ACUTE CORONARY SYNDROMES

Clinical Utility of Cardiac Troponin
Coronary heart disease (CHD) remains one of the major causes of death worldwide. Presentation with CHD, typically as chest pain, is one of the more common conditions seen in the Emergency Department (ED).

- Although chest pain is a common complaint, patients who have myocardial infarction (MI) are a relatively small percentage of all those who present with chest pain. Early recognition of those without MI is therefore as important as early identification of those who have MI.
- New developments in measurement methods mean that cardiac troponin (cTn) can be measured reliably and repeatedly at much lower levels than was previously possible. These methods are called high-sensitivity cardiac troponin (hs-cTn) assays.
- The use of hs-cTn measurement means it is possible to exclude myocardial infarction by measurement on admission to hospital and as little as 1-2 hours later.
- Rapid diagnostic pathways mean that both long waits in the ED while test results are awaited can be avoided and unnecessary hospital stays shortened.

This booklet provides clinicians and laboratory managers with concise, up-to-date information on the pathophysiology and diagnosis of myocardial infarction with special emphasis on the role of hs-cTn measurements for risk stratification and management of patients. Aspects of the laboratory and clinical factors affecting the routine measurement of cTn using hs-cTn assays are also discussed.
High mortality and morbidity

Globally, the total number of deaths due to ischemic heart disease (IHD) has risen steadily to reach 9.14 million in 2019. This makes IHD the leading cause of death in the world. Over the same time period the global age-standardized IHD death rate declined, indicating that, on average, global increase in IHD deaths has been due to population growth and aging.

In 2019, there were an estimated 197 million prevalent cases of IHD worldwide. In the 54 member countries of the European Society of Cardiology (ESC) alone there were 34.9 million people living with IHD in 2017. The societal impact of IHD is huge and the global burden of IHD, in terms of disability-adjusted life years (DALY’s), has increased since 1990 with IHD the leading cause of DALY’s in people 50 years and older. The DALY, a measure of the burden of a disease in populations, combines life expectancy (years of life lost) with adjusted quality of life (years lived with the disease).

Chest pain and acute coronary syndromes

Chest pain is the chief complaint in patients with cardiac ischemia.

Chest pain is among the top-10 reasons to visit an emergency department (ED), accounting for about 5% of all ED visits.

Among patients presenting with acute chest pain to the ED, disease prevalence can be expected as follows:

- Acute coronary syndromes (ACS) in 35%
  - ST-segment elevation myocardial infarction (STEMI) in 5-10%
  - Non-ST-segment elevation myocardial infarction (NSTEMI) in 15-20%.
  - Unstable angina (UA) in 10%
- Other cardiac conditions in 15%
- Non-cardiac diseases in 50%

Acute myocardial infarction (AMI: STEMI plus NSTEMI)* accounts for about 2/3 of AMI and UA for about 1/3 of ACS. There is a global trend of a decreasing incidence in STEMI with a concomitant increase in NSTEMI. STEMI is relatively more common in younger than in older people, and is more common in men than in women.

* The Universal Definition of Myocardial Infarction (currently in its 4th update) combines the ECG, clinical features and cardiac troponin (cTn) values above the 99th percentile upper reference limit (URL) with cTn changes (cTn kinetics, delta values) as an integral part of the definition. The shift to cTn testing has had an impact on the epidemiology of AMI by reclassifying patients previously diagnosed as unstable angina to NSTEMI.
**1 Definition, classification and pathophysiology**

The term **acute coronary syndromes** (ACS) refers to a constellation of clinical signs and symptoms due to acute **myocardial ischemia** that results from inadequate delivery of oxygen to the heart muscle. In myocardial ischemia there is an imbalance between myocardial oxygen supply and/or demand. This usually occurs due to reduced blood flow because of partial or complete blockage of the coronary arteries.

ACS may range from a potentially reversible phase (**unstable angina, UA**) to irreversible cell death (**myocardial infarction, MI**). The diagnosis of ACS requires the integration of clinical signs and symptoms, ECG and serial cardiac troponin (cTn) measurements (Figure 1).

- The ECG identifies approximately one quarter of ACS patients who present with persistent (>20 min) ST-segment elevation. These patients are diagnosed with **STEMI** and require immediate reperfusion.6
- The other three quarters of ACS patients are without persistent ST-segment elevations (NSTE-ACS; non-ST-elevation ACS). In these patients measurement of cTn is required to distinguish **NSTEMI** from UA (where there is myocardial ischemia in the absence of myocardial necrosis).8

The distinction between STEMI, NSTEMI and UA is clinically important and drives the decision for timing, type and intensity of therapeutic intervention.6,8

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**Figure 1. Diagnostic algorithm and triage in ACS.**8


<table>
<thead>
<tr>
<th>Level</th>
<th>Rule-out MI</th>
<th>Observe</th>
<th>Rule-in MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIGH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **STEMI**: STEMI
- **NSTEMI**: NSTEMI
- **UA**: UA
- **Noncardiac**: Noncardiac
- **Other cardiac**: Other cardiac
- **Unstable angina**: Unstable angina
- **NSTEMI**: NSTEMI
- **STEMI**: STEMI

*Noncardiac: thoracic diseases such as pneumonia or pneumothorax.
**Other cardiac: including amongst others, myocarditis, Takotsubo syndrome, congestive heart failure.
**Myocardial infarction and myocardial injury**

The 4th Universal Definition of Myocardial Infarction introduces a differentiation of myocardial infarction from myocardial injury. The term *myocardial injury* should be used when there is evidence of elevated cTn values with at least one value above the 99th percentile URL. Myocardial injury is considered acute if there is a rise and/or fall of cTn values. Myocardial injury, often acute, occurs in a wide range of conditions and is three times more common in the ED than a cTn elevation due to myocardial infarction (see below).

The term *acute myocardial infarction* (types 1, 2 and 3 MI) should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischemia.
- New ischemic ECG changes.
- Development of pathological Q waves.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

Depending on the underlying pathophysiological mechanism, 5 types of MI are distinguished including acute MI (types 1, 2 and 3 MI) and procedure-related MI (types 4 and 5 MI) (Table 1).

