Reviews

# A Review of Causes and Systemic Approach to Cardiac Troponin Elevation

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ABSTRACT

The first American College of Cardiology/European Society of Cardiology task force published recommendations for a universal definition of myocardial infarction (MI) in 2000 based on the measurement of troponin (Tn). Although this rapid and highly sensitive blood test is certainly valuable in the appropriate setting, its widespread use in variety of clinical scenarios may lead to the detection of Tn elevation in absence of thrombotic acute coronary syndrome. In 2007, the joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation task force proposed a new definition for acute MI based on detection of Tn and associated clinical evidence. The goal of this article is to review the universal definition of acute MI and to differentiate type 1 MI, type 2 MI, and non–acute coronary syndrome Tn elevations. The prognosis and a clinical approach to this differential diagnosis will be developed.

## Introduction

Cardiovascular disease is a global health problem causing nearly 1 in 3 deaths every year. Many of these deaths are due to coronary heart disease, and myocardial infarction (MI) is a major manifestation of coronary heart disease. In 1959, the World Health Organization defined MI as a combination of 2 of 3 characteristics: typical symptoms, enzyme rise, and a typical electrocardiographic (ECG) pattern involving the development of Q waves. Possible ischemic symptoms include various combinations of chest, epigastric, arm, wrist, or jaw discomfort with exertion or at rest, lasting for at least 20 minutes, with radiation to the arm, jaw, back, or shoulder, and may be associated with dyspnea, diaphoresis, nausea, vomiting,or lightheadedness. The discomfort is not positional and not affected by movement. These symptoms are not specific to MI and also can be caused by gastrointestinal, neurological, pulmonary, or musculoskeletal disorders; thus, additional evaluation is needed to supplement the clinical history.

In the recent past, clinicians have used different definitions of acute MI. Moreover, this occurred in some clinical trials involving therapeutic interventions for MI, which created confusion, as it was difficult to compare the results of these trials. The first American College of Cardiology/European Society of Cardiology (ACC/ESC) task force published recommendations for a universal definition of MI in 2000 based on the measurement of troponin (Tn).[1,2] This definition of MI was then updated in 2007, based on detection of Tn and associated clinical evidence. The development of a more sensitive and specific Tn assay has improved the accuracy of detective MI. Unfortunately, it also proved to be a major problem for some physicians, as an abnormal Tn level can occur as result of any process that involves myocardial damage.[3,4] The first report from the ACC/ESC emphasized that multiple factors could injure the myocardium. Despite this warning, many clinicians failed to apply clinical reasoning in situations where abnormal Tn levels were not suggestive of myocardial ischemia.

## Universal Definition of Myocardial Infarction

The term myocardialinfarction has major psychological and legal implications for the individual and society. It is an indicator of one of the leading health problems in the world, and it is an outcome measure in clinical trials and observational studies. With these perspectives, MI may be defined from a number of differentclinical, ECG, biochemical, imaging, and pathological characteristics (Table 1). This includes a typical rise and fall of Tn with $\geq$1 value above the 99th percentile of the upper reference limit and $\geq$1 of the following: clinical symptoms suggestive of ischemia, ECG changes, a new wall-motion abnormality on echocardiography, or new loss of viable myocardium on a nuclear scan. Based on the pathophysiology, MI has been classified into 5 different types,[5] as shown in Table 2. This same task force also defined the ECG criteria for ischemia (tables 3 and 4). The newer definition of acute MI as proposed by joint committee was an attempt to improve accuracy in diagnosis of acute MI. However, each component in this definition also has certain limitations.

