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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)

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Table 3 Clinical implications of high-sensitivity cardiac troponin assays

Compared with standard cardiac troponin assays, high-sensitivity assays:
• Have higher negative predictive value for acute MI.
• Reduce the "troponin-blind" interval leading to earlier detection of acute MI.
• Result in a ~4% absolute and ~20% relative increase in the detection of type 1 MI and a corresponding decrease in the diagnosis of unstable angina.
• Are associated with a 2-fold increase in the detection of type 2 MI.
Levels of high-sensitivity cardiac troponin should be interpreted as quantitative markers of cardiomyocyte damage (i.e. the higher the level, the greater the likelihood of MI):
• Elevations beyond 5-fold the upper reference limit have high (>90%) positive predictive value for acute type 1 MI.
• Elevations up to 3-fold the upper reference limit have only limited (50–60%) positive predictive value for acute MI and may be associated with a broad spectrum of conditions.
• It is common to detect circulating levels of cardiac troponin in healthy individuals.
Rising and/or falling cardiac troponin levels differentiate acute from chronic cardiomyocyte damage (the more pronounced the change, the higher the likelihood of acute MI).

MI = myocardial infarction.

Table 4 Conditions other than acute myocardial infarction type 1 associated with cardiac troponin elevation

Tachyarrhythmias
Heart failure
Hypertensive emergencies
Critical illness (e.g. shock/ sepsis/ burns)
Myocarditis[a]
Tako-Tsubo cardiomyopathy
Structural heart disease (e.g. aortic stenosis)
Aortic dissection
Pulmonary embolism, pulmonary hypertension
Renal dysfunction and associated cardiac disease
Coronary spasm
Acute neurological event (e.g. stroke or subarachnoid haemorrhage)
Cardiac contusion or cardiac procedures (CABG, PCI, ablation, pacing, cardioversion, or endomyocardial biopsy)
Hypo- and hyperthyroidism
Infiltrative diseases (e.g. amyloidosis, haemochromatosis, sarcoidosis, scleroderma)
Myocardial drug toxicity or poisoning (e.g. doxorubicin, 5-fluorouracil, herceptin, snake venoms)
Extreme endurance efforts
Rhabdomyolysis

Bold = most frequent conditions; CABG = coronary artery bypass surgery; PCI = percutaneous coronary intervention.
[a]includes myocardial extension of endocarditis or pericarditis.

obtain it within 10 min of the patient's arrival in the emergency room or, ideally, at first contact with emergency medical services in the pre-hospital setting and to have it immediately interpreted by a qualified physician.[28] While the ECG in the setting of NSTE-ACS may be normal in more than one-third of patients, characteristic abnormalities include ST depression, transient ST elevation and T-wave changes.[1,18] If the standard leads are inconclusive and the patient has signs or symptoms suggestive of ongoing myocardial ischaemia, additional leads should be recorded; left circumflex artery occlusion or right ventricular MI may be detected only in V_7–V_9 and V_{3R} and V_{4R}, respectively.[2] In patients with suggestive signs and symptoms, the finding of persistent ST elevation indicates STEMI, which mandates immediate reperfusion.[1] Comparison with previous tracings is valuable, particularly in patients with pre-existing ECG abnormalities. It is recommended to obtain additional 12-lead ECGs in the case of persistent or recurrent symptoms or diagnostic uncertainty. In patients with bundle branch block or paced rhythm, ECG is of no help for the diagnosis of NSTE-ACS.

