THE PRESENT AND FUTURE

JACC SCIENTIFIC EXPERT PANEL

Recommendations for Institutions Transitioning to High-Sensitivity Troponin Testing

JACC Scientific Expert Panel

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ABSTRACT

High-sensitivity cardiac troponin (hs-cTn) I or T methods have been in use in certain regions for years but are now increasingly globally adopted, including in the United States. Accordingly, inevitable challenges are created for institutions transitioning from conventional cardiac troponin (cTn) assays. hs-cTn assays have higher analytic precision at lower concentrations, yielding greater clinical sensitivity for myocardial injury and allowing accurate recognition of small changes in troponin concentration (rise or fall) within a short time frame. Although much of the knowledge regarding troponin biology that was applicable with older troponin assays still holds true, considerable education regarding the differences between conventional cTn and hs-cTn is needed before medical systems convert to the newer methods. This includes a basic understanding of how hs-cTn testing differs from conventional cTn testing and how it is best deployed in different settings, such as the emergency department and inpatient services. This Expert Panel will review important concepts for institutional transition to hs-cTn methodology, providing recommendations useful for education before implementation. (J Am Coll Cardiol 2019;73:1059–77) © 2019 by the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ADP = accelerated diagnostic protocol

AMI = acute myocardial infarction

CKD = chronic kidney disease

cTn = cardiac troponin

ECG = electrocardiogram

ED = emergency department

ESRD = end-stage renal disease

HF = heart failure

hs-cTn = high-sensitivity cardiac troponin

LoB = limit of blank

LoD = limit of detection

LoQ = limit of quantification

MI = myocardial infarction

NPV = negative predictive value

PCI = percutaneous coronary intervention

URL = upper reference limit

Although used for many years in several regions, including Europe, Australia, Asia, and Canada, high-sensitivity cardiac troponin (hs-cTn) I and T assays have only recently achieved regulatory approval in the United States and are in growing use in other global markets. With transition to more sensitive troponin assays comes the need to develop a consensus regarding aspects that medical systems should consider before implementation of these assays, which differ considerably from "conventional" cardiac troponin (cTn) methods. Additionally, even within the category of hs-cTnI or T assays, there will be variability in cutoff values, sensitivity, and specificity, as well as in the way in which these tests are interpreted.

This document, authored by an Expert Panel with a broad range of expertise, will provide suggestions to facilitate the transition from conventional cTn to hs-cTn methods, including necessary considerations for laboratory medicine, emergency medicine, cardiology, and those staffing inpatient services. A central theme is the need for collaborative preparation for the transition to hs-cTn methods and the necessity for extensive education. As with other Expert Panels in the *Journal*, this effort is intended to provide a framework for transition to hs-cTn testing based on the present evidence base; we also provide expert opinion in areas where evidence may be limited, new, and evolving, or where sufficient data to fully inform clinical decision making are lacking.

LABORATORY CONSIDERATIONS

With several hs-cTn assays available at the time of this writing and several others soon to be approved, laboratory medicine specialists should decide which assay meets institutional needs. As well, they represent an important source of education regarding how hs-cTnI or T assays contrast with conventional cTn methods (Online Table 1). Some basic education regarding analytic terminology, as illustrated in **Figure 1** and explained here, is helpful, because this clarifies how hs-cTn assays perform.

Limit of blank (LoB): The LoB is considered the background noise present in the analytical measurement system when no troponin is present (1).

Limit of detection (LoD): The LoD is the lowest concentration of analyte detectable in 95% of measurements (1). The imprecision at the LoD is often high, making measurements inaccurate.

Limit of quantitation (LoQ): LoQ is the lowest troponin concentration that can be reported as a number with specified certainty (1), for example, ≤ 20% imprecision.

Coefficient of variation: A measure of assay imprecision at any given concentration. The coefficient of variation value should be 10% or less at the 99th percentile upper reference limit (URL) for hs-cTn assays. Good precision allows for confident identification of small changes in biomarker concentration (2).

99th percentile clinical decision values: Like many biomarkers, troponin has no truly objective "gold standard" either for normality or for the diagnosis of acute myocardial infarction (MI). For troponin, the 99th percentile of normal healthy individuals was selected as a consensus decision point (3) because lower thresholds would have permitted excessive false positive results. Use of URLs at or near the 99th percentile leads to improved health outcomes (4,5); accordingly, this URL has been adopted in evidence-based guidelines developed by cardiology (6) and laboratory medicine (7) professional associations and endorsed by the Fourth Universal Definition of Myocardial Infarction Global Task Force (8). Determination of the 99th percentile URL is far from standardized because of varying criteria for defining a normal population (2).

Common questions from clinicians regarding hs-cTn methods include the following:

What makes an hs-cTn assay more sensitive? Assays for hs-cTnI or T measurement do not detect a novel troponin isoform. Rather, they enable more sensitive and precise detection at very low troponin concentrations. Although the

FIGURE 1 Various Analytic Definitions to Familiarize Clinicians

99th percentile (%tile) clinical decision values:
Male cut-offs >overall cut-offs > Female cut-offs
Sex-specific cut-offs should be used for interpretation with high-sensitivity cTn assays.

Limit of Quantitation (LoQ). Represents cTn value at which the value can be reliably reported as a number. LoQ is typically cTn concentration where assay's Total CV = 20%. LoQ always exceeds LoD.

Limit of Detection (LoD). The mean signal at which 5% of the frequency distribution is below the LoB, i.e., 95% Confidence that cTn is present in the sample. LoD always exceeds LoB.

Limit of Blank (LoB). Represents the 'noise' signal inherent in the analytical system. LoB is the 95th percentile of analytic signal when no cTn (0 ng/L) is present in samples tested, only matrix (serum or plasma).

An understanding of these terms facilitates transition to high-sensitivity cardiac troponin testing. %tile = percentile; cTn = cardiac troponin; CV = coefficient of variation; LoB = limit of blank; LoD = limit of detection; LoQ = limit of quantitation; Std. Dev. = standard deviation.

explicit details for how manufacturers achieve superior sensitivity are proprietary, an essential component is incorporation of antibody reagents that have far higher cTn avidity than contemporary assays, which helps optimize signal-to-noise ratio for hs-cTn tests (2).

How are troponin assays classified as high sensitivity? To be termed "high sensitivity," it has been proposed that assays allow establishment of sex-specific cutoffs, possess a low LoD, and be capable of measuring values > 50% in both healthy female and male populations with values greater than the LoD. A comparison between hs-cTn and conventional cTn methods is detailed in Online Table 1.

What issues should my laboratory consider before transition to hs-cTn? Clinical laboratory directors should consider the following:

- *Which assay should be chosen?* At the time of this writing, both hs-cTnI and T assays are available in the United States, with several other assays expected soon. Assay selection is typically based on which conventional cTn assay was run before the transition, along with considerations regarding which instrumentation is run in the laboratory. Because most point-of-care options do not achieve high-sensitivity performance, and rapid

protocols were defined using laboratory-based hs-cTn assays, the Writing Group does not presently advocate use of point-of-care troponin assays for these rapid protocols until point-of-care hs-cTn methods are both available and validated for such use.

- *Should different assays be available in different venues?* The transition to hs-cTn should be universal for all services within an institution. To avoid confusion, the Writing Group strongly recommends against availability of both hs-cTn and conventional methods or the use of multiple methods in different hospital venues (e.g., hs-cTn in the emergency department [ED] versus conventional cTn Inpatient settings).

- *Quality control utilization*: Clinical laboratories rely on control samples in testing to ensure that assays are performing up to specifications, as well as to monitor quality and consistency of results in the ranges that are important for clinical decision making (i.e., near 99th percentile URLs). The American Association of Clinical Chemistry and International Federation of Clinical Chemistry have recommendations to help ensure that quality control at the proper ranges is used (2). Also, it is recommended that clinicians be educated regarding the importance

FIGURE 2   The Laboratory Testing Cycle, Consisting of the Pre-Analytical Phase, the Analytical Phase, and the Post-Analytical Testing Phase

Pre-analytical phase:
--Clinical assessment
--Test request
--Blood collected

Analytical phase:
--Transport to lab
--Sample receipt
--Sample processing
--Analysis
--Result transmission

Post–analytical phase:
--Result seen by clinician
--Disposition decision

Errors in laboratory results in each testing phase are approximately 50%, 10% to 15%, and 30% to 40%, respectively.

of interference from substances such as anti-troponin antibodies, biotin, or substances released during hemolysis (Online Figure 1).

