

**SUMMARY**

Cardiac troponins have assumed important role in risk stratification of patients presenting in emergency room with acute chest pain. In the last fifteen years we have gained confidence in their clinical utility as markers of myocardial necrosis which is generally due to ischemia. They are more sensitive and specific than conventional markers like CK, CK-MB and LDH. Both quantitative and qualitative assays are available. Quantitative assays are point of care, relatively cheaper, results are more rapidly available and so are more popular. Qualitative assays are more sensitive, have to be conducted in the lab, blood sample collection is required and results are available after a certain period. So these are used as back up facility in most busy chest pain units.

Troponin T and I: both kind of evaluations are available and are well evaluated. However troponin T estimation is more standardized and thus more popular. The revised criteria for diagnosis of myocardial infarction by the ESC/ACC guidelines of year 2000 include troponins as important diagnostic criteria. Due to this, significant subset of patients who were earlier placed in NSTEMI are to be considered as myocardial infarction patients once they have positive troponins since these are markers of micro infarctions. Once this criteria is more widely applied in clinical use the concept of myocardial infarction is going to change.

Troponin estimations are important for risk stratifications of patients with chest pain and once they are negative in patients with normal electrocardiograms we can discharge patients from the emergency rooms. In coming times other markers like High sensitivity C reactive protein (hs-CRP) as marker of inflammation, Brain Natriuretic Peptide (BNP) as marker of heart

failure and Ischemia Modified Albumin (IMA) as marker of ischemia are likely to come up just as troponins have established their role as markers of necrosis. We will then be having a multimarker approach for management of these patients.

**CARDIAC TROPONINS—CURRENT STATUS**

Cardiac troponins have been in use for evaluation of patients with chest pain and acute coronary syndrome (ACS) for the last fifteen years. They have rapidly attained central role in diagnosis, prognostication and planning of therapeutic strategies in these patients. Presently, they are the most prominent biomarkers of cardiac injury and have relegated conventional biomarkers like creatine kinase (CK), CK-MB and LDH to second place. This is so because cardiac troponins are highly cardiac tissue specific unlike conventional biomarkers. The previous markers were detected using enzymatic activity. In troponins we are evaluating the concentration of specific proteins released consequent to myocardial necrosis<sup>1,2</sup>. A comparison of properties of various currently used cardiac markers is shown in Table 1.

The latest ESC/ACC guidelines have redefined acute myocardial infarction (AMI) in the year 2000 by incorporating cardiac troponins as a diagnostic criteria as shown in Table 2<sup>3-5</sup>. One cannot imagine a department admitting patients with chest pain without facility of troponin evaluation today. Among patients presenting in emergency with chest pain our aim is to stratify patients in various groups so as to enable us to discharge patients with no ischemia, manage optimally patients with ischemia but not at high risk and use invasive and aggressive therapeutic strategies in patients at high risk. Troponins as biomarkers of necrosis help us in subgrouping the patients in this setting<sup>6</sup>.

**Table 1:** Table showing properties of various cardiac markers currently used in patients presenting with acute chest pain

Protein	Molecular mass		Duration of detection	Sensitivity	Specificity
	(kD)	First detection*			
CK	96	4-6 hours	2-3 days	++	++
CK-MB	83	2-3 hours	1-2 days	+++	+++
Myoglobin	16	1.5-2 hours	8-12 hours	+++	+
Troponin I	33	3-4 hours	7-10 days	++++	++++
Troponin T	38	3-4 hours	7-14 days	++++	++++

\* Hours after symptom onset; CK - creatine kinase.

**Table 2 :** The Revised Definition of Myocardial Infarction according to the latest ESC/ACC guidelines on Myocardial Infarction; year 2000

Criteria for acute, evolving, or recent MI

Either one of the following criteria satisfies the diagnosis for an acute, evolving, or recent MI:

1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
  - a. Ischemic symptoms
  - b. Development of pathologic Q waves on the ECG reading
  - c. ECG changes indicative of ischemia (ST-segment elevation or depression)
  - d. Coronary artery intervention (e.g., coronary angioplasty)
2. Pathological findings of an acute MI

