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# Myocardial Injury in the Era of High-Sensitivity Cardiac Troponin Assays
## A Practical Approach for Clinicians

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**IMPORTANCE** Traditionally, elevated troponin concentrations were synonymous with myocardial infarction. But with improvements in troponin assays, elevated concentrations without overt myocardial ischemia are now more common; this is referred to as *myocardial injury*. Physicians may be falsely reassured by the absence of myocardial ischemia; however, recent evidence suggests that myocardial injury is associated with even more detrimental outcomes. Accordingly, this article reviews the definition, epidemiology, differential diagnosis, diagnostic evaluation, and management of myocardial injury.

**OBSERVATIONS** Current epidemiological evidence suggests that myocardial injury without overt ischemia represents about 60% of cases of abnormal troponin concentrations when obtained for clinical indications, and 1 in 8 patients presenting to the hospital will have evidence of myocardial injury. Myocardial injury is a concerning prognosis; the 5-year mortality rate is approximately 70%, with a major adverse cardiovascular event rate of 30% in the same period. The differential diagnosis is broad and can be divided into acute and chronic precipitants. The initial workup involves an assessment for myocardial ischemia. If infarction is ruled out, further evaluation includes a detailed history, physical examination, laboratory testing, a 12-lead electrocardiogram, and (if there is no known history of structural or valvular heart disease) an echocardiogram. Unfortunately, no consensus exists on routine management of patients with myocardial injury. Identifying and treating the underlying precipitant is the most practical approach.

**CONCLUSIONS AND RELEVANCE** Myocardial injury is the most common cause of abnormal troponin results, and its incidence will likely increase with an aging population, increasing prevalence of cardiovascular comorbidities, and greater sensitivity of troponin assays. Myocardial injury represents a challenge to clinicians; however, given its serious prognosis, it warrants a thorough evaluation of its underlying precipitant. Future strategies to prevent and/or manage myocardial injury are needed.

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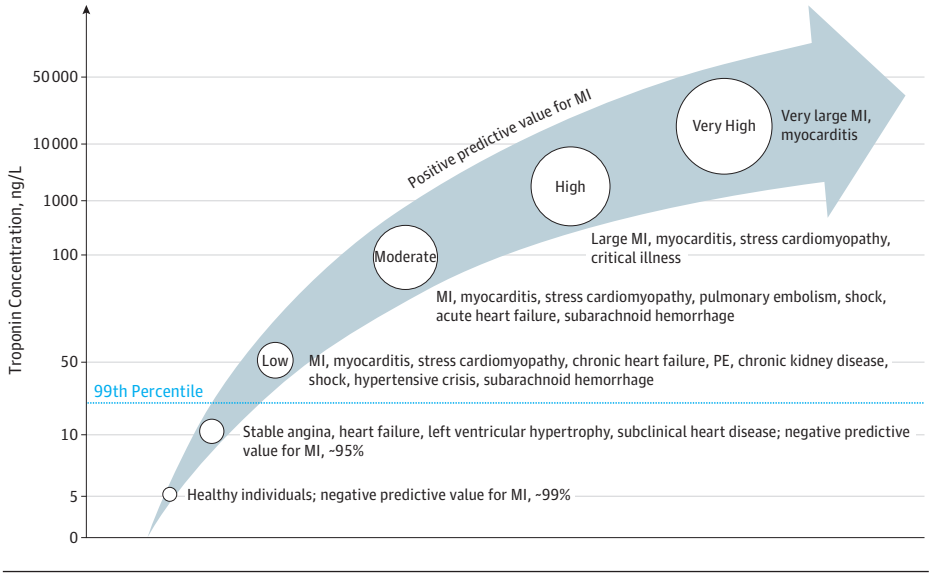
Cardiac troponin (cTn) was first discovered as a component of the myofibrillar apparatus in 1963.[1] However, it was a further 30 years before a reliable serum assay for cTn measurement was developed. These cTn assays were developed and validated to diagnose acute myocardial infarction (MI) and shown to detect MI with greater accuracy than creatine kinase because of their improved analytical performance, superior analytical sensitivity, and tissue specificity.[2] Most cTn in the cardiac myocyte is bound within the sarcomere, while approximately 5% remains free in the cytoplasm.[3] It is thought that under ischemic conditions, when MI occurs, free cytoplasmic cTn is released first, causing an initial rapid change in cTn concentration, while myofibrils are subsequently degraded over several days, resulting in a more stable and continuous cTn release.[3] With improvements in technology, cTn can now be quantified at levels greater than the limit of detection in 50% of healthy individuals or more by using high-sensitivity (hs) cTn assays[4]; some preclinical assays may reliably detect concentration of cTn in all normal individuals. The mechanism of cTn detection in healthy individuals is not fully understood but is hypothesized to be associated with myocyte turnover.[5] These advancements in analytical sensitivity have facilitated the early, rapid rule-in and rule-out of MI, with the ensuing potential to improve patient outcomes and decrease health care costs.[6]

However, the improved analytical sensitivity and the use of the 99th-percentile upper reference limit (URL) as the preferred concentration threshold for detecting myocardial injury comes with challenges, including increased recognition of cTn concentrations greater than the 99th percentile without overt myocardial ischemia.[7] This

Figure 1. Most Likely Causes of Myocardial Injury (MI), Stratified by Cardiac Troponin Concentration




PE indicates pulmonary embolism. SI conversion factor: To convert to µg/L, multiply by 0.001. Used with permission from Januzzi JL Jr, Mahler SA, Christenson RH, et al. Recommendations for institutions transitioning to high-sensitivity troponin testing: JACC Scientific Expert Panel. *JACC*. 2019;73(9):1059-1077.

circumstance, termed *myocardial injury*, is now acknowledged in the fourth universal definition of MI as a separate entity.[8] Several studies indicate that, when using contemporary and high-sensitivity assays, myocardial injury in the absence of ischemia is the most common cause of an increased cTn concentration.[9,10] Accustomed to the connotations that a diagnosis of MI carries, physicians may be falsely reassured by the absence of MI. Myocardial injury, however, is associated with even worse outcomes, with 5-year mortality rates and major adverse cardiovascular events (MACE) of approximately 70% and 30%, respectively, over the same period.[11] Notably, patients with myocardial injury without evidence of infarction may not necessarily derive benefit from traditional therapies for ischemia.[12,13]

Myocardial injury may be conceptually challenging and its evaluation difficult. While the term *myocardial injury* applies to any patient with an increased cTn level greater than the 99th-percentile value (including those with MI), the term is now endorsed as the preferred nomenclature to refer to patients with isolated cTn increases without MI. In this article, the definition, epidemiology, differential diagnosis, and prognosis of myocardial injury are reviewed, after which we provide a practical approach to its evaluation and management.

