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ESC GUIDELINES

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Diagnostic tools

Electrocardiogram

The resting 12-lead ECG is the first-line diagnostic tool in the assessment of patients with suspected ACS.

It is recommended to perform it within 10 min of the patient's arrival in the emergency room or, ideally, at first contact with the emergency medical services in the pre-hospital setting.

it to have it immediately interpreted by a qualified physician.

While the ECG in the setting of NSTE-ACS may be normal in more than 30% of patients.

characteristic abnormalities include ST-segment depression, transient ST-segment elevation, and T-wave changes.

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 may be detected only in V7V9 or right ventricular MI only in V3R and V4R.

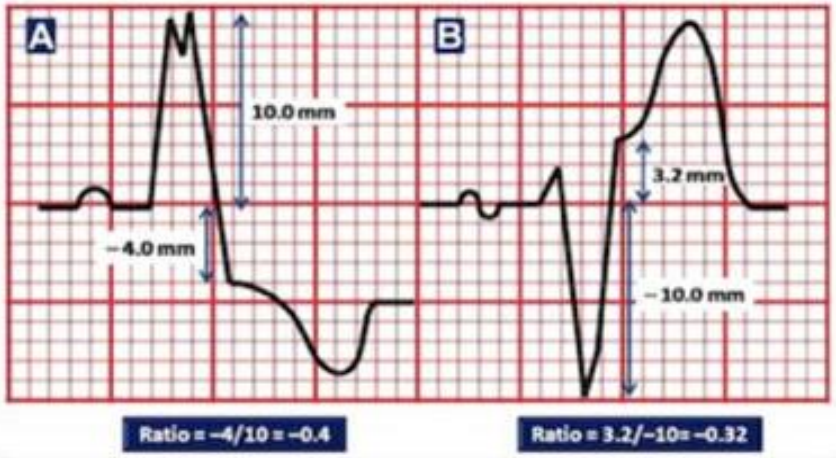
In patients with suggestive signs and symptoms, the finding of persistent ST-segment elevation indicates STEMI, which mandates immediate reperfusion.

It is recommended to obtain additional 12-lead ECGs in case of persistent or recurrent symptoms or diagnostic uncertainty In patients with left bundle branch block (LBBB), specific ECG criteria(Sgarbossa's criteria) may help in the detection of candidates for immediate coronary angiography.

Patients with a high clinical suspicion of ongoing myocardial ischaemia and LBBB should be managed in a way similar to STEMI patients, regardless of whether the LBBB is previously known

What is the new modified Sgarbossa Criteria?

- Concordant ST-segment elevation ≥ 1 mm in any lead
- Concordant ST-segment depression ≥ 1 mm in lead V1 – V3
- Discordant ST/S Ratio ≤ -0.25

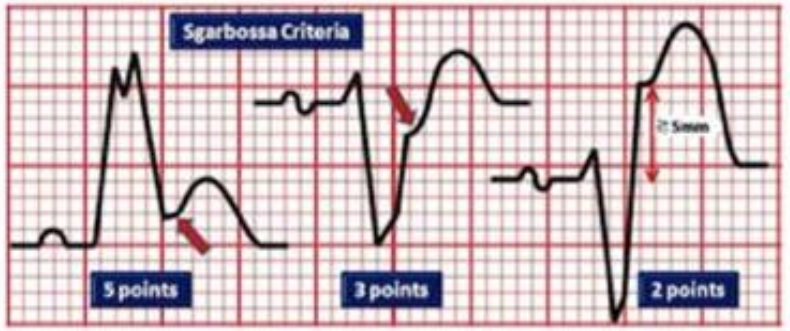


ST/S Ratio

Ratio of ST-segment elevation measured at the J point to the R or S wave, whichever was most prominent

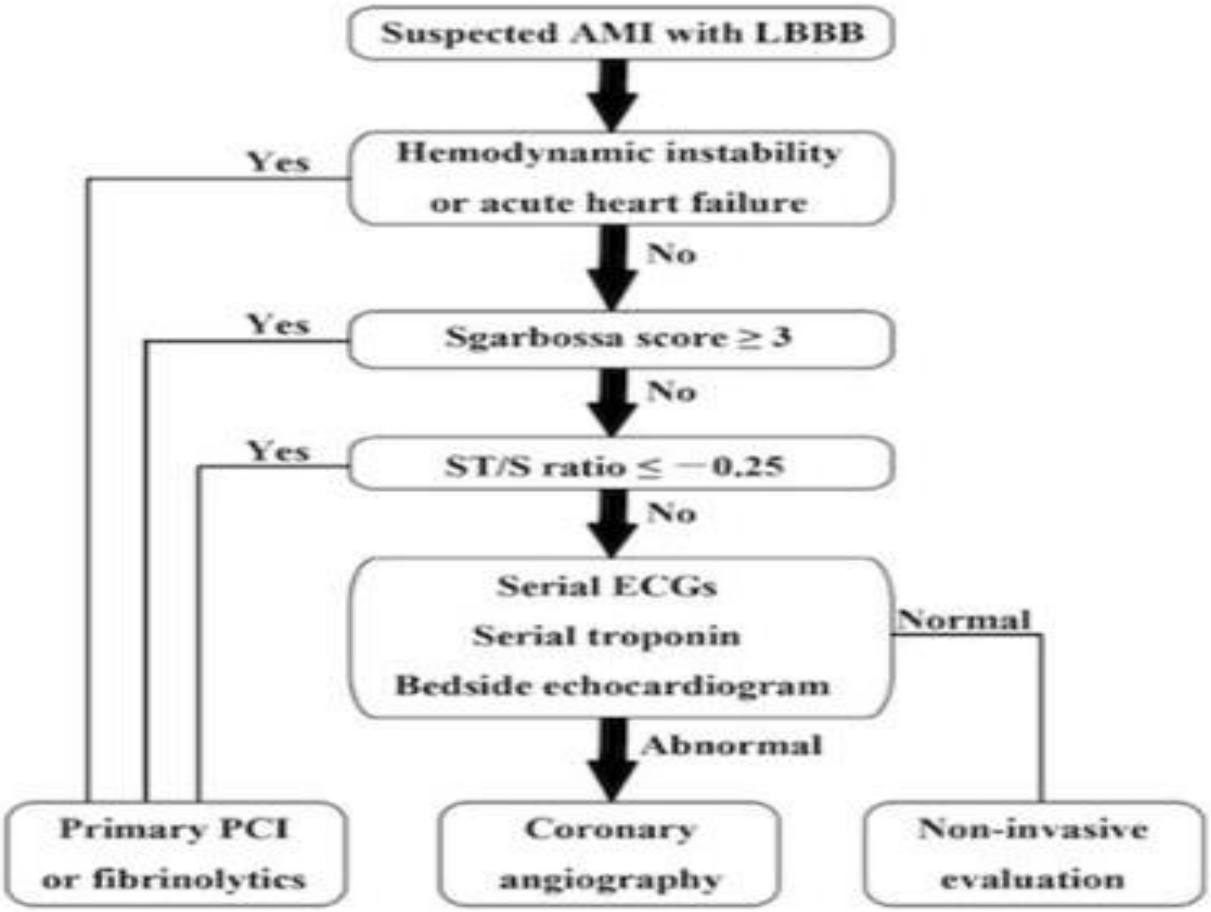
What are the original Sgarbossa Criteria?

- Concordant ST-segment elevation ≥ 1 mm in any lead = 5 points
- Concordant ST-segment depression ≥ 1 mm in lead V1 – V3 = 3 points
- Discordant ST-segment elevation ≥ 5 mm in any lead = 2 points



Sgarbossa ECG Criteria for LBBB	
Concordant STE ≥1mm	5 points
STD ≥1mm in V1 – V3	3 points
Discordant STE ≥5mm	2 points

- ST/S ratio ≤ -0.25 (Proposed, NOT Validated)



Diagnosis and triage algorithm for patients with suspected AMI and LBBB.

In contrast, haemodynamically stable patients presenting with chest pain and LBBB only have a slightly higher risk of having MI compared to patients without LBBB.

Therefore, the result of the hs-cTn T/I measurement at presentation should be integrated into the decision regarding immediate coronary angiography

In patients with right bundle brunch block (RBBB), ST-elevation is indicative of STEMI while ST-segment depression in lead I, aVL, and V5-6 is indicative of NSTE-ACS.

