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High-Sensitivity Cardiac Troponin Assays: Ready for Prime Time!

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Abstract

Rapid and accurate triage of patients presenting with chest pain to an emergency department (ED) is critical to prevent ED overcrowding and unnecessary resource use in individuals at low risk of acute myocardial infarction (AMI) and to efficiently and effectively guide patients at high risk to definite therapy. The use of biomarkers for rule-out or rule-in of suspected AMI has evolved substantially over the last several decades. Previously well-established biomarkers have been replaced by cardiac troponin (cTn). High-sensitivity cTn (hs-cTn) assays represent the newest generation of cTn assays and offer tremendous advantages, including improved sensitivity and precision. Still, implementation of these assays in the United States lags behind several other areas of the world. Within this educational review, we discuss the evolution of biomarker testing for detection of myocardial injury, address the specifics of hs-cTn assays and their recommended use within triage algorithms, and highlight potential challenges in their use. Ultimately, we focus on implementation strategies for hs-cTn assays, as they are now clearly ready for prime time.

INTRODUCTION

For patients presenting with suspected acute coronary syndromes (ACS), a rapid and accurate diagnosis or rule-out of acute myocardial infarction (AMI) is critical to aid emergency department (ED) triage. Cardiac troponins (cTns) have become the cornerstone of biomarker-based diagnosis and have replaced previously established biomarkers, including creatine kinase (CK) and CK-MB. Recent advances gave rise to high-sensitivity cTn (hs-cTn) I and T tests, exhibiting tremendous advantages for reliable ED-based rapid rule-out and rule-in of AMI. Clinical practice guidelines in both North America and Europe uniformly recommend preferred use of hs-cTn assays for management of suspected ACS. However, while hs-cTn assays are widely implemented in Europe and other parts of the Western world, implementation in the United States lags behind, mostly due to delayed approval of the first hs-cTn assay by the US Food and Drug Administration (FDA) in 2017. Herein, we summarize the evolution of hs-cTn assays and their advantages and potential limitations, discuss clinical practice algorithms for use of hs-cTn assays, provide an overview of the current status of implementation, particularly in the United States, and highlight nontraditional areas of use.

EVOLUTION OF CARDIAC BIOMARKER TESTING AND THE DEFINITION OF ACUTE MYOCARDIAL INFARCTION

Use of biomarkers for diagnosis or rule-out of suspected AMI has evolved substantially (**Figure 1**). First came the use of aspartate aminotransferase as the first biomarker of AMI in the early 1950s, followed by total enzymatic CK activity and lactate dehydrogenase subfractions, with myoglobin as an early-rising but nonspecific marker of muscle injury, and then the more cardiac-specific isoform of total CK, CK-MB, which was the workhorse of AMI diagnosis for several decades (1). Importantly, these early biomarkers of myocardial injury were all limited by a lack of myocardial

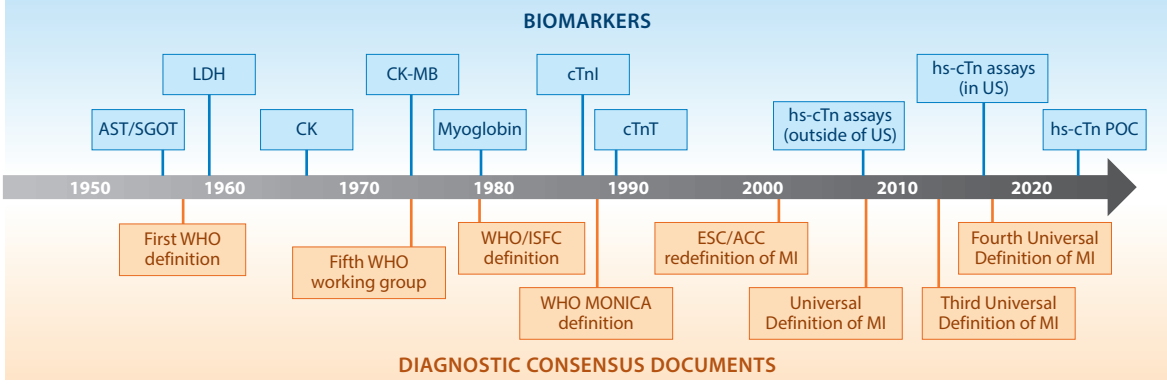


Figure 1

Timeline of developments in myocardial infarction diagnosis. Above the arrow, the introductions of several biomarkers are depicted. Below the arrow, several diagnostic consensus documents are highlighted. The 2000 ESC/ACC redefinition of MI document was based on the consensus of the First Global MI Task Force and was further redefined in 2007 by the Second Global MI Task Force culminating in the Universal Definition of MI endorsed by ESC, ACC, AHA and WHF. The development of more sensitive assays triggered another redefinition, termed the Third Universal Definition of MI, followed by the 2018 Fourth Universal Definition. Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; AST, aspartate aminotransferase; CK, creatine kinase; cTnI, cardiac troponin I; cTnT, cardiac troponin T; ESC, European Society of Cardiology; hs-cTn assays, high-sensitivity cardiac troponin assays; ISFC, International Society and Federation of Cardiology; LDH, lactate dehydrogenase; MI, myocardial infarction; MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease and Protocol; POC, point-of-care; SGOT, serum glutamic-oxaloacetic transaminase; WHF, World Heart Federation; WHO, World Health Organization.

specificity. Even CK-MB, predominantly found in myocardium, constitutes 5% of total CK in skeletal muscle. For a comprehensive review of biomarker-based ACS management, please refer to the overviews by Garg et al. (2) and Danese & Montagnana (3).

