Should the 1h algorithm for rule in and rule out of acute myocardial infarction be used universally?

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A key problem in the emergency department is the prompt identification of patients with myocardial infarction. While this is not a diagnostic challenge in ST elevation myocardial infarction as the ECG is usually unmistakable, in non ST elevation myocardial infarction (NSTEMI) the diagnosis is more complex and based on information derived from detailed clinical assessment, ECG and biomarkers. The ideal biomarker should allow an accurate and immediate identification of patients with NSTEMI. We do not have this ideal biomarker yet. The best approximation is currently represented by high sensitivity cardiac troponin (hs-cTn). In particular, the hs-cTn 0h/1h-algorithm proposed in the European Society of Cardiology Guidelines on the management of NSTEMI might allow a rapid ‘rule in’ and ‘rule out’ of a large proportion of patients with suspected NSTEMI.

A critical question is: ‘Should the 1h algorithm for rule in and rule out of acute myocardial infarction be used universally?’ This approach might substantially speed up the triage of patients with suspected NSTEMI. Yet, some concern has recently been raised on this universal application regardless of symptom duration, overall clinical risk and sex.

In the following debate key opinion leaders give their answers to this important question with major clinical implications. Finally, it is worth mentioning that this is a rapidly moving field and I anticipate that a new stimulating debate will soon be needed.

Sometimes earlier may not be better

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The recent European Society of Cardiology (ESC) guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (NSTE-ACS) added an avant-garde rapid one hour rule-in and rule-out algorithms using high sensitivity cardiac troponins (hs-cTn) as a clinical option. Although these algorithms may represent an advance in the early diagnosis of chest pain patients the guidelines, in our opinion, they overlook some gaps in the information that defined these approaches that could inadvertently disadvantage patients. Others report less optimistic results with hs-cTn assays with early approaches in ‘early presenters’ with ischaemia-induced myocardial injury. The following identifies our concerns about that guidelines so that clinicians can take them into account.

Gaps in the population providing the knowledge base

Guideline mandated diagnostic assessments should be applicable to all possible patients within a given disease state. To accomplish this goal, the one hour algorithm would have required a more extensive database than the one used. The studies relied on included large numbers of low risk patients presenting early after onset of symptoms but lacked substantial numbers of early patients with acute myocardial infarction (AMI). This group is critical to study to be sure that these patients manifest elevations even early after AMI so they can be distinguished from those without AMI. The largest number of
AMls in the studies evaluating the approach was 443 with only 106 patients presenting in ≤ 3 h after onset.3 How many presented in <2 h is unclear. Thus, we have insufficient knowledge about how the algorithm works in patients early after AMI. This is understandable given the CART analysis used to develop the protocol had only 75 AMls in the ‘derivation’ cohort and only 72 in the ‘validation’ cohort.4 That is why the data indicating that rapid biomarker protocols underestimate AMI is important albeit generated with a different model.2 The recent report from Shah et al. using a single measurement at admission supports this concern in a study with 782 AMI patients of whom 234 (personal communication per NLM) were evaluated within 2 h of onset of symptoms.5

The 1 h approach does not define the nature of the patients who ruled out. A low hs-cTn value in patients with normal ECGs and low GRACE scores is different than similar values in patients with high GRACE scores.6 An elevated hscTn value in a low risk patient should prompt a search for alternative explanations whereas a similar value in high risk patients may prompt clinicians to intensify treatment and consider intervention. However, these data are not available because risk stratification was not part of the approach. A recent analysis suggests that including stratification and ECG interpretation reduces the 30 day major adverse cardiac event rate in and negative predictive values in the rule out group and improves sensitivity in the rule in group.7

In selecting patients the studies used to develop this approach focused on patients whose primary problem was chest pain.3,4 Even those with chest pain alone may not always have high specificity for AMI.3 Patients with other presentations and possible AMI who are likely to be evaluated with this approach who have critical illnesses were likely under enrolled as were those with severe renal dysfunction and the elderly who often present atypically8 These patients often have values > 52 ng/L.13 These exclusions means that this approach will likely lack specificity when applied to all patients with possible AMI.

In patients who present at least 6 h after the onset of symptoms, conventional cTn assays do an excellent job at ruling out AMI and identifying those with a good prognosis.9 Therefore, although appropriate to enrol consecutive patients, the critical patients in studies looking at earlier approaches should have large numbers who present early after the onset of symptoms to make sure that the approach works in this group. As indicated above, this did not occur. The mean time to presentation in the studies used for these guidelines was usually 3–3.5 h.3 In TRAPID, the median time to presentation was 1.9 h but a median of 1.5 h to obtain the initial samples.10 By the time of the 1 h follow-up sample, many patients were close to the 6 h mark. This is important to appreciate.

