JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 70, NO. 8, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.07.718

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Clinical Use of High-Sensitivity Cardiac Troponin in Patients With Suspected Myocardial Infarction

Raphael Twerenbold, MD,[a] Jasper Boeddinghaus, MD,[a,b] Thomas Nestelberger, MD,[a] Karin Wildi, MD,[a] Maria Rubini Gimenez, MD,[a] Patrick Badertscher, MD,[a] Christian Mueller, MD[a]

ABSTRACT

High-sensitivity cardiac troponin (hs-cTn) assays have been used clinically by thousands of physicians in many countries throughout the world since their clinical introduction 7 years ago. In the early diagnosis of myocardial infarction (MI), beyond doubt, the most important indication of hs-cTn assays, these simple, inexpensive, and highly reproducible tools complement detailed clinical assessment including chest pain characteristics and the electrocardiogram. Hs-cTn assays for the first time allowed the precise quantification of cardiomyocyte injury around the 99th percentile and thereby substantially increased the accuracy of MI detection from blood obtained at presentation to the emergency department (ED). Higher accuracy at ED presentation enabled the development and extensive validation of early hs-cTn–based diagnostic algorithms, which substantially reduced the time required for the safe rule-out or rule-in of MI. This review summarizes key principles underlying the safe and effective use of hs-cTn in the ED in patients with suspected MI. (J Am Coll Cardiol 2017;70:996–1012) © 2017 by the American College of Cardiology Foundation.

About 20 million patients present with symptoms suggestive of myocardial infarction (MI) to emergency departments (EDs) in North America and Europe each year (1). Patients with MI may present with a wide variety of symptoms, such as chest pain, shortness of breath, weakness, nausea, and vomiting and even fatigue, making the diagnosis difficult (2,3). Demographics, traditional cardiac risk factors, chest pain characteristics, and physical examination can assist disposition decisions, but are insufficient by themselves to identify who does and does not have MI (4-7). Some patients may have objective evidence of a clear-cut diagnosis; however, the majority do not (8). Only a minority will be found to have MI and will instead have symptoms caused by noncardiac and often benign disorders such as musculoskeletal pain, pleuritis, or gastroesophageal reflux, highlighting the medical and economic need of rapid rule-out (9,10). Additionally, the early diagnosis of MI is crucial for the early initiation of evidence-based treatment. Missed MI has important medico-legal implications, being the highest single diagnosis in terms of dollars paid and third highest in terms of

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Cardiovascular Research Institute Basel (CRIB) and Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland; and the [b]Department of Internal Medicine, University Hospital Basel, University of Basel, Basel, Switzerland. Dr. Twerenbold has received research support from the Swiss National Science Foundation (P300PB-167803/1) and speaker honoraria/consulting honoraria from Roche, Abbott Diagnostics, Siemens, and BRAHMS Thermo Scientific. Dr. Boeddinghaus has received speaker honoraria from Siemens. Dr. Rubini Gimenez has received speaker honoraria from Abbott. Dr. Mueller has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the KTI, the Stiftung für kardiovaskuläre Forschung Basel; Abbott, Alere, AstraZeneca, 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, AstraZeneca, Biomerieux, Boehringer Ingelheim, Bristol-Myers Squibb, BRAHMS Thermo Scientific, Cardiorentis, Novartis, Roche, Siemens, and Singulex. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 15, 2017; revised manuscript received July 9, 2017, accepted July 10, 2017.

frequency of claims in malpractice against emergency physicians (11).

HIGH-SENSITIVITY CARDIAC TROPONIN

The clinical assessment, even combined with an electrocardiogram (ECG), is not sufficient to diagnose or exclude non-ST-segment-elevation myocardial infarction (NSTEMI) in most patients, and thus 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. Clinicians use cTn values to estimate the likelihood of MI and the short-term risk of death.

Advances in assay technology have led to a refinement in the clinical ability to detect and quantify cardiomyocyte injury (9,10,12–40). 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 MI (9,10,12–40). These improved assays are labeled "sensitive" when able to detect cTn in ~20% to 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 (10). 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, thereby reducing the time to diagnosis and improving efficiency in the ED (9,10,12–41).

Although hs-cTn assays have been used in Europe, Australia, New Zealand, Canada, and many other developed countries since 2010, the first hs-cTn assay has just received approval for clinical use in the United States in the spring of 2017. By contrast, sensitive cTn (s-cTn) assays are widely used in the United States.

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 s-cTnT and -I assays exactly quantify the amount of cardiomyocyte injury (12,27,41,42). 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 MI of only about 40% to 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. When referring to levels in the normal range, the same concept applies: the lower the cTn blood concentration, the lower the likelihood for MI. Continuous medical education and training of physicians in these concepts is essential to avoid inappropriate interpretation of chronic mild elevations of cTn associated with, for example, heart failure or other structural cardiac disorders such as valvular heart disease and left ventricular hypertrophy as signs of MI.

TRUE AND FALSE FALSE-POSITIVE hs-cTn MEASUREMENTS

In the absence of overt myocardial ischemia, elevated cTn levels are often labeled as "false-positive" hs-cTn results, which is a misleading term. 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, hypertensive heart disease, and chronic coronary artery disease (CAD). Many primarily cardiac disorders as well as noncardiac disorders with cardiac involvement may lead to substantial amounts of cardiomyocyte injury and thereby hs-cTn elevations (**Table 1**) (10,27). It is important to note that cTn elevations universally portend a worse prognosis than otherwise similar patients without a cTn elevation. This is true regardless of whether the patient has heart failure, renal dysfunction, gastrointestinal bleeding, sepsis, respiratory disease, pulmonary embolism, subarachnoid hemorrhage, or stroke, or whether the patient is asymptomatic without known cardiovascular disease (43). Obviously, the medical consequences of cardiomyocyte injury as quantified by cTn elevations will be highly individualized and different from that in patients with MI.

Nevertheless, 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 with heterophilic antibodies. In cases of striking discordance between cTn measurements and clinical presentation, analytical "false-positive" test results

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ADP = advanced diagnostic pathway

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

cTn = cardiac troponin

ECG = electrocardiogram

ED = emergency department

ESC = European Society of Cardiology

FDA = Food and Drug Administration

hs-cTn = high-sensitivity cardiac troponin

LBBB = left bundle branch block

MACE = major adverse cardiac event(s)

MI = myocardial infarction

NPV = negative predictive value

NSTEMI = non-ST-segment elevation myocardial infarction

PPV = positive predictive value

s-cTn = sensitive cardiac troponin

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

UA = unstable angina

TABLE 1 Conditions Other Than MI Associated With Cardiac Troponin Elevations

Tachyarrhythmias
Heart failure
Hypertensive emergencies
Critical illness (e.g., shock/sepsis/burns)
Myocarditis
Takotsubo cardiomyopathy
Structural heart disease (e.g., aortic stenosis)
Aortic dissection
Pulmonary embolism, pulmonary hypertension
Renal dysfunction and associated cardiac disease
Coronary spasm
Acute neurological event (e.g., stroke or subarachnoid hemorrhage)
Cardiac contusion or cardiac procedures (e.g., CABG, PCI, ablation, pacing, cardioversion, or endomyocardial biopsy)
Hypothyroidism and hyperthyroidism
Infiltrative diseases (e.g., amyloidosis, hemochromatosis, sarcoidosis, scleroderma)
Myocardial drug toxicity or poisoning (e.g., doxorubicin, 5-fluorouracil, Herceptin [trastuzumab], snake venoms)
Extreme endurance efforts
Rhabdomyolysis

Adapted with permission from Roffi et al. (27).

CABG = coronary artery bypass surgery; MI = myocardial infarction; PCI = percutaneous coronary intervention.

(e.g., due to heterophilic antibodies) must be considered. The following 2-step approach may facilitate further clinical workup: 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 nonrepeatable 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., heterophilic or troponin autoantibodies affecting cTnI or skeletal muscle disease affecting cTnT). In case of a match, chronic myocardial injury must be suspected and should be further elaborated with imaging techniques (44).