### Clinical criteria for MI

The clinical definition of MI denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia.

### Table 1. Etiological classification of myocardial infarction.

<table>
<thead>
<tr>
<th>Type 1 MI</th>
<th>MI caused by atherothrombotic coronary artery disease (CAD) and usually precipitated by atherosclerotic plaque disruption (rupture or erosion).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 MI</td>
<td>MI due to ischemic myocardial injury and evidence of an imbalance between myocardial oxygen supply and/or demand unrelated to coronary thrombosis</td>
</tr>
<tr>
<td>Type 3 MI</td>
<td>MI resulting in sudden cardiac death with symptoms suggestive of myocardial ischemia but without definitive cardiac biomarker evidence of MI (patients die before blood samples for cTn testing can be obtained or before increases in cTn can be identified).</td>
</tr>
<tr>
<td>Type 4 MI</td>
<td>MI associated with percutaneous coronary intervention (PCI; type 4a), stent thrombosis (type 4b) or restenosis (type 4c).</td>
</tr>
<tr>
<td>Type 5 MI</td>
<td>MI related to coronary artery bypass grafting (CABG).</td>
</tr>
</tbody>
</table>

The majority of MI patients present with type 1 MI, but type 2 MI is also a common subtype that may account for up to a third of all MI cases. Patients with type 2 MI are more frequently female and are older with more comorbidities; consequently they have an almost 2-fold poorer long-term survival than type 1 MI, with excess deaths due to non-cardiovascular causes.

The distinction between type 1 and type 2 MI and acute myocardial injury is clinically important because treatment is different.

Type 1 MI is caused by plaque rupture or erosion with atherothrombosis (Figure 2) and is treated by revascularization procedures and antithrombotic therapy. Plaque rupture is the most common cause both in STEMI and NSTEMI, but plaque erosion is more frequent in NSTEMI patients.

- **Plaque rupture** is the most common mechanism; it is associated with rupture of the thin fibrous cap of lipid-rich atherosclerotic plaques and exposure of the necrotic core to the vessel lumen leading to thrombus formation.
- **Plaque erosion** involves thrombus formation in an area of endothelial denudation adjacent to an atherosclerotic plaque without disruption of the fibrous cap.
Type 2 MI is the result of a mismatch between myocardial oxygen supply and demand in the absence of atherothrombosis (Figure 3) and consequently its treatment is based on the diagnosis of the underlying disorder. Underlying causes of type 2 MI are listed in Table 2.

MINOCA

It is increasingly recognized that there is a group of MI patients with no angiographic obstructive CAD, and the term myocardial infarction with non-obstructive coronary arteries (MINOCA) has been coined for this entity. Like the diagnosis of MI, the diagnosis of MINOCA indicates that there is an ischemic mechanism responsible for myocyte injury. Among patients diagnosed with MI, the prevalence of MINOCA is estimated to be 6-8%; more common in women and in patients presenting with NSTEMI.

Acute myocardial injury

The current update of the Universal Definition of Myocardial Infarction recognizes that myocardial injury may occur due to other pathologies than ischemic heart disease. Acute myocardial injury is suspected when there is a cTn elevation without symptoms of myocardial ischemia, or obvious CAD, or another clinical cardiologic diagnosis. It usually accompanies acute illness and requires treatment of the underlying medical condition. When it occurs, however, it indicates an adverse prognosis. It has been found that in the ED population, cTn elevation may be more common due to myocardial injury than myocardial infarction. Conditions associated with non-ischemic myocardial injury are listed in Table 2.

Table 2. Causes of myocardial injury with elevation of cTn.

<table>
<thead>
<tr>
<th>Causes of myocardial injury with elevation of cTn</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Myocardial injury related to acute myocardial ischemia</strong></td>
</tr>
<tr>
<td>Atherosclerotic plaque disruption with thrombosis (type 1 MI)</td>
</tr>
<tr>
<td>Oxygen supply/demand imbalance (type 2 MI)</td>
</tr>
<tr>
<td><strong>Reduced myocardial perfusion, e.g.</strong></td>
</tr>
<tr>
<td>- Coronary artery spasm, microvascular dysfunction</td>
</tr>
<tr>
<td>- Coronary embolism</td>
</tr>
<tr>
<td>- Coronary artery dissection</td>
</tr>
<tr>
<td>- Sustained bradyarrhythmia</td>
</tr>
<tr>
<td>- Hypotension or shock</td>
</tr>
<tr>
<td>- Respiratory failure</td>
</tr>
<tr>
<td>- Severe anemia</td>
</tr>
<tr>
<td><strong>Increased myocardial oxygen demand, e.g.</strong></td>
</tr>
<tr>
<td>- Sustained tachyarrhythmia</td>
</tr>
<tr>
<td>- Severe hypertension with or without left ventricular hypertrophy</td>
</tr>
<tr>
<td><strong>B. Other (non-ischemic) causes of myocardial injury</strong></td>
</tr>
<tr>
<td><strong>Cardiac conditions, e.g.</strong></td>
</tr>
<tr>
<td>- Heart failure</td>
</tr>
<tr>
<td>- Myocarditis</td>
</tr>
<tr>
<td>- Cardiomyopathy (any type)</td>
</tr>
<tr>
<td>- Takotsubo syndrome</td>
</tr>
<tr>
<td>- Coronary revascularization procedure</td>
</tr>
<tr>
<td>- Cardiac procedure other than revascularization</td>
</tr>
<tr>
<td>- Catheter ablation</td>
</tr>
<tr>
<td>- Defibrillator shocks</td>
</tr>
<tr>
<td>- Cardiac contusion</td>
</tr>
<tr>
<td><strong>Systemic conditions, e.g.</strong></td>
</tr>
<tr>
<td>- Sepsis, infectious disease (including COVID-19)</td>
</tr>
<tr>
<td>- Chronic kidney disease</td>
</tr>
<tr>
<td>- Stroke, subarachnoid hemorrhage</td>
</tr>
<tr>
<td>- Pulmonary embolism, pulmonary hypertension</td>
</tr>
<tr>
<td>- Infiltrative diseases, e.g. amyloidosis, sarcoidosis</td>
</tr>
<tr>
<td>- Chemotherapeutic agents</td>
</tr>
<tr>
<td>- Critically ill patients</td>
</tr>
<tr>
<td>- Strenuous exercise</td>
</tr>
</tbody>
</table>
Diagnosis