3.3.2 Biomarkers

Biomarkers complement clinical assessment and 12-lead ECG in the diagnosis, risk stratification and treatment of patients with suspected NSTE-ACS. Measurement of a biomarker of cardiomyocyte injury, preferably high-sensitivity cardiac troponin, is mandatory in all patients with suspected NSTE-ACS.[2,6,8] Cardiac troponins are more sensitive and specific markers of cardiomyocyte injury than creatine kinase (CK), its MB isoenzyme (CK-MB) and myoglobin.[6] If the clinical presentation is compatible with myocardial ischaemia, then a dynamic elevation of cardiac troponin above the 99th percentile of healthy individuals indicates MI.[2] In patients with MI, levels of cardiac troponin rise rapidly (i.e. usually within 1 h if using high-sensitivity assays) after symptom onset and remain elevated for a variable period of time (usually several days).[2,6] Advances in technology have led to a refinement in cardiac troponin assays and have improved the ability to detect and quantify cardiomyocyte injury.[2,6,8,10,29–37] In Europe, the vast majority of cardiac troponin assays run on automated platforms and are sensitive (i.e. allow for detection of cardiac troponin in ~20–50% of healthy individuals) or high-sensitivity (detection in ~50–90% of healthy individuals) assays. High-sensitivity assays are recommended over less sensitive ones.[2,6,8] The majority of currently used point-of-care assays cannot be considered sensitive or high-sensitivity assays.[8,35] Therefore the obvious advantage of point-of-care tests, namely the shorter turnaround time, is counterbalanced by lower sensitivity, lower diagnostic accuracy and lower negative predictive value. Overall, automated assays have been more thoroughly evaluated as compared with point-of-care tests.[2,6,8] As these techniques continue to improve and performance characteristics are both assay and hospital dependent, no recommendation regarding the site of measurement (central laboratory vs. bedside) can be given.[2,6,8,38] Data from large multicentre studies have consistently shown that sensitive and high-sensitivity cardiac troponin assays increase diagnostic accuracy for MI at the time of presentation as compared with conventional assays, especially in patients presenting early after chest pain onset, and allow for a more rapid 'rule-in' and 'rule-out' of MI (see section 3.3.3 and *Table 3*).[2,6,8,29–34]

In most patients with renal dysfunction, elevations in cardiac troponin should not be primarily attributed to impaired clearance and considered harmless, as cardiac conditions such as chronic coronary or hypertensive heart disease seem to be the most important contributor to troponin elevation in this setting.[41] Other life-threatening conditions presenting with chest pain, such as aortic dissection and pulmonary embolism, may also result in elevated troponin levels and should be considered as differential diagnoses (*Table 4*).

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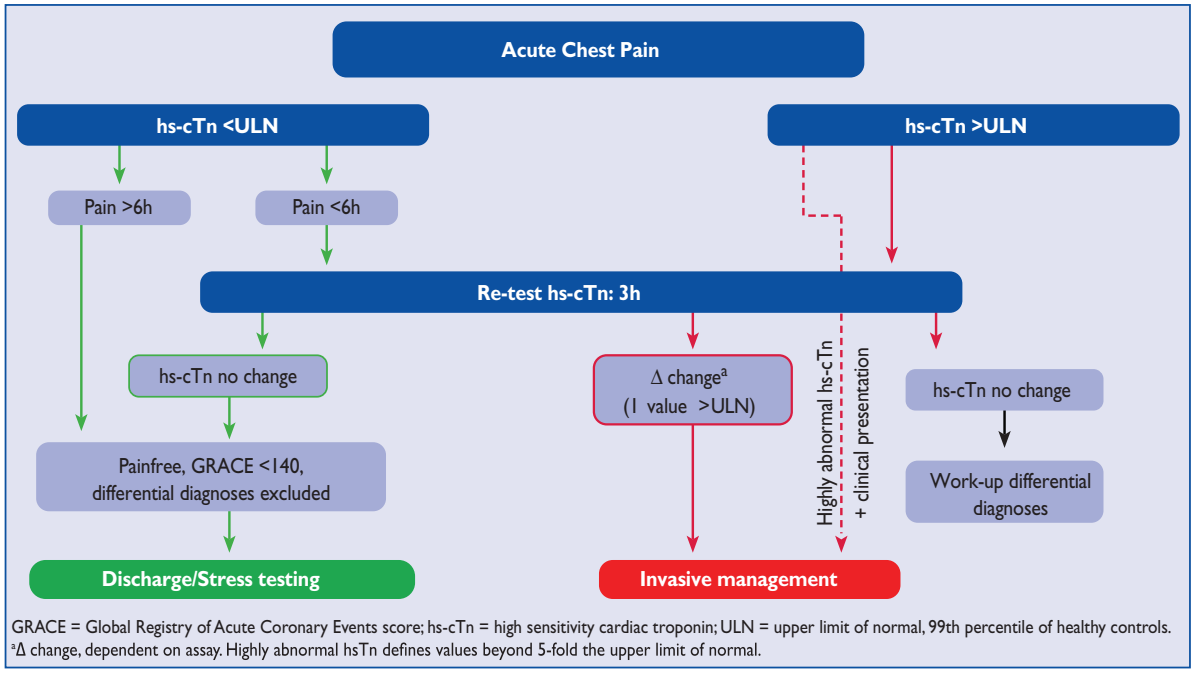
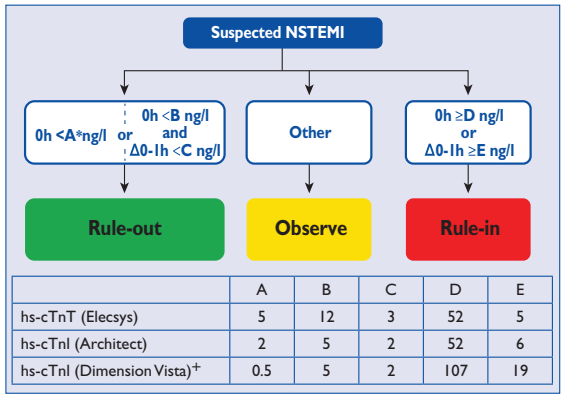


