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STATE-OF-THE-ART PAPER

Preparing the United States for High-Sensitivity Cardiac Troponin Assays

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It is only a matter of time before the use of high-sensitivity cardiac troponin assays (hs-cTn) becomes common throughout the United States. In preparation for this inevitability, this article raises a number of important issues regarding these assays that deserve consideration. These include: the need for the adoption of a universal nomenclature; the importance of defining uniform criteria for reference populations; the challenge of discriminating between acute and nonacute causes of hs-cTn elevations, and between type 1 and type 2 acute myocardial infarction (AMI); factors influencing the analytical precision of hs-cTn; ascertaining the optimal duration of the rule-out period for AMI; the need for further evaluation to determine the causes of a positive hs-cTn in non-AMI patients; and the use of hs-cTn to risk-stratify patients with disease conditions other than AMI. This review elaborates on these critical issues as a means of educating clinicians and researchers about them. (J Am Coll Cardiol 2013;61:1753–8) © 2013 by the American College of Cardiology Foundation

Recently, clinicians have begun to use the recommended cut-off values for current generation cardiac troponin (cTn) assays: the 99th percentile upper reference limit (URL). Previously, there was reluctance to use these cut-off values because they are associated with frequent elevations in cTn from non-acute ischemic heart disease conditions. Thus, there was a tendency to use cut-off values for troponin that equated with the prior gold standard diagnosis developed with less sensitive markers such as creatinine kinase-MB isoenzyme (CK-MB) or the lowest value at which assay achieved a 10% coefficient of variation (CV), which was thought to reduce false-positive elevations. The use of the 99th percentile URL increases the ability of these assays to detect both acute myocardial infarction (AMI) and structural cardiac morbidities (1). This change in practice should not be confused with newer-generation high-sensitivity assays.

Improvements in the analytic performance of cTn assays have resulted in superior sensitivity and precision. Improved sensitivity occurs because of more sensitive antigen binding and detection antibodies, increases in the concentration of the detection probes on the tag antibodies, increases in sample volume, and buffer optimization (2). Assays now are able to measure 10-fold lower concentrations with high precision (a CV <10% at the 99th percentile of the URL). The high-sensitivity cardiac troponin T (hs-cTnT) assay is already in clinical use throughout most of the world. It is only a matter of time before high-sensitivity assays are approved for use in the United States. In preparation for this, as well as the use of the 99th percentile URL with contemporary assays, there are a number of important issues that deserve consideration. Key concepts are included in Table 1.

Need for a Universally Accepted Nomenclature

The literature is replete with different terms used to refer to cTn assays. We advocate the use of the term "high-sensitivity cardiac troponin assays" (hs-cTn) for cTn assays that measure cardiac troponin values in at least 50% of a reference population (2,3). This policy we are informed has now been embraced by the journal *Clinical Chemistry*. High-sensitivity assays can be further categorized as well (Table 2).

Ideally, assays should have a CV of <10% at the 99th percentile value. Assays that do not achieve this level are less sensitive which protects against false-positive results, and they can be used (4).

Defining Uniform Criteria for Reference Populations

There is a lack of consistency in the types and numbers of subjects that should/can constitute a reference population (2). Often, participants are included after simple screening by check list but without a physical examination, electrocardiogram, or laboratory testing. At other times, a normal

