



# ANMCO-SIMEU Consensus Document: in-hospital management of patients presenting with chest pain

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**KEYWORDS**

Chest pain;  
Acute coronary syndromes;  
Differential diagnosis;  
Emergency department

Chest pain is a common general practice presentation that requires careful diagnostic assessment because of its diverse and potentially serious causes. However, the evaluation of acute chest pain remains challenging, despite many new insights over the past two decades. The percentage of patients presenting to the emergency departments because of acute chest pain appears to be increasing. Nowadays, there are two essential chest pain-related issues: (i) the missed diagnoses of acute coronary syndromes with a poor short-term prognosis; and (ii) the increasing percentage of hospitalizations of low-risk cases. It is well known that hospitalization of a low-risk chest pain patient can lead to unnecessary tests and procedures, with an increasing trend of complications and burden of costs. Therefore, the significantly reduced financial resources of healthcare systems induce physicians and administrators to improve the efficiency of care protocols for patients with acute chest pain. Despite the efforts of the Scientific Societies in producing statements on this topic, in Italy there is still a significant difference between emergency physicians and cardiologists in managing patients with chest pain. For this reason, the aim of the present consensus document is double: first, to review the evidence-based efficacy and utility of various diagnostic tools, and, second, to delineate the critical pathways (describing key steps) that need to be implemented in order to standardize the management of chest pain patients, making a correct diagnosis and treatment as uniform as possible across the entire country.

**Introduction**

'Chest pain' is the symptom causing 5-9% of admissions to hospital emergency departments (ED) in the western countries.<sup>1</sup> The most frequent cause of chest pain is acute coronary syndrome (ACS), at rates of up to 45%.<sup>2</sup> In about 2% of cases, ACS is not correctly detected and patients are mistakenly discharged,<sup>3</sup> at a cost estimated to be higher than 6 billion dollars,<sup>4,5</sup> with missed diagnoses of ACS triggering increases in legal and medical expenses.<sup>6</sup>

Issues associated with the management of these patients are two-fold, prompting the need: (i) on one hand, to avoid missed diagnoses of ACS, which has a high-mortality rate; and (ii) on the other, to avoid extensive hospitalization of cases at low risk.

The preparation of this consensus paper was prompted by the evolution and innovative implementation of diagnostic tools available in this setting of patients, following publication of the previous ANMCO-SIMEU Italian consensus document in 2009.<sup>7</sup>

The mentioned evolution is reflected in: (i) the introduction of high-sensitivity troponins and new biomarkers; (ii) the adoption of the newer ESC guidelines on ACS; (iii) the development of non-invasive imaging tests (at rest and with stress); and (iv) the need to introduce the concept of the 'Chest Pain Team'.

Technically, a chest pain is any pain occurring, anteriorly, between the base of the nose and the umbilicus and, posteriorly, between the occiput and the 12th vertebra, which has no traumatic or other clearly identifiable underlying cause.<sup>7</sup>

Among patients entering ED with chest pain, ACS is diagnosed and confirmed in 10-20% of cases.<sup>8</sup>

When a patient is admitted to ED because of acute chest pain, the true goal is to confirm or exclude an ACS [ST elevation myocardial infarction (STEMI), non ST elevation myocardial infarction (NSTEMI) unstable angina (UA)].

Among the causes of chest pain, there are life threatening conditions such as acute aortic syndrome (AAS), pulmonary embolism (PE), and hypertensive pneumothorax.

Aortic dissection and other AASs (aortic ulcer, intramural haematoma) are the causes of chest pain associated with the highest rate of mortality. PE may present with chest pain, dyspnoea, syncope, haemoptysis, cardiac arrest, or a combination of all these symptoms, which may be non-specific, hence the recommendation to use clinical predictive scores such as the Wells Score for PE.<sup>9</sup>

Table 1 shows a checklist of the causes of chest pain that must always be taken into consideration in a differential diagnosis with ACS.<sup>10</sup>

**Diagnostic tools****Clinical history (anamnesis) and physical examination**

A missed diagnosis of ACS can occur because uncorrected ECG interpretation, young age of the patient, inexperience of the physician, atypical symptoms presentation, missing ECG at first medical contact (FCM).<sup>11</sup>

In the absence of ECG abnormalities, the initial anamnestic evaluation also serves to sort the patients into different groups having a lesser or greater likelihood of ACS.

As reported in a meta-analysis of Fanaroff *et al.*,<sup>2</sup> the characteristics of chest pain/discomfort and the associated symptoms can be of used to obtain a probability stratification, but have no significant diagnostic power [LR + (positive likelihood ratio) < 3 for all assessed characteristics and for all associated symptoms]. Diaphoresis indicates a slightly higher probability of ACS (LR + 1.3-1.4). The presence of symptoms that derive benefit from taking sub-lingual nitrates or from resting is not a predictor of ACS.<sup>12</sup>

**Table 1** Modified from ACCA clinical decision-making toolkit<sup>10</sup>

Causes of chest pain/discomfort not related to ACS	
Cardiovascular	
Acute pericarditis, pericardial effusion	
Acute myocarditis	
Severe hypertensive crisis	
Stress induced cardiomyopathy (Takotsubo-like syndrome)	
Hypertrophic cardiomyopathy, aortic stenosis	
Acute left ventricular failure	
Acute aortic syndrome (dissection, aortic ulcer, intramural haematoma)	
Pulmonary embolism, pulmonary infarction, severe pulmonary hypertension	
Cardiac contusion	
Acute bio or mechanical prosthetic valve failure/malfunction	
Non-cardiovascular	
Oesophageal spasm, oesophagitis, gastroesophageal reflux disease	
Peptic ulcer, acute cholecystitis-pancreatitis	
Pneumonitis, bronchitis, asthma attack	
Pleurisy, pleural effusion, pneumothorax	
Chest injury	
Costochondritis, rib fracture	
Damage to cervical/thoracic vertebrae or discs	
Herpes zoster	
Anxiety, depression	

The presentation of symptoms is more atypical in elderly, where dyspnoea tends to dominate over the pain symptom, and also in women and in diabetics.