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Table 1. Definition of Myocardial Infarction

| Criteria for Acute MI (2007) |
|---|
| The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any 1 of the following criteria meets the diagnosis for MI. |
| 1. Detection of rise and/or fall of cardiac biomarkers (preferably Tn) with ≥1 value above the 99th percentile of the URL together with evidence of myocardial ischemia with ≥1 of the following:<br>a. Symptoms of ischemia<br>b. ECG changes indicative of new ischemia (new ST-T changes or new LBBB)<br>c. Development of pathological Q waves in the ECG<br>d. Imaging evidence of new loss of viable myocardium or new regional wall-motion abnormality |
| 2. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy; but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood. |
| 3. For PCI in patients with normal baseline Tn values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers >3 ×99th-percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized. |
| 4. For CABG in patients with normal baseline Tn of periprocedural myocardial necrosis. By convention, increases of biomarkers >5 ×99th-percentile URL + either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium, have been designated as defining CABG-related MI. |
| 5. Pathological findings of an acute MI. |
| Abbreviations: CABG, coronary artery bypass grafting; ECG, electrocardiogram; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention; Tn, troponin; URL, upper reference limit. Reprinted with permission from Thygesen et al.[5] Copyright © 2007 American Heart Association, Inc. |

## Symptoms

Not every patient with acute MI has typical symptoms as described above. The atypical symptoms include (but are not limited to) mental confusion, weakness, not feeling well, syncope, apprehension, and nervousness. Elderly, female, diabetic, and demented patients are likely to present with atypical symptoms.[6]

## Electrocardiographic

Apart from acute MI, there are multiple other causes of ST-segment elevation (Table 5). These include early repolarization, left bundle branch block (LBBB), pre-excitation, Brugada syndrome, pericarditis, myocarditis, pulmonary embolism, subarachnoid hemorrhage (SAH), lead transposition, cholecystitis, prior MI with Q waves and/or persistent ST elevation (left ventricular aneurysm), and a ventricular paced rhythm.[5]

Table 2. Clinical Classification of Different Types of MI

| |
|---|
| Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection. |
| Type 2: MI secondary to ischemia due to either increased oxygen demand or decreased supply (eg, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension). |
| Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy; but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood. |
| Type 4a: MI associated with PCI. |
| Type 4b: MI associated with stent thrombosis, as documented by angiography or at autopsy. |
| Type 5: MI associated with CABG. |
| Abbreviations: CABG, coronary artery bypass grafting; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention. Reprinted with permission from Thygesen et al.[5] Copyright © 2007 American Heart Association, Inc. |

Table 3. ECG Manifestations of Acute Myocardial Ischemia (in Absence of LVH and LBBB)

| |
|---|
| ST elevation |
| New ST elevation at the J-point in 2 contiguous leads with the cutoff points: ≥0.2 mV in men or ≥0.15 mV in women in leads $V_2$ through $V_3$ and/or ≥0.1 mV in other leads |
| ST depression and T-wave changes |
| New horizontal or downsloping ST depression ≥0.05 mV in 2 contiguous leads; and/or T inversion ≥0.1 mV in 2 contiguous leads with prominent R wave or R/S ratio >1 |
| Abbreviations: ECG, electrocardiographic; LBBB, left bundle branch block; LVH, left ventricular hypertrophy. Reprinted with permission from Thygesen et al.[5] Copyright © 2007 American Heart Association, Inc. |

Table 4. ECG Changes Associated With Prior MI

| |
|---|
| Any Q wave in leads $V_2$ through $V_3$ ≥0.02 s or QS complex in leads $V_2$ and $V_3$ |
| Q wave ≥0.03 s and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or $V_4$ through $V_6$ in any 2 leads of a contiguous lead grouping (I, aVL,$V_6$; $V_4$ through $V_6$; II, III, and aVF)[a] |
| R wave ≥0.04 s in $V_1$ through $V_2$ and R/S ≥1 with a concordant positive T wave in the absence of a conduction defect |
| Abbreviations: ECG, electrocardiographic; MI, myocardial infarctions. [a]The same criteria are used for supplemental leads $V_7$ through $V_9$, and for the Cabrera frontal plane lead grouping. Reprinted with permission from Thygesen et al.[5] Copyright © 2007 American Heart Association, Inc. |

## Troponin Assessment

Troponins are proteins involved in the regulation of cardiac and skeletal muscle contraction. The Tn complex modulates calcium-medicated actin and myosin interaction in striated muscle. The skeletal and cardiac isoforms of these proteins are formed by separate genes and differ in structure.[7] The