Discovery of Troponin and Evolution of Troponin Testing

Hs-cTn assays have been used in Europe and other parts of the world since around 2009 (**Figure 1**). The first hs-cTn assay was approved for use in the United States in 2017, nearly 10 years later. However, evolution of cTn testing to this point took decades. Troponin was first described in the 1960s as a novel protein in striated muscle (4). Soon thereafter, it was determined that troponin, a key structural and regulatory element of the thin filament of striated muscle, consisted of three components: troponin C, troponin I, and troponin T. These components exist in various isoforms, including cardiac muscle–specific isoforms of troponin I and T. Thus, troponin became an important biomarker candidate that would allow, for the first time, measurement of tissue-specific levels, improving specificity for myocardial (versus skeletal muscle) injury (3). In the late 1980s, Cummins et al. developed a cTnI radioimmunoassay and demonstrated elevated cTnI levels in patients a few hours after AMI that peaked at 18 h (5). Shortly thereafter, monoclonal antibodies against cTnI were described (6). The first-generation cTnT assays were developed by Katus et al. in 1989 (7). These cTn assays, even in early iterations, were more sensitive and more specific for myocardial injury than the "gold standard" CK-MB, necessitating redefinition of MI in 2000 (**Figure 1**) to a cTn gold standard.

Both cTnI and cTnT assays were optimized over subsequent decades, culminating in the current hs-cTnI and hs-cTnT assays (**Figure 1**) (8). These assays are approximately 100× more sensitive than earlier-generation assays and can detect circulating cTn in normal individuals. Not only can hs-cTn assays detect lower circulating cTn levels but they are also much more precise. This combination of increased sensitivity and increased precision means that the cTn level that defines the 99th percentile of the normal population, and even levels below the 99th percentile, can be measured with acceptable precision [i.e., an interassay coefficient of variation (CV) of 10% or less]. The currently accepted definition of an hs-cTn assay is that it detects cTn in at least 50% of individuals in a normal control population with a 10% CV or less at the 99th percentile (9). Most hs-cTn assays have a CV in the 2–5% range at the 99th percentile (9). By comparison, prior generation cTn assays used either a 10% CV threshold to define the upper reference limit (URL) or created a gray zone between the 10% CV level and an AMI diagnostic threshold.

Additionally, because of their increased sensitivity and specificity, both short- and long-term intra-individual variability in cTn levels is much less than inter-individual variability (10). In this situation, yes/no population thresholds to define AMI make less sense; rather, examining changes in levels within an individual over time becomes more relevant to define myocardial injury. The increased precision allows detection of even small changes in levels between baseline and 1 or 2 h or confident determination that levels are not changing. An important caveat in evolution of hs-cTn assays is that although they are now exquisitely sensitive for myocardial injury, they are not specific for the cause of myocardial injury, with AMI being a subset of all causes of myocardial injury. Sequential iterations of the universal definition of myocardial infarction (UDMI) have attempted to address the evolution of increasingly sensitive cTn assays, culminating in the most recent update in 2018 (11).

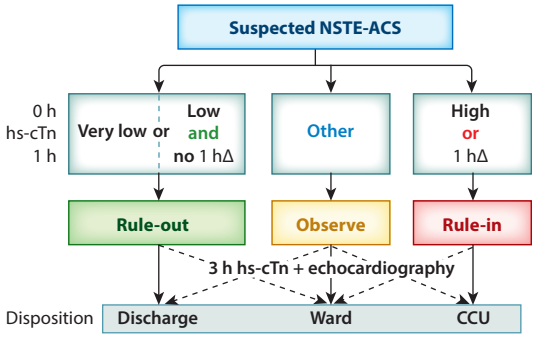
ADVANTAGES AND DISADVANTAGES OF HIGH-SENSITIVITY CARDIAC TROPONIN ASSAYS

Hs-cTn assays have clear advantages, including a very high negative predictive value, a reduced "troponin-blind" interval allowing earlier AMI detection, and expedited rule-in and rule-out using

algorithms that rely on two distinct measurements at presentation and 1 or 2 h later or based on just one measurement with a very low cTn level, below the assay limit of detection (12, 13). These features have consistently reduced ED length of stay and overall healthcare costs after implementation of hs-cTn assays, without increasing, and in some cases reducing, the use of noninvasive evaluation for ischemia or interventional procedures (14, 15). Reclassification of patients with elevated hs-cTn values previously not captured by less sensitive assays is also likely beneficial in prompting timely cardiovascular evaluation regardless of the etiology of myocardial injury (16, 17).