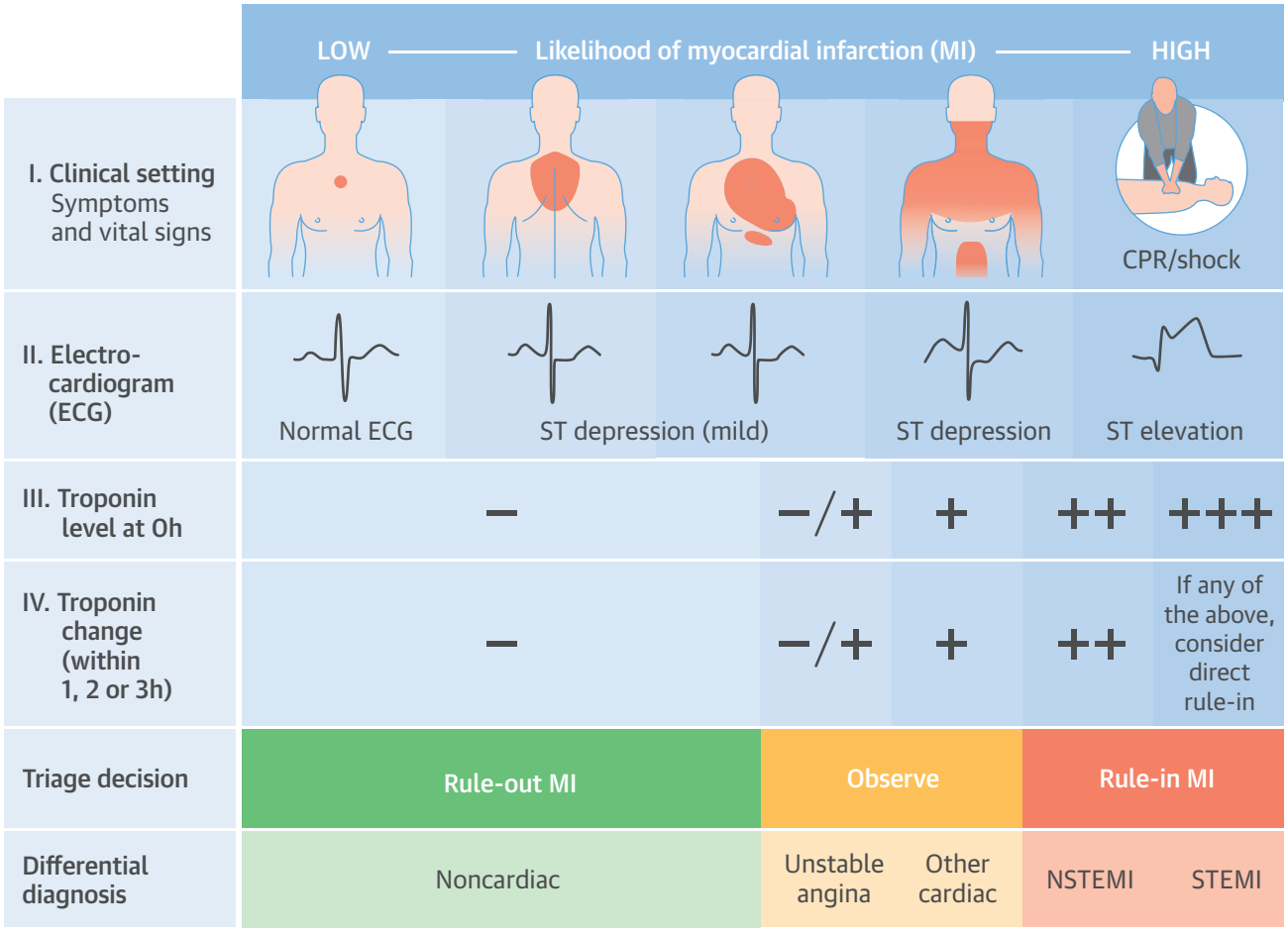
TROPONIN-BASED STRATEGIES FOR RAPID RULE-OUT OR RULE-IN OF MI

The most important clinical advantage of the new, more-sensitive cTn assays is their ability to substantially reduce the initial "troponin-blind" interval in the first hours after MI onset and to allow novel, rapid strategies for the early rule-out or rule-in of MI. Several troponin-based strategies rely on serial hs-cTn testing. Two of them, a 0-h to 1-h (0/1h) algorithm and a 0-h to 3-h (0/3h) algorithm, are recommended by the European Society of Cardiology (ESC) with a class I recommendation and deserve in-depth discussion. These novel strategies have been fine tuned to detect MI, but not unstable angina (UA), the acute coronary syndrome (ACS) phenotype at much lower short-term risk of death and/or major arrhythmias, but at substantial long-term risk of MI (45,46). Therefore, full cardiology workup and intensive lifestyle modification and medical therapy remain crucial in UA.

It is important to highlight 5 aspects when applying troponin-based strategies in clinical practice (**Central Illustration**). 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, because additional imaging tests, for example, invasive coronary angiography, stress testing, echocardiography, or computed tomography 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 cTn assay used, and the clinical setting, including the prevalence of MI (24,28). Fourth, these strategies should only be applied after the initial ECG has excluded ST-segment elevation myocardial infarction (STEMI) because these high-risk patients need prompt identification based on the ECG, and immediate reperfusion therapy, without the need for cTn testing (12). Some rule-out strategies require a completely normal ECG to be applied; others allow also for mild and nonspecific ECG abnormalities. Fifth, all triage strategies should be embedded in the local standard operating procedures of the ED.

Among the multitude of available triage algorithms for patients with suspected MI, 6 novel strategies based on cTn have been studied and validated in large, methodologically robust, multicenter diagnostic studies including several thousand patients and rigorous MI adjudication using serial hs-cTn testing. These warrant consideration for clinical use in the appropriate clinical setting of patients presenting to the ED with acute chest discomfort and/or suspected MI. The main performance metrics of the studies include safety (quantified by the negative

CENTRAL ILLUSTRATION **Patient Assessment With Suspected ACS**



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

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 ED and serially thereafter. "Other cardiac" includes, among other, myocarditis, Takotsubo cardiomyopathy, or congestive heart failure. "Noncardiac" 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 multidetector computed tomography angiography are recommended according to dedicated algorithms. Width of boxes represent the prevalence of the respective disorders among consecutive patients presenting with acute chest pain to the emergency department. ACS = acute coronary syndromes; CPR = cardio-pulmonary resuscitation; ECG = electrocardiography; hs-cTn = high-sensitivity cardiac troponin; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction. Adapted with permission from Roffi et al. (27).

predictive value [NPV] and sensitivity for MI) and efficacy (percentage of patients triaged early) for rule-out, as well as the PPV and specificity for MI (**Table 2**). Four algorithms use the absolute change between 2 measurements in addition to the hs-cTn concentrations determined at presentation to the ED to take advantage of the full diagnostic information provided. Rising and/or falling cTn levels differentiate acute from chronic myocardial injury. Absolute rather than relative changes seem to be the best metric to differentiate MI from other causes of chest pain (16,23-25). The larger the absolute (unsigned) cTn change within 1h, 2h, or 3h, the higher the likelihood for the presence of MI (16,23-25).

Two strategies require the use of a pre-defined risk score (0/3h-ESC algorithm and 2h advanced

TABLE 2 Summary of Biomarker Strategies for Rapid Assessment of Patients With Potential ACS in the ED

	Very Low cTn	0/1h-ESC Algorithm	Alternative 1h Algorithm	0/2h Algorithm	2h-ADP	0/3h-ESC Algorithm
Clinical scoring system	None	None	None	None	TIMI score ≤1 ECG Normal at 0 h/2 h	GRACE <140 and Pain Free
Number of blood draws	1	1 or 2	2	1 or 2	2	1 or 2
Indication	Rule-out	Rule-out and rule-in	Rule-out and rule-in	Rule-out and rule-in	Rule-out	Rule-out and rule-in
Negative predictive value for MI	98.5%–100%	99.1%–100%	99.2%–99.6%	99.5%–99.9%	99.1%–100%*	99.6%–100%
Eligible population size	+(+)	+++	+++	+++	++	++(+)
Biomarker rule-out criteria†						
High-sensitivity cardiac troponin T (hs-cTnT)	hs-cTnT <5 ng/l	hs-cTnT 0 h <12 ng/l AND 1-h change <3 ng/l	n.a.	hs-cTnT 0 h and 2 h <14 ng/l AND 2-h change <4 ng/l	hs-cTnT 0 h and 2 h <14 ng/l	hs-cTnT 0 h and 3 h <14 ng/l
High-sensitivity cardiac troponin I (hs-cTnI)	hs-cTnI 0 h <2–5 ng/l	hs-cTnI 0 h <5 ng/l AND 1-h change <2 ng/l	hs-cTnI 0 h ≤6 ng/l AND hs-cTnI 1 h ≤6 ng/l	hs-cTnI 0 h and 2 h <6 ng/l AND 2-h change <2 ng/l	hs-cTnI 0 h and 2 h <26 ng/l	hs-cTnI 0 h and 3 h <26 ng/l
Biomarker rule-in criteria†						
Using hs-cTnT	n.a.	hs-cTnT 0 h ≥52 ng/l OR 1-h change ≥5 ng/l	n.a.	hs-cTnT 0h ≥53 ng/l OR 2-h change ≥10 ng/l	n.a.	
Using hs-cTnI	n.a.	hs-cTnI 0 h ≥52 ng/l OR 1-h change ≥6 ng/l	hs-cTnI 1 h >6 ng/l AND 1-h change ≥12 ng/l	hs-cTnI 0 h ≥64 ng/l OR 2-h change ≥15 ng/l	n.a.	
Feasibility	High	High	High	High	Medium; requires use of TIMI score	Medium; requires GRACE score

Eligible population size is quantified by the percentage of consecutive chest pain patients eligible for this early triage strategy. + ≈20%; ++ ≈40%; +++ ≈50% to 75%. *For major adverse cardiac events (death, MI, major arrhythmias). †Characteristics are provided for the hs-cTnT (Elecsys) and hs-cTnI (Architect). Cutoff levels differ for other hs-cTn assays becoming available for clinical use in the future.

ACS = acute coronary syndrome; ADP = accelerated diagnostic pathway; cTn = cardiac troponin; ECG = electrocardiogram; ED = emergency department; ESC = European Society of Cardiology; GRACE = Global Registry of Acute Coronary Events; hs = high-sensitivity; LOD = lower limit of detection; MI = myocardial infarction; RCT = randomized controlled trial; TIMI = Thrombolysis In Myocardial Infarction.

