REVIEW ARTICLE

Use of cardiac troponin in the early diagnosis of acute myocardial infarction

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ABSTRACT
The diagnosis of coronary artery disease, which is one of the most common causes of death and disability worldwide, still remains a significant problem for clinicians. High-sensitivity cardiac troponin (hs-cTn) assays became the cornerstone in the diagnostic workup of acute myocardial infarction. Nowadays, they take an important position in diagnostic algorithms. However, there are still some unexplained issues in this field. This review summarizes and emphasizes the crucial role of hs-cTn in acute coronary syndromes. The 0/1-hour hs-cTn algorithm was mentioned for the first time in the 2015 official European Society of Cardiology guidelines on non–ST-segment-elevation acute coronary syndromes. It was derived, validated, and implemented for all clinically-available assays since then. In this review, troponin-based strategies for rapid rule-out or rule-in of non–ST-segment elevation myocardial infarction are gathered and compared with the update on the official European Society of Cardiology 0/1-hour pathway with the most recent values of hs-cTn. The document also focuses on the problem of possible analytic confounders (false--positive and false-negative results) and compares the usefulness of cTn to other diagnostic techniques (eg, magnetic resonance imaging). The review is divided into short, easy-to-read sections emphasizing 6 key messages on how to use and interpret hs-cTn base algorithms in clinical practice at the emergency department.

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Introduction Coronary artery disease (CAD) is one of the most common causes of death and disability worldwide, especially in developed countries. Although the mortality caused by CAD has declined over the past years, it still is the single most common cause of death in Europe.

Early detection of acute myocardial infarction Coronary artery disease is a multifaceted disorder. While the chronic form may steadily develop over decades, acute plaque rupture and / or fissure may suddenly convert into an acute life-threatening disease: acute myocardial infarction (AMI). The early diagnosis of AMI is of critical importance to maximally shorten the time to introduction of advanced AMI treatment, including electrocardiographic (ECG) rhythm monitoring, acetylsalicylic acid, β-blockers, statins, anticoagulants (eg, heparin), and coronary revascularization, after the onset of AMI to save as much myocardium at risk as possible ("time is muscle").[1] Accordingly, we review recent advances in the early diagnosis of AMI and highlight 6 key messages for clinicians.

Message 1: Early diagnosis of AMI is of critical importance to save as much myocardium at risk as possible ("time is muscle").

Detailed patient history including chest pain characteristics, physical examination, 12-lead ECG, and cardiac troponin T/I (cTnT/I) form the pillars of the early diagnosis of AMI (FIGURE 1). Among these diagnostic pillars, most of the recent advances were made in precise detection and quantification of cardiomyocyte injury by