The improved sensitivity of hs-cTn assays also creates potential clinical challenges, primarily that detection of myocardial injury is not specific for AMI. For example, the estimated positive predictive value for rule-in of the European Society of Cardiology (ESC) 0/1-h algorithm for AMI is ~70% (**Figure 2**) (18, 19). However, because cTn levels as measured by hs-cTn assays represent a quantitative marker of cardiomyocyte injury, one can gain some insight into the etiology of myocardial injury based on the magnitude of the values. As a general rule, greater cTn levels measured by hs-cTn assays are increasingly likely to represent AMI. However, there is no distinct cut-off for AMI diagnosis (2). Thus, it is imperative that clinicians consider the results of hs-cTn testing in the context of clinical presentation and the 12-lead electrocardiogram (ECG) to inform result interpretation (18, 20). Theoretical disadvantages may include overdiagnosis leading to inappropriate noninvasive and invasive workup and overtreatment with the potential risk of complications and increased hospitalization rates. However, most available studies of hs-cTn assay

a 0/1-h hs-cTn algorithm



b Assay-specific cut-off levels

0/1-hs-cTn algorithm	Very low	Low	No 1hΔ	High	1hΔ
hs-cTnT (Elecsys; Roche)	<5	<12	<3	≥52	≥5
hs-cTnI (Architect; Abbott)	<4	<5	<2	≥64	≥6
hs-cTnI (Centaur; Siemens)	<3	<6	<3	≥120	≥12
hs-cTnI (Access; Beckman Coulter)	<4	<5	<4	≥50	≥15
hs-cTnI (Clarity; Singulex)	<1	<2	<1	≥30	≥6
hs-cTnI (Vitros; Clinical Diagnostics)	<1	<2	<1	≥40	≥4
hs-cTnI (Pathfast; LSI Medience)	<3	<4	<3	≥90	≥20
hs-cTnI (Triage True; Quidel)	<4	<5	<3	≥60	≥8

c Risks associated with each category

Risk of	Low risk	Intermediate risk	High risk
MI at index visit	<0.3%	= 10%	>65%
30-day MACE	<0.5%	15–20%	>70%

Figure 2

The European Society of Cardiology (ESC) 0/1-h algorithm. (*a*) The depicted 0/1-h algorithm is the standard algorithm recommended by the most recent ESC guidelines, with blood draws at presentation and 60 min thereafter (18). Using the delta between the first and second value, patients with low baseline values and a delta below an empiric threshold can be safely ruled-out, and patients with a delta higher than the data-driven threshold are ruled-in. (*b*) Respective cut-off values for multiple available hs-cTn assays. (*c*) Risks associated with each category. Abbreviations: CCU, cardiac care unit; hs-cTn, high-sensitivity cardiac troponin assay; hs-cTnI, high-sensitivity cardiac troponin I assay; hs-cTnT, high-sensitivity cardiac troponin T assay; MACE, major adverse cardiovascular events; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome. Figure adapted from Reference 18 with permission.

implementation, especially when accompanied by educational efforts, have not confirmed this. Further, standardized diagnostic workups for patients who have elevated cTn levels detected by hs-cTn assays but no evidence of AMI have been helpful (21).

RELEASE AND BIOKINETICS OF CARDIAC TROPONIN

Because hs-cTn assays allow detection of cTn at levels within the normal range in a majority of the population, there has been renewed interest in the mechanism of cTn release from the myocardium (22). Transient elevation detected by hs-cTn assays has been observed after exercise (23), stress testing (24), or atrial pacing, challenging the assumption of myocardial necrosis as the sole mechanism of cTn release (22). Further, a recent study demonstrated an increase in cTn concentrations after a 30-s experimental coronary balloon occlusion in humans (25). The rapidity of release suggests that myocardial necrosis is not the sole mechanism of cTn release, especially when cTn is only modestly elevated. Because cTn is a quantitative biomarker, the likelihood of myocardial necrosis rises with higher cTn values and represents the most common final diagnosis in a majority of patients.

As previously outlined, the enhanced sensitivity and precision of hs-cTn assays allow detection (or exclusion) of significant changes in cTn concentrations in serial testing as early as 1–2 h after presentation, substantially earlier than with previously used, less sensitive and precise biomarkers of necrosis. However, the overall biokinetics of cTn release over the first 24–48 h after myocardial injury are not substantially different from other markers; CK peaks only slightly earlier than cTn (**Figure 3**) (18). Data are limited on the long-term kinetics of cTn as measured by hs-cTn assays. An observational analysis of the biokinetics of cTn measured by hs-cTn assays in ACS patients demonstrated a peak on day 1, followed by a gradual return to normal values. Levels of

