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High-Sensitivity Cardiac Troponin and the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guidelines for the Evaluation and Diagnosis of Acute Chest Pain

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ABSTRACT: The 2021 American Heart Association/American College of Cardiology/American Society of Echocardiography/American College of Chest Physicians/Society for Academic Emergency Medicine/Society of Cardiovascular Computed Tomography/Society for Cardiovascular Magnetic Resonance guidelines for the evaluation and diagnosis of acute chest pain make important recommendations that include the recognition of high-sensitivity cardiac troponin (hs-cTn) as the preferred biomarker, endorsement of 99th percentile upper reference limits to define myocardial injury, and the use of clinical decision pathways, as well as acknowledgment of the uniqueness of women and other patient subsets. Details on how to integrate hs-cTn into clinical practice are less extensively addressed. Clinicians should be aware of some of the analytical aspects related to hs-cTn assays regarding the limit of detection and the limit of quantitation and how they are used clinically, especially for the single sample strategy to rule out acute myocardial infarction. Likewise, it is important for clinicians to understand issues related to the derivation of the 99th percentile upper reference limit; the value of sex-specific 99th percentile upper reference limits; how to use changing concentrations (deltas) to facilitate diagnosis and risk stratification of patients with suspected acute coronary syndrome, including the differentiation of acute from chronic myocardial injury; and how to best integrate the use of hs-cTn with clinical decision pathways. With the use of hs-cTn, conditions such as type 2 myocardial infarction become more common, whereas others such as unstable angina become less frequent but still occur. Sections relating to these issues are included.

Key Words: chest pain ■ myocardial infarction ■ troponin

This evidence-based, multidisciplinary, critical appraisal of the acute chest pain and high-sensitivity cardiac troponin (hs-cTn) recommendations from the 2021 American Heart Association (AHA)/American College of Cardiology (ACC)/American Society of Echocardiography/American College of Chest Physicians/Society for Academic Emergency Medicine/Society of Cardiovascular Computed Tomography/Society for Cardiovascular Magnetic Resonance guidelines[1] for the evaluation and diagnosis of chest pain is endorsed by the International Federation of Clinical Chemistry and Laboratory Medicine Committee on Clinical Applications of Cardiac Bio-Markers (IFCC C-CB). Our appraisal involves laboratorians, emergency physicians, and noninvasive and interventional cardiologists. The recently published AHA/ACC guidelines[1] make important recommendations that include the recognition of hs-cTn as the preferred biomarker, endorsement of 99th percentile upper reference limits to define myocardial injury, the use of clinical decision pathways (CDPs), and acknowledgment of the uniqueness of women and other patient subsets. However, additional detail about how to integrate

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Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
ACS	acute coronary syndrome
AHA	American Heart Association
CDP	clinical decision pathway
cTn	cardiac troponin
ED	emergency department
ESC	European Society of Cardiology
FDA	Food and Drug Administration
HEART	History, ECG, Age, Risk Factors, Troponin
HiSTORIC	High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction
hs-cTn	high-sensitivity cardiac troponin
IFCC C-CB	International Federation of Clinical Chemistry and Laboratory Medicine Committee on Clinical Applications of Cardiac Bio-Markers
LoD	limit of detection
LoQ	limit of quantitation
MACE	major adverse cardiovascular event
MI	myocardial infarction
NT-proBNP	N-terminal pro–B-type natriuretic peptide
RCT	randomized clinical trial
TIMI	Thrombolysis in Myocardial Infarction
UDMI	Universal Definition of Myocardial Infarction

hs-cTn into clinical practice to assist with triage, diagnosis, and risk stratification of patients with suspected acute coronary syndrome (ACS) would be helpful. The goal of this IFCC C-CB–endorsed appraisal is to provide additional, constructive, evidence-based educational recommendations pertaining to cardiac troponin (cTn) that should be considered for integration into the guidelines and into clinical practice.

hs-cTn assays have been used clinically outside the United States for more than a decade. Data supporting their use have evolved from observational studies to randomized clinical trials (RCTs).[2–5] European Society of Cardiology (ESC) guidelines[6–8] have provided class I recommendations for hs-cTn since 2011 (Table 1). The 2020 ESC guidelines[8] recommend 0/1h and 0/2h early rule out algorithms with class IB recommendations. In contrast to the AHA/ACC guidelines,[1] the ESC[8] recommendations provide assay-specific risk stratification concentration thresholds that are helpful to clinicians (Figure 1).

Multiple hs-cTn assays have received 510(k) clearance by the US Food and Drug Administration (FDA) for clinical use in the United States since 2017.[9] The characteristics of all cTn assays are tabulated and updated every 4 months by the IFCC C-CB.[10] There are a paucity of US guidelines about how to incorporate cTn assays into clinical practice. This is an important gap given the broad clinical use of cTn testing[11,12] in the United States and the lower incidence of myocardial infarction (MI) in the United States compared with European studies.[13–15] This difference means that some of the thresholds that are derived from selected chest pain cohorts from Europe may not be as applicable in the all-comer, heterogeneous patient populations presenting to US emergency departments (EDs). Whereas the AHA/ACC guidelines reference data largely derived from European chest pain studies, there are an increasing number of US hs-cTn–based studies[13–24] that have evaluated these approaches as well.

The ACC/AHA guidelines[1] provide a class I recommendation to measure cTn in patients with chest pain and preferably to use hs-cTn assays. Opportunities exist, however, to educate clinicians more extensively about the analytics of hs-cTn assays,[25–28] many of which are important to understand how to best implement their use in clinical practice. The efficient assessment of patients with chest pain with hs-cTn assays requires the development and maintenance of evidence-based rapid risk-stratification protocols for acute MI, standardized sample collection processes with acceptable turnaround times that allow for rapid rule-in and rule-out algorithms, consistent reporting in electronic health records, and laboratory analytical quality control processes to ensure that hs-cTn results are reliable for decision-making.[28] The evaluation of patients with suspected ACS should integrate all aspects of these multiple processes and represent a multidisciplinary effort that involves partnership with laboratory medicine with clinicians from emergency medicine, internal and family medicine, and cardiology.

To provide a comprehensive education to clinicians, we have addressed the evidence-based literature, including several guidelines and expert consensus documents from professional organizations[29,30] (Table 2), as well as guidance documents from individual centers about how to use hs-cTn for the evaluation of patients with chest discomfort. Some of the information cited was published after the guidelines[1] were finished. We include some of those selected articles when they provide important insights related to hs-cTn assays. When we discuss these data, we acknowledge that these references were published after completion of the guidelines.

EVIDENCE-BASED APPRAISAL OF THE GUIDELINES RELATED TO THE USE OF HS-CTN

Analytical Issues

The AHA/ACC guidelines recognize hs-cTn as the preferred biomarker for the detection of myocardial injury

Table 1. European Society of Cardiology Recommendations on High-Sensitivity Cardiac Troponin Assays

ESC guidelines year	Recommendations
2011	▪ A rapid-rule out protocol (0 and 3 hours) is recommended when highly sensitive troponin tests are available. (Class IB)
2015	▪ A rapid rule-out protocol at 0 and 3 hours is recommended if high-sensitivity cardiac troponin tests are available. (Class IB) ▪ A rapid rule-out and rule-in protocol at 0 and 1 hour is recommended if a high-sensitivity cardiac troponin test with a validated 0/1h algorithm is available. Additional testing after 3 to 6 hours is indicated if the first 2 troponin measurements are not conclusive and the clinical condition is still suggestive of ACS. (Class IB)
2020	▪ The ESC 0/1h algorithm with blood sampling at 0 and 1 hour is recommended if a hs-cTn test with a validated 0/1h algorithm is available. (Class IB) ▪ Additional testing after 3 hours is recommended if the first 2 cardiac troponin measurements of the 0/1h algorithm are not conclusive and the clinical condition is still suggestive of ACS. (Class IB) ▪ As an alternative to the ESC 0/1h algorithm, it is recommended to use the ESC 0/2h algorithm with blood sampling at 0 and 2 hours, if a hs-cTn test with a validated 0/2h algorithm is available. (Class IB) ▪ As an alternative to the ESC 0/1h algorithm, a rapid rule-out and rule-in protocol with blood sampling at 0 and 3 hours should be considered, if a high-sensitivity (or sensitive) cardiac troponin test with a validated 0/3h algorithm is available. (Class IIa-B)

ACS indicates acute coronary syndrome; ESC, European Society of Cardiology; and hs-cTnT, high-sensitivity cardiac troponin T.

and endorse the assay-specific overall 99th percentile upper reference limits.[1] It should be noted that concentrations should be reported in ng/L units and concentrations rounded to whole numbers without decimals to avoid reporting or interpretation errors.[25–27] Using ng/L is a way to differentiate high-sensitivity from contemporary assays.

