

High-sensitivity cardiac troponin

High-Sensitivity Troponin Testing in Accordance with the 2018 Fourth Universal Definition of Myocardial Infarction

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Background: definition of myocardial infarction

The current definition of myocardial infarction (MI) involves 12-lead electrocardiogram (ECG), cardiac troponin (cTn) testing, and clinical assessment. Prior to 2000, MI diagnosis was based primarily on clinical evidence and ECG findings.¹⁻⁵ In 2000, the joint European Society of Cardiology (ESC) and the American College of Cardiology (ACC) committee redefined MI to include testing for abnormal cardiac biomarkers (myoglobin, CKMB, cTn).⁶ In 2007, an Expert Consensus Document provided an updated universal MI definition that included five MI subcategories, emphasis on abnormal cTn biomarker testing for rising/falling values in the setting of acute myocardial ischemia, and the need for better precision at the 99th percentile upper reference limit (URL).⁷ This 2007 universal definition document was endorsed by the ESC, ACC, the World Heart Federation (WHF), and the American Heart Association (AHA). With the advent of high-sensitivity cTn (hs-cTn) assays, the 2012 Third Universal Definition document included criteria for hs-cTn assay use and shorter 3-hour (h) algorithms.⁸ The 2018 Fourth Universal Definition of MI (ESC/ACC/AHA/WHF Expert Consensus Document) elaborates on the use of hs-cTn assays for differentiating myocardial injury due to ischemic MI and myocardial injury due to nonischemic conditions, both of which can cause elevated cTn concentrations.⁹

Nonischemic myocardial injury may be cardiac in origin, such as myocarditis, or noncardiac in origin, such as renal failure. The 2018 document also highlights analytical issues of cTn assays, benefits of hs-cTn assays, considerations for rapid rule-out and rule-in for diagnosing MI and myocardial injury, and concerns about cTn delta criteria for acute myocardial injury.⁹ Guidelines for the management of acute coronary syndromes in patients

with nonpersistent ST-segment elevation myocardial infarction (NSTEMI) patients were published by the ESC in 2011,¹⁰ updated in 2014 by the AHA/ACC,¹¹ and updated again in 2015 by the ESC.¹² Refer to Table 1 for a summary of the history of the universal definition of MI, guidelines for managing NSTEMI patients, and guidelines for the use of hs-cTn assays.^{13,14}

Table 1. History of the Universal Definition of Myocardial Infarction and guidelines for the management of NSTEMI patients.

Year	Document	Working Group	Highlights	Preferred Biochemical Marker
1960	First WHO ^a Definition ²	WHO	Clinical/ECG primarily	
1970s	Fifth WHO Definition ¹	WHO	Clinical/ECG primarily	
1979	Standardization of nomenclature ³	ISFC/WHO ^b Task Force	Clinical/ECG primarily	
1990s	WHO-MONICA ^c project ^{4,5}	WHO-MONICA	Clinical/ECG primarily	
2000	Redefinition of MI ⁶	ESC/ACC ^d	Biochemical and clinical	Myoglobin, CKMB, cTn
2007	Universal Definition of MI ⁷	Global MI Task Force ^e ESC/AAC/AHA/WHF endorsed by WHO	<ul style="list-style-type: none"> • 0, 6–9 h (rise/fall) • cTn one value >99th percentile URL • CV 10% • Five MI subcategories 	cTn
2011	ESC NSTEMI Guidelines ¹⁰	ESC	<ul style="list-style-type: none"> • Management of NSTEMI; rise/fall cTn 	
2012	Third Universal Definition of MI ⁸	Global MI Task Force ESC/ACC/AHA/WHF	<ul style="list-style-type: none"> • 0, 3–6 h (rise/fall) • s-cTn, hs-cTn; in ng/L • 99th percentile URL • One value >99th percentile URL • CV <10% at 99th percentile URL 	cTn
2014	Hs-cTn Assay Guidelines ¹¹	AHA/ACC/IFCC ^f		cTn
2014	Definition of hs-cTn assays ¹³	IFCC Task Force		cTn
2015	ESC NSTEMI Guidelines ¹²		<ul style="list-style-type: none"> • Management of NSTEMI; rise/fall cTn 	
2018	Fourth Universal Definition of MI ⁹	Global MI Task Force ESC/ACC/AHA/WHF	<ul style="list-style-type: none"> • MI vs. nonischemic myocardial injury (cardiac and noncardiac) • MI vs. myocardial injury after procedures (cardiac and noncardiac) • Analytical issues of cTn assays • Benefits of hs-cTn assays • Rapid rule-out/in for MI and myocardial injury considerations • Concerns about cTn delta criteria for acute myocardial injury 	cTn
2018	Recommendations for hs-cTn assay use ¹⁴	AACC/IFCC TF-CB ^g		cTn

