Cardiology Lab Essentials
Chapter 2

BIOMARKERS IN ACUTE CORONARY SYNDROME

Anna Wonnerth

DEFINING ACUTE CORONARY SYNDROME

Acute coronary syndrome (ACS) is a clinical term used to describe a spectrum of conditions with signs and symptoms of myocardial ischemia or infarction.

Symptoms include

- Chest pain
- Discomfort in the
  - upper left extremity
  - epigastric region
  - jaw
- Dyspnea
- Palpitations
- Fatigue

Sometimes there are no symptoms at all.

Requirements for diagnosing ACS

Clinical symptoms

Troponin testing

12-lead ECG

Based on the results of these tests, ACS can be divided into three distinct entities

- ST-elevation myocardial infarction (STEMI)
- Non-ST-elevation myocardial infarction (NSTEMI)
- Unstable angina

△ Troponin

STEMI / NSTEMI

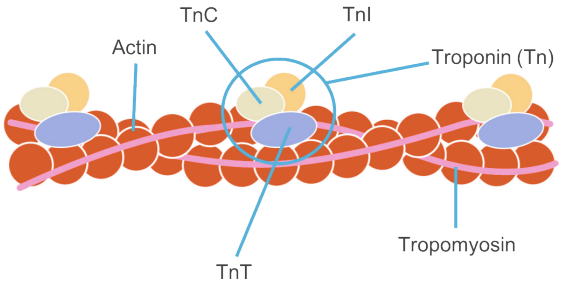
X Troponin

Unstable angina

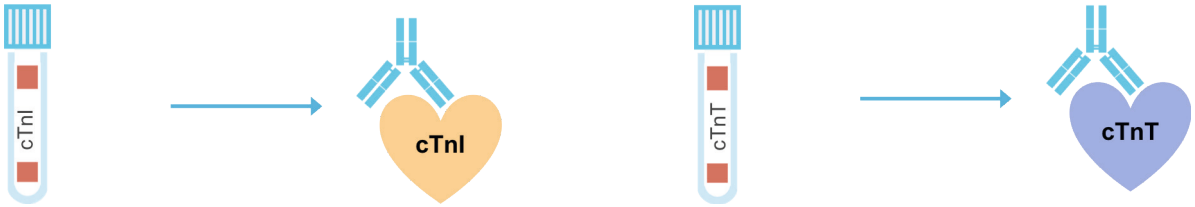
To diagnose myocardial infarction you always need significant changes in troponin levels, plus either symptoms or ECG changes suggestive of an acute myocardial infarction.

INTRODUCING TROPONINS

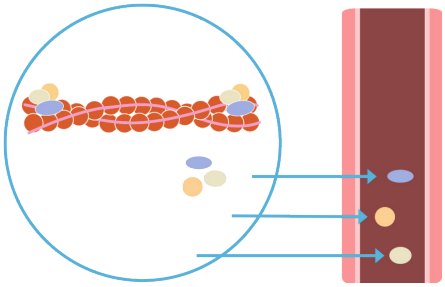
Myofibrils consist of the proteins actin, tropomyosin, and a troponin complex. This troponin complex consists of three subunits: troponin C, troponin I, and troponin T.



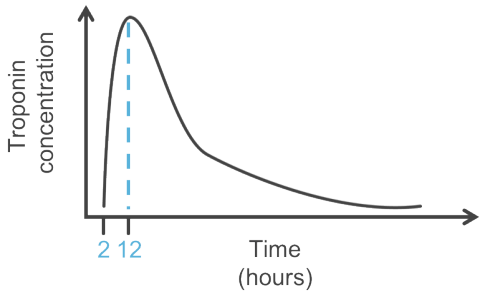
Only troponin I and troponin T have cardiac isoforms that are specific for the heart muscle. Clinical laboratory assays that measure troponin levels use antibodies to catch these cardiac-specific isoforms.



Troponins are localized either in the myofibrils or free in the cytoplasm. When there is ischemia or necrosis, troponins are set free into the circulation. Once they are released into the circulation, we can measure troponins using a simple blood test.