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Table 5. Common ECG Pitfalls in Diagnosing MI

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| False positives |
| Benign early repolarization |
| LBBB |
| Pre-excitation |
| Brugada syndrome |
| Peri-/myocarditis |
| PE |
| SAH |
| Metabolic disturbances such as hyperkalemia |
| Failure to recognize normal limits for J-point displacement |
| Lead transposition or use of modified Mason-Likar configuration[24] |
| Cholecystitis |
| False negatives |
| Prior MI with Q waves and/or persistent ST elevation |
| Paced rhythm |
| LBBB |

Abbreviations: ECG, electrocardiographic; LBBB, left bundle branch block; MI, myocardial infarction; PE, pulmonary embolism; SAH, subarachnoid hemorrhage. Reprinted with permission from Thygesen et al.[5] Copyright © 2007 American Heart Association, Inc.

cardiac troponin (cTn) complex is made of Tn I (inhibitory), Tn C (calcium-binding), and Tn T (tropomycin-binding) proteins.

Myocardial necrosis is signified by increased level of cTn.Cardiac troponin I (cTnI), in particular, is not expressed by injured or regenerating skeletal muscle, and is, therefore, exquisitely specific for myocardial injury.[8] In general, cTnI and cTnT provide comparable information, except in renal failure, where cTnT is more likely to be elevated.[9] Troponin elevation after myocardial necrosis occurs within 2–3 hours, reaches its peak in 24 hours, and remains elevated for 1 to 2 weeks. A multicenter study determining levels of TnI in 1818 consecutive patients with suspected acute MI upon admission and 3 hours and 6 hours after admission has found that 87% of patients with MI could be diagnosed if Tn levels were drawn within 6 hours, whereas the rate of diagnosis was almost 100% when these levels were drawn within 12 hours of presentation. The same study concluded that use of a sensitive assay for cTnI improves early diagnosis of acute MI and risk stratification, regardless of the time of chest-pain onset.[10] The high-sensitivity Tn assay is a very good screening test for myocardial injury, but the enhanced sensitivity results in many Tn elevations, and each of these requires careful clinical consideration. There have been multiple assays for cTnI, but only one CTnT assay. Currently, high-sensitivity assays are recommended.[11]

The joint ESC/ACC Committee for the Redefinition of Myocardial Infarction has defined MI as an increased cTn exceeding the 99th percentile of the distribution of cTnI in the reference group for that particular assay, with an imprecision limit of ≤10%. A recently published study determined that lowering the diagnostic threshold of Tn for diagnosis of MI could reduce morbidity and mortality[12]; however, the biggest challenge of lowering the diagnostic threshold of Tn for MI would be a greater number of patients with elevated cTn, including those due to nonthrombotic causes.

## Frequency of Troponin Elevation in the Real World

With implementation of high-sensitivity Tn assays, there has been a substantial rise in the incidence of MI diagnosis.[13–15] In fact, some centers reported a 100% increase in the incidence of MI since Tn measurement became the standard of care.[14] Many studies have described the presence of increased Tn levels in various cardiac and noncardiac conditions, in the absence of definite evidence to support a diagnosis of acute coronary syndrome (ACS).[16–27] A recently published study evaluated the incidence and type of acute MI in 2944 consecutive patients with cTnI measurement in a tertiary center. Fewer than one-third had acute MI, whereas more than two-thirds of the patients with an elevated cTnI had a non-MI cause of Tn increase. They did find that cTnI levels were higher in patients with acute MI.[28]

## Clinical Significance of Troponin Elevation in Absence of Acute Coronary Syndrome

The prevalence and determinant of chronic cTnT elevation was studied in a large, representative population consisting of 3557 subjects of the Dallas Heart Study. They concluded that cTnT elevation was associated with older age, black race, male sex, congestive heart failure, left ventricular hypertrophy, diabetes mellitus, and chronic kidney disease. In the general population, cTnT elevation is a rare in subjects without congestive heart failure, left ventricular hypertrophy, chronic kidney disease, or diabetes mellitus.[29] Most of the studies have shown that Tn release in heart failure (HF) occurs with and without obstructive epicardial coronary disease.[30]