Figure 2 0 h/3 h rule-out algorithm of non-ST-elevation acute coronary syndromes using high-sensitivity cardiac troponin assays.

Among the multitude of additional biomarkers evaluated for the diagnosis of NSTE-ACS, only CK-MB and copeptin seem to have clinical relevance.[2,6,8,10,44–50] CK-MB shows a more rapid decline after MI as compared with cardiac troponin and may provide added value for the timing of myocardial injury and the detection of early reinfarction.[2,6,8,10] Assessment of copeptin, the C-terminal part of the vasopressin prohormone, may quantify the endogenous stress level in multiple medical conditions including MI. As the level of endogenous stress appears to be invariably high at the onset of MI, the added value of copeptin to conventional (less sensitive) cardiac troponin assays is substantial.[44–50] Therefore the routine use of copeptin as an additional biomarker for the early rule-out of MI is recommended whenever sensitive or high-sensitivity cardiac troponin assays are not available. Copeptin may have some added value even over high-sensitivity cardiac troponin in the early rule-out of MI.[44–48]

3.3.3 'Rule-in' and 'rule-out' algorithms

Due to the higher sensitivity and diagnostic accuracy for the detection of acute MI at presentation, the time interval to the second cardiac troponin assessment can be shortened with the use of high-sensitivity assays. This may reduce substantially the delay to diagnosis, translating into shorter stays in the emergency department and lower costs.[2,6,8,10,29–36] It is recommended to use the 0 h/3 h algorithm (*Figure 2*). As an alternative, 0 h/1 h assessments are recommended when high-sensitivity cardiac troponin assays with a validated algorithm are available (*Figure 3*). The 0 h/1 h algorithms rely on two concepts: first, high-sensitivity cardiac troponin is a continuous variable and the probability of MI increases with increasing high-sensitivity cardiac troponin values;[39] second, early absolute changes of the levels within 1 h can be used as surrogates for absolute changes over 3 h or 6 h and provide incremental diagnostic value to the cardiac troponin assessment at presentation.[39] The cut-off levels within the 0 h/1 h algorithm are assay specific.[36,39,51–55] Those algorithms should always be integrated with a detailed



	A	B	C	D	E
hs-cTnT (Elecsys)	5	12	3	52	5
hs-cTnI (Architect)	2	5	2	52	6
hs-cTnI (Dimension Vista)+	0.5	5	2	107	19