Table 1. Definitions of Acute and Chronic Myocardial Injury and Myocardial Infarction Subtypes

| Condition | Definition[a] |
|---|---|
| Myocardial injury | |
| Acute | Dynamic rise and/or fall of troponin concentration attributable to cardiovascular or noncardiovascular causes |
| Chronic | Persistently elevated troponin concentration attributable to cardiovascular or noncardiovascular causes |
| Myocardial infarction, type[b] | |
| 1 | Myocardial infarction caused by plaque rupture, ulceration, or dissection |
| 2 | Myocardial infarction attributable to oxygen supply-demand mismatch |
| 3 | Sudden cardiac death with a causative mechanism that is most likely myocardial infarction |
| 4 | Myocardial infarction associated with percutaneous intervention or stent thrombosis |
| 5 | Myocardial infarction associated with cardiac surgery |

[a] All conditions are defined by a troponin concentration greater than the 99th percentile of the upper reference limit, regardless of cause.

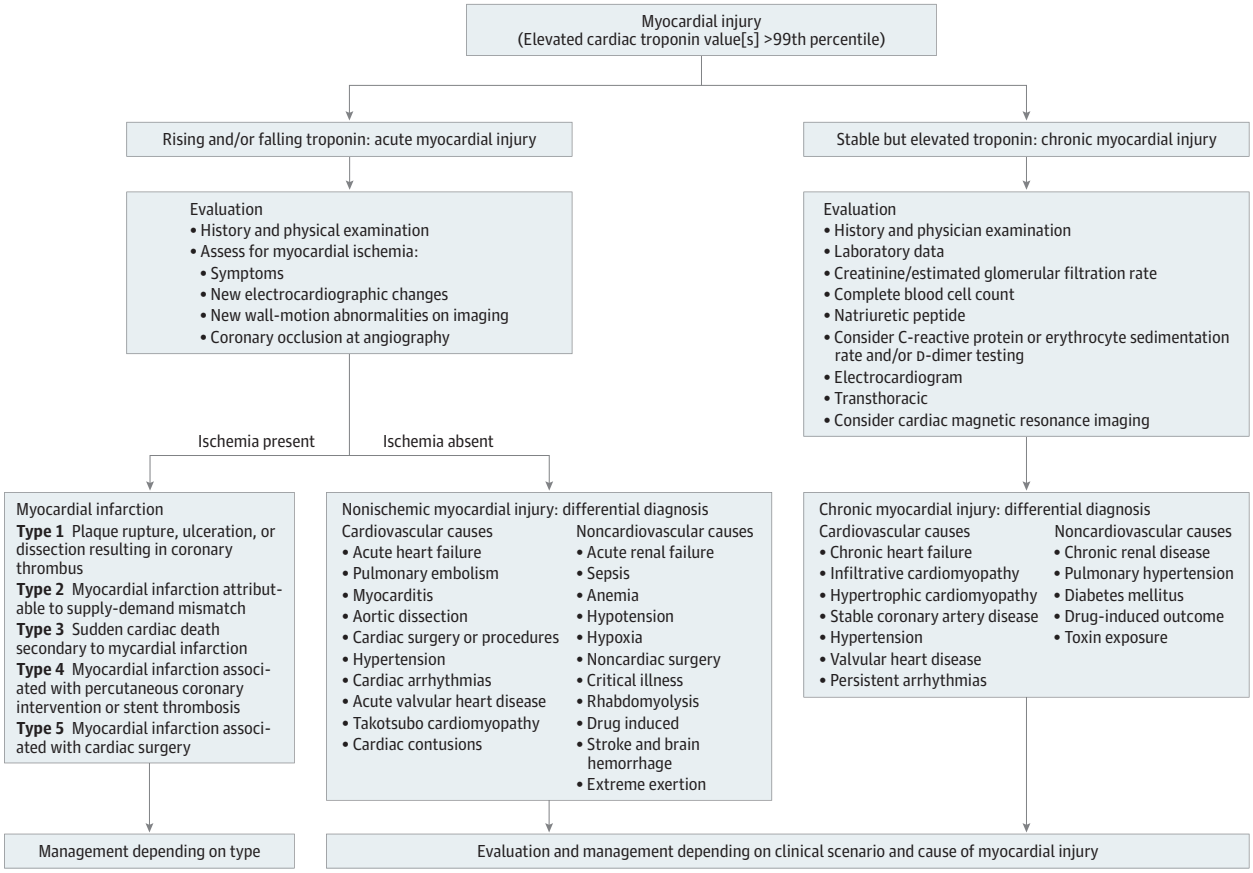
[b] Dynamic rise or fall of troponin concentration greater than the 99th percentile of the upper reference limit with myocardial ischemia per symptoms of ischemia, new ischemic electrocardiographic findings, new ischemic wall-motion abnormalities on echocardiogram, and/or a coronary thrombus visualized on coronary angiography.

## Defining Myocardial Injury

Myocardial injury is defined as any cTn concentration greater than the 99th-percentile URL.[8,14] Myocardial injury is considered acute if there is a rise and/or fall of cTn concentrations exceeding the biological and/or analytical variation.[15] No standard exists for how much rise and/or fall of hs-cTn concentration identifies an acute injury; typically, an increase in the cTn concentration greater than the reference change value (the biological variation of an assay) is considered acute for both cTnT and cTnI assays if the initial cTn value is less than the 99th-percentile value.[14] If the first cTn level is greater than the 99th-percentile value, then an increase of at least 50% of the 99th-percentile value or a change greater than 20% relative to the baseline value may be considered acute.[14] While small changes in cTn concentration have poor specificity, a large rise and/or fall is much more specific for acute myocardial injury, with the largest increases typically occurring in acute MI (**Figure 1**); the larger the rise and/or fall of cTn concentrations, the higher the positive predictive value for MI.[15]

To diagnose any of the 5 types of MI (**Table 1**), in addition to acute myocardial injury, there must be clinical evidence of acute myocardial ischemia. The diagnosis of myocardial ischemia

Figure 2. Evaluation, Differential Diagnosis, and Approach to Management of Acute and Chronic Myocardial Injury




requires that at least 1 of the following be observed: symptoms of myocardial ischemia, new ischemic electrocardiographic changes, new ischemic regional wall-motion abnormalities on cardiac imaging, and/or an acute coronary thrombus on coronary angiography.[8] In the absence of these prerequisites, MI cannot be diagnosed. Differentiating type 2 MI from myocardial injury can be particularly challenging. Both entities can have overlapping precipitants (eg, heart failure [HF] and sepsis), but they are differentiated by the presence of ischemia, which is needed to diagnose type 2 MI.[8] However, evaluating for the presence of ischemia can be challenging in certain situations, such as when a patient is intubated or atypical symptoms exist.