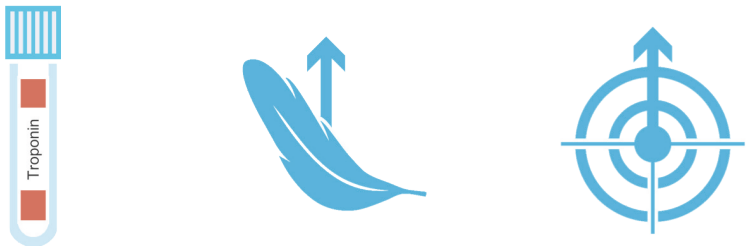


We can first detect a troponin elevation in the blood about two hours after cardiac muscle damage or death. Troponin levels then continue to rise, with a peak at about 12 hours, then gradually decrease over several days.

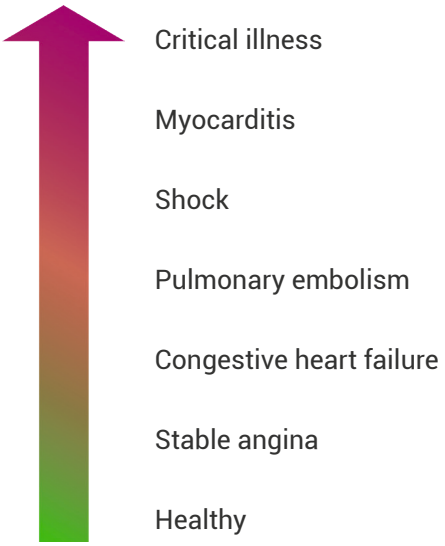


EXPLORING DIFFERENT TROPONIN ASSAYS

Cardiac troponin is the most sensitive and most specific marker in the detection of myocardial infarction.



Troponin assays have evolved over time. With the advent of the high-sensitive assays, we are now able to measure smaller concentrations of troponin than we could with previous generations of assays. As a consequence, troponins are not only detectable in patients with myocardial infarction, but very low levels of troponins can now also be found in patients with concomitant cardiac damage, those with chronic diseases, and even in healthy individuals.



For this reason, making serial measurements is often more important than a single measurement in order to evaluate changes in troponin levels over time.

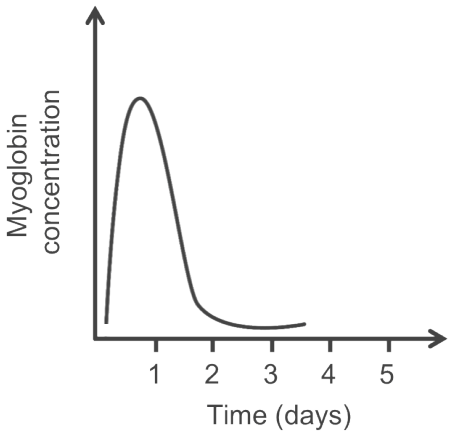
It is important to know that assays from different manufacturers have their own thresholds and specifications. Consequently, lab results from different assays cannot be compared with each other.

Using high-sensitive assays is faster and safer than using older generations.

INTRODUCING OTHER CARDIAC BIOMARKERS

Myoglobin

Myoglobin is an oxygen-binding protein related to hemoglobin. It is found in skeletal and cardiac muscle and is situated in the cytoplasm of myocytes. After muscle injury, myoglobin is released quickly into the bloodstream. However, myoglobin has a very short half-life in plasma, so it also quickly falls under the level of detection.

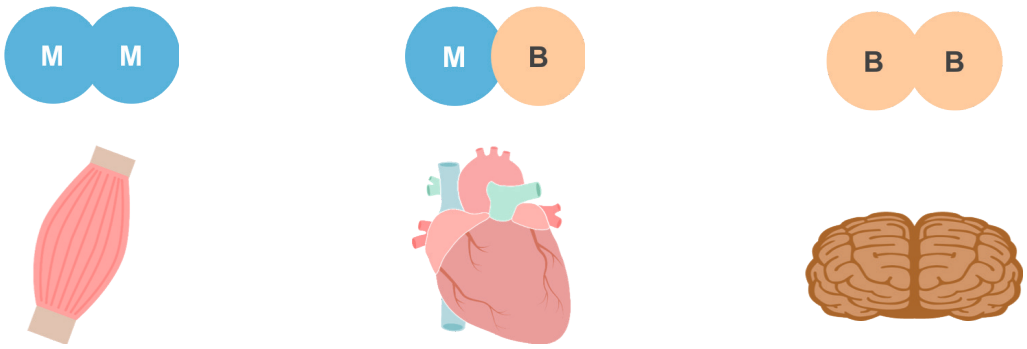


Due to its quick release, myoglobin was once the best marker for early detection of myocardial infarction. However, myoglobin is not cardiac specific, meaning it only indicates damage to muscle tissue, but cannot specifically tell you whether the damage occurred in the heart or in skeletal muscle.