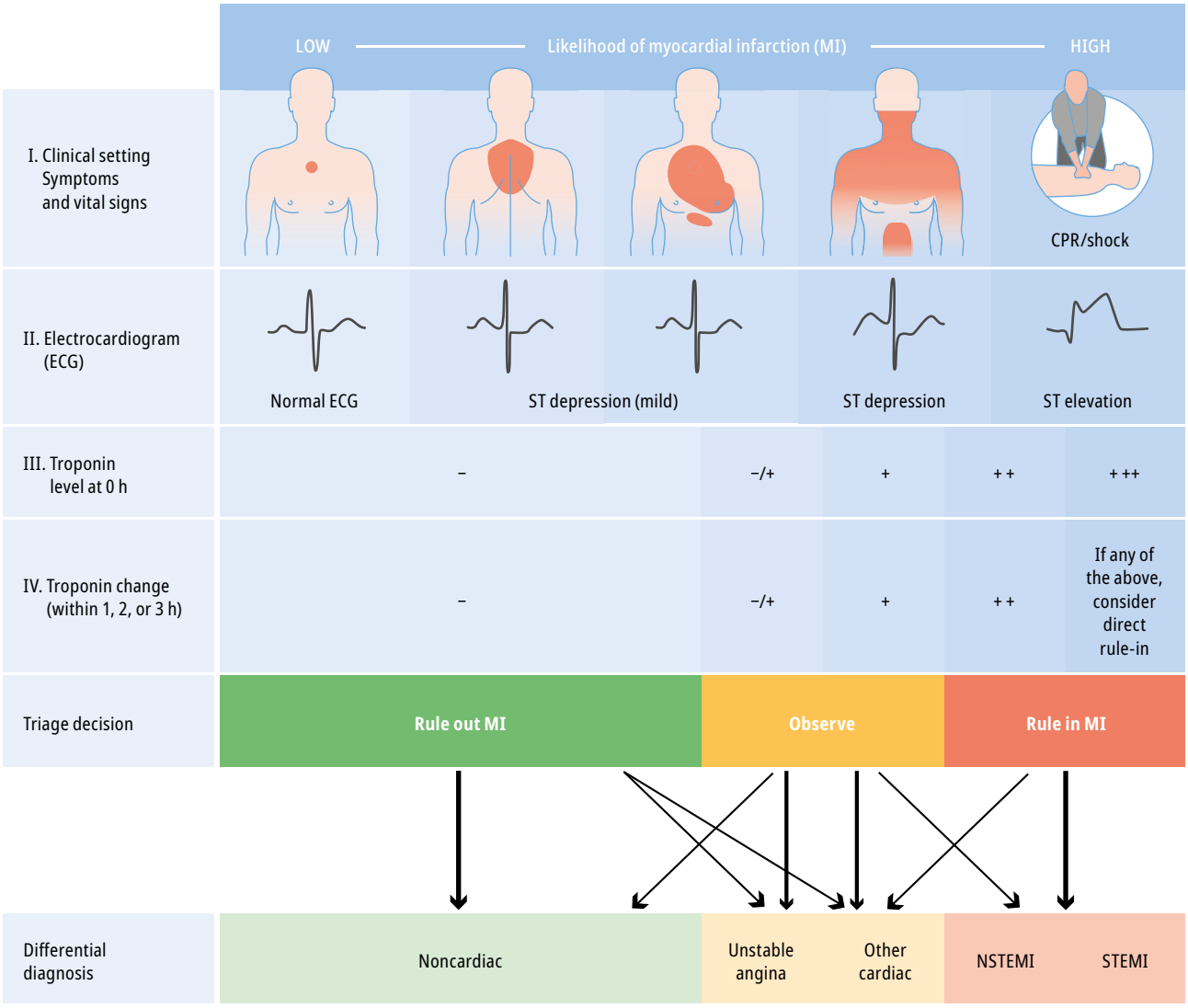

FIGURE 1 Diagnostic algorithm and triage in acute coronary syndrome (adapted from Roffi et al[3]). The initial assessment is based on the integration of low likelihood and / or high likelihood features derived from the clinical setting (ie, symptoms, vital signs), 12-lead electrocardiogram (ECG), and the cardiac troponin concentration determined at presentation to the emergency department and serially thereafter. "Other cardiac" diagnosis includes, among others, myocarditis, Takotsubo syndrome, or congestive heart failure. "Noncardiac" diagnosis refers to thoracic diseases such as pneumonia or pneumothorax. Cardiac troponin levels and their change during serial sampling should be interpreted as a quantitative marker: the higher the 0-hour level or the absolute change during serial sampling, the higher the likelihood of myocardial infarction. In patients presenting with cardiac arrest or hemodynamic instability of presumed cardiovascular origin, echocardiography should be performed / interpreted by trained physicians immediately following 12-lead ECG. If the initial evaluation suggests aortic dissection or pulmonary embolism, measurement of D-dimers and multidetector computed tomography angiography are recommended according to dedicated algorithms.[24-28] Abbreviations: CPR, cardiopulmonary resuscitation; Hs-cTn, high-sensitivity cardiac troponin; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction, STEMI, ST-segment elevation myocardial infarction

measuring systemic concentrations of cTnT/I, which are the preferred biomarkers for the early diagnosis of AMI. Accordingly, cTnT and cTnI are sensitive and specific biochemical markers of any type of cardiomyocyte injury, not only AMI. It is important to emphasize that both cTnT and cTnI have very high and comparable diagnostic accuracy at presentation for non–ST-segment elevation myocardial infarction (NSTEMI), which was confirmed in the European Society of Cardiology (ESC) guidelines and large diagnostic studies. There is no suggestion of superiority of any type of cTn in the diagnostic pathway of MI.[1-5]