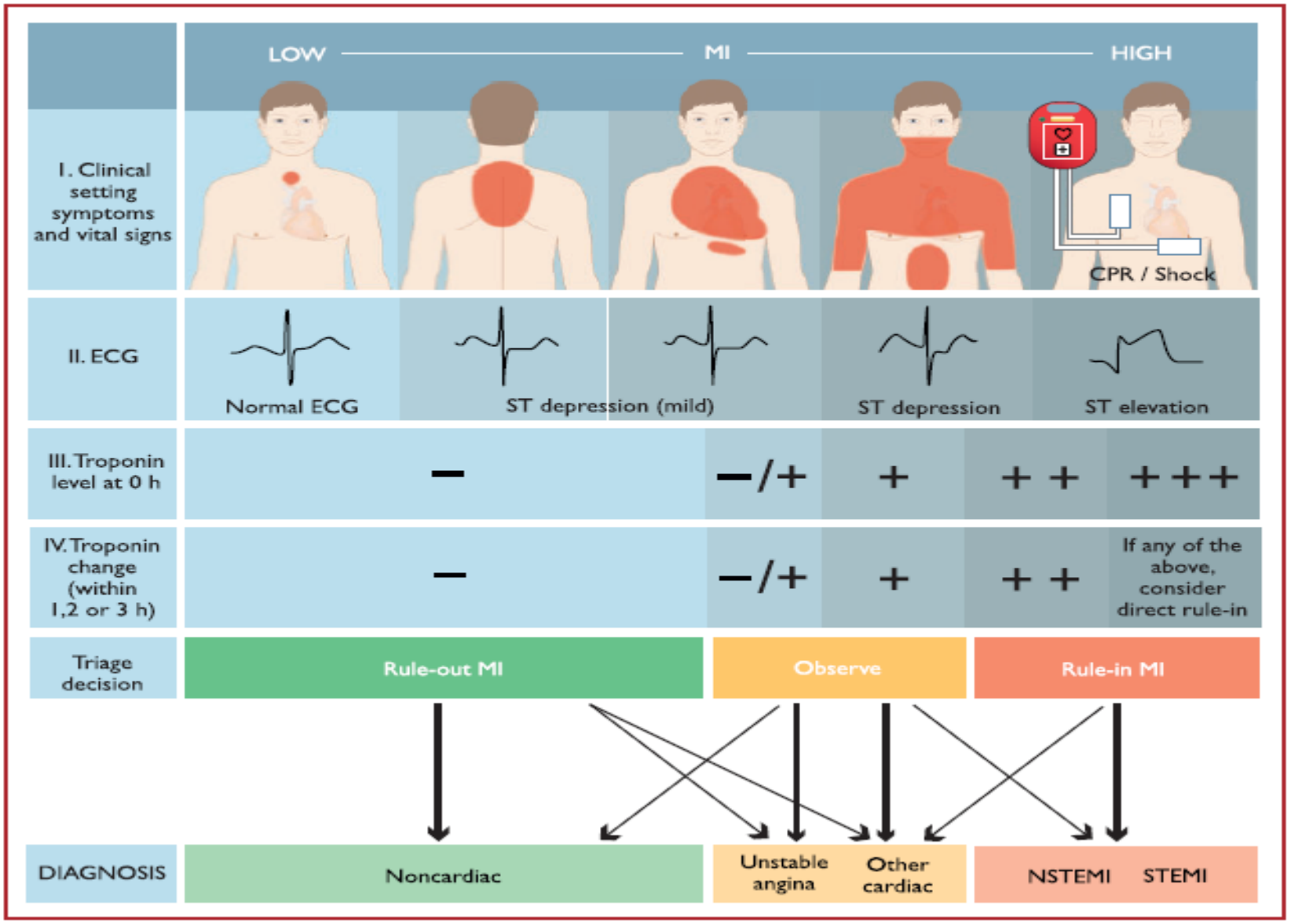
In patients with paced ventricular beats, the ECG is often of no help for the diagnosis of NSTE-ACS.

In general, it is advisable to perform ECG interpretation using remote technologies at the pre-hospital stage.

It is important to highlight that more than 50% of patients presenting with acute chest pain and LBBB to the emergency department or chest pain unit will ultimately be found to have a diagnosis other than MI.

Similarly, more than 50% of patients presenting with acute chest pain and RBBB to the emergency department will ultimately be found to have a diagnosis other than MI and should.

therefore, also await the result of the hs-cTn T/I measurement at presentation.


LOW
MI
HIGH
I. Clinical setting symptoms and vital signs
CPR / Shock
II. ECG
Normal ECG
ST depression (mild)
ST depression
ST elevation
III. Troponin level at 0 h
−
−/+
+
++
+++
IV. Troponin change (within 1,2 or 3 h)
−
−/+
+
++
If any of the above, consider direct rule-in
Triage decision
Rule-out MI
Observe
Rule-in MI
DIAGNOSIS
Noncardiac
Unstable angina
Other cardiac
NSTEMI
STEMI
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Biomarkers:

high-sensitivity cardiac troponin

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 hs-cTn, is mandatory in all patients with suspected NSTEACS.

Cardiac troponins are more sensitive and specific markers of cardiomyocyte injury than creatine kinase (CK), its myocardial band isoenzyme (CK-MB), and myoglobin

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.

In patients with MI, levels of cardiac troponin rise rapidly (i.e. usually within 1 h from symptom onset if using high-sensitivity assays) after symptom onset and remain elevated for a variable period of time (usually several days)

Advances in technology have lead to a refinement in cardiac troponin assays and have improved the ability to detect and quantify cardiomyocyte injury.

Data from large multicentre studies have consistently shown that hs-cTn assays increase diagnostic accuracy for MI at the time of presentation as compared with conventional assays (Figure in next slide), especially in patients presenting early after chest pain onset, and allow for a more rapid 'rule-in' and 'rule-out' of MI(Table3).

Overall, hs-cTn T and hs-cTn I assays seem to provide comparable diagnostic accuracy in the early diagnosis of MI

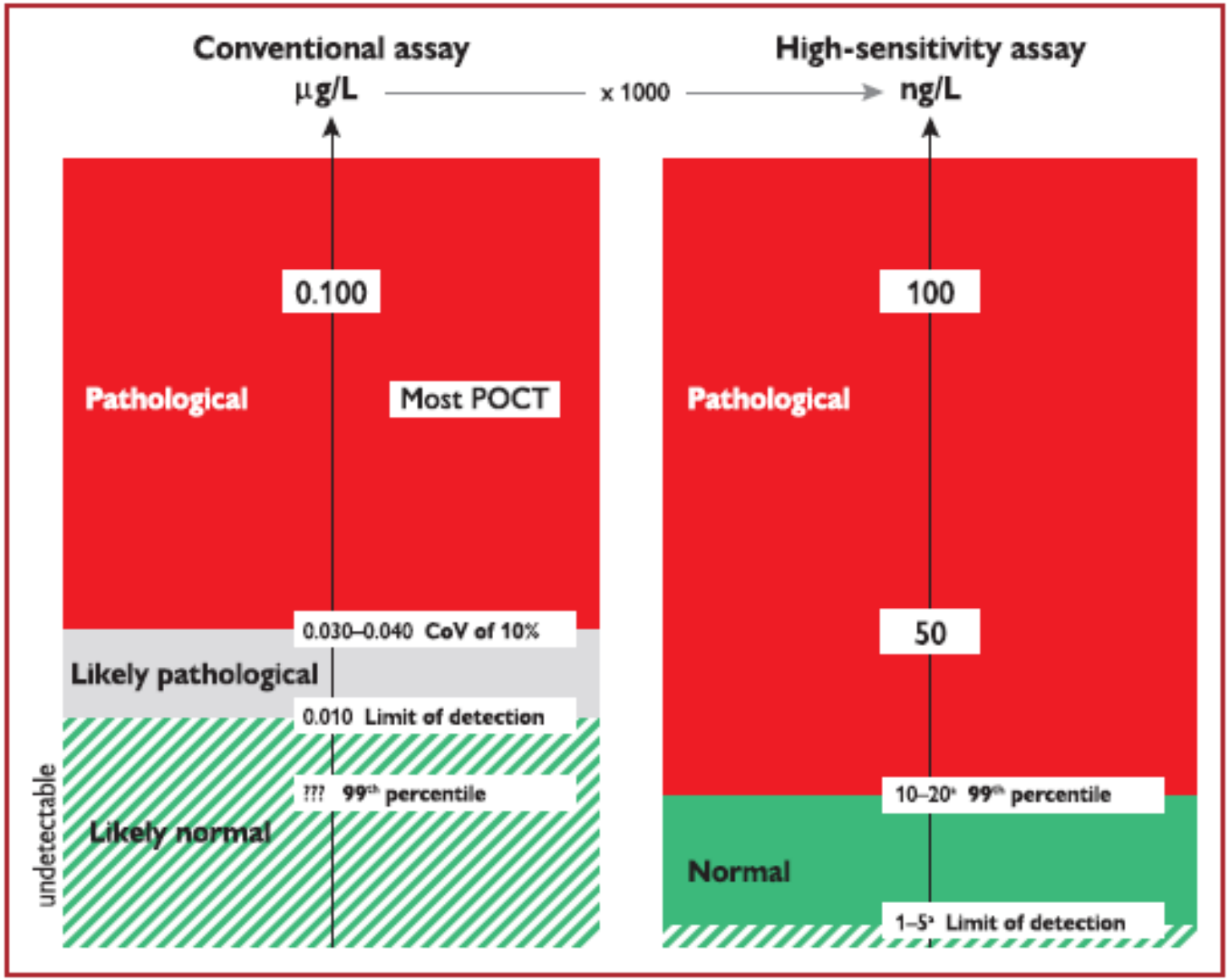
Conventional assay
µg/L
x 1000
High-sensitivity assay
ng/L
0.100
Pathological
Most POCT
0.030–0.040 CoV of 10%
Likely pathological
0.010 Limit of detection
??? 99th percentile
Likely normal
undetectable
100
Pathological
50
10–20* 99th percentile
Normal
1–5* Limit of detection
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Table 3 Clinical implications of high-sensitivity cardiac troponin assays

Compared with standard cardiac troponin assays, hs-cTn assays:
• Have higher NPV for AMI.
• Reduce the 'troponin-blind' interval leading to earlier detection of AMI.
• Result in ~4% absolute and ~20% relative increases 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 hs-cTn 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%) PPV for acute type 1 MI.
• Elevations up to 3-fold the upper reference limit have only limited (50–60%) PPV for AMI 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 (as in MI) from chronic cardiomyocyte damage (the more pronounced the change, the higher the likelihood of AMI).

