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

Myocardial Injury in the Era of High-Sensitivity Cardiac Troponin Assays: Guide for Clinicians

Cian P. McCarthy, M.B., B.Ch., B.A.O.[1]; Inbar Raber, M.D.[2]; Andrew R. Chapman, M.D., Ph.D.[3]; Yader Sandoval, M.D.[4]; Fred S. Apple, Ph.D.[5]; Nicholas L. Mills, M.D., Ph.D.[3, 6]; James L. Januzzi Jr, M.D.[7, 8].

[1] Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA.

[2] Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.

[3] British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, UK.

[4] Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA.

[5] Department of Laboratory Medicine and Pathology, Hennepin Healthcare/Hennepin County Medical Center & University of Minnesota, Minneapolis, Minnesota, USA.

[6] Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, UK.

[7] Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA.

[8] Baim Institute for Clinical Research, Boston, Massachusetts, USA.

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Corresponding Author:
James L. Januzzi Jr, MD
Massachusetts General Hospital
32 Fruit Street, Yawkey 5B
Boston, MA, 02114
P: +1-617-726-3443
F: +1-617-643-1620
E: jjanuzzi@mgh.harvard.edu

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Abstract

Importance: Traditionally, elevated troponin concentrations were synonymous with myocardial infarction. However, with improvements in troponin assays, elevated concentrations without overt myocardial ischemia is now more common; an entity 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, we review the definition, epidemiology, differential diagnosis, diagnostic evaluation, and management of myocardial injury.

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

Conclusion and Relevance: Myocardial injury is the most common etiology for 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 for its underlying precipitant. Future strategies to prevent and/or manage myocardial injury are needed.

Introduction

Cardiac troponin (cTn) was first discovered as a component of the myofibrillar apparatus in 1963.[1] It was, however, a further 30 years before a reliable serum assay for cTn measurement was developed. 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] The majority of cTn in the cardiac myocyte is bound within the sarcomere, while ~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 above the limit of detection in ≥50% of healthy individuals using high-sensitivity (hs) cTn assays;[4] some pre-clinical assays may reliably detect concentration of cTn in all normal subjects. The mechanism of cTn detection in healthy individuals is not fully understood but hypothesized to be related to myocyte turnover.[5] These advancements in analytical sensitivity have facilitated the early, rapid rule-in and rule-out of MI with ensuing potential to improve patient outcomes and decrease healthcare costs.[6]

The improved analytical sensitivity and the use of the 99th percentile upper-reference limit (URL) as the preferred concentration threshold for detecting myocardial injury, however, comes with challenges including increased recognition of cTn concentrations >99th percentile without overt myocardial ischemia.[7] This circumstance, termed *myocardial injury*, is now acknowledged in the Fourth Universal Definition of MI as a separate entity.[8] Several studies indicate that using contemporary and hs-assays, myocardial injury in the absence of ischemia is

the most common cause of an increased cTn.[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 ~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 >99th percentile (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.

Defining Myocardial Injury

Myocardial injury is defined as any cTn concentration above the 99th percentile URL.[8,14] Myocardial injury is considered *acute* if there is a rise and/or fall of cTn concentrations exceeding biological and/or analytical variation.[15] No standard exists for how much rise and/or fall of hs-cTn identifies acute injury; typically an increase in the cTn concentration greater than the reference change value (biological variation of an assay) is considered acute for both cTnT and cTnI assays if the initial cTn value is < 99th percentile.[14] If the first cTn level is > 99th percentile then an increase of at least 50% of the 99th percentile or a change > 20% 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, the higher the positive predictive value for MI.[15]

To diagnose any of the five 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 requires at least one of the following: 1) symptoms of myocardial ischemia, 2) new ischemic electrocardiographic changes, 3) new ischemic regional wall motion abnormalities on cardiac imaging, or 4) acute coronary thrombus on coronary angiography.[8] In the absence of these pre-requisites, MI cannot be diagnosed. Differentiating type 2 MI from myocardial injury can be particularly challenging. Both entities can have overlapping precipitants [e.g. 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 the intubated patient or when atypical symptoms exist.