Considerations regarding the assays

The 1 h approach depends on the use of hs-cTn assays.1 It does not work with non hscTn assays11

Most hs-cTn assays use sex specific cut off values. Recent data suggest they make the diagnostic evaluation of women better.12 To recognize sex differences, large study numbers of women with AMI are needed which are not the case in the studies that led to the 1 h algorithm.3,4 The cut-off value of 12 ng/L hs-cTnT reached by CART analysis9 may help deal with this issue since it is mid-way between the cut offs proposed for men and women.

An important caveat is whether the assays are capable analytically of making the distinctions proposed. From the published data, it does not appear to have the ability to distinguish between a change of 3 and 5 ng/L.13 The assay is even less precise when used on older instruments.14

When hs-cTn values are elevated, the use of change values improve specificity but reduce sensitivity.15 A change of 50–80% is needed to be sure that one has exceeded conjoint biological and analytical variation.15 But the use of large change values decreases sensitivity for detection of AMI. However, the use of very low change values as advocated by the 1 h algorithm diminishes specificity.15

This issue needs to be understood by clinicians.

Finally, extrapolation of the data partially validated predominately with the hs-cTnT assay to other assays was less than ideal. Choosing one assay (hs-cTnT) as the gold standard to determine assay values for another assay as done in the ESC guidelines biases the analysis against the non gold standard assay whenever there are discrepancies. This is particularly important given suggestions that the hs-cTnT assay may not be a high sensitivity assay.16 As such, the fact that there are more elevations of hs-cTnT in some studies4,17 despite the detection of many fewer normal subjects is of concern. The proper explanation for this is not clear. These concerns are furthered by the fact that analyses for hscTn were done on samples stored for long periods of time (years) after measurement of hscTnT which could well change the relationship between the values.17 The proper way to do such an analysis is with ‘fresh’ samples.

Precautions for clinicians

1. For now, only apply the rapid 1-h algorithm utilizing small changes to low risk patients. This will mitigate some of the concern about the paucity of data concerning patients with AMI who present early after the onset of symptoms2,12 until additional studies clarify this issue.

2. The use of a single cut-off value to diagnose AMI should be avoided. If used on an ‘all comers’ population, these values will include large numbers of patients with comorbidities and not AMI. The best way to diagnose AMI according to the guidelines is by observing a rising and/or falling pattern of cTn. This standard should be adhered to.

3. The low change values of 3 and 5 ng/L for hscTnT suggested are below the ability of most hs-cTn assays to provide accurate information if baseline values are low. Clinicians should be cautious about patients at high risk and those who came in early.25 If there are questions, one should obtain additional samples to make sure one is not missing a rising pattern of values.

4. It will take a longer time to rule in some patients with AMI; perhaps as long as 6 h.10

5. Cut-off values for assays other than hs-cTnT are insufficiently validated and should be used with caution if at all.

6. Sex specific cut-off values are recommended by the guidelines at present.4 Data evaluating women with AMI who present early after the onset of symptoms are needed.

It is likely that some components of the 1 h algorithm will work well. It may be that low hs-cTn values at presentation is a good way to exclude AMI, not because they are sensitive at detecting myocardial injury but because the risk factors associated with ischaemic heart disease cause increases in hscTnT within the normal range so baseline
values are not apt to be low. Thus, low values define a low risk group. However, we are less confident about some of the other recommendations such as utilizing a solitary fixed cut off for diagnosis of AMI and the application of this approach too all patients with possible AMI including those with renal failure, acute illness, the elderly and those who present early. Until these issues are clarified clinicians should take an extra caution in the interest of safe patient care.

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References


Background, fundamental concepts, and scientific evidence of the high-sensitivity cardiac troponin 0h/1h-algorithm for early rule-out or rule-in of acute myocardial infarction

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Early diagnosis of acute myocardial infarction

We appreciate the opportunity to explain in more detail the background, fundamental concepts, and scientific evidence of one of the diagnostic options recommended in the 2015 European Society of Cardiology (ESC) guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (NSTE-ACS): the high-sensitivity cardiac troponin (hs-cTn) 0h/1h-algorithm. We fully agree with Jaffe et al. that several important aspects of this novel approach require attention, particularly for physicians who did not previously have the opportunity to use hs-cTn assays. However, their editorial, both in the title and introductory statements, raises concerns about the hs-cTn 0h/1h-algorithm that are not substantiated by the data presented.

Background: The hs-cTn 0h/1h-algorithm was developed to optimize the management of patients presenting with acute chest pain and/or suspected acute myocardial infarction (AMI) to the emergency department (ED) by allowing safe rule-out and accurate rule-in of AMI more rapidly than with previous troponin-based algorithms. In addition, this approach should help to improve patient flow in the frequently busy ED and contribute to a more rational use of scarce health care resources. While rapid diagnosis of AMI is critical for the early initiation of evidence-based treatment, a timely rule-out is also of major relevance, as this may allow an early search for alternative diagnoses and/or patient discharge.