a World Health Organization;

b International Society and Federation of Cardiology/WHO;

c WHO-Multinational monitoring of trends and determinants in cardiovascular disease;

d European Society of Cardiology/American College of Cardiology;

e ESC/ACC/American Heart Association/World Heart Federation;

f AHA/ACC/International Federation of Clinical Chemistry and Laboratory Medicine;

g Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the IFCC;

ECG: electrocardiogram; URL: upper reference limit; CV: coefficient of variation; MI: myocardial infarction; cTn: cardiac troponin;

s-cTn: sensitive cTn; hs-cTn: high-sensitivity cTn; NSTEMI: Non ST-elevation myocardial infarction; CKMB: creatine phosphokinase MB (muscle/brain) isoenzyme.

Both acute ischemic (MI) and acute nonischemic (cardiac and noncardiac conditions) myocardial injury demonstrate cTn levels above the 99th percentile URL⁹

- Acute MI is diagnosed if there is evidence of myocardial necrosis (cell death due to injury) in a clinical setting consistent with myocardial ischemia. Cardiac troponins (cTnI and cTnT) are the preferred biomarkers to aid in the diagnosis of myocardial injury.
- The term myocardial injury comprises MI as well as other nonischemic cardiac and noncardiac conditions in which cTn values are above the 99th percentile URL.
- Both cTnI and cTnT are made by cardiac myocytic cells. Upon cell injury, circulating cTnI and cTnT concentrations rise. It has been reported that injured skeletal muscle contributes to the circulating levels of cTnT but not cTnI.
- In the case of MI, injury is acute and characterized by a significant rise and/or fall of cTn with at least one value above the 99th percentile URL of a healthy reference population (Figure 1).^{8,10-12}

- In the case of other cardiac and noncardiac conditions, the injury may be chronic, where cTn values do not show a significant rise and/or fall of cTn but remain elevated above the 99th percentile URL. Examples of the latter conditions include anemia, ventricular tachyarrhythmia, heart failure, kidney disease, hypotension/shock, and hypoxemia (Figure 1).
- Nonischemic acute myocardial injury may also be characterized by a significant rise and/or fall of cTn values above the 99th percentile URL; examples include acute heart failure and myocarditis. Thus, both acute ischemic (Type 1 and Type 2 MI) and acute nonischemic (acute heart failure, myocarditis) myocardial injury may demonstrate a significant rising/falling pattern of cTn (Figure 1).