At lower cTn concentrations, which are the kind most often frequently encountered in clinical practice, several mechanisms of acute myocardial injury besides ischemic mechanisms leading to acute MI have been described, including those that cause increased cTn release, such as myocardial strain,[16] inflammation,[17] apoptosis,[16] and cell injury,[18] or those that decrease cTn clearance, such as acute or chronic kidney injury (**Figure 2**).[19] All must be considered in the differential diagnosis if the presentation is ambiguous. A cTn result greater than the 99th-percentile URL without a rise and/or fall over a period of serial measurements (eg, more than 8 hours) is characteristic of chronic myocardial injury in the appropriate clinical setting.

## Epidemiology

The reported incidence of myocardial injury has varied according to the setting in which the cTn was measured (**Table 2**). In a cohort of 918 consecutive patients presenting to the emergency department (ED) without symptoms of MI, the incidence of myocardial injury was 12.4% (114 of 918 patients; of the 114, 5 [4.4%] had MI).[20] As expected, among patients presenting to the ED with suspicion of MI, the incidence of myocardial injury is higher. In the Use of Troponin in Acute Coronary Syndrome (UTROPIA) study, a prospective observational study of 1640 patients in the ED who were undergoing serial hs-cTnI measurements (with Abbott testing equipment) on clinical indication, Sandoval and colleagues[9] found that 25.7% of patients (n = 422) had at least 1 hs-cTnI test result greater than the 99th-percentile value, of whom 58% (or 14.9% of the total group) were determined to have myocardial injury without ischemia. The investigators found that the most frequent causative mechanisms of myocardial injury were renal failure, HF, and neurological conditions.[9] The High-Sensitivity Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome (High-STEACS) trial[21] was a stepped-wedge, cluster-randomized controlled trial that prospectively evaluated the implementation of an hs-cTnI assay among 48 282 consecutive patients presenting with

Table 2. Studies That Report Detection of Myocardial Injury in Various Settings

| Source | Participant Sample | Location | Assay | Incidence of Myocardial Injury, No. (%) | Rates of Nonischemic Myocardial Injury vs Myocardial Infarction, %:% |
|---|---|---|---|---|---|
| Lee et al[20] | 918 Consecutive patients presenting to the ED without symptoms of ACS | Scotland | Hs-cTnI (Abbott) | 114 (12.4) | 96:4 |
| Sandoval et al[9] | 1640 Patients presenting to the ED for suspicion of ACS | United States | Hs-cTnI (Abbott) | 422 (25.7) | 58:42 |
| Shah et al[21] | 48 282 Patients presenting to the ED for suspicion of ACS | Scotland | Hs-cTnI (Abbott) | 10 360 (21.5) | 31:69 |
| Kadesjo et al[22] | 39 558 Patients presenting to the ED for suspicion of ACS | Sweden | Hs-cTnT (brand name not reported) | 3855 (9.7) | 64.5[a]:35.5 |
| Sarkisian et al[23] | 3762 Patients with hs-cTn measured during their hospitalization | Denmark | Hs-cTnI (Abbott) | 1577 (41.9) | 69:31 |
| Dolci et al[24] | 1137 Patients with hs-cTn measured during their hospitalization | Italy | Hs-cTnT (Roche) | 1342 (58.7) | Not reported |
| McFalls et al[10] | 95 840 Patients with cTn measured during their index admission to the Veterans Affairs hospital who survived the hospitalization | United States | cTnI and cTnT (brand names not reported) | 21 688 (22.6) | 57:43 |

Abbreviations: ACS, acute coronary syndrome; cTn, cardiac troponin; cTnI, cardiac troponin I; cTnT, cardiac troponin T; ED, emergency department; hs-cTn, high-sensitivity troponin.

[a] Myocardial injury includes acute injury, 29.5%, and chronic injury, 35%.

suspected MI to 10 hospitals in Scotland. The investigators found the incidence of myocardial injury to be 21.5% (n = 10 360 of 48 282). They adjudicated the cause of myocardial injury in 9115 patients and reported that 6288 of these patients (69.0%) experienced MI (type 1 or type 2). Notably, few epidemiological studies to date have differentiated acute from chronic myocardial injury. Examining 39 558 patients presenting to the ED with chest pain, Kadesjo et al[22] found that 3855 patients (9.7%) had an hs-cTn concentration greater than the 99th-percentile value. Of these, 1118 (29.0%) had type 1 MI, 251 (6.5%) had type 2 MI, 1137 (29.5%) had acute myocardial injury, and the largest proportion (1349 patients [35.0%]) had chronic myocardial injury.

In the current era of hs-cTn assays, myocardial injury may now be the most common cause of increased cTn levels when examined in patients who are hospitalized. Using the Veterans Affairs centralized databases, McFalls et al[10] identified patients hospitalized with increased cTn concentrations in 2006. Among 95 840 patients who had a troponin (cTnT or cTnI) level measured during their index admission, 22.6% were diagnosed with myocardial injury; 12 400 of these 21 688 individuals with myocardial injury did not have an MI (57.2%).[10] Of the patients with noninfarction cTn increases, more than 40% carried a primary diagnosis of cardiac origin, such as HF and chronic coronary artery disease, while others were diagnosed with infections or diseases associated with the renal, gastrointestinal, and neurologic systems.[10] Similarly, examining 3762 patients with hs-cTnI levels measured during index hospitalization, Sarkisian et al[23] found the incidence of myocardial injury to be 41.9% (n = 1577), and only 488 of these patients (30.9%) were diagnosed with MI. Dolci et al[24] found the incidence of ischemic and nonischemic myocardial injury among 2287 patients who are hospitalized to be slightly higher, at 58.7% (n = 1342).

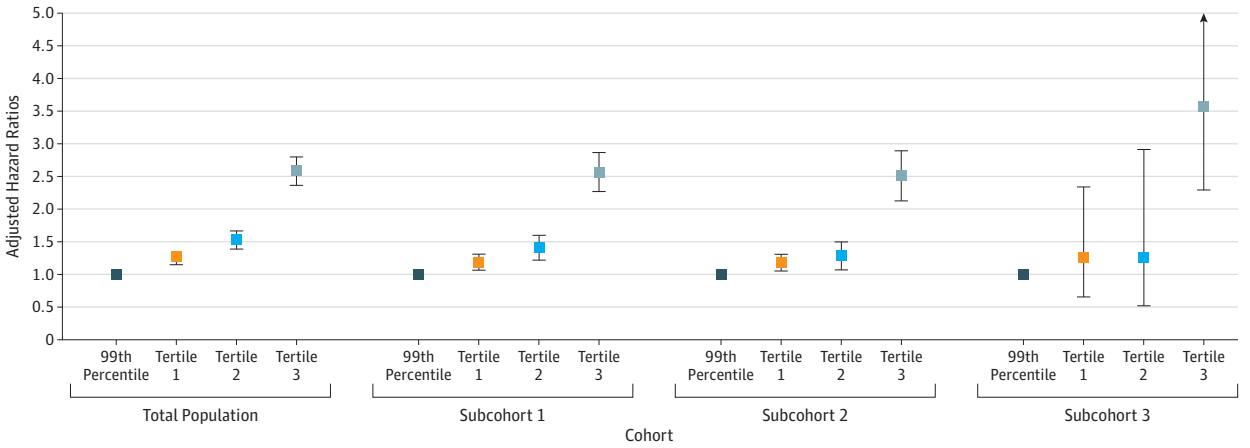
## Differential Diagnosis

The differential diagnosis for myocardial injury is broad. It can be divided into acute or chronic causes (Figures 1 and 2).