The 99th Percentile Upper Reference Limit

The new ACC/AHA guidelines,[1] as well as all other major guidelines[8,31] including the Universal Definition of Myocardial Infarction (UDMI),[32] recommend the 99th percentile upper reference limits as the threshold for myocardial injury and in the proper clinical setting to support the diagnosis of MI. However, there are some important issues of which clinicians should be aware. It is important to understand how these thresholds are derived because they influence the sensitivity with which myocardial injury is detected.[33,34] The most recent (2022) IFCC and American Association of Clinical Chemistry guidelines recommend that the 99th percentile upper reference limits be derived from a sample size of at least 400 male and 400 female healthy individuals who should be screened with the use of questionnaires to allow for exclusion of those with cardiovascular comorbidities and those on cardiovascular medications, as well as the use of biomarkers such as NT-proBNP (N-terminal pro–B-type natriuretic peptide), hemoglobin A1C, and estimated glomerular filtration rate to exclude people with subclinical disease.[25] Using rigorous selection criteria to define normality will result in lower 99th percentiles, whereas using less stringent criteria will result in higher 99th percentiles. Multiple studies demonstrate that the 99th percentile thresholds can vary significantly on the basis of the cohort selection.[35–37] If one is not cautious about the thresholds used, it can make comparisons between assays problematic.[35,38] Support by the guidelines for a consistent approach in this area would have helped the standardization of the 99th percentile upper reference limits.

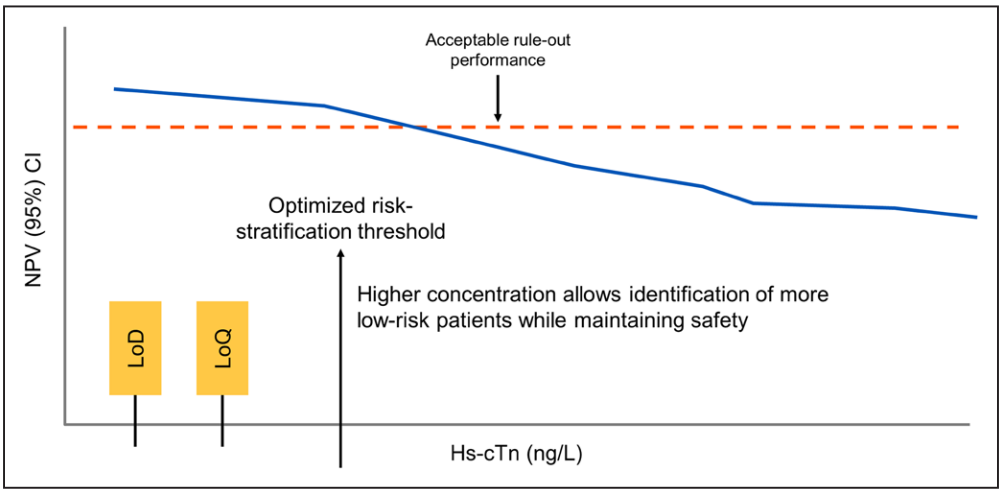

Figure 1. Use of optimized thresholds with high-sensitivity cardiac troponin assays.
Extensive data including observational studies, meta-analyses, and the largest high-sensitivity cardiac troponin (hs-cTn) randomized trial (HiSTORIC [High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction]) show that optimized rule-out thresholds (for selected hs-cTn assays thus far) represent a safe method to identify low-risk cases. LoD indicates limit of detection; LoQ, limit of quantitation; and NPV, negative predictive value.

Table 2. ACEP and SAEM Recommendations

ACEP clinical policy (2018)	SAEM GRACE-1 guidelines (2021)
In adult patients without evidence of ST-elevation ACS, the HEART score can be used as a clinical prediction instrument for risk stratification. A low score (<3) predicts 30-day MACE miss rate within a range of 0% to 2%.	In adult patients with recurrent, low-risk chest pain for >3 hours duration, we suggest a single, high-sensitivity troponin below a validated threshold to reasonably exclude ACS within 30 days.
In adult patients without evidence of ST-elevation ACS, other risk-stratification tools, such as TIMI, can be used to predict rate of 30-day MACE.	In patients with recurrent, low-risk chest pain and a normal stress test within the previous 12 months, we do not recommend repeat routine stress testing as a means to decrease rates of MACE at 30 days.
In adult patients with suspected acute NSTE-ACS, convention troponin testing at 0 and 3 hours with low-risk ACS (defined by HEART score 0 to 3) can predict an acceptable low rate of 30-day MACE.	In adult patients with recurrent, low-risk chest pain, there is insufficient evidence to recommend hospitalization (either standard inpatient admission or observation stay) versus discharge as a strategy to mitigate MACE within 30 days.
A single high-sensitivity troponin result below the level of detection on arrival to the ED or negative serial high-sensitivity troponin result at 0 and 2 hours is predictive of a low rate of MACE.	In adult patients with recurrent, low-risk chest pain and nonobstructive (<50% stenosis) CAD on previous angiography within 5 years, we suggest referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation.
In adult patients with suspected acute NSTE-ACS, determination of low risk on the basis of validated ADPs that include a nonischemic ECG result and negative serial high-sensitivity troponin testing results both at presentation and at 2 hours can predict a low rate of 30-day MACE, allowing for an accelerated discharge pathway from the ED.	In adult patients with recurrent, low-risk chest pain and no occlusive CAD (0% stenosis) on previous angiography within 5 years, we recommend referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation.
Do not routinely use further diagnostic testing (coronary CT angiography, stress testing, myocardial perfusion imaging) before discharge in low-risk patients in whom acute MI has been ruled out to reduce 30-day MACE.	In adult patients with recurrent, low-risk chest pain and previous CCTA within the past 2 years with no coronary stenoses, we suggest no further diagnostic testing other than a single, high-sensitivity troponin below a validated threshold to exclude ACS within that 2-year timeframe.
Arrange follow-up in 1 to 2 weeks for low-risk patients in whom MI has been ruled out. If no follow-up is available, consider further testing or observation before discharge.	In adult patients with recurrent, low-risk chest pain, we suggest the use of depression and anxiety screening tools as these might have an effect on health care use and return ED visits.
P2Y12 inhibitors and glycoprotein IIb/IIIa inhibitors may be given in the ED or delayed until cardiac catheterization.	In adult patients with recurrent, low-risk chest pain, we suggest referral for anxiety or depression management, as this might have an effect on health care use and return ED visits.

ACEP indicates American College of Emergency Physicians; ACS, acute coronary syndrome; ADP, accelerated diagnostic pathway; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT, computed tomography; ED, emergency department; GRACE, Guidelines for Reasonable and Appropriate Care in the Emergency Department; HEART, history, ECG, age, risk factors, troponin; MACE, major adverse cardiovascular event; MI, myocardial infarction; NSTE-ACS, non–ST-elevation acute coronary syndrome; SAEM, Society for Academic Emergency Medicine; and TIMI, Thrombolysis in Myocardial Infarction.

In addition, despite the fact that all major guidelines and the UDMI recommend use of the 99th percentile upper reference limits,[8,31,32] many medical centers still do not use this threshold.[39–42] Not only does this make the diagnosis of MI inconsistent with any given assay, but it also limits the applicability of recommended approaches in guidelines that are on the basis of the 99th percentile. All novel risk-stratification approaches using hs-cTn assays have been validated on the basis of the gold standard suggested by the UDMI,[32] which includes the appropriate 99th percentile upper reference limits.[34] Thus, opportunities exist to continue to educate clinicians about the importance of using the 99th percentile as an important criterion to standardize the diagnosis of MI for clinical, research, and regulatory purposes.[34] Sensitizing clinicians to the importance of this issue on the part of the guidelines would facilitate the standardization of the 99th percentile to support the diagnosis of acute MI.

Although the 2021 AHA/ACC guidelines[1] acknowledge and recommend that clinicians be "familiar with the analytical performance and the 99th percentile upper reference limit that defines myocardial injury for the cTn assay used at their institution" as a class I recommendation (Level of Evidence C-EO [expert opinion]), the clinical decision pathway table (Table 6 in the guidelines) reports hs-cTnT concentration thresholds that are not applicable for all assays given that cTn assays are not standardized. Given that 99th percentile upper reference limits are assay-specific, this area is one where clinicians would be well advised to use caution.

Sex-Specific 99th Percentile Upper Reference Limits

Class IB recommendations (Level of Evidence B-NR [nonrandomized])[1] are made that "women who present with chest pain are at risk for underdiagnosis, and potential cardiac causes should always be considered." The guidelines acknowledge sex-specific hs-cTn upper reference limits[1,43] but do not elaborate further or advocate their use. There are extensive data[35–37] documenting that women have lower 99th percentiles than men (Figure 2). That is why the Fourth UDMI,[32] as well as several guideline groups,[25] endorse sex-specific 99th percentiles for clinical practice. All FDA-cleared hs-cTn assays report sex-specific 99th percentiles[10] (Table 3). hs-cTnI and hs-cTnT sex-specific 99th percentiles improve the underdiagnosis of women.[14,43] The debate about their effect on outcomes is the focus of an ongoing RCT (CODE-MI [hs-cTn Optimizing the Diagnosis of Acute Myocardial Infarction/Injury in Women]; URL: https://www.clinicaltrials.gov; Unique identifier: NCT03819894).[44] If robust race-specific data

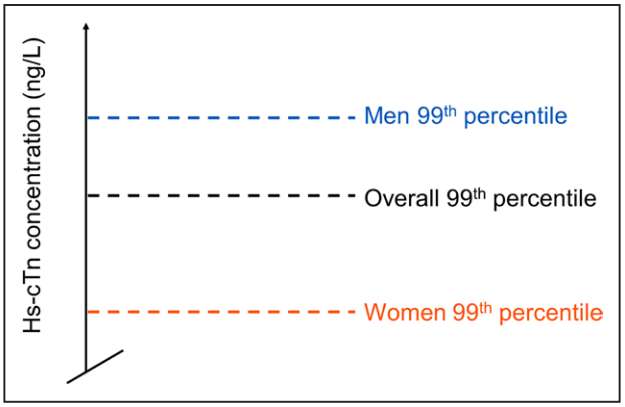

Figure 2. Sex-specific 99th percentile upper-reference limits for high-sensitivity cardiac troponin assays.
hs-cTn indicates high-sensitivity cardiac troponin.

become available, as has occurred with sex-specific data, they too would be relevant for consideration.