There are certain scores that integrate anamnesis with ECG and with the results of the first troponin test, introduced initially to assess the prognosis for known ACS: the PURSUIT score,<sup>13</sup> the TIMI risk score,<sup>14</sup> the HEART score,<sup>15</sup> and the GRACE score.<sup>16</sup>

The *physical examination* of patients with chest pain/discomfort and suspected ACS is very often normal or almost normal, and if there are signs of haemodynamic instability, or of heart failure, these indicate a particularly severe prognosis. Particular physical signs to look for are those indicating a disease not of myocardial ischaemic origin: pericarditis (pleuritic pain worsening by change in position, pericardial friction rub), PE (sudden onset of dyspnoea and pain, signs of right heart failure), aortic dissection (sudden onset pain often radiating to back, alterations of peripheral pulses) and those suggesting a suspicion of non-cardiac disorders: pneumothorax (abrupt onset of dyspnoea and pain), pneumonia (pleuritic pain, dyspnoea), musculoskeletal (intense fleeting pain), peptic ulcer, and pancreatitis (intense epigastric or substernal pain) diseases.<sup>17,18</sup>

### The electrocardiogram

When a patient has chest pain, 12-lead ECG should be performed within 10 min of the FMC. ECG can turn out to be normal in 1/5 of patients with chest pain caused by ACS.<sup>19</sup> In terms of electrocardiographic diagnosis, patients affected by ACS can be divided into two categories:

#### Anamnesis and physical examination. Executive summary

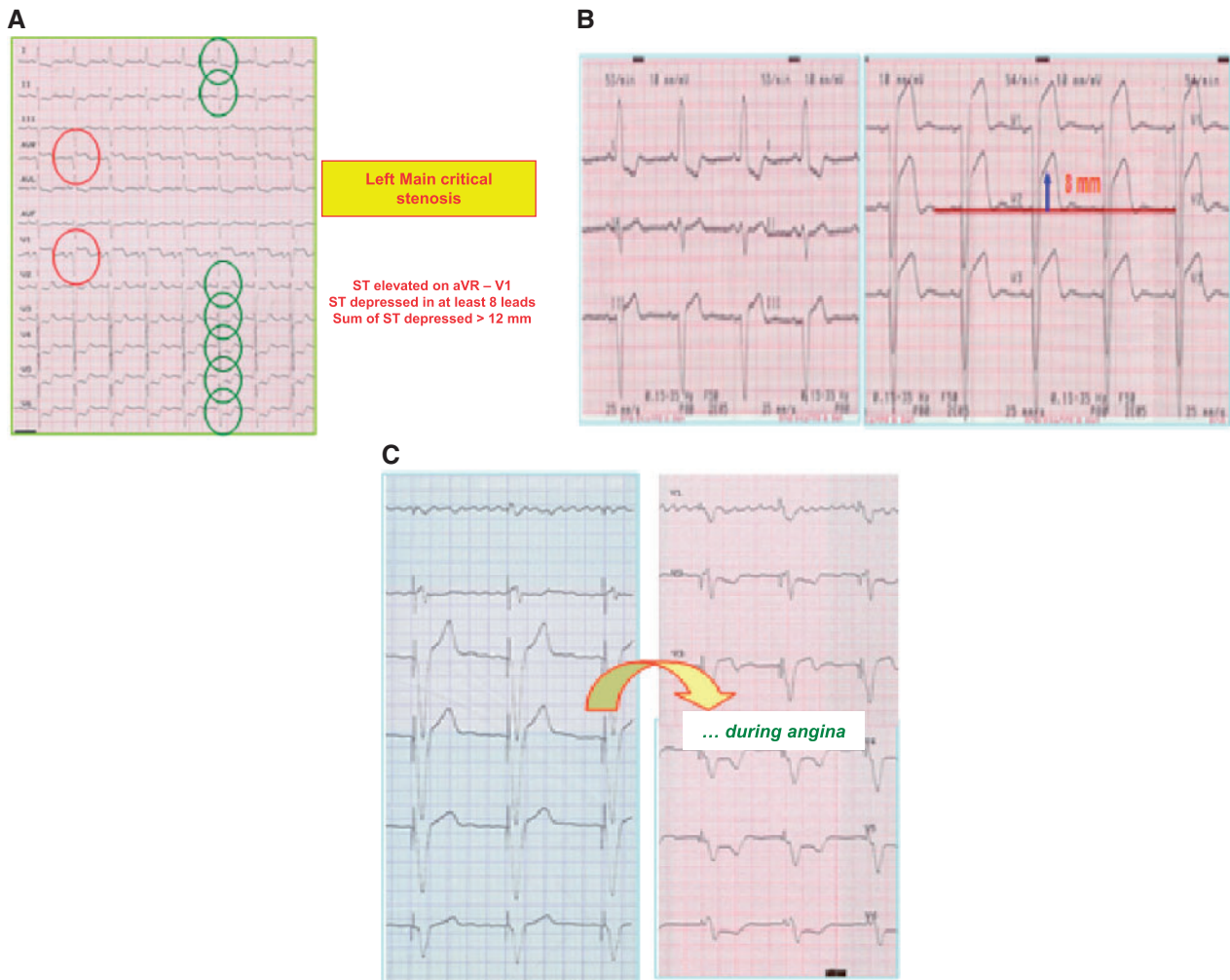
1. Recommended procedure: careful anamnestic assessment of symptoms at presentation, previous illnesses and risk factors, which can be integrated with an assessment of the likelihood of disease. Recommended procedure: calculation and use of risk/likelihood scores (GRACE, TIMI or HEART) associating anamnestic data with data relative to ECG and to initial troponin dosage.
2. Recommended procedure: baseline and serial assessment of vital parameters; search for signs possibly indicating life threatening severe diseases.

- (1) Patients with a persistent elevation of the ST segment (or new onset of left bundle branch block)<sup>20</sup> can be classified as STEMI-ACS;
- (2) Patients with ECG abnormalities other than elevation of the ST segment can be classified as NSTEMI-ACS.<sup>21</sup> ACS-NSTEMI can also progress in the absence of any ECG abnormalities.

In these cases, only increased biochemical markers of myocardial necrosis will allow a distinction between NSTEMI and UA.

The number of leads involved, the presence and magnitude of ST depression or a transient elevation are all indicative of the extent of the ischaemia and correlated likewise with the prognosis.<sup>21</sup>

Registry studies show that in 18.5% of cases, the ECG appears normal or doubtful on initial observation, and there is a minimal percentage of patients, with undiagnosed ACS as the result of an ECG having been incorrectly interpreted or badly performed.<sup>19</sup> Accordingly, where there is a high likelihood of ACS on the basis of anamnesis,



**Figure 1** Unusual ECG abnormalities during acute myocardial ischaemia. (A) Critical stenosis in the left main of the left coronary artery; (B) marked elevation of ST segment  $>5$  mm in leads V1-V2 with left bundle branch block and during chest pain; (C) significant abnormalities during chest pain under pace-maker rhythm.

the patient should be monitored continuously or serial 12-lead ECG should be taken. A 12-lead ECG must necessarily be taken in case of symptom recurrence or where symptoms worsen.<sup>22</sup> ESC guidelines<sup>21</sup> stress the importance of continuous 12-lead monitoring; for certain types of patients, moreover, comparison with previous ECGs is fundamentally important. In the case of left bundle branch block, indications of ischaemic damage will be given by a marked elevation of the ST segment beyond 5 mm in the right precordial leads or using the Sgarbossa criteria<sup>23</sup>: (i) ST elevation more than 1 mm and in the same direction (concordant) with the QRS complex, 5 points; (ii) ST depression more than 1 mm in leads V1-V3, 3 points; (iii) ST elevation more than 5 mm and in the opposite direction (discordant) with the QRS, 2 points. A score of 3 points is required to diagnose an acute myocardial infarction. Similarly, significant ST/T changes accompanying chest pain during right ventricular pacing ECG may be indicative of acute myocardial ischaemia (Figure 1).

When there is transmural necrosis of the antero-septal wall in a patient with right bundle branch block, there will

be a fall of the R wave in leads V1-V4 with appearance of the Q wave and simultaneous elevation of the ST segment.