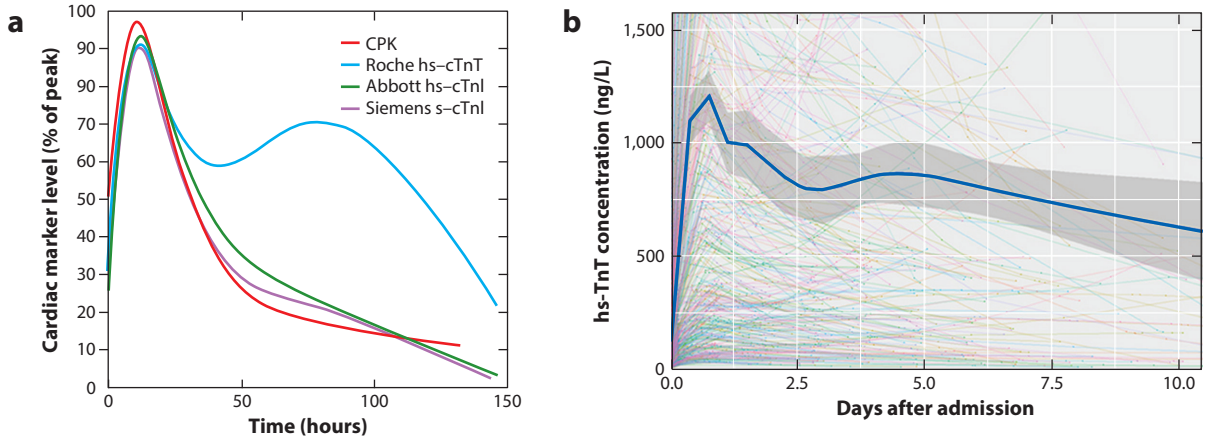


Figure 3

Biomarker kinetics. (*a*) Biomarker kinetics for CPK, hs-cTnT, hs-cTnI, and conventional cTnI testing in a cohort of 103 patients with anterior AMI undergoing PCI. All four biomarkers peaked at ~10 h and showed a log-linear decrease, while hs-cTnT results showed a plateau followed by a second peak at ~75 h after the index event. Note the rapid peak and normalization in this subset of patients with STEMI undergoing revascularization. Panel reprinted from Reference 28 with permission. (*b*) Biomarker kinetics of hs-cTnT in a mixed cohort of patients with type 1, type 2, and type 4 MI. Note the relatively slow normalization of values in this mixed cohort, providing additional evidence for a second hs-cTnT peak after ~5 days following MI in a subset of patients. Panel reprinted with permission from Reference 27. Abbreviations: AMI, acute myocardial infarction; CPK, creatine phosphokinase (an alternative name for creatine kinase); cTnI, cardiac troponin I; hs-cTnI, high-sensitivity cardiac troponin I assay; hs-cTnT, high-sensitivity cardiac troponin T assay; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

cTnI were below the URL on day 16 and levels of cTnT were below the URL on day 19, with a median time to stabilization of approximately 30–31 days (26). Another interesting analysis using hs-cTn assays investigated cTn biokinetics during the first 10 days after AMI, which demonstrated substantially elevated levels even 10 days after the index event. Furthermore, more than half of patients experienced a second peak of cTnT around day 5, an observation that was not associated with poorer outcome (27). Of interest, CK and CK-MB did not show this second peak. A previous similar study, involving ST-segment elevation AMI patients treated with percutaneous coronary intervention, demonstrated a similar second peak in cTnT, but not cTnI or CK, several days after the index event (28, 29). In summary, these studies suggest a significant time delay of several days to weeks until normalization of cTn values as measured by hs-cTn assays and even secondary, clinically nonsignificant peaks. If a fixed URL cut point is being used, this fluctuation of cTn could complicate hs-cTn-guided diagnosis of reinfarction. However, it also emphasizes two important points with regard to assessing possible recurrent ischemic events: (*a*) the importance of a symptom history and the ECG to guide additional clinical evaluation and (*b*) the importance of serial cTn testing rather than reliance on a fixed URL cut point to diagnose AMI with hs-cTn assays. In the context of ischemic symptoms and/or ECG changes, even if the baseline cTn level according to an hs-cTn assay is elevated at the time of evaluation of recurrent symptoms (time 0), a rise in the cTn level on serial testing (or by 20% if there is a markedly elevated level on the time 0 test), as described below, in validated testing algorithms is consistent with reinfarction. If the levels are flat or falling on serial testing, reinfarction is unlikely.

DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION AND THE USE OF VALIDATED RULE-IN AND RULE-OUT ALGORITHMS

The Fourth UDMI, produced jointly by the ESC, American Heart Association (AHA), American College of Cardiology (ACC), and World Heart Federation, defined type 1 (atherothrombotic) AMI as the "detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL in the context of at least one of the following: symptoms of acute myocardial ischemia; new ischemic ECG changes; development of pathologic Q waves; imaging evidence of loss of viable myocardium or new regional wall motion abnormalities with a typical ischemic pattern; identification of a coronary thrombus" (11, p. e624). Type 2 AMI is similarly defined but represents a supply–demand mismatch mechanism of ischemic injury. Laboratory detection of cTn values above the 99th percentile in the absence of supporting evidence of AMI is considered myocardial injury, with a rise and/or fall considered acute myocardial injury (11).