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Abbreviations and Acronyms

AMI = acute myocardial infarction

CV = coefficient of variation

hs = high sensitivity

cTn = cardiac troponin

URL = upper reference limit

creatinine and/or a normal natriuretic peptide value is required. Imaging to detect structural heart disease is rarely used. Because it is known that gender, age, race, renal function, heart failure, and structural heart disease, including increased left ventricular (LV) mass are associated with increased cTn concentrations (5–7) an assay's 99th percentile value depends on the composition of the reference group. Thus, the more criteria used, the lower the reference values (Fig. 1) (5). The appropriate reference value to use clinically also is far from a settled issue. It might be argued that using a higher 99th percentile value for the elderly allows comparison of the patient to his or her peers, but in raising the cut-off value, if the increases are caused by comorbidities, those who are particularly healthy will be disadvantaged (8). Gender and ethnicity are not comorbidities, and we would urge that those should be taken into account. It is clear that regardless of the assay, there will need to be 99th percentile values for men that are different for women (2). The reference population for assay validation studies should ideally be based on demographic characteristics that mirror the U.S. population and include subjects whose blood pressure, serum glucose, and creatinine and natriuretic peptide values are within the normal reference range and who take no cardiac medications. These subjects should be free from structural heart disease, documented by echocardiography, cardiac magnetic resonance imaging (MRI) or computed tomography (CT) angiography. Meeting these criteria will be a major challenge, especially for older individuals, although some initial studies have been performed (9). A conjoint pool of samples collected with the support of commercial manufacturers so that all companies could use the identical patient population for their reference ranges would be a major advance. One large national effort would probably be more cost-effective than multiple smaller efforts.

Table 1 Key Concepts

There is a need to develop a universal nomenclature for troponin assays.
There is a need for uniform criteria for selecting reference populations.
The optimal delta criteria for distinguishing between acute and chronic cardiac injury remain unclear and are likely to be assay-specific.
Distinguishing between type 1 and type 2 AMI is challenging, and more type 2 AMIs will be detected with hsTn assays.
Factors affecting the analytical precision of troponin assays (including how we collect samples) will become more important with the use of hs-cTn assays.
The optimal duration for ruling out AMI remains unclear; novel approaches to this issue are being developed.
Elevated hs-cTn, regardless of the cause, has important prognostic implications and deserves additional evaluation; many cases of chronic elevations can be evaluated in an outpatient setting.
Hs-cTn can be used to risk-stratify patients with non-ACS cardiovascular comorbidities.

ACS = acute coronary syndrome; AMI = acute myocardial infarction.

Table 2 Classification of High-Sensitivity Cardiac Troponin Assays

Category	Description
First Generation	Able to measure cTn in 50%–75% of a reference population
Second Generation	Able to measure cTn in 75%–95% of a reference population
Third Generation	Able to measure cTn in more than 95% of a reference population.

Adapted from Apple and Collinson (3).

Regardless of reference values, solitary elevations of hs-cTn values (>99th percentile) will be inadequate for clinical decision making (10). The exception may be very elevated values, which are most often caused by MI or myocarditis, once possible analytical confounding factors are eliminated. In other circumstances, serial changes in hs-cTn values will be required to determine whether acute myocardial injury is present.

Discriminating Between Acute and Nonacute Causes of hs-cTn Elevations

With the ability to precisely measure small concentrations of cTn, clinicians will be faced with the challenge of distinguishing patients who have acute problems from those with chronic elevations from other causes. Using the fourth-generation cTnT assay, approximately 0.7% of patients in the general population have modest elevations >99th percentile URL (11). In the same population, this number was 2% with the hs-cTnT assay (6). Of that number, only half had documentation (even with imaging) of cardiac abnormalities. If the prevalence of a positive cTnT is 2% in the general population, it will likely be 10% or 20% in the emergency department (ED) and even higher in hospitalized patients, as these patients often have cardiac comorbidities.

Measurement of changes in hs-cTn over time (δ hs-cTn) improves the specificity of hs-cTn for the diagnosis of acute cardiac injury (12,13). However, it does so at the cost of sensitivity. With contemporary assays, differences in analytical variation have been used to define an increasing pattern. At elevated values, CV for most assays is in the range of 5% to 7%, so a change of 20% ensures that a given change is not caused by analytical variation alone (10). At values near the 99th percentile URL, higher change values are necessary (13). The situation with hs-cTn assays is much more complex, as the following outline shows:

1. Change criteria are unique for each assay.
2. It will be easy to misclassify patients with coronary artery disease who may present with a noncardiac cause of chest pain but have elevated values. They could be having unstable ischemia or elevations caused by structural cardiac abnormalities and noncardiac discomfort. If hs-cTn is rising significantly, the issue is easy but if the

