Update on high-sensitivity cardiac troponin in patients with suspected myocardial infarction

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Disclosures:

Dr. Twerenbold received research support from the Swiss National Science Foundation (P300PB_167803), the Swiss Heart Foundation, the University Hospital of Basel and the University of Basel as well as speaker honoraria/consulting honoraria from Roche, Abbott, Siemens, Singulex and BRAHMS Thermo Scientific. Dr. Boeddinghaus received research support from the University Hospital of Basel (Division of Internal Medicine), the Swiss Academy of Medical Sciences, the Gottfried and Julia Bangerter-Rhyner Foundation, and speaker honoraria/consulting honoraria from Siemens. Dr. Mueller received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the KTI, the Stiftung für kardiovaskuläre Forschung Basel; Abbott, Alere, Astra Zeneca, Beckman Coulter, Biomerieux, BRAHMS Thermo Scientific, Roche, Siemens, Singulex, Sphingotec, and the Department of Internal Medicine, University Hospital Basel, as well as speaker honoraria/consulting honoraria from Abbott, Alere, Astra Zeneca, Biomerieux, Boehringer Ingelheim, BMS, BRAHMS Thermo Scientific, Cardiorentis, Novartis, Roche, Siemens, and Singulex. All other authors declare no conflicts of interest.

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ABSTRACT

High-sensitivity cardiac troponin (hs-cTn) assays have been used clinically in many countries throughout the world for years and complement detailed clinical assessment and the electrocardiogram in the early diagnosis of myocardial infarction (MI). Hs-cTn assays for the first time allow to precisely quantify cardiomyocyte injury around the 99th percentile and thereby substantially increase the accuracy for MI already for blood draws obtained at presentation to the emergency department (ED). Higher diagnostic accuracy at ED presentation enabled the development and extensive validation of early hs-cTn-based diagnostic algorithms, which substantially reduced the time required for safe rule-out or rule-in of MI.

High-sensitivity cardiac troponin

More than 20 million patients present with symptoms suggestive of myocardial infarction (MI) to emergency departments (ED) in Europe and North America each year.[1] Since the clinical assessment and electrocardiogram (ECG) alone are not sufficient to diagnose or exclude Non-ST-Segment-Elevation Myocardial Infarction (NSTEMI) in most patients, the addition of blood tests to measure the concentration of cardiac troponin (cTn) T or I form the cornerstone for the early diagnosis of MI.

Recent advances in cTn-assay technology have led to a refinement in the clinical ability to detect and quantify cardiomyocyte injury.[2-33] These assays increased diagnostic accuracy at presentation, substantially reduced the sensitivity deficit of cTn at presentation for MI and the associated "troponin-blind" interval, and allowed the recent development of several novel strategies for the early rule-out or early rule-in of NSTEMI.[2-33] These improved assays are labeled "sensitive" when able to detect cTn in ~20–50% of healthy individuals and "high-

sensitivity" if they detect a cTn level in >50% of reference (apparently healthy) subjects, and if they have a coefficient of variation of <10% at the 99th percentile upper reference limit of the assay.[3] High-sensitivity assays can accurately detect cTn at lower levels than older generation assays, giving them higher sensitivity for the detection of MI at presentation, which means that the time interval to the second measurement of high-sensitivity cTn (hs-cTn) can be significantly shortened. [2-35]

CTnT and I are structural proteins unique to the heart. Thereby, cTnT and I are organ-specific, but not disease-specific markers. High-sensitivity and sensitive cTnT and I assays exactly quantify the amount of cardiomyocyte injury.[4, 19, 34] They ought to be interpreted as quantitative variables and not in a binary fashion (negative/positive) like a pregnancy test. From a diagnostic perspective, it is highly inappropriate to label a patient as "cTn-positive", as this would lump together patients with only mildly elevated cTn levels barely above the 99th percentile and an associated positive predictive value (PPV) for NSTEMI of only about 40-50% with patients with markedly elevated cTn levels (e.g., about 5-times above the 99th percentile) and an associated PPV of 90%. The higher the cTn level, the higher is the likelihood for the presence of MI. Absolute rather than relative hs-cTn changes seem to be the best metric to differentiate MI from other causes of chest pain.[8, 15-17] The larger the absolute cTn change within 1h, 2h, or 3h, the higher the likelihood for the presence of MI.[8, 15-17] Continuous medical education and training of physicians in these concepts is essential to avoid inappropriate interpretation of chronic mild elevations of cTn associated with e.g. heart failure or other structural cardiac disorders as signs of MI.

