Critical Review Form

Prognosis

Cardiac-Specific Troponin I Levels to Predict the Risk of Mortality in Patients with Acute Coronary Syndromes, *NEJM* 1996; 335: 1342-1349

Objective: **"To evaluate the potential prognostic value of this marker (cardiac troponin I) in patients with unstable angina or non-Q-wave myocardial infarction". (p. 1342)**

Methods: **The data upon which this manuscript is based were collected as part of the Thrombolysis in Myocardial Ischemia Phase IIIB (TIMI IIIB) trial, a prospective, randomized multicenter U.S. and Canadian study of patients, with USA or NSTEMI conducted from October 1989 – June 1992. The trial was a factorial design to assess tissue plasminogen activator vs. placebo and early invasive vs. early conservative management strategies. Exclusion criteria included left bundle-branch block, documented MI in the preceding 21 days, treatable cause of angina, thrombolytic therapy within 72 hours or angioplasty within 6 months. The following definitions were used:**

> **Non-Q-wave infarction – elevated CK-MB level or total CK > twice normal (when no CK-MB was available) at presentation or within 12 hours thereafter.**
>
> **Unstable angina – everybody else.**

Investigators analyzed the 1404/1473 TIMI IIIB subjects who had plasma specimens available, including 845 who presented greater than six hours after the onset of chest pain. Specimens were originally collected in tubes containing aprotinin, EDTA, and D-phenylalanyl-L-pro-lyl-L-arginine. Specimen handling at collection, including storing at the site of collection at 4ºC before being shipped on dry ice to the Hematology Core Lab where they were stored at -70 ºC. They went through one cycle of thawing and refreezing before shipment in 1995 to the Brigham and Women's Hospital Cardiac Serum Core Laboratory.

Cardiac troponin I was measured by the Stratus II fluorometric enzyme immunoassay by technologists unaware of the clinical data. Since healthy persons should have no detectable troponin I in serum and the minimal level of detection for

the Stratus II is 0.35 ng/mL with within-run coefficient of variation of 13% and between-run variation 16%, a cutoff value of 0.4 ng/mL was selected for this study. The Brigham lab also tested for CK-MB using the Stratus instrument.

The troponin I levels measured were then merged with the clinical data at the Maryland Medical Research Center where statistical analysis was performed. After univariate analysis of patients with and without troponin at the cut-off level, multivariate analysis and Cox proportional-hazard models were performed for the primary outcome of 42-day mortality.

Guide		Comments
I.	**Are the results valid?**	
A.	**Was the sample of patients representative?** *In other words, how were subjects selected and did they pass through some sort of "filtering" system which could bias your results based on a non-representative sample. Also, were objective criteria used to diagnose the patients with the disorder?*	Not really. As demonstrated in Table 1 (p. 1344) subjects were primarily Caucasian (80%). In addition, investigators do not report on the prevalence of diabetes, hyperlipidemia, renal dysfunction, obesity, or any metrics of socio-economic status. All of these variables can impact ACS-mortality and could be important confounders if unequally distributed across troponin-level groups.
B.	**Were the patients sufficiently homogeneous with respect to prognostic risk?** *In other words, did all patients share a similar risk from during the study period or was one group expected to begin with a higher morbidity or mortality risk?*	Probably, although neglecting important prognostic variables like DM and hyperlipidemia levels open the possibility for unmeasured confounders.
C.	**Was follow-up sufficiently complete?** *In other words, were the investigators able to follow-up on subjects as planned or were a significant number lost to follow-up?*	No loss to follow-up at 42 days is reported.

D.	**Were objective and unbiased outcome criteria used?** Investigators should clearly specify and define their target outcomes before the study and whenever possible they should base their criteria on objective measures.	"Cardiac troponin I (was measured) by technologists unaware of the clinical data". (p.1343) The diagnosis of NSTEMI depended upon an elevated CK or CK-MB level, but the very hypothesis of this work is that troponin (found primarily in cardiac muscles) is more sensitive and specific than CK (found in skeletal and cardiac muscle). Therefore, in assessing the new test (troponin) to the old test (CK-MB) we are using an inferior criterion standard and the results should be interpreted accordingly.
II.	**What are the results?**	
A.	**How likely are the outcomes over time?**	• The mean age of the 1404 patients was 59 years and 38% were current smokers, 42% had HTN, and 40% had suffered a prior MI. Patients had a mean of 3.1 angina episodes in the preceding 24 hours lasting a mean of 1.9 hours for the qualifying episode and with 9.2 hours between first pain to treatment. • 948/1404 (68%) had USA and the remainder had non-Q-wave MI • The diagnosis of non-Q-wave MI or USA was only moderately correlated with troponin I greater than 0.4 ng/mL (Spearman rho = 0.465), but **25% of USA patients (i.e. no CK or CK-MB elevation) had troponin ≥ 0.4 ng/mL** • 29/1404 (2.1%) died within 42 days including 21/573 with troponin I ≥ to 0.4 ng/mL. The mortality risk was greatest for those enrolled between 6-24 hours post pain onset (4.0% vs. 0.4% mortality for troponin greater or equal to 0.4 ng/mL compared with 3.1% vs. 1.7% for those enrolled 0-