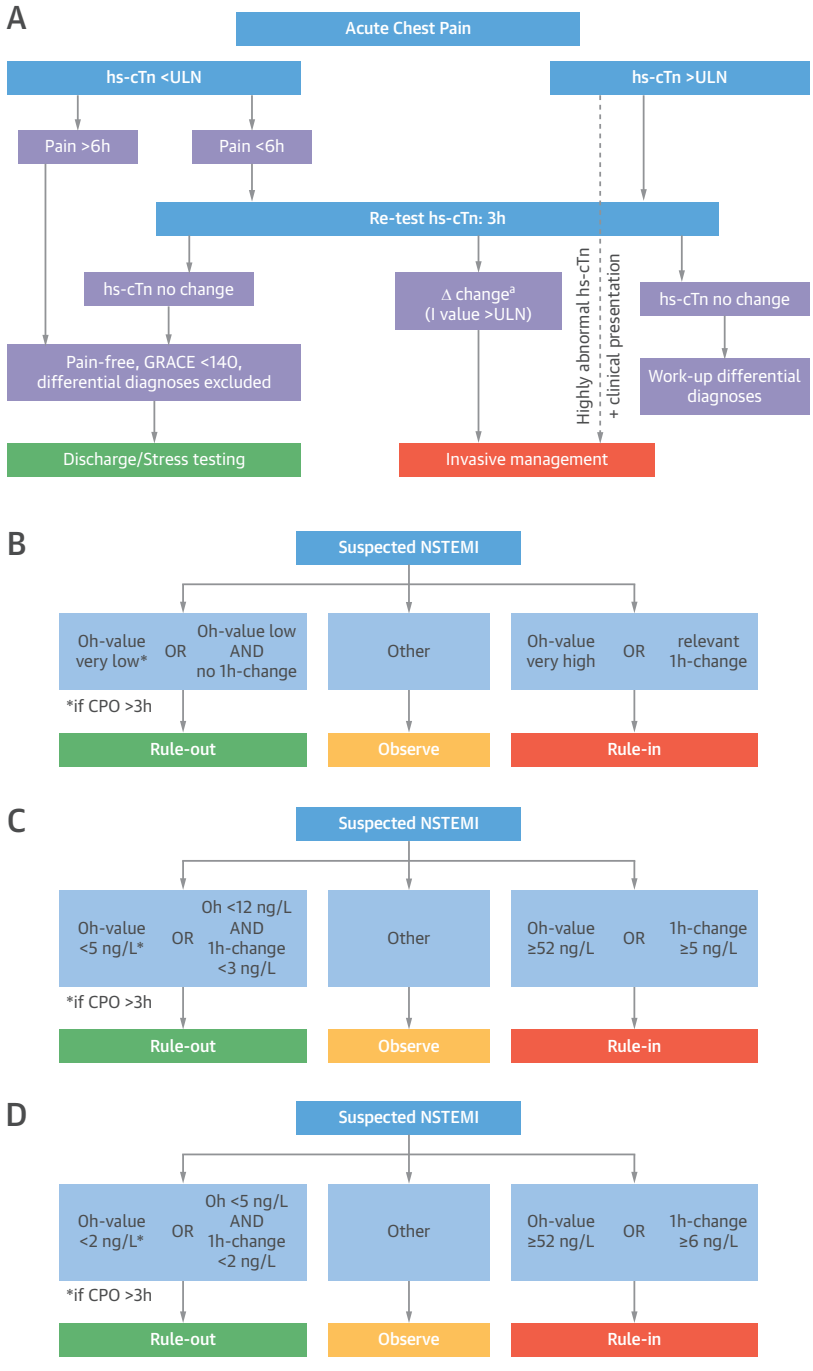
diagnostic pathways [ADP]), whereas the remaining 4 strategies do not.

0/3h-ESC ALGORITHM. MI is ruled out if concentrations of hs-cTn remain in the normal range (below the respective 99th percentiles) in the blood sample drawn at presentation and 3 h after presentation, and if the patient fulfils 2 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 (27). In patients presenting more than 6 h after chest pain onset, in whom chest pain onset can be reliably quantified, 1 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 3-h sample shows a relevant change. This approach has been recommended by the ESC guidelines since 2011 and is the standard of care in many institutions worldwide (**Figure 1A**) (10,27). Its use regarding rule-out of MI seems to be safe for all hs-cTn assays and possibly also some s-cTn assays (47). The exact performance for rule-in cannot be quantified, as no precise definitions of its rule-in cutoff levels are given. Given the average turnaround time for hs-cTn of about 1 h, the hs-cTn measurement performed at 3 h after ED presentation would become available at about 4 h after ED presentation and would allow clinical decision making regarding hospitalization versus outpatient management about 4 h 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 5 h in the overall population, and 4.5 h in those patients managed as outpatients (48).

An alternative 0/3h algorithm using lower cutoff criteria than the 99th percentile for rule-out has recently been developed specifically for hs-cTnI (49).

2h-ADP WITH RISK SCORES. This is the best validated strategy, combining serial cTn testing with a pre-defined clinical risk score, the Thrombolysis In Myocardial Infarction (TIMI) score (28–32). The TIMI score was developed about 2 decades ago as a prognostic score for patients with ACS to identify those who may benefit most from anticlotting therapy and was subsequently validated for the use in ED patients (50,51). The original 2h-ADP combines a TIMI score of 0 with a nonischemic ECG and negative

FIGURE 1 ESC Rapid Triage Algorithms



(A) The European Society of Cardiology (ESC) 0/3h rule-out and rule-in algorithm of non-ST-segment elevation acute coronary syndromes using high-sensitivity cardiac troponin (hs-cTn) assays. [a]Δ change, dependent on assay. Highly abnormal hsTn defines values beyond 5-fold the upper limit of normal. **(B)** The ESC 0/1h rule-out and rule-in algorithm using hs-cTn assays in patients presenting with suspected non-ST-segment elevation myocardial infarction (NSTEMI) to the emergency department. **(C)** The ESC 0/1h rule-out and rule-in algorithm with assay-specific cutoff values for the Elecsys hs-cTnT assay (Roche Diagnostics, Rotkreuz, Switzerland). **(D)** The ESC 0/1h rule-out and rule-in algorithm with assay-specific cutoff values for the Architect hs-cTnI assay (Abbott Laboratories, Chicago, Illinois). Adapted with permission from Roffi et al. (27). CPO = chest pain onset; GRACE = Global Registry of Acute Coronary events score; ULN = upper limit of normal.

conventional cTn testing at 0 and 2 h, classifying 9.8% of patients as low risk with a sensitivity and NPV for major adverse cardiac events (MACE) within 30 days of ≥99% (28). A modified protocol using hs-cTnI and a TIMI score of ≤1 could safely discharge 40% of patients with comparable MACE incidence (30).

0/2h ALGORITHM WITHOUT RISK SCORES. The alternative 0/2h strategy exclusively uses hs-cTn data to triage patients without the use of a specific clinical risk score and thereby achieves a comparable NPV and sensitivity for rule-out by also taking into account absolute concentration changes within 2 h (22,52,53). The lack of a relevant absolute change from presentation to 2 h combined with the fact that both concentrations need to be normal obviates the need of a pre-defined score and allows one to safely rule out MI even in patients with pre-existing CAD. Accordingly, this strategy is more effective and allows the rapid rule-out of MI in up to 60% of patients (22,52,53). Moreover, this strategy includes a rule-in algorithm that provides a PPV above 75% for MI and allows the early rule-in in about 10% to 15% of acute chest pain patients within 2 h to 3 h of presentation.

0/1h-ESC ALGORITHM. The concept of the 0/1h-ESC algorithm is identical to that of the 0/2h algorithm and is also based exclusively on information provided by hs-cTn blood concentrations (**Figure 1B**). The decision points derived and validated for each assay are assay-specific (**Figures 1C and 1D**) (24,27,34,35,54). The 0/1h-ESC algorithm obviates the need for formal use of clinical scores and allows safe rule-out of MI even in patients with pre-existing CAD or mild, nonspecific, and often pre-existing ECG abnormalities. Accordingly, this strategy is very effective and allows an accurate early triage in about 75% of patients: 60% towards rule-out and in 15% towards rule-in of MI. Again, given the average turnaround time for hs-cTn of about 1 h, the hs-cTn measurement performed at 1 h after ED presentation will become available at about 2 h after ED presentation and will facilitate clinical decision making regarding hospitalization versus outpatient management about 2 to 3 h after ED presentation in the majority of patients. The application of the 0/1h-ESC algorithm is also possible in institutions with a median turnaround time of more than 1 h because the 1 h only refers to the time interval between the serial blood sampling. In this situation, the second blood draw would need to be performed while still awaiting the results from the first blood draw. In order to further demonstrate the simplicity of the 0/1h-ESC algorithm, 5 common clinical scenarios are described as case reports in the Online Appendix.

ALTERNATIVE 1h ALGORITHM. A modification of the 0/1h-ESC algorithm has recently been developed for hs-cTnI (55). Safety of rule-out and overall efficacy are very high and comparable to the 0/1h-ESC algorithm. In contrast to the 0/1h-ESC algorithm, this algorithm does not allow for direct rule-out or rule-in on the basis of the 0 h sample only.

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% to 100%) NPV for MI. This approach has unique simplicity, as it requires only a single blood draw of an inexpensive and widely available biomarker. Because 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 a recent meta-analysis have provided consistent results for hs-cTnT, whereas 3 studies showed comparable findings for 3 hs-cTnI assays (36,37,56–60). Because 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 to 3 h before ED presentation, because safety was reduced in these very early presenters in a recent observation (60). 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 (27).

PROS AND CONS OF THE DIFFERENT EARLY ALGORITHMS

For all aforementioned diagnostic algorithms, 4 main differences need to be highlighted: First, some algorithms are exclusively cTn-based, whereas others use the combination of cTn with clinical risk scores. Although all algorithms, irrespective of being exclusively cTn-based or including a clinical risk score, need to be integrated and used in conjunction with all information available in the ED, the clinical utility and the need of formal risk scores is a matter of debate. Regarding the diagnosis of MI, the use of hs-cTn seems to obviate the need for routine assessment of formal risk scores because exclusively cTn-based algorithms provide similar NPV and sensitivity for the rule-out of MI as compared with algorithms additionally requiring a low risk score (22,24,29–31,34–37,47,52,53,55–61). However, clinical scores such as the TIMI or GRACE risk scores may help regarding selection of patients suitable for early discharge from the ED, which is a separate

management decision because these scores include variables such as known CAD, older age, and renal dysfunction indicating increased risk of future events (61).