True and false false-positive hs-cTn measurements

In the absence of overt myocardial ischemia, elevated cTn levels are often labelled as "false positive" hs-cTn results. This term should be avoided, as most of these unexpected hs-cTn elevations are "true-positive" for myocardial injury (rather than MI) and reflect previously undetected or underestimated cardiac disease including valvular heart disease, heart failure, and chronic coronary artery disease. Many cardiac and non-cardiac disorders may lead to substantial amounts of cardiomyocyte injury and thereby hs-cTn elevations.[3, 19] It is important to note that cTn elevations universally portend a worse prognosis than otherwise similar patients without a cTn elevation, irrespective of the underlying disease. This is true regardless of whether the patient has heart failure, renal dysfunction, gastrointestinal bleeding, sepsis, respiratory disease, pulmonary embolism, subarachnoid haemorrhage, or stroke or whether the patient is asymptomatic without known cardiovascular disease.[36] Obviously, the medical consequences of cardiomyocyte injury as quantified by cTn elevations will be highly individualized and different from that in patients with MI.

There are some rare circumstances when high or even very high cTn concentrations are observed in the absence of myocardial injury, for example due to analytical assay interferences. In cases of striking discordance between cTn measurements and clinical presentation, analytical "false-positive" test results (e.g., due to heterophilic antibodies) must be considered. The following two-step approach may facilitate further clinical work-up: First, cTn retesting using the same cTn assay should be performed. In case of a relevant change, acute myocardial injury must be excluded by imaging or invasive strategy. If no cause of myocardial injury can be detected by imaging and further serial cTn measurements remain in the normal range, the cTn result suspected to be false-positive can most probably be explained to be a non-repeatable

outlier. Second, if no cTn change after retesting can be observed, cTn should be measured using an alternative cTn assay (if available). In case of a cTn mismatch, contact the laboratory for ruling-out analytical interferences resulting in real but very rare "false-positive" cTn measurements (e.g., troponin auto-antibodies affecting cTnI or skeletal muscle disease affecting cTnT[37]). In case of a match, chronic myocardial injury must be suspected and should be further elaborated with imaging techniques.[38]

Troponin-based strategies for rapid rule-out or rule-in of NSTEMI

The most important clinical advantage of the new, more-sensitive cTn assays is their ability to substantially reduce the "troponin-blind" interval in the first hours of an MI and thereby do allow for novel strategies to early rule-out or rule-in of NSTEMI. Several troponin-based strategies rely on serial hs-cTn testing. Two of them, the 0/1h-algorithm and a 0/3h-algorithm, are currently recommended by the European Society of Cardiology (ESC) with a class I recommendation.

It is important to highlight five aspects when applying troponin-based strategies in clinical practice **(Figure 1)**: First, they should be used only in conjunction with full clinical assessment, including a pre-test probability assessment to identify those patients at high risk who may not be suitable for early discharge. Second, these strategies should be considered triage strategies rather than definite diagnostic strategies, as additional imaging tests e.g. invasive coronary angiography, stress testing, echocardiography or CT angiography may be necessary for a definite diagnosis. Third, the percentage of patients eligible for rule-out or rule-in varies widely from ≈9.8% to 77% depending on the underlying algorithm, the used cTn assay and the clinical setting including the prevalence of NSTEMI.[16, 20] Fourth, these strategies should only be applied after the initial ECG has excluded ST-Segment-Elevation Myocardial Infarction (STEMI) since

these high-risk patients need prompt identification based on the ECG and immediate reperfusion therapy without the need for cTn testing.[4] Fifth, all triage strategies should be embedded in the local standard operating procedures of the ED.

The main performance metrics of early triage strategies are safety of rule-out (quantified by the negative predictive value [NPV] and sensitivity for NSTEMI), 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 for NSTEMI), if the respective algorithms provides a rule-in strategy.