If, during an acute episode of chest pain, previously inverted T waves should return to be positive (pseudonormalization), the suspicion of transmural myocardial ischaemia is confirmed.

The need to comparison with previous ECG traces should encourage the use of electronic systems for electrocardiographic archiving. The launch of a national electrocardiography database (<https://www.bancadelcuore.it/>) by ANMCO is emblematic of the response to this need. With this project, the subject is provided with an electronic card called *BancomHeart*, allowing remote access to 12-lead electrocardiograms archive stored over time, by way of computer, tablet, and smartphone. An essential characteristic of these databases must be their ease of consultation, hence the possibility of using them via web tools.

For some clinical conditions, the 12-lead ECG can simulate transmural ischaemic myocardial lesion: acute pericarditis, ventricular pre-excitation, Brugada syndrome, early repolarization, electrolytic disorders.

If the 12-lead ECG results normal/non diagnostic, or not 'definitely ischaemic', it is better to have the interpretation confirmed as soon as possible by an expert.

Special care must be taken to ensure that the ECG is performed correctly. IEC Standards state that acquisition of the diagnostic ECG signal must be accomplished with a passband of 0.05-150 Hz for the diagnosis of ischaemia, infarction, etc. Many other diseases are detectable provided that measures are taken to ensure the quality of the electrical signal, which otherwise could occasion huge diagnostic errors, invalidity and possible legal consequences, as well as considerable ancillary costs. It is also essential that ergometric stress, Holter, telemetry and monitor traces are always ensured compliant with requirements for 12-lead diagnostic ECG, using unreconstructed signals, with a passband of at least 0.05 up to 150 Hz. The diagnostic electrocardiography signal must be acquired from 10 electrodes, using 12, simultaneous ECG leads: 6 peripheral, and 6 unipolar precordial.<sup>24,25</sup>

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#### 12-leads ECG—executive summary

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1. A 12-lead ECG must be performed on a patient with chest pain within 10' after the FMC, and the results interpreted immediately by an expert.
  2. Always perform V3R-4R in the case of inferior STEMI (to detect a possible lesion in the free wall of the right ventricle) and V7-V9 in the case of STEMI of the inferior and lateral wall, or of suspected posterior STEMI (to detect extension to the posterior myocardial tissue).
  3. A quick comparison should be made with previous traces, if possible using electronic archives that will allow fast retrieval and consultation of previous ECGs. This comparison is indispensable for patients with bundle branch block, pacing or previous myocardial infarction.
  4. For cases under observation in ED, continuous 12-lead ECG monitoring is recommended. Alternatively, serial 12-lead ECGs must be performed.
  5. It is important that a 12-lead trace be taken in the event of a recurrence or worsening of symptoms.
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### Biomarkers

Many biomarkers are related to diagnostic and prognostic processes associated with acute myocardial infarction. Diagnostic biomarkers for necrosis are creatine-kinase, troponin, Heart-Type Fatty Acid Binding Protein and Copeptin an Arginine Vasopressor Activation. Other biomarkers are related to prognostic process: brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) with biomechanical stress, high sensitive C-reactive protein (Hs-CRP) with inflammation, myeloperoxidase with neutrophilic activation, and endothelin with endothelial activation.<sup>26</sup>

### Cardiac troponin

Abnormal levels of cardiac troponin (cTn), type I (cTn-I) or type T (cTn-T) are considered the standard diagnostic indicator of acute myocardial infarction (AMI).<sup>27,28</sup> The third universal definition of myocardial infarction<sup>29</sup> considers the raised level of troponin, with a typical

**Table 2** Elevation of troponin due to causes other than myocardial ischaemia

Cardiovascular
Tachyarrhythmias
Acute cardiac insufficiency
Hypertensive crises
Myocarditis–pericarditis
Aortic dissection
Infiltration/accumulation diseases
Pulmonary embolism
Acute neurological episodes (stroke or subarachnoid haemorrhage)
Cardiac/thoracic contusion/trauma
Cardiac procedures: electrical cardioversion, ablation, endomyocardial biopsy
Systemic
Respiratory distress/bronchial pneumonia
Dehydration/cachexia
Systemic diseases (fever/infection/shock/burns)
Hypo and hyper thyroidism
Post-operative disorders
Severe anaemia/gastrointestinal bleeding
Use of cardiotoxic drugs
Kidney failure
Prolonged endurance sports
Rhabdomyolysis
Analytical
Poor analytical platform performance
Calibration errors/dilution problems
Limitations relating to sample collection: heterophile antibodies
Interfering substances (fibrin)

curve, as one of the elements indispensable to the diagnosis of AMI.

The elevation of troponin T or I occurs 2-4 h following the onset of symptoms.

Laboratory tests of high-analytical sensitivity are used to measure troponin I e T; these employ immunometric methods capable of measuring the 99th percentile of the reference population with an error equal to or less than 10%, as recommended by national guidelines.<sup>30</sup>

With the 'new' troponins, the negative predictive power of a single test is up to 95%, becoming 100% with 2 tests.<sup>31</sup> ESC 2015 guidelines on ACS-NSTEMI<sup>21</sup> recommend the use of *high-sensitivity cardiac troponin* (hs-cTn).

The kinetic pattern of hs-cTn is different to that of conventional cTn and consequently the timing of the measurements must be reviewed. Positivity with hs-cTn occurs much earlier than with conventional cTn, and there is evidence<sup>32</sup> to show that with this marker, it is possible to rule out AMI within 3 h after registration and triage, with a sensitivity and negative predictive values of around 100%.

An increase of cTn indicates only a cardiomyocyte damage and it can occur even in clinical situations other than ACS (Table 2). Being of lower specificity, these markers can cause a high and growing number of cases involving 'false positives', impacting adversely in terms of unsuitability and waste of resources.

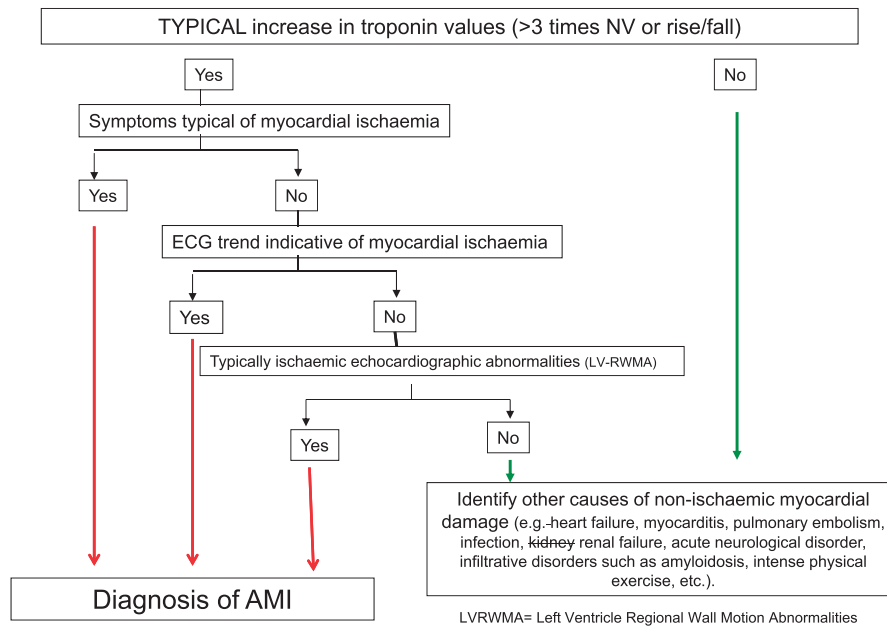


Figure 2 Interpretation of elevated troponin values.