The diagnosis of ACS (Figure 1) is based on the integration of:
- Clinical presentation (history, symptoms, signs, location and severity of pain)
- 12-lead ECG
- cTn measurement

Clinical presentation

Demographic and clinical features such as older age, male gender, family history of CAD, diabetes, hyperlipidemia, hypertension, renal insufficiency, previous manifestation of CAD as well as peripheral or carotid artery disease increase the likelihood of ACS.\(^5,8\) Conditions that may exacerbate or precipitate ACS include anemia, infection, inflammation, fever, and metabolic or endocrine (thyroid) disorders.\(^8\)

The typical **chief complaint** in ACS is angina (Table 3), defined as central chest pain or discomfort that occurs due to inadequate delivery of oxygen to the heart muscle. It has been likened to having a heavy weight pressing down inside the chest.

The pain may radiate to the neck, jaw or arm (usually the left). Typical stable angina (often called effort angina or angina pectoralis) is provoked by exertion or emotional stress and is relieved by rest or sublingual nitrates. This does not occur with unstable angina or myocardial infarction.

Often, the discomfort is diffuse (not localized, not positional) and may be accompanied by sweating, shortness of breath (dyspnea), nausea or fainting (syncope) (Table 3). Chest pain is not specific for ACS and may also occur in many other cardiac and non-cardiac conditions (Table 4). Like ACS, some of these conditions are also life-threatening, such as acute aortic dissection (AAD) and pulmonary embolism (PE).

Unfortunately, in patients with suspected ACS, elements of chest pain history alone are highly unlikely to confirm or exclude the diagnosis of ACS due to their limited sensitivity and specificity.\(^13,14\)

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**Table 3. Clinical presentation in suspected ACS.**\(^8\)

<table>
<thead>
<tr>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chest pain: retro-sternal pressure or heaviness (‘angina’) radiating to left arm, neck or jaw, which may be intermittent or persistent.</td>
<td>• Epigastric pain, recent onset indigestion, stabbing chest pain, chest pain with pleuritic features or increasing dyspnea.</td>
</tr>
<tr>
<td>• May be accompanied by sweating, nausea, abdominal pain, dyspnea or syncope.</td>
<td>• Often observed in younger (25-40 years) and older (&gt;75 years) patients, in women, and in patients with diabetes, chronic renal failure or dementia.</td>
</tr>
</tbody>
</table>

**Table 4. Differential diagnosis: causes of chest pain other than ACS.**\(^8\)

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Gastro-intestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopericarditis</td>
<td>Esophagitis, reflux or spasm</td>
</tr>
<tr>
<td>Cardiomyopathies</td>
<td>Peptic ulcer, gastritis</td>
</tr>
<tr>
<td>Tachyarrhythmias</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>Cholecystitis</td>
</tr>
<tr>
<td>Hypertensive emergencies</td>
<td></td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td></td>
</tr>
<tr>
<td>Takotsubo syndrome</td>
<td></td>
</tr>
<tr>
<td>Coronary spasm</td>
<td></td>
</tr>
<tr>
<td>Cardiac trauma</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary</th>
<th>Orthopedic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism (Tension)-Pneumothorax</td>
<td>Musculoskeletal disorders</td>
</tr>
<tr>
<td>Bronchitis, pneumonia</td>
<td>Chest trauma</td>
</tr>
<tr>
<td>Pleuritis</td>
<td>Muscle injury/inflammation</td>
</tr>
<tr>
<td></td>
<td>Costochondritis</td>
</tr>
<tr>
<td></td>
<td>Cervical spine pathologies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic dissection</td>
<td>Anxiety disorders</td>
</tr>
<tr>
<td>Symptomatic aortic aneurysm</td>
<td>Herpes zoster</td>
</tr>
<tr>
<td>Stroke</td>
<td>Anemia</td>
</tr>
</tbody>
</table>

**Bold:** common and/or important differential diagnoses.
ECG

The 12-lead ECG is the first-line diagnostic tool in the assessment of patients with suspected ACS (Figure 1). It should be recorded within 10 min of the patient’s arrival in the ED or at first prehospital medical contact. The ECG may be normal in more than one-third of suspected ACS patients. Characteristic ECG manifestations of acute myocardial ischemia include ST-depression, ST-elevation and T-wave changes.

The ECG may also provide information on the anatomic location, extent and severity of the coronary lesion as well as the presence of complications of acute MI with a poor prognosis (e.g. arrhythmias and conduction abnormalities).

The ECG diagnosis of AMI can be complicated in the presence of left bundle branch block (LBBB) or ventricular pacing. It is also important to be aware of conditions that mimic myocardial ischemia or MI on ECG. Examples of such false-positive ECG abnormalities include cardiomyopathy, cardiac amyloidosis, LBBB, ventricular hypertrophy, myocarditis, or hyperkalemia.

If the standard leads are inconclusive and the patient has signs or symptoms suggestive of ongoing myocardial ischemia, additional leads should be recorded.

Cardiac troponin

Cardiac troponin (I or T) is the preferred biomarker of cardiac necrosis. It needs to be integrated with clinical assessment and ECG in the diagnosis of patients with suspected ACS (Figure 1). See next chapter for further details on its use in diagnostic algorithms.

Figure 4. ECG tracings in ACS.