Cardiac troponins are the most useful diagnostic tool in the setting of chest pain with inconclusive ECG. Patients presenting with ST-segment elevation accompanying typical angina should be diagnosed as ST-segment elevation myocardial infarction (STEMI) and treated urgently and independently to the cTn concentrations.

Message 2: Elevated concentrations of cTnT and cTnI indicate cardiomyocyte injury, not necessarily AMI. Full clinical assessment including 12-lead ECG and use of cTnT/I as a quantitative variable are required to differentiate AMI from other causes of cardiomyocyte injury.

TABLE 1 Clinical implications of high-sensitivity cardiac troponin assays. Adapted from Roffi et al[3]

Compared with standard cardiac troponin assays, high-sensitivity cardiac troponin assays
• Have higher NPV for AMI.
• Reduce the "troponin-blind" interval leading to earlier detection of AMI.
• Result in a ~4% absolute and ~20% relative increase in the detection of type 1 AMI and a corresponding decrease in the diagnosis of unstable angina.
• Are associated with a 2-fold increase in the detection of type 2 AMI.
Levels of high-sensitivity cardiac troponin should be interpreted as quantitative markers of cardiomyocyte damage (ie, the higher the level, the greater the likelihood of AMI)
• Elevations beyond 5-fold the upper reference limit have high (>90%) PPV for acute type 1 AMI.
• 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 cardiomyocyte damage (as in AMI) from chronic cardiomyocyte damage (the more pronounced the change, the higher the likelihood of AMI).

Abbreviations: AMI, acute myocardial infarction; NPV, negative predictive value; PPV, positive predictive value

Before 2010, *c*TnT/I assays were unable to precisely quantify *c*TnT/I concentrations in the normal or mildly abnormal range.[6,7] Barely poor sensitivity of these assays for the early diagnosis of AMI could have been achieved only with serial sampling over 6 to 12 hours.[6] The "new" *c*Tn-assay technology allowed precise quantification of *c*TnT/I in the normal or mildly abnormal range, with the ability to quantify the concentration of *c*TnT/I concentrations in 50% or more of healthy individuals for high-sensitivity assays and in 20% to 50% of healthy individuals for sensitive assays. Improved sensitivity resulted in increased diagnostic accuracy for AMI at presentation to the emergency department (ED) and thereby allowed to substantially reduce the „troponin-blind" interval and the time necessary to rule-in or rule-out AMI (FIGURE 1).[2,3,6-34] High sensitive assays have been introduced worldwide gradually (eg, 2010 in Europe; 2017 in the United States in the routine clinical care).

Compared with conventional *c*TnT/I assays, the current ones improved particularly the rule--out process and thereby substantially reduced the need for cardiac stress testing and time to discharge from ED, thus reducing costs of outpatient management.[35]

Message 3: Hs-*c*TnT/I assays (vs conventional ones) increase the diagnostic accuracy for AMI at presentation, and thereby allows shortening the time to the second measurement.

In order to differentiate between acute and chronic cardiomyocyte injury, a second measurement is necessary in most patients. High--sensitivity of available *c*Tn assays allows for radical shortening of the time to the second measurement (0/1-hour, 0/2-hours, 0/3-hours algorithms etc).[1,4,7-9,36] Acute cardiac conditions show a rising / falling pattern, while chronic cardiac disorders such as chronic heart failure, left ventricular hypertrophy, valvular heart disease, or renal insufficiency usually exhibit rather stable elevations in the low pathological range, up to 2- or 3-fold upper limit of normal. In some patients, the rising pattern will not be seen in the short period of serial sampling in the ED, and may require a comparison with previous (lower) concentrations obtained in stable conditions or with (lower) concentrations obtained the next day in patients with near-peak *c*Tn concentrations.[8,9]

Message 4: Concentrations of hs-*c*TnT/I should always be considered as quantitative variables: the higher the concentration, the higher the likelihood of AMI.