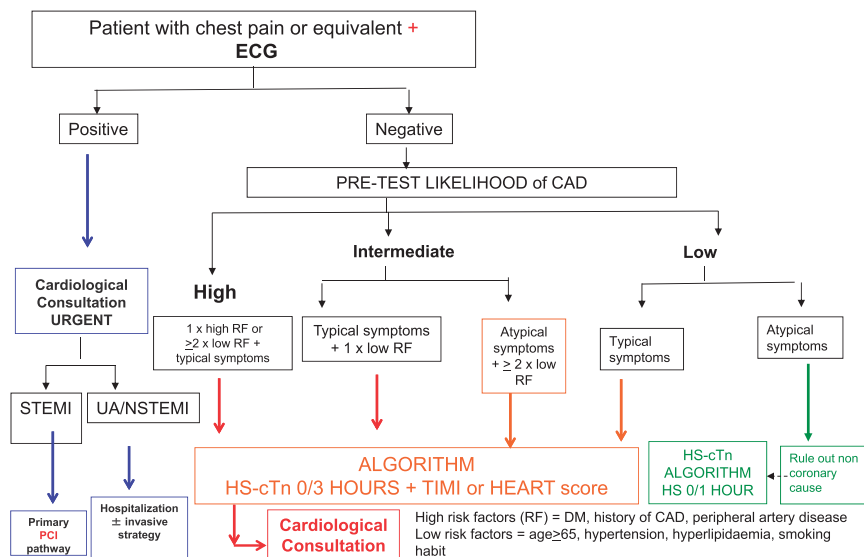


Figure 3 Selection of patient undergoing cardiac troponin assay in ED.

**Algorithms in using cTn**

**0-3 h Algorithm**

The 0-3 h algorithm (Figure 2) is currently the standard of reference for hs-cTn markers, and confirmed as such by the 2015 ESC Guidelines on ACS-NSTEMI.<sup>21</sup>

**0-1 h Algorithm**

An alternative algorithm validated and proposed more recently, of shorter duration with a 0/1 hour assessment, is based on a lower and more sensitive cut-off compared to that of the 99th percentile (6 ng/L).<sup>21</sup> This latter algorithm is based on the fact that hs-cTn is a continuous variable, and as its values increase, so does the probability of AMI. Moreover, this algorithm is based on the assumption that early absolute variations in levels at 1 h can be used as

surrogates for variations at 3 and 6 h, guaranteeing an incremental diagnostic value of the protocol. This protocol has proved useful especially in rule-out procedures, ensuring reliable early discharge of low-risk patients with negative troponin.

**0-6 h Algorithm**

To rule out acute infarction of the myocardium, the cTn assay, conducted utilizing methods of the latest generation, though not high sensitivity, should be performed at time 0 and after 6 h (considering measurement at 3 h as well, however, so as not to miss the peak of the curve). If all the values observed are ≤99th percentile and the variation in concentration is <50% (below the 99th percentile), the patient can be discharged.

If the onset of the symptom was  $>6$  h and the patient is asymptomatic, with a GRACE score of  $<140$ , and a differential diagnosis can be ruled out, discharge can be allowed possibly after a provocative test, or the test can be performed within a few days following discharge, as will be explained in due course.

Even using hs-cTn, but with tests not directly validated for the 0-1 h and 0-3 h algorithms, it is advisable to consider application of the 0-6 h algorithm.

### Novel biomarkers

Among the new biomarkers, copeptin appears to have the most scientific evidence in medical literature.<sup>33-37</sup> It represents the C-terminal portion of the pro-hormone of vasopressin secreted from the pituitary gland, and is able to quantify the level of endogenous stress characterizing many clinical conditions, including AMI. Owing to the rapid rise in the level of endogenous stress at the onset of ACS, copeptin immediately becomes positive even as the symptoms are first experienced, hence at the first blood test. A single copeptin assay is therefore sufficient, and this should always be employed in combination with troponin (*dual-marker strategy*). A patient dischargeable after the first blood test will therefore be one who is troponin-negative and copeptin-negative ( $<10$  pmol/L). This combination has a high negative predictive power in respect of AMI (close to 100%) and avoids the need for further troponin tests, thus speeding up management timescales considerably.

There are future developments in this field. There is an increasing interest in circulating microRNAs, non-coding small ribonucleic acid protein, as potential novel biomarkers for AMI. MicroRNAs increase their plasma levels shortly after the onset of a coronary event and certain isoforms appear exclusively after an AMI. Circulating miRNA seems to improve the diagnostic potential but at the moment the clinical data are very preliminary.<sup>38</sup>

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#### Biomarkers: executive summary

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1. The use of high-sensitivity cardiac troponin (hs-cTn) is recommended.
  2. The recommended algorithm is the 0-3 h type, using specifically validated hs-cTn.
  3. Whilst troponin is the diagnostic standard for AMI, it must be remembered that levels can be high in conditions other than ACS and an isolated increase does not allow the diagnosis of AMI, given that troponin is considered only to be a marker of myocardial damage.
  4. Stable values or inconsistent variations of troponin in the absence of dynamic variations in its plasma concentration (rise/fall with generation of a kinetic curve) do not constitute a marker of ACS.
  5. Practical cooperation with the blood analysis laboratory is essential, as also is knowledge of the diagnostic method (assay) utilized.
  6. Severe kidney failure causes cTn to increase (more so cTn-T than cTn-I). A higher cut-off value based on estimated glomerular filtration rate (eGFR) levels is needed for a more accurate diagnosis of AMI-NSTEMI in patients suffering from end-stage kidney failure.<sup>39</sup>
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### Exercise test

A maximal exercise test resulting negative for inducible ischaemia can help to avoid needless hospitalizations and allow patient discharge directly from Short-Stay Intensive Observation Unit.<sup>40</sup> In certain cases, the exercise test could also be scheduled within a few days following discharge.