At lower cTn concentrations, which are the most often frequently encountered in clinical practice; besides ischemic mechanisms leading to acute MI, several other mechanisms of acute myocardial injury have been described, including those that cause increase 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 above the 99th percentile URL without a rise and/or fall over a period of serial measurements (e.g. over 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% (of which 4% of patients were had MI).[20] Predictably, 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 1,640 ED patients undergoing serial hs-cTnI (Abbott) measurements on clinical indication, Sandoval and colleagues found that 26% of patients had at least one cTnI >99th percentile, of which 58% were determined to be myocardial injury.[9] The investigators found that the most frequent etiologies 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 was a stepped-wedge, cluster-randomized controlled trial that prospectively evaluated the implementation of a hs-cTnI assay among 48,282 consecutive patients presenting with suspected MI to ten hospitals in Scotland.[21] The investigators found the incidence of myocardial injury to be 21%, of which 69% were diagnosed with MI. 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 and colleagues found that 3,855 patients had a hs-cTn concentration greater than the 99th percentile. Of these, 29% had type 1 MI, 6.5% had type 2 MI, 29.5% had acute myocardial injury, and the majority (35%) had chronic myocardial injury.[22]

In the current era of hs-assays, myocardial injury may now be the most common cause of increased cTn when examined in hospitalized patients. Using the Veterans Affairs centralized databases, McFalls *et al.* identified patients hospitalized with increased cTn concentrations in

2006.[10] Among 100, 433 patients who had a troponin (cTnT or cTnI) measured during their index admission, 24% were diagnosed with myocardial injury; the majority (57%) were not found to have MI.[10] Of the patients with non-infarction cTn increases, more than 40% carried a primary diagnosis of cardiac origin, such as HF and chronic coronary artery disease (CAD), while others were diagnosed with infections or diseases related to the renal, gastrointestinal, and neurologic systems.[10] Similarly, examining 3,762 patients with hs-cTnI measured during index hospitalization, Sarkisian *et al.* found the incidence of myocardial injury to be 42% and only 31% of these patients were diagnosed with MI.[23] Dolci *et al.* found the incidence of ischemic and non-ischemic myocardial injury among hospitalized patients to be slightly higher at 59%.[24]

Differential Diagnosis

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

Acute Myocardial Injury

When a rise and/or fall of cTn with at least one concentration >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 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 (PE),[25] myocarditis,[17] and/or myopericarditis,[26] aortic dissection,[27] cardiac surgery,[28] or procedures[29] (e.g. cardioversion or ablation), hypertension,[16] arrhythmias,[30] acute HF,[31] acute valvular heart disease[32] (e.g.: aortic regurgitation or mitral regurgitation), Takotsubo cardiomyopathy,[33] and cardiac contusions[34] (including chest compressions). 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 due to myocardial ischemia, and when these patients are identified to have clinical evidence of myocardial ischemia, then acute MI is diagnosed. *Non-cardiovascular* causes and/or triggers of myocardial injury include acute renal failure,[35] sepsis,[36] anemia,[37] hypotension,[38] hypoxia,[39] non-cardiac surgery,[40] critical illness,[41] rhabdomyolysis,[42] drug induced (e.g. chemotherapy),[18] stroke,[43] and extreme exertion.[44] A common vexing issue is the effect of renal dysfunction on 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 CAD,[45] and left ventricular mass.[19]

Chronic Myocardial Injury

Cardiovascular causes of chronic myocardial injury include chronic HF,[46] infiltrative cardiomyopathies[47] (amyloidosis, hemochromatosis, and sarcoidosis), hypertrophic cardiomyopathy,[48] stable CAD,[49] hypertension,[50] valvular heart disease,[51] and persistent arrhythmias (e.g. atrial fibrillation).[52] *Non-cardiovascular* 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 versus chronic myocardial injury without infarction, and there remains limited data on differences in outcomes between these two entities.