AMI = acute myocardial infarction; hs-cTn = high-sensitivity cardiac troponin; MI = myocardial infarction; NPV = negative predictive value; PPV = positive predictive value.

Central laboratory vs. point-of-care:

The vast majority of cardiac troponin assays that are run on automated platforms in the central laboratory are sensitive (i.e. allow for detection of cardiac troponin in 20-50% of healthy individuals) or high-sensitivity (detection in 50-95% of healthy individuals) assays.

High-sensitivity assays are recommended over less sensitive ones, as they provide higher diagnostic accuracy at identical low cost

The majority of currently used point-of-care tests (POCTs) cannot be considered sensitive or high-sensitivity assays.

Therefore, the obvious advantage of POCTs, namely the shorter turn-around time, is counterbalanced by lower sensitivity, lower diagnostic accuracy, and lower negative predictive value (NPV).

Overall, automated assays have been more thoroughly evaluated than POCTs and seem to be preferable at this point in time.

The first hs-cTn I POCTs have recently been shown to provide **comparable performance characteristics** to that of central laboratory hs-cTn I/T assays.

Many cardiac pathologies other than MI also result in cardiomyocyte injury and, therefore, cardiac troponin elevations (Table 4).

Tachyarrhythmias, heart failure, hypertensive emergencies, critical illness, myocarditis, Takotsubo syndrome, and valvular heart disease are the most frequent ones.

Most often in elderly 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 syndromes (CCS) or hypertensive heart disease seem to be the most important contributor to cardiac troponin elevation in this setting.

Other life-threatening conditions presenting with chest pain, such as aortic dissection and pulmonary embolism, may also result in elevated cardiac troponinm concentrations and should be considered as differential diagnoses(Table 4).

Table 4 **Conditions other than acute type 1 myocardial infarction associated with cardiomyocyte injury (= cardiac troponin elevation)**

Tachyarrhythmias
Heart failure
Hypertensive emergencies
Critical illness (e.g. shock/sepsis/burns)
Myocarditis[a]
Takotsubo syndrome
Valvular heart disease (e.g. aortic stenosis)
Aortic dissection
Pulmonary embolism, pulmonary hypertension
Renal dysfunction and associated cardiac disease
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 graft(ing); PCI = percutaneous coronary intervention.
[a]Includes myocardial extension of endocarditis or pericarditis.

Other biomarkers

Compared with cardiac troponin, CK-MB shows a more rapid decline after MI and may provide added value for the timing of myocardial injury and the detection of early reinfarction.

However, it is important to highlight that little is known on how to best diagnose early reinfarction.

Myosin-binding protein C is more abundant than cardiac troponin and may therefore provide value as an alternative to, or in combination with, cardiac troponin.

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 high at the onset of MI in most patients, the added value of copeptin to conventional (less sensitive) cardiac troponin assays is substantial.

Therefore, the routine use of copeptin as an additional biomarker for the early rule-out of MI should be considered in the increasingly uncommon setting where hs-cTn assays are not available.

However, copeptin does not have relevant added value for institutions using one of the well-validated hs-cTn-based rapid protocols in the early diagnosis of MI.

Other widely available laboratory variables, such as estimated glomerular filtration rate (eGFR), glucose, and B-type natriuretic peptide (BNP) provide incremental prognostic information and may therefore help in risk stratification.

The determination of D-dimer is recommended in outpatients/emergency department patients with low or intermediate clinical probability, or those that are unlikely to have pulmonary embolism, to reduce the need for unnecessary imaging and irradiation.

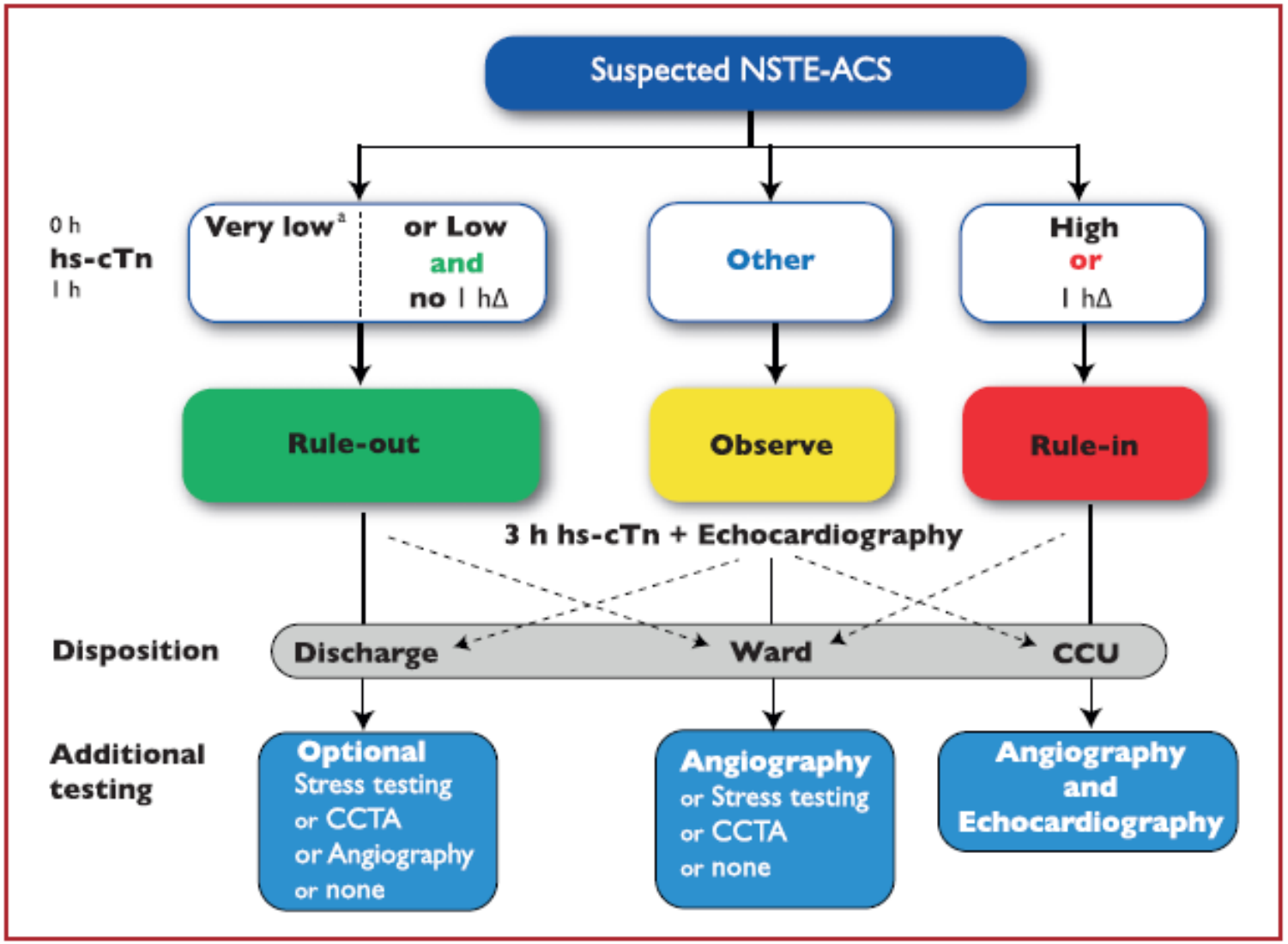
D-dimers are key diagnostic elements whenever pulmonary embolism is suspected

Rapid 'rule-in' and 'rule-out' algorithms

Due to the higher sensitivity and diagnostic accuracy for the detection of MI at presentation, the time interval to the second cardiac troponin assessment can be shortened with the use of hs-cTn assays.

This seems to substantially reduce the delay to diagnosis, translating into shorter stays in the emergency department and lower costs.

It is recommended to use the 0 h/1 h algorithm (best option, blood draw at 0 h and 1 h) or the 0 h/2 h algorithm (second best option, blood draw at 0 h and 2 h) (next figure).