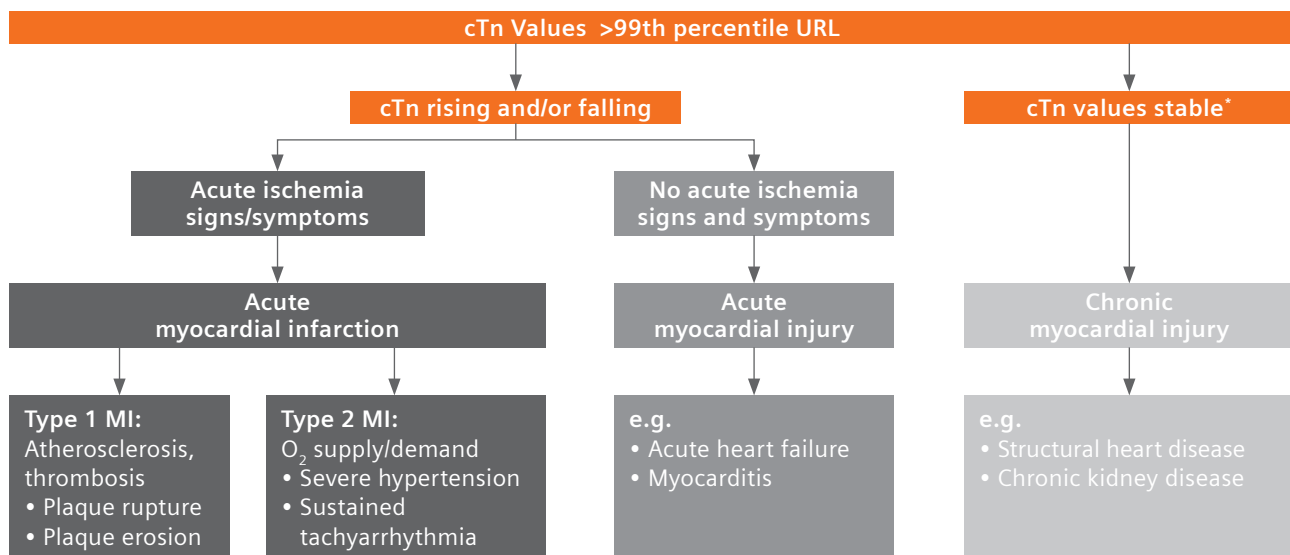


Figure 1. Myocardial injury model for acute ischemic, non-acute ischemic, and chronic types. cTn: cardiac troponin; O₂: Oxygen; MI: myocardial infarction; URL: upper reference limit.

A significant rising/falling pattern* of cTn above the 99th percentile URL using an hs-cTn assay may be demonstrated for:

- Acute ischemic (Type 1 and Type 2 MI) myocardial injury
- Acute nonischemic (acute heart failure, myocarditis) myocardial injury

Chronic cardiac and noncardiac conditions may show cTn above the 99th percentile URL using an hs-cTn assay, but not a significant rising/falling pattern;* cTn remains constant and elevated in conditions such as structural heart disease and chronic kidney disease.

*Stable cTn values refer to <20% changing pattern depending on clinical assessment.

Myocardial infarction typical clinical presentation includes chest pain and discomfort, but MI may present with atypical or no symptoms⁹

- Myocardial ischemia is caused by imbalance of oxygen supply and demand, leading to the development of MI. In a clinical setting, ischemia may be determined from patient history and ECG; however, symptoms such as chest pain and discomfort are not specific for myocardial ischemia.
- MI may present with atypical or no symptoms.
- An MI diagnosis involves identification of myocardial ischemia by clinical evaluation or ECG findings, as well as myocardial injury demonstrated by a significant rise and/or fall of cTn values.
- Examples of acute ischemic causes of MI include atherosclerotic plaque disruption with thrombosis; reduced myocardial perfusion (e.g., coronary artery spasm, microvascular dysfunction, coronary embolism, coronary artery dissection, sustained bradyarrhythmia, hypotension or shock, respiratory failure, severe anemia); and increased myocardial oxygen demand (e.g. sustained tachyarrhythmia and severe hypertension with or without left ventricular hypertrophy) (Table 2).⁹

Table 2. Examples of conditions that demonstrate elevations of cTn values due to myocardial injury.⁹

Myocardial injury related to acute myocardial ischemia	Other causes of myocardial injury
Atherosclerotic plaque disruption with thrombosis.	Cardiac <ul style="list-style-type: none"> • Heart failure • Myocarditis • Cardiomyopathy (any type) • Takotsubo syndrome • Coronary revascularization procedure • Cardiac procedure other than revascularization • Catheter ablation • Defibrillator shocks • Cardiac contusion Systemic <ul style="list-style-type: none"> • Sepsis, infectious disease • Chronic kidney disease • Stroke, subarachnoid hemorrhage • Pulmonary embolism, pulmonary hypertension • Infiltrative diseases (amyloidosis, sarcoidosis) • Chemotherapeutic agents • Critically ill patients • Strenuous exercise
Myocardial injury related to acute myocardial ischemia due to oxygen supply/demand imbalance	
Reduced myocardial perfusion <ul style="list-style-type: none"> • Coronary artery spasm, microvascular dysfunction • Coronary embolism • Coronary artery dissection • Sustained bradyarrhythmia • Hypotension or shock • Respiratory failure • Severe anemia Increased myocardial oxygen demand <ul style="list-style-type: none"> • Sustained tachyarrhythmia • Severe hypertension with or without left ventricular hypertrophy 	

Acute coronary syndrome comprises STEMI, NSTEMI, and stable angina, and MI falls into five categories based on pathology⁹

- The term acute coronary syndrome comprises three groups of patients based on ECG findings at presentation to the emergency department: those with new ST-segment elevations, termed ST-elevation MI (STEMI); those lacking ST-segment elevation, termed non-ST-elevation MI (NSTEMI); and stable angina.
- In addition, MI has been classified into five types, based in part on pathological findings (Table 3). Patients with suspected acute coronary syndrome that are ruled out for MI with normal cardiac biomarker values (<99th percentile URL) may have unstable angina or an alternative diagnosis.