The ergometric test (treadmill or bicycle) should be conducted once the patient has been asymptomatic for at least 12 h and showing no signs of heart failure for at least 48 h. Should the provocative test prove negative, the patient can be discharged directly and considered at low risk.<sup>41</sup>

The exercise ECG does not reveal high specificity or sensitivity. False responses can be produced in the case of bundle branch blocks or pacing, and reduced specificity of the findings is expected in case of former myocardial infarction. Nonetheless, one study documents a high-negative predictive value (99%) and high confidence in a population with a disease prevalence of 5%.<sup>42</sup> On the other hand, the appearance of angina or abnormalities of the ST segment during a low-work load would indicate a high likelihood of critical coronary disease.<sup>43</sup>

### Non-invasive imaging tests

#### Chest X-ray

The standard chest X-ray is diagnostic test performed frequently in a critical area on patients presenting with chest pain, especially to rule out pulmonary and vascular disorders.<sup>44</sup>

ESC guidelines on aortic dissection include the chest X-ray among the diagnostic tests.<sup>45</sup>

#### Rest echocardiography

Performing echocardiography quickly in ED was strongly recommended in the ANMCO-SIMEU position paper of 2009,<sup>4</sup> especially in cases with a combination of ongoing chest pain, non-diagnostic 12-lead ECG, and haemodynamic instability.<sup>46</sup> The latest 2015 ESC guidelines on ACS-NSTEMI<sup>21</sup> indicate echocardiography as having an essential role in the diagnosis of acute myocardial ischaemia, as it is able to detect regional wall motion abnormalities of the left ventricle (hypokinesia, akinesia), especially when symptoms are ongoing, and when the differential diagnosis of chest pain are non-coronary cardiovascular (aortic dissection, myocarditis-pericarditis, valve prosthetic dysfunction, etc.).<sup>47</sup>

Accordingly, an ultrasound scan, exploring not the 'organ' (heart, kidney, gall bladder, etc.) but the 'problem' (chest pain, haemodynamic instability, dyspnoea, etc.), is frequently performed by a cardiologist, or even by an emergency physician or resuscitator, using echocardiography to investigate not only chest pain but also dyspnoea, transient ischaemic attack (TIA)/stroke to identify cardioembolic sources, low-blood pressure, syncope, etc.<sup>48,49</sup>

There is still strong debate surrounding the echocardiographic diagnosis of acute myocardial infarction: studies on patients suffering chest pain, observed at a cardiologists-run Chest Pain Unit, showed the usefulness of serial echocardiographic scan of regional left ventricular wall motion in the final diagnosis of acute myocardial infarction, when 12-lead ECG and troponin were still

negative. Many other publications insist on the limitations and scant effectiveness of the method in this patient setting.<sup>50,51</sup>

### Stress echocardiography

Stress echocardiography is a technique used for the diagnosis, risk stratification, and prognosis of patients with known or suspected coronary disease employing various stressors that include inotropic drugs (dobutamine) or vasodilators (dipyridamole, adenosine) and also non-pharmacological stressors. Physical exercise is the most physiological stressor and consequently the most utilized and most recommended in literature.<sup>52</sup> Assessment is based on abnormalities in regional wall motion of the left ventricle during stress, compared to baseline, and the test is sometimes associated with the assessment of coronary flow reserve (CFR) on the anterior descending artery with adenosine.<sup>53</sup>

Numerous studies showed that a negative stress echo (using physical or pharmacological stressors) assumes a high negative predictive power and is associated with favourable outcome, as well as demonstrating a higher prognostic value than the ECG ergometric test.<sup>54,55</sup>

This operator-dependent technique also requires a suitable level of experience and skill which, as suggested by the major European and American scientific societies (European Association of CardioVascular Imaging, American Society of Echocardiography) is obtainable by performing and reporting >100 examinations per year.<sup>56</sup>

### Contrast echocardiography and strain imaging

Contrast echocardiography, in a setting of patients with chest pain, serves a dual purpose, allowing: (i) enhancement of the endocardial border during ventricular opacification, significantly improving the analysis of regional wall motion; and (ii) analysis of myocardial perfusion.<sup>57</sup>

The use of a contrast, which has the effect of enhancing the endocardial border, also increases the sensitivity of the stress echo, improving the *assessment* of all segments of the left ventricle wall, especially in patients having poor acoustic windows.

For the first time, the 2015 ESC Guidelines on ACS-NSTEMI<sup>21</sup> also mention Strain Imaging derived from 2D Speckle-Tracking echocardiography as a possible tool in detecting abnormalities of regional and global systolic function in patients with chest pain.

### Multislice coronary computed tomography

Coronary computed tomography (CT) using scanners with at least 64 rows of detectors will allow the identification of haemodynamically significant stenosis (>50%), in addition to an already high negative predictive value (higher than 90%) as well as a clear improvement in terms of positive predictive value and specificity.<sup>58</sup> This technique should be reserved for an extremely restricted population with a low to intermediate pre-test likelihood, quantifiable at between 20% and 70%.<sup>59</sup> This group also includes patients with chest pain not immediately identifiable using the more common diagnostic tools (ECG, biomarkers, blood gas analysis, chest X-ray), or who might be candidates for a triple rule-out (ACS, AAS, and PE) using a single diagnostic

test, albeit this approach remains controversial.<sup>60</sup> ROMICAT studies<sup>61,62</sup> comparing coronary CT with standard assessment procedure in the management of patients with chest pain, found that CT improved clinical decision making, reducing hospitalization time, but was also associated with an increase in downstream testing, exposure to radiation and higher care costs. Consequently, as of today there are no certainties on the real usefulness of coronary CT in decisional algorithms for acute chest pain.

### Cardiac magnetic resonance imaging

As of today there are no proofs to support the accuracy and the impact of magnetic resonance imaging (MRI) on the management of patients with acute chest pain.

The use of cardiac MRI on patients presenting with chest pain is referable almost exclusively to pharmacological stress testing with dobutamine.<sup>63,64</sup>

In images obtained during the course of a pharmacological stress test, any myocardial areas with low CFR will show a signal enhancement delayed and attenuated in relation to the surrounding myocardium (hypoperfusion area). A factor of fundamental importance in the interpretation of a myocardial perfusion scan during pharmacological stress is comparison with perfusion images obtained at rest and with delayed-enhancement images.

The capture of diagnostic quality coronary angio-MRI images from the single patient tends not to be constant, and generally will allow the identification of any significant stenoses (>50%) only along the proximal and medial segments of the large epicardial coronary vessels.

A meta-analysis,<sup>65</sup> conducted on 37 studies of cardiac MRI involving 2191 patients with known or suspected coronary disease, reported sensitivity, and specificity values of 83% and 86% respectively, in the case of kinematic stress, and of 91% and 81% respectively, in the case of perfusion stress tests. On the basis of these findings, the most recent ESC guidelines on myocardial revascularization indicate recommendation level IA for stress cardiac MRI in the case of symptomatic patients with intermediate pre-test likelihood of obstructive coronary disease, and attribute recommendation class IIB to coronary angio-MRI for the assessment of symptomatic patients examined for obstructive coronary disease.<sup>66</sup>

### Nuclear medicine tests

Myocardial tomoscintigraphy (SPECT) is used widely for assessing the perfusion of myocardial tissue, the extent of myocardial damage and its impact on cardiac function. In the PROMISE study,<sup>67</sup> nuclear tests were the ones most utilized in functional testing arm: 67% as against 22% for stress echo tests and 10% for ergometric tests.