When applying the results of Tn testing to acute-care medicine, the major differential diagnosis involves differentiating type 1, type 2, and non-MITn elevation. There are multiple causes of non-MI elevation of troponin (Table 6).[5,12–23,31–33] The postulated mechanisms involved in type 2 MI are listed in Table 2. These include mismatch between myocardial oxygen demand and supply in the absence of flow-limiting epicardial stenosis.[18,34] Likewise, the proposed causes for non-MITn increase include imbalance of the autonomic nervous system, with resulting excess of sympathetic activity and increased catecholamine effect on myocardial cells[35]; direct myocardial-cell injury by traumatic or inflammatory process; volume and pressure overload, resulting in an excessive increase in wall tension with secondary myofibrillary damage[36]; and impaired renal excretion.[37] In addition, cardiomyocyte damage from inflammatory cytokines or oxidative stress, hibernating myocardium, or apoptosis may produce an elevated Tn.[36,38–41] Cardiac troponin I release occurs frequently after subarachnoid hemorrhage (SAH) and has been associated with a neurogenic form of myocardial injury. It is primarily due to sympathetic overactivity leading to myocardial


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Table 6. Elevations of Troponin in the Absence of Overt Ischemic Heart Disease

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| Cardiac contusion, or other trauma including surgery, ablation, pacing, etc. |
| CHF (acute and chronic) |
| Aortic dissection |
| Aortic valve disease |
| Hypertrophic cardiomyopathy |
| Tachy- or bradyarrhythmias, or heart block |
| Apical ballooning syndrome |
| Rhabdomyolysis with cardiac injury |
| PE, severe pulmonary hypertension |
| Renal failure |
| Acute neurological disease, including stroke or SAH |
| Infiltrative diseases (eg, amyloidosis, hemochromatosis, sarcoidosis, and scleroderma) |
| Inflammatory diseases (eg, myocarditis or myocardial extension of endo-/pericarditis) |
| Drug toxicity or toxins |
| Critically ill patients, especially with respiratory failure or sepsis |
| Burns, especially if affecting >30% of body surface area |
| Extreme exertion |

Abbreviations: CHF, congestive heart failure; PE, pulmonary embolism; SAH, subarachnoid hemorrhage. Reprinted with permission from Thygesen et al.[5] Copyright © 2007 American Heart Association, Inc.

necrosis.[42] This overactivity of the sympathetic limb of the autonomic nervous system is a common phenomenon that leads to myocardial necrosis in neurological catastrophes such as SAH, cerebral infarction, status epilepticus, and head trauma. The prognostic significance and clinical impact of elevations of cTnI after SAH was assessed in a study of 253 patients. The study concluded that cTnI elevation after SAH is associated with an increased risk of cardiopulmonary complications, delayed cerebral ischemia, and death or poor functional outcome at discharge.[17,43]

Troponin elevation has also been reported in diabetic ketoacidosis. Metabolic derangement, fluid shifts, tachycardia, and increased sympathetic tone may trigger focal myocardial necrosis and Tn release. Acidosis also contributes in Tn release.[44] With sepsis, TNF-α and mediators produced by neutrophilic granulocytes may lead to anincreased permeability of the cardiomyocyte membrane formacromolecules and therefore leakage of Tn withoutmyocyte necrosis.[45]

Elevated cTnI has been associated with increased mortality in patients with[46–48] and without[17,49] ACS. Troponin elevation is a mortality risk factor for medical intensive care unit (ICU) patients admitted forreasons other than ACS. Mortality has been reported to be 4-fold higher and left ventricular ejection fraction significantly lower in Tn-positive patients without ACS as compared with Tn-negative critically ill patients.[13] Elevated cTn levels are commonly observed in the ICU. There are many non-ACS causes of cTn elevation in the ICU.[22,50] The clinical significance of elevated cTn level in patients in the ICU has been reviewed. In one study, the frequency of cTn elevation and its association with mortality and length of ICU stay in 58 consecutive critically ill patients without ACS was reviewed. This study concluded that elevated cTn measurements are associated with increased mortality and ICU length of stay.[51]