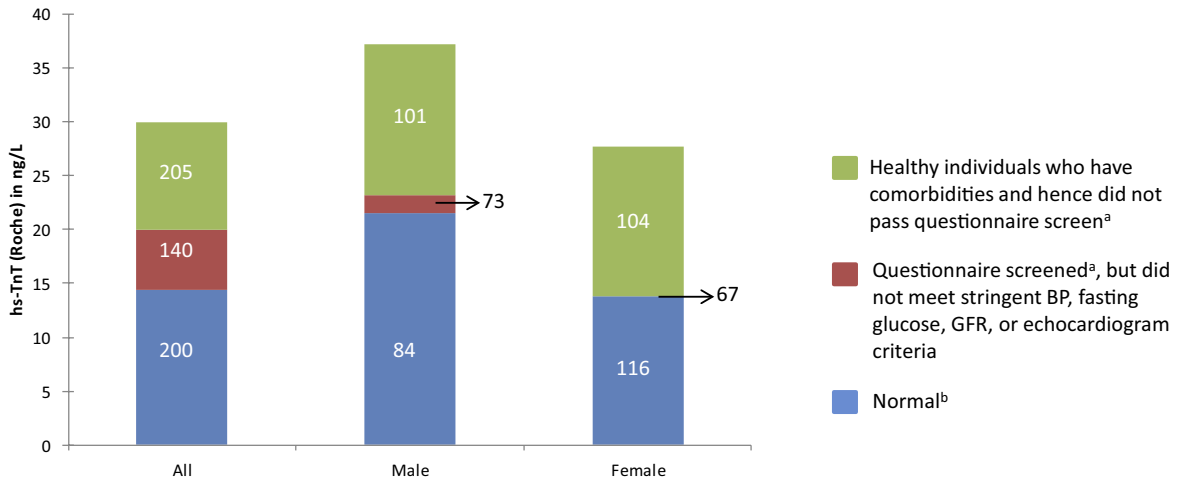

Figure 1 **Relationship Between Patient Characteristics and the 99% URL in Healthy Individuals**

Values for the 99th percentile URL go down with more rigorous screening.
Data from Collinson et al (5)
a = Have no history of vascular disease or diabetes, and not taking cardioactive drugs, based on questionnaire.
b = Normal defined as those individuals who had no history of vascular or cardiovascular disease, diabetes mellitus, hypertension, or heavy alcohol intake and who were receiving no cardiac medication AND had blood pressure ≤140/90 mmHg; fasting glucose <110 mg/dL; eGFR >60mL /min; LVEF > 50%; normal lung function; and no significant valvular heart disease, LVH, diastolic heart failure, or regional wall-motion abnormalities on echocardiography.

values are not rising, a diagnosis of AMI still might be made. If so, some patients may be included as having AMI without a changing pattern. This occurred in 14% patients studied by Hammarsten et al. (14). If patients with elevated hs-cTn without a changing pattern are not called AMI, should they be called patients with "unstable angina and cardiac injury" or patients with structural heart disease and noncardiac chest pain? Perhaps both exist?

3. The release of biomarkers is flow-dependent. Thus, there may not always be rapid access to the circulation. An area of injury distal to a totally occluded vessel (when collateral channels close) may be different in terms of the dynamics of hs-cTn change than an intermittently occluded coronary artery.
4. Conjoint biological and analytical variation can be measured. They are assay-dependent, and the reference change values range from 35% to 85% (2). The use of criteria less than that (which may be what is needed clinically) will thus likely include individuals with changes caused by conjoint biological and analytical variation alone. This has been shown to be the case in many patients with nonacute cardiovascular diagnoses (14,15).
5. Most evaluations have attempted to define the optimal delta, often with receiver operator curve analysis. Such an approach is based on the concept that sensitivity and specificity deserve equivalent weight. But higher deltas improve specificity more and lower ones improve sensitivity and it is not clear that all physicians want the same tradeoffs in this regard. ED physicians often prefer high-sensitivity so that their miss rate is low (<1%) (16), whereas hospital clinicians want increased specificity. This tension will need to be addressed in defining the optimal delta.
6. The delta associated with AMI may be different from that associated with other cardiac injury (14). In addition, women have less marked elevations of cTn in response to coronary artery disease (17) and in earlier studies were less apt to have elevated values (18). Given their pathology is at times different, it may be that different metrics may be necessary based on gender.
7. Some groups have assumed that if a change is of a given magnitude over 6 hours, it can be divided by 6 and the 1-h values can be used. This approach is not data driven, and biomarker release is more likely to be discontinuous rather than continuous (19). In addition, the values obtained with this approach are too small to be distinguished from a lack of change with most assays.