The severity of the patient's illness can influence the result of the test: the number of vessels affected influences results. In effect, sensitivity increases with the rise in the number of vessels affected, from around 85% to 95% if all the 3 main branches are involved. Similarly, the extent of the stenosis is critical in determining positivity. If the stenosis is severe, the test is positive in over 70% of cases. The vessels found most often to be stenotic are the anterior descending and the right coronary artery, on visual inspection, whereas the semi-quantitative method



**Table 3** Indications for correct and appropriate use of imaging tests in a setting of patients with chest pain

Appropriateness in non-invasive ultrasound procedures	ACR/ACC/AHA/AATS/ ACEP/ASNC/NASCI/ SAEM/SCCT/SCMR/SCPC/ SNMMI/STR/STS 2015	ASE 2013 (pericardium) 2015 (aorta)	ESC 2014 (Aorta PE) 2015 (ACS)	ANMCO-SIMEU 2016
STEMI-ACS (HUS)	R		A	A
ACS—certain (HUS)	R/M		A	A
ACS—probable (HUS)	M		A	A
ACS—possible (HUS)	R/M		A	A
PE low probability and DD—(CUS)	R		R	R
PE no low probability or DD+ (CUS)	M/A		M/A	A
PE no low probability or DD+ (HUS)			M/A	A
AAS possible/probable (HUS)	M	M	A	A
Pericarditis possible/probable (HUS)	A	A	A	A
Pnx possible/probable (TUS)				A
Not classified chest pain				A

ACS, acute coronary syndrome; HUS, heart ultra-sounds; CUS, compressive ultra-sounds; PE, Pulmonary Embolism; Pnx, pneumothorax; AAS, acute aortic syndrome; TUS, thorax ultra-sounds; DD, D-dimer; A, appropriate; M, intermediate appropriateness; R, rarely appropriate; O, not indicated.

functions better for the right and the circumflex. Indicators of triple vessel disease, in addition to diffuse deficits in the areas involved, include pulmonary capture of the radioactive drug and transient enlargement of the left ventricular lumen. The test should be restricted to those patients presenting with chest pain indicative of coronary disease, but without significant abnormalities on their ECG trace or without biomarker-related abnormalities, making it possible to identify patients at high risk, i.e. those with reversible perfusion defects rather than those who do not have perfusion defects or those who have irreversible perfusion defects as from former necrosis.<sup>67,68</sup>

#### Comparison between anatomical and functional testing and appropriateness in the use of imaging tests for patients with chest pain

The PROMISE study<sup>69</sup> was the first to draw a real comparison between anatomical tests (multislice coronary CT) and functional tests (nuclear, stress-echo, ergometric) conducted on patients with chest pain and suspected coronary disease. The primary hypothesis of the study was that cardiac events (combination of death from whatever cause, myocardial infarction, hospitalization for unstable angina, and major peri-procedural complications) at 2 years into follow-up would be fewer in the CT group than in the functional testing group. The study, which enrolled 5000 patients for each arm, showed no difference in predetermined outcomes, legitimating the use of functional tests for the initial diagnosis of symptomatic patients for suspected coronary disease. In short, the study rehabilitated the clinical procedure that had always been practised (and suggested by guidelines) before multislice coronary imaging was made possible by the groundbreaking advent of coronary CT. It is reasonable to concur with Gaibazzi<sup>70</sup> in saying that functional tests will never attain the diagnostic accuracy of multislice coronary CT if compared with the gold standard of 'coronarography', likewise anatomical, but their capacity for the stratification of patients

according to the presence and extent of reversible ischaemia places them notionally on a higher level of usefulness than an anatomical test such as coronary CT.

The paper entitled '2015 ACR/ACC/AHA/AATS/ACEP/ASNC/NASCI/SAEM/SCCT/SCMR/SCPC/SNMMI/STR/STS Appropriate Utilization of Cardiovascular Imaging in Emergency Department Patients With Chest Pain'<sup>71</sup> provides indications for correct and appropriate use of imaging tests in a setting of patients with chest pain.

It assesses the appropriateness of tests on the basis of four diagnostic entry points: (i) suspected ACS; (ii) suspected PE; (iii) suspected AAS; and (iv) patients for whom it is not possible to establish a probable diagnosis. The grading of tests adopted in the paper is A = appropriate, M = may be appropriate, R = rarely appropriate. Starting from this statement, in this document we report a modified table summarizing the appropriateness of the different non-invasive ultrasound test in the daily management of chest pain patients (*Table 3*).

#### Proposal of in-hospital diagnostic pathway

The diagnostic pathway for chest pain patients proposed in this document has the following goals:

- to identify patients with a high probability of ACS (STEMI, NSTEMI, unstable angina) with the aim of ensuring timely reperfusion of STEMI patients and initiating the appropriate specialist procedure for those with NSTEMI and unstable angina;
- to identify other diseases of non-coronary origin requiring emergency or urgent treatment procedures;
- to assess the likelihood of ACS in patients with chest pain having no clear cause and with non-diagnostic or normal 12-lead ECG on initial assessment.

The diagnostic pathway proposed in this consensus document will be divided into single steps.

##### Step 1: triage

The following actions are recommended at triage (by nurses):

Steps	Actions	Timing
1. Assessment on the door	Assessment of symptoms type	Immediate
2. Targeted collection of clinical/ anamnestic data	Recording of data. Fill an anamnestic questionnaire form if necessary	Within 10'
3. Perform 12-lead ECG	Consider performing V3R-4R and V7-9; acquisition of report.	Within 10', or immediately if patient is in pain
4. Brief physical examination to assess vital parameters	Fill in report indicating vital parameters	
5. Assign priority colour code <sup>72</sup>	For method of assignment, see text	After steps 1, 2, and 3
6. Re-assessment	Yellow codes Green codes	→ After 10' → After 30'

### Step 2: ED—emergency room (ER)

In the ER, the following actions should be performed.

Actions	Description	Indications
Venous access	Cannulation of antecubital vein	Always
12-lead ECG	Interpret, report, repeat or perform for first time if not performed during triage period	Always
Anamnesis	Collection of complete anamnestic data, expanding on details recorded at triage <sup>73</sup>	Always
Physical examination	Assess 'vital parameters' sheet filled in during triage, perform a complete physical examination, drafting structured second report if appropriate	Always
Take blood for troponin	The troponin (T or I) utilized should preferably be high sensitivity (hs-cTn) <sup>74</sup>	See Figure 3
Other blood-chemical tests	Complete blood count, coagulation, creatinine, plasma electrolytes, others according to clinical suspicion	Always
Blood gas analysis	Arterial blood sample	If respiratory insufficiency or suspicion of pleuro-pulmonary disease or PE
Bedside ultrasound scan	Protocol as per guidelines	According to cases, not least to rule out causes other than ACS
Request radiology exams	Chest X-ray, chest angio CT, multislice coronary CT	According to clinical suspicion
Activate consultations	Cardiac consultation and/or transthoracic-transoesophageal echocardiogram	According to cases, during the diagnostic orientation process

### Step 3: diagnostic orientation and in-hospital observation protocol

The main decision-making crossroads coincide with: (i) 12-lead ECG acquiring; and (ii) cardiac troponin dosage.