Second, the early rule-out (and rule-in) algorithms differ in time points chosen for first and serially thereafter performed (hs)-cTn measurements. Single cutoff strategies rule out patients with a single measurement at presentation, the other algorithms use different time intervals between the first and the second measurement of cardiac troponin concentrations (1 h, 2 h, and 3 h) (**Figure 2**). Third, although the 0/1h, 0/2h, and 0/3h algorithms have the potential to triage patients toward rule-out and rule-in of MI, the other 2 described algorithms can only be used for early rule-out of MI. Fourth, patients presenting very early after chest pain onset require particular attention in order not to miss late rises in hs-cTn. In general, rule-out based on a single measurement approach is *not* possible in early presenters (≤3 h after chest pain onset) (**Figure 3**) (27,60). Although pilot data suggest that using very low concentrations of hs-cTnI (2 ng/l or less) may also allow very high NPV in early presenters, further studies seem necessary to confirm the safety of this approach in early presenters.

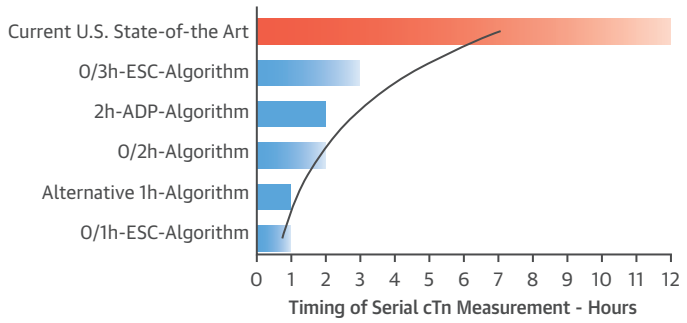
The clinical value of early rule-out algorithms for safe rule-out of MI is helping guide clinicians identifying patients at very low risk for MI and MACE. However, the decision, which of the available strategies for rapid triage of suspected MI should be used in clinical practice, must be made by each institution individually depending on the locally used cTn assay (sensitive vs. 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?

Although some rapid strategies provide guidance for rule-out only, 4 strategies also provide detailed guidance for rule-in of MI. In addition to the rule-out and rule-in zone, these strategies leave up to one-third of patients in an observe zone (24,34,35,52,53,55,62). Although patients' management is largely defined and simplified in patients assigned to rule-out and rule-in, it remains highly personalized and sometimes challenging in those assigned to the observe zone. These patients are typically elderly men with pre-existing CAD and were shown to have increased long-term mortality (63). Detailed clinical assessment, additional hs-cTn measurement at 3 h, and cardiac imaging are integral for accurate diagnosis in these patients. The clinical interpretation of mildly abnormal hs-cTn levels is crucial for physicians in the ED due to the fact that still up to one-third of patients triaged to the observe zone are finally diagnosed with MI or UA. Therefore, further serial hs-cTn retesting at 3 h should be performed to better differentiate an acute cardiac disease (such as MI) associated with a dynamic hs-cTn course, from a chronic cardiac disease reflected by a stable hs-cTn course. Depending on the clinical picture and the course of hs-cTn during serial sampling, coronary angiography (in those with high likelihood for MI), echocardiography, and functional stress imaging (in those with low likelihood for MI) seem to be the preferred tests in observe-zone patients (62).

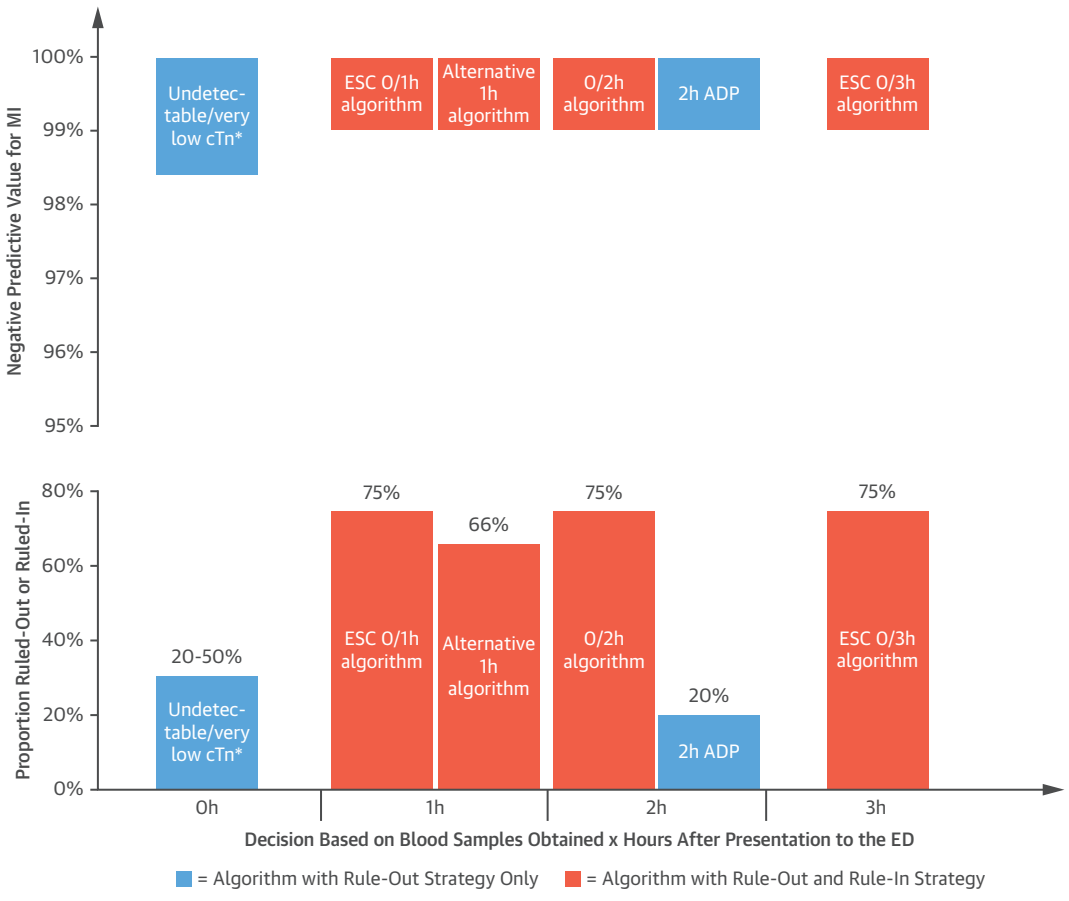
Due to the characteristics of patients in the observe zone with their high prevalence of pre-existing CAD, coronary computed tomography angiography (CCTA) seems a suitable imaging modality in only a minority (64). A randomized controlled trial recently investigated whether a diagnostic strategy supplemented by routine early CCTA is superior to standard optimal care encompassing hs-cTnT in patients with suspected ACS in the ED. It showed no benefit of routine CCTA use regarding identification of significant CAD requiring revascularization within 30 days, duration of hospital stay, or direct discharge from the ED (65). Functional instead of anatomic 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 (63).

FIGURE 2 Timing of Serial hs-cTn Measurements According to Underlying Algorithm



Orange bar indicates current state-of-the art in the United States. **Blue bars** indicate timing of second hs-cTn measurement in multiple rapid triage algorithms. **Blue bars with fading colors to the right end** indicate algorithms allowing direct rule-out and direct rule-in acute myocardial infarction in some patients based on hs-cTn measurements obtained at presentation only, whereas **saturated blue bars** do not allow direct rule-out/rule-in of myocardial infarction. ADP = accelerated diagnostic pathway; cTn = cardiac troponin; ESC = European Society of Cardiology.

FIGURE 3 Diagnostic Performance of Troponin-Based Algorithms and Their Timing of Blood Resampling



Algorithms in **blue boxes** contain a rule-out strategy only, algorithms in **orange boxes** contain both a rule-out and a rule-in strategy. **Upper panel** displays negative predictive values, **lower panel** displays proportions of patients eligible for rule-out or rule-in (if applicable) (22,24,29–31,34–37,47,52,53,55–61). *Should only be used in patients with chest pain onset of at least 3 h before presentation to the ED. ADP = advanced diagnostic pathway; ED = emergency department; ESC = European Society of Cardiology; MI = myocardial infarction; other abbreviations as in Figure 2.

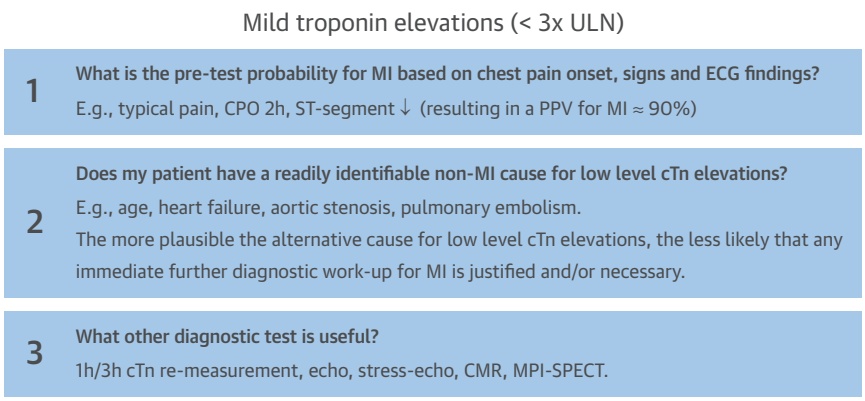
OVER-RULING THE TRIAGE RECOMMENDATIONS

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 MI. 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 3 h. In the vast majority of patients, the 3-h measurement will then confirm the rule-out of MI. However, because the novel hs-cTn-based rule-out algorithms have very high, but not perfect, NPV and sensitivity, over-ruling will detect a rare late-rising patient with MI.