The 2020 ESC guidelines for management of non-ST-segment elevation ACS and the 2021 ACC/AHA chest pain guidelines both recommend use of hs-cTn assays for evaluation of potential ACS. The ESC guidelines further recommend use of a 0/1-h hs-cTn testing algorithm (**Figure 2**), with blood draws at presentation and 60 min thereafter as the best option, and use of a 0/2-h algorithm (blood draw at presentation and 120 min thereafter) if 0/1-h testing is not feasible (18). In developing these algorithms, thresholds for AMI rule-out and rule-in required a minimum negative predictive value of 99% and a minimum positive predictive value of 70%, respectively. Both the 0/1 and 0/2 algorithms were rigorously validated using large cohorts and central adjudication processes and were recently tested in implementation studies (30, 31). Recent evidence suggests that the previously recommended 0/3-h algorithm is inferior to the 0/1-h algorithm with respect to both safety and efficacy (32). The foundational concepts of these algorithms are observations that cTn levels are continuous variables, with higher values making an AMI more likely, and that very early absolute changes reflect changes over the next few hours because troponin release is roughly linear over the first 8 h after myocardial injury. Such rapid algorithms

reduce the troponin-blind interval for detection of myocardial injury and improve rule-out efficiency, resulting in shorter ED lengths of stay and potentially lower costs (19, 33). For an extensive overview of the various algorithms as well as the assay-specific cut-off concentrations, we refer the reader to the 2020 ESC guidelines (18).

When applying these algorithms, the baseline (0 h) value is classified as high, resulting in immediate rule-in categorization; very low, resulting in immediate rule-out; low, requiring a second value; or intermediate, also requiring a second value (18). Using the difference between the first and second value, patients with low baseline values and a delta below an empiric threshold can be safely ruled-out, and patients with a delta higher than the data-driven threshold are ruled in. **Figure 2** shows this algorithm for multiple available hs-cTn assays, as well as corresponding risks associated with each category. Patients who do not fulfill criteria for rapid rule-in or rapid rule-out are assigned to the "observe" category. About 25–30% of patients are assigned to this heterogeneous group that has a 15% incidence of non-ST-segment elevation myocardial infarction (34). Importantly, the "observe" category has a similar mortality rate as the rule-in group (8.1% 1-year mortality and 14% 2-year mortality) (34). Noninvasive imaging with echocardiography and repeat hs-cTn measurement at 3 h should be performed in "observe" patients (18). In the unlikely event that presentation is <1 h from symptom onset, a 3-h test should also be considered (19). Validated cut-offs for a 3-h cTnT level and 0/3-h absolute change provide further guidance for management of this challenging patient group (35).

A challenging situation for cardiologists is unexpected troponin results (36). It is estimated that detection of myocardial injury in the absence of AMI has increased by approximately threefold with introduction of hs-cTn assays (37), with 1 in 20 unselected in- and outpatients having cTn levels above the URL (38). The list of differential diagnoses is long, and a clinical approach to such patients has recently been proposed (36), requiring skillful evaluation by experienced providers.

It is also important to be aware of clinical characteristics that affect cTn levels, particularly as assessed by hs-cTn assays, including age, sex, and renal impairment. While the effect of sex is modest (male levels higher than female), older age and renal impairment can have substantial effects on cTn levels and can result in baseline levels chronically above the 99th percentile (39, 40). However, in the absence of acute myocardial injury, serial testing will yield changes in cTn levels that do not exceed recommended algorithm values. The ESC guidelines recommend uniform algorithm cut-offs due to the complexity of incorporating all confounders into a clinical practice algorithm (18). These guidelines also advise that the relative change on serial testing is more relevant than the baseline value relative to the 99th percentile (18). However, the Fourth UDMI encourages use of sex-specific cut-offs for the 99th percentile, while acknowledging lack of evidence as to whether this approach would yield valuable additional information (11). A novel approach to overcome those limitations could be the use of machine learning. The recently developed Collaboration for the Diagnosis and Evaluation of Acute Coronary Syndrome (CoDE-ACS) machine learning model integrates single or serial hs-cTn assay results with clinical features. The model has already undergone external validation and demonstrated superiority over pathways using fixed hs-cTn thresholds in a variety of healthcare systems (41).

RELEASE OF CARDIAC TROPONIN IN OTHER CARDIOVASCULAR DISEASE STATES

Myocardial injury is a nonspecific term describing the elevation of cTn levels above the 99th percentile URL. In the setting of evidence of ischemia, a rise and/or fall in cTn levels represents AMI. However, many other conditions can cause myocardial injury in the absence of ischemia (11).