## STRUCTURE

The troponins are a complex of three proteins (I, C, and T) that regulate the calcium mediated interaction of actin and myosin. Tissue-specific isoforms of each troponin exist. However, the cardiac form of troponin C is shared by smooth muscle, so it lacks cardiac specificity. The cardiac troponin-I (cTnI) and troponin – T (cTnT) are not found in any tissue outside the heart. So these have unique specificity for the heart. In addition these two proteins have high sensitivity. Most of the troponin is complexed to the contractile apparatus. A small amount (3% for cTnI and 6% for cTnT) exists which is not structurally bound. This “small amount” has been termed the ‘cytosolic pool’. Although its localization is not proved definitively, the cytosolic pool permits the early kinetics of release similar to that of CK-MB or even earlier with more sensitive assays. However, it takes 5-6 hours for troponins to be released and detectable in blood following an ischaemic necrosis injury. Subsequently, prolonged elevation of troponins occurs

as a result of degradation of the contractile pool in the area that has been injured. The persistence of elevation is due to release from this structural pool, since the half life of troponin in the circulation is short. The duration for which levels remain high is 7-10 days for troponin – I and 10–14 days for troponin-T<sup>7,8</sup>. A comparison of various features of cardiac troponins is shown in Table 3.

## MEASUREMENT

**Two kinds of assays:** Qualitative and quantitative are available. Over the past 15 years, immunoassays have been developed for the cardiac troponins T and I. While several manufacturers have produced assays for troponin I, patent protection has meant that only Roche Diagnostics (Basel, Switzerland; formerly Bioehringer Mannheim, Germany) has produced a troponin T assay. There have been three generations of this laboratory assay. The current point-of-care (bedside) assay and the laboratory troponin T assay (ELISA assay) have a high degree of correlation. It is recommended that for a positive result the upper limit be defined as the 99<sup>th</sup> percentile. This is ~ 3 SDs above the mean for the normal

**Table 3:** Showing comparison of characteristics of troponin I and troponin T

Feature	cTnT	cTnI
Molecular weight (kDa)	33	23.5
Cardiac Specific	+++	+++
Affected by renal function	Yes	Yes
Initial detection	4-6 hours	4- 6 hours
Duration of elevation	10 – 14 days	7 – 10 days
Cytoplasmic pool	6 %	3 %
Rapid laboratory assay	Yes	Yes
Bedside assay	Yes	Yes

range. This should be along with an acceptable level of analytical variability of less than 10%. Point-of-care cardiac marker testing provides results within minutes, and should be used when the delay in obtaining laboratory results is likely to exceed 60 minutes<sup>9</sup>.

Different manufacturers have used different antibodies raised against different epitopes on cardiac troponin I, and there is no standardization between the different troponin I assays, which complicates their use. Troponin-I values may also be affected by heterophil antibodies. Thus at present, no troponin-I assay meets the ACC/ESC criteria for diagnosis of MI. Also fibrin can confound the assay of cTnI and heparinized plasma is preferred for this assay. This is not necessary for assessment of cTnT.

The 2002 ESC/ACC guideline update for patients presenting with unstable angina and NSTEMI states that "Point of care assays at present are qualitative or at best semiquantitative. A positive bedside test should be confirmed by a conventional quantitative test." Cardiac TnT is detectable at slightly lower serum levels than most TnI assays. The GUSTO – II investigators compared TnI and TnT in short term risk stratification of ACS patients. They observed that troponin-T showed a greater association with 30 day mortality than TnI. Meta-analysis have helped in assessment of the 'degree of risk' value of troponins in risk stratification<sup>10</sup>. In an analysis by Wu the odd ratio for AMI or deaths from hospital discharge to 34 months was 4.3 and need for revascularization was 4.4. In another analysis of 18,000 patients in 21 acute coronary syndrome studies troponin positive patients had an odds ratio of 3.4 for death or MI at 30 days.

## CLINICAL UTILITY

The troponins have revolutionized the risk stratification of chest pain patients and are now a corner stone for evaluation of patients admitted with chest pain<sup>11,12</sup>. They are markers of myocardial necrosis. These markers are tissue specific but are not specific regarding cause of injury. Hence these are also elevated in patients with: tachycardia with or without hypotension, pulmonary emboli with right ventricular infarction, cardiac failure with myocardial necrosis due to raised LV end diastolic pressures, direct trauma to the heart, myocardial toxins like adriamycin and 5 – fluorouracil, myocarditis, cardiac surgery and also in renal failure in which the cause of myocardial necrosis is not established.

