Critical Review Form
Prognosis

Quantitative troponin and death, cardiogenic shock, cardiac arrest and new heart failure in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS): insights from the Global of Acute Coronary Events, *Heart* 2011; 97: 197-202

Objective: **"To determine if the extent of troponin concentration elevation in patients presenting with (1) in-hospital complications such as cardiogenic shock, new onset heart failure, and cardiac arrest and (2) mortality after accounting for other established risk variables." (p. 197)**

Methods: **A sampling of patients were used from the Global Registry of Acute Coronary Events (GRACE), a 14-country collaboration. The sample included 16318 patients from 95 hospitals enrolled between July 2000 and December 2007 with non-ST-segment elevation acute coronary syndrome (NSTE ACS). Excluding subjects with LBBB or STE, subjects were identified by clinical history of ACS along with at least one of the following: EKG changes consistent with ACS, serial increases in cardiac biomarkers (troponin or CK-MB), or documented history of CAD**

Follow-up at 6-months was conducted by interview (patient, family, or healthcare provider) or medical record review. Initial troponin T or I levels were obtained along with peak levels up to 24 hours. Outcomes assessed included in-hospital death, new onset CHF, cardiogenic shock, and cardiac arrest or sustained ventricular tachycardia. Investigators also assessed all-cause 14-day and, 6-month mortality. Recurrent MI required ECG changes along with CK changes either twice the upper limit of normal (ULN) and increased over 25% from previous peak or >1.5x ULN and 50% over previous peak and after CABG > 5x ULN.

The following definitions were used:

> **Cardiogenic Shock – SBP < 80 mm Hg with pulmonary edema and hypo perfusion.**
>
> **Heart failure – signs or symptoms of Killip Class II or greater heart failure.**
>
> **Cardiac arrest – VF or rapid VT with hemodynamic instability, asystole or PEA requiring CPR. (p. 198)**

For analysis of crude rates, each outcome was assessed against troponin level stratified by ratios 1, 10, 100, 1000, or > 1000. Stepwise logistic regression models were then used with log base 10 of the troponin level for each outcome adjusted for hospital cluster age, cardiac arrest prior to admission, ST depression, Killip Class, SBP, pulse, and creatinine level. Unadjusted association of troponin and all-cause mortality was assessed with Kaylan-Meier plots. Adjusted associations were evaluated with Cox regression models, adjusting for hospital cluster and the above GRACE risk score variables. The final Cox model separated early (< 14 days) and late (15 – 180 days) mortality because the effect of troponin elevation was not uniform over time.

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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?*	Yes. 16286 patients from 95 hospitals with available troponin assay after NSTE ACS. Mean age 68 with 65% males, 24% smokers and 30% with prior MI and 28% diabetes.
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?*	Investigators do not disclose any associated randomization scheme or interventions (fibrinolytics, angioplasty) so presumably all patients entered the hospital with similar NSTE ACS prognosis prior to knowledge of troponin level.
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?*	Yes. "The in-hospital outcomes of death, new-onset congestive heart failure, cardiogenic shock, and cardiac arrest/sustained ventricular tachycardia (VT)/ventricular fibrillation (VF) was examined in addition, we evaluated all-cause mortality at 14 days and 6-months". (p. 198). No loss to follow-up was 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.	Yes, using the definitions provided above "trained site abstractors used standard event definitions in the GRACE registry". (p. 202)
II.	**What are the results?**	
A.	**How likely are the outcomes over time?**	• Most patients had troponin-I (76%) rather than troponin-T (24%). • As demonstrated in Table 1 (p. 199) patients in the group with highest troponin elevations (troponin ratio >1000 which was 107/16286 or 0.65% of the cohort) were less likely to have had prior MI, PCI or coronary bypass surgery. They were also older (74 vs. 66 years in the lowest troponin ratio group), more likely to smoke and more likely to present with ST-depression (51% vs. 17%), and severe CHF (Killip Class 4 4.7% vs. 0.1%) • The unadjusted rates of complications increased progressively across the five troponin groups (p <0.0001 for trend) • Logistic regression models adjusting for GRACE risk score variables (age, cardiac arrest prior to admission, ST depression, Killip Class, SBP, pulse and creatinine level) identified the following outcomes independently associated with an elevated troponin ratio:

In-Hospital Events by Troponin Group (%)