Suspected NSTE-ACS
0 h
hs-cTn
1 h
Very low[a]
or Low
and
no 1 hΔ
Other
High
or
1 hΔ
Rule-out
Observe
Rule-in
3 h hs-cTn + Echocardiography
Disposition
Discharge
Ward
CCU
Additional testing
Optional
Stress testing
or CCTA
or Angiography
or none
Angiography
or Stress testing
or CCTA
or none
Angiography
and
Echocardiography
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These have been derived and well-validated in large multicentre diagnostic studies using central adjudication of the final diagnosis for all currently available hs-cTn assays.

Optimal thresholds for rule-out were selected to allow for a minimal sensitivity and NPV of 99%.

Optimal thresholds for rule-in were selected to allow for a minimal positive predictive value (PPV) of 70%.

The algorithms were developed in large derivation cohorts and then validated in large independent validation cohorts.

As an alternative, the previous European Society of Cardiology (ESC) 0 h/3 h algorithm should be considered.

However, three recent large diagnostic studies have suggested that the ESC 0 h/3 h algorithm seems to balance efficacy and safety less well in comparison to more rapid protocols using lower rule-out concentrations including the ESC 0 h/1 h algorithm.

Moreover, the very high safety and high efficacy of applying the ESC 0 h/1 h algorithm has recently been confirmed in three real-life implementation studies, including one randomized controlled trial (RCT)

The 0 h/1 h and 0 h/2 h algorithms rely on two concepts:

first, hscTn is a continuous variable and the probability of MI increases with increasing hs-cTn values, second, early absolute changes of the levels within 1 h or 2 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.

The cut-off concentrations within the 0 h/1 h and 0 h/2 h algorithms are assay specific(Table in next slide).

Table 5 Assay specific cut-off levels in ng/l within the 0 h/1 h and 0 h/2 h algorithms

0 h/1 h algorithm	Very low	Low	No 1hΔ	High	1hΔ
hs-cTn T (Elecsys; Roche)	<5	<12	<3	≥52	≥5
hs-cTn I (Architect; Abbott)	<4	<5	<2	≥64	≥6
hs-cTn I (Centaur; Siemens)	<3	<6	<3	≥120	≥12
hs-cTn I (Access; Beckman Coulter)	<4	<5	<4	≥50	≥15
hs-cTn I (Clarity; Singulex)	<1	<2	<1	≥30	≥6
hs-cTn I (Vitros; Clinical Diagnostics)	<1	<2	<1	≥40	≥4
hs-cTn I (Pathfast; LSI Medience)	<3	<4	<3	≥90	≥20
hs-cTn I (TriageTrue; Quidel)	<4	<5	<3	≥60	≥8
0 h/2 h algorithm	**Very low**	**Low**	**No 2hΔ**	**High**	**2hΔ**
hs-cTn T (Elecsys; Roche)	<5	<14	<4	≥52	≥10
hs-cTn I (Architect; Abbott)	<4	<6	<2	≥64	≥15
hs-cTn I (Centaur; Siemens)	<3	<8	<7	≥120	≥20
hs-cTn I (Access; Beckman Coulter)	<4	<5	<5	≥50	≥20
hs-cTn I (Clarity; Singulex)	<1	TBD	TBD	≥30	TBD
hs-cTn I (Vitros; Clinical Diagnostics)	<1	TBD	TBD	≥40	TBD
hs-cTn I (Pathfast; LSI Medience)	<3	TBD	TBD	≥90	TBD
hs-cTn I (TriageTrue; Quidel)	<4	TBD	TBD	≥60	TBD

These cut-offs apply irrespective of age and renal function. Optimized cut-offs for patients above 75 years of age and patients with renal dysfunction have been evaluated, but not consistently shown to provide better balance between safety and efficacy as compared to these universal cut-offs.[35,36,69] The algorithms for additional assays are in development.

hs-cTn = high-sensitivity cardiac troponin; TBD = to be determined.[35–37,39,40,68,69,75–84]

The NPV for MI in patients assigned ‘ruleout’ exceeded 99% in several large validation cohorts.

Used in conjunction with clinical and ECG findings, the 0 h/1 h and 0 h/2 h algorithm will allow the identification of appropriate candidates for early discharge and outpatient management.

Even after the ruleout of MI, elective non-invasive or invasive imaging may be indicated according to clinical assessment. Invasive coronary angiography (ICA) will still be the best option in patients with very high clinical likelihood of unstable angina, even afterNSTEMI has been ruled out.

In contrast, stress testing with imaging or coronary computed tomography angiography (CCTA) will be the best option in patients with low-tomodest clinical likelihood of unstable angina. No testing is necessary in patients with a clear alternative diagnosis

The PPV for MI in patients meeting the ‘rule-in’ criteria is about Most of the ‘rule-in’ patients with diagnoses other than MI did have conditions that usually still require ICA or cardiac magnetic resonance (CMR) imaging for accurate diagnosis, including Takotsubo syndrome and myocarditis.

Therefore, the vast majority of patients triaged towards the rule-in group are candidates for early ICA and admission to a coronary care unit (CCU).

These algorithms should always be integrated with a detailed clinical assessment and 12-lead ECG, and repeat blood sampling is mandatory in case of ongoing or recurrent chest pain.

The same concept applies to the 0 h/2 h algorithm. Cut-off levels are assay-specific and shown in Table 5.

Cut-off levels for other hscTn assays are in development

Observe:

Patients who do not qualify for 'rule-out' or 'rule-in', are assigned to observe.

They represent a heterogeneous group that usually requires a third measurement of cardiac troponin at 3 h and echocardiography as the next steps.

ICA should be considered in patients for whom there is a high degree of clinical suspicion of NSTE-ACS (e.g. relevant increase in cardiac troponin from presentation to 3 h),

while in patients with low-to-intermediate likelihood for this condition according to clinical judgment, non-invasive imaging using CCTA or stress testing [stress echocardiography, positron emission tomography, singlephoton- emission tomography (SPECT), or CMR for the detection of ACS features (oedema, late gadoliniumenhancement, perfusion defect, etc.)] should be considered after discharge from the emergency department to the ward.

No further diagnostic testing is indicated when alternative conditions, such as rapid ventricular rate response to atrial fibrillation (AF) or hypertensive emergency, have been identified.

Caveats of using rapid algorithms. 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. The ESC 0 h/1h and 0 h/2 h algorithms apply to all patients irrespective of chest pain onset. The safety (as quantified by the NPV) and sensitivity are very high (>99%), including in the subgroup of patients presenting very early (e.g. <2 h). However, due to the time dependency of troponin release and the only moderate number of patients presenting <1 h after chest pain onset in previous studies, obtaining an additional cardiac troponin concentration at 3 h in patients presenting <1 h and triaged towards rule-out should be considered.

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

Confounders of cardiac troponin concentration

In patients presenting with suspected NSTE-ACS, beyond the presence or absence of MI, four clinical variables affect hs-cTn concentrations:

i. Age (to a large extent as a surrogate for pre-existing cardiac disease).

ii. Renal dysfunction (to a large extent as a surrogate for pre-existing cardiac disease).

iii. Time from chest pain onset.

iv. Sex.

The effect of age (differences in concentration between healthy very young vs. healthy very old individuals up to 300%), renal dysfunction (differences in concentration between otherwise healthy patients with very high vs. very low eGFR up to 300%), and chest pain onset (>300%) is substantial, and modest for sex (40%).

Until information technology tools that allow the incorporation of the effect of all four variables are available, the use of uniform cut-off concentrations should remain the standard of care in the early diagnosis of MI

Practical guidance on how to implement the European Society of Cardiology 0 h/1 h algorithm:

In order to maximize the safety and feasibility of the process, the nursing team should, in general, obtain blood samples for hs-cTn at 0 h and 1 h irrespective of other clinical details and pending results.

This introduces unnecessary cardiac troponin measurements in perhaps 10-15% of patients with very low 0 h concentrations and chest pain onset >3 h, but substantially facilitates the process and thereby further increases patient safety.

Documentation of the time of the 0 h blood draw allows exact determination of the time window (± 10 min) of the 1 h blood draw.