- *Result turnaround time:* Establishing and maintaining turnaround time is more important in the hs-cTn era so that the enhanced precision of hs-cTn assays can be translated into earlier rule-out and disposition protocols (9,10). Practice guidelines suggest a turnaround time of 60 min or less from receipt of the sample in the laboratory (2,11), a goal that necessarily engages numerous stakeholders in the pre-analytical, analytical, and post-analytical phases to avoid errors, delays, and slow result reporting (**Figure 2**). Although point-of-care troponin testing can reduce turnaround times, the present use of point-of-care assays in accelerated protocols or together

with an automated hs-cTn assay is not recommended because of lack of sufficient data.

- *Units for reporting high-sensitivity cardiac troponin (ng/l):* The American Association of Clinical Chemistry and International Federation of Clinical Chemistry recommend reporting hs-cTnI or T results in nanograms per liter. Thus, instead of fractional results (e.g., 0.025 ng/ml), hs-cTnI or T data will be reported as integers (i.e., 25 ng/l) (2). The larger numerical result is often perturbing to clinicians, but the consensus is that reporting hs-cTn results as integers will be clearer and safer for interpretation (12). Consistent communication regarding the specific assay used and testing units is vital, particularly in institutions and health care systems that use multiple cTn assays or receive transfers from external institutions. When transitioning to high-sensitivity assays, the Writing Group suggests teaching clinicians how to "translate" previous conventional cTn results to the newer hs-cTn method being implemented, because harmony is often not perfect between conventional and high-sensitivity assays.

- *Which 99th percentile URL should be used?* The 99th percentile URLs for hs-cTnI or T are assay and population dependent but are nonetheless relatively portable. Institutions must consider either sex-independent 99th percentile URLs or sex-based cutoff values (which typically have lower threshold values for women than for men). Effects of sex on troponin concentrations are much smaller than those of age, presence of kidney disease or heart failure (HF), or duration since chest discomfort onset; however, they are nonetheless important. The Writing Group recognizes the increased complexity and potentially controversial nature of this issue; however, given the influence of sex on 99th percentile decision limits for hs-cTn, use of sex-specific cutoffs is reasonable, as recommended by the Fourth Universal Definition of MI (8). More data are needed to provide further clarity on this topic.

CLINICAL CONSIDERATIONS

Before institutional transition to hs-cTn testing, it is important to establish core concepts regarding troponin and how hs-cTn methods differ in terms of deployment and interpretation. The Writing Group

has provided consensus knowledge regarding important topics for clinician education.

TROPONIN AND ACUTE MI. The Fourth Joint European Society of Cardiology/American College of Cardiology/American Heart Association/World Heart Foundation Task Force for the Universal Definition of MI (8) has provided accepted criteria for diagnosis of acute MI (AMI): the diagnosis is made based on a rise or fall of troponin I or T, with at least 1 measurement exceeding the 99th percentile of a normal population (indicating the presence of myocardial injury), in the context of reasonable suspicion for coronary ischemia (e.g., typical symptoms, changes on electrocardiography, evidence for loss of myocardial function, or demonstration of obstructive coronary artery disease). Henceforth in this document, an hs-cTn concentration exceeding the 99th percentile of a normal population will be referred to as elevated or abnormal. Although changes below the 99th percentile may reveal acute coronary events, use of such lower concentrations is not yet endorsed by the Fourth Universal Definition of MI.

If AMI is diagnosed, it can be classified into 1 of 5 different types (Online Table 2); type 1 and type 2 MI are most commonly encountered. However, a central tenet articulated by the Universal Definition of MI is that although abnormal hs-cTn values reflect injury to myocardial cells, an elevated hs-cTn does not indicate the underlying cause of injury. AMI is an important cause of troponin release; however, clinicians are cautioned that many other processes can lead to myocardial injury and troponin elevation in the absence of AMI (**Table 1**). In some cases, this myocardial injury is chronic and relatively static, such that hs-cTn values remain elevated but do not change substantially over hours to days. In contrast, acute myocardial injury typically causes a changing pattern of hs-cTn values and might be due to ischemic or nonischemic causes. The Fourth Universal Definition of MI provides for the diagnosis of acute or chronic myocardial injury when at least 1 hs-cTn value is above the 99th percentile URL. The myocardial injury is considered acute if there is a rise or fall of cTn values. The diagnosis of MI, including type 2 MI, requires clinical evidence of myocardial ischemia. If there is no evidence to support the presence of myocardial ischemia, a diagnosis of myocardial injury should be made.

Therefore:

1. An abnormal hs-cTn is central to the diagnosis of AMI, but MI is a clinical diagnosis that is not defined by troponin alone. To diagnose an AMI,

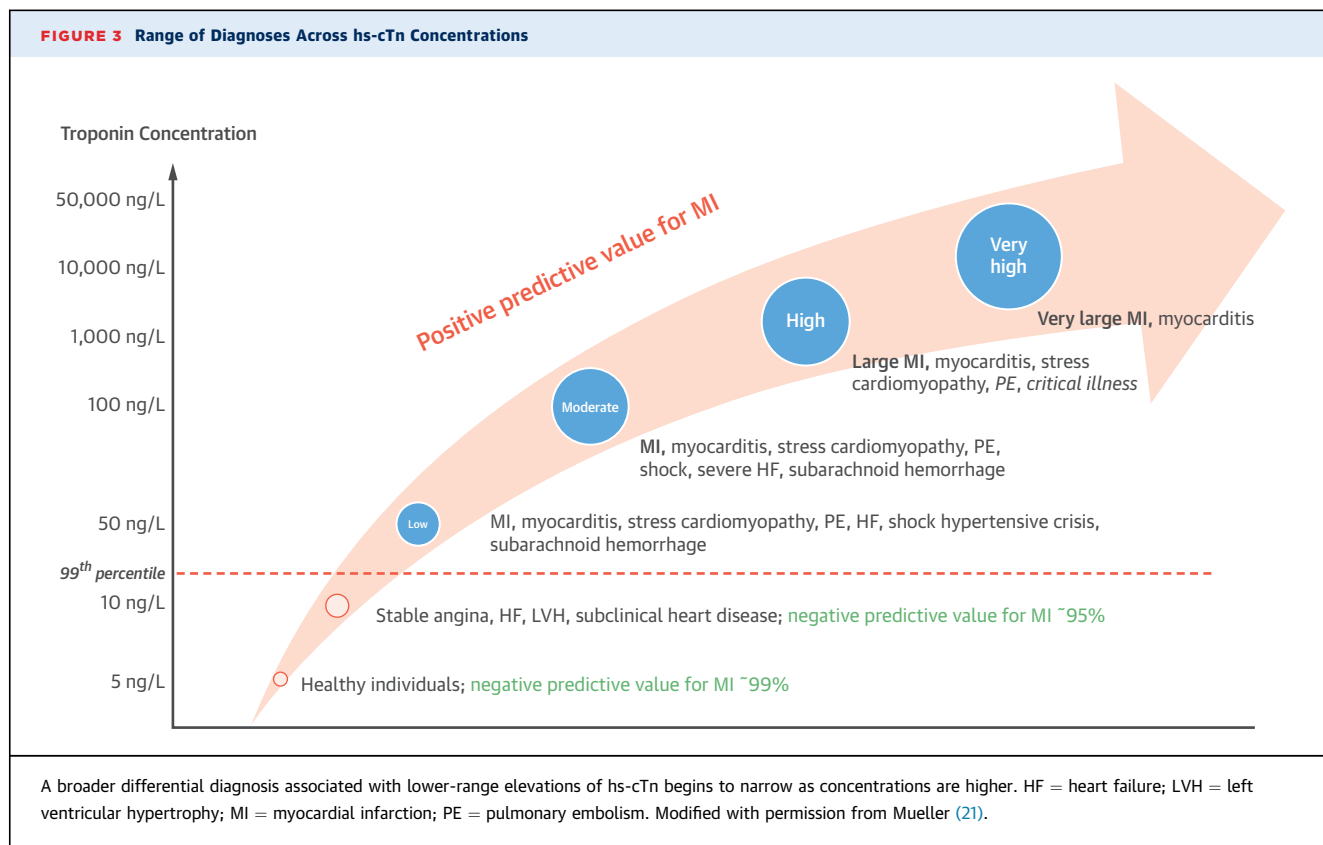| TABLE 1 Differential Diagnosis for an Elevated hs-cTn Result |
|---|
| **Injury related to primary myocardial ischemia** |
| Plaque rupture |
| Intraluminal thrombus |
| **Injury related to myocardial oxygen supply/demand imbalance** |
| Tachy/bradyarrhythmias |
| Aortic dissection or severe aortic valve disease |
| Hypertrophic cardiomyopathy |
| Cardiogenic, hypovolemic, or septic shock |
| Severe respiratory failure |
| Severe anemia |
| Hypertension with or without left ventricular hypertrophy |
| Coronary endothelial dysfunction, spasm, or dissection |
| **Injury not related to myocardial ischemia** |
| Cardiac contusion, surgery, ablation, pacing or defibrillation |
| Rhabdomyolysis with cardiac involvement |
| Myocarditis |
| Cardiotoxic agents (e.g., anthracyclines, Herceptin) |
| **Multifactorial or indeterminate myocardial injury** |
| Heart failure |
| Stress cardiomyopathy |
| Pulmonary embolism |
| Pulmonary hypertension |
| Sepsis |
| Critical illness |
| Renal failure |
| Severe acute neurological disease (e.g., stroke, subarachnoid hemorrhage) |
| Infiltrative cardiomyopathies (e.g., amyloidosis, sarcoidosis) |
| Strenuous exercise |