	Troponin ratio 0.01 to ≤ (n=6328)	Troponin ratio >1 to ≤ 10 (n=4222)	Troponin ratio >10 to ≤ 100 (n=4057)
New-onset CHF†	2.5	5.1	7.4
Cardiogenic shock‡	0.5	1.4	2.0
Cardiac arrest/VF or sustained VT‡	1.0	2.4	3.4
Death	0.8	2.2	3.0
Recurrent MI	1.6	2.3	2.3
Death or recurrent MI	2.2	4.2	5.0

	Troponin ratio >100 to ≤ 1000 (n=1403)	Troponin ratio >1000 (n=107)	P Value for trend*
New-onset CHF†	11.6	15.8	<0.001
Cardiogenic shock‡	4.4	12.7	<0.001
Cardiac arrest/VF or sustained VT‡	5.9	13.4	<0.001
Death	5.3	14.0	<0.001

Outcome	Odds Ratio (95% CI)
New CHF in-hospital*	1.57 (1.45-1.71)
New cardiogenic shock†	1.87 (1.61-2.18)

Recurrent MI	**1.5**	**5.8**	**0.035**
Death or recurrent MI	**6.5**	**19.4**	**<0.001**

Cox Hazards Model Predictors of Mortality

Variable	Odds Ratio (95% CI)
Troponin Early (0-14 days) Mortality	1.61 (1.44-1.81)
Troponin Late (15-180 days) Mortality	1.18 (1.07-1.30)
ST depression	1.53 (1.31-1.79)
Age (per 5 year increase)	1.43 (1.38-1.48)
Killip Class	1.79 (1.62-1.97)
Serum creatinine	1.25 (1.19-1.31)
Cardiac arrest at presentation	4.58 (3.20-6.55)
Systolic BP (per 5mm/Hg ↑	0.95 (0.94-0.96)
Heart rate (per 10 beat ↑	1.05 (1.02-1.08)
New cardiac arrest‡	1.56 (1.39-1.74)

* Excluded 2197 patients who presented with heart failure.

† Excluded 55 patients who presented with cardiogenic shock.

‡ Excluded 164 patients who presented with cardiac arrest

- The results for in-hospital outcomes were consistent for both troponin I and troponin T.
- 755 of patients with an outcome event during the initial hospitalization had only one event.
- Using Kaplan-Meier **the unadjusted mortality for all patients with NSTE ACS was 2.6% at 14 days and 7.3% at 180 days from presentation** to the hospital.
- Cox proportional hazards model identified the independent predictors for mortality noted to the left.

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 details are provided on where these patients presented (first world nation hospital? Cardiac cath lab availability? Academic or community hospital?) or what interventions occurred (ASA, ß-blocker, TPA, etc.). "However, the external validity of these registry data may be greater as they come from a broad-based population, and the subjects are likely to be less selected than those populations included in randomised controlled trials" (p. 202)
B.	**Was the follow-up sufficiently long?**	Yes, 6-month follow-up is sufficient for EM purposes.
C.	**Can I use the results in the management of patients in my practice?**	Uncertain. The investigators do not provide any idea for altering NSTE ACS management based upon troponin results. Since nobody is likely to discharge an ACS patient with a troponin elevation, the question becomes how does one alter inpatient management of NSTE ACS for varying degrees of troponin elevation to alter the observed mortality? Ideas might include early PCI, prolonged telemetry or more aggressive early medical management, but with trial data the current paper does not tell us if any of these interventions would reduce mortality.

Limitations

1) **Troponin measurement not performed at central lab so subject to variability.**

2) **The timing of in-hospital complication was not reported so the cause-effect relationship of troponin elevation could not be determined.**

3) **No protocol for the frequency of troponin measurements was reported.**

4) **Non-fatal events were not adjudicated by an independent committee.**

5) **Management interventions were not incorporated into the model, although hospital cluster was not an independent predictor for any of the measured outcomes.**

6) **No recommendations were provided on how to use this information.**

Bottom Line

The extent of elevation of troponin is an independent predictor of mortality and in-hospital development of new CHF, cardiogenic shock or cardiac arrest in patients following NSTE ACS. Since the overall (unadjusted) 14 day mortality rate is 2.6% (with in-hospital death rates of 14% in those with troponin ratio >1000), future interventional trials are needed to identify effective management mechanisms incorporating the prognostic information provided by the degree of troponin elevation.