RULE-OUT FOR MI DOES NOT ALWAYS EQUAL OUTPATIENT MANAGEMENT

Because the novel strategies were developed to safely rule out MI, but not other disorders that still may require hospital admission such as UA, pulmonary embolism, aortic dissection, or severe sepsis from pneumonia, the percentage of patients that can possibly be managed as outpatients is smaller than the percentage of patients ruled out for MI. Besides, standard operating procedures should be in place to

FIGURE 4 3 Key Questions to Facilitate Work-Up of Patients Presenting With Mild Elevations of hs-cTn



Three key questions to facilitate work-up of patients presenting with mild elevations of hs-cTn. CMR = cardiac magnetic resonance imaging; MPI-SPECT = myocardial perfusion imaging single-photon emission computed tomography; PPV = positive predictive value; ST-segment ↓ = ST-segment depression; other abbreviations as in Figures 1 to 3.

ensure appropriate follow-up of patients rapidly discharged from the ED, which often will include outpatient functional cardiac stress testing.

WHAT TO DO IN PATIENTS WITH MILD hs-cTn ELEVATIONS?

Mild cTn elevations are those just above the 99th percentile (e.g., up to 3 times the 99th percentile) and have a broad differential diagnosis (27). In patients presenting with acute chest pain, the PPV of mild cTn elevations for MI is only about 50% (66). In patients in whom mild cTn elevations are detected for other presenting symptoms or possibly during screening with an even lower pre-test probability for MI, the PPV of mild cTn elevations for MI is even lower. The following 3 key questions should help to rapidly identify the underlying cause of mild cTn elevations and to guide optimal management of these challenging patients (**Figure 4**) (67).

First, what is the pre-test probability for MI based on symptoms, signs, and ECG findings? For example, in a patient with typical acute chest pain that started only 2 h ago and is associated with ST-segment depression, mild cTn elevations perfectly match the clinical scenario of MI, because cardiomyocyte injury is a time-dependent phenomenon in MI. This patient has a >95% likelihood of MI and requires immediate treatment for MI.

Second, is there a readily identifiable non-MI cause for the observed mild cTn elevation? Basic clinical assessment for age often provides important clues, such as pre-existing structural heart disease, including left ventricular hypertrophy, or obvious non-MI acute cardiac disorders such as acute heart failure, acute tachyarrhythmia, severe sepsis, or acute pulmonary embolism. The more plausible the alternative cause for mild cTn elevations, the less likely that any immediate further diagnostic workup for MI is justified and/or necessary.

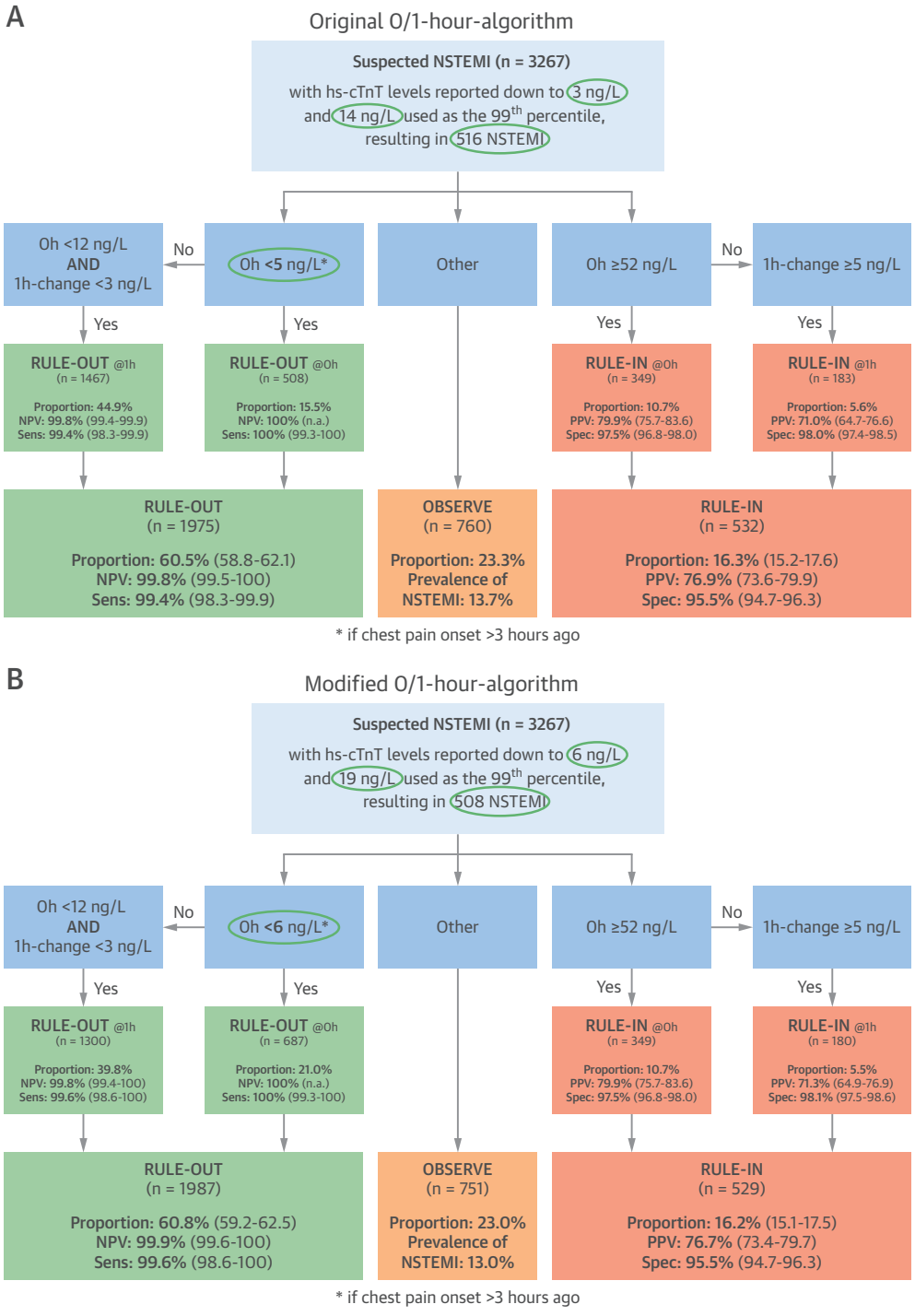
Third, which additional diagnostic test is useful? In nearly all patients, changes in cTn should be assessed by repeating the cTn measurement after 1 h (66). The higher the change in cTn within 1 h, the higher the likelihood of MI. Echocardiography will be helpful, if, for example, valvular heart disease or heart failure is the suspected cause of symptoms and cTn elevation. Cardiac magnetic resonance imaging is helpful to differentiate coronary from other patterns of cardiomyocyte injury and can thereby avoid coronary angiography in many patients with a low likelihood of MI.

Last, but not least, it is important to remember that mild cTn elevation indicates an increased risk for death irrespective of its cause and should always trigger a search for treatable causes.

UNIFORM VERSUS SEX-SPECIFIC CUTOFF LEVELS

In patients presenting with suspected MI, beyond the presence or absence of MI, 4 clinical variables seem to impact on hs-cTn concentrations: age, sex, renal dysfunction, and time from chest pain onset (68–77). Accordingly, 3 strategies can be considered:

FIGURE 5 Diagnostic Performance of the Original and Modified 0/1h-Algorithm



Diagnostic performance of **(A)** the original 0/1h-ESC-algorithm and **(B)** the 0/1h-ESC-algorithm modified according to the Food and Drug Administration (FDA) regulatory requirements for rapid rule-out and rule-in of NSTEMI using high-sensitivity cardiac troponin T (hs-cTnT). The underlying differences between the original and the modified algorithm are **circled in green**. @0h = based on 0-h blood sample obtained at presentation to the ED only (direct rule-out or direct rule-in); @1h = based on 0- and 1-h blood samples; 1h-change = absolute (unsigned) change of hs-cTnT within 1 h; NPV = negative predictive value; PPV = positive predictive value; Sens = sensitivity; Spec = specificity; other abbreviations as in Figures 1 and 3. Adapted with permission from Twerenbold et al. (115).

1. First, a sophisticated one individualizing hs-cTn cutoff levels in the ED for all 4 confounders. Once automatized with a laboratory software tool, this approach may be feasible and could present a valid alternative to the current way of using 1 uniform cutoff value.
2. Second, using sex-specific cutoff levels, but ignoring the possibly larger confounding effect of age and renal dysfunction. Recent studies have highlighted that women presenting with suspected MI are on average 5 to 8 years older than men presenting with suspected MI (77–82). The higher age of female patients associated with higher hs-cTn levels seemed to well compensate the effect of female sex, which per se is associated with lower hs-cTn levels, obviating the need to adjust cutoff values. 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 (68–77,82). In the largest and methodologically most robust study, including 2,734 patients, the use of sex-specific cutoff values of hs-cTnT resulted in only an upgrade of 2 women from UA to NSTEMI and a downgrade of 1 man from NSTEMI to UA (77). Identical findings emerged from a second large diagnostic study using hs-cTnT (82). By contrast, controversies remain for hs-cTnI (71,79,81), which seem at least in part related to its rather high uniform 99th percentile recommended by the manufacturer (83). Clearly, further studies are necessary to elucidate benefits and/or harms of sex-specific cutoff levels in the diagnosis of MI. The use of lower hs-cTn cutoff levels in women would invariably increase the number of women classified as MI. The resulting impact of the obligatory drop in specificity and the associated increased rate of elevated hs-cTn levels in absence of myocardial ischemia in women, as well as the corresponding lower number of men detected with MI by using higher hs-cTn cutoff levels in men, requires more in-depth analyses.
3. Third, the traditional one using a uniform cutoff value. Given the uncertainties and obvious limitations of the second option, the preference of the current ESC guidelines is to continue using uniform cutoff levels (27). Because 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 (27).