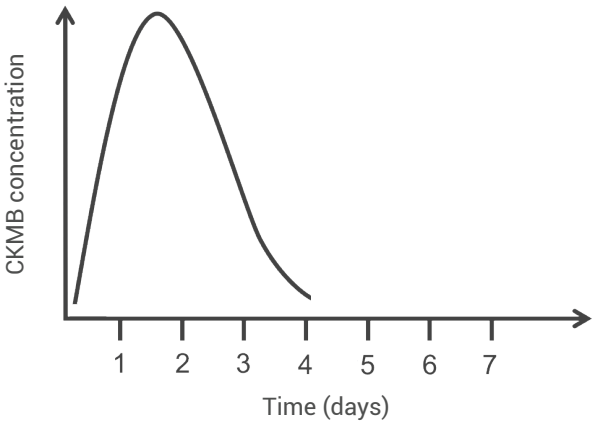
Since contemporary troponin assays can detect cardiac injury as fast as myoglobin, testing for myoglobin is no longer recommended in the setting of ACS diagnostics.

Creatine kinase isoenzyme MB (CKMB)

Creatine kinase (CK) is an enzyme, which has important implications in energy metabolism within cells. CKs are found in the cytosol as well as associated with the mitochondrial membrane. Cytosolic CK exists as a dimer, made up of any combination of the muscle-type (M) and brain-type (B) subunits. The isoform creatine kinase MB (CKMB) is the dominant isoform in cardiac muscle. However, no isoform shows 100% organ specificity, meaning that CKMB is also found in other muscle tissues, but at lower levels than in the heart.



CKMB levels begin to rise about 4–6 hours after myocardial infarction, reaching maximum levels around 24 hours. The levels return to baseline 3–4 days later.



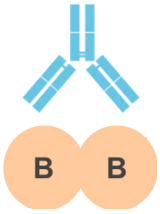
CKMB used to be the gold standard in ACS diagnostics. Nowadays, all major guidelines state that cardiac troponin is the marker of choice and only mention using CKMB in special situations, like detecting myocardial infarction after percutaneous coronary intervention, or possibly to detect a recurrent infarction.

AVOIDING PITFALLS

When you test for creatine kinase MB you need to be aware of two specific pitfalls.

Macroenzyme CK (macro-CK)

Macroenzyme CK are enzymes with an increased molecular mass as compared to normal CK enzymes. There are two types of macro-CK.



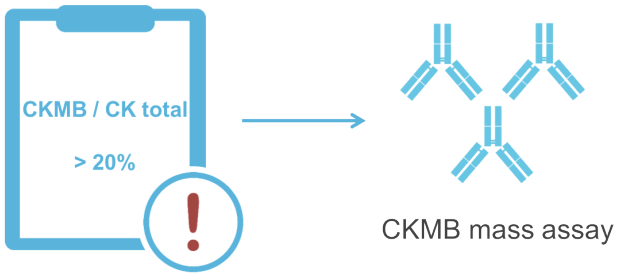
Type 1 macro-CK

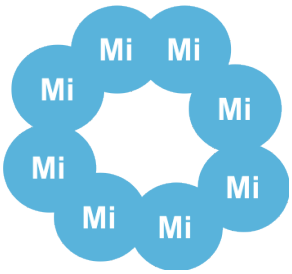
Type 1 macro-CK is a complex of a CK isoenzyme and an immunoglobulin.

Type 1 macro-CK are shown to occur in 1–2% of the screened population and are present more often in women than in men. Type 1 macro-CK complexes are of no clinical significance, **but** they interfere with CKMB activity assays and cause falsely increased results.

You should suspect your CKMB results to be falsely increased because of type 1 macro-CK if your CKMB activity makes up 20% or more of your total creatine kinase activity results.

In these cases, you should order a CKMB mass test or make a CK isoenzyme electrophoresis to rule out interference.