One small retrospective study showed that patients with non-cardiac precipitating factors for their increased cTnI at presentation have higher in-hospital mortality (26.7% vs. 13.4%, p=0.002) compared to cardiac-related precipitants.[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 concentration, and a history of HF were predictive of 2-year mortality.[9] Longer term outcomes were examined by Chapman and colleagues, who found that 5-year mortality was as high as 72%.[11] The long-term mortality from myocardial injury was mostly driven from non-cardiovascular causes (62%).[11] Accordingly, some of this mortality risk may not be modifiable. Cardiovascular event rates, however, are also high among this population. The 5-year MACE rates were 31% with 28% of patients experiencing a cardiovascular death.[11] Over 5-years, 4.8% of patients with myocardial injury experience a non-fatal MI, 5.6% a HF hospitalization, and 3.9% a stroke.[11] Patients with myocardial injury in the absence of MI, had a higher risk of all-cause mortality compared to type 1 MI (adjusted relative risk: 2.09; 95% confidence interval, 1.72-2.55) but a lower risk of MACE (adjusted relative risk 0.77 95% confidence interval, 0.66-0.89). A large retrospective analysis of 9,800 patients with myocardial injury without MI, diagnosed by either conventional or hs-cTn, included in the SWEDEHEART registry (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) found similarly morbid long term outcomes; with 15.4% of patients having MACE (composite of all-cause mortality, MI, readmission for HF, or stroke at a median follow-up 4.9 years). Furthermore, they reported that the magnitude of myocardial injury was an important predictor of mortality, with successive increases in hazard ratios across troponin tertiles, even when adjusting for presence of cardiovascular disease or prevalent comorbidities.[58] Examining outcomes among patients with myocardial injury

diagnosed in the ED, Kadesjo *et al.* found that patients with acute myocardial injury had a 21% higher risk of all-cause mortality and a 30% higher risk of HF compared to patients with chronic myocardial injury over a median follow-up of 3.9 years.[22]

Myocardial injury occurs in a heterogeneous group of patients; consisting of both cardiac and non-cardiac types of insult; which likely confer different prognostic implications. A prospective study on patients with myocardial injury categorized patients based on etiology: ischemic, non-ischemic cardiac (e.g. major cardiac surgery), noncardiac (e.g. infection) or multifactorial (at least 2 cardiac or non-cardiac conditions) conditions.[59] Researchers found that after adjusting for covariates, cardiac ischemic and non-ischemic patients had similar mortality rates. However, diagnoses of noncardiac and multifactorial causes of myocardial injury carried higher mortality compared to cardiac ischemic types of injury (hazard ratio 1.39, 95% confidence interval 1.06-1.80; p =0 .02).[59] Patients with chronic HF often have evidence of myocardial injury and a meta-analysis of 9,289 patients found that cTn increases predicted all-cause mortality (hazard ratio (HR) 1.48, p<0.001), cardiovascular death (HR 1.40, p<0.001), and cardiovascular hospitalization (HR 1.42, p<0.001).[46]

Troponin levels may correlate with clinical prognosis in some cases. Increases in cTnI concentrations in patients undergoing high dose chemotherapy for aggressive malignancies 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 were found to be strong predictors of all-cause mortality. Troponin detection can also be induced by exercise, though the clinical implication of the cTn elevation not well understood.[44] Prognostication using cTn certainly does not apply for all causes of

myocardial injury nor would 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 post-discharge facilitating surveillance for symptoms of ischemia, HF, and optimization of preventative therapies. The TARRACO (Troponin Assessment for Risk stRatification of patients without Acute COronary athero-thrombosis) 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 predictors of adverse cardiovascular events in this population, including age, hypertension, absence of chest pain, dyspnea, and anemia. MACE events were five times higher in the high-risk patients compared to the lowest risk patients based on this score.[64] The utility of this score to alter the prognosis of patients (by guiding further investigation or therapeutic intervention) will however need evaluation in a clinical trial.