Table 1 Other conditions associated with myocardial injury

Acute conditions	Chronic conditions
(Peri-)Myocarditis	Severe chronic coronary artery disease
Tachyarrhythmias	Chronic heart failure
Acute heart failure	Chronic kidney disease
Hypertensive emergencies	Left ventricular hypertrophy?
Takotsubo syndrome	Subclinical heart disease
Coronary spasm	Older age
Cardiac trauma	
Pulmonary embolism	
Aortic dissection	
Cardiac surgery or procedure	
Acute valvular heart disease	
Sepsis	
Subarachnoid hemorrhage	
Critical illness	

Nonischemic myocardial injury may be detected in a wide variety of disease states, including both primarily myocardial and primarily nonmyocardial etiologies (21). **Table 1** provides an overview of disease states other than AMI that are characterized by chronically or acutely elevated cTn levels (i.e., nonischemic myocardial injury).

IS ONE BIOMARKER (TROPONIN) ENOUGH?

ACC/AHA and ESC practice guidelines discourage use of additional biomarkers, including CK, CK-MB, and copeptin (18, 20). With use of hs-cTn assays that have superior sensitivity and precision and are capable of detecting circulating cTn earlier after presentation compared with CK-MB assays, there is no role for CK-MB in diagnosis or risk stratification, and testing only adds cost (42). Copeptin, the C-terminal portion of provasopressin, is a reliable biomarker for endogenous stress (43) and represents an ideal add-on biomarker to conventional cTn assays, offering substantial added value in early detection of ACS and AMI (44, 45); however, copeptin adds no value to validated hs-cTn algorithms (18).

POINT-OF-CARE TROPONIN TESTS

When central laboratory services may not be available or access to testing is delayed, point-of-care (POC) tests that allow very short turnaround times have increasingly been used (46). However, POC assays generally have lower sensitivity and diagnostic accuracy, translating into lower negative predictive values (47). Experience with conventional-sensitivity POC cTn assays showed that they reduced time to first cTn result, time from first medical contact to final disposition, and use of ED and hospital resources; moreover, patients identified as low risk had no major adverse cardiac events in short-term follow-up (48, 49). Newer POC assays have discrimination close to that of laboratory-based hs-cTnI assays, with turnaround times <15 min (50, 51). A POC hs-cTnI assay–based pathway showed rapid, safe, and accessible exclusion of AMI in two ED cohorts (52). The ARTICA and PRESTO trials are testing POC hs-cTn-based protocols (53, 54). ARTICA will apply an early rule-out strategy for low-risk patients using POC testing and a modified HEART (history, EKG, age, risk factors, and troponin) score, randomizing patients to ED evaluation or primary care follow-up, with a primary outcome of cost-effectiveness (54). PRESTO will evaluate prehospital POC testing for early AMI diagnosis (53).

IMPLEMENTATION OF HIGH-SENSITIVITY CARDIAC TROPONIN ASSAYS

The Transition to High-Sensitivity Cardiac Troponin Assays: an International Experience

While hs-cTn assays have clear advantages, fears that limited diagnostic specificity could result in inappropriate resource use and hospitalizations delayed implementation of these assays in practice, particularly in the United States. Several well-planned implementation efforts involving a variety of stakeholders, and including providers from laboratory medicine, EDs, and general and interventional cardiology, as well as cardiology consult teams, have applied rigorous pre- and postimplementation data collection to resolve many of these concerns.

An early analysis from Italy showed a higher rate of positive results when using hs-cTn assays at the 99th percentile, and an accompanying increase in ED use, but not intensive care or general ward hospitalizations (55). In the SWEDEHEART registry, a pre-/postimplementation study in more than 35,000 coronary care unit admissions showed that transition to hs-cTn assays was associated with an increase in AMI diagnoses, without inappropriate increases in hospital resource utilization, and with better identification and allocation of patients for beneficial therapies (56). Another Swedish analysis suggested a reduction in reinfarction and a slight, but significant, increase in use of coronary angiographies and revascularizations (57, 58). A 10-year experience from 12 Dutch hospitals demonstrated that hs-cTn implementation resulted in a doubling in AMI diagnoses but a substantial reduction in mortality (59).

An elegant Scottish implementation analysis using more sensitive cTn assays evaluated the effects on hard outcomes of lowering the AMI diagnostic threshold. Patients were stratified into three groups according to their respective cTn values: <0.05 ng/mL, between 0.05 and 0.2 ng/mL, and above 0.2 ng/mL, the latter being the prior AMI cut-off. During the validation phase, only values above the original 0.2 ng/mL cut-off were reported to clinicians (60). Interestingly, patients with cTn values between 0.05 and 0.2 ng/mL had the highest rate of death or recurrent AMI. During the implementation phase, lowering the threshold to 0.05 ng/mL strongly lowered the risk of death or recurrent AMI in 0.05–0.2 ng/mL group, in conjunction with an increase in use of guidelines-recommended treatments. These results suggest that more sensitive cTn assays reclassify patients at elevated risk, who otherwise would not be identified or treated. However, High-STEACS, a stepped-wedge, 10-center cluster-randomized trial including nearly 50,000 patients with paired cTn measurements, did not confirm these results (61). During the validation phase, results from hs-cTn assays were concealed from treating providers and only contemporary cTn values given. Hospitals were randomly assigned to either early ($n = 5$) or late ($n = 5$) implementation of hs-cTn assays. Seventeen percent of patients were reclassified based on hs-cTn results, but there was no difference in AMI or cardiovascular death after hs-cTn implementation.