### Acute Myocardial Injury

When a rise and/or fall of cTn level with at least 1 concentration greater than the 99th-percentile URL is encountered, acute MI is a primary consideration; the larger the magnitude of the cTn increase, the more likely acute MI is to be the cause. That said, even when faced with moderate degrees of injury, a broad range of precipitants of myocardial injury should be considered. Cardiovascular causes of acute myocardial injury include MI,[8] pulmonary embolism,[25] myocarditis[17] and/or myopericarditis,[26] aortic dissection,[27] cardiac surgery[28] or procedures (eg, cardioversion or ablation),[29] hypertension,[16] arrhythmias,[30] acute HF,[31] acute valvular heart disease (eg, aortic regurgitation or mitral regurgitation),[32] takotsubo cardiomyopathy,[33] and cardiac contusions (including chest compressions).[34] If accompanying clinical evidence of acute myocardial ischemia is identified, then acute MI should be diagnosed. For example, in the absence of overt myocardial ischemia, most patients with acute HF should be categorized as having myocardial injury; however, acute HF can occur because of myocardial ischemia, and when these patients are identified to have clinical evidence of myocardial ischemia, then acute MI is diagnosed. Noncardiovascular causes and/or triggers of myocardial injury include acute renal failure,[35] sepsis,[36] anemia,[37] hypotension,[38] hypoxia,[39] noncardiac surgery,[40] critical illness,[41] rhabdomyolysis,[42] drug-induced causes (eg, chemotherapy),[18] stroke,[43] and extreme exertion.[44]

Figure 3. Multivariable-Adjusted Hazard Ratios (With 95% CIs) of Major Cardiovascular Adverse Events in Patients With Troponin Elevation Without Specific Diagnosis and in Subcohorts




In all cohorts, the risk of major adverse cardiovascular events increased in a stepwise fashion across higher (assay-specific) cardiac troponin levels, with patients in the highest tertile being at particularly high risk. Patients with cardiac troponin concentrations at or less than the 99th-percentile value were used as a reference group. All analyses are adjusted for age, sex, admission year, hospital, and cardiac troponin assay. Subcohort 1 excludes patients with previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, stroke, or heart failure. Subcohort 2 excludes all of those excluded by subcohort 1, plus patients with estimated glomerular filtration rates less than 60/mL/min/1.73 $m^2$. Subcohort 3 excludes all those excluded by the other 2 subcohorts, plus patients with left ventricular ejection fraction of 50% or less or significant coronary stenosis. Used with permission from Eggers et al.[58]

A common, vexing issue is the association of renal dysfunction with cTn concentrations. One prevalent hypothesis is that myocardial injury in patients with advanced kidney disease is a consequence of decreased clearance of cardiac troponin. However, its presence is likely multifactorial and also influenced by other factors, such as underlying coronary artery disease[45] and the presence of a left ventricular mass.[19]

### Chronic Myocardial Injury

Cardiovascular causes of chronic myocardial injury include chronic HF,[46] infiltrative cardiomyopathies (amyloidosis, hemochromatosis, and sarcoidosis),[47] hypertrophic cardiomyopathy,[48] stable coronary artery disease,[49] hypertension,[50] valvular heart disease,[51] and persistent arrhythmias (eg, atrial fibrillation).[52] Noncardiovascular causes include chronic renal disease,[53] pulmonary hypertension,[54] toxins,[55] and diabetes mellitus.[56]

## Prognosis

Emerging evidence from several observational studies indicates that myocardial injury pertains a concerning prognosis (**Figure 3**). Most studies have not delineated acute vs chronic myocardial injury without infarction, and there remain limited data on differences in outcomes between these 2 conditions.

One small retrospective study showed that patients with noncardiac precipitating factors compared with cardiac-associated precipitants for their increased cTnI concentration at presentation have higher in-hospital mortality rates (26.7% vs 13.4%; $P = .002$).[57] Beyond the initial hospitalization, myocardial injury has high short-term mortality (11% at 6 months and 26% at 2 years).[9] Age, maximum cTnI concentrations, and a history of HF were prognosticative of mortality at 2 years.[9] Longer-term outcomes were examined by Chapman et al,[11] who found that the 5-year mortality rate was as high as 72.4% (n = 378 of 522). The long-term mortality from myocardial injury was mostly driven by noncardiovascular causes (218 of 378 [57.7%]).[11] Accordingly, some of this mortality risk may not be modifiable. However, cardiovascular event rates are also high among this population. The 5-year MACE rates were 31.0% (n = 162 of 522), with 27.8% of all patients (n = 145 of 522) experiencing death from a cardiovascular cause.[11] Over 5 years, 35 of 522 patients (6.7%) with myocardial injury experienced a nonfatal MI and 48 of 522 (9.2%) had an HF hospitalization.[11] Patients with myocardial injury in the absence of MI, compared with those with type 1 MI, had a higher risk of all-cause mortality (adjusted relative risk, 2.09 [95% CI, 1.72-2.55]) but a lower risk of MACE (adjusted relative risk, 0.77 [95% CI, 0.66-0.89]). A large retrospective analysis of 9800 patients with myocardial injury without MI, diagnosed by either conventional or hs-cTn assays, who were included in the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry, found similarly morbid long-term outcomes, with 15.4% of patients having MACE (a composite of all-cause mortality, MI, readmission for HF, or stroke at a median follow-up of 4.9 years). Furthermore, they reported that the magnitude of myocardial injury was an important factor associated with mortality, with successive increases in hazard ratios across troponin tertiles, even when adjusting for the presence of cardiovascular disease or prevalent comorbidities.[58] Examining outcomes among patients with myocardial injury diagnosed in the ED, Kadesjo et al[22] found that patients with acute myocardial injury had a 21% higher risk of all-cause mortality (adjusted hazard ratio, 1.21 [95% CI, 1.08-1.37]) and a 24% higher risk of HF (adjusted haz-

ard ratio, 1.24 [95% CI, 1.07-1.43]), compared with patients with chronic myocardial injury over a median follow-up of 3.9 years.