These issues pose a major challenge even for defining the ideal delta change value and provide the reasons why the use of this approach will reduce sensitivity (20,21) (Fig. 2).

In addition, there is controversy in regard to the metrics that should be used with high-sensitivity assays. The Australian-New Zealand group proposed a 50% change for hs-cTnT for values below 53 ng/l and a 20% change above that value (22). The 20% change is much less than conjoint biological and analytical variation. A number of publications have suggested the superiority of absolute δ cTn compared to relative δ cTn in discriminating between AMI and non-AMI causes of elevated cTn (23–25). However, the utility of the absolute or relative δ cTn appears to depend on the

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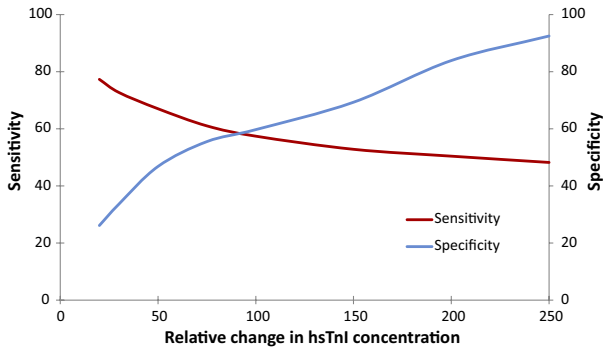

Figure 2 **Defining the Optimal Delta: Tension Between Sensitivity and Specificity**

There is a reciprocal relationship between sensitivity and specificity. With marked percentage changes, specificity is improved at the expense of sensitivity, and at lower values, the opposite occurs. Data from Keller et al. (20).

initial cTn concentration, and the major benefit may be at higher values (23). A recent publication by Apple et al. (26) calculates deltas in several different ways with a contemporary assay and provides a template for how to do such studies optimally (26). If all studies were carried out in a similar fashion, it would help immensely. In the long run, institutions will need to define the approach they wish to take. We believe this discussion is a critical one and should include laboratory, ED, and cardiology professionals.

Distinguishing Between Type 1 and Type 2 AMI

Although δ cTn is helpful in distinguishing between AMI and nonacute causes of Tn release, it may or may not be useful in discerning type 1 from type 2 AMI. As assay sensitivity increases, it appears that the frequency of type 2 AMI increases. However, making this distinction is not easy. Type 1 AMI is caused by a primary coronary event, usually plaque rupture. It is managed acutely with aggressive anticoagulation and revascularization (percutaneous coronary intervention or coronary artery bypass) (10). Type 2 AMI typically evolves secondary to ischemia from an oxygen demand/supply mismatch such as severe tachycardia and hypo- or hypertension and the like, with or without a coronary abnormality. These events usually are treated by addressing the underlying abnormalities. They are particularly common in patients who are critically ill and those who are postoperative (27). However, autopsy studies from patients with postoperative AMI often manifest plaque rupture (28). Thus, the more important events, even if less common, may be type 1 AMIs. Type 2 events seem more common in women, who tend to have more endothelial dysfunction, more plaque erosion, and less fixed coronary artery disease (28–30). Additional studies are needed to determine how best to make this clinical distinction. For now, clinical judgment is recommended.

