

# Troponin Marks the Spot!

Cardiac troponins I and T are highly specific markers for myocardial injury. Furthermore, their diagnostic and prognostic capabilities in ACS have been well established and are important to recognize with regards to treatment options for high-risk patients.

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## *What is troponin?*

Cardiac troponin I (cTnI) and T (cTnT) are regulatory proteins that control the calcium-mediated interaction of actin and myosin. cTnI has been shown to be found only in cardiac muscle and studies have failed to identify any cTnI outside of the heart.<sup>1</sup> Newer second- and third-generation assays do not detect cTnT isoforms re-expressed in response to injury (*i.e.*, skeletal muscle injury), therefore, the specificity of cTnI and cTnT in assessing cardiac injury should be considered comparable.

*The new ESC/ACC definition of AMI has increased the detection of AMI by up to 25%; this translates into improved identification of high-risk patients who warrant more aggressive therapy.*

A multitude of assays are in use across institutions. In fact, upper limits of normal can vary not only between different assays, but also the same assay used at different sites confusing our interpretation of troponin levels. In an attempt to standardize the assays, the 2000 joint European Society of Cardiology and the American College of Cardiology (ESC/ACC) Committee on Redefinition of Myocardial Infarction consensus document recommended that the upper reference

limit be set at the 99th percentile ( $> 3$  SD above normal) of the reference population measured with a level of imprecision (coefficient of variation)  $< 10\%$ .<sup>2</sup> Most assays are still working at achieving this goal.

## *What is the diagnostic role of troponin in ACS?*

Until recently, the diagnosis of an acute myocardial infarction (AMI) was generally made using the revised 1979 World Health Organization (WHO) criteria. These criteria were based on the combination of typical symptoms, typical electrocardiogram (ECG) pattern (with an injury current and/or Q waves), and a rise in enzymes (*i.e.*, creatine kinase (CK)-MB). cTnI and cTnT have since been demonstrated as being highly sensitive and specific biomarkers of myocardial necrosis, and valuable prognostic indicators in patients with acute coronary syndrome (ACS). This discovery led the joint ESC/ACC committee to establish a new definition of AMI in 2000 (Table 1).<sup>2</sup> This new definition has increased the detection of AMI, in some centres, by up to 25% through the identification of microscopic infarcts that previously may have been labelled as unstable angina under the WHO criteria.<sup>2</sup> This translates into the improved identification

Table 1

## 2000 joint ESC/ACC redefinition of MI

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:

- Ischemic symptoms
- Development of pathologic Q waves on the ECG
- ECG changes indicative of ischemia (ST segment elevation or depression)
- Coronary artery intervention (e.g., angioplasty)

ESC: European Society of Cardiology  
ACC: American College of Cardiology  
MI: Myocardial infarction  
ECG: Electrocardiogram

of high-risk patients who warrant more aggressive therapy.

In a review of 471 consecutive patients admitted to the hospital because of chest pain, patients with AMI identified by the revised ESC/ACC AMI criteria had more comorbidities, a similar rate of in-hospital adverse cardiac events, and a higher six-month mortality compared with those diagnosed by the WHO criteria.<sup>3</sup>

The near absolute tissue specificity of the troponins compared with CK-MB, and other conventional markers, is well established. It is now clear that when conjoint skeletal muscle and cardiac injury is present, the improved specificity of the troponins reduces the number of false positive results.<sup>4</sup>

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The clinical sensitivity of troponin for detection of myocardial injury is also well established. It has been reported to be as high as 100%, compared with 81.8% for CK-MB mass, at 36 hours following the onset of symptoms.<sup>5</sup> Troponin appears three to 12 hours after onset of cardiac injury, peaks at 18 to 24 hours, and can remain elevated for seven to 10 days. CK-MB has similar kinetics, but unlike troponin, remains elevated for only 36 to 48 hours. This prolonged time window, during which troponin markers are elevated, also makes troponin a preferred marker.