Accumulating evidence suggests that patients with acute and chronic HF may have measurable levels of circulating cTn, whose detection and magnitude may have prognostic implications. Furthermore, as new, more sensitive cTn assays are being developed, larger numbers of HF patients are found to have detectable cTn, with a persistent relationship between magnitude and outcome.[30] An elevated Tn level in HF correlates with advanced disease and acute decompensation and indicates worst prognosis.[30]

It is very important for clinicians to understand that an elevated Tn level is a relatively common finding in hospitalized patients. Although Tn elevation is an essential requirement for the diagnosis of MI, it is not sufficient without confirmation, either by ECG, clinical history, or a new echocardiographic or nuclear finding. There have been a few studies that assessed the possible variables that could predict diagnosis of ACS. The predictors that can help rule in or rule out the diagnosis of ACS in the presence of an elevated Tn level are age, hypertension, and history of ischemic heart disease, renal function, and a maximal cTn level.[52] These predictors can increase diagnostic accuracy and guide the appropriate treatment.The high early and late mortality rate among the patients with non-ACScTn elevation indicates that Tn level serves as an indicator of a critical state in a noncardiac condition.[17]

## Approach to Increased Troponin: Potential Treatment Strategies

The assessment of whether a Tn elevation is aresult of ACS or non-ACS eventhas become a major challenge and has great implications for both in-hospital and long-term management. Thesituation is more complicated in critically ill patients, where the history is usually limited and the diagnosis is based on objective laboratory and imaging testresults, such as Tn elevation and ECG changes. In some cases, a misdiagnosis of AMI that is only based on the elevated Tn levelmay lead to inappropriate and sometimes harmful management, such as antithrombotic therapy inthe presence of bleeding or a coronary angiogram in thepresence of renal failure.

A slight elevation in Tn level is common in hospitalized patientswithin a large spectrum of clinical settings.It is very important for clinicians to develop a systemic approach to cTn elevation. Even if we have a diagnostic test for ACS with a known excellent sensitivity and specificity, we should not ignore the pretest probability of coronary artery disease. A positive Tn test result mustbe interpreted in the context of the presenting symptomsand other clinical predictors to improve the accuracy ofthe diagnosis. There are few predictors that can help rule out or rule in the diagnosis of ACS in thepresence of an elevated Tn level. As patient