Taken together, these trends in morbidity and mortality underscore the reality that myocardial injury with ‘negative’ ischemic work-up does not offer reassurance; rather, a careful evaluation for alternate etiologies should be considered. Furthermore, trivializing such circumstances 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 healthcare 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 past medical history and cardiovascular risk factors, 3) serial 12-lead electrocardiograms, 4) serial cTn measurements assessed over 3-12 hour periods depending on sensitivity of the assay, 5) imaging: 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 (computerized tomography or invasive).

If the patient reports symptoms of angina—even atypical—they nominally meet the Universal Definition for acute MI, and an ischemic evaluation should be undertaken, if not previously performed. If myocardial infarction is excluded the subsequent assessment includes a comprehensive history and physical examination, laboratory testing, and where appropriate, cardiac imaging.

History and Physical Examination

Inquiring about the presence and nature of chest discomfort is important. Pleuritic discomfort may suggest PE, pneumonia, or myocarditis. Discomfort radiating to the back may suggest aortic dissection. Symptoms suggestive of HF (dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema), valvular heart disease (syncope, angina, and dyspnea), cardiac arrhythmias (palpitations), and infections (fevers, chills) should be explored. Recent procedures (cardiac and non-cardiac), use of cardiotoxic medications (in particular chemotherapy and substance abuse), activity (intense exercise regimens), life stressors (Takotsubo cardiomyopathy), recent travel, and past medical history (specifically cardiovascular, pulmonary, and renal comorbidities) should be reviewed.

The physical examination must include an appraisal of the patients' vital signs, cardiovascular system (heart rate and rhythm, murmurs, presence of congestion), pulmonary system (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 early and late presenters or in those in whom symptom onset is uncertain and distinguishing acute vs. chronic injury from infarction remains uncertain, a 3rd sample can be helpful as up to 26% of patients with acute MI may not demonstrate a significant 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 signs of conduction or structural disease (e.g. left ventricular hypertrophy). We recommend assessment of renal function and measurement of a natriuretic peptide to provide complementary information regarding common causes of non-MI related injury, such as chronic kidney disease or HF, respectively). A complete blood count (anemia or infection) should be attained. Additional laboratory testing such as d-dimer (considering PE and aortic dissection), and infectious/inflammatory markers (e.g. 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 (e.g. 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 (e.g.: anemia, tachycardia, hypotension, etc.) leading to myocardial ischemia. The DEtermining the Mechanism of myocardial injury AND role of coronary disease in type 2 Myocardial Infarction (DEMAND MI; NCT03338504) trial is attempting to improve our 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 angiography (or computed tomography angiography) within 5 days of randomization versus conservative management (with or without functional testing at clinician discretion) with a primary endpoint of all-cause mortality at 2 years.[68] Cost-effectiveness will be determined based on clinical events, quality of life, and resource utilization over 24 months.[68]

Beyond those patients with ischemic myocardial injury, unfortunately, no consensus exists regarding routine management of patients with myocardial injury. The management of myocardial injury may thus focus on the identification and treatment of the underlying precipitant (e.g. HF).

Whether therapies to attenuate injury itself are of benefit remains unclear and data are largely retrospective and/or inconclusive. The WOSCOPS (West of Scotland Coronary Prevention Study) investigators found pravastatin reduced hs-cTnI concentrations in an ambulatory population free of prior MI by an average of 13%, and change in troponin 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 non-ischemic myocardial injury is uncertain. The MANAGE (Management of Myocardial Injury After Noncardiac Surgery) trial found that dabigatran lowered major vascular event rates when compared with placebo (11% versus 15%, p=0.02) among patients with myocardial injury after noncardiac surgery.[70] Nonetheless, the results of this trial should be interpreted cautiously as the trial was terminated early and medication discontinuation rates were high. Further, given the heterogeneity in etiologies, it is difficult to conceive that one-single approach can be used for all patients and the primary composite endpoint was broad (vascular mortality, non-fatal MI, non-hemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism). Lastly, sodium-glucose cotransporter 2 inhibitors (SGLT2i) 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 when compared to placebo.[72] Thus, these agents, along with others with alter hemodynamic stress, warrant investigation among patients with myocardial injury.

