Frequently Asked Questions Regarding the Use of Troponin in the Clinical Setting

What does an elevated troponin level mean?
• Elevated troponin is a sensitive and specific indicator of cardiac myonecrosis, with troponin release from myocytes into the systemic circulation. In and of itself, elevated troponin does not indicate MI (myonecrosis due to ischemia); rather, it is nonspecific relative to the etiology of cardiac myonecrosis. Troponin elevation occurs in many nonischemic clinical conditions. As assays become more sensitive, more conditions that result in low-level troponin elevations will be identified.

When should a troponin level be obtained?
• Because it is not specific for MI, troponin evaluation should be performed only if clinically indicated for suspected MI. An elevated troponin level must always be interpreted in the context of the clinical presentation and pre-test likelihood that it represents MI. Troponin is recommended for diagnosis of MI in CKD patients with symptoms of MI regardless of the severity of renal impairment. Dynamic changes in troponin values of ≥20% over 6 to 9 h should be used to define acute MI in ESRD patients. In the absence of specific interventions based on the results, routine troponin testing is not recommended for nonischemic clinical conditions except: FDA-approved troponin testing for prognosis in CKD patients. Treatment of patients undergoing chemotherapy who have drug-induced cardiac injury.

What is the prognostic significance of an elevated troponin level?
• Troponin elevation imparts a worse prognosis, irrespective of the underlying etiology. For patients with non-ST-segment elevation ACS, global risk assessment rather than any single risk marker, best affirms prognosis and is preferred to guide therapeutic decisions.

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WHO Universal Definition of Myocardial Infarction

1979 WHO:
2 of 3 Features:
1. Clinical history
2. Electrocardiographic findings
3. Temporal changes in serum enzymes

2007 Global Task Force:
The term MI is used in a clinical setting (History and ECG) consistent with myocardial infarction associated with criteria for MI as defined:
1. A rise and/or fall of biomarkers (preferably troponin)
2. Sudden Cardiac Death
3. Elevations in biomarkers after Percutaneous Coronary Intervention (PCI) in patients with normal pre-intervention markers
4. Elevations of biomarkers in patients after Coronary Artery Bypass Grafting (CABG) with normal baseline troponin levels
5. Pathologic findings of acute MI

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Analytical Issues

- **What is a Temporal Rise and/or Fall in Troponin?**
  - A 20% change at 3 to 6 hours from the prior sample
  - Recommended times: Baseline, 3-6h (6-9 hours, 12-24 hours)
  - Time 0 is onset of symptoms or arrival in ER if uncertain

- **Problems with troponin assays** –
  - Differing susceptibility to interfering substances (e.g., heterophile antibodies and rheumatoid factor)
  - Variability in Sensitivity over time and at the expense of specificity
  - Problems defining the “reference control populations”
  - Lack of standardization of troponin assays

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**Statistical Issues – Bayes Theorem**

- Pre-test likelihood determines post-test likelihood
- What are you testing for? Acute coronary syndrome (ACS) or myocardial infarction from any cause?
- Pre-test likelihood is influenced by prevalence of the disease in the population and clinical indicators (age; sex; risk factors; quality of presenting symptoms – typical, atypical, non-cardiac, none; ischemic ECG changes; new wall-motion abnormalities; history of known CAD)
- Post-test likelihood is also influenced by the “extent of positivity of the troponin” (more predictive with higher troponin and less predictive with lower troponins)
- Troponin kinetics over time – “smoldering abnormal” vs. “dynamic changing troponins” (>20% change)
Semi quantitative Summary of Positive and Negative Predictive Accuracies of Troponin Testing in Various Scenarios