Figure 3 0 h/1 h rule-in and rule-out algorithms using high-sensitivity cardiac troponins (hs-cTn) assays in patients presenting with suspected non-ST-elevation myocardial infarction (NSTEMI) to the emergency department. 0 h and 1 h refer to the time from first blood test. NSTEMI can be ruled-out already at presentation, if the hs-cTn concentration is very low. NSTEMI can also be ruled-out by the combination of low baseline levels and the lack of a relevant increase within 1 h. Patients have a high likelihood for NSTEMI if the hs-cTn concentration at presentation is at least moderately elevated or hs-cTn concentrations show a clear rise within the first hour. Cut-off levels are assay-specific. Cut-off levels for other hs-cTn assays are in development. *Only applicable if chest pain onset >3h, +At the time of the publication of the guideline not yet commercially available.

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clinical assessment and 12-lead ECG and repeat blood sampling is mandatory in case of ongoing or recurrent chest pain (*Table 5*, see Web addenda).

***Table 5* (see Web addenda) Characteristics of the 0 h/3 h and 0 h/1 h algorithms**

The negative predictive value for MI in patients assigned 'rule-out' exceeded 98% in several large validation cohorts.[30–34,36,39,51–55] Used in conjunction with clinical and ECG findings, the 0 h/1 h algorithm may allow the identification of candidates for early discharge and outpatient management. The positive predictive value for MI in those patients meeting the 'rule-in' criteria was 75–80%.[30–34,39,53–55] Most of the 'rule-in' patients with diagnoses other than MI did have conditions that usually require inpatient coronary angiography for accurate diagnosis, including Tako–Tsubo cardiomyopathy and myocarditis.[39,53–55] Patients who do not qualify for 'rule-out' or 'rule-in' represent a heterogeneous group that may require further investigations if no alternative explanation for the cardiac troponin elevation is identified. A large proportion of these patients may require a further high-sensitivity cardiac troponin assessment (e.g. at 3 h). Coronary angiography should be considered in patients for whom there is a high degree of clinical suspicion of NSTE-ACS, while in patients with low to intermediate likelihood for this condition, computed tomography (CT) coronary angiography should be considered. No further diagnostic testing in the emergency department is indicated when alternative conditions such as rapid ventricular rate response to atrial fibrillation or hypertensive emergency have been identified.

For rapid rule-out, two alternative approaches to the 0 h/1 h or 0 h/3 h algorithms have been adequately validated and may be considered. First, a 2 h rule-out protocol combining the Thrombolysis in Myocardial Infarction (TIMI) risk score with ECG and high-sensitivity cardiac troponin at presentation allowed a safe rule-out in up to 40% of patients.[56–58] Second, a dual-marker strategy combining normal levels of cardiac troponin together with low levels of copeptin (<10 pmol/L) at presentation showed very high negative predictive value for MI, obviating the need for serial testing in selected patients.[44–50] When using any algorithm, three main caveats apply: (i) algorithms should only be used in conjunction with all available clinical information, including detailed assessment of chest pain characteristics and ECG; (ii) in patients presenting very early (e.g. within 1 h from chest pain onset), the second cardiac troponin level should be obtained at 3 h, due to the time dependency of troponin release; (iii) as late increases in cardiac troponin have been described in ~1% of patients, serial cardiac troponin testing should be pursued if the clinical suspicion remains high or whenever the patient develops recurrent chest pain.[52,54] High-sensitivity cardiac troponin assays also maintain high diagnostic accuracy in patients with renal dysfunction. To ensure the best possible clinical use, assay-specific optimal cut-off levels, which are higher in patients with renal dysfunction, should be used.[59]

3.3.4 Non-invasive imaging

3.3.4.1 Functional evaluation

Transthoracic echocardiography should be routinely available in emergency rooms and chest pain units and performed/interpreted by trained physicians in all patients during hospitalization for NSTE-ACS. This imaging modality is useful to identify abnormalities suggestive of myocardial ischaemia or necrosis (i.e. segmental hypokinesia or akinesia). In the absence of significant wall motion abnormalities, impaired myocardial perfusion detected by contrast echocardiography or reduced regional function using strain and strain rate imaging might improve the diagnostic and prognostic value of conventional echocardiography.[60,61] Moreover, echocardiography can help in detecting alternative pathologies associated with chest pain, such as acute aortic dissection, pericardial effusion, aortic valve stenosis, hypertrophic cardiomyopathy or right ventricular dilatation suggestive of acute pulmonary embolism. Similarly, echocardiography is the diagnostic tool of choice for patients with haemodynamic instability of suspected cardiac origin.[62] Evaluation of left ventricular (LV) systolic function, at the latest by the time of hospital discharge, is important to estimate prognosis, and echocardiography (as well as other imaging modalities) can provide this information.