Conclusion

The 4th Universal Definition of MI recently considered the phenomenon of myocardial injury as a separate, unique entity. Myocardial injury is the most common etiology for 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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Figure Legends

Figure 1: Figure illustrating most likely causes of myocardial injury stratified by cardiac troponin concentration. Abbreviations: HF= heart failure, LVH= left ventricular hypertrophy, MI= myocardial infarction, PE= pulmonary embolism. Taken with permission from Januzzi JL Jr et al; Recommendations for Institutions Transitioning to High-Sensitivity Troponin Testing: JACC Scientific Expert Panel. *JACC:*2019;73(9):1059-1077.

Figure 2: Figure illustrating the evaluation, differential diagnosis, and approach to management of acute and chronic myocardial injury. Abbreviations: ECG= electrocardiogram, PCI= percutaneous coronary intervention, TTE= transthoracic echocardiogram.

Figure 3: Multivariable-adjusted hazard ratios (with 95% CIs) of major adverse events in patients with troponin elevation without specific diagnosis and in subcohorts. In all cohorts, the risk of major adverse events increased in a stepwise fashion across higher assay-specific cardiac troponin (cTn) levels, with patients in the highest tertile being at particularly high risk. Patients with cTn ≤99th percentile were used as reference group. All analyses are adjusted for age, sex, admission year, hospital, and cTn assay. CABG = coronary artery bypass grafting; CI = confidence interval; cTn = cardiac troponin; eGFR = estimated glomerular filtration rate; HR = hazard ratio; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention. Taken with permission from Eggers et al; Cardiac troponin Elevation in Patients Without Specific Diagnosis. *JACC:*2019;73:1-9.