<table>
<thead>
<tr>
<th>Typical Anginal Symptoms</th>
<th>Ischemic ECG or Echocardiogram Findings</th>
<th>History of Risk Factors for Coronary Artery Disease</th>
<th>Pre-Test Probability of Acute Myocardial Infarction</th>
<th>Cardiac Troponin Value</th>
<th>Diagnostic Evaluation for Nonischemic Etiology</th>
<th>Prognostic Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>High (50%)</td>
<td>Positive</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Low (&lt;4%)</td>
<td>Negative</td>
<td>High NPV</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>High (50%)</td>
<td>Positive</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Low (&lt;4%)</td>
<td>Negative</td>
<td>High NPV</td>
<td>No</td>
</tr>
</tbody>
</table>
High Sensitivity Troponins

- 16 to 66% of "subjects in the general population" had detectable troponins in various studies. Underlying or preclinical "disease" was felt to be the etiology.
- Higher % in clinically ill patients
- Associated with Diabetes, LVH, CKD, hypertension, CAD, pulmonary embolism, heart failure, sepsis, chemotherapy-associated cardiac toxicity (anthracyclines, cyclophosphamide, platinum-based)

Non-ACS Ischemic Troponin Elevations

- Paroxysmal Atrial Fibrillation, Supraventricular Tachycardia
- Ventricular Tachycardia
- Hypoxia
- Severe Anemia
- Gastrointestinal Hemorrhage (hypertension and anemia)
- Hypertension (small vessel, wall stress)
- Spasm
- Coronary Embolism
- Procedure Related – PCI, CABG
- Cocaine, methamphetamine

CLINICAL PRESENTATION helps distinguish ACS from Non-ACS troponin elevations and determines the extent of further workup

Non-ischemic Troponin Elevations

- Pulmonary embolism
- Heart failure (wall stress, hypoxia, demand > supply)
- Chronic Kidney Disease (CKD)
- Sepsis
- Chemotherapy-associated Cardiac toxicity (anthracyclines, cyclophosphamide, platinum)
- Myocarditis: Infections (HIV, vaccinations) and Toxic agents (Not associated with acute rheumatic fever, dengue fever, Plasmodium falciparum)
- Myopericarditis
- Amyloidosis
- Cardiac Transplant monitoring (for rejection)
- Blunt Cardiac Injury
- Non-cardiac surgery
- Subarachnoid hemorrhage
- Stroke
- Endocarditis
Non-ischemic Troponin Elevations

- Cardiac Tumors and Systemic Malignancies
- Hematologic Conditions (hemophagocytic lymphohistiocytosis, thrombotic thrombocytopenia purpura, thrombotic microangiopathy)
- Neuromuscular and Myopathic Conditions
- Autoimmune and Connective Tissue Disorders (Sarcoid, systemic sclerosis, inclusion body myositis, polymyositis/dermatomyositis, Wegener’s granulomatosis, giant cell myocarditis)
- Arrhythmia treatment – ablations, placement of pacing or defibrillator leads
- Metabolic disorders: Diabetic ketoacidosis, severe hyperglycemia
- COPD – multiple etiologies like hypoxia, acidosis, pulmonary hypertension
- Autonomically Mediated Disorders: Stress (Takotsubo’s) cardiomyopathy, pheochromocytoma, catecholamine excess with subarachnoid hemorrhage
- Pregnancy: oxytocin? Tocolytic agents, co-morbidities (hypertension, pre-eclampsia, eclampsia, obesity, diabetes, early CAD), peripartum cardiomyopathy
- Stressful Exercise
- Rhabdomyolysis
- Aortic Dissection – rarely coronary dissection, frequently hypotension and catecholamines