A key knowledge point is an elevated hs-cTn identifies the presence of myocardial injury but not the mechanism.

hs-cTn = high-sensitivity cardiac troponin.

evidence of myocardial ischemia is required. An elevated hs-cTnI or T without other corroborating evidence is not sufficient for a diagnosis of AMI, even if a rise or fall is detected.

2. Changes in hs-cTn are critically important to identify acute myocardial injury, which in the context of acute myocardial ischemia may qualify for AMI. When determining whether there has been a rise or fall of troponin on serial sampling, absolute change in troponin concentration has greater diagnostic accuracy for AMI than relative change criteria (13). The changes may be a rise or a fall depending on the timing of the event and its evaluation; however, the clinical significance is identical. Clinicians should be aware that the rise in troponin concentration as detected by an hs-cTn assay can be faster than the fall in values, whose reduction are in part related to vessel patency or size of MI.

The cutoff quantity for defining a rise or fall must be determined for each individual troponin assay. One approach for interpretation at lower values suggests that a change threshold be set at 50% to 80% of the baseline concentration (which comports to the sum of analytic and biological

FIGURE 3   Range of Diagnoses Across hs-cTn Concentrations

A broader differential diagnosis associated with lower-range elevations of hs-cTn begins to narrow as concentrations are higher. HF = heart failure; LVH = left ventricular hypertrophy; MI = myocardial infarction; PE = pulmonary embolism. Modified with permission from Mueller (21).

variation) (12). For example, for hs-cTnT, a change of 7 ng/l from a baseline of 14 ng/l would be significant (13,14). Present data and the Universal Definition of MI (8) suggest that the use of absolute values rather than percentages provides better diagnostic information (13). We endorse that approach.

Serial testing becomes even more important in patients with chronic comorbid conditions, such as the elderly and those with chronic kidney disease (CKD) (15) or HF. In patients with CKD, a recent study suggested both a relative and absolute change in hs-cTnT concentration improved diagnostic accuracy for AMI over admission values (area under the curve: 0.90; 95% confidence interval [CI]: 0.82 to 0.96; p < 0.001 for relative change vs. 0.68; 95% CI: 0.62 to 0.74; p < 0.001 for admission concentration, and 0.88 [95% CI: 0.82 to 0.94; p < 0.001] for absolute change vs. 0.68 [95% CI: 0.62 to 0.74; p < 0.001] for admission level, respectively) (16). However, no hs-cTnI or T change criteria have perfect sensitivity and specificity for AMI, and thus, clinician judgment remains essential to confirm or refute the diagnosis. In general, with lower change criteria, sensitivity is higher and specificity is lower.

3. The "differential diagnosis" of abnormal hs-cTn is broad at lower concentrations. With higher values, the differential diagnosis narrows (**Figure 3**). Although a rise or fall in troponin concentration suggests acuity, it is not etiologically specific. Rising or falling hs-cTn patterns result from a variety of underlying conditions, including pulmonary embolus, myocarditis, or sepsis, as well as AMI. The absolute baseline concentration, as well as the change in hs-cTn, is often one indication of whether an AMI has occurred versus another disease state (17,18). For instance, when type 1 MI has occurred, it is common to see rapid and substantial increases in hs-cTn over a few hours (19). Fewer things mimic such magnitude of increase; however, acute myocarditis can also cause large rises in hs-cTn, with a distribution that overlaps with that for type 1 MI, as can systemic inflammatory response syndromes, such as that associated with sepsis. Chronic cardiac disease and many type 2 MIs will demonstrate both lower baseline hs-cTn concentrations and smaller changes in hs-cTn over the first few hours (20). It is imperative that

clinicians perform a thorough evaluation, including consideration of the clinical syndrome that prompted ordering the hs-cTn test, and maintain a broad differential diagnosis when evaluating hs-cTn rise or fall. The clinician might need to use several tools to make or exclude the final diagnosis of AMI. If, for instance, the patient has a rise or fall of hs-cTn that exceeds the 99th percentile but the results of coronary angiography or stress testing are normal, other studies, including an echocardiogram, pulmonary embolism evaluation, or cardiac magnetic resonance imaging, might be considered based on the patient's clinical presentation. Recognition of acute or chronic myocardial injury attributable to conditions other than MI (e.g., pulmonary embolism, myocarditis, severe valvular heart disease, atrial fibrillation, and acute HF) can also aid in risk stratification and, in some cases, therapeutic decision making (e.g., pulmonary embolism) (8,21).

4. There are many reasons why patients might have chronic hs-cTn elevations above the 99th percentile. Chronic troponin elevation is a common finding when hs-cTn tests are used and can be associated with presence of comorbidities such as CKD, diabetes mellitus, significant left ventricular hypertrophy, HF, and other causes. To be explicitly clear, such injury is a valid finding and should not be considered a false positive. Myocardial injury outside that occurring in the setting of AMI can create diagnostic challenges but should not be discarded as a nuisance abnormality, because it is associated with a poor cardiovascular prognosis. Colloquialisms such as "troponin leak," "troponinemia," or "troponinitis" are unadvisable because such terms trivialize the prognostic meaning of myocardial injury.

USE OF hs-cTn TESTING IN THE ED. Troponin testing is commonly used to diagnose or exclude AMI in patients presenting to the ED with symptoms compatible with acute coronary syndrome (ACS). This is a common ED presentation and a frequent reason for further evaluations (22). However, the prevalence of AMI among such patients ranges as low as 5% to 20% (23-25). Given the low prevalence of disease and the growing problem of ED and hospital crowding, there is a need to safely increase the efficiency and rapidity of evaluations for ACS. Accelerated diagnostic protocols (ADPs) that allow ACS to be quickly excluded (ruled out) and identified (ruled in) could improve health care system resource utilization. ADPs should not only have a high sensitivity and negative predictive value (NPV)

for MI but should also identify patients at low risk for cardiac complications post-discharge to be considered safe. The optimal use of a given score may be dependent on the population seen in a given facility.

ADPs have been implemented successfully in other countries, but some may be concerned about the acceptable miss rate, especially in the litigious society of the United States. An international survey asked emergency physicians to state the acceptable risk of a patient developing a major adverse cardiac event within 30 days. Only approximately 40% would accept a risk of 1% or more, which suggests a high degree of risk aversion. However, Australian emergency physicians were considerably more risk averse than those in North America (26), which does not necessarily suggest that ADPs will be less successful in the United States.

Analytical characteristics of hs-cTn assays have opened new possibilities for ADPs, including single-measurement protocols and more rapid serial measurement approaches with the time interval between serial samples reduced.