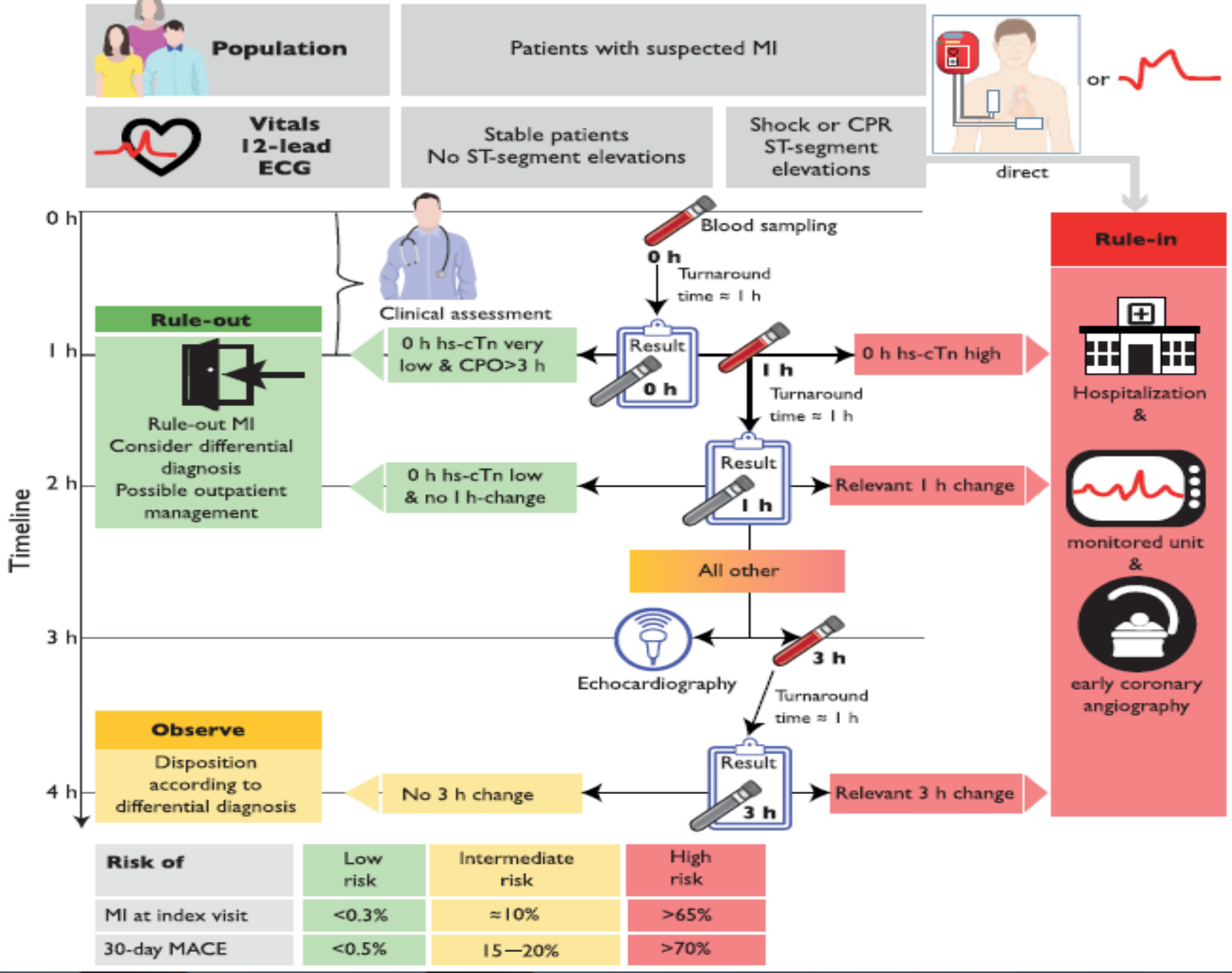
If the 1 h (± 10 min) blood draw was not feasible, then blood should be drawn at 2 h and the ESC 0 h/2 h algorithm applied.

Avoiding misunderstandings: time to decision=time of blood draw+turn-around time

The use of the ESC 0 h/1 h algorithm is irrespective of the local turn around time.

0 h and 1 h refer to the time point at which blood is taken (Figure 4).

The clinical and economic benefit of the ESC 0 h/1 h algorithm vs. the ESC 0 h/3 h algorithm or other algorithms with the second blood draw later than 1 h is therefore independent of the local turn-around time.



Risk of	Low risk	Intermediate risk	High risk
MI at index visit	<0.3%	≈10%	>65%
30-day MACE	<0.5%	15—20%	>70%

Non-invasive imaging

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 contrast echocardiography might improve the diagnostic and prognostic value of conventional echocardiography.

-detecting alternative pathologies associated with chest pain, such as acute aortic dissection, pericardial effusion, aortic valve stenosis, hypertrophic cardiomyopathy, mitral valve prolapse, 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.

-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 normal hs-cTn, who are free from chest pain for several hours, stress imaging can be performed during hospitalization or shortly after discharge.

Stress imaging is preferred over exercise ECG due to its greater diagnostic accuracy.

Various studies have shown that normal exercise or dobutamine or dipyridamole stress echocardiograms have high NPV for ischaemia and are associated with excellent patient outcomes.

Moreover, stress echocardiography has demonstrated superior prognostic value over exercise ECG.

If the acoustic window is not adequate to assess regional wall motion abnormalities, the use of echocardiographic contrast is recommended to improve the accuracy of such an assessment and facilitate the detection of ischaemia.

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 mid-term prognosis.

Additionally, CMR permits detection of scar tissue (using late gadolinium enhancement) and can differentiate this from recent infarction (using T2-weighted imaging to delineate myocardial oedema).

Moreover, CMR can facilitate the differential diagnosis between infarction, myocarditis, or Takotsubo syndrome, among others.

Similarly, SPECT has been shown to be useful for the risk stratification of patients with acute chest pain suggestive of ACS.

Resting myocardial scintigraphy, by detecting fixed perfusion defects suggestive of myocardial necrosis, can be helpful for the initial triage of patients presenting with chest pain without ECG changes or elevated cardiac troponins.

Combined stressrest imaging and/or stress-only imaging may further enhance assessment of ischaemia, while a normal study is associated with an excellent outcome.

Stressrest imaging modalities are usually not widely available on 24 h service and some (e.g. SPECT) are associated with substantial radiation exposure.

Anatomical evaluation

CCTA allows visualization of the coronary arteries and a normal scan excludes CAD.

CCTA has a high NPV to exclude ACS (by excluding CAD) and an excellent outcome in patients presenting to the emergency department with low-to-intermediate pre-test probability for ACS and a normal CCTA.

Seven RCTs have tested CCTA vs. usual care in the triage of low-to-intermediate-risk patients presenting with acute chest pain to emergency departments without signs of ischaemia on ECG and normal cardiac troponins. At a follow-up of 16 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, postdischarge emergency department visits, or re-hospitalizations) and showed that CCTA was associated with a reduction in emergency department costs and length of stay.

However, none of these studies used hs-cTn assays, which also reduce hospital stay.

In a randomized study, in which the standard of care included hs-cTn, CCTA was no longer able to improve patient flow.

It was also noted that CCTA was associated with an increase in the use of invasive angiography.

In contrast, in a recent randomized trial of unclear NSTEMI diagnosis, upfront imaging with CCTA reduced the need for ICA Similar results were observed in a sub-analysis of the Very EaRly vs Deferred Invasive evaluation using Computerized Tomography (VERDICT) trial, where upfront CCTA in NSTE-ACS patients had an NPV of 90.9%.

However, a relatively large patient group had to be excluded for specific reasons and an NPV of 90.9% is not entirely perfect.

Accordingly, CCTA can be used to exclude CAD and is thus less useful in patients with known CAD. Other factors limiting CCTA include severe calcifications (high calcium score) and elevated or irregular heart rate; in addition, a 24 h service is currently not widely available.

Finally, the use of CCTA in the acute setting in patients with stents or previous CABG has not been validated. Importantly, computed tomography (CT) imaging can effectively exclude other causes of acute chest pain that, if untreated, are associated with high mortality, namely pulmonary embolismand aortic dissection

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.

Several cardiac and non-cardiac conditions maymimic 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 origin.

Takotsubo syndrome has recently been observed more often as a differential diagnosis and usually requires coronary angiography to rule out ACS

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

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

Bold = common and/or important differential diagnoses.

[a]Dilated, hypertrophic and restrictive cardiomyopathies may cause angina or chest discomfort.

Chest X-ray is recommended in all patients in whom NSTEACS is considered unlikely in order to detect pneumonia, pneumothorax, rib fractures, or other thoracic disorders.

Stroke may be accompanied by ECG changes, myocardial wall motion abnormalities, and cardiomyocyte injury (= increase in cardiac troponin concentrations).

The majority of patients presenting to the emergency department with acute chest pain have non-cardiac conditions causing the chest discomfort.

In many instances, the pain is musculoskeletal and is therefore benign, selflimiting, and does not require hospitalization.

Chest pain characteristics help to some extent in the early identification of these patients.

Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected non-ST-segment elevation acute coronary syndrome

Recommendations	Class[a]	Level[b]
Diagnosis and risk stratification		
It is recommended to base diagnosis and initial short-term risk stratification on a combination of clinical history, symptoms, vital signs, other physical findings, ECG, and laboratory results including hs-cTn.[3]	I	B
It is recommended to measure cardiac troponins with high-sensitivity assays immediately after admission and obtain the results within 60 min of blood sampling.[3,10–13,29–31,34]	I	B
It is recommended to obtain a 12-lead ECG within 10 min after first medical contact and to have it immediately interpreted by an experienced physician.[21]	I	B
It is recommended to obtain an additional 12-lead ECG in case of recurrent symptoms or diagnostic uncertainty.	I	C
The ESC 0 h/1 h algorithm with blood sampling at 0 h and 1 h is recommended if an hs-cTn test with a validated 0 h/1 h algorithm is available.[30,33,35,36,39,68,69,75,76]	I	B
Additional testing after 3 h is recommended if the first two cardiac troponin measurements of the 0 h/1 h algorithm are not conclusive and the clinical condition is still suggestive of ACS.[85]	I	B
As an alternative to the ESC 0 h/1 h algorithm, it is recommended to use the ESC 0 h/2 h algorithm with blood sampling at 0 h and 2 h, if an hs-cTn test with a validated 0 h/2 h algorithm is available.[33,39,75,78,84]	I	B
Additional ECG leads (V3R, V4R, V7–V9) are recommended if ongoing ischaemia is suspected when standard leads are inconclusive.	I	C
As an alternative to the ESC 0 h/1 h algorithm, a rapid rule-out and rule-in protocol with blood sampling at 0 h and 3 h should be considered, if a high-sensitivity (or sensitive) cardiac troponin test with a validated 0 h/3 h algorithm is available.[70–73]	IIa	B
The routine use of copeptin as an additional biomarker for the early rule-out of MI should be considered where hs-cTn assays are not available.	IIa	B
It should be considered to use established risk scores for prognosis estimation.	IIa	C
For initial diagnostic purposes, it is not recommended to routinely measure additional biomarkers such as h-FABP or copeptin, in addition to hs-cTn.[47,48,51,52,54,118]	III	B

Imaging		
In patients presenting with cardiac arrest or haemodynamic instability of presumed cardiovascular origin, echocardiography is recommended and should be performed by trained physicians immediately following a 12-lead ECG.	I	C
In patients with no recurrence of chest pain, normal ECG findings, and normal levels of cardiac troponin (preferably high sensitivity), but still with a suspected ACS, a non-invasive stress test (preferably with imaging) for inducible ischaemia or CCTA is recommended before deciding on an invasive approach.[91,92,98,101,105–108]	I	B
Echocardiography is recommended to evaluate regional and global LV function and to rule in or rule out differential diagnoses.[c]	I	C
CCTA is recommended as an alternative to ICA to exclude ACS when there is a low-to-intermediate likelihood of CAD and when cardiac troponin and/or ECG are normal or inconclusive.[105,108,110–114]	I	A
Monitoring		
Continuous rhythm monitoring is recommended until the diagnosis of NSTEMI has been established or ruled out.	I	C
It is recommended to admit NSTEMI patients to a monitored unit.	I	C
Rhythm monitoring up to 24 h or to PCI (whichever comes first) is recommended in NSTEMI patients at low risk for cardiac arrhythmias.[d]	I	C
Rhythm monitoring for >24 h is recommended in NSTEMI patients at increased risk for cardiac arrhythmias.[e]	I	C
In the absence of signs or symptoms of ongoing ischaemia, rhythm monitoring in unstable angina may be considered in selected patients (e.g. suspicion of coronary spasm or associated symptoms suggestive of arrhythmic events).	IIb	C

0 h = time of first blood test; 1 h, 2 h, 3 h = 1, 2, or 3 h after the first blood test.

ACS = acute coronary syndromes; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ECG = electrocardiogram/electrocardiography; ESC = European Society of Cardiology; GRACE = Global Registry of Acute Coronary Events; h-FABP = heart-type fatty acid-binding protein; hs-cTn = high-sensitivity cardiac troponin; ICA = invasive coronary angiography; LV = left ventricular; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

[a]Class of recommendation.

[b]Level of evidence.

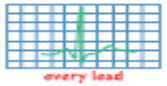
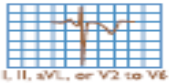
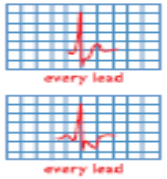
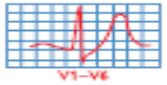
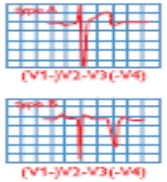
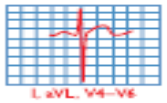
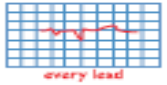
[c]Does not apply to patients discharged the same day in whom NSTEMI has been ruled out.

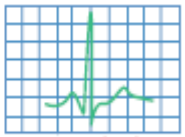
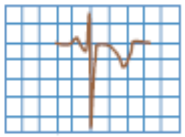
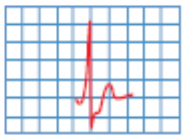
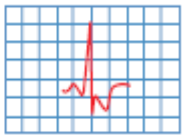
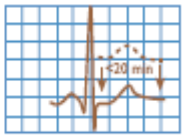
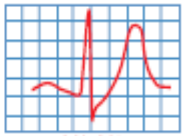
[d]If none of the following criteria: haemodynamically unstable, major arrhythmias, LVEF <40%, failed reperfusion, additional critical coronary stenoses of major vessels, complications related to percutaneous revascularization, or GRACE risk score >140 if assessed.

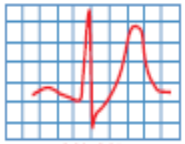
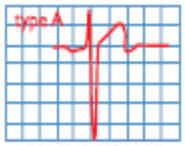
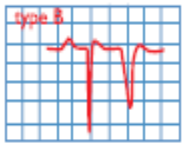
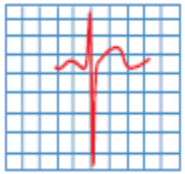
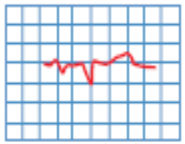
[e]If one or more of the above criteria are present.

Risk assessment and outcomes

1-Electrocardiogram indicators:

	ECG pattern	Criteria	Signifying	Figure
a	Normal ECG		No clue	
b	Isolated T-wave inversion	T-wave inversion >1 mm in ≥5 leads considering I, II, aVL, and V2–V6	Only mildly impaired prognosis	
c	ST-segment depression	J point depressed by ≥0.05 mm in leads V2 and V3 or ≥1 mm in all other leads followed by a horizontal or downsloping ST-segment for ≥0.08 s in ≥1 leads (except aVR)	More severe ischaemia	
d	Transient ST-segment elevation	ST-segment elevation in ≥2 continuous leads of ≥0.25 mV in men <40 years, ≥2 mm in men ≥40 years, or ≥0.15 mV in women in leads V2 through V3 and/or ≥0.1 mV in other leads lasting <20 min	Only mildly impaired prognosis	
e	De Winter ST-T	1–3 mm upsloping ST-segment depression at the J point in leads V1–V6 that continue into tall, positive, and symmetrical T waves	Proximal LAD occlusion/severe stenosis	
f g	Wellens sign	isoelectric or minimally elevated J point (<1 mm) + biphasic T wave in leads V2 and V3 (type A) or symmetric and deeply inverted T waves in leads V2 and V3, occasionally in leads V1, V4, V5, and V6 (type B)	Proximal LAD occlusion/severe stenosis	
h	Resting U wave inversion	discrete negative deflection in the T-P segment (negative in comparison to the following P-R segment) no initial positive U wave deflection not obscured by fusion with terminal T wave or following P wave in I, aVL, and V4 through V6	Occlusion or severe stenosis of the left main artery or LAD	
i	Low QRS voltage	peak to peak QRS complex voltage <0.5 mV in all limb leads and <1.0 mV in all precordial leads	High risk for in-hospital mortality	

	ECG pattern	Criteria	Signifying	Figure
a	Normal ECG		No clue	 every lead
b	Isolated T-wave inversion	T-wave inversion >1 mm in ≥5 leads considering I, II, aVL, and V2–V6	Only mildly impaired prognosis	 I, II, aVL, or V2 to V6
c	ST-segment depression	J point depressed by ≥0.05 mm in leads V2 and V3 or ≥1 mm in all other leads followed by a horizontal or downsloping ST-segment for ≥0.08 s in ≥1 leads (except aVR)	More severe ischaemia	 every lead  every lead
d	Transient ST-segment elevation	ST-segment elevation in ≥2 continuous leads of ≥0.25 mV in men <40 years, ≥2 mm in men ≥40 years, or ≥0.15 mV in women in leads V2 through V3 and/or ≥0.1 mV in other leads lasting <20 min	Only mildly impaired prognosis	 <20 min every lead
e	De Winter ST-T	1–3 mm upsloping ST-segment depression at the J point in leads V1–V6 that continue into tall, positive, and symmetrical T waves	Proximal LAD occlusion/severe stenosis	 V1–V6

e	De Winter ST-T	1–3 mm upsloping ST-segment depression at the J point in leads V1–V6 that continue into tall, positive, and symmetrical T waves	Proximal LAD occlusion/severe stenosis	
f g	Wellens sign	isoelectric or minimally elevated J point (<1 mm) + biphasic T wave in leads V2 and V3 (type A) or symmetric and deeply inverted T waves in leads V2 and V3, occasionally in leads V1, V4, V5, and V6 (type B)	Proximal LAD occlusion/severe stenosis	 
h	Resting U wave inversion	discrete negative deflection in the T-P segment (negative in comparison to the following P-R segment) no initial positive U wave deflection not obscured by fusion with terminal T wave or following P wave in I, aVL, and V4 through V6	Occlusion or severe stenosis of the left main artery or LAD	
i	Low QRS voltage	peak to peak QRS complex voltage <0.5 mV in all limb leads and <1.0 mV in all precordial leads	High risk for in-hospital mortality	

Supplementary Figure 2 Electrocardiogram indicators of risk in patients with non-ST-segment elevation acute coronary syndrome ECG = electrocardiogram; LAD = left anterior descending.