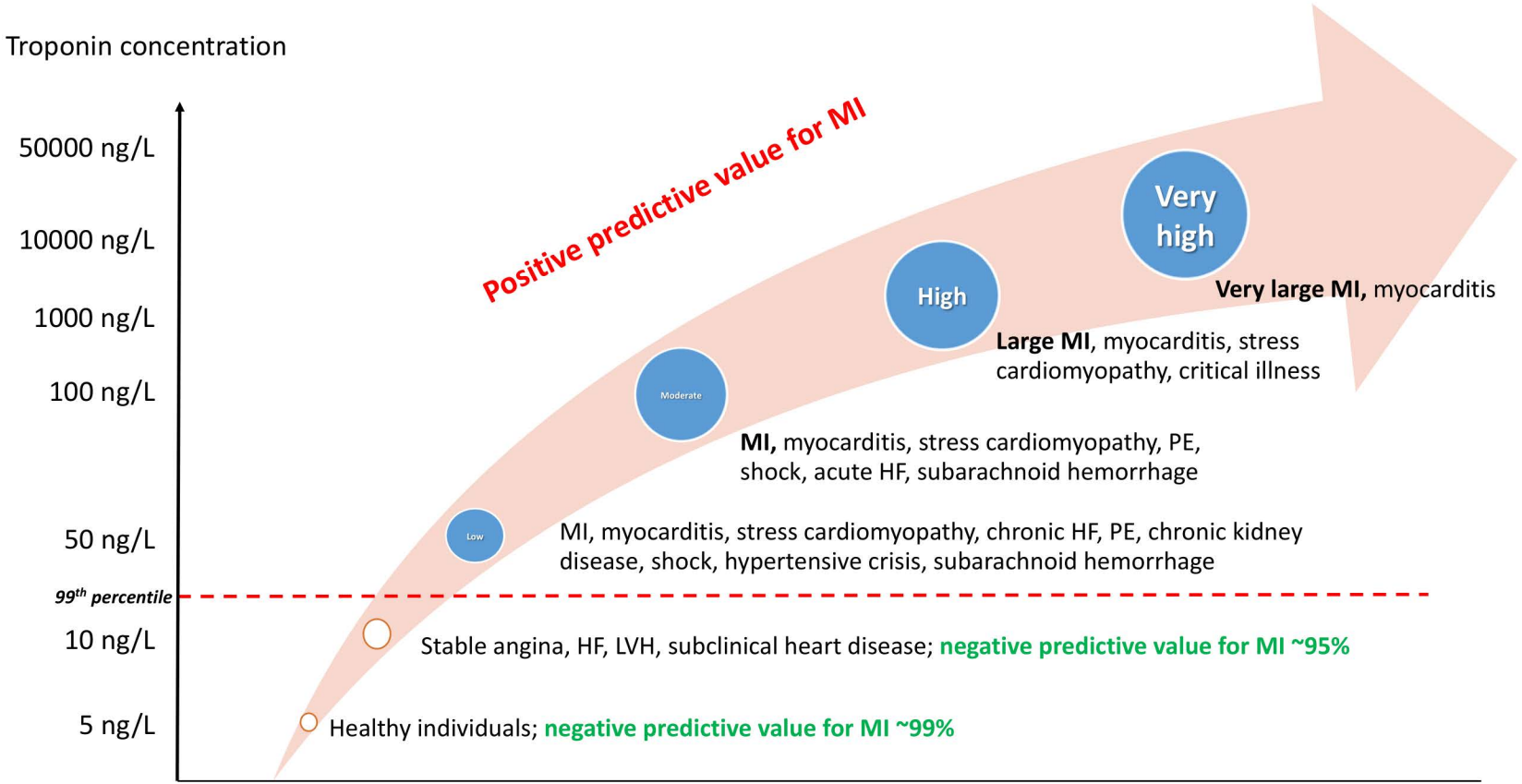
Table 1: Definitions of Acute and Chronic Myocardial Injury and the Subtypes of Myocardial Infarction