EXCLUDING AMI WITH A SINGLE BLOOD TEST. Evidence from multiple observational studies suggests that when using a cutoff set at the LoD, a single blood test could be sufficient to rule out the diagnosis of AMI in a sizable proportion of patients presenting to the ED. Multiple studies have now demonstrated that a cutoff set at the LoD of the hs-cTnT assay (5 ng/l) achieves very high NPV for AMI, especially among patients with no ischemia on an electrocardiogram (ECG) (27,28). Similarly, a cutoff set at the LoD of the Abbott ARCHITECT hs-cTnI assay (1.2 ng/l) has a sensitivity of 99.0% for MI with 99.5% NPV, although a more liberal cutoff set at 5 ng/l was shown to have only 94.5% sensitivity (29). However, the incidence of other major cardiovascular events has not always been presented. In some studies, the number of patients presenting early after symptom onset has been limited, and the NPV could be lower in these patients (30,31). Subsequent studies have substantiated these data for most hs-cTn assays, although data on the incidence of other major cardiovascular events have not always been presented. Thus, at present, the use of this diagnostic strategy is recommended only in patients who present >3 h after symptom onset.

Problematically, the U.S. Food and Drug Administration approved the use of the hs-cTnT assay but has restricted the reporting of results to concentrations of 6 ng/l (LoQ) or greater. Therefore, the single-test hs-cTnT strategy in its widely reported form

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TABLE 2 Summary of hs-cTn Rapid Rule-Out and Rule-In Accelerated Diagnostic Panels

	0/3h	High STEACS	0/2h	0/1h
Rule-out criteria				
hs-cTnT	<14 ng/l at 0 and 3 h* and GRACE score <140	NA	<14 ng/l at 0 and 2 h and Δ <4 ng/l	<12 ng/l at 0 and 1 h Δ <3 ng/l
hs-cTnI†	<26 ng/l at 0 and 3 h* and GRACE score <140	<5 ng/l at 0 h or a 3-h value: <16 ng/l in women <34 ng/l in men and Δ <3 ng/l	<6 ng/l at 0 and 2 h and Δ <2 ng/l	<5 ng/l at 0 and 1 h Δ <2 ng/l
NPV for MI	98.3%–100%	99.5%	99.4%– 99.9%	98.9%–100%
Sensitivity for MI	98.9%–100%	97.7%	96.0%–99.6%	96.7%–100%
Proportion ruled out	39.8%–49.1%	74.2%	56.0%–77.8%	47.9%–64.2%
Rule-in criteria				
hs-cTnT	>14 ng/l at 0 or 3 h	N.A.	≥53 ng/l at 0 h or ≥10 ng/l Δ at 2 h	≥52 ng/l at 0 h or 1 h Δ ≥ 5 ng/l
hs-cTnI	>26 ng/l at 0 or 3 h	>16 ng/l in women >34 ng/l in men at 0 or 3 h	≥64 ng/l at 0 h or ≥15 ng/l Δ at 2 h	≥52 ng/l at 0 h or 1 h Δ ≥ 6 ng/l
PPV for MI	72.0%–83.5%	59.5%	75.8%–85.0%	63.4%–84.0%
Specificity for MI	96.7%–98.2%	87.6%	95.2%–99.0%	93.8%–97%
Proportion ruled-in	9.7%%–38.2%	22.0%	7.7%–16.7%	13.1%–23.0%

*In patients with ≥6 h of pain, only a single value below this threshold is required. †Abbott ARCHITECT hs-cTnI.

0/1h = accelerated diagnostic protocol to rule out MI in patients presenting >3 h from symptoms using a single hs-cTn measurement at presentation, whereas for other patients, an absolute hs-cTn at presentation and 1-h delta are used to rule out or rule in MI or to place patients in an observational zone; 0/2h = accelerated diagnostic protocol that uses maximal levels and absolute delta hs-cTnI or T concentrations at 0 and 2 h to rule out or rule in MI or place patients in an observational zone; 0/3h = accelerated diagnostic protocol that incorporates hs-cTn at 0 and 3 h, hs-cTn change, and time since pain onset to determine which patients are appropriate for discharge or stress testing versus invasive management; GRACE = Global Registry of Acute Coronary Events; High STEACS = High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; MI = myocardial infarction; NA = not applicable; NPV = negative predictive value; PPV = positive predictive value.

(cutoff 3 ng/l) cannot be used in the United States. To date, 2 studies have evaluated diagnostic accuracy at the 6 ng/l hs-cTnT cutoff (32,33). Although the sensitivity to exclude AMI and the NPV are high at the LoQ concentration, a larger body of evidence will be required before a recommendation for the routine use of this cutoff can be endorsed.

ACCELERATED DIAGNOSTIC PROTOCOLS. Protocols to rapidly exclude MI should have a high sensitivity and NPV to be clinically useful. They should also identify patients at low risk for cardiac complications post-discharge to be considered safe.

ADPs are care algorithms that combine clinical data to stratify ED patients with symptoms of possible myocardial ischemia according to risk and determine their disposition. There are 3 categories of ADPs: 1) rapid rule-out strategies, developed on the basis of assay-specific hs-cTn cutpoints and change values (deltas); 2) ADPs that incorporate a risk score or decision aid and focus on prediction of adverse cardiac events over a relatively short time horizon (e.g., 30 days); and 3) a combination of the two. Commonly used decision aids include the TIMI (Thrombolysis In Myocardial Infarction) and GRACE (Global Registry of Acute Coronary Events) risk scores, which were derived and validated among patients with ACS, and newer aids, including ADAPT (2-h Accelerated Diagnostic Protocol to Assess Patients With Chest Pain

Symptoms), the HEART (History, ECG, Age, Risk Factors, and Troponin) score and pathway, T-MACS (Troponin-only Manchester Acute Coronary Syndromes), and EDACS (Emergency Department Assessment of Chest Pain Score), derived and validated in ED patients with undifferentiated chest pain. These scores predict various outcomes; for example, the TIMI and GRACE scores predict risk for subsequent mortality, whereas newer aids predict risk for prevalent or incident major adverse cardiovascular events. The ADAPT score predicts risk for MI, emergency revascularization, death, ventricular arrhythmia, cardiac arrest, cardiogenic shock, or high-degree atrioventricular block, whereas the HEART score predicts all-cause mortality, MI, or coronary revascularization. T-MACS predicts risk for MI or incident death, or coronary revascularization, and EDACS was developed to predict risk for MI, emergency revascularization, death from cardiovascular causes, ventricular arrhythmia, cardiac arrest, cardiogenic shock, or high-degree atrioventricular block. The optimal use of a given score may be dependent on the population seen in a given facility and on which outcomes are to be predicted.

TROPONIN-ONLY ADPs. Other troponin-only ADPs use serial troponin testing over 1 to 3 h. Changes in hs-cTnI or T concentrations used in various troponin-only ADPs are summarized in **Table 2**.

TABLE 3 The HEART Score for Evaluation of Patients With Suspected Acute Coronary Ischemia

Variables	Points
History	
Highly suspicious	2
Moderately suspicious	1
Slightly suspicious	0
ECG	
Significant ST-segment depression	2
Nonspecific abnormalities	1
Normal	0
Age, yrs	
>65	2
45–65	1
<45	0
Risk factors	
3 or more risk factors	2
1 or 2 risk factors	1
No risk factors	0
Troponin	
>3 × normal limit	2
1–3 × normal limit	1
≥ Normal limit	0
Total	Range 0–10

Low risk is 0 to 3 points, moderate risk 4 to 6 points, and high risk ≥7 points.
ECG = electrocardiogram; HEART = history, ECG, age, risk factors, and troponin.

The High STEACS (High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome) pathway uses hs-cTn measures at presentation and 3 h to identify a low-risk group and can provide NPV >99% for 30-day cardiac death or MI. However, among early presenters (< 2 h from symptom onset), NPV drops to 97.6% (10). In a recent validation study, the High STEACS pathway excluded MI in 40.7% at presentation and a total of 74.2% at 3 h with 99.5% NPV for 30-day cardiac death or MI (31). Use of the GRACE score in combination with the High STEACS pathway was associated with an incremental increase in NPV (99.7%) (10,31).