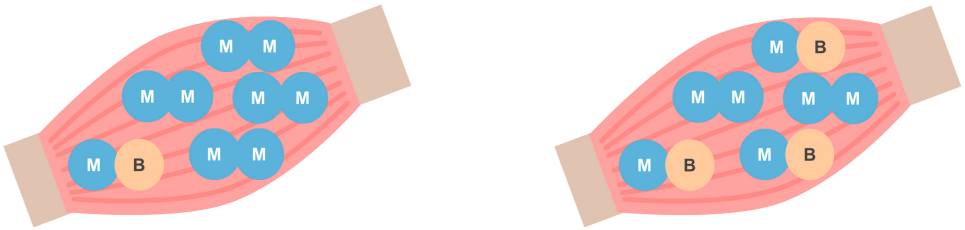
Type 2 macro-CK

Type 2 macro-CK are oligomeric complexes of mitochondrial CK.

Type 2 macro-CK molecules can be found in severely ill patients with malignancies or liver diseases and have been associated with poor prognosis. However, they do not interfere with CKMB testing, so they are of no concern in myocardial infarction diagnostics.

Skeletal muscle disease

Skeletal muscle damage or disease can lead to changes in the distribution of CK isoenzyme within skeletal muscle. In these cases, more B subtypes are expressed than normal, which in turn leads to an increase in CKMB in these individuals. This may explain rare cases of increased CKMB concentrations without the presence of myocardial infarction.



Healthy

Diseased

This has been shown to occur in myopathies, like muscular dystrophies or polymyositis, and can also result from chronic damage to skeletal muscle, as seen, for example, after extreme exercise.

DIAGNOSING NON-ST-ELEVATION MYOCARDIAL INFARCTION (NSTEMI)

Requirements for diagnosing NSTEMI

Clinical presentation and history

ECG testing

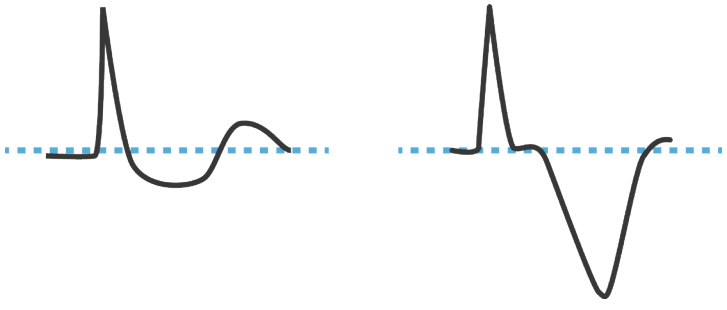
Troponin testing

Symptoms

The leading symptom of NSTEMI is chest pain, also called angina, but some patients might present with atypical symptoms like nausea, dizziness, dyspnea or abdominal pain.

12-lead ECG

The ECG should be performed within the first ten minutes of the patient's admission to hospital or after the patient first reports their symptoms. The most prominent ECG findings in non-ST-elevation myocardial infarction are ST segment depression or a T wave inversion.



ST depression

T wave inversion

Unfortunately, sometimes ECG findings can initially be nondiagnostic. If you continue to suspect ACS, repeat the ECG at 15–30 minute intervals during the first hour, especially if symptoms reoccur.

However, a normal ECG does not exclude the diagnosis of ACS.

Troponin testing

According to the most recent guidelines, cardiac troponin—either troponin I or troponin T—is the single biomarker of choice. Sensitive or high-sensitive troponin assays have a high negative predictive value. So if your patient has troponin levels below the cutoff value, and there is no further suspicion for myocardial infarction, it is reasonable to conclude that there is nothing wrong cardio-wise.

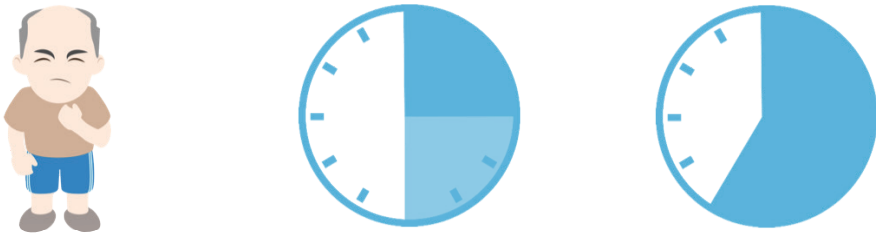
On the other hand, sensitive or high-sensitive troponin assays have a rather poor positive predictive value. The positive predictive value of troponin testing can be increased by looking at the delta change in troponin levels of serial measurements. How large this delta change must be in order to indicate pathology depends on the assay you use. This information should be provided by your local lab.