In different clinical settings the utility of cardiac troponins is of a different level. The current clinical

utility of cardiac troponins in various kinds of presentations is being described in detail.

### a. *Patients with ST-segment elevation myocardial infarction*

Patients with acute ST-segment elevation myocardial infarction do not need biomarker measurements before therapy. In this situation troponin elevation however does identify patients at high risk for adverse events. Patients with elevated troponins have lower rate of recanalization with thrombolysis or PCI, lower TIMI flow grade with reperfusion and adverse short and long term prognosis. This possibly is due to the fact that patients with elevated troponins at admission already have symptoms for a longer duration.

### b. *High risk patients with ACS*

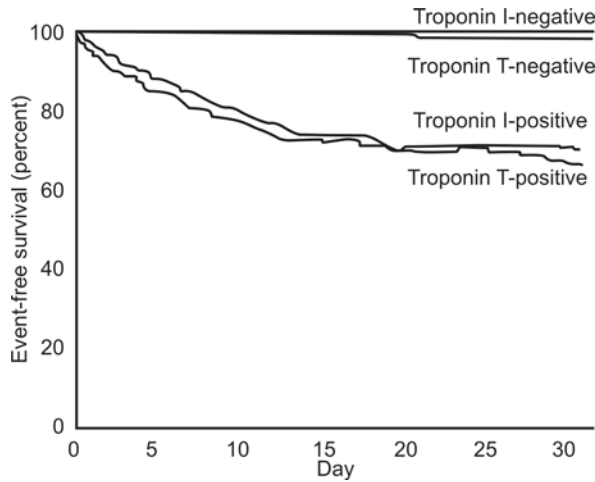
The high risk patients are those who are; elderly, have chest pain at rest, have ST changes or bundle branch block on ECG with hemodynamic instability and arrhythmias. 50-60% of these patients have elevated troponins. According to the new definition of non STEMI by the ECS/ACC guideline these individuals fulfill the definition of myocardial infarction. In this subset elevated troponins further indicate individuals with high risk and provide important information to guide the therapy. Those with elevated troponins have adverse coronary anatomy on angiogram with more thrombus and reduced TIMI grade of flow. They have more complex lesions and more extensive disease. So, these patients have better outcomes if they are treated with low molecular weight heparin rather than unfractionated heparin. Gp IIb/IIIa agents also help positive patients more as compared to Trop-T negative patients. These more aggressive therapies are not only not beneficial but in some studies seem to be detrimental if applied to patients without cardiac troponin elevations.

### c. *Intermediate and low risk patients*

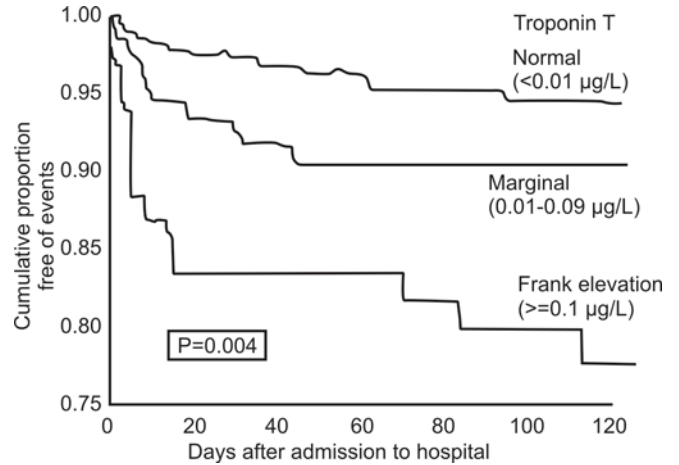
The intermediate risk patients do not have rest pain, lack ECG change, but have high probability of coronary artery disease. The low risk patients in addition to above features do not have significant risk factors also. Again in this setting also troponins are the markers of choice. The landmark study of 733 consecutive patients who presented with chest discomfort conducted by Hamm and colleagues demonstrated that all the patients at short term risk could be identified using troponins, provided these are done six hours after the onset of symptoms as

shown in Fig. 1<sup>6</sup>. Even marginal elevations of cTnT and cTnI levels have prognostic significance, though less prominent than among those with frank elevations (Figs 2,3)<sup>13,14</sup>. In another study of low risk patients, Galveston evaluated 400 patients, with low risk history and normal and near normal ECG. Then they conducted angiograms in all the patients and found that those patients who had troponins positive had a 90% frequency of angiographic coronary artery