Adapted from www.thrombosisadviser.com/acute-coronary-syndrome

Persistent ST-segment elevation is the hallmark finding in STEMI. ST-depression and T-wave inversion are notable signs of cardiac ischemia in NSTEMI.
1 Biochemistry and pathophysiology

The troponin complex consists of 3 subunits (I, T and C) and is essential for the regulation of skeletal and cardiac muscle contraction. In contrast to troponin C, cardiac-specific isoforms of troponin T and I exist. The release of cTnI and cTnT from cardiomyocytes is highly specific for myocardial injury (Figure 5). However, any type of injury, not just ischemic injury, can result in the release of cTn into the blood circulation. Consequently, cTn can also be elevated in other conditions than MI (Table 2).

The troponin complex is the regulatory complex of the myofibrillar thin filament (consisting of actin and tropomyosin) that plays a critical role in regulating Ca2+-mediated excitation-contraction coupling in the heart. There is one troponin complex bound to every seventh actin monomer. The troponin complex consists of 3 subunits: troponin C (TnC, 18 kDa), the Ca2+-binding subunit; troponin I (TnI, 23 kDa), the inhibitory subunit that prevents contraction in the absence of Ca2+-binding to TnC; and troponin T (TnT, 35 kDa), the subunit that attaches troponin to tropomyosin and to the myofibrillar thin filament. The cytosol of the cardiac myocyte contains free unbound troponins which are released into the circulation upon damage. After AMI, cTnI is present in serum as ternary T-I-C and binary I-C complexes, whereas cTnT is present as a combination of T-I-C and free cTnT.

2 Assays

Specific antibodies have been raised against the cardiac-specific cTn isoforms, the basis of widely available quantitative cTnI and cTnT assays. Advances in technology have led to an improvement of the ability of cTn assays to detect and quantify cardiomyocyte injury. Because of their increased analytical power, allowing accurate measurement below the 99th percentile URL as well as accurate measurement of small absolute changes, high-sensitivity cTn (hs-cTn) assays enable earlier detection of AMI with shortening of the time window for serial testing (Figure 6).

The classical viewpoint is that cTn release from cardiomyocytes is caused by irreversible injury resulting in cardiac necrosis. However, the release of cTn does not always require myocardial cell death and there are clinical scenarios with cTn increase despite a low clinical likelihood of myocardial necrosis. Examples include extraordinary endurance exercise (e.g. marathon), after reversible ischemia in an exercise or dobutamine stress test, after rapid atrial pacing, in severe chronic stable heart failure and in severe chronic stable artery disease.


3 Role of cardiac troponin in diagnosis of ACS

**Interpretation and serial measurements**

Troponin levels together with kinetic changes need to be integrated with clinical assessment and the ECG in the diagnosis of patients with suspected ACS (Figure 1). In its interpretation, cTn should be considered as a quantitative marker of cardiac injury with the likelihood of AMI increasing with the level of cTn (Figure 7).22

![Figure 7. cTn as a quantitative marker of cardiac injury.](image)

**Table 5. Algorithms for rule-out and rule-in of AMI for hs-cTn assays.**23, 24

<table>
<thead>
<tr>
<th>Prediction of AMI</th>
<th>hsTN concentration</th>
<th>Likelihood of AMI (differential diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rule-in</td>
<td>Very high</td>
<td>Very large AMI myocarditis</td>
</tr>
<tr>
<td>PPV &gt;95%</td>
<td>...</td>
<td>Large AMI myocarditis, Takotsubo, PE, critical illness</td>
</tr>
<tr>
<td>PPV 80%</td>
<td>High</td>
<td>Small AMI early large AMI, myocarditis, Takotsubo, PE, shock, heart failure, S aureus bacteremia (SAB),...</td>
</tr>
<tr>
<td>PPV 50% NPV 95%</td>
<td>...</td>
<td>Micro AMI early large AMI, myocarditis, Takotsubo, PE, shock, heart failure, hypertensive crisis, SAB, stable CAD,...</td>
</tr>
</tbody>
</table>

**99th percentile URL**

| Rule-out | NPV 98% | ... | Stable angina, heart failure, LVH, subclinical heart disease, ... |
| NPV 99%  | Very low| Healthy individuals |

The lower the level of cTn, the lower the likelihood and the higher the negative predictive value (NPV) for the presence of AMI. In contrast, the higher the level, the higher the likelihood and the higher the positive predictive value (PPV) for the presence of AMI. Elevations above 5-fold the URL have a high (>90%) positive predictive value (PPV) for AMI. Elevations up to 3-fold the URL have only limited PPV (50-60%) for acute MI and may be associated with a broad spectrum of conditions.

Furthermore, it is important to consider the difference between serial measurements (delta) to differentiate chronic from acute conditions22:

- Absolute changes in cTn provide a higher diagnostic accuracy for AMI as compared to relative changes. A caveat is that patients with AMI may show no or only a minimal change when troponin levels are measured around the peak of cTn release.

- The higher the absolute change, the higher the likelihood for AMI. However, there are several other acute cardiac conditions including tachyarrhythmias, myocarditis, hypertensive crisis, and Takotsubo cardiomyopathy that may also present with substantial cTn changes.

**Algorithms for rule-in and rule-out of AMI**

Based on a decision limit as well as criteria for a difference (delta) between serial measurement of cTn, algorithms have been designed and validated for rule-out and rule-in of AMI:

- **Rule-out algorithms** are optimized for sensitivity to minimize false-negatives.23
- **Rule-in algorithms** are optimized for specificity to minimize false-positives.24

Algorithms are based on the following two approaches (Table 5):

1. **Fixed threshold based on the 99th percentile URL**: decision within 3-6 hours from admission.
   - This is the classical approach as recommended in the Universal Definition of MI.7 For the diagnosis of MI, serial measurement of cTn is needed for detection of a dynamic changing pattern of cTn with at least one value above the 99th percentile URL.
   - With conventional cTn assays a time window of 6 hours or more from admission is needed.25
   - Compared with conventional assays, hs-cTn assays allow earlier detection of acute MI, with shortening of the time window for serial testing to 3 hours.5,20