USING DIAGNOSTIC ALGORITHMS

Timing of troponin testing

Troponin levels should be tested at presentation. If the troponin levels are not above the critical threshold, troponin should be retested again 3–6 hours after symptom onset. If troponin levels are still not above the critical threshold, and the delta change is insignificant, but the suspicion for ACS remains, then additional testing beyond six hours after symptom onset is indicated.

If the time of symptom onset is unclear, the time of presentation should be considered the time of onset.



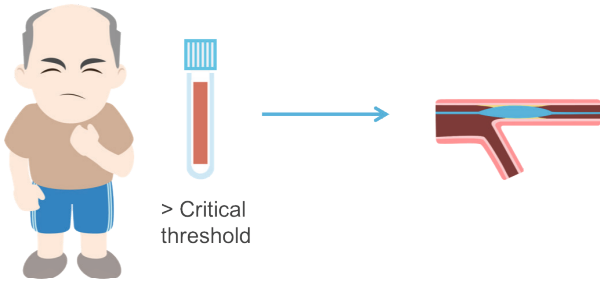
Presentation

3–6 hours
after symptom onset

> 6 hours

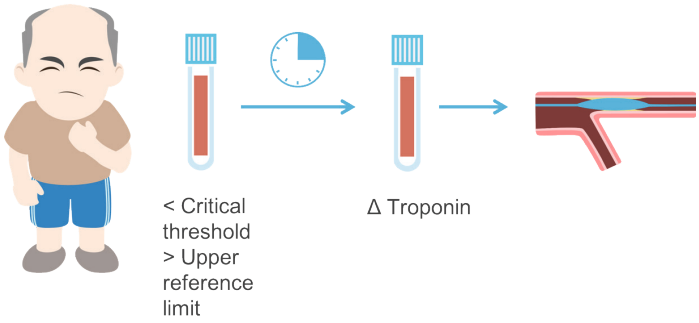
Interpretation of troponin results

If the clinical presentation is consistent with myocardial infarction, and the baseline troponin test shows levels beyond a certain critical threshold, invasive management should be organized immediately, and another retest is not necessary.

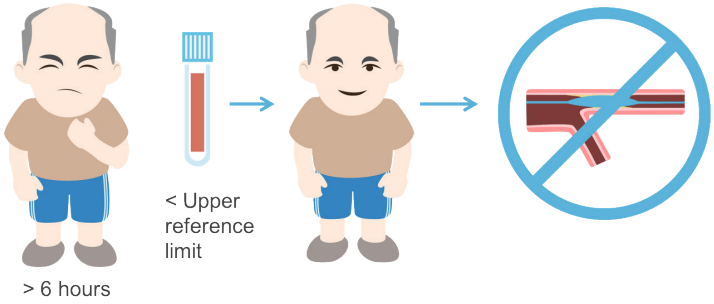


> Critical
threshold

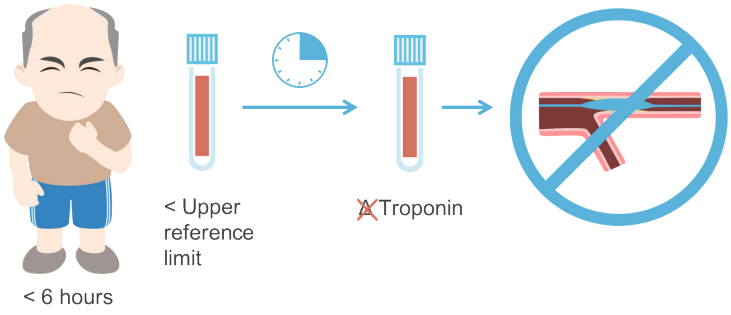
If the baseline troponin concentration is not above the critical threshold but is above the upper reference level, and the retest, three hours from the first blood test, shows a significant change compared to the first result, invasive management is recommended. The critical threshold and the value indicating a significant change in troponin are assay specific and should be provided by the laboratory.



If the patient began experiencing pain more than six hours ago and the troponin levels at presentation are below the upper reference limit, a retest is not needed. If the ischemic risk assessment shows negative results, your patient is pain-free, and differentials were excluded, you can consider noninvasive testing or even discharge.



If the pain started less than six hours ago and troponin levels at presentation are below the upper reference limit, it still may be too early to detect a rise in troponin levels. Thus, retesting three hours later is indicated. If there is no significant change, nonurgent evaluation can be supported as long as the patient is pain-free, differentials were excluded, and risk assessment shows favorable results.



If the patient still experiences symptoms, has an abnormal ECG or abnormal risk assessment results, invasive strategies should be reconsidered.