Single-Sample Rule-Out of Acute MI Using hs-cTnI and hs-cTnT Assays

Among patients who are not early presenters (symptom onset >2 hours), extensive data exist to support the use of a single low hs-cTn measurement to identify patients with a low risk for acute MI.[3–5,16,17,19,45–47] These patients have been shown to be unlikely to have major adverse cardiovascular events during short- and long-term follow-up.[45,48] This is a valuable strategy for clinicians to understand and use because it can reduce hospital overcrowding and facilitate the early discharge of selected low-risk patients. A "very low" hs-cTn concentration often refers to either an analytical threshold such as the limit of detection (LoD) or limit of quantitation (LoQ) or may refer to a validated hs-cTn concentration that is higher than the LoD or LoQ that is optimized to maximize the proportion of eligible low-risk patients while maintaining safety. The guideline[1] recommendations are focused on the LoD analytical threshold. However, despite extensive validation of the approach, the 2021 AHA/ACC guidelines[1] provide only a class 2a recommendation (Level of Evidence NR [nonrandomized]) that "for patients with acute chest pain, a normal electrocardiogram (ECG), and symptoms suggestive of ACS that began at least 3 hours before ED arrival, a single hs-cTn concentration that is below the limit of detection on initial measurement (time zero) is reasonable to exclude myocardial injury." On the basis of their recommendation to use of the LoD for hs-cTn assays and the large number of available studies including meta-analyses,[45–47] randomized trials,[3,4] and United States–based cohort trials,[16,19] a higher recommendation than class 2a (Level of Evidence B-NR [nonrandomized]) would have been appropriate.

A critically important educational caveat, however, is the fact that none of the hs-cTn assays cleared by the FDA is allowed to report to the LoD.[9,49] hs-cTn assays are only FDA-cleared to report to the LoQ, the lowest concentration with a 20% coefficient of variation.[28,49,50] The LoQ concentration threshold is invariably above the LoD,[51] although some companies, by reporting ranges from across their studies or rounding up to whole numbers, can give the false impression that the LoD and LoQ are the same.[10] Although the difference between the LoD and LoQ can be small for some assays, the thresholds are unequivocally distinct in their definition[51] (Figure 3), imprecision standards, concentrations[10] (Table 3), and evidence base support for their clinical use. Therefore, the AHA/ACC recommendation to use the LoD is not clinically applicable in the United States. There are some data[17,18,20,52,53] indicating that use of the LoQ is safe for this purpose. Recent US data confirm the safety of the use of a value at the LoQ (<6 ng/L) for the single sample rule out using the hs-cTnT assay.[56]

We emphasize that there are robust clinical data for some hs-cTn assays suggesting that hs-cTn concentrations well above both the LoD and LoQ are of value in

Table 3. FDA-Cleared High-Sensitivity Cardiac Troponin Assay Thresholds

Assay	LoD, ng/L	LoQ, ng/L	Overall 99th percentile, ng/L	Sex-specific 99thpercentiles, F/M, ng/L
Abbott ARCHITECT hs-cTnI	1.7	2.3	28	17/35
Beckman Coulter Access 2 hs-cTnI (plasma)	1.0–2.0	0.9–2.3	17.5	11.6/19.8
Beckman Coulter Access 2 hs-cTnI (serum)	1.0–2.0	0.9–2.3	18.2	11.8/19.7
Beckman Coulter DxI Access hs-cTnI (plasma)	1.5–2.3	1.2–2.3	17.9	14.9/19.8
Beckman Coulter DxI Access hs-cTnI (serum)	1.5–2.3	1.2–2.3	18.1	13.6/19.8
Roche cobas e601, e602, E170/TnT Gen 5 STAT	3; 5 for e411	6	19	14/22
Siemens ATELLICA high-sensitivity TnI (TNIH)	1.6	2.50	45.4	38.6/53.5
Siemens ADVIA Centaur XP/XPT/CP high-sensitivity TnI (TNIH)	1.6	2.50	46.5	39.6/58.0
Siemens Dimension VISTA high-sensitivity TnI (TNIH)	2.0	3.0	58.9	53.7/78.5
Siemens Dimension ExL high-sensitivity TnI (TNIH)	2.7	4.0	60.4	51.4/76.2

Limit of detection (LoD), limit of quantitation (LoQ), and 99th percentile upper reference limits according to the insert package information. Source: reference 10. Beckman-Coulter has chosen to report their LoD as equal to the LoQ for ease of reporting. FDA indicates Food and Drug Administration; and hs-cTnI, high-sensitivity cardiac troponin I.

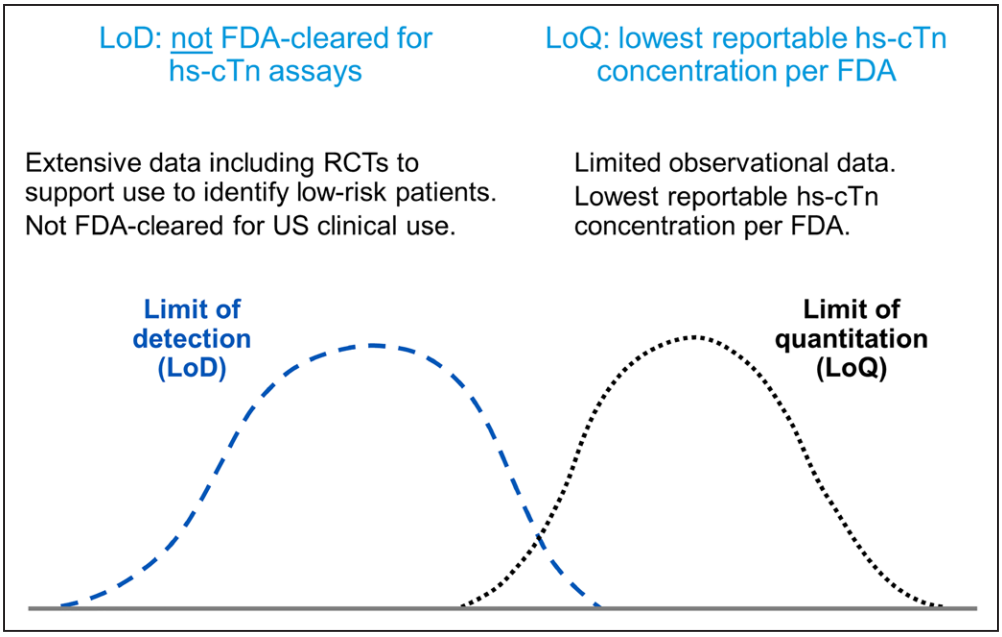

Figure 3. Lowest clinically relevant analytical thresholds with high-sensitivity cardiac troponin assays.
FDA indicates Food and Drug Administration; hs-cTn, high-sensitivity cardiac troponin; and RCT, randomized controlled trial.

ruling out MI.[5,16,19,45,54] For example, the High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome) rule-out pathway,[45,55] which evaluated an optimized concentration of <5 ng/L to exclude MI with the Abbott hs-cTnI assay, was validated for safety and efficacy in the HiSTORIC trial (High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction; 31 492 patients),[5] which was published after the guidelines were completed. The study showed an adverse event rate of only 0.3% (56 of 16 792; MI or cardiac death) at 30 days.[5] There were validation studies before HiSTORIC, including the US data,[19] and a meta-analysis[45] of 22 457 patients across 19 cohorts to support this approach. This approach is also applicable using other hs-cTnI assays.[16] This is an approach that might be worth considering when centers are using hs-cTn assays with the appropriate evidence base to support implementation. Point of care assays may facilitate this approach.

Information About a Changing Pattern of Values (Deltas)

It would have been educational to provide some guidance regarding the changing pattern (deltas) of cTn values because this element is critical when serial measurements are used.[27,57] These considerations are complex and assay-dependent, but some principles have been published by the biomarker group of the Acute Cardiovascular Care Association[57] and by the IFCC-CB.[27] Validated assay-specific deltas for low and high risk as recommended by the ESC guidelines[8] are worth considering in the United States, assuming centers use the appropriate 99th percentile upper reference limits upon which the data are based.