Myocardial injury occurs in a heterogeneous group of patients, consisting of both cardiac and noncardiac types of insult, which likely confer different prognostic implications. A prospective study on patients with myocardial injury categorized patients based on causative mechanisms: ischemic, nonischemic cardiac (eg, major cardiac surgery), noncardiac (eg, infection), or multifactorial (at least 2 cardiac or noncardiac conditions).[59] Researchers found that after adjusting for covariates, patients with cardiac-ischemic and nonischemic causes had similar mortality rates. However, diagnoses of noncardiac and multifactorial causes of myocardial injury were associated with higher mortality rates compared with cardiac ischemic types of injury (hazard ratio [HR], 1.39 [95% CI, 1.06-1.80]; $P = .02$).[59] Patients with chronic HF often have evidence of myocardial injury, and a meta-analysis of 9289 patients found that cTn increases were associated with greater all-cause mortality (HR, 1.48 [95% CI, 1.41-1.55]; $P < .001$), cardiovascular death (HR, 1.40 [95% CI, 1.33-1.48]; $P < .001$), and cardiovascular hospitalization (HR, 1.42 [95% CI, 1.36-1.49]; $P < .001$).[46]

Troponin levels may correlate with clinical prognosis in some cases. Increases in cTnI concentrations in patients undergoing high-dose chemotherapy for aggressive malignant conditions have been correlated with future reductions in left ventricular ejection fraction.[60] In patients with chronic kidney disease and end-stage renal disease, increased cTn concentrations are associated with higher rates of all-cause mortality.[61,62] In patients with amyloidosis[47] or pulmonary embolism,[63] detection of cTn was found to be strongly associated with all-cause mortality. Troponin detection can also be induced by exercise, though the clinical implications of the cTn elevation are not well understood.[44] Prognostication using cTn measurement certainly does not apply for all causes of myocardial injury, nor would a peak cTn level necessarily enable prognostication across various causes of myocardial injury, which can cause vastly different levels of cTn elevation.

Risk stratification for patients with myocardial injury and identification of patients would benefit from close monitoring and further testing is an area of ongoing investigation, especially given the evidence that increased cTn concentrations carry prognostic significance. Risk stratification may guide frequency of follow-up visits postdischarge facilitating surveillance for symptoms of ischemia, HF, and optimization of preventative therapies. The Troponin Assessment for Risk Stratification of Patients Without Acute Coronary Atherothrombosis (TARRACO) risk score was recently developed to risk stratify patients with type 2 MI or myocardial injury and externally validated in a cohort of 401 patients.[64] The score combines incorporates cTn concentrations and factors associated with adverse cardiovascular events in this population, including age, hypertension, absence of chest pain, dyspnea, and anemia. Major adverse cardiovascular events were 5 times higher in the patients at high risk compared with the patients at lowest risk, based on this score.[64] The utility of this score to alter the prognosis of patients (by guiding further investigation or therapeutic intervention) will need evaluation in a clinical trial, however.

Taken together, these patterns of morbidity and mortality underscore the reality that myocardial injury with negative ischemic workup does not offer reassurance; rather, a careful evaluation for alternate causative mechanisms should be considered. Furthermore, trivializing such circumstances with terms such as a *troponin leak* or *troponinemia* is strongly discouraged. Although prospective studies are needed to demonstrate that outcomes for patients with myocardial injury are indeed modifiable, the consistency of the evidence that myocardial injury is associated with very poor outcomes across a broad range of health care settings requires clinicians to take elevated troponin seriously.

## Evaluating Myocardial Injury

The initial assessment of myocardial injury focuses on the (1) assessment of ischemic symptoms, (2) review of the patients' medical history and cardiovascular risk factors, (3) serial 12-lead electrocardiograms, (4) serial cTn measurements assessed over periods of 3 to 12 hours, depending on sensitivity of the assay, (5) an echocardiogram to assess for regional wall-motion abnormalities and exclude the presence of cardiomyopathy and/or structural heart disease, and/or (6) coronary angiography (whether by computerized tomography or an invasive procedure). If the patient reports symptoms of angina, even atypical angina, they nominally meet the universal definition for acute MI, and an ischemic evaluation should be undertaken if it has not previously performed. If myocardial infarction is excluded, the subsequent assessment includes a comprehensive history and physical examination, laboratory testing, and cardiac imaging, if appropriate.

### History and Physical Examination

Inquiring about the presence and nature of chest discomfort is important. Pleuritic discomfort may suggest pulmonary embolism, pneumonia, or myocarditis. Discomfort radiating to the back may suggest aortic dissection. Symptoms suggestive of HF (eg, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema), valvular heart disease (eg, syncope, angina, and dyspnea), cardiac arrhythmias (eg, palpitations), and infections (eg, fevers, chills) should be explored. Recent procedures (eg, cardiac and noncardiac), use of cardiotoxic medications (in particular chemotherapy and substance abuse), activity (eg, intense exercise regimens), life stressors (eg, takotsubo cardiomyopathy), recent travel, and medical history (specifically cardiovascular, pulmonary, and renal comorbidities) should be reviewed. The physical examination must include an appraisal of the patient's vital signs, cardiovascular system (eg, heart rate and rhythm, murmurs, presence of congestion), pulmonary system (eg, wheezing, rhonchi, and crackles), and potential sources of infection.

### Laboratory Data and Imaging

Serial cTn measurements are informative to differentiate acute from chronic myocardial injury when using hs-cTn assays. In patients who presented early and late or those in whom symptom onset is uncertain and distinguishing acute injury or chronic injury from infarction remains uncertain, a third sample can be helpful. This is because up to 26% of patients with acute MI may not demonstrate a substantial rise and/or fall.[65] A 12-lead electrocardiogram should be obtained at presentation and reviewed for signs of ischemia, infarction, arrhythmias, acute right ventricular strain, and conduction or structural disease (eg, left ventricular hypertrophy). We recommend assessment of renal function and measurement of a natri-

uretic peptide to provide complementary information regarding common causes of injury that are not associated with MI (such as chronic kidney disease or HF, respectively). A complete blood cell count (anemia or infection) should be attained. Additional laboratory testing, such as a D-dimer (considering pulmonary embolism and aortic dissection), and infectious and inflammatory markers (eg, C-reactive protein) can be guided by clinical assessment. An echocardiogram should be obtained to assess for systolic or diastolic dysfunction, left ventricular hypertrophy, wall-motion abnormalities, or valvular abnormalities. Further imaging, such as cardiac magnetic resonance imaging, may be obtained, depending on the clinical scenario (eg, suspected myocarditis or infiltrative cardiomyopathy).

## Treatment

For type 1 MI, an evidence-based treatment is well established.[66,67] For type 2 MI, present recommendations are to individualize care and correct the supply-demand alteration (eg, anemia, tachycardia, hypotension) leading to myocardial ischemia. The Determining the Mechanism of Myocardial Injury and Role of Coronary Disease in Type 2 Myocardial Infarction trial (DEMAND MI; NCT03338504) is attempting to improve the understanding of the mechanisms of ischemic myocardial injury by engaging computed tomography, coronary angiography, invasive coronary angiography, and cardiac magnetic resonance imaging. The Appropriateness of Coronary Investigation in Myocardial Injury and Type 2 Myocardial Infarction (ACT-2) trial is randomizing 300 patients with myocardial injury to invasive or computed tomography angiography within 5 days of randomization vs conservative management (with or without functional testing at clinician discretion), with a primary end point of all-cause mortality at 2 years.[68] Cost-effectiveness will be determined based on clinical events, quality of life, and resource use over 24 months.[68]

Unfortunately, beyond guidelines for treating these patients with ischemic myocardial injury, no consensus exists regarding the routine management of patients with myocardial injury. The management of myocardial injury may thus focus on the identification and treatment of the underlying precipitant (eg, HF).