The 0/2h ADP uses maximal levels and absolute delta hs-cTnI or T concentrations at 0 and 2 h to rule out or rule in MI or place patients in an observational zone. In the derivation and validation cohorts, 60% and 78% of patients, respectively, were ruled out, with NPVs for MI approaching 100% (32,34). Compared with ADAPT, the 0/2h algorithm (using either hs-cTnT or I) ruled out 18% to 27% more patients while producing a similar NPV (≥ 99%) for MI (35). In a Canadian cohort (N = 722), the 0/2h hs-cTnT algorithm was 98.7% and 97.6% sensitive to exclude 7-day and 30-day MI, respectively (36).

The 0/1h ADP rapid rule-out strategy is endorsed as an alternative to the 0/3h algorithm by the 2015
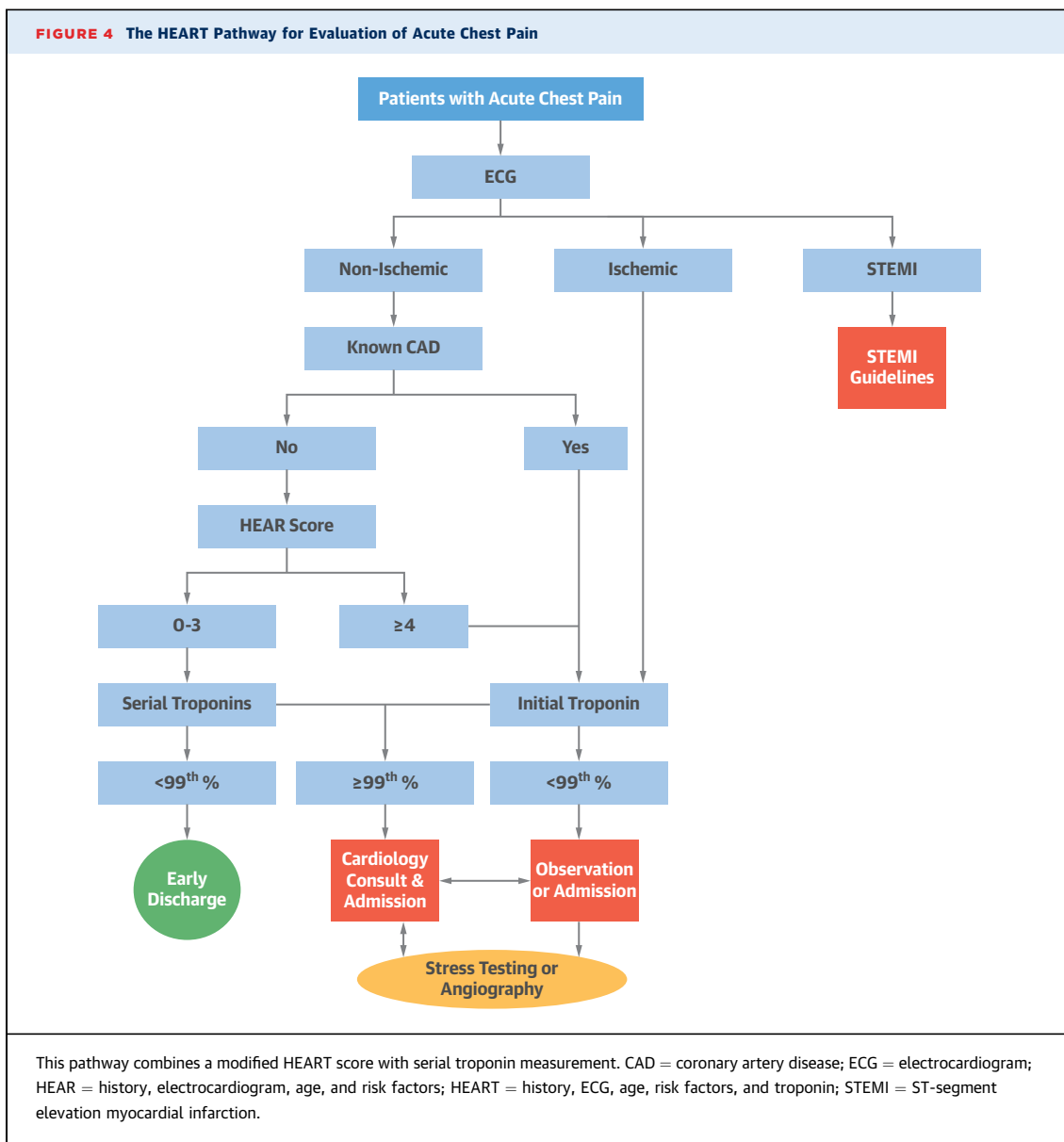
European Society of Cardiology guidelines (37). With this approach, MI in patients with > 3 h of symptoms can be ruled out using a single hs-cTn measurement at presentation. In other patients, an absolute hs-cTn at presentation and 1-h delta is used to rule out or rule in MI or to place patients in an observational zone. The approach ruled out 60% of patients with 100% sensitivity and NPV for MI (38). This was validated in separate cohorts with 99.1% to 100% NPV (37,39-41) in studies examining both hs-cTnT and hs-cTnI. Recent analyses suggest this ADP maintains a high NPV for MI among elderly patients and early presenters (42,43).

Although these studies provide a body of evidence supporting rapid rule-out ADPs, some have questioned their generalizability (44). Another limitation is that guidelines recommend using these ADPs in conjunction with all available clinical data, such as the patient's ECG and historical data, but no specific guidance is given regarding how to incorporate these data into the algorithm. Finally, studies evaluating the 0/1h and other rapid rule-out algorithms have been largely observational.

An important caveat that is often missed with rapid protocols is that patients who are on the downslope of the time-concentration curve (which often moves more slowly than the upslope) might not manifest a falling pattern over short periods of time. Thus, in patients in whom the index of suspicion is high and the initial values are increased without a clear cause, a later sample can be informative; in some series, up to 26% of patients with AMI may fit into this category (45).

ADPs INCORPORATING A RISK SCORE/DECISION AID WITH TROPONIN TESTING. The 0/3h ADP incorporates hs-cTn at 0 and 3 h, hs-cTn change, and time since pain onset (24) to determine which patients are appropriate for discharge or stress testing versus invasive management. In an observational study of 2,727 patients with possible ACS, the 0/3h ADP had an NPV > 99.5% for MI among early (<6 h since pain onset) and late (≥6 h) presenters (46,47). Use of the 0/3h ADP was associated with an increase in outpatient management of patients, reduction in stress testing rates, and decreased length of stay compared with usual care with contemporary cTn measures (27). However, 2 analyses evaluating this algorithm found it might be insufficiently sensitive for MI (30,31).

The TIMI risk score for non–ST-segment elevation ACS is frequently used for early risk stratification in the ED (48). It is insufficiently sensitive to be used alone with a single hs-cTn measurement (49,50). Combining a TIMI score of 0 with hs-cTnT or I less

FIGURE 4 The HEART Pathway for Evaluation of Acute Chest Pain

This pathway combines a modified HEART score with serial troponin measurement. CAD = coronary artery disease; ECG = electrocardiogram; HEAR = history, electrocardiogram, age, and risk factors; HEART = history, ECG, age, risk factors, and troponin; STEMI = ST-segment elevation myocardial infarction.

than or equal to the LoD yielded sensitivities of 99.5% and 98.9%, respectively, for 30-day events but identified just 17.9% and 21% as low risk (51).

ADAPT combines a TIMI score of 0, a nonischemic ECG, and negative serial troponin measures at 0 and 2 h to identify low-risk patients. In an observational study, ADAPT ruled out MI in 20% of patients, with 99.7% sensitivity and 99.7% NPV for 30-day adverse cardiac events (52). In a North American retrospective validation (N = 1,140), ADAPT had a sensitivity of 83% and NPV of 99.1% for major adverse cardiac events (53). However, in a randomized trial, ADAPT increased the early discharge rate by only 8.3% (54). ADAPT has been validated for use with hs-cTn (22,54).

With hs-cTn assays, patients with a TIMI score <2 can be discharged while maintaining sensitivity (at 100% and 97.4% in 2 respective cohorts). This approach identifies more patients as low risk (34.5% and 40.3%, respectively) (25).