ESC 0/3h-algorithm: NSTEMI is ruled-out if hs-cTn concentrations remain in the normal range (below the respective assay-specific 99th percentile) in the blood samples drawn at presentation and 3h after presentation, and if the patient fulfils two additional requirements: to be pain-free and to be at low-risk of in-hospital mortality as quantified by a Global Registry of Acute Coronary Events (GRACE)-score below 140.[19] In patients presenting more than 6h after chest pain onset, in whom chest pain onset can be reliably quantified, one single blood draw at presentation is considered to be sufficient. Patients are ruled-in if they have a clearly elevated hs-cTn blood concentration at presentation, or if the 3h sample shows a relevant change. This approach has been recommended by the ESC Guidelines since 2011 and is still the most-widely used algorithm in Europe.[3, 19] Its use regarding rule-out of MI seems to be acceptably effective and safe for all hs-cTn assays and possibly also some sensitive cTn assays.[39] The exact performance for rule-in cannot be quantified, as no precise definitions of its rule-in cut-off levels are given. Given the average turn-around time for hs-cTn of about 1h, the hs-cTn measurement performed at 3h after ED presentation would become available at about 4h after ED presentation

and would allow clinical decision making regarding hospitalization versus outpatient management about 4h after ED presentation in the majority of patients. In a recent study, this strategy enabled outpatient management in 56% of patients, with a median time in the ED of about 5h in the overall population, and 4 1/2h in those patients managed as out-patients.[40]

0/2h-algorithm (± clinical risk scores): Several algorithms based on hs-cTn-resampling after 2 hours have been developed, some of them with[20-24] and some without[14, 41, 42] the additional use of a specific clinical risk score. The latter exclusively use hs-cTn concentrations at ED presentation and their absolute change within 2h to triage patients without the use of a specific clinical risk score and thereby achieve a high NPV and sensitivity comparable to the ones using a clinical risk scores.[14, 41, 42] Accordingly, the 0/2h-algorithms without the need for clinical risk scores are easier applicable than the ones with a risk score and allow for rapid rule-out of NSTEMI in up to 60% of patients.[14, 41, 42] In addition, they also include a rule-in strategy that provides a PPV above 75% for NSTEMI and allows the early rule-in in about 10-15% of acute chest pain patients[14, 41, 42] whereas the 2h-algorithms with the clinical risk scores do only provide a rule-out strategy.[20-24]

ESC 0/1h-algorithm: The concept of the ESC 0/1h-algorithm is identical to that of the 0/2h-algorithm and is also exclusively based on information provided by hs-cTn concentrations and their absolute 1h-change, using assay-specific cutoffs.[16, 19, 26, 27, 43] The 0/1h-ESC-algorithm results in safe rule-out of NSTEMI (NPV 99-100%) and allows an accurate early triage in about 75% of patients: 60% towards rule-out and in 15% towards rule-in of NSTEMI. The application of the ESC 0/1h-algorithm is also possible in institutions with a median turn-around time of more than 1h since the 1h only refers to the timing of the serial sample. In these institutions, the

second blood draw would simply need to be performed while still awaiting the results from the first blood draw.

Direct rule-out based strategy on undetectable/very low baseline hs-cTn concentrations:

Undetectable or very low blood concentrations of hs-cTn at presentation to the ED have a very high (98.6-100%) NPV for NSTEMI. This approach has unique simplicity, as it requires only a single blood draw of an inexpensive and widely available biomarker. As the lower limit of detection is assay-dependent and varies among the clinically available hs-cTn assays, "very low concentrations e.g. below the 30% percentile of healthy individuals" may be the preferred metrics to identify biological-equivalent values. Four large studies and three recent meta-analysis have provided consistent results for hs-cTnT and hs-cTnI assays.[28, 29, 44-49] As the release of cTn is a time-dependent phenomenon, this approach should only be used in patients with a chest pain onset of at least 2-3h prior to ED presentation, as safety was reduced in the very early presenters in a recent observation.[48] In the 2015 ESC guidelines, this approach is recommended in combination with the 0/1h-algorithm as the preferred rule-out strategies due to their excellent balance between speed and accuracy.[19]