- (1) The 12-lead ECG must answer the following questions:
- (2) are there signs of acute transmural ischaemia (ACS-STEMI) detectable in the 12-lead ECG? If so, initiate a fast track cardiac care pathway (referral to the cathlab for primary PCI or to the reference STEMI network) in order to ensure reperfusion in the shortest time possible (door-to-balloon time, ideally <90 min); refer to specific ESC guidelines<sup>20</sup> (Figure 4);
- (3) are there signs of acute non transmural ischaemia (ACS-NSTEMI) detectable in the 12-lead ECG? If so, initiate a cardiac care pathway with transfer to

- Intensive Cardiac Care Unit and/or cathlab; refer to specific ESC guidelines<sup>21</sup> (Figure 4);
- (4) if the answer to both of the above questions is no, but there are signs of haemodynamic instability (resuscitated cardiac arrest, cardiogenic shock scenario, acute pulmonary oedema, low blood pressure, etc.) assess differential diagnosis with other acute and life threatening diseases (by way of echocardiogram and/or CT scan or other diagnostic procedures)<sup>75,76</sup> (Figure 4)
- (5) if the answer to all the above questions is no, but pain is persistent and ongoing at the time of observation, a more specific fast track diagnosis pathway must be put in hand (echocardiogram and/or CT scan and/or urgent coronary angiography if indicated.

If the answer to all the above questions is no and there are no signs of haemodynamic instability, a specific

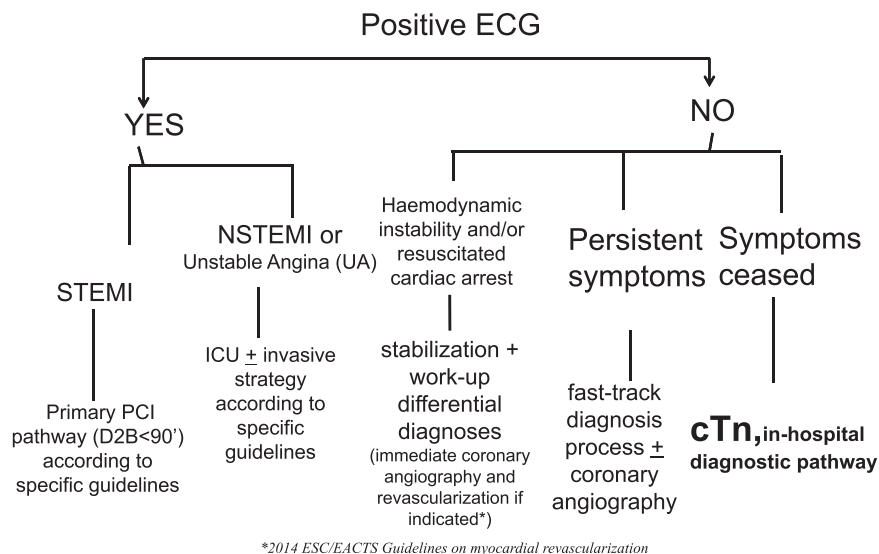


Figure 4 Decision-making on the basis of 12-lead ECG.

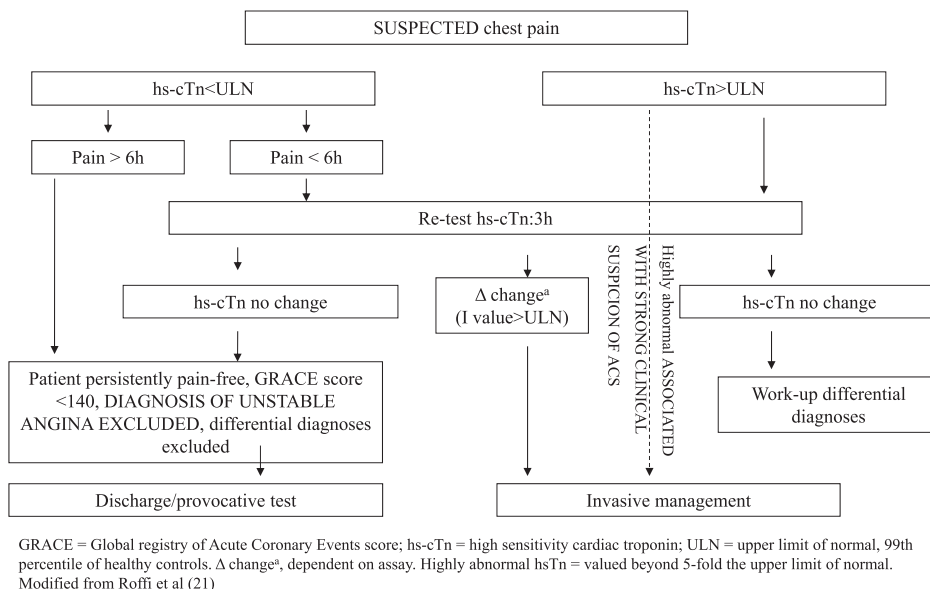


Figure 5 High sensitivity troponin algorithm 0 h/3 h.

diagnostic pathway should be initiated, which will include a troponin assay (Figures 4 and 5).

- Whilst an increase in troponin plasma level may be indicative of myocytes damage, it does not provide any information about the underlying mechanism responsible for such damage.

Small amounts of myocardial damage associated with necrosis can occur in patients with heart failure, kidney failure, myocarditis, arrhythmias, PE, or even during the course of percutaneous coronary or uncomplicated surgical procedures. In these cases, there is no question of infarction, but only of myocardial damage. Accordingly, to have a diagnosis of AMI there must be (even if this alone is not sufficient) a very high initial value of troponin or at least a

three-fold increase at the second determination, or, better still, a typical troponin curve showing a rise followed by a fall, and evidence of at least one value higher than the values indicating normality, associated with symptoms or ECG abnormalities suggesting ischaemia, or with positive imaging tests or angiographic data.

A ‘routine’ approach and an unreasoned assessment of troponin plasma levels will result inevitably in:

- inappropriate recourse to cardiological consultations;
- inappropriate hospitalizations, often with occupation of intensive care beds;
- erroneous diagnostic pathway of the patient, who is labelled wrongly as suffering from acute coronary

syndrome, with the real risk that other acute pathological conditions could be underestimated or left undiagnosed.

Figure 3 illustrates the decision-making process with regards to selection of the patient who should undergo a troponin assay. The flow chart delineates, first, the assessment of pre-test likelihood of coronary disease (high, intermediate, and low) and thus identifies a subgroup of patients on which the test is not to be performed (low likelihood, atypical symptoms). For this category of patients, if anything, the 0-1 h algorithm, indicated in the 2015 ESC guidelines on ACS-NSTEMI, could be applicable.<sup>21</sup> For the remaining categories of patients, the 0-3 h algorithm with hs-cTn must be integrated with clinical/anamnestic prediction tools such as HEART score or TIMI score.

Values of cTn must be determined on the basis of the 0-3 h algorithm (Figure 5) in accordance with ESC guidelines. If the high sensitivity test is not available, the 0-6 h algorithm can be used. During this period, the patient must be kept under observation by monitoring the 12-lead ECG continuously, or alternatively, by taking serial traces (every hour). It is important that an ECG trace is acquired immediately in case of recurrence/worsening of symptoms. The administration of ASA is advisable.