Fundamental concepts: The hs-cTn 0h/1h-algorithm is based on the same fundamental concepts as the hs-cTn 0h/3h-algorithm, which has been recommended for the first time in the 2011 ESC NSTE-ACS guidelines and remains a valid option in the 2015 edition. First, early diagnosis of AMI is based on the careful integration of all information derived from detailed clinical assessment, including chest pain characteristics, vital signs, ECG, and blood concentration of cTn T or I (Figure 1). Therefore, the hs-cTn 0h/1h-algorithm (Figure 2) provides detailed guidance on how to interpret one of the three key diagnostic variables. Second, both algorithms are applied after the initial 12-lead ECG has ruled-out the presence of significant ST-segment elevation, which should trigger the immediate transfer to the cardiac catheterization laboratory. Third, both the hs-cTn 0h/3h- and hs-cTn 0h/1h-algorithms have been validated and can be applied to unselected patients presenting with acute chest pain and/or suspected AMI in the ED. In contrast, their use is unlikely to be helpful in patients, in whom the clinical utility of cTn in general is questionable, such as critically ill patients. Fourth, compared with conventional cTn assays, hs-cTn assays increase diagnostic accuracy at presentation by substantially reducing the sensitivity deficit of standard cTn at presentation for AMI and the associated ‘troponin-blind’ interval (i.e. time delay between cardiomyocyte necrosis and troponin detection in the blood), and increase the accuracy in the identification of patients at very low risk of death and/or future AMI suitable for outpatient management. Fifth, due to the higher sensitivity for AMI at presentation as well as for detection of cTn levels, hs-cTn assays allow for a shorter time interval to the second troponin measurement. This results in a substantial reduction in the time to diagnosis and/or therapeutic decision as well as ED stay and costs.

Sixth, hs-cTn should be considered as a quantitative marker of cardiomyocyte injury. The higher the blood hs-cTn concentration, the higher the likelihood for AMI. Vice versa, the lower the blood hs-cTn concentration, the lower the likelihood for AMI. Accordingly, very low hs-cTn concentrations at presentation have shown a very high negative predictive value (NPV) for AMI and were associated with extremely low mortality rates at 30 days. Seventh, absolute changes in hs-cTn within the 1st hour of observation in the ED, as compared to relative changes, have higher diagnostic accuracy and provide incremental value to the blood hs-cTn concentration at presentation. Again, the more pronounced the change in hs-cTn levels, the higher the likelihood for AMI. Eighth, both the hs-cTn 0h/3h- and the hs-cTn 0h/1h-algorithm allow for a safe and early triage of patients, but do not allow for a 1:1 diagnosis label. Accordingly, while the hs-cTn 0h/1h-algorithm allows for a safe and rapid rule-out of AMI in up to 60% of unselected ED patients presenting with chest pain and/or suspected AMI, full clinical assessment is still needed to determine whether the final diagnosis is an anxiety disorder, musculoskeletal chest pain, reflex disorder, or pneumonia. Similarly, a patient presenting with acute chest pain to the ED and being assigned the ‘rule-in’ pathway by the hs-cTn 0h/1h-algorithm (or hs-cTn 0h/3h-algorithm) is not automatically diagnosed as AMI. However, in this setting AMI is very likely (positive predictive value [PPV] 75–80%, specificity about 96%), the patient should be transferred to a monitored unit, antithrombotic therapy should be started, and he should undergo early coronary angiography.