Pros and cons of the different early algorithms

There are some main differences between the above listed algorithms that have to be mentioned: First, direct rule-out strategies rule-out patients with a single hs-cTn measurement at ED presentation, whereas the other algorithms require serial sampling at 1, 2 or 3h. While the ESC 0/1- and 0/2h-algorithms (without risk scores) incorporate both the hs-cTn-concentration at ED presentation and its absolute change during resampling, the ESC 0/3h-algorithm and the 2h-

algorithm (with risk scores) rely on the assay-specific 99th percentile, only. The integration of absolute changes in the ESC 0/1h- and 0/2h-algorithms has the potential to improve safety and efficacy compared with the ESC 0/3h-algorithm. However, as direct head-to-head comparisons are still missing, their impact could not been quantified yet. Second, while the 0/1h-, 0/2h-, and 0/3h-algorithms have the potential to triage patients towards rule-out and rule-in of NSTEMI, the other two described algorithms (direct rule-out strategy and 2h-algorithm with clinical risk score) can only be used for early rule-out of NSTEMI. Third, by incorporating the time since chest pain onset, the ESC 0/1h-algorithm take advantage of patients presenting very early after chest pain onset, a subgroup of patients requiring particular attention in order not to miss late rises in hs-cTn.[19, 48]

The clinical value of early rule-out algorithms for safe rule-out of MI is helping guide clinicians identifying patients at very low risk for NSTEMI and MACE. However, the decision, which of the available strategies for rapid triage of suspected MI should be used in clinical practice, must be made by each institution individually depending on the locally used cTn assay (sensitive versus high-sensitivity), wish for additional rule-in guidance and individual preferences regarding targeted balance between safety and efficacy.

What to do in the observe-zone

The ESC 0/1h-algorithms[16, 19, 26, 27, 43] as well as some of the 0/2h-algorithms[14, 41, 42] provide detailed guidance for rule-in of NSTEMI in addition to a rule-out strategy. Thereby, an intermediate-risk group has been created, leaving up-to one third of patients in this observe-zone.[14, 16, 19, 26, 27, 41, 42] These patients are typically elderly men with pre-existing coronary artery disease and were shown to have increased long-term mortality.[50] Detailed clinical assessment,

additional hs-cTn measurement at 3h, and cardiac imaging are key for accurate diagnosis in these patients. The clinical interpretation of mildly abnormal hs-cTn levels is crucial for physicians in the ED since still up to one-third of patients triaged to the observe-zone are finally diagnosed with NSTEMI or unstable angina. Therefore, further serial hs-cTn retesting at 3h should be performed to better differentiate an acute cardiac disease (such as NSTEMI) associated with a dynamic hs-cTn course from a chronic cardiac disease reflected by stable hs-cTn course. Coronary angiography (in those with high likelihood for NSTEMI), echocardiography, and functional stress imaging (in those with low likelihood for NSTEMI) seem to be the preferred tests in observe patients.(62)

Coronary computed tomography angiography (CCTA) seems a suitable imaging modality in only a minority.[51] A randomized-controlled trial recently showed no benefit of routine CCTA over standard optimal care encompassing hs-cTnT in patients with suspected acute coronary syndrome regarding identification of significant CAD requiring revascularization within 30 days, duration of hospital stay or direct discharge from the ED.[52] Functional instead of anatomical testing is mandatory to differentiate coronary lesions resulting in myocardial ischemia and acute chest pain at rest from lesions that are innocent bystanders regarding the acute chest pain episode leading to ED presentation.[50]

Over-ruling the triage recommendations

Hs-cTn-based triage algorithms must always be used in conjunction with detailed clinical assessment and thorough interpretation of the ECG. This synthesis may well result in over-ruling a “rule-out” recommendation provided by the hs-cTn-based algorithms in some patients perceived to be at high-risk of NSTEMI. Over-ruling should then lead to the identical process

described for patients assigned the observe-zone and should always include an additional hs-cTn measurement at 3h.

Rule-out for MI does not always equal outpatient management: As the novel strategies were developed to safely rule-out NSTEMI, but not other disorders that still may require hospital admission such as e.g. unstable angina, pulmonary embolism, aortic dissection, or severe sepsis from pneumonia. Accordingly, the percentage of patients that can possibly be managed as out-patients is smaller as the percentage of patients ruled-out for NSTEMI. Besides, standard operating procedures should be in place to ensure appropriate follow-up of patients rapidly discharged from the ED, which often will include outpatient functional cardiac stress testing.