Concentrations of high sensitivity (hs) *c*TnT/I should always be considered as quantitative variables and rather absolute than relative hs-*c*Tn changes should be preferred as criteria to discriminate acute from chronic myocardial injury (TABLE 1).[8,9] The higher the change of concentration is, the higher the likelihood of acute myocardial injury including AMI, myocarditis, and Takotsubo syndrome.[4,8,9,37] Proper interpretation of elevation in *c*Tn levels (high vs chronic / mild) seems to be fundamental in everyday clinical practice. The possibility of a falling pattern of *c*Tn concentrations during the ACS should also attract clinicians' attention.

False-positive results In the era of hs-*c*TnT/I, clinicians have to deal with a high number of patients with elevated hs-*c*TnT/I concentrations. In some of them, an elevated hs-*c*TnT/I concentration is unexpected and may be the first hint towards the presence of relevant cardiac disease. As the sensitivity of hs-*c*TnT/I for cardiomyocyte

injury is much higher as compared with all currently available cardiac imaging techniques, including cardiac magnetic resonance imaging, the vast majority of unexpected elevations in hs-cTnT/I concentrations are true-positive, and not false-positive results. While an unexpected elevation in hs-cTn level most often is the manifestation of cardiac disorders different from AMI, such as arrhythmias, cardiomyopathies, strenuous exercise, and so on,[1,37] it is the result of cardiomyocyte injury and therefore a true reflection of cardiac health / disease. Therefore, the term false-positive should be avoided, or at least used with extreme caution. In such subgroup of patients, coronary angio-CT, a fast and widely available test, should be considered as a valuable diagnostic tool, particularly in the setting of the observe zone.

Message 5: As the sensitivity of hs-cTnT/I for cardiomyocyte injury is much higher compared with all available cardiac imaging techniques, including cardiac magnetic resonance imaging, the vast majority of unexpected elevations in hs-cTnT/I concentrations are true-positive, and not false-positive results.

High-sensitivity assays are optimized to reduce analytic confounders, which are the most common causes of true false-positive results by using chimeric mouse–human antibodies and by the addition of heterophilic antibodies blocking antibodies to assay reagents.[38] However, in rare cases, false-positive or even false-negative results still may occur due to these analytic confounders.

Sometimes, clinicians have to deal with random nonrepeatable false-positive results not due to analytical reasons, which are called outliers. The best way to reveal them is retesting the sample.[39] Another possible confounder is hemolysis, which is a particularly common phenomenon in blood samples taken in the ED. Hemolysis seems to lead in a reduction with some[12,40] and a rise with other[41] cardiac troponin assays. A recent prospective study in patients presenting to the ED with suspected AMI reassuringly found that the amount of hemolysis usually present in blood samples does not seem to cause a relevant problem, with both hs-cTnT and hs-cTnI maintaining very high diagnostic accuracy for AMI, even when measured from hemolytic samples.[42]

Recently, ultra-high supplemental doses of biotin have been suggested to interfere by competition between the biotin labelled troponin antibody and the streptavidin-coated microparticles.[43] Some of patients have auto-antibodies to cTnI (eg, in dilated cardiomyopathy) which can also interfere and cause false-negative results.[44-47] It becomes a significant issue when concentrations are low, as the epitope targets of assay antibodies can be masked.[7] In the presence of heterophilic antibodies (cTnI), skeletal myopathies (mainly cTnT) or macrotroponin I (an analyte bound to analyte-specific autoantibodies, more common with hs-cTnI) there is a chance to obtain truly false-positive results.[48-51] This issue seems to be especially highlighted when the clinical presentation does not match with obtained cTn results, usually with relevant discrepancy between cTnI and cTnT.[38] In case of such a phenomenon, an additional blood sample should be obtained to exclude random error. If there is a relevant change, acute myocardial injury must be excluded by imaging or invasive strategy.[32] If this does not solve the problem, recentrifugation, dilution, or incubation with heterophilic blocking reagents or measurement with another assay should be performed.[38]