The ESC/ACC document makes it clear that an elevation of cTnT or cTnI above the 99th percentile on at least one occasion in the first 24 hours is the preferred biomarker for diagnosis of AMI. In the absence of troponin testing, an elevation of CK-MB mass above the 99th percentile on two successive samples is recommended. The sampling frequency should be at admission, at two to four hours, and at six to nine hours, with an optional 12-hour to 24-hour sample.<sup>2</sup> Increased sensitivity of troponin allows us to detect a spectrum of myocardial injury. Accordingly, the ACC recommends a two-cutoff designation for cardiac troponin:

- a low limit that detects a small amount of myocardial injury, but classifies those patients at high risk (> 97.5th percentile), and
- a higher limit, with the amount of injury present reflective of definite AMI (> 99th percentile).<sup>2</sup>

Several markers should no longer be used to evaluate cardiac disease. These include total CK, aspartate aminotransferase, total lactate dehydrogenase, and lactate dehydrogenase isoenzymes. These markers have poor specificity for the detection of cardiac injury because of their wide tissue distribution. CK-MB isoforms, although a highly specific and sensitive marker of myocardial injury, are not in use because of a lack of clinical availability.

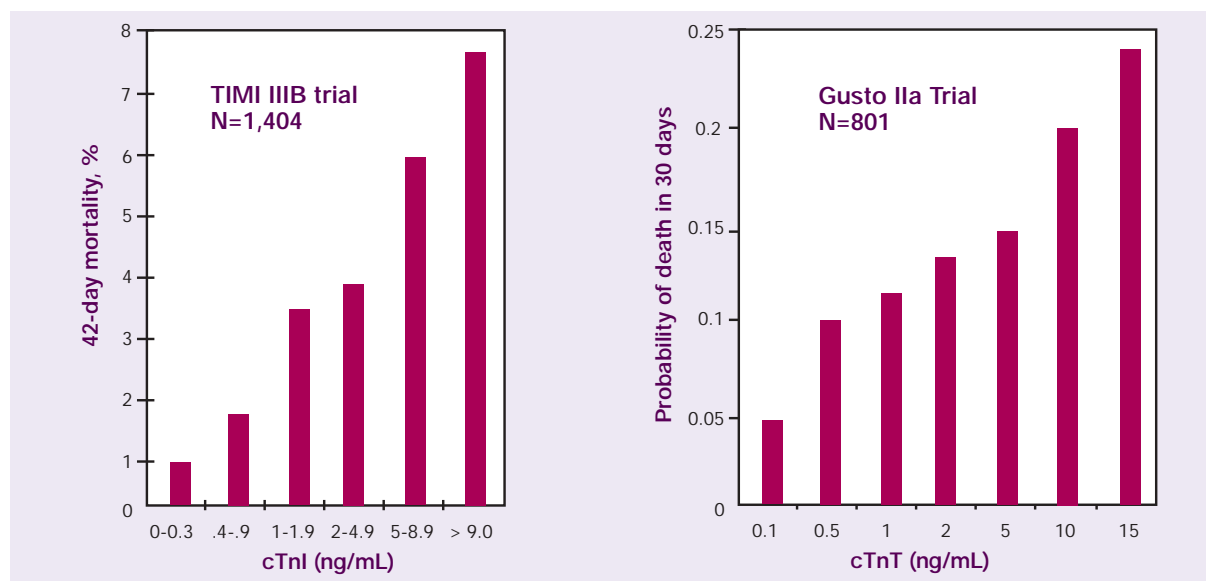


Figure 1. Prognostic value of the degree of troponin elevation in ACS.

### *What is the prognostic role of troponin elevation in ACS?*

The prognostic value of elevated serum troponins has been well established in patients with ST segment elevation MI (STEMI), non-ST elevation MI (NSTEMI), and unstable angina.<sup>4,5</sup> A pooled analysis of 21 studies involving 18,982 patients with ACS found that an elevated serum concentration of cTnI or cTnT was associated with an increased risk of cardiac death or reinfarction at 30 days.<sup>6</sup> Elevated troponins were also predictive of the composite end point over a longer followup (five months to three years) in those with a STEMI or NSTEMI. A negative predictive value for cardiac event/mortality at three to six months has been shown to be as high as 98.9 % for cTnT and 99.7 % for cTnI.<sup>7</sup>

The degree of elevation of cTnI or cTnT in ACS also has prognostic value, as illustrated by the results from a num-