The HEART score (**Table 3**) has 5 factors: history, ECG, age, risk factors, and troponin, with each scored 0, 1, or 2, making the scoring system easy to remember without a computer (55). Meta-analysis of 12 studies (N = 11,217) found that HEART had a pooled sensitivity of 96.7% for major adverse cardiac events (56), which might be considered unacceptable to clinicians (26). Limitations of the HEART score include the subjective nature of the history and that patients

TABLE 4 Simplified Checklist for the Single-Test Acute Coronary Syndrome Rule Out Using the T-MACS Accelerated Diagnostic Protocol

Variable	Score
Visible sweating	1 point
Systolic blood pressure <100 mm Hg	1 point
Pain radiation to the right arm or right shoulder	1 point
Chest discomfort associated with vomiting	1 point
Worsening angina	1 point
Acute ischemia on electrocardiogram	1 point
cTn > 9 ng/l*	1 point
Total	Range 0–7

Those with 0 points are eligible for immediate discharge. *Currently validated for use with the Siemens hs-cTnI and Roche hs-cTnT assays.

T-MACS = Troponin-only Manchester Acute Coronary Syndromes; other abbreviations as in **Tables 1 and 2**.

TABLE 5 EDACS Accelerated Diagnostic Protocol

Variable	Score
Age, yrs	
18–45	2
46–50	4
51–55	6
56–60	8
61–65	10
66–70	12
71–75	14
76–80	16
81–85	18
≥86	20
Male sex	6
Known CAD or ≥ 3 risk factors	4
Diaphoresis	3
Radiates to arm or shoulder	5
Pain occurred or worsened with inspiration	−4
Pain is reproducible with palpation	−6
Total	Range −4 to +28

Low-risk patients meet all criteria: score <16, normal electrocardiogram, and negative serial high-sensitivity cardiac troponin.

CAD = coronary artery disease; EDACS = Emergency Department Assessment of Chest Pain Score.

with troponin elevations or acute ischemic ECGs can have low-risk scores.

The HEART Pathway (**Figure 4**) combines a modified HEART score with serial troponin measurements and improves sensitivity and NPV of the basic HEART score [57]. For a patient to be considered low risk and eligible for early discharge, the HEART Pathway requires a history, electrocardiogram, age, and risk factors (HEAR) score of 0 to 3, a nonischemic ECG, no prior coronary artery disease events, and negative serial troponins. In a recent prospective study, the HEART Pathway identified 30.7% of patients as low risk with an NPV of 99.6% for 30-day death or MI [58].

The T-MACS decision aid (**Table 4**) is a single-test ADP that calculates probability of ACS using elements of the history, physical examination, ECG ischemia, and cTn concentration measured at the time of arrival in the ED. On prospective validation (N = 1,459), T-MACS had 99.3% NPV and 98.1% sensitivity, ruling out ACS in 40.4% of patients. T-MACS also rules in ACS with over 90% positive predictive value [59]. Use of T-MACS increased safe early discharges in a pilot randomized controlled trial (26% vs. 8% for control, p = 0.004) [44] and has been validated with hs-cTnT and cTnI [60].

The EDACS ADP (**Table 5**) incorporates a risk score, 0 and 2 h cTn results, and ECG findings. In derivation studies, EDACS classified 42% to 51% of ED patients as low risk for 30-day events, with a sensitivity ≥99% [61]. Validation results had sensitivities of 100% and 88% for 30-day events in Canadian (N = 763) and U.S. (N = 282) cohorts [62,63]. A study from Australia and New Zealand (N = 2536) found that an EDACS score <16 combined with an initial hs-cTnI <7.0 ng/l or hs-cTnT <8.3 ng/l classified approximately 30% as low risk, with sensitivities for 30-day events of 98.5%

and 98.7% [51]; use of EDACS with hs-cTn at 5 hospitals was associated with increased early discharge rates and a high NPV [64].

USING hs-cTn TO GUIDE APPLICATION OF NONINVASIVE TESTING. Stress testing and coronary computed tomography angiography are recommended by guidelines to exclude myocardial ischemia or obstructive coronary artery disease among patients with acute chest pain [65]. This paradigm is associated with overtesting, a low yield of true positive findings, ED and observation unit overcrowding, radiation exposure, and high cost [66-68]. Although it is possible that introduction of more sensitive assays for cTn might increase the use of additional noninvasive or invasive evaluation for ischemia, experience with implementation of hs-cTn using hs-cTn ADPs in Europe has reduced the rates of noninvasive testing and overall cost, without an increase in the use of invasive angiography [20,27]. Recent interest has focused on use of hs-cTn together with imaging. Ferencik et al. [69] proposed an approach designed to identify patients suitable for noninvasive testing: patients did not require imaging if they had <2 traditional cardiovascular risk factors and a baseline hs-cTnI <4 ng/l or a second hs-cTnI with 0% relative change. This ADP identified 34% of patients as not requiring noninvasive testing with 100% NPV for index visit ACS [69]. Additional prospective evaluations are needed before clinical use.

FIGURE 5   A Stepwise Approach for the Consultant to Confront Unexpectedly Abnormal hs-cTn Concentrations

1   What is the pre-test probability for MI based on chest pain onset, signs and ECG findings?
E.g., typical pain, CPO 2h, ST-segment ↓ (resulting in a PPV for MI ≈ 90%)

2   Does my patient have a readily identifiable non-MI cause for low level cTn elevations?
E.g., age, heart failure, aortic stenosis, pulmonary embolism.
The more plausible the alternative cause for low level cTn elevations, the less likely that any immediate further diagnostic work-up for MI is justified and/or necessary.

3   What other diagnostic test is useful?
1h/3h cTn re-measurement, echo, stress-echo, CMR, MPI-SPECT.

Considerations include pre-test probability for MI, timing of chest pain onset (CPO), presence of other diagnostic abnormalities that can increase positive predictive value (PPV) for MI, as well as judicious use of other diagnostic tests such as imaging. CMR = cardiac magnetic resonance; echo = echocardiography; MPI-SPECT = myocardial perfusion imaging-single photon emission computed tomography; other abbreviations as in Figures 1, 3, and 4.

CLINICAL OUTCOMES. Although the use of hs-cTn–based ADPs can improve diagnostic accuracy, increase outpatient versus inpatient management of patients with suspected MI, and decrease length of stay compared with usual care with conventional cTn, it remains uncertain as to whether implementation of hs-cTn testing in the ED can reduce the rate of major cardiovascular events in this population. An important nonrandomized study using conventional cTn demonstrated an association between implementation of URLs at or near the 99th percentile and a lower rate of recurrent MI or death (4,5). However, in a stepped-wedge, cluster-randomized controlled trial of implementation of an hs-cTnI assay in Scotland, overall reclassification of myocardial injury or infarction (not identified by a conventional assay) occurred in only ~4% of consecutive patients admitted to the EDs with suspected ACS; hs-cTnI testing reduced length of stay but did not reduce an endpoint of cardiovascular death or MI at 1 year (70).

TESTING OUTSIDE OF THE ED

Understanding of hs-cTn is necessary when measured outside the ED, including in hospital inpatients with signs or symptoms of coronary ischemia and in those found to have an elevated hs-cTn in the context of medical illness, patients with possible MI after noncardiac surgery, and those with possible MI after coronary revascularization. Additionally, questions are commonly asked about the possible utility of hs-cTn testing for patients encountered in the outpatient setting. The concepts articulated for ED-based testing still hold outside of the more urgent setting; however, some special considerations do exist.

INPATIENT TESTING FOR PATIENTS WITH SUSPECTED MI. A frequent inpatient cardiology consultation might involve evaluation and management of acutely ill patients who have an elevated troponin identified either because of the development of ischemic signs or symptoms or for other reasons. There are similarities between those patients seen with suspected MI in the ED and those who develop acute symptoms during an inpatient hospital stay. Thus, many of the factors that determine the clinical specificity of hs-cTn for diagnosis of MI, such as advanced CKD, are in play in hospitalized patients as well. Moreover, the prevalence of such factors is even higher than in ED patients, which results in more frequent elevations of hs-cTn. Furthermore, the time from symptom or sign onset to recognition and evaluation may be slower among hospitalized patients.