There also are important concepts that underlie the use of changing patterns (Figure 4). For patients without myocardial injury, the absence of significant cTn concentration changes over time identifies lower-risk patients.[58] The presence of changes identifies higher-risk patients and improves diagnostic specificity.[15,59] Even with the use of delta changes, the positive predictive value and specificity for MI are far from perfect.[15,59] Clinicians need to be aware that these change criteria define acute myocardial injury, which can occur for many reasons other than MI.[32] The increase in specificity and positive predictive value necessary to diagnose MI must come from other clinical data such as the history, ECG, or imaging. For patients without cTn increases above the 99th percentile at baseline or only modest increases, absolute concentration deltas are superior to relative (percent) changes.[57,60] Among patients with chronic increases above the 99th percentile, the absence of significant changes (in this instance a percentage change <20% delta) is indicative of chronic myocardial injury in the appropriate clinical context.[32] Because hs-cTn assays detect more chronic myocardial injury,[61] the importance of differentiating between acute and chronic injury with serial sampling should be emphasized[32] (Figure 4).

The Fourth UDMI[32] suggests that rising and falling patterns have similar importance but reflect different timing, but definitive evidence is needed. In the interim, the approach suggested in the UDMI is reasonable for clinicians to follow. Whereas hs-cTn assays measure very low cTn concentrations and detect changes (deltas) with higher precision than contemporary assays (which are

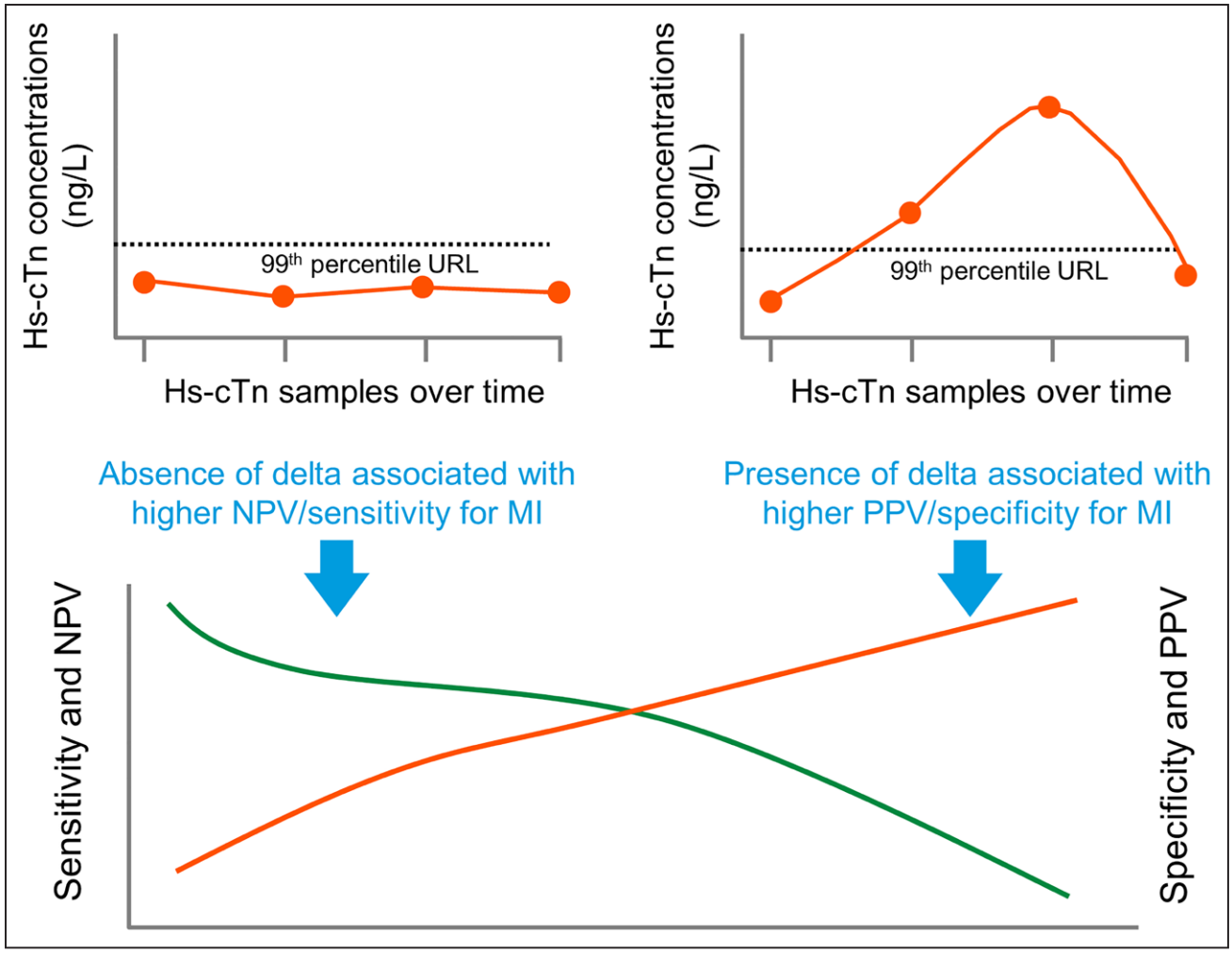

Figure 4. Use of a changing pattern of high-sensitivity cardiac troponin concentrations.
Importance of changing patterns over time to distinguish acute from chronic myocardial injury (**top**). In addition, note the balance between sensitivity and specificity for any given delta value (**bottom**). Adapted from Keller et al.[59] hs-cTn indicates high-sensitivity cardiac troponin; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value; and URL, upper reference limit.

being phased out by manufacturers), there is concern that very small deltas may not be detected with adequate precision,[62–64] which leads to the potential for patient misclassification.

Single-Sample hs-cTn for Identification of High-Risk Patients on the Basis of Higher Concentrations

Increased baseline cTn concentrations above the 99th percentile are specific for myocardial injury[32] and identify high-risk patients. Higher concentrations such as those endorsed by the ESC help identify even higher-risk patients.[8,65] However, with the broader use of hs-cTn testing in the United States, clinicians need to be aware that although they are specific for myocardial injury, these approaches may lack specificity for MI, especially in elderly patients, those with critical illness, and those with end-stage renal disease.[66,67] In these situations, assessing changes over serial measurements (deltas) becomes even more important to improve diagnostic specificity.[15,27,57,58]

Clinical Decision Pathways and Risk Stratification Groups

One of the benefits of hs-cTn assays is that they expedite the evaluation of patients with suspected ACS,[3,5] predominantly because of the early identification of low-risk patients eligible for early discharge. This reduces ED overcrowding without increasing resource use.[14,23] The AHA/ACC recommendations[1] for the intermediate group may do the opposite, unless hs-cTn results are considered. CDP and risk scores are used by ED physicians to evaluate undifferentiated patients. There are guidelines that suggest how to integrate them with hs-cTn assays.[29,30] The American College of Emergency Physicians recommends the HEART (History, ECG, Age, Risk Factors, Troponin) and TIMI (Thrombolysis in Myocardial Infarction) scores to predict the rate of 30-day major adverse

cardiovascular event (MACE).[29] The American College of Emergency Physicians policy[29] suggests patients are eligible for accelerated discharge when they are at low risk for 30-day MACE on the basis of a nonischemic ECG and "negative" serial hs-cTn results at presentation and 2 hours. The Society for Academic Emergency Medicine guidelines,[30] which focus on recurrent, low-risk chest pain (i.e., HEART score <4), provide similar guidelines.

Integration of hs-cTn With Risk Scores for the Intermediate Risk Group

The 2021 AHA/ACC guidelines[1] provide a class 1B recommendation (Level of Evidence B-NR [nonrandomized]) that "in patients presenting with acute chest pain and suspected ACS, clinical decision pathways (CDPs) should categorize patients into low, intermediate, and high-risk strata to facilitate disposition and subsequent diagnostic evaluation." The low-risk group is well-defined, but the definitions for intermediate and high-risk groups are less definitive. One could be designated at intermediate risk on the basis of a risk score alone even with hs-cTn concentrations below the 99th percentile. However, in most situations, the presence or absence of myocardial injury on the basis of cTn concentrations above or below the 99th percentile is a key element that predicts adverse events.[32] Thus, should patients with an intermediate risk score (e.g. HEART score of 4 to 6) without myocardial injury have the same risk profile and care recommendations as a patient with increased cTn concentrations above the 99th percentile? We would suggest these groups are likely different, and that patients with increased cTn above the 99th percentile upper reference limit indicative of myocardial injury are likely at different risk depending on whether the changes are acute or chronic,[60,67-69] as well as their magnitude.[64,70]

Because there are multiple ways to be designated intermediate risk, should the class I recommendations for transthoracic echocardiography, coronary computed tomography angiography, and stress testing be applied to all intermediate patients irrespective of their hs-cTn results? To our knowledge, there are no strong data for those without myocardial injury. Noninvasive evaluations in those with elevated risk scores but nonischemic ECGs and nonelevated cTn concentrations <99th percentile upper reference limit have a low diagnostic yield without evidence for improved clinical outcomes.[71–74] This potential for overtesting could exacerbate ED and hospital overcrowding and increase length of stay. In addition, it is unclear whether all or only a subset of those at intermediate risk should be admitted to observation units. The guidelines state with a 2a recommendation "for intermediate-risk patients with acute chest pain, management in an observation unit is reasonable to shorten length of stay and lower cost relative to an inpatient admission."[1] In a large multisite study of ED patients without an initial diagnosis of MI, there appeared to be no benefit in 30-day outcomes associated with observation or hospital admission.[75] Another large multisite study of ED patients without an initial diagnosis of MI found wide variation in physicians' admission rates and no improvement in patient outcomes related to higher admission rates.[76] Our concern is that patients without myocardial injury, even if intermediate risk on the basis of a risk score, do not necessarily require additional evaluations either in an observation unit or the hospital. There may be some patients who need evaluation in the outpatient setting.