2. **Threshold NOT based on the 99th percentile URL**: decision in 2 hours, or less, from admission.
   - The introduction of hs-cTn assays, with accurate measurement below the 99th percentile URL and detection of small absolute changes within 1 or 2 hours, has led to the development of rapid rule-out/rule-in strategies with substantial reduction in the time to decision.23,24

![Table 5. Algorithms for rule-out and rule-in of AMI for hs-cTn assays.](image)

<table>
<thead>
<tr>
<th>Classical approach</th>
<th>Decision limit</th>
<th>Serial measurement</th>
<th>Time for decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>99th percentile URL</td>
<td>Yes</td>
<td></td>
<td>3 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Accelerated approach</th>
<th>Decision limits plus early absolute changes (cutoff levels are assay specific)</th>
<th>Serial measurement</th>
<th>Time for decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 2 hours</td>
<td>Yes (single sample rule-out on admission may also be used)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Considerations for the use of cTn in diagnostic algorithms

Initial management of a patient with suspected ACS relies on clinical assessment plus 12-lead ECG for rapid detection of STEMI. If no immediate threat is detected, NSTEMI should be considered and the decision-making process is guided by triage algorithms that rely on measurement of cTn by hs-cTn assays. With hs-cTn assays the following triage algorithms are endorsed by ESC guidelines:

- Standard algorithm (99th percentile URL): 0 h/3 h (Figure 8)
- Rapid algorithms: 0 h/1 h (Figure 9) or 0 h/2 h

Because of lack of standardization, decision limits (thresholds) and delta values are assay specific. Consequently, algorithms are also assay-specific with a very low cut-off for rule-out, a high cut-off for rule-in and delta values based on the absolute change between two consecutive measurements to make further decisions on rule-out or rule-in. If hs-cTn is below the lower cutoff and remains low, the risk for 30-day adverse outcome is low and AMI is ruled out. If the cTn concentration is above the high threshold, the probability for AMI is high and the patient should undergo CCTA within 48 hours (see flow chart in Figure 10).

Algorithms should always be used in conjunction with all available clinical information. Special attention should be paid to time of chest pain onset as it impacts interpretation of the results and the need for further serial measurements. For very early presenters (<1 h from chest pain onset) an additional sample will be needed at 3 hours. Late increases of cTn may occur in 1% of patients. Therefore, repeat testing at later time points (3-6 hours) is advised if first measurements are not conclusive and clinical suspicion remains high.
Patients presenting with chest pain. ACS?

ECG indicates STEMI

STEMI pathway
Troponin measurement on admission and 6-24 h to confirm diagnosis

cTn >High (above URL)

High risk Rule-in

Delta positive

Medical assessment
Further cardiac investigation

NESTEMI

Myocardial injury

Delta negative

Chronic myocardial injury

Intermediate risk Repeat cTn

Delta positive

Delta intermediate and cTn >Very Low

Admit Acute cardiac injury

Further investigation

Repeat Troponin 3-6 h

Low risk Rule-out

Delta negative and cTn <Low

Low risk Rule-out

Discharge

cTn <Very Low (close to LoD)

Discharge

Consider further cardiac investigation

ECG does not show STEMI

Measure troponin

cTn High – Very Low (between LoD and URL)

Intermediate risk Repeat cTn

Delta positive

Medical assessment Further cardiac investigation

NSTEMI

Myocardial injury

Delta negative

Medical assessment Further cardiac investigation

Consider further cardiac investigation

Follow-up medical decisions for patients categorized as high risk (rule-in), intermediate risk and low risk (rule-out).

ACS, acute coronary syndrome; cTn, cardiac troponin; ECG, electrocardiogram; LoD, limit of detection; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; URL, upper reference limit

Adapted from Collinson P. Clin Biochem. 2021;S0009-9120(21)00047-3
4 Guide to interpretation

Pre-analytical and analytical considerations

▶ Sample type

Serum, plasma, or anticoagulated whole blood (point-of-care tests) are acceptable specimens for the analysis of cTn, but different specimen types should not be used interchangeably. Depending on the assay, differences may exist between serum and plasma samples. Also, there may be an influence of the type of anticoagulant that is used for sample collection with lower values in EDTA- vs. lithium heparin plasma.

Rapid processing of samples is important and results should be obtained within 60 minutes of blood collection. Therefore, whole blood and plasma are the specimens of choice for the emergency laboratory to avoid delays due to serum preparation.

▶ Precision

More sensitive assays provide better precision at low values and facilitate the detection of changing values within 1 or 2 hours of admission. Key criteria for a hs-cTn assay are:

- Analytical imprecision (% CV) at its established 99th percentile URL ≤10%.
- Ability to quantify troponin levels in the majority (>50%) of healthy subjects.

▶ Standardization

In contrast to cTnT, with only one supplier, there are many cTnI assays commercially available. These assays use different calibrators and have a variable immunoreactivity to the various circulating forms of cTnI. Consequently, the standardization of cTnI assays remains a huge challenge. Therefore, despite correlation between methods, reported values of cTnI results differ across measurement platforms and each assay will have its own assay specific clinical decision limits.

Expected values

▶ Impact of age, gender and ethnicity

With hs-cTn assays a difference between men and women becomes apparent with higher values in men compared with women. This is biologically plausible because of the larger heart mass in men. Furthermore, in adults cTn increases with age in both men and women. The reverse trend is seen in healthy children, with highest values in the first month of life and a gradual decline until adolescence. Concerning ethnicity, higher values have been reported in African-Americans compared with Caucasians.

Laboratory practice guidelines recommend that manufacturers report sex-specific 99th percentile URL’s for their hs-cTn assay. Specific URLs by age or by ethnicity are currently not recommended. Despite clear sex differences in URL’s, the clinical superiority of sex-specific URL’s have not been definitely proven.

▶ Causes of elevated cTn

It is important to consider cTn as a quantitative marker of cardiac injury: the higher the level, the higher the likelihood of AMI (Figure 7). Elevated cTn (i.e. above the 99th percentile URL) is not specific for AMI and can be observed in numerous conditions.