Whether therapies to attenuate injury itself are of benefit remains unclear and data are largely retrospective and/or inconclusive. The West of Scotland Coronary Prevention Study (WOSCOPS) investigators found that pravastatin reduced hs-cTnI concentrations in an ambulatory population free of prior MI by a mean of 13%, and a change in troponin concentration at 1 year was associated with future MI risk reduction, independent of cholesterol lowering.[69] However, this was a primary prevention study, and the applicability of these findings to patients with acute nonischemic myocardial injury is uncertain. The Management of Myocardial Injury After Noncardiac Surgery (MANAGE) trial found that dabigatran lowered major vascular event rates when compared with placebo (97 of 877 [11%] vs 133 of 877 [15%]; hazard ratio, 0.72 [95% CI, 0.55-0.93]; $P = .01$) among patients with myocardial injury after noncardiac surgery.[70] Nonetheless, the results of this trial should be interpreted cautiously, because the trial was terminated early and medication discontinuation rates were high. Furthermore, given the heterogeneity in causes, it is difficult to conceive that a single approach can be used for all patients, and the primary composite end point was broad (eg, vascular mortality, nonfatal MI, nonhemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism). Lastly, sodium-glucose cotransporter 2 inhibitors have been shown to enhance diuresis, reduce blood pressure, and improve left ventricular remodeling.[71] In patients with diabetes mellitus, canagliflozin delayed a rise in troponin over 2 years compared with placebo.[72] Thus, these agents, along with others with alter hemodynamic stress, warrant investigation among patients with myocardial injury.

## Conclusions

The fourth universal definition of MI recently considered the phenomenon of myocardial injury as a separate, unique entity. Myocardial injury is the most common cause of abnormal hs-cTn results, and its incidence will likely increase with an aging population, increasing prevalence of cardiovascular comorbidities, and greater sensitivity of hs-cTn assays. Myocardial injury represents a challenge to clinicians; however, given its serious prognosis, it warrants a thorough evaluation for its underlying precipitant. Future strategies to prevent and/or manage myocardial injury are needed.

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Dr Sandoval reports present participation in an advisory board for Abbott Diagnostics and past, nonsalaried advisory board participation for Roche Diagnostics. No other disclosures were reported.

## REFERENCES


1. Ebashi S. Third component participating in the superprecipitation of 'natural actomyosin'. *Nature*. 1963;200:1010. doi:10.1038/2001010a0

2. Wu AH, Feng YJ, Contois JH, Pervaiz S. Comparison of myoglobin, creatine kinase-MB, and cardiac troponin I for diagnosis of acute myocardial infarction. *Ann Clin Lab Sci*. 1996;26(4):291-300.

3. Katus HA, Remppis A, Scheffold T, Diederich KW, Kuebler W. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. *Am J Cardiol*. 1991;67(16):1360-1367. doi:10.1016/0002-9149(91)90466-X

4. Apple FS, Sandoval Y, Jaffe AS, Ordonez-Llanos J; IFCC Task Force on Clinical Applications of Cardiac Bio-Markers. Cardiac troponin assays: guide to understanding analytical characteristics and their impact on clinical care. *Clin Chem*. 2017;63(1):73-81. doi:10.1373/clinchem.2016.255109

5. Bergmann O, Bhardwaj RD, Bernard S, et al. Evidence for cardiomyocyte renewal in humans. *Science*. 2009;324(5923):98-102. doi:10.1126/science.1164680

6. Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *JAMA*. 2011;306(24):2684-2693. doi:10.1001/jama.2011.1896

7. Sandoval Y, Thygesen K. Myocardial infarction type 2 and myocardial injury. *Clin Chem*. 2017;63(1):101-107. doi:10.1373/clinchem.2016.255521

8. Thygesen K, Alpert JS, Jaffe AS, et al; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72(18):2231-2264. doi:10.1016/j.jacc.2018.08.1038

9. Sandoval Y, Smith SW, Sexter A, et al. Type 1 and 2 myocardial infarction and myocardial injury: clinical transition to high-sensitivity cardiac troponin I. *Am J Med*. 2017;130(12):1431-1439.e4. doi:10.1016/j.amjmed.2017.05.049

10. McFalls EO, Larsen G, Johnson GR, et al. Outcomes of hospitalized patients with non-acute coronary syndrome and elevated cardiac troponin level. *Am J Med*. 2011;124(7):630-635. doi:10.1016/j.amjmed.2011.02.024

11. Chapman AR, Shah ASV, Lee KK, et al. Long-term outcomes in patients with type 2 myocardial infarction and myocardial injury. *Circulation*. 2018;137(12):1236-1245. doi:10.1161/CIRCULATIONAHA.117.031806

12. Everett BM, Brooks MM, Vlachos HEA, Chaitman BR, Frye RL, Bhatt DL; BARI 2D Study Group. Troponin and cardiac events in stable ischemic heart disease and diabetes. *N Engl J Med*. 2015;373(7):610-620. doi:10.1056/NEJMoa1415921

13. Omland T, Pfeffer MA, Solomon SD, et al; PEACE Investigators. Prognostic value of cardiac troponin I measured with a highly sensitive assay in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2013;61(12):1240-1249. doi:10.1016/j.jacc.2012.12.026

14. Wu AHB, Christenson RH, Greene DN, et al. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: expert opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. *Clin Chem*. 2018;64(4):645-655. doi:10.1373/clinchem.2017.277186

15. Twerenbold R, Jaffe A, Reichlin T, Reiter M, Mueller C. High-sensitive troponin T measurements: what do we gain and what are the challenges? *Eur Heart J*. 2012;33(5):579-586. doi:10.1093/eurheartj/ehr492

16. Weil BR, Suzuki G, Young RF, Iyer V, Canty JM Jr. Troponin release and reversible left ventricular dysfunction after transient pressure overload. *J Am Coll Cardiol*. 2018;71(25):2906-2916. doi:10.1016/j.jacc.2018.04.029

17. Lauer B, Niederau C, Kühl U, et al. Cardiac troponin T in patients with clinically suspected myocarditis. *J Am Coll Cardiol*. 1997;30(5):1354-1359. doi:10.1016/S0735-1097(97)00317-3