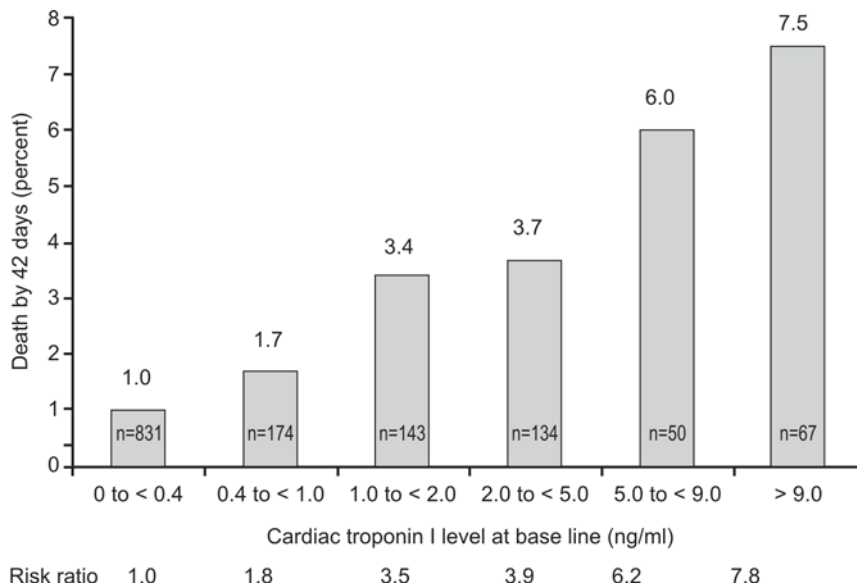
disease. Thus it shows the importance of elevated troponin in patients who present with chest pain even among those who clinically are a low risk group. In this subset of low risk individuals a negative troponin enables us to discharge patients from the emergency triage and thus avoid medico legal complications while keeping the costs low at the same time (Fig. 4)<sup>15</sup>.



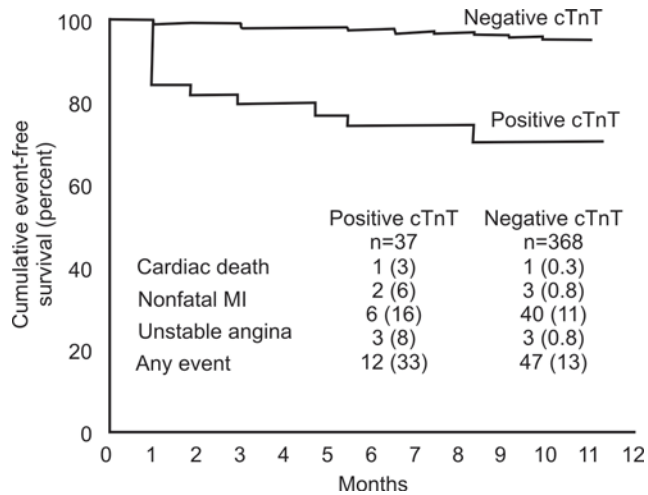
**Fig. 1:** Survival among patients with intermediate risk acute coronary syndrome: as stratified with use of cardiac troponins. (N Engl J Med 1997;337:1648-53).



**Fig. 2:** Relationship of troponin T levels (marginal and frank) at admission with cardiac events over 120 days. (Am J Cardiol 2004; 93:275-9).



**Fig. 3:** Relationship of cardiac troponin I levels in NSTEMI patients with 2-day mortality as seen in TIMI – IIIB trial. (N Engl Med 1996;335:1342-9)



**Fig. 4:** Prognostic significance of troponin elevation in patients presenting with chest pain with normal or near normal electrograms. (J Am Coll Cardiol 2000;35:1827-34).