In patients without ischaemic changes on 12-lead ECGs and negative cardiac troponins (preferably high-sensitivity) who are free of chest pain for several hours, stress imaging can be performed during admission or shortly after discharge. Stress imaging is preferred over exercise ECG due to its greater diagnostic accuracy.[63] Various studies have shown that normal exercise, dobutamine or dipyridamole stress echocardiograms have high negative predictive value for ischaemia and are associated with excellent patient outcomes.[64,65] Moreover, stress echocardiography demonstrated superior prognostic value over exercise ECG.[64,66] The addition of contrast may improve endocardial border detection, which may facilitate detection of ischaemia.[67]

Cardiac magnetic resonance (CMR) can assess both perfusion and wall motion abnormalities, and patients presenting with acute chest pain with a normal stress CMR have an excellent short- and midterm prognosis.[68] CMR also permits detection of scar tissue (using late gadolinium enhancement) and can differentiate this from recent infarction (using T2-weighted imaging to delineate myocardial oedema).[69,70] Moreover, CMR can facilitate the differential diagnosis between infarction and myocarditis or Tako–Tsubo cardiomyopathy.[71] Similarly, nuclear myocardial perfusion imaging has been shown to be useful for risk stratification of patients with acute chest pain suggestive for ACS. Resting myocardial scintigraphy, by detecting fixed perfusion defects suggestive of myocardial necrosis, can be helpful for initial triage of patients presenting with chest pain without ECG changes or elevated cardiac troponins.[72] Combined stress–rest imaging may further enhance assessment of ischaemia, while a normal study is associated with excellent outcome.[73,74] Stress–rest imaging modalities are usually not widely available on 24 h service.

3.3.4.2 Anatomical evaluation

Multidetector computed tomography (MDCT) allows for visualization of the coronary arteries and a normal scan excludes CAD. A meta-analysis of nine studies ($n = 1349$ patients) has reported overall high negative predictive values to exclude ACS (by excluding CAD) and excellent outcome in patients presenting to the emergency department with low to intermediate pre-test probability for ACS and a normal coronary CT angiogram.[75] Four randomized controlled trials (RCTs) have tested MDCT ($n = 1869$ patients) vs.

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usual care ($n = 1397$) in the triage of low- to intermediate-risk patients presenting with acute chest pain to emergency departments without signs of ischaemia on ECG and/or inconclusive cardiac troponins.[76–79] At a follow-up of 1–6 months, there were no deaths, and a meta-analysis demonstrated comparable outcomes with the two approaches (i.e. no difference in the incidence of MI, post-discharge emergency department visits or rehospitalizations) and showed that MDCT was associated with a reduction in emergency department costs and length of stay.[80] However, none of these studies used high-sensitivity cardiac troponin assays, which also may reduce hospital stay. It was also noted that MDCT was associated with an increase in the use of invasive angiography {8.4% vs. 6.3%; odds ratio [OR] 1.36 [95% confidence interval (CI) 1.03, 1.80], $P = 0.030$}.[80] Accordingly, MDCT coronary angiography can be used to exclude CAD (and MDCT is thus not useful in patients with known CAD). Other factors limiting MDCT coronary angiography include severe calcifications (high calcium score) and elevated or irregular heart rate; in addition, a sufficient level of expertise is needed and 24 h service is currently not widely available. Finally, the use of MDCT coronary angiography in the acute setting in patients with stents or previous CABG has not been validated. Importantly, CT imaging can effectively exclude other causes of acute chest pain that, if untreated, are associated with high mortality, namely pulmonary embolism, aortic dissection and tension pneumothorax.[81]

3.4 Differential diagnosis

Among unselected patients presenting with acute chest pain to the emergency department, disease prevalence can be expected to be the following: 5–10% STEMI, 15–20% NSTEMI, 10% unstable angina, 15% other cardiac conditions and 50% non-cardiac diseases.[48,51,52,56–58] Several cardiac and non-cardiac conditions may mimic NSTE-ACS (*Table 6*).