In the multinational APACE study, transition to hs-cTn increased AMI rates, while coronary angiography rates were similar after implementation and rates of stress testing were substantially reduced. Median time to ED discharge decreased by nearly 80 min and mean total costs were reduced by 20% with hs-cTn assays (62).

Current State of Implementation in the United States

With approval of the first hs-cTn assay by the FDA in 2017, and subsequent additional approvals (63, 64), US hospitals have a tremendous opportunity to incorporate the vast experience and evidence generated in Europe and other countries. Still, US adoption of hs-cTn assays has been slow (65). Despite the European experience, there remains considerable apprehension that implementation would increase hospital lengths of stay and cascade testing in a population with more

prevalent disease and risk factors. Further, with the much higher sensitivity and lack of etiologic specificity of these assays and the more indiscriminate ED cTn testing patterns in the United States, there are concerns that hospital wards and cardiac catheterization laboratories could be overwhelmed with cases of elevated cTn in the absence of AMI or other serious cardiac illness.

Several analyses of hs-cTn assay implementation by early adopters in either single hospitals or hospital systems in the United States have not confirmed these fears, reporting outcomes similar to the European experience. In a single-center experience, transition to hs-cTn assays was associated with increased ED length of stay, outweighed by fewer hospital admissions and no changes in stress testing or cardiology consultations (66). Implementation of hs-cTn in a larger system including five EDs resulted in more upfront tests (e.g., additional cTn tests or ECGs) but fewer admissions, stress tests and PCIs (67). A transition analysis from Wisconsin showed an increase in AMI and myocardial injury diagnoses, while overall resource use did not increase, with the exception of coronary angiography (37). Another analysis from the Mayo Clinic Health System hospitals described a successful transition to hs-cTn assays, based on extensive multidisciplinary collaborative and educational efforts (68). While use of hs-cTn assays slightly increased the number of AMI diagnoses, mostly accounted for by type 2 MI events, no increase in resource use or hospital admissions was noted. Similar observations were made in the University of Texas–Southwestern Medical Center collaborative implementation program, in which ED length of stay and inpatient admissions were reduced with no increase in AMI readmission or death (69).

A recent analysis from the National Cardiovascular Data Registry (NCDR) Chest Pain–MI registry provided much-needed US-wide insight into hs-cTn assay implementation. In 550 participating hospitals and 251,000 patients, there was an increase in hs-cTn assay use from 3.3% of hospitals in the first quarter of 2019 to 32.6% in the third quarter of 2021 (64). While hs-cTn assay use was associated with more use of echocardiography among patients with a final diagnosis of non-ST-segment elevation acute coronary syndrome, use of invasive angiography among low-risk patients was lower, hospital length of stay was slightly shorter, and mortality was similar between hospitals that used hs-cTn assays and those that did not. These registry results, with diversity in geographic locations and hospital types, provide reassurance that implementation of hs-cTn assays in the United States has not increased resource use, similar to experiences in other parts of the world. Still, even among hospitals participating in the NCDR Chest Pain–MI registry, uptake of hs-cTn testing is slow and remains low; two-thirds of hospitals are still not using hs-cTn assays and accruing their benefits.

Overcoming Barriers to Implementation in the United States

An important first step to implementation of hs-cTn assays and overcoming existing concerns is dissemination of data from large registries and hospital systems that have successfully transitioned to hs-cTn assays. Further, major clinical practice guidelines are now well aligned on the preference for hs-cTn assays and can be used to set quality benchmarks (11, 18, 20). In addition, several guidance documents have been published to provide support for clinicians and hospital or system administrators in the transition to hs-cTn assays (70, 71). The recent expert consensus document on hs-cTn implementation by Januzzi et al. is an excellent resource (70). This document discusses many important considerations, including (*a*) laboratory perspectives and educational efforts with regard to analytic terminology and reporting, (*b*) issues regarding the choice of assay and quality control, and (*c*) the importance of collaboration between clinical and laboratory staff with regard to turnaround times and results interpretation. It further highlights the most important clinical considerations and educational efforts for clinical interpretation of hs-cTn results and use of diagnostic protocols. Overall, we believe that the main key to a successful transition is education, broad institutional collaboration, and preparation involving all key stakeholders.