Uniform versus sex-specific cutoff levels

Beyond the presence or absence of NSTEMI, four clinical variables impact on hs-cTn concentrations: age, sex, renal function, and time since chest pain onset.[53-62] Accordingly, three strategies can be considered: First, a sophisticated one individualizing hs-cTn cutoff levels in the ED for all four confounders. Once automatized within a lab-software tool, this approach may be feasible and could present a valid alternative to the current way of using one uniform cutoff value. Second, using sex-specific cutoff levels. Recent studies have highlighted that women presenting with suspected NSTEMI are on average 5-8 years older than men presenting with suspected NSTEMI.[62-67] The higher age of female patients associated with higher hs-cTn levels seemed to well compensate the effect of female sex. Accordingly, the use of sex-specific cutoff levels was associated with only a negligible number of patients reclassified as compared with the use of a uniform cutoff level when using hs-cTnT.[53-62, 67] Controversies remain for hs-cTnI,[56, 64,

[66] which seem at least in part related to its rather high uniform 99th percentile recommended by the manufacturer.[68] Third, the traditional one using one uniform cutoff value. Given the uncertainties and obvious limitations of the second option, the preference of e.g. the current ESC guidelines is to continue using uniform cutoff levels. [19] As increased complexity in the ED is closely linked with an increased rate of errors, the simplest option of continuing to use uniform cutoff levels at this point in time seems also the safest.[19]

It is important to highlight that the possible clinical use of hs-cTn is currently explored in several additional indications beyond the diagnosis of NSTEMI and that pros and cons of using sex-specific cutoff values may differ in other emerging indications.

Hs-cTn in patients with renal dysfunction

Patients with suspected NSTEMI and renal dysfunction are at substantial higher risk of NSTEMI as compared to patients with normal renal function.[69-71] Accurate rule-out and rule-in of NSTEMI is of paramount importance since patients with renal dysfunction are more prone to adverse events related to cardiovascular medication (e.g. anticoagulation), as well as to cardiovascular procedures including coronary angiography and coronary intervention.[19, 34] However, rapid and accurate diagnosis of NSTEMI is challenging in this vulnerable patient subgroup, since they often present with chronically elevated troponin levels (10-20% using s-cTn, up to 70% using hs-cTn) even in conditions other than acute myocardial ischemia, which are still associated with poor prognosis.[71, 72] The underlying pathophysiological mechanism is poorly understood and not primarily explained by reduced glomerular filtration rate.[35, 73-75]

In general, the high diagnostic utility of hs-cTn in patients with renal dysfunction can be maintained if adjusted decision levels higher than the assay-specific 99th percentiles are

considered.[71] A recent international analysis addressed the question whether the ESC 0/1-algorithm can safely be used also in patients with renal dysfunction.[76] High safety of rule-out (sensitivity 100% for hs-cTnT, 98.6% for hs-TnI) was documented, supporting the use of the ESC 0/1h-algorithm also in patients with renal dysfunction. However, specificity of rule-in and efficacy of rule-out were decreased as fewer patients with renal dysfunction presented with low hs-cTn blood concentrations. Modifications of the rule-in and rule-out thresholds did not improve the specificity or overall efficacy of the 0/1h-algorithm.

Hs-cTn in the elderly patient

Similar to patients with renal dysfunction, mild hs-cTn elevations are common observed in elderly non-MI patients, indicating chronic cardiomyocyte injury. The exact pathophysiological mechanisms resulting in cardiomyocyte injury in the aging heart are incompletely understood. Beyond the higher burden of cardiovascular diseases (e.g. previous MI, structural heart disease, myocardial fibrosis)[3, 19, 74] and renal dysfunction, chronic elevations in hs-cTnT concentrations may also partly be explained by the higher prevalence of non-cardiovascular comorbidities (e.g. chronic obstructive pulmonary disease)[77]

Using the uniform assay-specific 99th percentiles as a binary decision level to rule-out or rule-in NSTEMI based on a single blood sample obtained at presentation to the ED is of limited diagnostic value in the elderly, particularly due to a substantially reduced specificity. However, high diagnostic accuracy of hs-cTn can be maintained if age-adjusted decision levels higher than the assay-specific 99th percentiles are used.[9] While differences in baseline hs-cTn concentrations exist between middle-aged and elderly patients, absolute hs-cTn changes during serial sampling

do not differ in NSTEMI-patients. Therefore, the diagnostic information of absolute changes during serial sampling, a relevant element of the ESC 0/1h- and 0/2h-algorithm, is maintained.