18. Kitayama H, Kondo T, Sugiyama J, et al. High-sensitive troponin T assay can predict anthracycline- and trastuzumab-induced cardiotoxicity in breast cancer patients. *Breast Cancer*. 2017;24(6):774-782. doi:10.1007/s12282-017-0778-8

19. deFilippi C, Seliger SL, Kelley W, et al. Interpreting cardiac troponin results from high-sensitivity assays in chronic kidney disease without acute coronary syndrome. *Clin Chem*. 2012;58(9):1342-1351. doi:10.1373/clinchem.2012.185322

20. Lee KK, Noaman A, Vaswani A, et al. Prevalence, determinants, and clinical associations of high-sensitivity cardiac troponin in patients attending emergency departments. *Am J Med*. 2019;132(1):110.e8-110.e21. doi:10.1016/j.amjmed.2018.10.002

21. Shah ASV, Anand A, Strachan FE, et al; High-STEACS Investigators. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *Lancet*. 2018;392(10151):919-928. doi:10.1016/S0140-6736(18)31923-8

22. Kadesjo E, Roos A, Siddiqui AJ, Desta L, Lundback M, Holzmann M. Acute versus chronic myocardial injury and outcomes. *J Am Coll Cardiol*. 2019;73(9)(suppl 1):105. doi:10.1016/S0735-1097(19)30713-2

23. Sarkisian L, Saaby L, Poulsen TS, et al. Clinical characteristics and outcomes of patients with myocardial infarction, myocardial injury, and nonelevated troponins. *Am J Med*. 2016;129(4):446.e5-446.e21. doi:10.1016/j.amjmed.2015.11.006

24. Dolci A, Braga F, Valente C, Guzzetti S, Panteghini M. Impact of implementation of the high-sensitivity cardiac troponin T assay in a university hospital setting. *Clin Chem*. 2011;57(8):1211-1212. doi:10.1373/clinchem.2011.164426

25. Douketis JD, Crowther MA, Stanton EB, Ginsberg JS. Elevated cardiac troponin levels in patients with submassive pulmonary embolism. *Arch Intern Med*. 2002;162(1):79-81. doi:10.1001/archinte.162.1.79

26. Kobayashi D, Aggarwal S, Kheiwa A, Shah N. Myopericarditis in children: elevated troponin I level does not predict outcome. *Pediatr Cardiol*. 2012;33(7):1040-1045. doi:10.1007/s00246-012-0222-y

27. Vagnarelli F, Corsini A, Bugani G, et al. Troponin T elevation in acute aortic syndromes: Frequency and impact on diagnostic delay and misdiagnosis. *Eur Heart J Acute Cardiovasc Care*. 2016;5(7):61-71. doi:10.1177/2048872615590146

28. Januzzi JL, Lewandrowski K, MacGillivray TE, et al. A comparison of cardiac troponin T and creatine kinase-MB for patient evaluation after cardiac surgery. *J Am Coll Cardiol*. 2002;39(9):1518-1523. doi:10.1016/S0735-1097(02)01789-8

29. Yoshida K, Yui Y, Kimata A, et al. Troponin elevation after radiofrequency catheter ablation of atrial fibrillation: relevance to AF substrate, procedural outcomes, and reverse structural remodeling. *Heart Rhythm*. 2014;11(8):1336-1342. doi:10.1016/j.hrthm.2014.04.015

30. Thelin J, Melander O. Dynamic high-sensitivity troponin elevations in atrial fibrillation patients might not be associated with significant coronary artery disease. *BMC Cardiovasc Disord*. 2017;17(1):169. doi:10.1186/s12872-017-0601-7

31. Peacock WF IV, De Marco T, Fonarow GC, et al; ADHERE Investigators. Cardiac troponin and outcome in acute heart failure. *N Engl J Med*. 2008;358(20):2117-2126. doi:10.1056/NEJMoa0706824

32. Olaf S, Debora B, Ricarda B, et al. Exercise tolerance in asymptomatic patients with moderate-severe valvular heart disease and preserved ejection fraction. *Arch Med Sci*. 2012;8(6):1018-1026. doi:10.5114/aoms.2012.32409

33. Madhavan M, Borlaug BA, Lerman A, Rihal CS, Prasad A. Stress hormone and circulating biomarker profile of apical ballooning syndrome (takotsubo cardiomyopathy): insights into the clinical significance of B-type natriuretic peptide and troponin levels. *Heart*. 2009;95(17):1436-1441. doi:10.1136/hrt.2009.170399

34. Müllner M, Oschatz E, Sterz F, et al. The influence of chest compressions and external defibrillation on the release of creatine kinase-MB and cardiac troponin T in patients resuscitated from out-of-hospital cardiac arrest. *Resuscitation*. 1998;38(2):99-105. doi:10.1016/S0300-9572(98)00087-2

35. Song D, de Zoysa JR, Ng A, Chiu W. Troponins in acute kidney injury. *Ren Fail*. 2012;34(1):35-39. doi:10.3109/0886022X.2011.623440

36. Ammann P, Fehr T, Minder EI, Günter C, Bertel O. Elevation of troponin I in sepsis and septic shock. *Intensive Care Med*. 2001;27(6):965-969. doi:10.1007/s001340100920

37. Bellotto F, Fagiuoli S, Pavei A, et al. Anemia and ischemia: myocardial injury in patients with gastrointestinal bleeding. *Am J Med*. 2005;118(5):548-551. doi:10.1016/j.amjmed.2005.01.026

38. Klein Gunnewiek JMT, van de Leur JJJPM. Elevated troponin T concentrations in critically ill patients. *Intensive Care Med*. 2003;29(12):2317-2322. doi:10.1007/s00134-003-1953-2

39. Brekke PH, Omland T, Holmedal SH, Smith P, Søyseth V. Troponin T elevation and long-term mortality after chronic obstructive pulmonary disease exacerbation. *Eur Respir J*. 2008;31(3):563-570. doi:10.1183/09031936.00015807

40. Puelacher C, Lurati Buse G, Seeberger D, et al; BASEL-PMI Investigators. Perioperative myocardial injury after noncardiac surgery: incidence, mortality, and characterization. *Circulation*. 2018;

137(12):1221-1232. doi:10.1161/CIRCULATIONAHA.117.030114

**41**. Lim W, Qushmaq I, Devereaux PJ, et al. Elevated cardiac troponin measurements in critically ill patients. *Arch Intern Med*. 2006;166(22):2446-2454. doi:10.1001/archinte.166.22.2446

**42**. Punukollu G, Gowda RM, Khan IA, et al. Elevated serum cardiac troponin I in rhabdomyolysis. *Int J Cardiol*. 2004;96(1):35-40. doi:10.1016/j.ijcard.2003.04.053

**43**. Sandhu R, Aronow WS, Rajdev A, et al. Relation of cardiac troponin I levels with in-hospital mortality in patients with ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. *Am J Cardiol*. 2008;102(5):632-634. doi:10.1016/j.amjcard.2008.04.036

**44**. Fortescue EB, Shin AY, Greenes DS, et al. Cardiac troponin increases among runners in the Boston Marathon. *Ann Emerg Med*. 2007;49(2):137-143, 143.e1. doi:10.1016/j.annemergmed.2006.09.024

**45**. deFilippi C, Wasserman S, Rosanio S, et al. Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. *JAMA*. 2003;290(3):353-359. doi:10.1001/jama.290.3.353

**46**. Aimo A, Januzzi JL Jr, Vergaro G, et al. Prognostic value of high-sensitivity troponin t in chronic heart failure: an individual patient data meta-analysis. *Circulation*. 2018;137(3):286-297. doi:10.1161/CIRCULATIONAHA.117.031560

**47**. Qian G, Wu C, Zhang Y, Chen YD, Dong W, Ren YH. Prognostic value of high-sensitivity cardiac troponin T in patients with endomyocardial-biopsy proven cardiac amyloidosis. *J Geriatr Cardiol*. 2014;11(2):136-140.