First, cTn is not only elevated in the classical type 1 MI (atherothrombosis) but also in type 2 MI due to a myocardial oxygen supply-demand mismatch associated with a variety of underlying disorders (Table 2). Besides type 1 and type 2 MI, there are a number of other cardiac and non-cardiac conditions where elevated cTn levels can occur (Table 2). Elevated cTn in critical care is indicative of myocardial injury and an adverse prognosis.

This has also been reported for the most recent respiratory pathogen SARS-CoV-2 (COVID-19).
**FREQUENTLY ASKED QUESTIONS**

1. **What is the difference between cTnI and cTnT?**
   Guidelines do not differentiate between cTnI and cTnT as a tool in the diagnosis and prognosis of suspected ACS. In a direct comparison both hs-cTnI and hs-cTnT provided overall similar high diagnostic and prognostic accuracy, albeit that cTnI showed a somewhat higher diagnostic accuracy for early presenters and cTnT for late presenters, and also cTnT showed a higher prognostic accuracy for all-cause mortality.

   The following are notable differences between cTnI and cTnT:
   - After AMI, cTnI increases tend to continue for longer than cTnT increases.
   - Elevated dysfunction leads more frequently to elevations in cTnT than cTnI.
   - cTnT, but not cTnI, shows a diurnal rhythm characterized by gradually decreasing concentrations throughout daytime, rising concentrations during night-time, with peak concentrations in the morning.
   - There is only one supplier of cTnT assays but multiple suppliers of cTnI assays, each with their own monoclonal antibodies and calibrators. This variability in source materials, combined with a lack of standardization, results in a large heterogeneity and poor concordance between cTnI assays. Consequently, for cTnI, results are not transferable from one assay to another.

2. **Can false-negative or false-positive cTn results be expected?**
   A false-positive result is a test result above the decision threshold in the absence of disease, whereas a false-negative result is a test result below the decision threshold in the presence of disease. However, it is important to realize that although cTn is highly specific for cardiac damage it has only moderate specificity for AMI and can be elevated in many other clinical settings (Table 2). Here, the term false-positive is misleading because in these clinical settings an elevated cTn test result, as a marker of cardiac damage, is associated with adverse outcomes.

   The importance of a significant change in cTn levels upon serial testing is a key consideration in distinguishing AMI from other causes of cardiac damage. Furthermore, serial testing is also important to avoid false-negatives which may occur in very early presenters or due to late increases in cTn. Therefore, repeat testing at later time points is always needed if first measurements are not conclusive and clinical suspicion remains high.

   Analytical interferences are a rare cause of false results but should be considered when test results and clinical presentation are discordant. Most often these issues cause increased cTn values that do not change acutely over time. Possible reasons for erroneous results include the following:
   - Analytical interferences due to pronounced hemolysis, hyperlipidemia or hyperbilirubinemia.
   - Non-reproducible increases in concentrations, referred to as ‘flyers’ or ‘outliers.’
   - Presence of heterophilic or human anti-mouse antibodies.
   - Presence of auto-antibodies against cTnI or cTnT. These antibodies can directly interfere with the assay or their binding to cTn can result in high molecular weight complexes (macrotroponins) that are cleared more slowly from the circulation, resulting in persistently elevated cTn concentrations.

   In the case of erroneous and discordant results, it is important to consult the lab to investigate and eliminate potential analytical interferences.

3. **How is the 99th percentile URL for cTn assays determined?**
   The 99th percentile URL need to be determined for both men and women which requires at least 300 normal adult individuals of each sex with a diverse distribution of ages from 18 to over 70 years. Apart from age and gender, cTn levels may be influenced by underlying factors with impact on cardiac structure and function. A critical element, therefore, is the definition of ‘normal,’ because studies have shown that a more rigorous selection based on eliminating potential comorbidities will lower the URL.

   Currently, there is no uniform consensus on how to select ‘cardiac healthy’ individuals, but experts have proposed the following exclusion criteria:
   - History of cardiovascular disease and medication usage.
   - Diabetes (HbA1c ≥6.5%).
   - Renal dysfunction (eGFR <60 mL / min / 1.73 m²).
   - Elevated NT-proBNP as a surrogate marker of cardiac dysfunction (>125 pg/mL for age <75 years and >450 pg/mL for age ≥75 years).

4. **What are the clinical implications of high-sensitivity cTn assays?**
   The clinical implications of hs-cTn assays are summarized in Table 6. Compared with conventional cTn assays, the new generation of hs-cTn assays have improved diagnostic and prognostic properties with the following impact on clinical management:
FREQUENTLY ASKED QUESTIONS

5. Is there a role for cTn in the distinction between type 1 and type 2 MI?

Following the introduction of hs-cTn assays the incidence of type 2 MI and ischemic myocardial injury is projected to increase. The distinction between type 1 and type 2 MI and ischemic myocardial injury remains a challenge but is critically important because of differences in therapy. The differential diagnosis between type 1 and 2 MI can only be done with coronary angiography, but such invasive approach is not warranted or can even be harmful in type 2 MI patients. Therefore, there is a clinical need for a rapid non-invasive differentiation of both MI types.

In general, cTn values are higher in type 1 than in type 2 MI. Yet, no cut-off has been defined to accurately discriminate between both types and also the use of delta values is not helpful. Compared with type 1 MI, patients with type 2 MI are more often female and are more often not presenting with typical radiating chest pain. These observations have led to the development of a simple binary score to predict the probability of type 2 MI with highest probability (72%) when all 3 predictors are positive: female sex, absence of radiating chest pain and hs-cTn ≤40.8 ng/L. This score still requires external validation, including appropriateness of this cut-off with other hs-cTnI assays.

6. How do I select the most optimal rule-out/rule-in algorithm?

Several elements are important to consider in this selection process. In the ED setting of patients with chest pain and suspected ACS the most valuable application is rapid and safe rule-out. This requires an informed balance between safety (NPV for the presence of AMI) and efficacy (proportion triaged towards rule-out). Furthermore, it is important to consider the user friendliness of the choice of algorithm and the impact on patient flow and staff workload, hence it is dependent on the process of the particular hospital.