Table 2

## Possible etiologies for troponin elevation in non-ACS states

- Congestive heart failure
- Pericarditis
- Myocarditis
- Iatrogenic (ablation, pacing, defibrillation discharge, electrical cardioversion, endomyocardial biopsy, cardiac surgery)
- Arrhythmias
- Trauma (cardiac contusion)
- Thermal injury
- Rhabdomyolysis with cardiac injury
- Critical illness (sepsis)
- Stroke
- Acute neurologic disease (subarachnoid bleed, stroke)
- Renal failure
- Pulmonary embolism
- Lobar pneumonia
- Cirrhosis
- Human immunodeficiency virus
- Endocrine disorders (hypothyroidism)

ACS: Acute coronary syndrome

ber of major trials (Figure 1).<sup>8,9</sup> Troponin elevation after coronary artery bypass surgery has been associated with an increase in adverse clinical outcomes relative to those instances in which no elevation has been found. It is also now generally recognized that elevations of troponin do occur after percutaneous coronary intervention in the absence of clearly definable clinical events, and that such elevations are associated with increased costs and adverse clinical outcomes, including death. Any amount of ischemic myocardial damage, as detected by troponin, implies a worsened long-term outcome for the patient.

## Troponin elevation in non-ACS states

Troponin elevation can also occur in individuals who experience cardiac injury not due to ischemic injury. This can occur in scenarios atypical of ACS (*i.e.*, in patients with atypical symptoms and/or equivocal ECG changes) which is a reminder not to make the diagnosis of AMI solely on the presence of increased markers. Table 2 lists some of the documented conditions in which a rise of non-ACS-related troponin can occur. The exact pathogenesis of such troponin elevation is largely unknown, but some of the proposed mechanisms include:

- left ventricular hypertrophy,
- coronary artery endothelial dysfunction,
- loss of cardiac myocyte membrane integrity,
- stretch mediated troponin release from cardiac muscle,
- impaired renal excretion, and
- cardiac myocyte apoptosis.

A number of studies have explored troponin elevation in these non-ACS states. Khan et al. studied 102 consecutive patients, with a troponin greater than the upper reference limit, and found that 35% of patients did not have ACS.<sup>10</sup> The mean value of cTnI was significantly higher in the ACS versus non-ACS group. In these instances, troponin release may be a result of the mechanisms discussed. Unfortunately, there is minimal outcome data for non-ACS states, with the exception of renal insufficiency, heart failure, and pulmonary embolism (PE).

### Renal insufficiency

The appropriate use of troponin in patients with renal insufficiency is not clearly understood, as elevations are commonly observed in those who do not have clinical evidence of myocardial damage. This is especially true of cTnT, which is more frequently elevated than cTnI among asymptomatic patients with renal insufficiency. This is thought to be due to

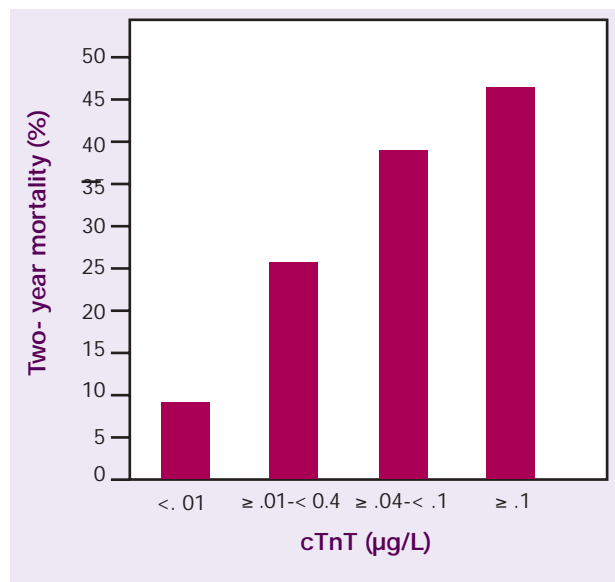


Figure 2A: Prognostic value of cTnT elevation in ESRD.