2-Biomarkers

Beyond diagnostic utility, initial cardiac troponin levels add prognostic information in terms of short- and long-term mortality to clinical and ECG variables.

While hs-cTn T and I have comparable diagnostic accuracy, hs-cTn T has greater prognostic accuracy.

Serial measurements are useful to identify peak levels of cardiac troponin for risk stratification purposes in patients with established MI. The higher the hs-cTn levels, the greater the risk of death.

However, evidence is limited regarding the optimal time points of serial hs-cTn measurement.

Serum creatinine and eGFR should also be determined in all patients with NSTE-ACS because they affect prognosis and are key elements of the Global Registry of Acute Coronary Events (GRACE) risk score.

Similarly, natriuretic peptides [BNP and N-terminal pro-BNP (NT-proBNP)] provide prognostic information regarding the risk of death, acute heart failure, as well as the development of AF in addition to cardiac troponin

In addition, quantifying the presence and severity of haemodynamic stress and heart failure using BNP or NT-proBNP concentrations in patients with left main CAD or three-vessel CAD without NSTEACS may help the heart team to select either PCI or CABG as the revascularization strategy of choice.

However, this needs confirmation in randomized trials and has not been tested in NSTEACS patients so far. Similarly, natriuretic peptides provide prognostic information on top of cardiac troponin.

Other biomarkers, such as high-sensitivity C-reactive protein, mid-regional pro-adrenomedullin, growth differentiation factor 15 (GDF-15), heart-type fatty acid-binding protein (h-FABP), and copeptin may also have some prognostic value.

However, the assessment of these markers has, so far, not been shown to improve patient management and their added value in risk assessment on top of the GRACE risk calculation and/or BNP/NT-proBNP seems marginal.

At the present time, the routine use of these biomarkers for prognostic purposes is not recommended.

Clinical scores for risk assessment

A number of prognostic models that aim to estimate the future risk of all-cause mortality or the combined risk of all-cause mortality or MI have been developed. These models have been formulated into clinical risk scores and, among these, the GRACE risk score offers the best discriminative performance.

It is important to recognize, however, that there are several GRACE risk scores, and each refers to different patient groups and predicts different outcomes.

The GRACE risk score models have been externally validated using observational data.

The nomogram to calculate the original GRACE risk score, which estimates the risk of in-hospital death, is shown in Supplementary Figure 3 and online risk calculators are available for other GRACE risk scores: https://www.out

comes-umassmed.org/risk_models_grace_orig.aspx for the GRACE risk score 1.0 and www.outcomes-umassmed.org/grace/ acs_risk2/index.html for the GRACE risk score 2.0

Supplementary Table I **Clinical scores for risk assessment**

Version	Method of calculation	Derivation cohort	Number of variables	Outcome	Model assumption	Model output	c statistics for NSTE-ACS population in derivation cohort
1.0	Pencil-and-paper calculator	11 389 patients enrolled from April 1999 to March 2001[30]	8	Risk of in-hospital death	Linear association between continuous predictor and risk[30,32,37]	Score is transferred to cumulative risk in percent by means of a nomogram	0.83[30]
	Pencil-and-paper calculator	15 007 patients enrolled from April 1999 to March 2002[32]	9	Risk of death from hospital discharge to 6 months			0.78[32]
	Web calculator or iPhone/iPad calculator	21 688 patients enrolled from April 1999 to September 2005[37]	8	Risk of in-hospital death			Unknown
			8	Risk of death from hospital admission to 6 months			0.79[37]
			8	Risk of death or MI from hospital admission to 6 months			0.70[37]
2.0	Web calculator or iPhone/Android application	Unknown	8	Risk of in-hospital death	Linear association between continuous predictor and risk	Unknown	Unknown
		Unknown	8	Risk of death from hospital admission to 6 months	Linear association between continuous predictor and risk	Score is transferred to cumulative risk in percent by means of a nomogram; risk is adjusted by 80/91 to reflect overall death rates in different populations	Unknown
		32 037 patients enrolled from January 2002 to December 2007[38]	8	Risk of death from hospital admission to 1 year	Non-linear association between predictor and risk[38]	Model estimates are directly used to compute cumulative risk in percent	0.829[38]
			8	Risk of death or MI from hospital admission to 1 year			0.746[38]
		1274 patients enrolled in the UK[38,39]	8	Risk of death from hospital admission to 3 years			0.782[38]

MI = myocardial infarction; NSTE-ACS = non-ST-elevation acute coronary syndrome.

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			8	Risk of death or MI from hospital admission to 6 months			0.70[37]

2.0	Web calculator or iPhone/ Android application	Unknown	8	Risk of in-hospital death	Linear association between continuous predictor and risk	Unknown	Unknown
		Unknown	8	Risk of death from hospital admission to 6 months	Linear association between continuous predictor and risk	Score is transferred to cumulative risk in percent by means of a nomogram; risk is adjusted by 80/91 to reflect overall death rates in different populations	Unknown
		32 037 patients enrolled from January 2002 to December 2007[38]	8	Risk of death from hospital admission to 1 year	Non-linear association between predictor and risk[38]	Model estimates are directly used to compute cumulative risk in percent	0.829[38]
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		1274 patients enrolled in the UK[38,39]	8	Risk of death from hospital admission to 3 years			0.782[38]

MI = myocardial infarction; NSTE-ACS = non-ST-elevation acute coronary syndrome.

1. Find points for each predictive factor:

Killip Class	Points	SBP, mm Hg	Points	Heart Rate, Beats/min	Points	Age, y	Points	Creatinine Level, mg/dL	Points
I	0	≤80	58	≤50	0	≤30	0	0–0.39	1
II	20	80–99	53	50–69	3	30–39	8	0.40–0.79	4
III	39	100–119	43	70–89	9	40–49	25	0.80–1.19	7
IV	59	120–139	34	90–109	15	50–59	41	1.20–1.59	10
		140–159	24	110–149	24	60–69	58	1.60–1.99	13
		160–199	10	150–199	38	70–79	75	2.00–3.99	21
		≥200	0	≥200	46	80–89	91	>4.0	28
						≥90	100		

Other Risk Factors	Points
Cardiac Arrest at Admission	39
ST-Segment Deviation	28
Elevated Cardiac Enzyme Levels	14

2. Sum points for all predictive factors:

Killip Class	+	SBP	+	Heart Rate	+	Age	+	Creatinine Level	+	Cardiac Arrest at Admission	+	ST-Segment Deviation	+	Elevated Cardiac Enzyme Levels	=	Total Points

3. Look up risk corresponding to total points:

Total Points	≤60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	≥250
Probability of In-Hospital Death, %	≤0.2	0.3	0.4	0.6	0.8	1.1	1.6	2.1	2.9	3.9	5.4	7.3	9.8	13	18	23	29	36	44	≥52

For example, a patient has Killip class II, SBP of 100 mm Hg, heart rate of 100 beats/min, is 65 years of age, has serum creatinine level of 1 mg/dL, did not have a cardiac arrest at admission but did have ST-segment deviation and elevated enzyme levels.
His score would be: 20 + 53 + 15 + 58 + 7 + 0 + 28 + 14 = 196
This person would have about a 16% risk of having an in-hospital death.

Similarly, a patient with Killip class I, SBP of 80 mm Hg, heart rate of 60 beats/min, is 55 years of age, has serum creatinine level of 0.4 mg/dL, and no risk factors would have the following score:
0 + 58 + 3 + 41 + 1 = 103, which gives approximately a 0.9% risk of having an in-hospital death.

Supplementary Figure 3 Clinical scores for risk assessment. The figure shows a nomogram for calculation of the GRACE risk score and was adapted by Granger *et al.*[30] SBP = systolic blood pressure.

1. Find points for each predictive factor:

Killip Class	Points	SBP, mm Hg	Points	Heart Rate, Beats/min	Points	Age, y	Points	Creatinine Level, mg/dL	Points
I	0	≤80	58	≤50	0	≤30	0	0–0.39	1
II	20	80–99	53	50–69	3	30–39	8	0.40–0.79	4
III	39	100–119	43	70–89	9	40–49	25	0.80–1.19	7
IV	59	120–139	34	90–109	15	50–59	41	1.20–1.59	10
		140–159	24	110–149	24	60–69	58	1.60–1.99	13
		160–199	10	150–199	38	70–79	75	2.00–3.99	21
		≥200	0	≥200	46	80–89	91	>4.0	28
						≥90	100		

Other Risk Factors	Points
Cardiac Arrest at Admission	39
ST-Segment Deviation	28
Elevated Cardiac Enzyme Levels	14

2. Sum points for all predictive factors:

Killip Class	+	SBP	+	Heart Rate	+	Age	+	Creatinine Level	+	Cardiac Arrest at Admission

+	ST-Segment Deviation	+	Elevated Cardiac Enzyme Levels	=	Total Points

3. Look up risk corresponding to total points:

Total Points	≤60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	≥250
Probability of In-Hospital Death, %	≤0.2	0.3	0.4	0.6	0.8	1.1	1.6	2.1	2.9	3.9	5.4	7.3	9.8	13	18	23	29	36	44	≥52

For example, a patient has Killip class II, SBP of 100 mm Hg, heart rate of 100 beats/min, is 65 years of age, has serum creatinine level of 1 mg/dL, did not have a cardiac arrest at admission but did have ST-segment deviation and elevated enzyme levels.
His score would be: 20 + 53 + 15 + 58 + 7 + 0 + 28 + 14 = 196
This person would have about a 16% risk of having an in-hospital death.