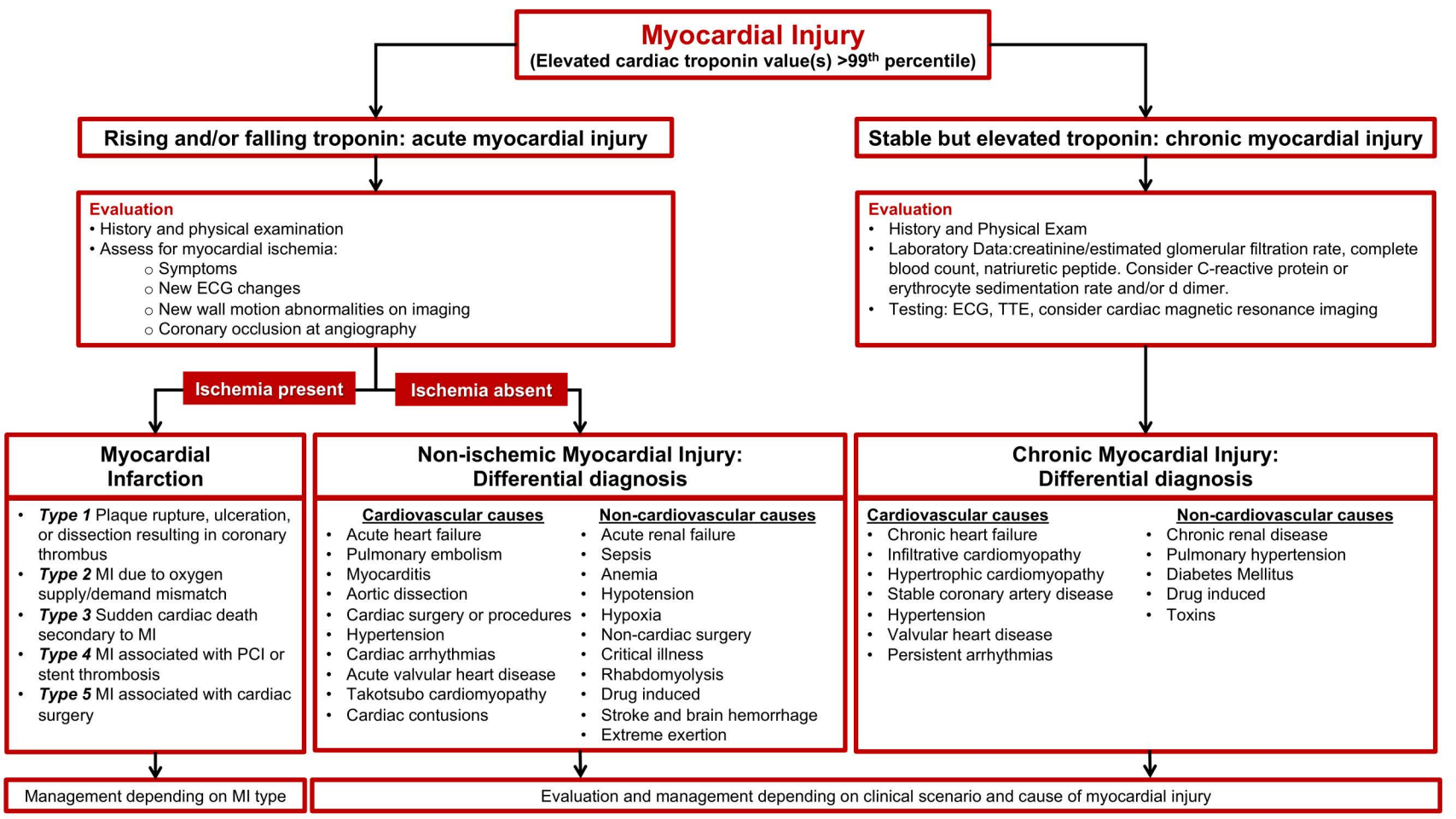
Myocardial Injury	*Troponin concentration above the 99th percentile URL, regardless of cause*	
	Acute	Dynamic rise and/or fall of troponin concentration due to cardiovascular or non-cardiovascular causes
	Chronic	Persistently elevated troponin concentration due to cardiovascular or non-cardiovascular causes
Myocardial Infarction	*Dynamic rise or fall of troponin concentration above 99th percentile URL with myocardial ischemia evidenced by 1) symptoms of ischemia, 2) new ischemic electrocardiographic findings, 3) new ischemic wall motion abnormalities on echocardiogram, 4) coronary thrombus visualized on coronary angiography*	
	Type 1	Myocardial infarction caused by plaque rupture, ulceration, or dissection
	Type 2	Myocardial infarction due to oxygen supply-demand mismatch
	Type 3	Sudden cardiac death with etiology most likely myocardial infarction
	Type 4	Myocardial infarction associated with percutaneous intervention or stent thrombosis
	Type 5	Myocardial infarction associated with cardiac surgery

Table 2: Table showing studies which report detection of myocardial injury in various settings. Abbreviations: ACS=acute coronary syndrome, cTn= cardiac troponin, ED= emergency department, hs-cTn=high sensitivity troponin, MI=myocardial infarction, VA=veterans affairs.

Study	**Setting**	**Location**	**Assay**	**Incidence of Myocardial injury**	**Cause of myocardial injury**	**Reference**
Lee *et al.*	918 consecutive patients presenting to the ED *without* symptoms of ACS	Scotland	Hs-cTnI (Abbott)	12%	- Non-ischemic myocardial injury= 96%. - MI= 4%.	[20]
Sandoval *et al.*	1,640 patients presenting to the ED for suspicion of ACS	United States	Hs-cTnI (Abbott)	26%	- Non-ischemic myocardial injury= 58% - MI= 42%	[9]
Shah *et al.*	48,282 patients presenting to the ED for suspicion of ACS	Scotland	Hs-cTnI (Abbott)	21%	- Non-ischemic myocardial injury= 31% - MI= 69%	[21]
Kadesjo *et al.*	39,558 patients presenting to the ED for suspicion of ACS	Sweden	Hs-cTnT	10%	- Non-ischemic myocardial injury 64.5% (29.5% acute injury and 35% chronic injury) - MI= 35.5%	[22]
Sarkisian *et al.*	3,762 patients with hs-cTn measured during	Denmark	Hs-cTnI (Abbott)	42%	- Non-ischemic myocardial injury= 69%	[23]