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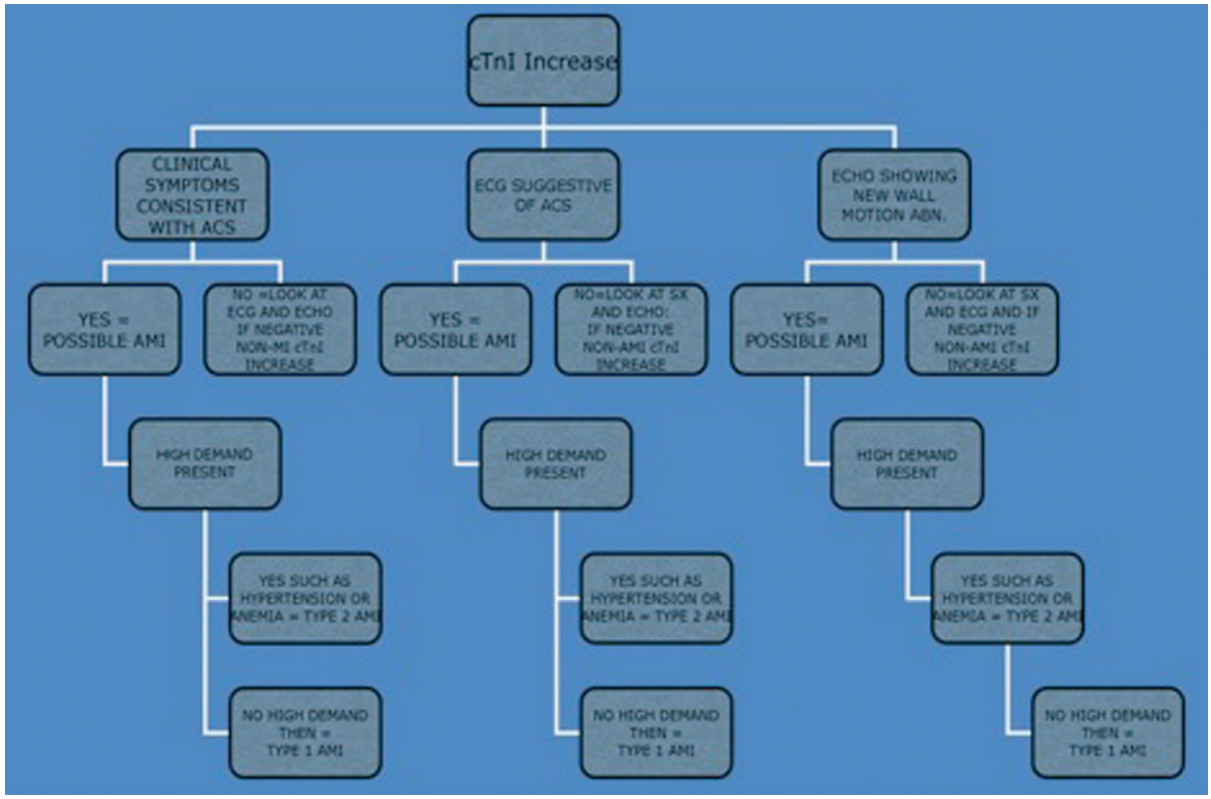


Figure 1. Proposed algorithm for the management of patients with an elevated troponin T level. Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; cTnI, cardiac troponin I; ECG, electrocardiogram; ECHO, echocardiogram.

age 40–70 years, history of hypertension or ischemic heart disease, normal renal function, anda cTn level >1 ng/mL favors ACS, extreme age (<40 y, >80 y) and impaired renal function favors non-ACScTn elevation.[52]

A diagnosis of MI requires combination of clinical history, ECG changes, Tn increase, and/or a new wall-motion abnormality on echocardiogram or nuclear scan showing new loss of viable myocardium. A Tn elevation should be divided into ACS and non-ACS based on clinical history and available diagnostic tools. If probability of ACS is low, then the abovementioned predictors should be considered to proceed with appropriate treatment (see algorithm; Figure 1).

Type 2 MI (demand ischemia) should also be differentiated from noncardiac causes of cTn elevation. This type of MI is the result of an imbalance between myocardial oxygen requirement and supply. Non-ACSTn elevation is due to myocardial injury resulting from variety of mechanisms, such as sympathetic overactivity in SAH or the effect of different inflammatory markers in HF and sepsis.

In conclusion, an elevated Tn level is a relatively common finding in hospitalized patients. Although cTn elevation is an essential requirement forthe diagnosis of MI, it is not sufficient alone. Clinicians must incorporate sound clinical reasoning before making a diagnosis of ACS based on elevated cTn. Patients with cTn elevation unrelated to ACS define a high-riskgroup with poor short-term (in-hospital) and long-term (30 mo from discharge) outcomes.Troponin should not be used as a screening test in patients with a low pretest probability for coronary artery disease, as this approach may leadto inappropriate diagnosis, treatment, and interventions.