It is important to highlight that the possible clinical use of hs-cTn is currently explored in several additional indications beyond the diagnosis of MI 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 MI and renal dysfunction are at substantial higher risk of MI as compared with patients with normal renal function (84–86). Accurate rule-out and rule-in of MI is of paramount importance because 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 (27,41). However, rapid and accurate diagnosis of MI is challenging in this vulnerable patient subgroup for several reasons: First, patients with renal dysfunction more frequently present with atypical clinical presentation of MI (87,88). Second, left ventricular hypertrophy is common in renal dysfunction and often results in ECG changes that may mimic or obscure MI. Third, baseline concentrations of cTn are often chronically elevated in patients with renal dysfunction (10% to 20% using s-cTn, up to 70% using hs-cTn) even in conditions other than acute myocardial ischemia and are associated with poor prognosis (86,89). The underlying pathophysiological mechanism is poorly understood, yet. Initially, it has been hypothesized that hs-cTn elevations are a direct result of reduced glomerular filtration rate. However, data from several studies suggest that elevated levels of cTn, similar to natriuretic peptides, are only to a lesser extent explained by reduced renal clearance (about 20%), particularly because the molecular size of the intact molecule is too large to be filtrated by glomeruli (90–93). It could be demonstrated that cTnT molecules may be degraded into smaller fragments that are small enough to be filtered by the kidney and can still be detected by cTn assays (94). However, the renal elimination and half-life of these cTn fragments do not differ between renal dysfunction and normal renal function (95). Furthermore, in a study examining patients with end-stage renal disease undergoing renal transplantation, levels of cTn did not decrease in the vast majority (82%) after renal transplantation despite substantially improved renal function, further advocating against the concept of

elevated cTn concentrations being primarily explained by reduced renal clearance (90). Recent studies have hypothesized that the underlying mechanism of chronic cTn release may be caused by some forms of cardiorenal syndrome triggered by unknown inflammatory processes leading to chronic myocardial injury and consecutive chronic cTn release in renal dysfunction (96,97).

Using the uniform assay-specific 99th percentiles as a binary decision level to rule out or rule in MI on the basis of a single blood sample obtained at presentation to the ED is of limited diagnostic value in patients with renal dysfunction (86). However, it was demonstrated in a large multicenter study investigating the diagnostic utility of 7 more sensitive cTn assays in patients with renal dysfunction and normal renal function that high diagnostic accuracy of hs-cTn can be maintained if adjusted decision levels higher than the assay-specific 99th percentiles are used in renal dysfunction (86). Although differences in baseline hs-cTn concentrations exist between patients with renal dysfunction and normal renal function, absolute hs-cTn changes during serial sampling do not differ between MI patients with renal dysfunction and normal renal function (86). Therefore, the diagnostic information of absolute changes during serial sampling is maintained.

Can the different hs-cTn-based rule-out strategies safely be used also in patients with renal dysfunction? These strategies were derived and validated in mixed, all-comers populations including patients with renal dysfunction. Patients requiring dialysis were mostly excluded from the analyses. Safety of all the 6 mentioned rule-out strategies is high in mixed populations and seems to be maintained also in patients with renal dysfunction, according to subgroup analyses (55,60). However, the efficacy of rule-out is lower because fewer patients have low hs-cTn blood concentrations. Whether the application of hs-cTn-based strategies using renal function-adjusted cutoff values or uniform cutoff levels is more favorable regarding the balance of safety and efficacy needs to be investigated in future studies.

hs-cTn IN PATIENTS WITH LEFT BUNDLE BRANCH BLOCK

Patients with suspected MI and left bundle branch block (LBBB) present a unique diagnostic and therapeutic challenge for clinicians in the ED. It is currently unknown whether patients presenting with acute chest pain and presumably new LBBB should also receive immediate coronary angiography and/or thrombolysis therapy such as those with clear STEMI. This major uncertainty is highlighted by divergent recommendations given by the respective guidelines in the United States and Europe (98,99). In recent years, most patients presenting with suspected MI and LBBB have been found to have diagnoses other than MI, probably based on the more accurate classification of MI in the primary PCI era (100). The distribution of new or presumably new versus known LBBB has changed over the years. Although chronic LBBB has become more common, incident LBBB in MI has decreased (101). Several studies have demonstrated no difference in the prevalence of MI between patients with presumably new or known LBBB, suggesting that true MI related LBBB is indeed rare (102,103).

Due to their high specificity, specific ECG criteria including Sgarbossa, Smith, and Selvester criteria should be used to triage patients toward rule-in of MI and immediate coronary angiography such as patients with STEMI (104,105). Despite the present evidence supporting the use of these ECG criteria in new or indeterminate-age LBBB, it must be stated that current guidelines do not specifically include this application of the criteria in their recommendations. Patients not meeting these ECG criteria have only a slightly higher overall prevalence of MI as compared with patients without LBBB and should undergo standard serial testing for hs-cTn (102,103).

SHOULD WE MEASURE hs-cTn IN PATIENTS WITH LOW PRE-TEST PROBABILITY?

There is concern that hs-cTn may have low diagnostic accuracy in patients with low pre-test probability for ACS. Concern of misinterpretation of these hs-cTn elevations as MI and patient harm associated with potential unnecessary therapies such as anticoagulation and coronary angiography has led some experts to recommend withholding cTn testing in patients with low pre-test probability for ACS (106,107). By contrast, practice guidelines highlight that MI frequently presents with atypical symptoms (e.g., in women and elderly patients), and mandate high scrutiny for MI, which means ECG and cTn testing also in patients with atypical symptoms (27,41). These divergent recommendations result in uncertainty in clinical practice regarding cTn testing in patients with low pre-test probability for ACS.

Previous research focused predominantly on the evaluation of elevated cTn levels in unselected patients (108–111). Patients with high initial cTn levels had a much higher incidence of Type I MI and that

sensitivity and specificity of s-cTn increased with serial testing (108). Thus, the implementation of the kinetics of the marker could provide some reassurance regarding the widespread concern of too many false-positive results in patients with low likelihood of ACS. A recent retrospective analysis reported low specificity for hs-cTnT to diagnose MI when grouping ED patients with suspected MI with patients with acute heart failure and patients with documented pulmonary embolism (109). Hence, it is very important to highlight that diagnostic testing with hs-cTn should be applied to the correct population, at the optimal time and in the appropriate clinical context. In patients presenting with acute chest discomfort at least possibly suggestive of MI, the standard of care using clinical assessment and the 12-lead ECG in conjunction with hs-cTn should be applied also in a rather low pre-test probability setting. This recommendation is specific for patients presenting with any kind of chest discomfort to the ED and do not apply to patients without any chest pain, for example, patients with a stroke (112) or critically ill patients in the intensive care unit (113). Although useful in patients presenting with acute chest pain, hs-cTn should not be used as a general screening test for MI in an unselected ED population.

APPLICATION OF RAPID, TROPONIN-BASED TRIAGE ALGORITHMS IN THE UNITED STATES

In the spring of 2017, the Food and Drug Administration (FDA) approved the hs-cTnT assay as the first clinically available, more sensitive cTn assay in the United States (114). The FDA-approved use of hs-cTnT differs in 2 important details from the contemporary use of hs-cTnT in most other countries. First, very low concentrations are only reported down to the limit of quantification (6 ng/l) as compared with the limit of blank (3 ng/l). Second, the FDA required the determination of the assay-specific 99th percentile upper-reference limit in an age-matched population to that of patients presenting to the ED with suspected MI, whereas the 99th percentile upper-reference limit for use outside the United States was determined in healthy and often younger individuals. As a consequence, the FDA-approved uniform 99th percentile upper-reference limit (19 ng/l) is slightly higher as compared with the 99th percentile upper-reference limit used outside the United States (14 ng/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 0/1h-ESC-algorithm in a large international diagnostic multicenter study enrolling 3,267 unselected patients presenting with suspected MI to the ED (115). The original 0/1h-ESC algorithm was adapted to the FDA setting by lifting the direct rule-out criterion at presentation from <5 ng/l to <6 ng/l, because hs-cTnT levels are only reported down to 6 ng/l in the United States. Rule-out safety, as well as rule-in performance, of the original and the modified algorithm were very high and comparable (NPV 99.8% vs. 99.9%; $p = 0.928$; sensitivity 99.4% vs. 99.6%; $p = 0.667$; PPV 76.9% vs. 76.7%; $p = 0.969$; specificity 95.5% for both algorithms; $p = 0.929$) (**Figure 5**). Both algorithms allowed rapid rule-out and rule-in of MI in 3 of 4 patients. These findings confirm the concept of the 0/1h-ESC algorithms and suggest that the 0/1h algorithm using hs-cTnT as approved by the FDA seems to provide high safety and high efficacy for the triage toward rapid rule-out or rule-in of MI.

CONCLUSIONS

hs-cTn assays improve and accelerate the early management of patients presenting with suspected MI and complement assessment using clinical signs and the ECG. The increased sensitivity reduces the "troponin-blind" interval early after onset of MI and allows to substantially shorten the timing of serial hs-cTn remeasurement. 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 ischemic from nonischemic causes of chest pain and mild 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 and safe rule-out and, depending on which algorithm, also rule-in of MI within a few hours. Such an approach will not only allow an increase in patients' safety as compared with conventional, less sensitive cTn assays, but also substantially reduce duration of stay in the ED and costs. Once a process of ≥24 h, many patients can now have MI rapidly and safely excluded already in the ED.