Conditions that should always be considered in the differential diagnosis of NSTE-ACS, because they are potentially life-threatening but also treatable, include aortic dissection, pulmonary embolism and tension pneumothorax. Echocardiography should be performed urgently in all patients with haemodynamic instability of suspected cardiovascular (CV) origin.[62]

Chest X-ray is recommended in all patients in whom NSTE-ACS is considered unlikely in order to detect pneumonia, pneumothorax, rib fractures or other thoracic disorders. Tako–Tsubo cardiomyopathy and coronary artery spasm are briefly described in section 5.6.4.2, Web addenda. Stroke may be accompanied by ECG changes, myocardial wall motion abnormalities and an increase in cardiac troponin levels.[2,6] The majority of patients presenting with acute chest pain to the emergency department have non-cardiac conditions causing the chest discomfort. In many instances the pain is musculoskeletal, and therefore benign, self-limiting and does not require hospitalization. Chest pain characteristics help to some extent in the early identification of those patients.[24]

4. Risk assessment and outcomes

4.1 Clinical presentation, electrocardiogram and biomarkers

4.1.1 Clinical presentation

In addition to some universal clinical markers of risk, such as advanced age, diabetes and renal insufficiency, the initial clinical presentation is highly predictive of early prognosis.[82] Chest pain at rest carries a worse prognosis than symptoms elicited during physical exertion. In patients with intermittent symptoms, an increasing number of episodes preceding the index event also adversely affects prognosis. Tachycardia, hypotension, heart failure and new mitral regurgitation at presentation predict poor prognosis and call for rapid diagnosis and management.[25,82–84]

4.1.2 Electrocardiogram

The initial ECG is predictive of early risk.[18] Patients with ST depression have a worse prognosis than patients with a normal ECG.[85,86] The number of leads showing ST depression and the magnitude of ST depression are indicative of the extent of ischaemia and correlate with prognosis on the one hand, and benefit from an invasive treatment strategy on the other.[87] ST depression $\geq$0.05 mV in two or more contiguous leads, in the appropriate clinical context, is suggestive of NSTE-ACS and linked to adverse prognosis.[85] ST depression combined with transient ST elevation identifies a high-risk subgroup,[88] while associated T-wave inversion does not alter the prognostic value of ST depression. While isolated T-wave inversion on admission has not been associated with worse prognosis compared with the absence of ECG abnormalities, it frequently triggers a more rapid diagnosis and treatment.[86]

Table 6 Differential diagnoses of acute coronary syndromes in the setting of acute chest pain

Cardiac	Pulmonary	Vascular	Gastro-intestinal	Orthopaedic	Other
Myopericarditis Cardiomyopathies[a]	**Pulmonary embolism**	**Aortic dissection**	**Oesophagitis, reflus or spasm**	**Musculoskeletal disorders**	**Anxiety disorders**
Tachyarrhythmias	**(Tension)-Pneumothorax**	Symptomatic aortic aneurysm	Peptic ulcer, gastritis	Chest trauma	Herpes zoster
Acute heart failure	Bronchitis, pneumonia	Stroke	Pancreatitis	Muscle injury/ inflammation	Anaemia
Hypertensive emergencies	Pleuritis		Cholecystitis	Costochondritis	
Aortic valve stenosis				Cervical spine pathologies	
Tako-Tsubo cardiomyopathy					
Coronary spasm					
Cardiac trauma					

Bold = common and/or important differential diagnoses.
[a]Dilated, hypertrophic and restrictive cardiomyopathies may cause angina or chest discomfort.

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