		6 hours post pain onset) reflecting the delay between myocardial injury and detectable troponin in serum. • There was a **statistically significant increase in unadjusted mortality with increasing levels of troponin I** (Fig. 3 p. 1347): Troponin I ng/mL / 42 Day Mortality / Risk Ratio (95% CI) < 0.4 / 1.0 / 1.0 0.4-1.0 / 1.7 / 1.8 (05.-6.7) 1.0-2.0 / 3.4 / 3.5 (1.2-10.6) 2.0-5.0 / 3.7 / 3.9 (1.3-11.7) 5.0-9.0 / 6.0 / 6.2 (1.7-22.3) ≥ 9.0 / 7.5 / 7.8 (2.6-23.0) • Multivariate adjustment for prognostic variable found to be associated with 42 day mortality on univariate analysis (Table 1 p. 1344) included smoking status, history of angina, HTN, MI or known angiographic CAD, pre-existing use of nitrates, ß-blockers, CCB, or aspirin, duration of angina symptoms, and transient ST-segment elevation or depression. Multivariate analysis left the following independent predicators for 42 day mortality: ST-depression at entry (RR 4.63, 95% CI 2-10), age ≥ 65 (RR 2.34, 95% CI 1-5), and troponin I increase of 1 ng/mL (RR 1.03, 95% CI 1-1.05. The latter variable did not increase when looking at the subject with symptoms lasting longer than six hours.
B.	**How precise are the estimates of likelihood?** *In other words, what are the confidence intervals for the given outcome likelihoods?*	See 95% CI above

III.	How can I apply the results to patient care?	
A.	**Were the study patients and their management similar to those in my practice?**	No. Although "all the patients received intravenous heparin and aspirin and other standard medical therapy" (p. 1343) the authors do not provide prognostic results stratified by or adjusted for the experimental interventions received (tissue plasminogen activator vs. placebo, early aggressive angioplasty intervention) so prognosis may be skewed by factors other than age, ST-deviation and troponin-I elevation. Furthermore, investigators do not report on important pre-existing prognostic confounding variables (DM, hyperlipidemia, obesity, etc.) and the patient population is not representative of a typical urban sampling.
B.	**Was the follow-up sufficiently long?**	Yes, 42-days is sufficiently long for emergency medicine purposes since patients ought to be able to obtain follow-up and definitive interventions within that time frame.
C.	**Can I use the results in the management of patients in my practice?**	Yes. In the search for optimal biomarkers to denote myocardial injury that correlates with patient-important outcomes, CK-MB should be replaced by troponin I. Furthermore, non-AMI patients with troponin-I $\geq$ 0.4 ng/mL should be considered at increased risk for 42-day mortality, especially if the troponin is obtained > six hours after symptom onset.

Limitations

1) **Incomplete assessment of recognized important prognostic variables for ACS mortality: DM, hyperlipidemia, obesity, renal dysfunction and socio-economic status. Although it is important to distinguish risk factors for the development of disease from conditions/exposures that portend a poor prognosis after the disease state has developed, in the case of coronary artery disease there is**

overlap between these risk factors. In other words, patients with DM and hyperlipidemia are both more likely to develop CAD than those without DM or hyperlipidemia. And once CAD develops, those with HTN and DM are more likely to suffer adverse consequences from their CAD than those without HTN or DM. Therefore, these are important prognostic variables that ought to be considered in any statistical evaluation of a new test's prognostic characteristics.

2) **Selection bias with primarily Caucasian sampling and uncertain external validity for other ethnic groups.**

3) **Up to six years between specimen collection and troponin assay with stated stability of frozen sample only extending to 16 months.**

4) **No stratified reporting or adjustment for the experiment's interventional arm (TPA, early catheterization) on 42-day mortality.**

Bottom Line

Troponin-I should replace CK-MB as a diagnostic and prognostic marker to distinguish unstable angina from non-Q-wave myocardial infarction. In both forms of ACS (USA and NSTEMI), increasing levels of troponin are significantly associated with an increased 42-day mortality. Future studies are needed to assess the independent prognostic power of troponin when adjusted for the full spectrum of confounding baseline and interventional variables. Since biomarker elevation is part of the definition distinguishing USA from non-Q-wave MI, an RCT design allocating physicians to be aware or not aware of troponin-I levels will probably never occur so the additive benefit of the biomarker above EKG and clinical gestalt will remain unknown.