One-hour algorithm

For some high-sensitive assays, it is recommended that you retest troponin levels after one hour, instead of three hours.

(Reference: *Roffi et al., 2016*)

Ischemic risk assessment

Risk assessment tools help to provide information on outcome prognosis and are superior to clinical assessment alone. They are based on a specific combination of variables.

Common examples of these assessments are the GRACE Risk Score 2.0 or the TIMI score.

To calculate the GRACE Risk Score 2.0, the following variables are used

- Age
- Heart rate
- Systolic blood pressure value
- Creatinine concentration or history of renal dysfunction
- Killip class or use of diuretics
- ECG ST segment deviation at presentation
- Elevation of biomarkers of cardiac necrosis
- Cardiac arrest at admission

To calculate the TIMI score, the following variables are used

- Age
- Hypertension
- Hypercholesterolemia
- Diabetes
- Family history of coronary artery disease
- Smoking status
- Known coronary artery disease with a stenosis ≥ 50%
- Use of acetylsalicylic acid (ASA) in the past seven days
- Number of episodes of angina in prior 24 hours
- ECG ST segment deviation at presentation
- Elevation of biomarkers of cardiac necrosis

There are online calculators and mobile apps to help you calculate and interpret your patient's risk.

DIAGNOSING PERIPROCEDURAL MYOCARDIAL INFARCTION

Periprocedural myocardial infarction (pMI, which occurs during or after percutaneous coronary intervention (PCI), can be difficult to diagnose based on cardiac biomarkers. You can find two opposing recommendations on which biomarker to use in this situation.

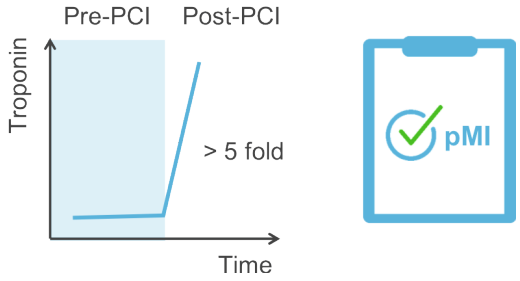
Recommendation 1—cardiac troponin

In 2018, a joint task force of global cardiology societies published a consensus on the definition of myocardial infarction, in which periprocedural myocardial infarction was discussed.
(Reference: *Thygesen et al., 2018*)

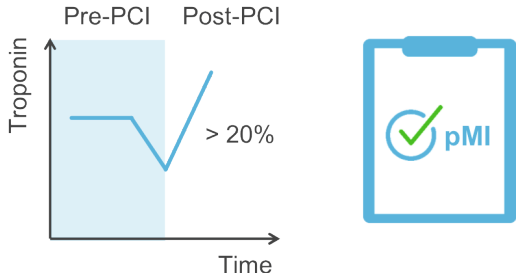
This consensus recommends the use of cardiac troponins to diagnose pMI.

Interpretation of troponin results

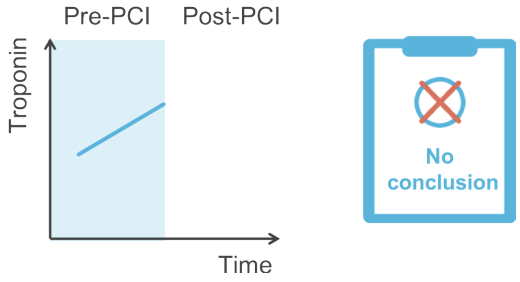
If the preprocedural value is normal, a 5-fold elevation of the upper reference limit is suggestive of pMI, if in addition there are other factors suggesting myocardial infarction, like clinical symptoms, associated ECG findings or imaging evidence of a new loss of myocardial tissue.



If the baseline troponin levels are elevated, but stable or falling, then a troponin rise of 20% or more is needed to diagnose pMI.



If the baseline troponin levels are elevated and rising before the PCI, no conclusion can be drawn.