Perioperative myocardial injury and MI associated with noncardiac procedures⁹

In addition to myocardial injury and MI associated with cardiac procedures (Table 3, Type 4 and 5 MI), perioperative MI is a common complication of major noncardiac surgery, with poor prognosis. Baseline hs-cTn values should be obtained to know which patients have chronic cTn elevation prior to surgery and those at higher risk during and after surgery. Postoperative hs-cTn values exceed the 99th percentile URL in about 35% of patients. The pathophysiological mechanism of perioperative myocardial injury may be MI (Type 1 or Type 2) or nonischemic in nature.

Myocardial infarction with nonobstructive coronary arteries⁹

Myocardial infarction with nonobstructive coronary arteries (MINOCA) comprises a group of MI patients without angiographic obstructive CAD for whom nonischemic causes (e.g., myocarditis) have been ruled out. Possible causes of MINOCA include Type 1 and/or Type 2 MI and other causes. MINOCA is present in about 7% of MI patients, more so in NSTEMI vs. STEMI patients and in women.

Myocardial injury associated with nonischemic cardiac causes⁹

- Myocardial injury or MI may be associated with heart failure. cTn concentrations above the 99th percentile URL measured with an hs-cTn assay may be present in patients with heart failure, especially severe cases (e.g., acutely decompensated heart failure). In the case of acutely decompensated heart failure, the possibility of MI should be investigated if symptoms, ECG, and biomarker rise/fall cause suspicion.⁹

Table 3. Myocardial infarction comprises five categories based on pathology.

Myocardial Infarction Type	Mechanism	cTn/hs-cTn Delta [†]	Biomarker cTn Assay	ECG	Imaging
Type 1	Plaque rupture/erosion with occlusive or nonocclusive thrombus	Yes Rise/fall	Yes One value >99th percentile URL	STEMI/ NSTEMI	Yes
Type 2	<ul style="list-style-type: none"> • Atherosclerosis and/or oxygen supply/demand imbalance • Vasospasm or coronary microvascular dysfunction • Nonatherosclerotic coronary dissection 	Yes Rise/fall	Yes One value >99th percentile URL	3–24% have STEMI	Yes
Type 3	<ul style="list-style-type: none"> • Cardiac death, with suspected MI before biomarker testing • MI is detected by autopsy examination 	N.A.	N.A.	N.A.	N.A.
Type 4a	Percutaneous coronary intervention (PCI)-related MI reflects cTn concentrations >5x the 99th percentile URL in patients with normal values at baseline. In patients with high stable preprocedure cTn (<20% variation) or falling, cTn must increase by >20% post-procedure and still be >5x the 99th percentile URL. In addition, ECG and imaging evidence are required.	Yes <48 h post-op	Yes	Yes	Yes
Type 4b	Stent/scaffold thrombosis associated with PCI	Yes Rise/fall	Yes One value >99th percentile URL	STEMI/ NSTEMI/ autopsy	Yes
Type 4c	Restenosis associated with PCI	Yes Rise/fall	Yes One value >99th percentile URL	STEMI/ NSTEMI	Yes
Type 5	Coronary artery bypass grafting (CABG)-related MI reflects cTn concentrations >10x the 99th percentile URL in patients with normal values at baseline. In patients with high stable preprocedure cTn (<20% variation) or falling, cTn must increase by >20% postprocedure and still be >10x the 99th percentile URL. In addition, pathological Q waves and imaging evidence are required.	Yes <48 h post-op	Yes	Yes	Yes

†A serial change (delta value) will likely not be demonstrated shortly after chest pain onset, at the peak of cTn release, and when cTn is on the decline part of the curve. N.A.: not applicable; Post-op: postoperative.