Can the different hs-cTn-based rule-out strategies safely be applied also in the elderlies? These strategies were derived and validated in mixed, all-comers populations with a median age of about 65 years, reflecting a standard chest pain population presenting to the ED in most developed health care settings. Subgroup analysis of the ESC 0/1h-algorithm indicated very high safety also in the challenging subgroup of elderly patients.[48] Due to the higher prevalence of chronically elevated hs-cTn blood concentrations, however, fewer elderly patients seem to be eligible for rule-out. Whether the application of hs-cTn-based strategies using age-adjusted, higher cutoff values or uniform cutoff levels is more favorable regarding the balance of safety and efficacy, needs to be investigated in future studies.

Application of rapid, troponin-based triage algorithms in the United States of America (USA)

Although hs-cTn assays have been widely used since 2010 in Europe and many other countries outside the United States of America (USA), the first hs-cTn assay has just received approval by the Food and Drug Administration (FDA) for clinical use in the USA in spring 2017. The FDA-approved use of hs-cTnT differs in two important details from its contemporary use in most other countries: First, low concentrations are only reported down to 6ng/L as compared to 3ng/L and second, a higher age-matched 99th percentile upper-reference limit of 19ng/L is suggested as compared with 14ng/L. Both changes could potentially impact the safety and/or efficacy of rapid triage algorithms defined previously in a non-FDA setting. A recent analysis aimed to quantify the impact of the FDA-approved use of hs-cTnT on the safety and efficacy of the ESC 0/1h-

algorithm.[78] The original ESC 0/1h-algorithm was minimally adapted to the FDA-setting by lifting the direct rule-out criteria at presentation from <5ng/L to <6ng/L, since hs-cTnT levels are only reported down to 6ng/L in the USA. Rule-out safety as well as rule-in accuracy of the original and the modified algorithm were very high and comparable (NPV 99.8% versus 99.9%, PPV 76.9% versus 76.7%). Both algorithms allowed rapid rule-out and rule-in of NSTEMI in three patients out of four.

CONCLUSIONS

Hs-cTn assays improve and accelerate the early management of patients with suspected NSTEMI and complement assessment using clinical presentation and the ECG. Reduction of the "troponin-blind" interval allows to substantially shorten timing of serial hs-cTn re-measurement. Many factors other than acute myocardial ischemia may cause cardiomyocyte injury and therefore mild hs-cTn elevations. Dynamic changes of hs-cTn during serial sampling help to distinguish acute from chronic causes of chest pain and troponin elevations. To maximally profit from hs-cTn assays in clinical practice, they should best be used embedded in an institutional standard operating procedure of the ED and in conjunction with a rapid triage algorithm enabling rapid decision making within few hours. Such an approach will allow not only to increase patients' safety as compared with conventional, less sensitive cTn assays, but also to substantially reduce duration of stay on the ED and costs. Once a process of ≥24 hours, many patients can now have NSTEMI rapidly and safely excluded already in the ED.