Integration of hs-cTn With Risk Scores for the High-Risk Group

The guidelines[1] provide a class I recommendation that "for patients with acute chest pain and suspected ACS who are designated as high risk, invasive coronary angiography is recommended." Our concern is that this recommendation includes those with increased risk scores on the basis of age and comorbidities without myocardial injury. Studies suggest that for patients with ACS and hs-cTn concentrations below the 99th percentile, there is no benefit from a routine invasive approach.[77]

Discordance With ESC Guidelines

There is discordance between the 2020 ESC[8] and the 2021 AHA/ACC[1] guidelines. The ESC guidelines[8] provide class I recommendations for the 0/1h and 0/2h algorithms. They have downgraded the 0/3h algorithm on the basis of multiple studies[46,78-81] demonstrating a reduced ability to exclude MI. The latter likely occurs because of an improved rule-out performance when incorporating the single sample rule out, which is advocated in the 0/1h and 0/2h algorithms but not the 0/3h algorithm.[7,8] The AHA/ACC guidelines do not make this distinction when tabulating the available hs-cTn protocols, but it is important to acknowledge that the 0/3h algorithm has been downgraded because of the data[46,78-81] showing it is not as safe as the 0/1h and 0/2h algorithms.

OTHER GAPS

Definition of MACE and Acceptable Miss Rates

Defining what constitutes an acceptable miss rate is critical. Previous surveys[82] have suggested that the accepted miss rate for ED physicians is 1%. The 2018 American College of Emergency Physicians policy[29] indicated that "any discussion of accuracy in ED testing for potential NSTEMI needs to include discussion of acceptable rate of missed diagnosis" and recommended a miss rate of 1% to 2% for 30-day MACE. They defined MACE as Q-wave MI, non–Q-wave MI (non–ST-segment–elevation MI), death, or target lesion

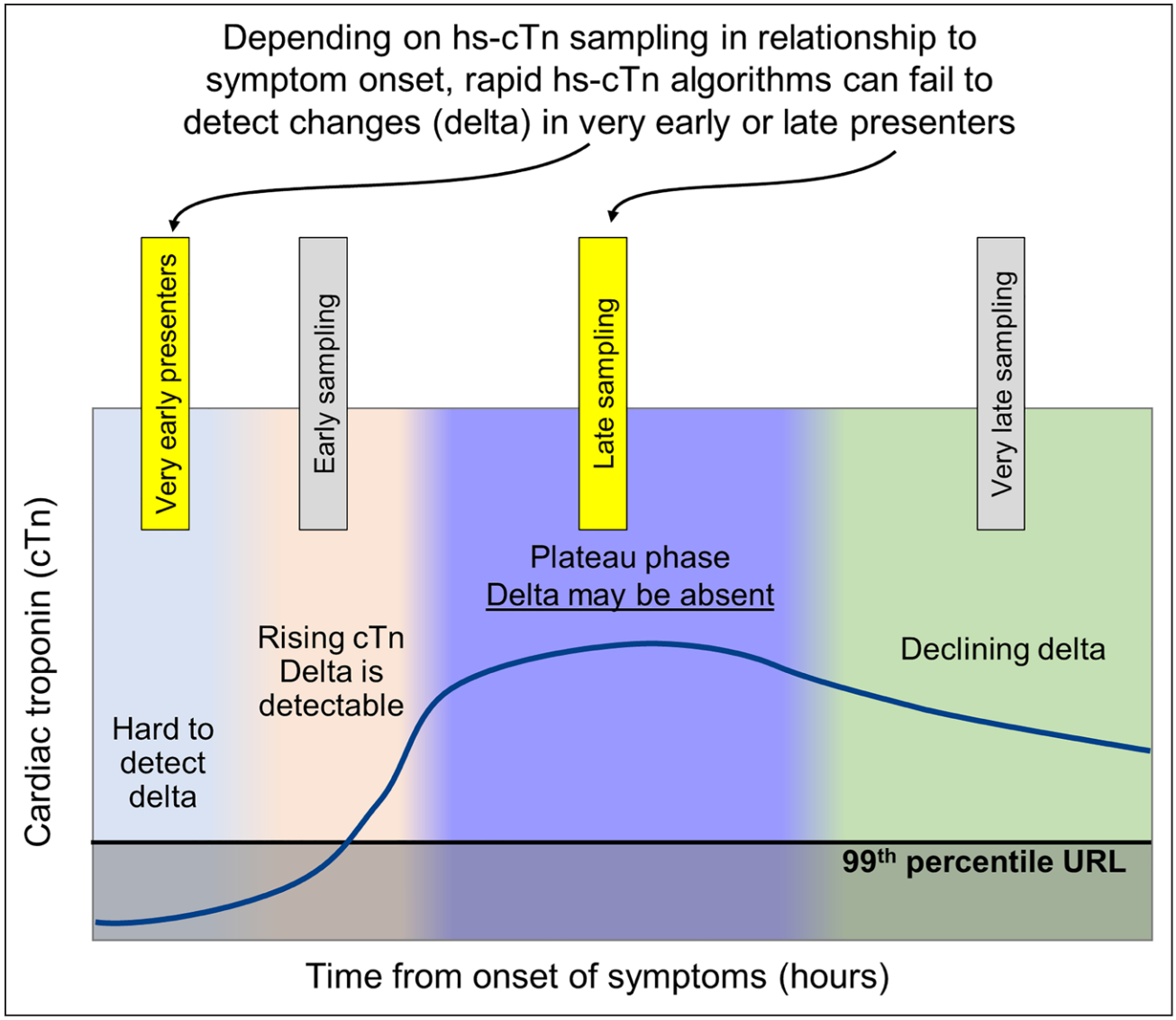

Figure 5. Time concentration curve in patients with myocardial infarction.
Note the differences in the rapidity of the upslope compared with the downslope. hs-cTn indicates high-sensitivity cardiac troponin; and URL, upper reference limit. Adapted from the UDMI.[32]

revascularization within 30 days after the ED evaluation.[29] The inclusion of revascularization after an ED presentation was controversial as an end point because it may not reflect information from the clinical presentation but be related in some cases more to information derived during the evaluation itself. The 2021 AHA/ACC chest pain guidelines[1] indicate that patients with a 30-day risk of death or MACE <1% should be potentially designated as low risk but do not indicate what constitutes MACE, which would have been informative.

Requiem for Unstable Angina: Not Yet

Unstable angina is diagnosed less frequently using hs-cTn assays, but the entity has not yet disappeared.[83–85] Education on this fact would be helpful because it alerts clinicians that although hs-cTn assays are excellent in ruling out acute MI, unstable angina presentations and severe stable obstructive coronary artery disease still occur. [84,85] We would hasten to add that the presence of coronary artery disease alone in the age of widespread use of coronary computed tomography angiography is insufficient to diagnose unstable angina in the absence of appropriate symptoms. Some caution is necessary in this area. There are good data that patients benefit from an invasive strategy when they have an increased cTn value.[8] In some studies, however, they do not benefit when the cTn is not increased[86,87] and in some studies, there have been claims of detriment.[77,88]

Type 2 MI Is Common

With hs-cTn assays, the major increase in MI diagnoses is largely attributable to type 2 events.[89,90] In the United

States, some of the data indicate there may be more type 2[14,24] than type 1 MIs. In the absence of robust data and heterogeneity intrinsic to this patient population, expert recommendations are to focus on treating the underlying supply–demand imbalances/triggers. For selected patients, such as those with microvascular disease or epicardial vasospasm, spontaneous coronary artery dissection, or coronary embolus, angiography is needed.[90]

cTn Sampling in Relation to Symptom Onset

Rapid hs-cTn algorithms can fail in patients who present early[54] (<2 to 3 hours) or in those who present late (>12 hours, although there is no consensus). It may take time for cTn signals to develop in the patients who present early and more time and additional samples to observe a declining pattern indicative of an acute event in those who present late (Figure 5). Both cautions are included in the UDMI.[32]

CONCLUSION

We have provided evidence-based perspectives to assist with the evaluation of patients with suspected ACS and the proper use of hs-cTn assays to integrate them into the recent ACC/AHA guidelines. It is encouraging and a good start to see hs-cTn incorporated into new guidelines. Their use should be coordinated globally across all medical disciplines. Opportunities exist to address many key elements that we have articulated in upcoming policy documents from the major societies.