- Myocardial injury is associated with Takotsubo syndrome, whose presentation is difficult to distinguish from MI, especially when coronary artery disease is also present. Monitoring for QTc prolongation >500 ms during the acute phase and the recovery of LV function over 2–4 weeks may help to distinguish Takotsubo syndrome from MI diagnosis. Takotsubo syndrome is present in 1–2% of suspected STEMI patients and is typically caused by severe physical or mental stress. Half of patients have cardiovascular complications, 44% have ST-segment elevation, and mortality is similar to STEMI (4–5%).
- Other examples of nonischemic cardiac causes of myocardial injury include myocarditis, cardiomyopathy, coronary revascularization procedure, cardiac procedure other than revascularization, catheter ablation, defibrillator shocks, and cardiac contusion (Table 2).⁹

Myocardial injury associated with nonischemic, noncardiac (systemic) causes (e.g., chronic kidney disease)

- Cardiovascular disease is a common complication in chronic kidney disease (CKD) patients. Likely causes include left ventricular hypertrophy, cardiomyocyte apoptosis, coronary obstruction, anemia, and uremic effects. Myocardial injury is demonstrated by elevation of cTn values in CKD patients, and when using hs-cTn assays, elevations above the 99th percentile URL patients have been observed in most end-stage renal disease patients.
- cTnI and cTnT are the preferred biomarkers for the evaluation of myocardial injury. However, biochemical data indicates that injured skeletal muscle expresses proteins that are detected by the cTnT assay.
- Many patients with CKD have elevations of cTnT, which is more often elevated than cTnI.

- A changing pattern of values (delta value) for diagnosing MI is as important for the CKD and the dialysis population as it is for patients with normal renal function. Evaluation of delta values must include consideration of the timing of the event, the same as for patients with normal renal function. Patients who present early, late, or at the peak of cTn release may not demonstrate a significant serial change.
- A significant rise/fall of cTn could indicate MI, but also acute volume overload or congestive heart failure. An MI diagnosis is likely if a significant rise/fall of cTn using an hs-cTn assay is accompanied by ischemic symptoms and ECG changes. If cTn levels are unchanging upon serial measurements and timing is taken into account, elevated levels likely reflect chronic myocardial injury.
- Other examples of noncardiac (systemic) causes of myocardial injury include sepsis, infectious disease, stroke, subarachnoid hemorrhage, pulmonary embolism, pulmonary hypertension, infiltrative diseases (e.g., amyloidosis, sarcoidosis), chemotherapeutic agents, critically ill patients, and strenuous exercise (Table 2).⁹

Biochemical approach for diagnosing myocardial injury and MI⁹

Cardiac troponin I and T are the recommended biomarkers to aid in ruling in and ruling out myocardial injury and MI. As mentioned above, a cTn rising/falling pattern along with clinical evaluation and ECG are essential for the diagnosis of acute MI. Due to lack of standardization, cTn values for the different assays will be different and cannot be compared. When evaluating a rising/falling pattern, several considerations should be noted:

- Most biomarker release depends on coronary blood flow—which may be low or high, producing variability in the time cTn takes to peak velocity—to exceed the 99th percentile URL or observe a rise/fall in values. As mentioned above, in people with MI who present early, if blood flow is low, patients at risk may be missed because the biomarker is not yet detected (Figure 2).
- Changing pattern values may not be detected readily in patients presenting at the peak of cTn release, or after the peak when cTn release is declining slowly, because they cannot overcome analytical and biological variation (Figure 2).
- In order to overcome analytical and biological variation (which is in the range of 50–60%), guidelines have recommended >50% changing pattern when baseline values are <99th percentile URL, and >20% when baseline values are >99th percentile URL. Absolute changes appear to be superior to relative percent changes but are assay-specific.

Analytical issues regarding cardiac troponins (optimal imprecision and criteria for defining hs-cTn assays)

- Optimal imprecision for assays is described by a coefficient of variation (CV) of $\leq 10\%$ at the 99th percentile URL. This allows for adequate discrimination between normal and abnormal values and detection of significant changing values. Assays with CV $>20\%$ at the 99th percentile URL are not recommended for use. Assays are clinically usable if the CV is >10 to $<20\%$.¹⁴
- Prior to 2009, uniform criteria for defining cTn, sensitive-cTn, and hs-cTn assays were lacking in the literature. In 2009, assays were defined by the number of healthy people who had detectable cTn concentrations.¹⁵ “Contemporary” assays were assays that measure cTn in $<50\%$ healthy subjects; “hs-cTn” assays measured cTn in $>50\%$ of healthy subjects (men and women combined). A 2018 Expert Consensus Document has updated recommendations for hs-cTn assays to detect cTn in $>50\%$ women and $>50\%$ men.^{14,16,17} In addition, previous imprecision criteria were endorsed.^{14,15}

The 99th percentile URL value differs for each manufacturer; clinicians should rely on changing values to aid in the diagnosis of myocardial injury and MI^{9,14}