It is also worth noting that other acute conditions common at the ED, such as acute pulmonary embolism, aortic dissection, stroke, and acute cholecystitis, which can also occur with the rise of cTn values, may lead to misdiagnosis and particular attention should be paid during the differential diagnostic workup. The time since the onset of chest pain is also one of the most common and important confounders.

Each approved diagnostic algorithm emphasize the need of serial sampling of cTn, especially when we consider presence of the "troponin-blind" interval (eg, in the ESC 0/1-hour algorithm, given that rapid rule-out values should be evaluated in addition with the information about the onset of chest pain, preferably at least 3 hours prior to the admission, as shown in FIGURE 2). Moreover, the number of "early presenters" (within 1–2 hours) in the researches validating these pathways was not high, which further confirms the need for additional blood sampling in this group of patients, particularly with a high pre-test probability for AMI.[3,52] On the other hand, clinicians have to remember about the potential falling pattern of cTn values ("late presenters").

Irrespective of cTn, initial ECG changes (QRS complexes, ST-T wave) could be potentially misleading since those abnormalities are commonly met in many other cardiac conditions, such as pre-excitation, cardiomyopathies, amyloidosis, pericarditis, left / right ventricular hypertrophy or electrolyte imbalance.

Troponin-based strategies for rapid rule-out or rule-in of NSTEMI Due to their increased sensitivity and accuracy for detection of AMI from samples obtained at presentation, hs-cTnT/I assays have allowed to substantially shorten the time to the second blood draw and the time to decision. This reduced the time to the initiation of therapy and time to discharge from the ED, and thereby also treatment cost in the ED.[6,7,17,35]

As the majority of patients presenting to the ED with acute chest pain are eventually

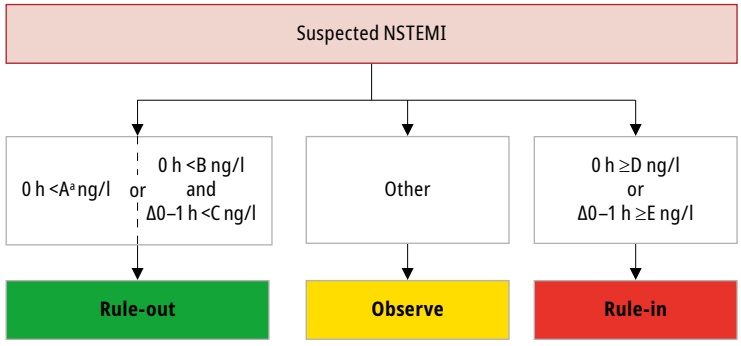

FIGURE 2 The template of the European Society of Cardiology 0/1-h algorithm using high-sensitivity cardiac troponin (hs-cTn) assays in patients presenting with suspected non–ST-segment-elevation myocardial infarction (NSTEMI; adapted from Roffi et al[3]). "0 h" and "1 h" refer to the time from first blood test. NSTEMI can be ruled-out already at presentation if the hs-cTn level is very low. NSTEMI can also be ruled out by the combination of low baseline levels and lack of a relevant increase within 1 hour. There is a high likelihood of NSTEMI if the hs-cTn level at presentation is at least moderately elevated or hs-cTn levels show a clear rise within the first hour. Cutoff levels are assay-specific. Letters A–E correspond with the cTn values provided in the TABLE 2.
a Only applicable if chest pain onset >3 hours.
Abbreviations: see FIGURE 1

found to have noncardiac and often benign causes, the reduction in the time needed for the safe rule-out of AMI was the most important clinical implication of rapid hs-*c*TnT/I based algorithms.