The latest 2020 ESC Guidelines for the management of ACS in patients presenting without persistent ST-segment elevation clearly recommend the use of a 0 h/2 h algorithm as an alternative to a validated 0 h/1 h algorithm. The accelerated algorithm implemented on a particular site will depend on the test available at the central laboratory (hs-cTnI or hs-cTnT). It will also be influenced by the ability of the laboratory to return results within 45 minutes of blood draw.

Both accelerated (0 h/1 h or 0 h/2 h) and 0 h/3 h algorithms are recommended by the ESC for early rule-out of AMI. These are completely different protocols. The accelerated algorithms are based on hs-cTn levels at
presentation and absolute changes within the first 1 or 2 hours. They are based on the ability to predict that the patient will rule-in or rule-out for MI according to the Universal Definition of MI on further testing. This is discussed in more detail below. The 0 h/3 h algorithm uses the fixed 99th percentile URL threshold in conjunction with clinical criteria (GRACE score) and is based directly on the Universal Definition of MI. From a direct comparison of both approaches it was concluded that the accelerated algorithms are superior because they more favorably combine safety with efficacy. Advantages of the accelerated algorithms are that they allow earlier clinical decision making and do not require a specific risk score which increases its feasibility.

The 0 h/1 h approach has been questioned on the basis of patient flow and ED and laboratory logistics related to sampling at this short time interval. Consequently, a 2-hour protocol may be more suitable for some institutions.

7 What are the limitations of rapid rule-out/rule-in algorithms?

As a critical principle it is important to emphasize that AMI remains a clinical diagnosis and that the results of cTn testing need to be interpreted in conjunction with all other available information such as 12-lead ECG, patient history and examination and other diagnostic investigations. Rapid cTn testing algorithms are very useful to triage about 70% of suspected patients towards either AMI rule-out or AMI rule-in. This is not synonymous with a final diagnosis for presence or absence of AMI, but only informs about the probability of having AMI which aids in making decisions on the next course of action in the clinical management of the patient.

AMI rule-out

In this case, the decision to discharge home from the ED must not be solely based on cTn testing. Repeat cTn testing at later time points may be required if first measurements are not conclusive and clinical suspicion for ACS remains high, for example in the case of early presenters (<2 hours from onset of chest pain). AMI rule-out does not mean ACS rule-out and, therefore, further investigations such as functional cardiac stress testing may be needed to rule-out UA. Also, in the case of chest pain, it is important to be aware of other life-threatening disorders such as AAD or PE.

In the context of AMI rule-out, a clinical risk score may provide incremental value for the selection of patients who are also candidates for rapid discharge from the ED and outpatient management. For this reason, the GRACE score is already integrated in the 3-hour ESC algorithm (Figure 8). Compared with a 2-hour rule-out protocol, a 2-hour protocol that combined cTn testing with the TIMI score was superior for selection of patients for early discharge from the ED.

The HEART score outperformed both TIMI and GRACE in its capacity to predict major adverse cardiac events (MACE) after 30 days from presentation to the ED. The HEART score integrates cTn testing with ECG, age and clinical predictors. A single cTn at presentation and a HEART score of ≤3 demonstrated NPV of ≥99.5% for 30-day MACE, which suggests that this a threshold for safe discharge.

AMI rule-in

In this case the PPV is only about 75-80%. This is enough as a working diagnosis and is helpful for the physician to make a decision for coronary angiography and start of certain medical therapies. Conditions like Takotsubo cardiomyopathy and myocarditis can also be associated with substantial elevations and changes in cTn (Figure 7). To differentiate AMI from these conditions early coronary angiography is the general clinical consequence of triage towards AMI rule-in.

Observational zone

Diagnostic uncertainty remains in approximately 25-30% of suspected patients. Patients in the observational zone are typically elderly men with pre-existing CAD and have a similar high long-term mortality as patients triaged towards AMI rule-in. Additional diagnostic investigations are needed in this group, including cTn testing at later time points (3-6 hours), functional stress imaging and coronary angiography in order to discriminate ACS (21% UA, 15% AMI) from non-cardiac disease (38%) and non-coronary cardiac disease (24%).

8 Should early presenters be managed differently?

Early presenters are patients with suspected ACS that are seen in the ED <2 hours from chest pain onset. High-sensitivity assays detect changes in troponin earlier and therefore improve the diagnostic accuracy for MI in these patients.

In early presenters, better diagnostic accuracy has been reported for cTnI as compared to cTnT.

The 0/3h algorithm allows longer time for clinical assessment and later sequential measurements, and will safely rule out ACS patients among early presenters.

The ESC 0 h/1h and 0 h/2h algorithms can also be used in these patients as safety (negative predictive value and sensitivity) is maintained for these strategies.

However, due to the kinetics of cTn release following MI, it is recommended that sequential measurements of hs-cTn are used in patients that present very early (<1h) after chest pain onset, especially if the first result is inconclusive and there is clinical suspicion of ACS. Although changes within the reference interval can be detected within 1-2 hours of MI, values above the 99th percentile can be reliably detected only 3 hours or more from symptom onset.
9 Which patients pose a challenge for the diagnosis of AMI by cTn?

Special attention is required for suspected patients presenting with renal dysfunction (eGFR <60 mL / min / 1.73 m²) or symptoms other than typical chest pain such as dyspnea.

**Renal dysfunction** may occur in 16% of patients presenting with symptoms of suspected AMI. These patients more frequently present with atypical symptoms and the proportion of diagnosed AMI is 2-fold higher than in suspected patients without renal function. These patients pose a diagnostic challenge because, even in the absence of AMI, ECG abnormalities (ST-segment depression/T-wave inversion) and elevations of cTn above the 99th percentile URL are more frequently observed. Yet, the diagnostic utility of hs-cTn assays is retained in patients with renal dysfunction as long as test specific optimized cut-off levels are used (2 to 3-fold higher than 99th percentile URL).