#### d. **Renal Failure**

Traditional serum markers of myocardial necrosis such as CK, CK-MB and myoglobin are commonly increased in renal failure, even in the absence of clinically suspected myocardial ischemia. Cardiac troponins are considered markers of myocardial necrosis. However, we now realize that even cardiac troponins are elevated in some patients with renal failure in the absence of ischemia.

Cardiac disease accounts for 50% patient deaths in chronic renal failure and conventional methods for diagnosis of ischemia like chest pain and ECG changes may be equivocal. We are just beginning to understand the clinical relevance of serum troponin elevation in patients with chronic renal failure. Serum troponin-T is more frequently increased than troponin-I in patients with renal failure which has made some physicians to doubt its specificity for diagnosis of myocardial infarction in patients of renal failure.

Despite persistent uncertainty about the mechanism of elevated serum troponins in patients with renal failure, data suggests that these are associated with high risk, including an increase in mortality. The serum troponin-T may be elevated due to,

- Uremic skeletal myopathy causing skeletal muscle source
- Small areas of silent myocardial necrosis (micro infarctions)
- Heart failure and raised end diastolic pressure in patients with renal failure

- Left ventricular hypertrophy which is common in patients of renal failure and lastly also less likely due to
- Decreased clearance by the failing kidney.

The negative predictive value of troponins is even more highly useful in patients with chronic renal failure. Further studies are ongoing and required to delineate the exact role of serum troponins in this subset of patients<sup>16-18</sup>.

#### e. **Patients undergoing PCI:**

An elevation of C Tn has been reported in 24-40% of patients after successful PCI in stable and unstable coronary artery disease. Possible reasons for appearance of C Tn include side branch occlusion, coronary dissection, bulky devices causing transient ischemia and microembolisms. In direct comparison C Tn were more sensitive for detection of minor injury and hence detectable more frequently than CK or CK-MB after elective PCI. However, the relationship between magnitude of CK-MB and future prognosis is seemingly more robust and consistent than the relationship of troponins with outcomes in this setting<sup>19</sup>.

#### f. **Patients after CABG**

Patients who undergo cardiac surgery have some amount of C Tn and CK-MB release. The higher the value, the worse the associated injury and high values presage subsequent events, including death. Elevations have been related to surgical approach, extent of cross clamp and bypass time, the nature of cardioplegia and nature of procedure (valves and coronaries vs. CABG alone). MRI studies suggest that most of the injury is subendocardial and apical. Graft occlusion as a cause of injury does not seem to be common. Lehrke et al. defined a C TnT concentration  $\geq 0.46$  ng/ml 48 hours after open heart surgery as being predictive for long term mortality<sup>20</sup>.

## CONCLUSIONS

Cardiac troponins today offer clinicians a valuable tool for diagnosis of myocardial infarction even at the level of microinfarction. They provide independent prognostic information regarding subsequent events and mortality in patients with all subset of acute coronary syndromes including; ST elevation acute myocardial infarction, non-STEMI, intermediate and low risk chest pain patients, patients with renal failure and those undergoing therapeutic procedures likes PCI, and CABG. We have been able to reach a stage where their exact role is quite distinctly delineated in various subset of presentations.

Quantitative assays are more expensive and the reporting is often delayed. However these are more sensitive than qualitative kit assays which are of course very handy, provide instant report and can be repeated in the emergency room. This is the first cardiac biomarker which a clinician can use at the bedside of the patient for risk stratification and diagnosis. Other markers of myocardial necrosis have been relegated to second place by troponins. In the coming times we will be looking at multi marker approach for management of these patients since markers of ischemia, Ischemia Modified Albumin (IMA) is being evaluated though its exact clinical utility and position will take sometime. Similarly markers of inflammation like High Sensitivity C Reactive Protein (hs-CRP) is being already evaluated and Brain Natriuretic Peptide (BNP) is also in use clinically as a marker of heart failure which can be there in some of these patients. Thus we today have various methods like clinical history, electrocardiographic abnormalities, cardiac biomarkers and echocardiography for immediate evaluation for diagnosis and risk stratification of patients coming to our emergency room with chest pain syndrome.

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