The main performance metrics of early triage strategies towards NSTEMI are safety of rule-out (quantified by the negative predictive value [NPV] and sensitivity), overall efficacy (percentage of patients triaged either towards rule-out or rule-in), as well as accuracy of rule-in (quantified by the positive predictive value [PPV] and specificity), if the respective algorithms provide a rule-in strategy.[53]

European Society of Cardiology 0/1-hour and 0/2-hour algorithms Several hs-*c*TnT/I–based rapid algorithms have been developed in the last decade.[3,18,20,28,54-58] The first was the ESC 0/3-hour algorithm, introduced in the 2011 ESC guidelines for non–ST-segment-elevation (NSTE) ACS. It was the first hs-*c*TnT/I–based rapid algorithm that was used widely throughout the world.[3] The NPV of this tool in rule-out exceeded 98%. It should be noted that the rule-out protocol is not only based on hs-*c*Tn but it also requires patients to be pain free and have the GRACE score of less than 140.[6]

However, 4 recently published large diagnostic studies suggested that the balance between efficacy and safety of the ESC 0/3-hour algorithm might be improved with more rapid protocols based on lower rule-out concentrations, including the ESC 0/1-hour algorithm introduced in the NSTE-ACS guidelines in 2015.[59-62]

Moreover, the very high safety and high efficacy of applying the ESC 0/1-hour algorithm was recently confirmed in 3 real-life implementation studies, including 1 randomized controlled trial.[62-64] Thus, the ESC 0/1-hour algorithm should be considered as the preferred rapid algorithm, according to both ESC and ESC Acute Cardiovascular Care Association (ACCA) statements.[3,52]

Message 6: The ESC 0/1-hour algorithm (published in the NSTE-ACS guidelines in 2015) is currently the preferred rapid algorithm, as it balances safety and efficacy most optimally, and has been derived and validated for all clinically available hs-*c*TnT/I assays.

It can therefore be applied in all institutions which use hs-*c*TnT/I assays, truly allowing generalization of this approach to all developed countries (FIGURE 2 and TABLE 2 should be interpreted simultaneously).[3,59-68] As the best alternative, the 0/2-hour algorithm is recommended.[18,52] The 0/1-hour and 0/2-hour algorithms rely on 2 concepts. First, hs-*c*Tn is a continuous variable and the probability of AMI increases with increasing hs-*c*Tn values. Second, early absolute changes of the levels within 1 hour or 2 hours (both rise or fall) can be used as surrogates for absolute changes over 3 or 6 hours and provide incremental diagnostic value to the *c*Tn assessment at presentation.[3,4,19,26,27] The cutoff concentrations within the 0/1-hour and 0/2-hour algorithms are assay specific. The NPV for AMI in patients assigned rule-out exceeded 99% in

TABLE 2 High-sensitivity cardiac troponin values (letters A–E; all values in ng/l) applicable in the ESC 0/1-hour algorithm[3,59-68,86]

Troponin (assay)	A	B	C	D	E
hs-cTnT (Roche Elecsys)	5	12	3	52	5
hs-cTnI (Abbott Architect)	4	5	2	64	6
hs-cTnT (Siemens Centaur)	3	6	3	120	12
hs-cTnI (Beckman Access)	4	5	4	50	15
hs-cTnI (VITROS)	1	2	1	40	4
hs-cTnI (Quidel TriageTrue)	4	5	3	60	8

Letters A–E should be considered together with the ESC 0/1-hour algorithm provided in FIGURE 2.

several large validation studies. Used in conjunction with clinical and 12-lead ECG findings, the 0/1-hour and 0/2-hour algorithm will allow the identification of appropriate candidates for early discharge and outpatient management. The PPV for AMI in those patients meeting the rule-in criteria was about 70% to 75%. Most of the rule-in patients with diagnoses other than AMI still had acute life-threatening conditions that required invasive coronary angiography or cardiac magnetic resonance 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 invasive coronary angiography and admission to the coronary care unit.

