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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