**Dyspnea** may occur in 17-49% of patients with suspected ACS but the prevalence of diagnosed ACS is much lower than in patients presenting with typical chest pain. This high-risk cohort poses a challenge for the diagnosis of AMI because of the low pre-test probability and the lower specificity of cTn. Higher cut-offs at presentation and serial measurements over 6 hours may help to identify NSTEMI in this population.

10 What is the prognostic utility of cTn?

It is recommended to use established risk scores (e.g. GRACE) for prognosis estimation. These scores integrate hs-cTn test results with clinical factors. Invasive coronary angiography has a central role in the management of patients with NSTE-ACS and the timing of this intervention is guided by risk stratification. An early invasive strategy, defined as coronary angiography within 24 hours of hospital admission, is required in the presence of high-risk criteria, including a dynamic rise or fall in cTn compatible with MI.

Irrespective of the presence of AMI, any elevated cTn is predictive of an adverse outcome. The HEART score, which integrates cTn and hs-cTn testing with ECG, age and clinical predictors, is a useful tool to select MI rule-out patients for safe discharge.

11 Is there a role for cTn testing in other diseases?

Information on an elevated cTn (>99th percentile URL) may be helpful in the management of the following cardiovascular diseases:

**Heart failure**

Elevated cTn is frequently observed in both acute and chronic HF due to cardiac or non-cardiac mechanisms. In the case of acute HF, cTn should be measured to confirm or exclude MI as the precipitating cause. In this setting, an elevated cTn is associated with a more decompensated profile and a higher risk for an adverse outcome. The 10% of acute HF patients with cTn below the 99th percentile URL are at very low risk for a short-term adverse event and may be eligible for early discharge. An elevated cTn has independent prognostic value in chronic HF, but data are lacking about specific therapeutic interventions in such cases.

**Pulmonary embolism**

Approximately 50% of acute PE patients show elevated cTn values on admission and these patients have a worse prognosis. Decisions on clinical management of PE in the acute phase are guided by the assessment of the patient’s early death risk. This risk assessment integrates clinical parameters, assessment of right ventricular dysfunction (RVD) by echocardiography and measurement of cardiac biomarkers (cTn or natriuretic peptides). Absence of an elevated cTn has a high NPV (>98%) for a complicated course. Patients stratified as low risk based on a low clinical score, absence of RVD and normal cTn may be potential candidates for early discharge and home treatment.

**Atrial fibrillation**

Currently, a clinical score is recommended for stroke risk prediction in patients with AF in order to select patients for oral anticoagulant therapy. In AF patients on oral anticoagulation it is important to identify modifiable risk factors for major bleeding. Higher concentrations of hs-cTn in AF patients are independently associated with increased risk for stroke, cardiac mortality or bleeding. Because of this additional prognostic information in AF patients, a biomarker-based risk score for stroke as well as for bleeding may prove helpful for better risk stratification.
REFERENCES

REFERENCES


### LIST OF ABBREVIATIONS & ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAD</td>
<td>acute aortic dissection</td>
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<td>ACS</td>
<td>acute coronary syndromes</td>
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<td>AF</td>
<td>atrial fibrillation</td>
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<td>AMI</td>
<td>acute myocardial infarction</td>
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<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
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<td>CAD</td>
<td>coronary artery disease</td>
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<td>CCTA</td>
<td>coronary computed tomography angiography</td>
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<tr>
<td>CCU</td>
<td>coronary care unit</td>
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<tr>
<td>cTn</td>
<td>cardiac troponin</td>
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<tr>
<td>CV</td>
<td>coefficient of variation</td>
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<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>ED</td>
<td>emergency department</td>
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<tr>
<td>EDTA</td>
<td>ethylene diamine tetra-acetic acid</td>
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<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
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<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
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<td>GRACE score</td>
<td>Global Registry of Acute Coronary Events; the GRACE risk score has been developed to assess the risk of mortality in patients with ACS <a href="http://www.mdcalc.com/grace-acs-risk-mortality-calculator">www.mdcalc.com/grace-acs-risk-mortality-calculator</a></td>
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<tr>
<td>HEART score</td>
<td>Score to assess risk of major adverse cardiac events (MACE) in ED patients with chest pain based on the following 5 predictors: History, ECG, Age, Risk factors and Troponin <a href="http://www.heartscore.nl">www.heartscore.nl</a></td>
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<tr>
<td>HF</td>
<td>heart failure</td>
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<tr>
<td>hs-cTn</td>
<td>high-sensitivity cardiac troponin</td>
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<td>IHD</td>
<td>ischemic heart disease</td>
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<tr>
<td>kDa</td>
<td>kilo Dalton (unit of molecular weight)</td>
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<td>LBBB</td>
<td>left bundle branch block</td>
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<td>LoD</td>
<td>limit of detection</td>
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<td>MACE</td>
<td>major adverse cardiac events</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>MINOCA</td>
<td>myocardial infarction with non-obstructive coronary arteries</td>
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<td>NPV</td>
<td>negative predictive value</td>
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<td>NSTE-ACS</td>
<td>non-ST-segment elevation acute coronary syndromes</td>
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<td>NSTEMI</td>
<td>non-ST-segment elevation myocardial infarction</td>
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<tr>
<td>NT-proBNP</td>
<td>N-terminal pro B-type natriuretic peptide</td>
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<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<tr>
<td>PE</td>
<td>pulmonary embolism</td>
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<tr>
<td>PPV</td>
<td>positive predictive value</td>
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<td>RVD</td>
<td>right ventricular dysfunction</td>
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<td>STEMI</td>
<td>ST-segment-elevation myocardial infarction</td>
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<td>TIMI score</td>
<td>Thrombolysis in Myocardial Infarction; the TIMI risk score has been developed to assess mortality risk in patients with ACS <a href="http://www.mdcalc.com/timi-risk-score-ua-nstemi">www.mdcalc.com/timi-risk-score-ua-nstemi</a> <a href="http://www.mdcalc.com/timi-risk-score-stemi">www.mdcalc.com/timi-risk-score-stemi</a></td>
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