These algorithms should always be integrated with a detailed clinical assessment and 12-lead ECG with mandatory repeat blood sampling in case of ongoing or recurrent chest pain.[3,4,19,26,27] If the onset of pain was more than 3 hours prior to the ED admission and cTn concentrations are very low (below assay specific limit of detection), AMI can be excluded with only one blood test. AMI can be also excluded in case of low baseline levels and no relevant increase within 1 hour. AMI can be ruled-in when hs-cTn is at least moderately elevated at admission or shows the relevant delta in 1-hour observation. In any other case, the patient "falls" into the observe zone and the diagnostic process has to be continued.[3,19]

A recent study proposed the addition of clinical judgement and ECG findings to further improve the performance of the 0/1-hour algorithm in the prediction of major adverse cardiovascular events (MACE). The ESC hs-cTn 0/1-hour algorithm alone balanced efficacy and safety in the prediction of MACE better than the extended protocol, whereas additional use of clinical assessment and ECG to the ESC hs-cTnI 0/1-hour algorithm revealed to be a better option for the rule-out of 30-day MACE and unstable angina than the ESC algorithm alone.[5]

Open questions The following questions and aspects remain controversial at the time of writing this study and are further explored in ongoing studies: 1) Should the use of uniform cutoff levels remain the standard of care, or are sex-specific cutoffs of medical value in the early diagnosis of AMI?[1,69-76] 2) Given the fact that age and renal dysfunction are much stronger confounders of cTnT/I concentrations versus sex, other researchers have suggested the use of age-adjusted and / or renal function–adjusted cutoffs.[1,14,70,76-80] 3) Even more dramatic, the use of the 99th percentile of healthy individuals as a condition sine qua non in the universal definition of AMI has been questioned. An alternative may be the use of an individualized baseline concentration and the use of an absolute increase above that baseline to rule-in AMI. This concept has already been used in the detection of perioperative myocardial infarction / injury.[81] 4) Information technology–based solutions may allow to integrate all known confounders and ultimately provide even more accurate estimates for the presence or absence of AMI among patients presenting with acute chest discomfort.[4,82] While substantial advances have been made in the use of cTn, novel approaches in the interpretation of the 12-lead ECG are evolving.[83] 5) Although the hs-cTn are nowadays the golden standard for the diagnosis of MI, clinicians worldwide are still looking for more sensitive and specific biomarker of myocardial injury. Usefulness of the heart-type fatty acid-binding protein (h-FABP) was recently assessed in several studies. The issue is still developing and data are ambiguous (no significant improvement vs higher sensitivity in the early diagnosis of AMI).[84,85] Surely, more clinical research is needed to confirm the utility of novel biomarkers in the early diagnosis of ACS.

Conclusions The early diagnosis of AMI is of critical importance to save as much myocardium at risk as possible ("time is muscle"). Elevated concentrations of cTnT and I indicate cardiomyocyte injury, not necessarily AMI. Full clinical assessment including 12-lead ECG and the use of cTnT/I as a quantitative variable are required to differentiate AMI from other causes of cardiomyocyte injury. The use of hs-cTnT/I assays (as compared with conventional assays) increases the diagnostic accuracy for AMI at presentation, and thereby allows shortening the time interval to the second measurement. Concentrations of hs-cTnT/I should always be considered as quantitative variables: the higher the concentration, the higher the likelihood of AMI. As the sensitivity of hscTnT/I for cardiomyocyte injury is much higher as compared with all currently available cardiac imaging techniques including cardiac magnetic resonance imaging, the vast majority of unexpected elevations in hs-cTnT/I are true-positive, and not false-positive results. The ESC 0/1-hour algorithm is currently the preferred rapid algorithm, as it best balances safety and efficacy, and as it has been derived and validated for all clinically available hs-cTnT/I assays.

ARTICLE INFORMATION

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