	their hospitalization.				- MI= 31%	
Dolci *et al.*	1,137 patients with hs-cTn measured during their hospitalization.	Italy	Hs-cTnT (Roche).	59%	Not provided	[24]
McFall *et al.*	100, 433 VA patients with cTn measured during their index admission	United States	cTnI and cTnT	24%	- Non-ischemic myocardial injury= 57% - MI= 43%	[10]


Troponin concentration
50000 ng/L
10000 ng/L
1000 ng/L
100 ng/L
50 ng/L
99th percentile
10 ng/L
5 ng/L
Positive predictive value for MI
Very high
High
Moderate
Low
Very large MI, myocarditis
Large MI, myocarditis, stress cardiomyopathy, critical illness
MI, myocarditis, stress cardiomyopathy, PE, shock, acute HF, subarachnoid hemorrhage
MI, myocarditis, stress cardiomyopathy, chronic HF, PE, chronic kidney disease, shock, hypertensive crisis, subarachnoid hemorrhage
Stable angina, HF, LVH, subclinical heart disease; negative predictive value for MI ~95%
Healthy individuals; negative predictive value for MI ~99%


Myocardial Injury
(Elevated cardiac troponin value(s) >99th percentile)
Rising and/or falling troponin: acute myocardial injury
Stable but elevated troponin: chronic myocardial injury
Evaluation
• History and physical examination
• Assess for myocardial ischemia:
○ Symptoms
○ New ECG changes
○ New wall motion abnormalities on imaging
○ Coronary occlusion at angiography
Evaluation
• History and Physical Exam
• Laboratory Data:creatinine/estimated glomerular filtration rate, complete blood count, natriuretic peptide. Consider C-reactive protein or erythrocyte sedimentation rate and/or d dimer.
• Testing: ECG, TTE, consider cardiac magnetic resonance imaging
Ischemia present
Ischemia absent
Myocardial Infarction
• Type 1 Plaque rupture, ulceration, or dissection resulting in coronary thrombus
• Type 2 MI due to oxygen supply/demand mismatch
• Type 3 Sudden cardiac death secondary to MI
• Type 4 MI associated with PCI or stent thrombosis
• Type 5 MI associated with cardiac surgery
Non-ischemic Myocardial Injury: Differential diagnosis
Cardiovascular causes
• Acute heart failure
• Pulmonary embolism
• Myocarditis
• Aortic dissection
• Cardiac surgery or procedures
• Hypertension
• Cardiac arrhythmias
• Acute valvular heart disease
• Takotsubo cardiomyopathy
• Cardiac contusions
Non-cardiovascular causes
• Acute renal failure
• Sepsis
• Anemia
• Hypotension
• Hypoxia
• Non-cardiac surgery
• Critical illness
• Rhabdomyolysis
• Drug induced
• Stroke and brain hemorrhage
• Extreme exertion
Chronic Myocardial Injury: Differential diagnosis
Cardiovascular causes
• Chronic heart failure
• Infiltrative cardiomyopathy
• Hypertrophic cardiomyopathy
• Stable coronary artery disease
• Hypertension
• Valvular heart disease
• Persistent arrhythmias
Non-cardiovascular causes
• Chronic renal disease
• Pulmonary hypertension
• Diabetes Mellitus
• Drug induced
• Toxins
Management depending on MI type
Evaluation and management depending on clinical scenario and cause of myocardial injury