Where values are above the normality range, the first step is to establish whether or not the increase can be considered *typical* of ACS (at least a three-fold increase, or a rise/fall type pattern). The delta change depends on the used assay.

If the cTn increase is *typical* (Figure 2), in a patient with a high clinical likelihood of ACS, or an ECG trend appearing positive for ischaemia, or alternatively, an echocardiographic assessment showing positive for left ventricle regional wall motion abnormalities, then a diagnosis of AMI can be given. The inclusion of rest echocardiography in the decision-making pathway is a true novelty in this document.

If the increased troponin level is *not typical*, other causes of myocardial damage must be considered (heart failure, myocarditis, PE, infection, kidney failure, acute neurological disorder, infiltrative disorders such as amyloidosis, intense physical exercise, etc.).

If a diagnosis of AMI is formulated, the next step in ED (Pathway A, Figure 6) is to look for possible factors that might have produced a discrepancy between the demand and supply of O<sub>2</sub> (anaemia, hypoxaemia, tachyarrhythmia, etc.). If any one of these factors is found to be present, the diagnosis will be *AMI type 2*.<sup>28</sup> In this case, the possibility of hospitalization in Cardiology ward can be considered especially for a patient with haemodynamic instability or very elevated values of troponin, or persistent ischaemia, or where an extensive ischaemic area is identified (by ECG or echocardiogram). Alternatively, and in the absence of the above criteria, the patient could be hospitalized in an Emergency or Internal Medicine Unit, where steps will be taken promptly to correct the precipitating factors. If factors responsible for the discrepancy between the demand and supply of O<sub>2</sub> are not identified, the patient can be diagnosed with myocardial infarction *type 1* and must be admitted to a ICU and/or referred to the Cath-lab.

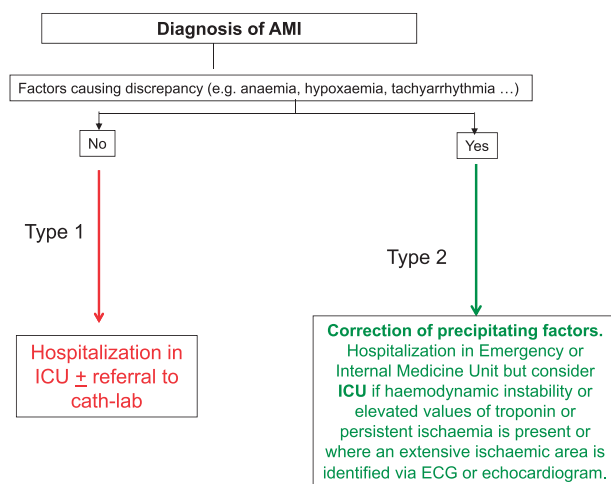


Figure 6 In-hospital pathway through ED (A).

If no diagnosis of myocardial infarction is made (Pathway B, Figure 7), and both 12-lead ECG and troponin assays give negative results, the next step in ED is to establish whether or not a clinical diagnosis of unstable angina may be possible. If the answer is yes, the patient should be hospitalized in Cardiology ward. If the answer is no and the patient has had no symptoms for a number of hours (at least 6), given a GRACE score of <140 with cTn and ECG both stable, a provocative test can be performed either immediately or after discharge (within a few days), depending on the case.

If the answer is no but there remains a strong suspicion of non-coronary disease or ACS continues to be suspected or the GRACE score is >140, the patient can be observed for a period (8-12 h depending on local logistics) in Short Stay Intensive Observation, Chest Pain Unit or ED. Steps that must be taken during this stage of the pathway include 12-lead ECG monitoring, additional troponin tests if opportune, the administration of aspirin if opportune, and any other diagnostic test (including chest X-ray) that could be of use in formulating a definitive diagnosis. This stage likewise can be concluded with a provocative test before discharge or thereafter (within a few days), depending on the case, favouring a test before discharge if the patient has a history of coronary artery disease.

The management of patients with chest pain in an ED setting needs a close integration and cooperation between emergency physicians and cardiologists, together with nursing staff, especially triage nurses. A prerequisite for such integration is that the organization

should hinge on a shared awareness of the diagnostic pathway. This is the basis for proposing the creation of a *Chest Pain Team*—comprising an emergency physician, a cardiologist and a triage nurse—in every hospital facility.

## Conclusions

Although the many advances and innovations of recent years, the assessment of patients with chest pain continues to be a daily challenge. Given the economic impact and the risk of complications induced by inappropriate tests and examinations carried out on a patient with chest pain,

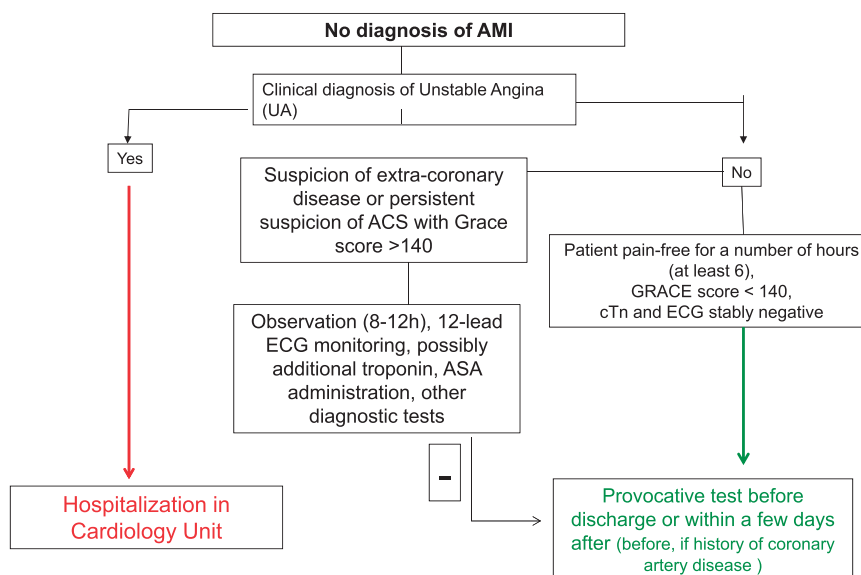


Figure 7 In-hospital pathway through ED (B).

better pathways must be studied, not least in order to avoid pointless examinations and unnecessary hospitalizations.

This document embraces and applies the new proposals offered by medical literature in matters of diagnostic testing and clinical/anamnestic assessment, in seeking to formulate a rule-in/rule-out process for ACS that is both modern and efficient. Above all, the introduction of hs-cTn assays has allowed healthcare professionals to identify a higher number of ACS cases, improving the sensitivity of rule-in/rule-out tests in particular, but has led at the same time to overestimations in diagnosis, and very often to unnecessary hospitalizations, accompanied by a significant waste of economic resources.

The role of this document is to provide operators in the field with guidance on making the right choices, so that the results of different diagnostic tests can be balanced and integrated correctly.

The organization of ED and cardiology departments around a shared diagnostic pathway is the first step in ensuring efficient management of patients with chest pain.

The main purpose of the document is to promote a nationwide standardization of diagnosis and care protocols for patients with chest pain, with the aim of improving outcomes.

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