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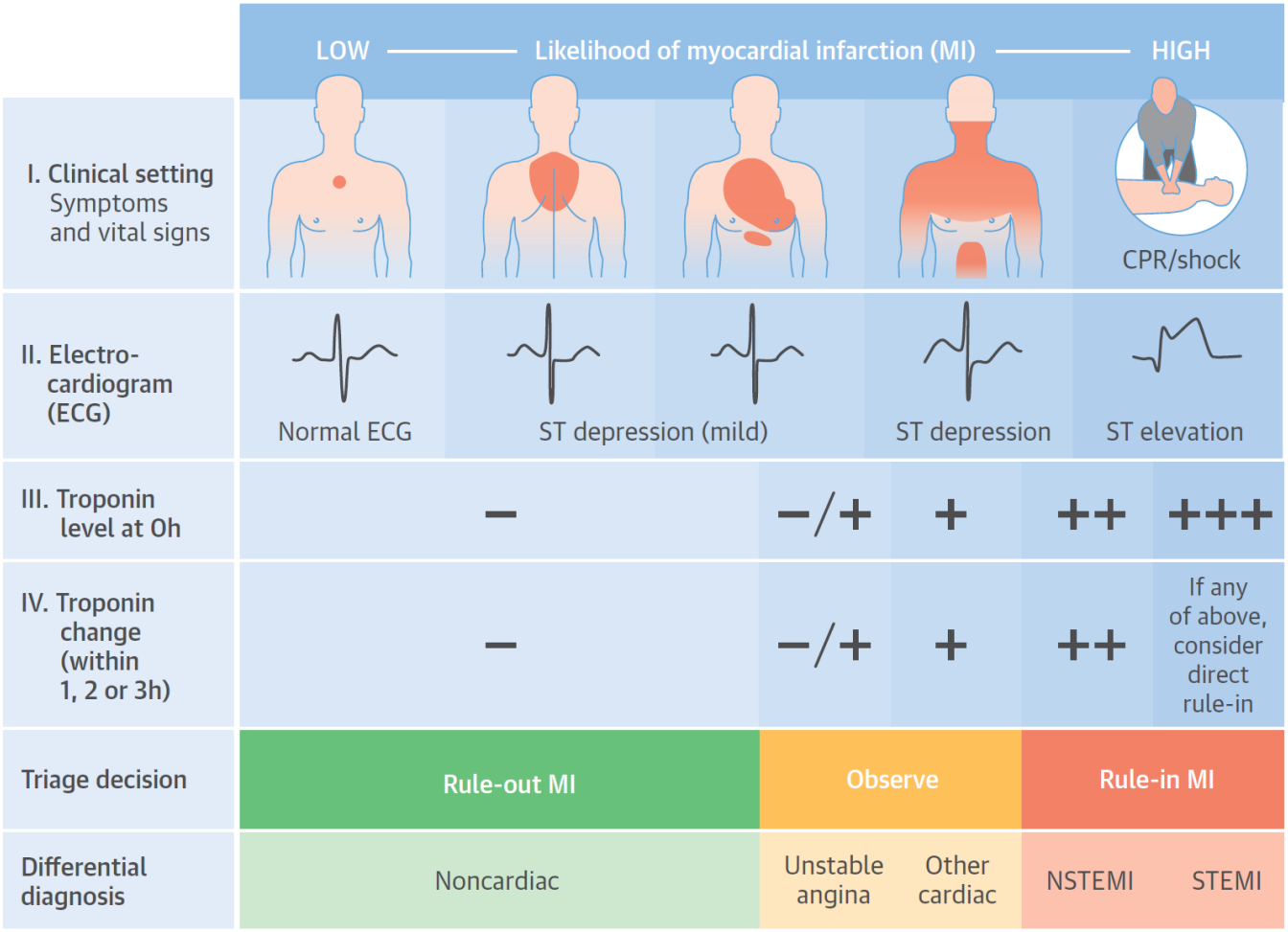
Figure Legend



Twerenbold, R. et al. J Am Coll Cardiol. 2017;70(8):996-1012.

Figure 1 **Patient assessment in suspected acute coronary syndrome**

The initial assessment is based on the integration of low likelihood and/or high likelihood features derived from clinical setting (i.e., symptoms, vital signs), 12-lead ECG, and cardiac troponin determined at presentation to the emergency department and serially thereafter. “Other cardiac” includes, among other, myocarditis, Tako-Tsubo cardiomyopathy, or congestive heart failure. “Non-cardiac” refers to thoracic diseases such as pneumonia or pneumothorax. Cardiac troponin and its change during serial sampling should be interpreted as a quantitative marker: the higher the 0h-level or the absolute change during serial sampling, the higher the likelihood for the presence 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 a 12-lead ECG. If the initial evaluation suggests aortic dissection or pulmonary embolism, D-dimers and multi-detector computed tomography angiography are recommended according to dedicated algorithms.

CPR=cardio-pulmonary resuscitation; ECG=electrocardiogramm; MI=myocardial infarction; NSTEMI=Non-ST-Segment-Elevation Myocardial Infarction; STEMI=ST-Segment-Elevation Myocardial Infarction.

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