- The clinical decision level for MI, the 99th percentile URL, must be determined independently for each assay. Values for the 99th percentile URL are found in manufacturers’ Instructions for Use, publications, and the IFCC website. No uniform criteria exist for how to determine the 99th percentile URL, and the value has been found to change depending on the criteria used.
- Although higher 99th percentile URL values are obtained in patients with comorbidities and age over 60 years, age-dependent cutoff points are not recommended at present.¹⁴ Instead, clinicians should rely on changing values during serial measurements of cTn for the diagnosis of acute myocardial injury, including MI.
- Sex-specific 99th percentile URLs are recommended for hs-cTn assays because lower values are observed among women compared with men for some hs-cTn assays.¹⁴ Use of these assays by not applying sex-specific cutoffs may disadvantage women with possible MI.

Proposed algorithms for myocardial injury and MI

For a diagnosis of acute MI, guidelines recommend cTn measurements at presentation (0 h) and after 3 h to 6 h, along with a rise and/or fall in cTn values with at least one value above the 99th percentile URL. In addition, clinical and ECG likelihood are needed.^{8,10-12} With the advent of hs-cTn assays, shorter 0/1-h and 0/2-h algorithms have been investigated[‡] and are also considered in new ESC guidelines; however, rapid algorithms and cutoff values must be developed for each assay, and several points kept in mind, some mentioned above:

- Sampling may be needed after 6 h in those for whom suspicion of acute MI remains high, despite no changing pattern in early sampling.
- Acute injury is distinguished from chronic conditions (e.g., structural heart disease) by a rising and/or falling pattern (Figure 1). Some acute MI patients, presenting late after onset of acute MI (>12–18 h), may show a slow decline in cTn values and a changing pattern only after longer time periods; it may be hard to detect a changing pattern over short time periods (Figure 2).
- These late NSTEMI presenters may be difficult to distinguish from patients with unstable angina symptoms and increased hs-cTn due to structural heart disease.
- Acute MI patients presenting very early may not demonstrate elevated hs-cTn (Figure 2).
- With hs-cTn assays, unstable angina patient numbers will decrease and NSTEMI patient numbers will increase.
- Patients not meeting the delta or 99th percentile URL cutoff values will need to depend on clinical assessment for triage.
- For ruling out acute MI and myocardial injury, a strategy of very low levels of hs-cTn on presentation or absence of delta after 1 h to 2 h has been proposed.
- A single-sample rule-out strategy using a very low value or LoD has high sensitivity for myocardial injury and high negative predictive value for ruling out acute MI. It should be used only for those presenting >2 h after onset of chest pain; precision of the assays must allow differentiation of small differences.
- 0/1-h and 0/2-h strategies for rule-in of acute MI will include subjects with diagnoses other than acute MI, and other causes of acute myocardial injury must be considered.
- End-stage renal disease and critically ill patients will likely need altered cutoff values. Renal failure patients may have significant elevated chronic increases in cTn values that do not demonstrate a changing pattern.

‡A single sample strategy for rule-out and 0/1-h and 0/2-h strategies for rule-in of acute MI has not been cleared by the FDA for use with Siemens High-Sensitivity Troponin I assays.

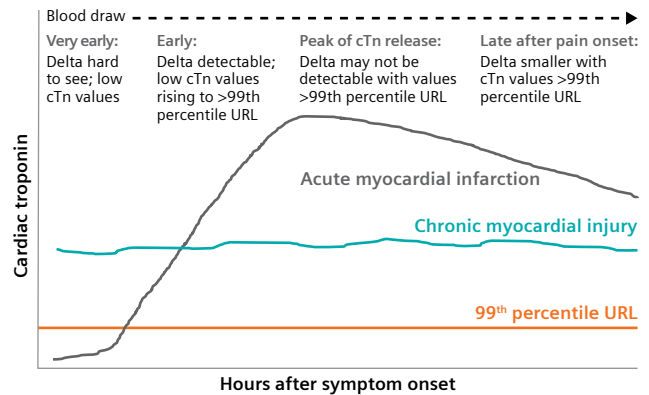


Figure 2. Schematic for time course of cTn release into the circulation after myocardial injury and acute MI. Some myocardial injury conditions are characterized by cTn levels that are chronically elevated and greater than the 99th percentile URL. A changing pattern of cTn values can distinguish those with elevations due to acute MI and those with elevations due to chronic conditions.

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