ADDRESS FOR CORRESPONDENCE: Prof. Christian Mueller, CRIB and Department of Cardiology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland. E-mail: christian.mueller@usb.ch.

REFERENCES

1. Blomkalns AL, Gibler WB. Chest pain unit concept: rationale and diagnostic strategies. Cardiol Clin 2005;23:411–21.

2. Lee TH, Rouan GW, Weisberg MC, et al. Clinical characteristics and natural history of patients with acute myocardial infarction sent home from the emergency room. Am J Cardiol 1987;60:219–24.

3. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000;342:1163–70.

4. Goldman L, Cook EF, Brand DA, et al. A computer protocol to predict myocardial infarction in emergency department patients with chest pain. N Engl J Med 1988;318:797–803.

5. Lee TH, Juarez G, Cook EF, et al. Ruling out acute myocardial infarction. A prospective multicenter validation of a 12-hour strategy for patients at low risk. N Engl J Med 1991;324:1239–46.

6. Hutter AM Jr., Amsterdam EA, Jaffe AS. 31st Bethesda Conference. Emergency Cardiac Care. Task Force 2: acute coronary syndromes: section 2B-chest discomfort evaluation in the hospital. J Am Coll Cardiol 2000;35:853–62.

7. Lee TH, Cook EF, Weisberg M, Sargent RK, Wilson C, Goldman L. Acute chest pain in the emergency room. Identification and examination of low-risk patients. Arch Intern Med 1985;145:65–9.

8. Hollander JE, Robey JL, Chase MR, Brown AM, Zogby KE, Shofer FS. Relationship between a clear-cut alternative noncardiac diagnosis and 30-day outcome in emergency department patients with chest pain. Acad Emerg Med 2007;14:210–5.

9. Thygesen K, Mair J, Katus H, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J 2010;31:2197–204.

10. Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J 2012;33:2252–7.

11. Freeman L, Antill T. Ten things emergency physicians should not do: unless they want to become defendants. Foresight 2000;49:1–10.

12. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.

13. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858–67.

14. Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med 2009;361:868–77.

15. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56:254–61.

16. Haaf P, Drexler B, Reichlin T, et al. High-sensitivity cardiac troponin in the distinction of acute myocardial infarction from acute cardiac noncoronary artery disease. Circulation 2012;126:31–40.

17. Reiter M, Twerenbold R, Reichlin T, et al. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. Eur Heart J 2011;32:1379–89.

18. Reiter M, Twerenbold R, Reichlin T, et al. Early diagnosis of acute myocardial infarction in patients with pre-existing coronary artery disease using more sensitive cardiac troponin assays. Eur Heart J 2012;33:988–97.

19. Apple FS. A new season for cardiac troponin assays: it's time to keep a scorecard. Clin Chem 2009;55:1303–6.

20. Rubini Gimenez M, Twerenbold R, Reichlin T, et al. Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction. Eur Heart J 2014;35:2303–11.

21. Reichlin T, Twerenbold R, Reiter M, et al. Introduction of high-sensitivity troponin assays: impact on myocardial infarction incidence and prognosis. Am J Med 2012;125:1205–13.e1.

22. Reichlin T, Cullen L, Parsonage WA, et al. Two-hour algorithm for triage toward rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Am J Med 2015;128:369–79.e4.

23. Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011;124:136–45.

24. Reichlin T, Schindler C, Drexler B, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Arch Intern Med 2012;172:1211–8.

25. Mueller M, Biener M, Vafaie M, et al. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. Clin Chem 2012;58:209–18.

26. Mueller C. Biomarkers and acute coronary syndromes: an update. Eur Heart J 2014;35:552–6.

27. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267–315.

28. Than M, Cullen L, Reid CM, et al. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. Lancet 2011;377:1077–84.

29. Than M, Cullen L, Aldous S, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. J Am Coll Cardiol 2012;59:2091–8.

30. Cullen L, Mueller C, Parsonage WA, et al. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. J Am Coll Cardiol 2013;62:1242–9.

31. Than M, Aldous S, Lord SJ, et al. A 2-hour diagnostic protocol for possible cardiac chest pain in the emergency department: a randomized clinical trial. JAMA Intern Med 2014;174:51–8.

32. Meller B, Cullen L, Parsonage WA, et al. Accelerated diagnostic protocol using high-sensitivity cardiac troponin T in acute chest pain patients. Int J Cardiol 2015;184:208–15.

33. Hammarsten O, Fu ML, Sigurjonsdottir R, et al. Troponin T percentiles from a random population sample, emergency room patients and patients with myocardial infarction. Clin Chem 2012;58:628–37.

34. Reichlin T, Twerenbold R, Wildi K, et al. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. CMAJ 2015;187:E243–52.

35. Rubini Gimenez M, Twerenbold R, Jaeger C, et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. Am J Med 2015;128:861–70.e4.

36. Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. J Am Coll Cardiol 2011;58:1332–9.

37. Rubini Gimenez M, Hoeller R, Reichlin T, et al. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. Int J Cardiol 2013;168:3896–901.

38. Schoenenberger AW, Stallone F, Walz B, et al. Incremental value of heart-type fatty acid-binding protein in suspected acute myocardial infarction early after symptom onset. Eur Heart J 2016;5:185–92.

39. Hollander JE, Than M, Mueller C. State-of-the-art evaluation of emergency department patients presenting with potential acute coronary syndromes. Circulation 2016;134:547–64.

40. Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA 2011;306:2684–93.

41. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139–228.

42. Reinstadler SJ, Feistritzer HJ, Klug G, et al. High-sensitivity troponin T for prediction of left ventricular function and infarct size one year following ST-elevation myocardial infarction. Int J Cardiol 2016;202:188–93.

43. Hollander JE. Managing troponin testing. Ann Emerg Med 2016;68:690–4.

44. Mair J, Lindahl B, Muller C, et al. What to do when you question cardiac troponin values. Eur Heart J Acute Cardiovasc Care 2017 May 1 [E-pub ahead of print].

45. Reichlin T, Twerenbold R, Maushart C, et al. Risk stratification in patients with unstable angina using absolute serial changes of 3 high-sensitive troponin assays. Am Heart J 2013;165:371–8.e3.

46. Braunwald E, Morrow DA. Unstable angina: is it time for a requiem? Circulation 2013;127:2452–7.

47. Wildi K, Nelles B, Twerenbold R, et al. Safety and efficacy of the 0 h/3 h protocol for rapid rule out of myocardial infarction. Am Heart J 2016;181:16–25.

48. Twerenbold R, Jaeger C, Rubini Gimenez M, et al. Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction. Eur Heart J 2016;37:3324–32.

49. Chapman AR, Anand A, Boeddinghaus J, et al. Comparison of the efficacy and safety of early rule-out pathways for acute myocardial infarction. Circulation 2017;135:1586–96.

50. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000;284:835–42.

51. Hess EP, Agarwal D, Chandra S, et al. Diagnostic accuracy of the TIMI risk score in patients with chest pain in the emergency department: a meta-analysis. CMAJ 2010;182:1039–44.

52. Druey S, Wildi K, Twerenbold R, et al. Early rule-out and rule-in of myocardial infarction using sensitive cardiac Troponin I. Int J Cardiol 2015;195:163–70.

53. Boeddinghaus J, Reichlin T, Cullen L, et al. Two-hour algorithm for triage toward rule-out and rule-in of acute myocardial infarction by use of high-sensitivity cardiac troponin I. Clin Chem 2016;62:494–504.

54. Mueller C, Giannitsis E, Christ M, et al. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. Ann Emerg Med 2016;68:76–87.e4.

55. Neumann JT, Sorensen NA, Schwemer T, et al. Diagnosis of myocardial infarction using a high-sensitivity troponin I 1-hour algorithm. JAMA Cardiol 2016;1:397–404.

56. Zhelev Z, Hyde C, Youngman E, et al. Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: systematic review and meta-analysis. BMJ 2015;350:h15.

57. Body R, Burrows G, Carley S, et al. High-sensitivity cardiac troponin t concentrations below the limit of detection to exclude acute myocardial infarction: a prospective evaluation. Clin Chem 2015;61:983–9.

58. Bandstein N, Ljung R, Johansson M, Holzmann MJ. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. J Am Coll Cardiol 2014;63:2569–78.

59. Shah AS, Anand A, Sandoval Y, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet 2015;386:2481–8.

60. Boeddinghaus J, Nestelberger T, Twerenbold R, et al. Direct comparison of 4 very early rule-out strategies for acute myocardial infarction using high-sensitivity cardiac troponin I. Circulation 2017;135:1597–611.

61. Wildi K, Cullen L, Twerenbold R, et al. Direct comparison of two rule-out strategies for acute myocardial infarction: 2h-accelerated diagnostic protocol versus 2h-algorithm. Clin Chem 2017;63:1227–36.

62. Lindahl B, Jernberg T, Badertscher P, et al. An algorithm for rule-in and rule-out of acute myocardial infarction using a novel troponin I assay. Heart 2017;103:125–31.

63. Nestelberger T, Wildi K, Boeddinghaus J, et al. Characterization of the observe zone of the ESC 2015 high-sensitivity cardiac troponin 0h/1h-algorithm for the early diagnosis of acute myocardial infarction. Int J Cardiol 2016;207:238–45.

64. Schlett CL, Hoffmann U, Geisler T, Nikolaou K, Bamberg F. Cardiac computed tomography for the evaluation of the acute chest pain syndrome: state of the art. Radiol Clin North Am 2015;53:297–305.