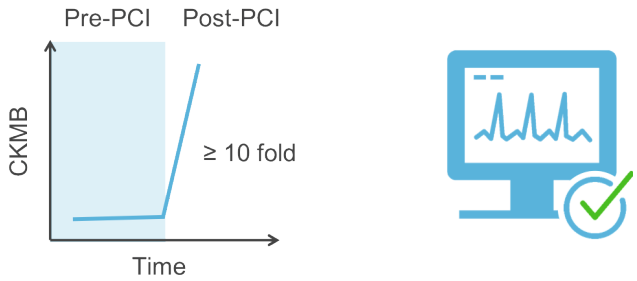
Recommendation 2—creatine kinase MB

In 2013 the Society for Cardiovascular Angiography and Interventions (SCAI published their consensus on the topic of periprocedural myocardial infarction.
(Reference: *Moussa et al., 2013*)

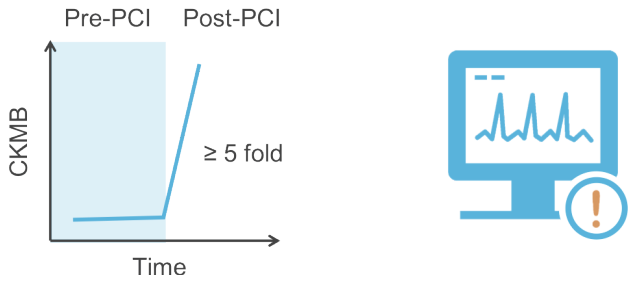
The SCAI recommends the use of CKMB to diagnose pMI.

Interpretation of CKMB results

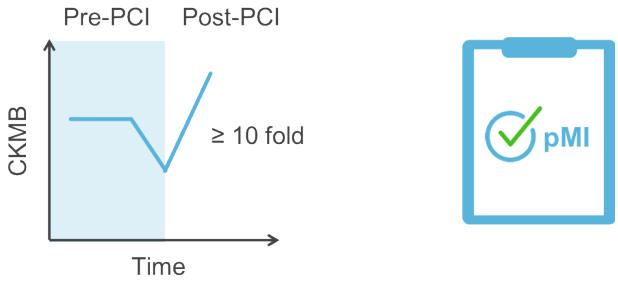
If the baseline CKMB value is normal, a new 10-fold increase in CKMB is needed to diagnose pMI when no ECG changes are present.



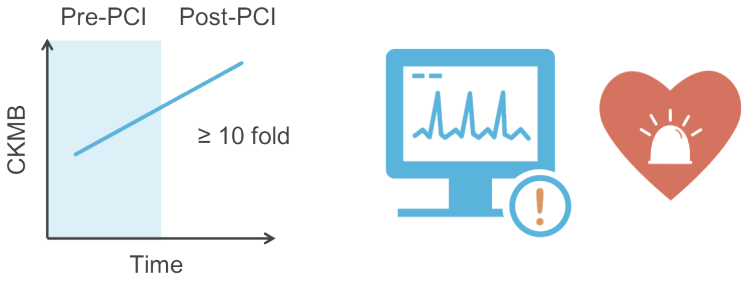
If the baseline CKMB value is normal and new ECG changes are present, then a 5-fold increase in CKMB is sufficient to diagnose pMI.



If the baseline value is elevated but stable or falling, a 10-fold increase in CKMB is necessary to diagnose pMI.



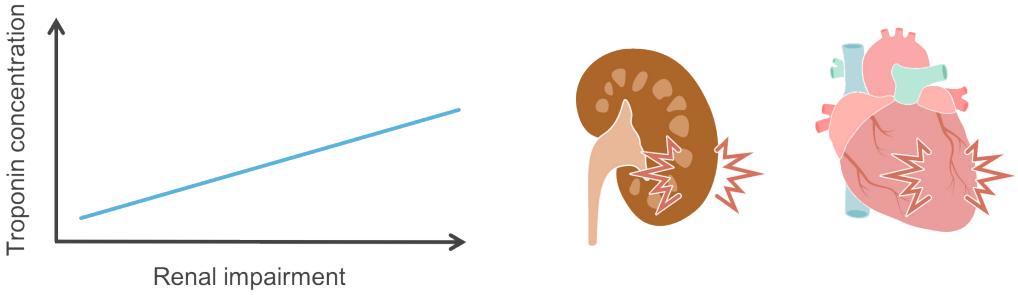
If the baseline value is elevated but rising, a 10-fold increase in CKMB, plus new ECG changes, and significant signs of myocardial infarction (such as worsening of heart failure or sustained hypotension) must be present in order to diagnose pMI. Chest pain is not enough in this scenario.



The SCAI also states cutoff levels for cardiac troponin that roughly correspond to these CKMB levels.

