC curves were also constructed. Two Cox regression models were assessed to determine the association of Troponin-I Ultra and Troponin-I with 30-day outcomes. One model adjusted for gender and age. The second model adjusted for gender, age, BMI, HTN, DM, smoking, hyperlipidemia, GFR and "electrocardiogram".

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Yes, these were adults with new onset chest pain. Clinicians had to establish the diagnosis and treatment plan using only clinical exam, ECG, and routine labs up to 12 hours from presentation to chest pain units – almost always prior to the definitive diagnostic study.
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. "the final discharge diagnosis was based on all available clinical, laboratory, and imaging findings, was adjudicated by an expert committee of two independent cardiologists who were unaware of the results of the troponin I assays". (p. 869)
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. The results of the ultra-sensitive troponin did not impact how the final diagnosis was determined.
II.	**What are the results?**	

A.

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

* LR^+ and LR^- are not reported in the manuscript so 2x2 tables were re-constructed to compute them. For example, for <3º presentation

Ultra-sen Trop-I	MI	No MI
>0.04	347	96
<0.04	66	1309

- 1818 patients were enrolled with a mean age 61 years and 66% were male with mean BMI 28 kg/m^2. Co-morbid illnesses included DM 16%, HTN 74%, and hyperlipidemia 73%. 36% had a previous diagnosis of CAD. 74% had presented less than 12 hours after the onset of chest pain and 38% in less than 3 hours.
- 22.7% (413/1818) had the final discharge diagnosis of AMI including 7.2% with STEMI. 13.2% (240/1818) were diagnosed with USA.
- Several patients had an elevated troponin with non-cardiac etiology of chest pain: PE (19), acute CHG (18), myocarditis (17), aortic dissection (6), and decompensated aortic value stenosis (2).
- Compared with troponin T the ultra sensitive Troponin I had the following diagnostic test characteristics.

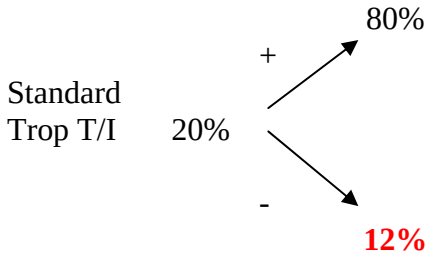
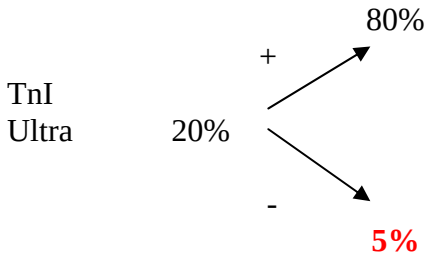
	Ultra Trop I (95% CI)	Trop T (95% CI)
Present.<3º		
Sen	84.0 (78-89)	55.2 (47-63)
Spec	93.2 (90-95)	95.7 (93-97)
LR^+*	12.3(10.5-14.2)	12.7 (10-16)
LR^-*	**0.17** (0.14-0.21)	**0.47** (0.44-0.50)
AUC	0.95	0.76
Present<6º		
Sen	86.8 (82-91)	62.1 (56-68)
Spec	92.2 (90-94)	94.9 (93-96)
LR^+*	11.1 (9.7-12.6)	12.1 (9.7-15.1)
LR^-*	**0.14** (0.12-0.18)	**0.40** (0.37-0.44)
AUC	0.95	0.79
All Patients		
Sen	90.7 (87-93)	72.7 (68-77)
Spec	90.2 (88-92)	94.1 (93-95)
LR^+	9.2 (8.3-10.1)	12.3 (10.2-14.9)
LR^-	0.11 (0.08-0.14)	0.29 (0.26-0.33)
AUC	0.96	0.85

- To differentiate USA from non-coronary chest pain the AUC was 0.62.

		• 81% of MI patients presenting within 3 hours of chest pain had an elevated ultra-Trop I on admission and 95% if presenting within 6-12 hours. • For the composite outcome the Cox hazards model demonstrated no significant differences between Ultra Trop-I and Trop-T

	Model 1 HR (95% CI)	Model 2 HR (95% CI)
UltraTrop I <0.04		
At Adm.	1.96 (1.27-3.05)	1.72 (1.06-2.81)
3º after Adm.	2.16 (1.36-3.41)	2.01 (1.21-3.34)
6º after Adm.	2.06 (1.29-3.29)	1.90 (1.13-3.19)
Trop T >0.01		
At Adm.	1.91 (1.22-3.01)	1.63 (0.99-2.68)
3º after Adm.	2.09 (1.34-3.28)	1.81 (1.11-2.96)
6º after Adm.	1.95 (1.23-3.08)	1.61 (0.96-2.7)

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 add TnI ultra assay to the diagnostic tests that can be ordered.
B.	**Are the results applicable to the patients in my practice?**	Uncertain. These were no ED patients; they were chest pain units in Germany presumably staffed by Cardiologists. Although the investigators do not quantify "high-risk" for ACS, these patients probably are higher risk than the typical U.S. ED chest pain patient. The authors note "the relatively low number of patients with decompensated heart failure was explained by the primary admission of such patients to the general emergency department". (p. 870)
C.	**Will the results change my management strategy?**	Not unless TnI ultra assay becomes available in our ED.

D.	**Will patients be better off as a result of the test?**	Yes for earlier diagnosis. If the standard Troponin T or Troponin I test is used for a patient presenting within 3 hours of angina onset, the post-test probability to <u>rule out</u> myocardial infarction would be reduced significantly consistent with TnI ultra. Pre-test probability AMI 20%   **Who wants to send the extra 7% home with a false-negative troponin?** However, "Future studies will be needed to determine whether the early diagnosis of myocardial infarction facilitates rapid use of invasive strategies and thus improves the outcome in patients with myocardial infarction". (p. 877)

Limitations

1) **Failure to report 2x2 tables or LR's.**

2) **Failure to discuss properties of the new assay distinguishing it from standard troponin assays.**

3) **Uncertain external validity to US ED's given the different German acute care model.**

4) **No quantitative description of "high risk" for AMI.**

Bottom Line

A single sensitive troponin I at the time of admission substantially improves diagnostic accuracy for AMI compared with conventional troponin T. In fact, measurement of sensitive troponin I within 3 hours of admission detected 100% of MI's with increasing false-positive rates. Future diagnostic-interventional trials are needed to determine whether earlier detection improves patient-oriented outcomes in MI.