Similarly, a patient with Killip class I, SBP of 80 mm Hg, heart rate of 60 beats/min, is 55 years of age, has serum creatinine level of 0.4 mg/dL, and no risk factors would have the following score:
0 + 58 + 3 + 41 + 1 = 103, which gives approximately a 0.9% risk of having an in-hospital death.

upplementary Figure 3 Clinical scores for risk assessment. The figure shows a nomogram for calculation of the GRACE risk score and wa: dapted by Granger *et al.*[30] SBP = systolic blood pressure.

Given that the GRACE risk score predicts clinical outcomes, it is possible to stratify patients according to their estimated risk of future ischaemic events.

A GRACE risk score-based risk assessment has been found to be superior to (subjective) physician assessment for the occurrence of death or MI.

Moreover, it is well recognized that the delivery of guideline-directed care is inversely related to the estimated risk of the patient with NSTE-ACS143 the so called 'risk-treatment paradox'.

Guideline-directed care is associated with proportionally greater survival gains among those with higher baseline risk, therefore objective risk assessment may help to identify NSTE-ACS patients who would benefit from risk-determined care interventions.

The Australian GRACE Risk score Intervention Study (AGRIS)146 and the ongoing UK GRACE Risk score Intervention Study (UKGRIS)147 have or are for the first time investigating the impact of the utilization of the GRACE risk score on outcomes of patients with NSTE-ACS in a randomized manner.

The AGRIS cluster-randomized trial failed to demonstrate any add-on value, especially for the guideline-directed treatments with the routine implementation of the GRACE risk score.

This was largely explained by better-than-expected performance of the control hospitals.

Given temporal improvements in early mortality from NSTE-ACS, the prediction of long-term risk is important.

Deaths in the early phase following NSTE-ACS are more attributable to ischaemia/thrombosis-related events, whereas in the later phase they are more likely to be associated with the progression of atherosclerosis and non-cardiovascular causes.

Recommendations on biomarker measurements for prognostic stratification

Recommendations	Class[a]	Level[b]
Beyond its diagnostic role, it is recommended to measure hs-cTn serially for the estimation of prognosis.[12,13,119,120]	I	B
Measuring BNP or NT-proBNP plasma concentrations should be considered to gain prognostic information.[121,125,126]	IIa	B
The measurement of additional biomarkers, such as mid-regional pro-A-type natriuretic peptide, high-sensitivity C-reactive protein, mid-regional pro-adrenomedullin, GDF-15, copeptin, and h-FABP is not recommended for routine risk or prognosis assessment.[50,127,129]	III	B
Score to risk stratify in NSTE-ACS		
GRACE risk score models should be considered for estimating prognosis.[137–139]	IIa	B
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations may be considered.[153,154]	IIb	A
To estimate bleeding risk, the use of scores may be considered in patients undergoing coronary angiography.[155,156]	IIb	B

BNP = B-type natriuretic peptide; DAPT = dual antiplatelet therapy; GDF-15 = growth differentiation factor 15; GRACE = Global Registry of Acute Coronary Events; h-FABP = heart-type fatty acid-binding protein; hs-cTn = high-sensitivity cardiac troponin; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

[a]Class of recommendation.

[b]Level of evidence.

Bleeding risk assessment

Major bleeding events are associated with increased mortality in NSTE-ACS.

In order to estimate bleeding risk in this setting, scores such as the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/American Heart Association (AHA) guidelines (CRUSADE; https://www.mdcalc.

com/crusade-score-post-mibleeding-risk) and the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) bleeding risk scores have been developed.

Overall, the two scores have reasonable predictive value for major bleeding in ACS patients undergoing coronary angiography, with CRUSADE being the most discriminatory.

Changes in interventional practice, such as the use of radial access for coronary angiography and PCI, as well as in antithrombotic treatment, may modify the predictive value of risk scores.

In addition, in medically treated patients or those on oral anticoagulants(OACs), the predictive value of these scores has not been established.

Given these limitations, the use of the CRUSADE bleeding risk score may be considered in patients undergoing coronary angiography to quantify bleeding risk

An alternative to these scores may be the assessment of bleeding risk according to the Academic Research Consortium for High Bleeding Risk (ARC-HBR) (Table 7).

This consensus definition of patients at high bleeding risk (HBR) was recently developed to provide consistency for clinical trials evaluating the safety and effectiveness of devices and drug regimens for patients undergoing PCI.

This proposed ARC-HBR represents a pragmatic approach that includes the most recent trials performed in HBR patients, who were previously excluded from clinical trials of dual antiplatelet therapy(DAPT) duration or intensity (Table 7).

However, bleeding risk assessment based on ARC-HBR criteria may be difficult to apply in routine clinical practice as several of the criteria are quite detailed and so far, this score has not been validated.

Table 7 Major and minor criteria for high bleeding risk according to the Academic Research Consortium for High Bleeding Risk at the time of percutaneous coronary intervention (bleeding risk is high if at least one major or two minor criteria are met)

Major	Minor
• Anticipated use of long-term OAC[a]	• Age ≥ 75 years
• Severe or end-stage CKD (eGFR <30 mL/min)	• Moderate CKD (eGFR 30–59 mL/min)
• Haemoglobin <11 g/dL	• Haemoglobin 11–12.9 g/dL for men or 11–11.9 g/dL for women
• Spontaneous bleeding requiring hospitalization and/or transfusion in the past 6 months or at any time, if recurrent	• Spontaneous bleeding requiring hospitalization and/or transfusion within the past 12 months not meeting the major criterion
• Moderate or severe baseline thrombocytopenia[b] (platelet count <100 × 10^9/L)	• Chronic use of oral non-steroidal anti-inflammatory drugs or steroids
• Chronic bleeding diathesis	• Any ischaemic stroke at any time not meeting the major criterion
• Liver cirrhosis with portal hypertension	
• Active malignancy[c] (excluding non-melanoma skin cancer) within the past 12 months	
• Previous spontaneous intracranial haemorrhage (at any time) • Previous traumatic intracranial haemorrhage within the past 12 months • Presence of a brain arteriovenous malformation • Moderate or severe ischaemic stroke[d] within the past 6 months	
• Recent major surgery or major trauma within 30 days prior to PCI • Non-deferrable major surgery on DAPT	

CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; OAC = oral anticoagulation/anticoagulant; PCI = percutaneous coronary intervention.

[a]This excludes vascular protection doses.[162]

[b]Baseline thrombocytopenia is defined as thrombocytopenia before PCI.

[c]Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).

[d]National Institutes of Health Stroke Scale score >5.

Integrating ischaemic and bleeding risks

Major bleeding events affect prognosis in a similar way to spontaneous ischaemic complications. Given the trade-off between ischaemic vs. bleeding risks for any antithrombotic regimen, the use of scores might prove useful to tailor antithrombotic duration, as well as intensity, to maximize ischaemic protection and minimize bleeding risk in the individual patient.

Specific risk scores have been developed for patients on DAPT following PCI, in the setting of both CCS as well as ACS.

To date, no risk score has been tested in patients requiring long-term anticoagulation.

The DAPT and the PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy (PRECISE-DAPT) scores have been designed to guide and inform decision making on DAPT duration.

The applicability of the PRECISE-DAPT score is at patient discharge, while the DAPT score is a bleeding risk estimation to be calculated at 1 year from the index event.

The usefulness of the PRECISE-DAPT score was retrospectively assessed within patients randomized to different DAPT durations (n = 10 081) to identify the effect on bleeding and ischaemia of a long (12-24 months) or short (36 months) treatment duration in relation to baseline bleeding risk.

Among HBR patients based on PRECISE-DAPT (i.e. PRECISE-DAPT score>_25), prolonged DAPT was associated with no ischaemic benefit but a large bleeding burden.

Conversely, longer treatment in patients without HBR (i.e. PRECISE-DAPT score <25) was associated with no increase in bleeding and a significant reduction in the composite ischaemic endpoint of MI, definite stent thrombosis, stroke, and target vessel revascularization.

The findings remained valid in analyses restricted to ACS. However, for the majority of patients in the study, DAPT consisted of aspirin and clopidogrel.

An external validation of the PRECISE-DAPT score in ACS patients undergoing PCI and treated with prasugrel or ticagrelor showed a modest predictive value for major bleeding at a median follow-up of 14 months (c-statistic = 0.653).

In addition, none of these risk prediction models have been prospectively tested in RCTs, therefore, their value in improving patient outcomes remains unclear.

The DAPT study has been less well validated, with a retrospective analysis in 1970 patients and a score calculation at a different time point (6 vs. 12 months) than in the derivation cohort used to generate the score.