65. Dedic A, Lubbers MM, Schaap J, et al. Coronary CT angiography for suspected ACS in the era of high-sensitivity troponins: randomized multicenter study. J Am Coll Cardiol 2016;67:16–26.

66. Boeddinghaus J, Reichlin T, Nestelberger T, et al. Early diagnosis of acute myocardial infarction in patients with mild elevations of cardiac troponin. Clin Res Cardiol 2017;106:457–67.

67. Mueller CE. MY APPROACH to low-level troponin elevations. Trends Cardiovasc Med 2015;25:373.

68. Apple FS, Sandoval Y, Jaffe AS, Ordonez-Llanos J, IFCC Task Force on Clinical Applications of Cardiac Bio-Markers. Cardiac troponin assays: guide to understanding analytical characteristics and their impact on clinical care. Clin Chem 2017;63:73–81.

69. Mueller C, Kavsak PA. Sex-specific cutoffs for cardiac troponin using high-sensitivity assays - Is there clinical equipoise? Clin Biochem 2015;48:749–50.

70. Gore MO, Seliger SL, Defilippi CR, et al. Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. J Am Coll Cardiol 2014;63:1441–8.

71. Cullen LA, Mills NL. Point: the use of sex-specific cutpoints for high-sensitivity cardiac troponin assays. Clin Chem 2017;63:261–3.

72. Giannitsis E. Counterpoint: potential concerns regarding the use of sex-specific cutpoints for high-sensitivity troponin assays. Clin Chem 2017;63:264–6.

73. Giannitsis E. Sex-specific troponin measures for diagnosis of acute coronary syndrome. Heart 2016;102:91–2.

74. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin Chem 2012;58:1574–81.

75. Koerbin G, Tate J, Potter JM, Cavanaugh J, Glasgow N, Hickman PE. Characterisation of a highly sensitive troponin I assay and its application to a cardio-healthy population. Clin Chem Lab Med 2012;50:871–8.

76. Krintus M, Kozinski M, Boudry P, et al. European multicenter analytical evaluation of the Abbott ARCHITECT STAT high sensitive troponin I immunoassay. Clin Chem Lab Med 2014;52:1657–65.

77. Rubini Gimenez M, Twerenbold R, Boeddinghaus J, et al. Clinical effect of sex-specific cutoff values of high-sensitivity cardiac troponin T in suspected myocardial infarction. JAMA Cardiol 2016;1:912–20.

78. Rubini Gimenez M, Reiter M, Twerenbold R, et al. Sex-specific chest pain characteristics in the early diagnosis of acute myocardial infarction. JAMA Intern Med 2014;174:241–9.

79. Cullen L, Greenslade JH, Carlton EW, et al. Sex-specific versus overall cut points for a high sensitivity troponin I assay in predicting 1-year outcomes in emergency patients presenting with chest pain. Heart 2016;102:120–6.

80. Shah AS, Griffiths M, Lee KK, et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. BMJ 2015;350:g7873.

81. Trambas C, Pickering JW, Than M, et al. Impact of high-sensitivity troponin I testing with sex-specific cutoffs on the diagnosis of acute myocardial infarction. Clin Chem 2016;62:831–8.

82. Mueller-Hennessen M, Lindahl B, Giannitsis E, et al. Diagnostic and prognostic implications using age- and gender-specific cut-offs for high-sensitivity cardiac troponin T - Sub-analysis from the TRAPID-AMI study. Int J Cardiol 2016;209:26–33.

83. Wildi K, Gimenez MR, Twerenbold R, et al. Misdiagnosis of myocardial infarction related to limitations of the current regulatory approach to define clinical decision values for cardiac troponin. Circulation 2015;131:2032–40.

84. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–305.

85. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351:1285–95.

86. Twerenbold R, Wildi K, Jaeger C, et al. Optimal cutoff levels of more sensitive cardiac troponin assays for the early diagnosis of myocardial infarction in patients with renal dysfunction. Circulation 2015;131:2041–50.

87. Aronow WS, Ahn C, Mercando AD, Epstein S. Prevalence of coronary artery disease, complex ventricular arrhythmias, and silent myocardial ischemia and incidence of new coronary events in older persons with chronic renal insufficiency and

with normal renal function. Am J Cardiol 2000; 86:1142–3.A9.

88. Nakamura S, Uzu T, Inenaga T, Kimura G. Prediction of coronary artery disease and cardiac events using electrocardiographic changes during hemodialysis. Am J Kidney Dis 2000;36:592–9.

89. deFilippi CR, Herzog CA. Interpreting cardiac biomarkers in the setting of chronic kidney disease. Clin Chem 2017;63:59–65.

90. Bozbas H, Korkmaz ME, Atar I, et al. Serum levels of cardiac enzymes before and after renal transplantation. Clin Cardiol 2004;27:559–62.

91. Friden V, Starnberg K, Muslimovic A, et al. Clearance of cardiac troponin T with and without kidney function. Clin Biochem 2017;50:468–74.

92. Irfan A, Twerenbold R, Reiter M, et al. Determinants of high-sensitivity troponin T among patients with a noncardiac cause of chest pain. Am J Med 2012;125:491–8.e1.

93. Mueller C, Laule-Kilian K, Scholer A, et al. B-type natriuretic peptide for acute dyspnea in patients with kidney disease: insights from a randomized comparison. Kidney Int 2005;67:278–84.

94. Diris JH, Hackeng CM, Kooman JP, Pinto YM, Hermens WT, van Dieijen-Visser MP. Impaired renal clearance explains elevated troponin T fragments in hemodialysis patients. Circulation 2004;109:23–5.

95. Ellis K, Dreisbach AW, Lertora JL. Plasma elimination of cardiac troponin I in end-stage renal disease. South Med J 2001;94:993–6.

96. Wong CK, Szeto CC, Chan MH, Leung CB, Li PK, Lam CW. Elevation of pro-inflammatory cytokines, C-reactive protein and cardiac troponin T in chronic renal failure patients on dialysis. Immunol Invest 2007;36:47–57.

97. D'Marco L, Bellasi A, Raggi P. Cardiovascular biomarkers in chronic kidney disease: state of current research and clinical applicability. Dis Markers 2015;2015:586569.

98. American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.

99. Task Force on the management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.

100. Neeland IJ, Kontos MC, de Lemos JA. Evolving considerations in the management of patients with left bundle branch block and suspected myocardial infarction. J Am Coll Cardiol 2012;60:96–105.

101. Jolobe OM. Bundle branch block old and new in myocardial infarction. Am J Emerg Med 2010; 28:749.e5.

102. Chang AM, Shofer FS, Tabas JA, Magid DJ, McCusker CM, Hollander JE. Lack of association between left bundle-branch block and acute myocardial infarction in symptomatic ED patients. Am J Emerg Med 2009;27:916–21.

103. Kontos MC, Aziz HA, Chau VQ, Roberts CS, Ornato JP, Vetrovec GW. Outcomes in patients with chronicity of left bundle-branch block with possible acute myocardial infarction. Am Heart J 2011;161:698–704.

104. Smith SW, Dodd KW, Henry TD, Dvorak DM, Pearce LA. Diagnosis of ST-elevation myocardial infarction in the presence of left bundle branch block with the ST-elevation to S-wave ratio in a modified Sgarbossa rule. Ann Emerg Med 2012; 60:766–76.

105. Gregg RE HE, Zhou SH. Combining Sgarbossa and Selvester ECG criteria to improve STEMI detection in the presence of LBBB. Comput Cardiol 2010;37:277–80.

106. Baxi S, Lakin J, Stapleton S, Redberg R. High-sensitivity troponin: elevated without infarction, is the horse out of the barn? Emerg Med J 2014;31:354–5.

107. Jarolim P. High sensitivity cardiac troponin assays in the clinical laboratories. Clin Chem Lab Med 2015;53:635–52.

108. Yiadom MY, Jarolim P, Jenkins C, Melanson SE, Conrad M, Kosowsky JM. Diagnostic implications of an elevated troponin in the emergency department. Dis Markers 2015; 2015:157812.

109. Haider DG, Klemenz T, Fiedler GM, Nakas CT, Exadaktylos AK, Leichtle AB. High sensitive cardiac troponin T: Testing the test. Int J Cardiol 2017; 228:779–83.

110. Javed U, Aftab W, Ambrose JA, et al. Frequency of elevated troponin I and diagnosis of acute myocardial infarction. Am J Cardiol 2009; 104:9–13.

111. Alcalai R, Planer D, Culhaoglu A, Osman A, Pollak A, Lotan C. Acute coronary syndrome vs nonspecific troponin elevation: clinical predictors and survival analysis. Arch Intern Med 2007;167: 276–81.

112. Scheitz JF, Endres M, Mochmann HC, Audebert HJ, Nolte CH. Frequency, determinants and outcome of elevated troponin in acute ischemic stroke patients. Int J Cardiol 2012;157: 239–42.

113. Lim W, Qushmaq I, Devereaux PJ, et al. Elevated cardiac troponin measurements in critically ill patients. Arch Intern Med 2006;166:2446–54.

114. US Food & Drug Administration.510(k) Substantial Equivalence Determination Decision Summary. FDA. Available at: https://www.accessdata.fda.gov/cdrh_docs/reviews/K162895.pdf. Accessed April 13, 2017.

115. Twerenbold R, Badertscher P, Boeddinghaus J, et al. Impact of the FDA regulatory approach on the performance of the 0/1-hour-algorithm for rapid diagnosis of myocardial infarction. J Am Coll Cardiol 2017. In press.

KEY WORDS algorithm, diagnostic algorithms, emergency department, high-sensitivity cardiac troponin, rule-in, rule-out

APPENDIX For patient case presentations, please see the online version of this article.