Analytical Imprecision in Cardiac Troponin Assays

All analytical problems will be more critical with hs-cTn assays. Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are measured using enzyme linked immunosorbent assays. As with all immunoassays, quantification of hs-cTn can be influenced by interference between reagent antibodies and the analyte (cTn), leading to false-positive or negative results (31). Autoantibodies to cTnI or cTnT are found in 5% to 20% of individuals and can reduce detection of cTn (32,33). Additionally, fetal cTn isoforms can be re-expressed in diseased skeletal muscle and detected by the cTnT assays, resulting in false-positive values (34). Several strategies, including the use of blocking reagents, assay redesign, and use of antibody fragments, have been used to reduce interference (35). However, these strategies do not completely eliminate them. Furthermore, there are differences in measured cTn values based on specimen type (serum versus heparinized plasma versus EDTA plasma). In addition, hemolysis may affect the accuracy of cTn measurement on some platforms (37), and it is hard to avoid especially with blood draws from peripheral IV lines, which are common especially in intensive care units.

Ruling Out AMI

Studies evaluating the diagnostic performance of hs-cTn assays for the early diagnosis of AMI usually define AMI on the basis of a rising and/or falling pattern of current generation cTn values (21,38). However, defining AMI on the basis of the less sensitive current generation assay results in an underestimation of the true prevalence of AMI and an overestimation of negative predictive value of the experimental assay. It also significantly shortens the time it takes to rule in all the AMIs and thus to definitively exclude AMI as it ignores the new AMIs more sensitively detected by the hs-cTn assay. Thus, in the study by Hammarsten et al. (14), the time to exclude all AMIs was 8.5 hours when all of the AMIs detected with the high-sensitivity assay were included, whereas others that do not include these additional events report this can be done in 3 to 4 hours (21,29,38). In our view, Hammarsten is correct.

This does not mean that hs-cTn cannot help in excluding AMI. Body et al. (39) reported that patients who present with undetectable values (less than the LOB of the hs-cTnT assay) were unlikely to have adverse events during follow-up. If that group of patients is added to those who present later than 6 hours, then perhaps a significant proportion of patients with possible acute coronary syndrome (ACS) could have that diagnosis excluded with the initial value (40). Studies need to continue to evaluate cTn values for at least 6 h to define the frequency of additional AMIs detected in that manner. Using follow-up evaluations of patients with small event rates who are likely to have additional care during the follow-up period are likely to be underpowered. It may be that better initial risk

stratification may help with this, as recently reported (16,41). Low-risk patients who have good follow-up after an ED visit may be a group that can be released as early as 2 h after presentation (16).

Investigating the Causes of Positive Troponin Values in Non-AMI Patients

Elevated Tn values (including those obtained with high-sensitivity assays) are associated with a 2-fold higher risk for longer-term all-cause mortality and cardiovascular death than a negative troponin values (6,42–44). This association is dose-dependent. If values are rising, they are indicative of acute cardiac injury. Those patients should be admitted because the risk is often short-term. However, if the values are stable, assuming the timing of any acute event would allow detection of a changing pattern, the risk, although substantive, in our view, often plays out in the longer term (44). Many of these individuals, assuming they are doing well clinically, can be evaluated outside of the hospital, in our view. However, because such elevations are an indicator of a subclinical cardiovascular injury, such evaluations should be early and aggressive. Data from several studies suggest that there may well be risk far below the 99th percentile URL value. Thus, it may evolve that patients in the upper ranges of the normal range also require some degree of cardiovascular evaluation.

Risk Stratifying Patients With Nonacute Coronary Syndrome Conditions

Patients who have a rising pattern of values have a higher risk of mortality than those with negative values regardless of the cause. Investigations are ongoing to determine how well results from hs-cTn testing help to risk-stratify patients with pulmonary embolism (45), congestive heart failure (46), sepsis (47), hypertensive emergency (48), and chronic obstructive pulmonary disease (49). Presently, the studies suggest that cTn values classify patients into clinically relevant risk subgroups. Studies are needed to evaluate the incremental prognostic benefit of hs-cTn.

Conclusions

Routine use of hs-cTn assays in the United States is inevitable. These assays hold the promise of improving the sensitivity of AMI diagnoses, shortening the duration of AMI evaluation and improving the risk stratification of other noncardiac diagnoses. However, to be able to fully realize their potential, additional studies are needed to address the knowledge gaps we have identified. In the interim, clinicians need to learn how to use the 99th% URL and the concept of changing values so when the day comes that hs-cTn assays are available, they will have experience with the important basic concepts.

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