## References


1. Thygesen K, Alpert JS. Myocardial infarction redefined: a consensus document of the joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J.* 2000;21:1502–1513.
2. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined: a consensus document of the joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction [published correction appears in *J Am Coll Cardiol.* 2001;37:973]. *J Am Coll Cardiol.* 2000;36:959–969.
3. Blich M, Sebbag A, Attias J, et al. Cardiac troponin I elevation in hospitalized patients without acute coronary syndromes. *Am J Cardiol.* 2008;101:1384–1388.
4. Agzew Y. Elevated serum cardiac troponin in non–acute coronary syndrome. *Clin Cardiol.* 2009;32:15–20.
5. Thygesen K, Alpert JS, White JD. Universal definition of myocardial infarction. *Circulation.* 2007;116:2634–2653.
6. Canto JG, Goldberg RJ, Hand MM, et al. Symptom presentation of women with acute coronary syndromes: myth vs reality. *Arch Intern Med.* 2007;167:2405–2413.
7. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction—summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol.* 2002;40:1366–1374.
8. Adams JE III, Bodor GS, Dávila-Román VG, et al. Cardiac troponin I: a marker with high specificity for cardiac injury. *Circulation.* 1993;88:101–106.




Published online in Wiley Online Library (wileyonlinelibrary.com)
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9. Needham DM, Shufelt KA, Tomlinson G, et al. Troponin I and T levels in renal failure patients without acute coronary syndrome: a systematic review of the literature. *Can J Cardiol.* 2004;12:1212–1218.
10. Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med.* 2009;361:868–877.
11. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med.* 2009;361:858–867.
12. Mills NL, Churchhouse AM, Lee KK, et al. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA.* 2011;305:1210–1216.
13. Kontos MC, Fritz LM, Anderson FP, et al. Impact of the troponin standard on the prevalence of acute myocardial infarction. *Am Heart J.* 2003;146:446–452.
14. Ferguson JL, Beckett GJ, Stoddart M, et al. Myocardial infarction redefined: the new ACC/ESC definition, based on cardiac troponin, increases the apparent incidence of infarction. *Heart.* 2002;88:343–347.
15. Amit G, Gilutz H, Cafri C, et al. What have the new definition of acute myocardial infarction and the introduction of troponin measurement done to the coronary care unit? Impacts on admission rate, length of stay, case mix and mortality. *Cardiology.* 2004;102:171–176.
16. Ammann P, Fehr T, Minder EI, et al. Elevation of troponin I in sepsis and septic shock. *Intensive Care Med.* 2001;27:965–969.
17. Ammann P, Maggiorini M, Bertel O, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. *J Am Coll Cardiol.* 2003;41:2004–2009.
18. Bakshi TK, Choo MK, Edwards CC, et al. Causes of elevated troponin I with a normal coronary angiogram. *Intern Med J.* 2002;32:520–525.
19. Burness CE, Beacock D, Channer KS. Pitfalls and problems of relying on serum troponin. *QJM.* 2005;98:365–371.
20. Diris JH, Hackeng CM, Kooman JP, et al. Impaired renal clearance explains elevated troponin T fragments in hemodialysis patients. *Circulation.* 2004;109:23–25.
21. James P, Ellis CJ, Whitlock RM, et al. Relation between troponin T concentration and mortality in patients presenting with an acute stroke: observational study. *BMJ.* 2000;320:1502–1504.
22. Jeremias A, Gibson CM. Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. *Ann Intern Med.* 2005;142:786–791.
23. La Vecchia L, Ottani F, Favero L, et al. Increased cardiac troponin I on admission predicts in-hospital mortality in acute pulmonary embolism. *Heart*. 2004;90:633–637.
24. Moller N, Foss AC, Gravholt CH, et al. Myocardial injury with biomarker elevation in diabetic ketoacidosis. *J Diabetes Complications.* 2005;19:361–363.
25. Spies C, Haude V, Fitzner R, et al. Serum cardiac troponin T as a prognostic marker in early sepsis. *Chest.* 1998;113:1055–1063.
26. Edouard AR, Benoist JF, Cosson C, et al. Circulating cardiac troponin I in trauma patients without cardiac contusion. *Intensive Care Med*. 1998;24:569–573.