The consultant called to evaluate an elevated hs-cTn result should consider both the clinical scenario and the confounding conditions that can result in baseline elevations in hs-cTn (Figure 5). Taking advantage of the magnitude of the hs-cTn elevation and information on change in concentration during serial testing, as described in previous sections, will assist the consultant with formulating recommendations.

Given the potential for a falsely low hs-cTn concentration if measured too soon after onset of symptoms, for evaluation of hospitalized patients, a baseline-3 h sampling protocol is prudent to evaluate for possible AMI.

hs-cTn TESTING AFTER NONCARDIAC SURGERY.
Perioperative cardiovascular events are a major cause of morbidity and mortality among patients undergoing noncardiac surgery (71). Although conventional cTn assays might not often detect cardiac injury in the post-operative setting, hs-cTn measurement often reveals a surprisingly high incidence of post-operative cardiac injury, and such injury is of prognostic importance. For example, in one study, approximately 35% of patients had post-operative hs-cTnT concentrations above the 99th percentile value of 14 ng/l (72). Thirty-day mortality for patients with values <14 ng/l was .01% to .05%; with mild elevations (14 to 20 ng/l), it was 1.1%; with values 21 to 64 ng/l, it was 3.0%; for values from 65 to 999 ng/l, it was 9.1%; and for values ≥1,000 ng/l, it was 29.6%. The investigators also found the larger the change from baseline, the worse the prognosis (72). Besides AMI, it is reasonable to assume multiple causes of troponin elevation (such as pulmonary embolism, HF, sepsis) were present: only 7% of patients in this study acknowledged ischemic symptoms, and the ECGs were often not informative (72). Among those thought to have AMI, most were assumed to be type 2 MIs (73,74); however, it has been noted in small studies that 50% of the events that lead to mortality are plaque rupture events (75).

When confronted with an elevated hs-cTnI or T concentration after noncardiac surgery, to avoid misdiagnosis of MI, clinicians must incorporate the entire clinical picture into decision making, while not underestimating the importance of a modest to larger rise in hs-cTn concentration. Many have recommended a baseline, pre-operative sample in patients deemed at risk to facilitate interpretation (8).

MEASUREMENT AFTER PERCUTANEOUS CORONARY INTERVENTION. It is common to detect increase in troponin concentration after percutaneous coronary intervention (PCI); this is more common when using hs-cTn assays. Often the rise in troponin occurs absent an obvious complication such as a type 4 MI. Unfortunately, given heavy reliance on biomarker testing to identify such periprocedural MI events, concerns regarding overdiagnosis of post-PCI MI has led many institutions to measure creatine kinase-MB as the gold standard biomarker for post-PCI surveillance. With thoughtful deployment, however, there is no reason why hs-cTn might not be used for this indication.

There are important considerations when measuring hs-cTn after PCI. Knowledge of the pre-PCI troponin concentration and of whether the marker was rising before PCI is important, because a continued positive delta is expected for those with rising concentration before the procedure. On the basis of the Universal Definition of MI, criteria for a type 4A MI include elevation of cardiac troponin values >5 times the 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cardiac troponin values >20% if the baseline values were elevated and are stable or falling (8). However, abnormal hs-cTn alone is not diagnostic of a type 4A MI, because the definition requires: 1) new ischemic ECG changes; 2) angiographic findings consistent with a procedural flow-limiting complication; or 3) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality. Without one of these major criteria, a PCI-related MI cannot be reliably diagnosed.

CONFOUNDING VARIABLES AND DIAGNOSES.
Chronic diseases such as CKD or HF can be associated with elevated background concentrations of hs-cTn. Thus, assessment of acute symptoms in affected patients can be challenging. Although detection of chronic myocardial injury identifies a patient at higher risk, a standard approach for evaluation of such patients remains undefined.

Chronic kidney disease. Patients with CKD and end-stage renal disease (ESRD) have high mortality rates. Cardiovascular disease is the predominant cause of death in ESRD patients, accounting for 43% of all-cause mortality. Patients with advanced CKD also experience higher rates of morbidity and mortality after MI (76). Early diagnosis and invasive management have been shown to improve outcomes among patients with CKD and ESRD presenting with MI, regardless of CKD severity (77).

Interpretation of elevations of hs-cTnI or T can be difficult in patients with CKD or ESRD, because concentrations are frequently above the 99th percentile value in the absence of AMI (78). Compared with hs-cTnI, hs-cTnT concentrations above the 99th percentile were more frequent among CKD patients in the absence of AMI (68% vs. 38% of CKD patients, respectively) (78). However, it is important to emphasize that the diagnosis of AMI is not made based on a single hs-cTn value above the 99th percentile but requires a characteristic rise or fall on serial sampling. Although the more frequent elevation of hs-cTnT above the 99th percentile might create some diagnostic confusion, these elevations are prognostically relevant and must be interpreted in clinical context. As the severity of CKD progresses, baseline levels of both hs-cTnT and hs-cTnI gradually rise (79). Furthermore, interpreting hs-cTn levels in ESRD patients can be complex if they have been

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recently dialyzed. In a small study of ESRD patients, recent hemodialysis resulted in decreases in hs-cTnT by up to 10% to 12% (80). Mechanistic explanations for abnormal hs-cTn values in patients with advanced CKD include increased myocardial release secondary to underlying structural heart disease (79), along with a small contribution of decreased clearance (80). Kidney disease itself can foster myocardial injury.

Despite these issues, accurate use of hs-cTn to identify or exclude AMI in those with CKD is still possible; however, differences in optimal cutoffs might exist. A recent analysis of patients with and without kidney dysfunction with suspected ACS suggested the 99th percentile levels and optimized cutoff concentrations for various hs-cTnI and T assays were higher in those with kidney dysfunction (17). The Writing Group does not endorse specific cutoffs in those with CKD because of concerns for false negative diagnoses; however, it emphasizes that absolute changes in hs-cTnI or T concentrations during serial sampling do not differ between MI patients with and without CKD (15), which indicates the proper way to diagnose AMI relies on serial changes in such patients. A recent prospective, European multicenter study demonstrated that when using hs-cTnT in a 0/1h triage algorithm for patients with CKD, there was overall similar sensitivity of rule out but lower specificity of rule in and lower overall efficacy (81). Careful consideration of the clinical scenario and serial changes in hs-cTn concentrations are needed to successfully diagnose AMI in this population. However, although specificity and positive predictive value for AMI might be lower, potentially creating the need for additional evaluative studies or admission, it is reassuring that the sensitivity and NPV remain adequate for early rule out. We recommend that for CKD patients with a single value above algorithmic thresholds, serial testing be used to look for dynamic changes consistent with acute injury/MI. Additional studies to tailor algorithm rule-in thresholds for the available hs-cTn assays (T or I) for use in CKD patients would be a useful contribution.

Heart failure. AMI is an important cause of decompensated HF; thus, troponin measurement is recommended as a routine part of the evaluation of patients presenting with signs or symptoms of acute HF (82). Importantly, when using hs-cTn assays, concentrations above the 99th percentile cutoff are common among patients with HF, and a rise or fall can often be encountered in those with acute decompensation of HF. Though this makes diagnostic evaluation for AMI more challenging, abnormal results with hs-cTn assays are an important prognostic indicator in HF.

Abnormal cTn can occur from myocardial ischemia, myocardial stress, cardiomyocyte apoptosis and autophagy, and exosomal release of cytosolic troponin (82). Abnormal hs-cTnI or T concentrations in patients with HF predict adverse ventricular remodeling, future HF hospitalization, and death (83,84). Similar to patients with CKD, serial testing of hs-cTn concentrations can help differentiate MI from chronic hs-cTn elevations due to HF (82). Even with serial testing, it can be difficult to distinguish hs-cTn elevations due to acute myocardial stress from AMI, and type 2 MI can be difficult to exclude. Clinicians should be reminded that the criteria to diagnose a type 2 MI are similar to those for type 1 MI; a rise in hs-cTn alone should not qualify the patient for a diagnosis of MI.