ARTICLE INFORMATION

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REFERENCES

1. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, Blankstein R, Boyd J, Bullock-Palmer RP, Conejo T, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation.* 2021;144:e368–e454. doi: 10.1161/CIR.0000000000001030
2. Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Chapman AR, Sandeman D, Stables CL, Adamson PD, Andrews JPM, et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *Lancet.* 2018;392:919–928. doi: 10.1016/S0140-6736(18)31923-8
3. Chew DP, Lambrakis K, Blyth A, Seshadri A, Edmonds MJR, Briffa T, Cullen LA, Quinn S, Karnon J, Chuang A, et al. A randomized trial of a 1-hour troponin T protocol in suspected acute coronary syndromes: the Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department With High-Sensitivity Troponin T study (RAPID-TnT). *Circulation.* 2019;140:1543–1556. doi: 10.1161/CIRCULATIONAHA.119.042891
4. Carlton EW, Ingram J, Taylor H, Glynn J, Kandiyali R, Campbell S, Beasant L, Aziz S, Beresford P, Kendall J, et al. Limit of detection of troponin discharge strategy versus usual care: randomised controlled trial. *Heart.* 2020;106:1586–1594. doi: 10.1136/heartjnl-2020-316692
5. Anand A, Lee KK, Chapman AR, Ferry AV, Adamson PD, Strachan FE, Berry C, Findlay I, Cruikshank A, Reid A, et al. High-sensitivity cardiac troponin on presentation to rule out myocardial infarction: a stepped-wedge cluster randomized controlled trial. *Circulation.* 2021;143:2214–2224. doi: 10.1161/CIRCULATIONAHA.120.052380
6. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:2999–3054. doi: 10.1093/eurheartj/ehr236
7. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, 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. doi: 10.1093/eurheartj/ehv320
8. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021;42:1289–1367. doi: 10.1093/eurheartj/ehaa575
9. Apple FS, Fantz CR, Collinson PO. Implementation of high-sensitivity and point-of-care cardiac troponin assays into practice: some different thoughts. *Clin Chem.* 2021;67:70–78. doi: 10.1093/clinchem/hvaa264
10. International Federation of Clinical Chemistry and Laboratory Medicine Committee on Clinical Applications of Cardiac Bio-Markers (C-CB).

Accessed November 18, 2021. https://www.ifcc.org/ifcc-education-division/emd-committees/committee-on-clinical-applications-of-cardiac-bio-markers-c-cb/
11. Makam AN, Nguyen OK. Use of cardiac biomarker testing in the emergency department. *JAMA Intern Med.* 2015;175:67–75. doi: 10.1001/jamainternmed.2014.5830
12. Shah ASV, Sandoval Y, Noaman A, Sexter A, Vaswani A, Smith SW, Gibbins M, Griffiths M, Chapman AR, Strachan FE, et al. Patient selection for high sensitivity cardiac troponin testing and diagnosis of myocardial infarction: prospective cohort study. *BMJ.* 2017;359:j4788. doi: 10.1136/bmj.j4788
13. Vigen R, Kutscher P, Fernandez F, Yu A, Bertulfo B, Hashim IA, Molberg K, Diercks DB, Metzger JC, Soto J, et al. Evaluation of a novel rule-out myocardial infarction protocol incorporating high-sensitivity troponin T in a US hospital. *Circulation.* 2018;138:2061–2063. doi: 10.1161/CIRCULATIONAHA.118.033861
14. Ola O, Akula A, De Michieli L, Dworak M, Crockford E, Lobo R, Rastas N, Knott JD, Mehta RA, Hodge DO, et al. Clinical impact of high-sensitivity cardiac troponin T implementation in the community. *J Am Coll Cardiol.* 2021;77:3160–3170. doi: 10.1016/j.jacc.2021.04.050
15. Sandoval Y, Smith SW, Thordsen SE, Bruen CA, Carlson MD, Dodd KW, Driver BE, Jacoby K, Johnson BK, Love SA, et al. Diagnostic performance of high sensitivity compared with contemporary cardiac troponin I for the diagnosis of acute myocardial infarction. *Clin Chem.* 2017;63:1594–1604. doi: 10.1373/clinchem.2017.272930
16. Sandoval Y, Nowak R, deFilippi CR, Christenson RH, Peacock WF, McCord J, Limkakeng AT, Sexter A, Apple FS. Myocardial infarction risk stratification with a single measurement of high-sensitivity troponin I. *J Am Coll Cardiol.* 2019;74:271–282. doi: 10.1016/j.jacc.2019.05.058
17. Allen BR, Christenson RH, Cohen SA, Nowak R, Wilkerson RG, Mumma B, Madsen T, McCord J, Huis In't Veld M, Massoomi M, et al. Diagnostic performance of high-sensitivity cardiac troponin T strategies and clinical variables in a multisite US cohort. *Circulation.* 2021;143:1659–1672. doi: 10.1161/CIRCULATIONAHA.120.049298
18. Vigen R, Diercks DB, Hashim IA, Pandey A, Zhong L, Kutscher P, Fernandez F, Yu A, Bertulfo B, Molberg K, et al. Association of a novel protocol for rapid exclusion of myocardial infarction with resource use in a US safety net hospital. *JAMA Netw Open.* 2020;3:e203359. doi: 10.1001/jamanetworkopen.2020.3359
19. Sandoval Y, Smith SW, Love SA, Sexter A, Schulz K, Apple FS. Single high-sensitivity cardiac troponin I to rule out acute myocardial infarction. *Am J Med.* 2017;130:1076–1083.e1. doi: 10.1016/j.amjmed.2017.02.032
20. Peacock WF, Baumann BM, Bruton D, Davis TE, Handy B, Jones CW, Hollander JE, Limkakeng AT, Mehrotra A, Than M, et al. Efficacy of high-sensitivity troponin T in identifying very-low-risk patients with possible acute coronary syndrome. *JAMA Cardiol.* 2018;3:104–111. doi: 10.1001/jamacardio.2017.4625
21. Ford JS, Chaco E, Tancredi DJ, Mumma BE. Impact of high-sensitivity cardiac troponin implementation on emergency department length of stay, testing, admissions, and diagnoses. *Am J Emerg Med.* 2021;45:54–60. doi: 10.1016/j.ajem.2021.02.021
22. Mumma BE, Casey SD, Dang RK, Polen MK, Kaur JC, Rodrigo J, Tancredi DJ, Narverud RA, Amsterdam EA, Tran N. Diagnostic reclassification by a high-sensitivity cardiac troponin assay. *Ann Emerg Med.* 2020;76:566–579. doi: 10.1016/j.annemergmed.2020.06.047
23. Ganguli I, Cui J, Thakore N, Orav EJ, Januzzi JL, Baugh CW, Sequist TD, Wasfy JH. Downstream cascades of care following high-sensitivity troponin test implementation. *J Am Coll Cardiol.* 2021;77:3171–3179. doi: 10.1016/j.jacc.2021.04.049
24. Sandoval Y, Askew JW 3rd, Newman JS, Clements CM, Grube ED, Ola O, Akula A, Dworak M, Wohlrab S, Karon BS, et al. Implementing high-sensitivity cardiac troponin T in a US regional healthcare system. *Circulation.* 2020;141:1937–1939. doi: 10.1161/CIRCULATIONAHA.119.045480
25. Aakre KM, Saenger AK, Body R, Collinson P, Hammarsten O, Jaffe AS, Kavsak P, Omland T, Ordonez-Lianos J, Apple FS. Analytical considerations in deriving 99th percentile upper reference limits for high-sensitivity cardiac troponin assays: educational recommendations from the IFCC committee on clinical application of cardiac bio-markers [published online June 18, 2022]. *Clin Chem.* doi: 10.1093/clinchem/hvac092
26. Apple FS, Sandoval Y, Jaffe AS, Ordonez-Llanos J. Cardiac troponin assays: guide to understanding analytical characteristics and their impact on clinical care. *Clin Chem.* 2017;63:73–81. doi: 10.1373/clinchem.2016.255109
27. Apple FS, Jaffe AS, Collinson P, Mockel M, Ordonez-Llanos J, Lindahl B, Hollander J, Plebani M, Than M, Chan MH. IFCC educational materials on selected analytical and clinical applications of high sensitivity cardiac troponin assays. *Clin Biochem.* 2015;48:201–203. doi: 10.1016/j.clinbiochem.2014.08.021
28. Januzzi JL Jr, Mahler SA, Christenson RH, Rymer J, Newby LK, Body R, Morrow DA, Jaffe AS. Recommendations for institutions transitioning to high-sensitivity troponin testing: *JACC* scientific expert panel. *J Am Coll Cardiol.* 2019;73:1059–1077. doi: 10.1016/j.jacc.2018.12.046
29. Tomaszewski CA, Nestler D, Shah KH, Sudhir A, Brown MD. Clinical policy: critical issues in the evaluation and management of emergency department patients with suspected non-ST-elevation acute coronary syndromes. *Ann Emerg Med.* 2018;72:e65–e106. doi: 10.1016/j.annemergmed.2018.07.045
30. Musey PI Jr, Bellolio F, Upadhye S, Chang AM, Diercks DB, Gottlieb M, Hess EP, Kontos MC, Mumma BE, Probst MA, Stahl JH, et al. Guidelines for reasonable and appropriate care in the emergency department (GRACE): recurrent, low-risk chest pain in the emergency department. *Acad Emerg Med.* 2021;28:718–744. doi: 10.1111/acem.14296
31. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, 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. *Circulation.* 2014;130:e344–e426. doi: 10.1161/CIR.0000000000000134
32. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Fourth universal definition of myocardial infarction (2018). *Circulation.* 2018;138:e618–e651. doi: 10.1161/CIR.0000000000000617
33. Sandoval Y, Apple FS. The global need to define normality: the 99th percentile value of cardiac troponin. *Clin Chem.* 2014;60:455–462. doi: 10.1373/clinchem.2013.211706
34. Sandoval Y, Apple FS, Saenger AK, Collinson PO, Wu AHB, Jaffe AS. 99th percentile upper-reference limit of cardiac troponin and the diagnosis of acute myocardial infarction. *Clin Chem.* 2020;66:1167–1180. doi: 10.1093/clinchem/hvaa158
35. Apple FS, Wu AHB, Sandoval Y, Sexter A, Love SA, Myers G, Schulz K, Duh SH, Christenson RH. Sex-specific 99th percentile upper reference limits for high sensitivity cardiac troponin assays derived using a universal sample bank. *Clin Chem.* 2020;66:434–444. doi: 10.1093/clinchem/hvz029
36. Collinson PO, Heung YM, Gaze D, Boa F, Senior R, Christenson R, Apple FS. Influence of population selection on the 99th percentile reference value for cardiac troponin assays. *Clin Chem.* 2012;58:219–225. doi: 10.1373/clinchem.2011.171082
37. 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;58:1574–1581. doi: 10.1373/clinchem.2012.192716
38. Wildi K, Gimenez MR, Twerenbold R, Reichlin T, Jaeger C, Heinzelmann A, Arnold C, Nelles B, Druey S, Haaf P, et al. Misdiagnosis of myocardial infarction related to limitations of the current regulatory approach to define clinical decision values for cardiac troponin. *Circulation.* 2015;131:2032–2040. doi: 10.1161/CIRCULATIONAHA.114.014129
39. Hachey BJ, Kontos MC, Newby LK, Christenson RH, Peacock WF, Brewer KC, McCord J. Trends in use of biomarker protocols for the evaluation of possible myocardial infarction. *J Am Heart Assoc.* 2017;6:e005852. doi: 10.1161/JAHA.117.005852
40. Collinson P, Hammerer-Lercher A, Suvisaari J, Apple FS, Christenson RH, Pulkki K, van Dieijen-Visser MP, Duff CJ, Baum H, Stavljenic-Rukavina A, et al. How well do laboratories adhere to recommended clinical guidelines for the management of myocardial infarction? The Cardiac Marker Guidelines Uptake in Europe Study (CARMAGUE). *Clin Chem.* 2016;62:1264–1271. doi: 10.1373/clinchem.2016.259515
41. Bagai A, Alexander KP, Berger JS, Senior R, Sajeev C, Pracon R, Mavromatis K, Lopez-Sendón JL, Gosselin G, Diaz A, et al. Use of troponin assay 99th percentile as the decision level for myocardial infarction diagnosis. *Am Heart J.* 2017;190:135–139. doi: 10.1016/j.ahj.2017.04.016
42. Anand A, Shah ASV, Beshiri A, Jaffe AS, Mills NL. Global adoption of high-sensitivity cardiac troponins and the universal definition of myocardial infarction. *Clin Chem.* 2019;65:484–489. doi: 10.1373/clinchem.2018.298059
43. Shah AS, Griffiths M, Lee KK, McAllister DA, Hunter AL, Ferry AV, Cruikshank A, Reid A, Stoddart M, Strachan F, et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ.* 2015;350:g7873. doi: 10.1136/bmj.g7873
44. Zhao Y, Izadnegahdar M, Lee MK, Kavsak PA, Singer J, Scheuermeyer F, Udell JA, Robinson S, Norris CM, Lyon AW, et al. High-Sensitivity Cardiac Troponin–Optimizing the Diagnosis of Acute Myocardial Infarction/Injury in Women (CODE-MI): rationale and design for a multicenter, stepped-wedge,