27. Edouard AR, Felten ML, Hebert JL, et al. Incidence and significance of cardiac troponin I release in severe trauma patients. *Anesthesiology.* 2004;101:1262–1268.
28. Blich M, Sebbag A, Attias J, et al. Cardiac troponin I elevation in hospitalized patients without acute coronary syndromes. *Am J Cardiol.* 2009;104:9–13.
29. Wallace TW, Abdullah SM, Drazner MH, et al. Prevalence and determinants of troponin T elevation in the general population. *Circulation.* 2006;113:1958–1965.
30. Kociol RD, Pang PS, Gheorghiade M, et al. Troponin elevation in heart failure: prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol.* 2010;56:1071–1078.
31. Kligfield P, Gettes LS, Bailey JJ, et al. Recommendations for the standardization and interpretationof the electrocardiogram—part I: the electrocardiogram and its technology. A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the HeartRhythm Society, endorsed by the International Society for Computerized Electrocardiology. *Circulation.* 2007;115:1306–1324.
32. Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease. *J Am Coll Cardiol.* 2006;48:1–11.
33. French JK, White HD. Clinical implications of the new definition ofmyocardial infarction. *Heart.* 2004;90:99–106.
34. Hamwi SM, Sharma AK, Weissman NJ, et al. Troponin-I elevation in patients with increased left ventricular mass. *Am J Cardiol.* 2003;92:88–90.
35. Tung P, Kopelnik A, Banki N, et al. Predictors of neurocardiogenic injury after subarachnoid hemorrhage. *Stroke.* 2004;35:548–551.
36. Logeart D, Beyne P, Cusson C, et al. Evidence of cardiac myolysis in severe nonischemic heart failure and the potential role of increased wall strain. *Am Heart J.* 2001;141:247–253.
37. Frankel WL, Herold DA, Ziegler TW, et al. Cardiac troponin T is elevated in asymptomatic patients with chronic renal failure. *Am J Clin Pathol.* 1996;106:118–123.
38. Brawnwald E. Biomarkers in heart failure. *N Engl J Med.* 2008;358:2148–2159.
39. Levine B, Kalman J, Mayer L, et al. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med.* 1990;323:236–241.
40. Narula J, Haider N, Virmani R, et al. Apoptosis in myocytes in end-stage heart failure. *N Engl J Med.* 1996;335:1182–1189.
41. Olivetti G, Abbi R, Quaini F, et al. Apoptosis in the failing human heart. *N Engl J Med.* 1997;336:1131–1141.
42. Samuels MA. The brain-heart connection. *Circulation.* 2007;116:77–84.
43. Naidech AM, Kreiter KT, Janjua N, et al. Cardiac troponin elevation, cardiovascular mortality, and outcome after subarachnoid hemorrhage. *Circulation.* 2005;112:2851–2856.
44. Al-Mallah M, Zuberi O, Arida M, et al. Positive troponin in a diabetic ketoacidosis without evident acute coronary syndrome predicts adverse cardiac events. *Clin Cardiol.* 2008;31:67–71.
45. Wu AH, Ford L. Release of cardiac troponin in acute coronarysyndromes: ischemia or necrosis? *Clin Chim Acta.* 1999;284:161–174.
46. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndrome. *N Engl J Med.* 1996;335:1342–1349.
47. Heidenreich PA, Alloggiamento T, Melsop K, et al. The prognostic value of troponin in patients with non–ST-elevation acute coronary syndromes: meta-analysis. *J Am Coll Cardiol.* 2001;38:478–485.
48. Morrow DA, Cannon CP, Rifai N, et al. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non–ST-elevation myocardial infarction. *JAMA.* 2001;286:2405–2412.
49. Guest TM, Ramanathan AV, Tuteur PG, et al. Myocardial injury in critically ill patients: a frequent unrecognized complication. *JAMA.* 1995;273:1945–1949.
50. Roongsritong C, Warraich I, Bradley C. Common causes of troponin elevations in the absence of acute myocardial infarction: incidence and clinical significance. *Chest.* 2004;125:1877–1884.
51. Lim W, Qushmaq I, Devereaux PJ, et al. Elevated cardiac troponin measurements in critically ill patients. *Arch Intern Med.* 2006;166:2446–2454.
52. Alcalai R, Planer D, Culhaoglu A, et al. Acute coronary syndrome vs nonspecific troponin elevation: clinical predictors and survival analysis. *Arch Intern Med.* 2007;167:276–281.



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