**48**. Kubo T, Kitaoka H, Yamanaka S, et al. Significance of high-sensitivity cardiac troponin T in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2013;62(14):1252-1259. doi:10.1016/j.jacc.2013.03.055

**49**. Januzzi JL Jr, Suchindran S, Coles A, et al. High-sensitivity troponin I and coronary computed tomography in symptomatic outpatients with suspected coronary artery disease: insights from the PROMISE trial. *JACC Cardiovasc Imaging*. 2019;12(6):1047-1055. doi:10.1016/j.jcmg.2018.01.021

**50**. Aeschbacher S, Schoen T, Bossard M, et al. Relationship between high-sensitivity cardiac troponin I and blood pressure among young and healthy adults. *Am J Hypertens*. 2015;28(6):789-796. doi:10.1093/ajh/hpu226

**51**. Røsjø H, Andreassen J, Edvardsen T, Omland T. Prognostic usefulness of circulating high-sensitivity troponin T in aortic stenosis and relation to echocardiographic indexes of cardiac function and anatomy. *Am J Cardiol*. 2011;108(1):88-91. doi:10.1016/j.amjcard.2011.02.346

**52**. van den Bos EJ, Constantinescu AA, van Domburg RT, Akin S, Jordaens LJ, Kofflard MJ. Minor elevations in troponin I are associated with mortality and adverse cardiac events in patients with atrial fibrillation. *Eur Heart J*. 2011;32(5):611-617. doi:10.1093/eurheartj/ehq491

**53**. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. *Circulation*. 2002;106(23):2941-2945. doi:10.1161/01.CIR.0000041254.30637.34

**54**. Heresi GA, Tang WH, Aytekin M, Hammel J, Hazen SL, Dweik RA. Sensitive cardiac troponin I predicts poor outcomes in pulmonary arterial hypertension. *Eur Respir J*. 2012;39(4):939-944. doi:10.1183/09031936.00067011

**55**. Riley ED, Hsue PY, Vittinghoff E, et al. Higher prevalence of detectable troponin I among cocaine-users without known cardiovascular disease. *Drug Alcohol Depend*. 2017;172:88-93. doi:10.1016/j.drugalcdep.2016.11.039

**56**. Segre CAW, Hueb W, Garcia RM, et al. Troponin in diabetic patients with and without chronic coronary artery disease. *BMC Cardiovasc Disord*. 2015;15:72. doi:10.1186/s12872-015-0051-z

**57**. Ilva TJ, Eskola MJ, Nikus KC, et al. The etiology and prognostic significance of cardiac troponin I elevation in unselected emergency department patients. *J Emerg Med*. 2010;38(1):1-5. doi:10.1016/j.jemermed.2007.09.060

**58**. Eggers KM, Jernberg T, Lindahl B. Cardiac troponin elevation in patients without a specific diagnosis. *J Am Coll Cardiol*. 2019;73(1):1-9. doi:10.1016/j.jacc.2018.09.082

**59**. Sarkisian L, Saaby L, Poulsen TS, et al. Prognostic impact of myocardial injury related to various cardiac and noncardiac conditions. *Am J Med*. 2016;129(5):506-514.e1. doi:10.1016/j.amjmed.2015.12.009

**60**. Cardinale D, Sandri MT, Martinoni A, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol*. 2000;36(2):517-522. doi:10.1016/S0735-1097(00)00748-8

**61**. Michos ED, Wilson LM, Yeh HC, et al. Prognostic value of cardiac troponin in patients with chronic kidney disease without suspected acute coronary syndrome: a systematic review and meta-analysis. *Ann Intern Med*. 2014;161(7):491-501. doi:10.7326/M14-0743

**62**. Sandoval Y, Herzog CA, Love SA, et al. Prognostic value of serial changes in high-sensitivity cardiac troponin I and T over 3 months using reference change values in hemodialysis patients. *Clin Chem*. 2016;62(4):631-638. doi:10.1373/clinchem.2015.251835

**63**. 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(6):633-637. doi:10.1136/hrt.2003.019745

**64**. Cediel G, Sandoval Y, Sexter A, et al. Risk estimation in type 2 myocardial infarction and myocardial injury: the TARRACO risk score. *Am J Med*. 2019;132(2):217-226. doi:10.1016/j.amjmed.2018.10.022

**65**. Bjurman C, Larsson M, Johanson P, et al. Small changes in troponin T levels are common in patients with non-ST-segment elevation myocardial infarction and are linked to higher mortality. *J Am Coll Cardiol*. 2013;62(14):1231-1238. doi:10.1016/j.jacc.2013.06.050

**66**. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61(4):e78-e140. doi:10.1016/j.jacc.2012.11.019

**67**. Amsterdam EA, Wenger NK, Brindis RG, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130(25):e344-e426.

**68**. Lambrakis K, French JK, Scott IA, et al. The appropriateness of coronary investigation in myocardial injury and type 2 myocardial infarction (ACT-2): A randomized trial design. *Am Heart J*. 2019;208:11-20. doi:10.1016/j.ahj.2018.09.016

**69**. Ford I, Shah ASV, Zhang R, et al. High-sensitivity cardiac troponin, statin therapy, and risk of coronary heart disease. *J Am Coll Cardiol*. 2016;68(25):2719-2728. doi:10.1016/j.jacc.2016.10.020

**70**. Devereaux PJ, Duceppe E, Guyatt G, et al; MANAGE Investigators. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. *Lancet*. 2018;391(10137):2325-2334. doi:10.1016/S0140-6736(18)30832-8

**71**. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. *J Am Coll Cardiol*. 2019;73(15):1931-1944. doi:10.1016/j.jacc.2019.01.056

**72**. Januzzi JL Jr, Butler J, Jarolim P, et al. Effects of canagliflozin on cardiovascular biomarkers in older adults with type 2 diabetes. *J Am Coll Cardiol*. 2017;70(6):704-712. doi:10.1016/j.jacc.2017.06.016