cluster-randomized trial. *Am Heart J.* 2020;229:18–28. doi: 10.1016/j.ahj.2020.06.013
45. Chapman AR, Lee KK, McAllister DA, Cullen L, Greenslade JH, Parsonage W, Worster A, Kavsak PA, Blankenberg S, Neumann J, et al. Association of high-sensitivity cardiac troponin I concentration with cardiac outcomes in patients with suspected acute coronary syndrome. *JAMA.* 2017;318:1913–1924. doi: 10.1001/jama.2017.17488
46. Chiang CH, Chiang CH, Pickering JW, Stoyanov KM, Chew DP, Neumann JT, Ojeda F, Sörensen NA, Su KY, Kavsak P, et al. Performance of the European Society of Cardiology 0/1-hour, 0/2-hour, and 0/3-hour algorithms for rapid triage of acute myocardial infarction: an international collaborative meta-analysis. *Ann Intern Med.* 2022;175:101–113. doi: 10.7326/M21-1499
47. Pickering JW, Than MP, Cullen L, Aldous S, Ter Avest E, Body R, Carlton EW, Collinson P, Dupuy AM, Ekelund U, et al. Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin T measurement below the limit of detection: a collaborative meta-analysis. *Ann Intern Med.* 2017;166:715–724. doi: 10.7326/M16-2562
48. Than MP, Aldous SJ, Troughton RW, Pemberton CJ, Richards AM, Frampton CMA, Florkowski CM, George PM, Bailey S, Young JM, et al. Detectable high-sensitivity cardiac troponin within the population reference interval conveys high 5-year cardiovascular risk: an observational study. *Clin Chem.* 2018;64:1044–1053. doi: 10.1373/clinchem.2017.285700
49. Sandoval Y, Smith SW, Apple FS. Present and future of cardiac troponin in clinical practice: a paradigm shift to high-sensitivity assays. *Am J Med.* 2016;129:354–365. doi: 10.1016/j.amjmed.2015.12.005
50. Sandoval Y, Jaffe AS. Using high-sensitivity cardiac troponin T for acute cardiac care. *Am J Med.* 2017;130:1358–1365.e1. doi: 10.1016/j.amjmed.2017.07.033
51. Armbruster DA, Pry T. Limit of blank, limit of detection and limit of quantitation. *Clin Biochem Rev.* 2008;29:S49–S52.
52. Chapman AR, Sandeman D, Ferry AV, Stewart S, Strachan FE, Wereski R, Bularga A, Anand A, Shah ASV, Mills NL. Risk stratification using high-sensitivity cardiac troponin T in patients with suspected acute coronary syndrome. *J Am Coll Cardiol.* 2020;75:985–987. doi: 10.1016/j.jacc.2019.12.036
53. Twerenbold R, Badertscher P, Boeddinghaus J, Nestelberger T, Wildi K, Rubini Gimenez M, Miró Ò, Martín-Sánchez FJ, Reichlin T, Mueller C. Effect of the FDA regulatory approach on the 0/1-h algorithm for rapid diagnosis of MI. *J Am Coll Cardiol.* 2017;70:1532–1534. doi: 10.1016/j.jacc.2017.07.746
54. Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, Chapman AR, Langdon T, Sandeman D, Vaswani A, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. *Lancet.* 2015;386:2481–2488. doi: 10.1016/S0140-6736(15)00391-8
55. Chapman AR, Anand A, Boeddinghaus J, Ferry AV, Sandeman D, Adamson PD, Andrews J, Tan S, Cheng SF, D'Souza M, et al. Comparison of the efficacy and safety of early rule-out pathways for acute myocardial infarction. *Circulation.* 2017;135:1586–1596. doi: 10.1161/CIRCULATIONAHA.116.025021
56. Sandoval Y, Lewis B, Mehta R, Ola O, Knott J, De Michieli L, Akula A, Lobo R, Yang E, Gharacholou S, et al. Rapid exclusion of acute myocardial injury and infarction with a single high sensitivity cardiac troponin T in the emergency department: a multicenter United States evaluation. *Circulation.* 2022;145:1708–1719. doi: 10.1161/CIRCULATIONAHA.122.059235
57. Jaffe AS, Moeckel M, Giannitsis E, Huber K, Mair J, Mueller C, Plebani M, Thygesen K, Lindahl B. In search for the Holy Grail: suggestions for studies to define delta changes to diagnose or exclude acute myocardial infarction: a position paper from the study group on biomarkers of the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care.* 2014;3:313–316. doi: 10.1177/2048872614541906
58. Korley FK, Jaffe AS. Preparing the United States for high-sensitivity cardiac troponin assays. *J Am Coll Cardiol.* 2013;61:1753–1758. doi: 10.1016/j.jacc.2012.09.069
59. Keller T, Zeller T, Ojeda F, Tzikas S, Lillpopp L, Sinning C, Wild P, Genth-Zotz S, Warnholtz A, Giannitsis E, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *JAMA.* 2011;306:2684–2693. doi: 10.1001/jama.2011.1896
60. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, Bassetti S, Steuer S, Winkler K, Peter F, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation.* 2011;124:136–145. doi: 10.1161/CIRCULATIONAHA.111.023937
61. Chapman AR, Adamson PD, Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Berry C, Findlay I, Cruikshank A, et al. High-sensitivity cardiac troponin and the universal definition of myocardial infarction. *Circulation.* 2020;141:161–171. doi: 10.1161/CIRCULATIONAHA.119.042960
62. Saenger AK, Beyrau R, Braun S, Cooray R, Dolci A, Freidank H, Giannitsis E, Gustafson S, Handy B, Katus H, et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. *Clin Chim Acta.* 2011;412:748–754. doi: 10.1016/j.cca.2010.12.034
63. Donato LJ, Wockenfus AM, Katzman BM, Baumann NA, Jaffe AS, Karon BS. Analytical and clinical considerations in implementing the Roche Elecsys troponin T Gen 5 STAT assay. *Am J Clin Pathol.* 2021;156:1121–1129. doi: 10.1093/ajcp/aqab082
64. Jaffe AS, White H. Ruling-in myocardial injury and ruling-out myocardial infarction with the European Society of Cardiology 1-hour algorithm. *Circulation.* 2016;134:1542–1545. doi: 10.1161/CIRCULATIONAHA.116.024687
65. Reichlin T, Twerenbold R, Wildi K, Gimenez MR, Bergsma N, Haaf P, Druey S, Puelacher C, Moehring B, Freese M, 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–E252. doi: 10.1503/cmaj.141349
66. Gunsolus I, Sandoval Y, Smith SW, Sexter A, Schulz K, Herzog CA, Apple FS. Renal dysfunction influences the diagnostic and prognostic performance of high-sensitivity cardiac troponin I. *J Am Soc Nephrol.* 2018;29:636–643. doi: 10.1681/ASN.2017030341
67. Twerenbold R, Wildi K, Jaeger C, Gimenez MR, Reiter M, Reichlin T, Walukiewicz A, Gugala M, Krivoshei L, Marti N, 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;131:2041–2050. doi: 10.1161/CIRCULATIONAHA.114.014245
68. Kadesjö E, Roos A, Siddiqui AJ, Sartipy U, Holzmann MJ. Causes of death in patients with acute and chronic myocardial injury. *Am J Med.* 2020;133:590–598.e2. doi: 10.1016/j.amjmed.2019.09.030
69. Bardají A, Bonet G, Carrasquer A, González-Del Hoyo M, Vásquez-Nuñez K, Ali S, Boqué C, Cediel G. Clinical features and prognosis of patients with acute and chronic myocardial injury admitted to the emergency department. *Am J Med.* 2019;132:614–621. doi: 10.1016/j.amjmed.2018.11.037
70. Melki D, Lugnegård J, Alfredsson J, Lind S, Eggers KM, Lindahl B, Jernberg T. Implications of introducing high-sensitivity cardiac troponin t into clinical practice: data from the SWEDEHEART registry. *J Am Coll Cardiol.* 2015;65:1655–1664. doi: 10.1016/j.jacc.2015.02.044
71. Hermann LK, Newman DH, Pleasant WA, Rojanasarntikul D, Lakoff D, Goldberg SA, Duvall WL, Henzlova MJ. Yield of routine provocative cardiac testing among patients in an emergency department-based chest pain unit. *JAMA Intern Med.* 2013;173:1128–1133. doi: 10.1001/jamainternmed.2013.850
72. Reinhardt SW, Lin CJ, Novak E, Brown DL. Noninvasive cardiac testing vs clinical evaluation alone in acute chest pain: a secondary analysis of the ROMICAT-II randomized clinical trial. *JAMA Intern Med.* 2018;178:212–219. doi: 10.1001/jamainternmed.2017.7360
73. Foy AJ, Liu G, DavidsonSciamanna WRC, Leslie DL. Comparative effectiveness of diagnostic testing strategies in emergency department patients with chest pain: an analysis of downstream testing, interventions, and outcomes. *JAMA Intern Med.* 2015;175:428–436. doi: 10.1001/jamainternmed.2014.7657
74. Sandhu AT, Heidenreich PA, Bhattacharya J, Bundorf MK. Cardiovascular testing and clinical outcomes in emergency department patients with chest pain. *JAMA Intern Med.* 2017;177:1175–1182. doi: 10.1001/jamainternmed.2017.2432
75. Sharp AL, Kawatkar AA, Baecker AS, Redberg RF, Lee MS, Ferencik M, Wu YL, Shen E, Zheng C, Park S, et al. Does hospital admission/observation for chest pain improve patient outcomes after emergency department evaluation for suspected acute coronary syndrome? *J Gen Intern Med.* 2022;37:745–752. doi: 10.1007/s11606-021-06841-2
76. Natsui S, Sun BC, Shen E, Redberg RF, Ferencik M, Lee MS, Musigdilok V, Wu YL, Zheng C, Kawatkar AA, et al. Higher emergency physician chest pain hospitalization rates do not lead to improved patient outcomes. *Circ Cardiovasc Qual Outcomes.* 2021;14:e006297. doi: 10.1161/CIRCOUTCOMES.119.006297
77. Giannitsis E, Wallentin L, James SK, Bertilsson M, Siegbahn A, Storey RF, Husted S, Cannon CP, Armstrong PW, Steg PG, et al. Outcomes after planned invasive or conservative treatment strategy in patients with non-ST-elevation acute coronary syndrome and a normal value of high sensitivity troponin at randomisation: a Platelet Inhibition and Patient Outcomes (PLATO) trial biomarker substudy. *Eur Heart J Acute Cardiovasc Care.* 2017;6:500–510. doi: 10.1177/2048872616641901