Adverse Outcomes Among Heart Failure Patients With Elevated Troponin Levels

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type</th>
<th>Troponin</th>
<th>% With Elevated</th>
<th>Endpoint</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setsuta</td>
<td>79</td>
<td>T</td>
<td>56</td>
<td>54%</td>
<td>Death, heart failure admit</td>
<td>7.0</td>
</tr>
<tr>
<td>La Vecchia</td>
<td>80</td>
<td>I</td>
<td>34</td>
<td>29%</td>
<td>Death</td>
<td>6.9</td>
</tr>
<tr>
<td>Ishii</td>
<td>81</td>
<td>T</td>
<td>100</td>
<td>35%</td>
<td>Cardiac death, heart failure admit</td>
<td>3.1</td>
</tr>
<tr>
<td>Taniguchi</td>
<td>71</td>
<td>T</td>
<td>71</td>
<td>28%</td>
<td>Heart failure death, heart failure admit</td>
<td>∼3.0</td>
</tr>
<tr>
<td>Perna</td>
<td>2005</td>
<td>T</td>
<td>184</td>
<td>32%</td>
<td>Death, heart failure admit</td>
<td>1.7</td>
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<tr>
<td>Ilva</td>
<td>83</td>
<td>T</td>
<td>364</td>
<td>30%</td>
<td>Death</td>
<td>2.6†</td>
</tr>
<tr>
<td>Ilva</td>
<td>83</td>
<td>I</td>
<td>364</td>
<td>51%</td>
<td>Death</td>
<td>2.0†</td>
</tr>
<tr>
<td>Horwich</td>
<td>84</td>
<td>I</td>
<td>238</td>
<td>49%</td>
<td>Death</td>
<td>1.85</td>
</tr>
<tr>
<td>Miller</td>
<td>85</td>
<td>T (serial)</td>
<td>150</td>
<td>27%, all values elevated</td>
<td>Death, transplant</td>
<td>3.77</td>
</tr>
<tr>
<td>Sato</td>
<td>86</td>
<td>T (serial)</td>
<td>60</td>
<td>28%, all values elevated</td>
<td>Cardiac death or hospital admit</td>
<td>7.6</td>
</tr>
<tr>
<td>Perna</td>
<td>2004</td>
<td>T (serial)</td>
<td>115</td>
<td>46%, ≥1 value elevated</td>
<td>Death or hospital admit</td>
<td>1.09</td>
</tr>
<tr>
<td>Hudson</td>
<td>88</td>
<td>T</td>
<td>136</td>
<td>24%</td>
<td>Death</td>
<td>4.2</td>
</tr>
<tr>
<td>Lantini</td>
<td>42</td>
<td>T</td>
<td>4,053</td>
<td>10%</td>
<td>Death</td>
<td>2.08</td>
</tr>
</tbody>
</table>

Summary Points

- Elevated troponin in and of itself does not indicate an MI but does indicate myonecrosis
- MI is myonecrosis from ischemia (MI, types 1 through 5)
- MI is not synonymous with ACS (plaque rupture, thrombosis)
- Bayes Theorem matters. Clinical presentation matters (“When in doubt, ask the patient”)
- hs-Troponins are “abnormal” in many clinical and subclinical situations and “normal” has yet to be standardized and may be dependent on a number of factors. Significance of the abnormalities outside of ACS is often unknown.
- Therefore, back to basics. MI is diagnosed with: temporal biomarker changes, ECG changes, clinical presentation (history and risk factors)
- When to order the test? When you need to diagnose (or not) MI dictated by the CLINICAL situation. It is NOT a screening test.
- What’s wrong with “screening”? Unnecessary downstream testing and potential harm
Study Population

The selection of the study population and number of patients at different levels of high-sensitivity cardiac troponin T (hs-cTnT), which are reported in nanograms per liter. ED = emergency department.

Figure Legend:

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The selection of the study population, and number of patients at different levels of high-sensitivity cardiac troponin T (hs-cTnT), which are reported in nanograms per liter. ED = emergency department.

Figure Legend:

Patients With Undetectable High-Sensitivity Cardiac Troponin T and Myocardial Infarction Within 30 Days

Patients with an initial high-sensitivity cardiac troponin T (hs-cTnT) < 5 ng/l and an electrocardiogram (ECG) without ST-segment elevation or depression, but myocardial infarction (MI) within 30 days of follow-up. LAD = left anterior descending artery, LCX = left circumflex artery, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction, NSTEMI = non-ST-segment elevation myocardial infarction, other abbreviations as in Figure 1.