Coronary angiography will then help to differentiate AMI from other conditions such as Takotsubo cardiomyopathy or myocarditis. Ninth, the hs-cTn 0h/1h-algorithm on its own already provides a very high NPV for AMI (99–100%). In addition, the 2015 ESC guidelines explicitly state in the recommendation table that ‘additional testing after 3–6h is indicated if the first two troponin measurements are not conclusive and the clinical condition is still suggestive of ACS’. This caveat particularly applies to patients presenting very early after chest pain onset, as cTn release from cardiomyocytes into blood is a time-dependent phenomenon. Tenth, both algorithms need to be embedded carefully into the network of local standard operating procedures. Meticulous outpatient follow-up with functional or anatomical imaging tests such as stress echocardiography, myocardial perfusion imaging or CT angiography will be required in a proportion of patients, in whom these early algorithms have rapidly and safely ruled-out AMI in the ED. Accordingly, these algorithms do rule out AMI, not coronary artery disease. In fact, a patient with cardiovascular risk factors presenting with typical symptoms has a high probability of coronary disease even if the hs-cTn is negative. Eleventh, hs-cTn assays also maintain high diagnostic accuracy in elderly patients and in patients with renal dysfunction. While the rule-out of AMI in elderly patients or patients with renal dysfunction can be done exactly as in young patients and patients with normal renal function, rule-out requires higher hs-cTn cut-off values in order to maintain comparable PPV and specificity.
perspective with efforts to also achieve biological-equivalent 99th percentiles, as currently approved 99th percentile have recently been found to not be biological-equivalent, irrespective of whether the uniform or sex-specific 99th percentile were used. This problem relates to differences in the composition of the cohorts of healthy individuals used to define the 99th percentiles. Finally, the hs-cTn 0h/1h should be considered a refinement of the hs-cTn 0h/3h-algorithm as it provides more detailed guidance regarding rule-in. The hs-cTn 0h/3h-algorithm recommends early coronary angiography in patients with typical symptoms, a ‘highly abnormal’ hs-cTn and ‘relevant’ hs-cTn changes within 3h, but does not quantify exactly what levels would qualify for these terms. Due to the poor harmonization among hs-cTn assays, detailed guidance, as now provided in the hs-cTn 0h/1h-algorithm, is assay-specific. While at first sight, this increases complexity, clinicians should only focus on the numbers specific for the hs-cTn assay used at their institution.

Scientific evidence: Hs-cTn assays have been available for clinical research since 2007 and were introduced into clinical practice in Europe, Australia, New Zealand, Canada, and many other countries since 2010. Over the years, the evidence for the diagnostic utility of hs-cTn in general and the hs-cTn 0h/1h-algorithm in particular has become very solid. The hs-cTn 0h/1h-algorithm recommended in the 2015 ESC guidelines combines two approaches. The first is the use of a single measurement of very low blood concentrations of hs-cTn at ED presentation to rule-out AMI. This approach has been shown to allow early triage towards rule-out in 10–60% of ED patients with acute chest pain and provide a very high NPV (98–100%) for AMI in multiple diagnostic studies with the meticulous adjudication of AMI being performed by multiple independent cardiologists using all clinical information including full clinical assessment, the ECG, imaging including coronary angiography, serial measurements of (hs)-cTn, and clinical follow-up. Overall, more than 12 000 ED patients were enrolled in these studies, of whom more than 1400 had AMI. As the release of cTn is a time-dependent phenomenon, the 2015 guidelines state that this approach should only be used in patients with chest pain onset of at least 3h prior to ED presentation. A recent study, published after the release of the guidelines, provided additional support for the very high NPV of blood concentrations at ED presentation below 2ng/L for hs-cTnI (Architect) and suggested that a NPV above 99.5% can also be achieved by blood concentrations below 5ng/L (thereby extending the very early rule-out option to patients presenting hs-cTnI blood concentrations of 2.0–4.9 ng/L) with this assay. The second approach uses blood hs-cTn concentrations at presentation and their absolute changes within the first hour as quantitative variables to take full advantage of their diagnostic information. This approach has been consistently shown to allow early triage towards rule-out or rule-in in about 75% of ED patients with acute chest pain. For the triage towards rule-out, both criteria must be met in order to maximize safety, especially in early presenters. Accordingly, in contrast to the first approach (very low blood concentrations), this approach does not seem to have a less favourable NPV in patients presenting very early after chest pain onset. However, as stated above, we fully agree with Jaffe et al. that particular caution (and often a 3h sample) is advisable in very early presenters due to the time-dependency of cTn release into the circulation. Within large international multicentre diagnostic studies these algorithms were derived to achieve predefined very high NPVs and PPVs. These studies use meticulous adjudication of AMI being performed by independent cardiologists using all clinical information including full clinical assessment, the ECG, imaging including coronary angiography, serial measurements of the local (hs)-cTn and additionally serial measurements of (hs)-cTn from study blood samples, and clinical follow-up. These algorithms were then validated in separate cohorts. This approach achieved very high NPV for the

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/37/44/3316/2733195)
triate towards rule-out of AMI of 99–100% and also high accuracy for rule-in with a PPV of about 75% and a specificity of about 96%. Overall, more than 4000 ED patients were enrolled in these studies, of whom more than 800 had AMI. One of these studies, including 1282 patients, was specifically designed to maximize the inclusion of patients presenting very early after chest pain onset, resulting in a median time from chest pain onset or peak to ED presentation of 1.8h (interquartile range 1.0–2.9h).

In summary, the 2015 ESC NSTE-ACS guidelines propose two hs-cTn-based diagnostic algorithms for patients presenting with acute chest pain and/or suspected AMI to the ED. By including the new hs-cTn 0h/1h-algorithm, the guidelines try to carefully balance diagnostic accuracy and speed and guide physicians regarding the best possible clinical use of hs-cTn blood concentrations.

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