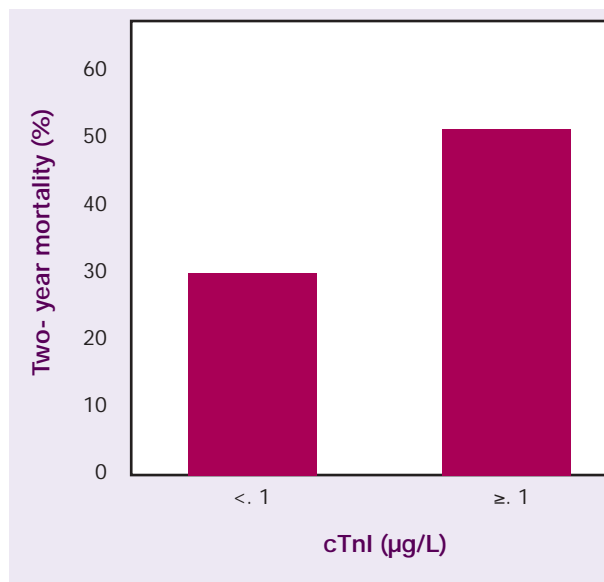


Figure 2B: Prognostic value of cTnI elevation in ESRD.

the relatively higher levels of an unbound cystolic pool of cTnT and decreased renal clearance related to a higher molecular weight. There is a growing body of evidence demonstrating that elevations in serum troponin levels in stable asymptomatic patients with end-stage renal disease (ESRD) are predictive of worse long-term cardiovascular outcomes.

A well-designed prospective study of 733 asymptomatic patients with ESRD found that increased levels of both cTnT and cTnI were associated with a twofold to fivefold enhanced risk of mortality at two years (Figure 2).<sup>11</sup> Presumably, this increased mortality is a translation of underlying coronary disease.

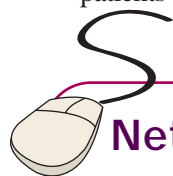
Another prospective study followed 224 ESRD patients with elevated cTnT levels and no ischemic

symptoms.<sup>12</sup> In these patients, progressively higher quartiles of cTnT predicted an increased risk of death and angiographically documented multivessel coronary artery disease (CAD).

Further study is required to determine whether a more aggressive approach to treatment should be employed among asymptomatic patients with ESRD and elevated troponins. The most specific marker for ACS among patients with ESRD appears to be serial measurements of cTnI. If not available, a sequential rise in cTnT can help determine the presence or absence of ACS in patients with renal insufficiency.

### Heart failure

The prognostic role of troponin elevation in non-ischemic heart failure has also been acknowledged. Hudson et al. prospectively collected data from 136



### Net Readings

1. American College of Cardiology:  
[www.acc.org](http://www.acc.org)
2. European Society of Cardiology:  
[www.escardio.org](http://www.escardio.org)

## Take-home message

- Both cTnI and cTnT are highly specific markers of myocardial injury.
- The diagnostic and prognostic capabilities of troponin in ACS have been well established and are important to recognize.
- Troponin is not always a marker of ischemic injury and the clinical challenge is differentiating ischemic vs. non-ischemic myocardial injury.
- There are many conditions in which troponin elevation can occur, but preliminary outcome data only exists for renal insufficiency, heart failure, and PE.


ambulatory patients with heart failure and found that 24% had an elevated cTnT. Elevated cTnT concentrations were associated with increased relative risks of death or hospitalization during a one-year followup.<sup>13</sup>

Another similar study performed multiple measurements of cTnT in 60 patients with non-ischemic dilated cardiomyopathy.<sup>14</sup> The cardiac event-free survival and ejection fraction (EF) at two-year followup were significantly higher in the cTnT < 0.02 ng/mL group versus the group that had cTnT levels persistently > 0.02 ng/mL. It is reasonable to infer that patients with low left ventricular EF and chronic heart failure can be risk stratified for future cardiac events based on cardiac troponin levels; however, there is insufficient evidence to make this a firm recommendation.

### Pulmonary embolism

Serum cTnI and cTnT are elevated in 30% to 50% of patients with a moderate to large PE. Although not useful for diagnosis, elevated troponins are predictive of an adverse prognosis, being associated with marked increases in the incidence of prolonged hypotension and in-hospital mortality.

The Management strategies And Prognosis of Pulmonary Embolism Trial (MAPPET) is one of several looking at troponin elevation in PE.<sup>15</sup> It prospectively studied 106 consecutive patients with

confirmed PE and found that both cTnI and cTnT were elevated in 41% and 37% of patients respectively, and were associated with increased overall in-hospital mortality. Troponin elevations also significantly correlated with right ventricular dysfunction on echocardiogram. Troponins should be performed in patients with PE for risk stratification. 

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