78. Pickering JW, Greenslade JH, Cullen L, Flaws D, Parsonage W, George P, Worster A, Kavsak PA, Than MP. Validation of presentation and 3 h high-sensitivity troponin to rule-in and rule-out acute myocardial infarction. *Heart.* 2016;102:1270–1278. doi: 10.1136/heartjnl-2015-308505
79. Chapman AR, Hesse K, Andrews J, Lee KK, Anand A, Shah ASV, Sandeman D, Ferry AV, Jameson J, Piya S, et al. High-sensitivity cardiac troponin I and clinical risk scores in patients with suspected acute coronary syndrome. *Circulation.* 2018;138:1654–1665. doi: 10.1161/CIRCULATIONAHA.118.036426
80. Badertscher P, Boeddinghaus J, Twerenbold R, Nestelberger T, Wildi K, Wussler D, Schwarz J, Puelacher C, Rubini Giménez M, Kozhuharov N, et al. Direct comparison of the 0/1h and 0/3h algorithms for early rule-out of acute myocardial infarction. *Circulation.* 2018;137:2536–2538. doi: 10.1161/CIRCULATIONAHA.118.034260
81. Sandoval Y, Smith SW, Schulz K, Sexter A, Apple FS. Comparison of 0/3-hour rapid rule-out strategies using high-sensitivity cardiac troponin I in a US emergency department. *Circ Cardiovasc Qual Outcomes.* 2020;13:e006565. doi: 10.1161/CIRCOUTCOMES.120.006565
82. Than M, Herbert M, Flaws D, Cullen L, Hess E, Hollander JE, Diercks D, Ardagh MW, Kline JA, Munro Z, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the emergency department? A clinical survey. *Int J Cardiol.* 2013;166:752–754. doi: 10.1016/j.ijcard.2012.09.171
83. Braunwald E, Morrow DA. Unstable angina: is it time for a requiem? *Circulation.* 2013;127:2452–2457. doi: 10.1161/CIRCULATIONAHA.113.001258
84. Sandoval Y, Apple FS, Smith SW. High-sensitivity cardiac troponin assays and unstable angina. *Eur Heart J Acute Cardiovasc Care.* 2018;7:120–128. doi: 10.1177/2048872616658591
85. Puelacher C, Gugala M, Adamson PD, Shah A, Chapman AR, Anand A, Sabti Z, Boeddinghaus J, Nestelberger T, Twerenbold R, et al. Incidence and outcomes of unstable angina compared with non-ST-elevation myocardial infarction. *Heart.* 2019;105:1423–1431. doi: 10.1136/heartjnl-2018-314305
86. Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban: PRISM Study Investigators: Platelet Receptor Inhibition in Ischemic Syndrome Management. *Lancet.* 1999;354:1757–1762. doi: 10.1016/s0140-6736(99)10285-x
87. Kastrati A, Mehilli J, Neumann FJ, Dotzer F, ten Berg J, Bollwein H, Graf I, Ibrahim M, Pache J, Seyfarth M, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA.* 2006;295:1531–1538. doi: 10.1001/jama.295.13.joc60034
88. Wiviott SD, Cannon CP, Morrow DA, Murphy SA, Gibson CM, McCabe CH, Sabatine MS, Rifai N, Giugliano RP, DiBattiste PM, et al. Differential expression of cardiac biomarkers by gender in patients with unstable angina/non–ST-elevation myocardial infarction: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18) substudy. *Circulation.* 2004;109:580–586. doi: 10.1161/01.CIR.0000109491.66226.26
89. Sandoval Y, Jaffe AS. Type 2 myocardial infarction: *JACC* review topic of the week. *J Am Coll Cardiol.* 2019;73:1846–1860. doi: 10.1016/j.jacc.2019.02.018
90. DeFilippis AP, Chapman AR, Mills NL, de Lemos JA, Arbab-Zadeh A, Newby LK, Morrow DA. Assessment and treatment of patients with type 2 myocardial infarction and acute nonischemic myocardial injury. *Circulation.* 2019;140:1661–1678. doi: 10.1161/CIRCULATIONAHA.119.040631