EVALUATION OF PATIENTS WITH EVIDENCE OF CHRONIC MYOCARDIAL INJURY

Although elevations in hs-cTn have a useful role in predicting 1-year adverse cardiovascular outcomes in a broad range of acute and chronic diagnoses, insufficient evidence exists to recommend a standard approach to such patients. Individualized evaluation is recommended for patients found to have elevated hs-cTn in the absence of obvious acute coronary ischemia, particularly because the meaning of such elevations can vary by disease state and the specific assay being used. Such evaluation should include consideration of the broad range of medical conditions known or suspected to lead to myocardial injury (listed in **Table 1**). A cardiovascular history and physical are often all that may be needed. Diagnostic testing, including echocardiographic or magnetic resonance imaging, stress testing, or other such evaluation, might be reasonable in certain cases. Currently, there is no consensus on specific management strategies for these patients with stable elevations in hs-cTn. Although there are no specific guidelines for how to manage patients with hs-cTn elevations in the observation zone, we recommend considering the patient's HEART score to determine an immediate strategy for further evaluation. If the patient has a high-risk HEART score (7 to 10 points), stress testing or coronary computed tomography angiography or cardiology consultation could be considered before the patient is released from the ED, and a medium-risk HEART score (4 to 6 points) should prompt at least early follow-up as an outpatient with cardiology.

Beyond this, therapeutic strategies to mitigate increased risk associated with chronic myocardial

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CENTRAL ILLUSTRATION Algorithm for Transition to High-Sensitivity Cardiac Troponin Testing

Clinical Laboratory Preparation

☐ Is the Clinical Laboratory ready to provide necessary analytical education?

☐ Has an assay been selected?

☐ Was assay performance acceptable in the local Clinical Laboratory?

☐ Which 99th percentile cut-off will be used?

☐ Is the Clinical Laboratory able to process samples within a reasonable time-frame?

☐ Is the reporting of results integrated well with the electronic health record?

Emergency Department/Hospital Preparation

☐ Have there been sessions to educate clinicians regarding the transition?

☐ Will an ADP be used in the Emergency Department?

☐ What will the process be for the blood draw in the Emergency Department? Will this occur in Triage or once patient is roomed?

☐ Do clinicians understand basic concepts of how high sensitivity troponin differs from previous troponin methods?

☐ Do clinicians understand the distinction between injury and infarction?

☐ Do clinicians understand the differential diagnosis of an abnormal hs-cTn concentration?

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A careful, collaborative approach across specialties is strongly recommended.

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injury should similarly be individualized. Given the knowledge of the higher risk and poor 1-year outcomes of these patients, at a minimum, consideration of outpatient follow-up and risk assessment to identify and address any potentially modifiable risk factors seems reasonable. Recent data suggested lipid lowering might double the number of patients whose hs-cTnI fell by >25% after treatment, also reducing the risk for cardiovascular events (85). In a similar fashion, greater physical activity lowered hs-cTnT concentrations in a cohort of older adults (86).

OUTPATIENT TESTING

Clinicians occasionally measure troponin concentrations to evaluate ambulatory outpatients with subacute chest symptoms. Given the potential frequency of chronic myocardial injury (leading to a result >99th percentile), caution is advised with respect to use of single hs-cTn measurements for this application. If contemplated to evaluate patients with symptoms suspicious for ACS, serial hs-cTn measurements and an ED evaluation are advised. None of the ADPs discussed above are validated for outpatient testing.

The Writing Group is aware that clinicians may be interested in emerging applications for hs-cTn testing in stable patients (87) (Online Table 3). Epidemiological studies of hs-cTnI or T among population-based cohorts with established cardiovascular disease or risk factors have revealed associations with underlying structural heart disease and a proclivity to develop it (88,89). These findings have motivated investigations of hs-cTn as a prognostic indicator in patients with known cardiovascular diseases, such as coronary heart disease, atrial fibrillation, and valvular heart disease, as well as those potentially at risk. The recent use of hs-cTnI or T for prognostication in the outpatient setting remains nascent, and no guidance can be offered at present about implementation in the outpatient arena (90).

OVERALL RECOMMENDATIONS FOR TRANSITION TO hs-cTn TESTING

Each institution should implement a testing strategy that meets the needs of the local environment. Suggested points to consider are detailed in the **Central Illustration**.

Together with consultation from other services, members from the clinical laboratory should recommend which hs-cTn assay best fits institutional needs and should prepare to work with colleagues from other services to provide necessary education regarding how hs-cTn assays differ from conventional

versions. As above, the Writing Group recommends transition to hs-cTn for all hospital services.

For ED-based testing, current evidence supports excluding MI by use of a rapid algorithm (e.g., baseline plus 1-, 2-, or 3-h second sample) for hs-cTn alongside a validated risk score such as EDACS or HEART to identify patients suitable for early discharge. Compared with other rule-out strategies, the serial testing approach for hs-cTn is less likely to miss MI among early presenters and uses a change value that is less susceptible to assay imprecision. For patients presenting >3 h from symptom onset, a 0/1h algorithm (particularly when paired with an ADP) can provide acceptable sensitivity and NPV. For those presenting >3 h from symptom onset and with a low-risk presentation and very low hs-cTn concentration (e.g., < LoD), the single-test approach is reasonable; because evidence suggests that the single-test approach might have lower sensitivity in patients presenting <3 h from symptom onset, serial testing is still recommended in this group. The Writing Group, although cognizant of controversy, agrees with the Universal Definition of MI (8) and recommends use of sex-based 99th percentile URLs and has provided recommended values for "significant" changes of hs-cTn to be nested within the strategies used for AMI evaluation. Currently, institutions in the United States have instituted algorithms using hs-cTn; 2 are detailed in Online Figure 2A and 2B.

For inpatient testing of acute chest discomfort or other signs of myocardial ischemia, it is reasonable to use a 3-h approach, with the recognition that the rapid response for inpatients might run the potential risk of early false negative testing and that at times, there are difficulties in seeing a delayed falling pattern. In contrast to the ED setting, a substantially greater percentage of patients in the hospital setting are likely to have significant, acute comorbid medical conditions that can cause myocardial injury. Thus, clinicians should be mindful of the caveats offered in this document regarding how to approach short-term hs-cTn changes, how to differentiate long-term hs-cTn elevations, the logic regarding coronary versus noncoronary myocardial injury, and distinctions between type 1 and type 2 MI.

Although a common source of interest, information is insufficient regarding use of hs-cTn testing for stable outpatients. In outpatients with chest symptoms, a single outpatient measurement for evaluating chest discomfort is not presently supported; generally, such testing should probably be reserved for the ED environment.

EDUCATION AND IMPLEMENTATION

Given substantial differences between conventional and high-sensitivity assays for troponin measurement, the Writing Group strongly advises against conversion to hs-cTn without a gradual, phased educational process that involves all clinical services affected by this change. This effort should include an assessment of current knowledge, development of strategies for effective knowledge transfer, and ongoing efforts to ensure success (Online Figure 3). This approach is critical to avoid confusion, controversy, and potential patient harm.

Educational efforts surrounding conversion to hs-cTn should emphasize understanding of basic laboratory medicine concepts, methods for interpreting hs-cTn concentrations, and strategies for approaching confusing results. Institutions should adapt knowledge regarding hs-cTn to local context and assess barriers to use. Once an understanding of local systems of care is established, optimal approaches to tailor change of practice should be identified. Specifically, decisions regarding which strategies to use in various environments (ED, hospital-based testing) should be individualized based on local preference and involve key members from the clinical laboratory, ED, cardiology, hospital medicine, surgery, anesthesia, critical care, nursing, or other important specialties, as appropriate. Educational efforts should include didactic lectures, enduring materials (including electronic and print media and laminated cards detailing important information), and frequent reminders before launch.

The Writing Group strongly recommends against transition to hs-cTn without preparation. The collaborative educational process should take at least several weeks to months, to allow for preparation in the clinical laboratory and provide time for busy clinicians to familiarize themselves with the knowledge regarding the change.

Once implemented, knowledge use—specifically patterns of hs-cTn ordering, interpretation, and patient treatment—should be monitored and outcomes evaluated. Such ongoing evaluation with a focus on continuous quality improvement is critical to optimal deployment.

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KEY WORDS laboratory testing, myocardial infarction, troponin

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APPENDIX For supplemental tables and figures, please see the online version of this paper.