INTERPRETING TROPONIN IN CHRONIC KIDNEY DISEASE

Even in the absence of any clinical evidence of myocardial damage, troponin elevations are common in patients with chronic kidney disease (CKD), especially as renal impairment progresses. These elevations are not caused solely by the impaired renal function and decreased renal clearance, but chronic myocardial injury or structural heart disease also contribute.

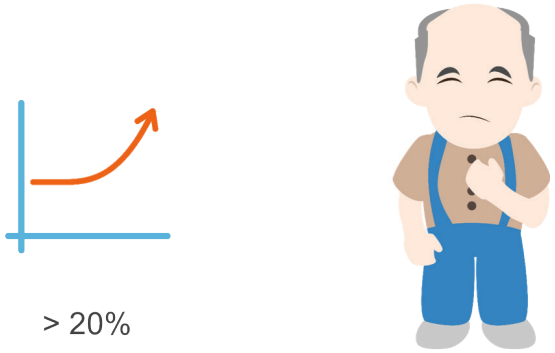


Stably elevated troponin concentrations have been shown to be associated with a poor long-term survival in CKD patients.

Diagnosing acute myocardial infarction in CKD patients

Similar to individuals with no renal impairment, troponin is the preferred marker to diagnose acute myocardial infarction in patients with CKD. The changes in troponin level should be assessed using serial troponin measurements.

In patients with chronically elevated troponin levels, > 20% increase in serially measured troponin is generally accepted as the threshold for indicating an acute myocardial infarction.



READING LIST

Amsterdam, EA, Wenger, NK, Brindis, RG, et al. 2014. 2014 AHA/ACC guidelines 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. *J Am Coll Cardiol.* **64:** e139–e228. https://www.ncbi.nlm.nih.gov/pubmed/25260718

Antman, EM, Cohen, M, Bernink, PJ, et al. 2000. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. **284:** 835–842. https://www.ncbi.nlm.nih.gov/pubmed/10938172

Fox, KAA, FitzGerald, G, Puymirat, E, et al. 2014. Should patients with acute coronary syndrome be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open.* **4:** e004425.

Garg, P, Morris, P, Fazlanie, AL, et al. 2017. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. *Intern Emerg Med.* **12:** 147–155. https://www.ncbi.nlm.nih.gov/pubmed/28188579

Huang, W, FitzGerlad, G, Goldberg, RJ, et al. 2016. Performance of the GRACE risk score 2.0 simplified algorithm for predicting 1-year death following hospitalization for an acute coronary syndrome in a contemporary multiracial cohort. *Am J Cardiol.* **118:** 1105–1110. https://www.ncbi.nlm.nih.gov/pubmed/27561191

Jaffe, AS, Babuin, AL, Apple, FS. 2006. Biomarkers in acute cardiac disease: the present and the future. *J Am Coll Cardiol.* **48:** 1–11. https://www.ncbi.nlm.nih.gov/pubmed/16814641

Klinkenberg, LJJ. 2016. High-sensitivity cardiac troponins in health and disease. *Ned Tijdschr Klin Chem Labgeneesk.* **41:** 235–241.

McLaurin, MD, Apple, FS, Falahati, A, et al. 1998. Cardiac troponin I and creatine kinase-MB mass to rule out myocardial injury in hospitalized patients with renal insufficiency. *Am J Cardiol.* **82:** 973–975. https://www.ncbi.nlm.nih.gov/pubmed/9794355

Moussa, ID, Klein, LW, Shah, B, et al. 2013. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol.* **62:** 1563–1570. https://www.ncbi.nlm.nih.gov/pubmed/24135581

Newby, LK, Jesse, RL, Babb, JD, et al. 2012. ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation task force on Clinical Expert Consensus Documents. *J Am Coll Cardiol.* **60:** 2427–2463. https://www.ncbi.nlm.nih.gov/pubmed/23154053

Rifai, N, et al. 2018. *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics*. 6th edition. Amsterdam: Elsevier.

Roffi, M, Patrono, C, Collet, JP, et al. 2016. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* **37:** 267–315. https://www.ncbi.nlm.nih.gov/pubmed/26320110

Thygesen, K, Alpert, JS, Jaffe, AS, et al. 2018. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol.* **pii:** S0735–1097. https://www.ncbi.nlm.nih.gov/pubmed/30153967

Tricoci, P. 2017. Consensus or controversy?: evolution of criteria for myocardial infarction after percutaneous coronary intervention. *Clin Chem.* **63:** 82–90. https://www.ncbi.nlm.nih.gov/pubmed/28062613