NONTRADITIONAL USE OF HIGH-SENSITIVITY CARDIAC TROPONIN ASSAYS

Cardio-Oncology

Cancer therapy–related cardiovascular toxicity (CTR-CVT) is a major contributor to non-cancer-related death among cancer survivors. In 2022, the ESC published inaugural guidelines on cardio-oncology, recommending cTn measurement using hs-cTn assays in all cancer patients at risk for CTR-CVT before initiation of potentially cardiotoxic anticancer therapies to stratify risk for cardiovascular toxicity and during therapy to detect subclinical CTR-CVT (72). However, there are no universally accepted cut-offs for elevated baseline risk or for diagnosing CTR-CVT, and optimal timing of biomarker testing during treatment is unknown. The same issues with lack of etiologic specificity of cTn elevation also challenge results interpretation and subsequent treatment decisions. Ongoing studies are evaluating use of hs-cTn assays for risk stratification, CTR-CVT diagnosis, and most importantly, use of cTn levels as triggers for initiation or intensification of cardiovascular preventive therapies.

Noncardiac Surgery

A rise of cTn levels after noncardiac surgery, termed perioperative myocardial injury (PMI), is strongly associated with mortality, even in the absence of additional criteria for AMI diagnosis (73). In a prospective study of >2,000 patients undergoing noncardiac surgery, PMI (defined as an absolute increase in hs-cTn level by ≥URL value on day 1 or 2 postsurgery versus preop) occurred in 16% and was associated with dramatically higher mortality (8.9%) versus no PMI (1.5%) (74). The 2022 ESC guidelines on cardiovascular assessment and management of patients undergoing noncardiac surgery recommend routine assessment of PMI using hs-cTn assays preoperatively and 24 and 48 h after surgery in patients with known cardiovascular disease (CVD), cardiovascular risk factors (including age >65 years), or symptoms suggestive of CVD before intermediate- and high-risk noncardiac surgery (75). Testing is not recommended in low-risk patients undergoing low- or intermediate-risk noncardiac surgery. PMI diagnosis triggers further clinical work-up as outlined in the guidelines.

Screening of the General Population

In early analyses, cTn levels within the normal range were associated with higher risk of cardiovascular events than nondetectable levels (76, 77). In a large meta-analysis (>150,000 individuals), hs-cTn assays detected cTn in 80% of patients (cTnI 82.6%, cTnT 69.7%) (78). Individuals with cTnT in the top one-third (>8 ng/L) were at 67% greater risk for fatal CVD and 59% greater risk for coronary heart disease compared with those in the bottom one-third (<5 ng/L). Additional studies showed that risk stratification with hs-cTn testing in asymptomatic individuals extended to patients with chronic coronary disease (79, 80). The Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) project assayed cTn in nearly 75,000 individuals free from CVD from 10 prospective population-based studies using hs-cTn assays in a central laboratory (81). The median value was 2.7 ng/L. Individuals in the highest quintile (5.9 ng/L) had 160% higher cardiovascular mortality and a 92% higher risk for first cardiovascular event compared with individuals in the lowest tertile (2.5 ng/L). Importantly, the addition of hs-cTnI to established risk scores improved cardiovascular risk prediction. Additionally, among JUPITER trial participants, statin treatment was associated with a greater absolute cardiovascular risk reduction among those with baseline cTnI >6 ng/L versus those with cTnI <6 ng/L (81). However, whether individuals with detectable cTn levels within the normal range would benefit from intensified therapy such

as statins has not been studied in prospective trials. Therefore, routine use of hs-cTn assays in cardiovascular risk prediction in the general population is currently not recommended (82).

CONCLUSION

Hs-cTn assays exhibit superior characteristics for rapid rule-in or rule-out of AMI in patients presenting to the ED with chest pain but without signs of acute ST-segment elevation. More than a decade of experience with hs-cTn assays in Europe and other parts of the world has consistently shown improved diagnostic utility without a meaningful increase in inappropriate diagnostics or hospital admissions. Although implementation of hs-cTn assays lags behind in the United States, several position documents provide guidance for successful implementation, and the early clinical implementation experience mirrors that in Europe and other areas. We therefore believe that the widespread use of hs-cTn assays is ready for prime time!

OUTLOOK

Biomarker assessment for diagnosis, triage, and risk stratification of ED patients with possible ACS continues to evolve. Even as hs-cTn assays are being implemented, ultrasensitive cardiac troponin (us-cTn) assays that enable detection of circulating cTn in almost every individual are being developed. By reliably detecting concentrations as low as <0.1 ng/L (83), these assays may be particularly useful in primary prevention risk stratification in the general population. Cardiac myosin-binding protein C (cMyC) is an intracardiac protein that is involved in sarcomere organization and is crucial for normal cardiac function. It is more abundant than cTn in myocardium and is released even more rapidly (84). In a direct comparison, measurement of cMyC and cTnT and cTnI by hs-cTn assays provided comparable discriminatory power for AMI, but cMyC was particularly helpful in early presenters (85). More dedicated research on the use of cMyC in early presenters, or other clinical indications, is needed. It is possible that cMyC testing could augment or replace hs-cTn assays in the continued evolution of biomarkers of myocardial injury for a variety of indications.

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