High-Sensitivity Cardiac Troponin: Hype, Help, and Reality

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Articles in *The New England Journal of Medicine* get tremendous publicity, some justified and some not. Recently, 2 articles and an editorial (1–3) were published about the use of “high-sensitivity” cardiac troponin (cTn). These articles are welcome because they emphasize important concepts for clinicians. Some aspects, however, require clarification. Here we examine these articles and separate out new data from hype.

Are the Assays “High-Sensitivity” (hs) Assays?

No. Most of the assays used are contemporary assays (4), including the Siemens Ultra and Abbott Architect assays. Two new assays were included, both from Roche: a hs-cTnT assay (1) and a first description of a cTnI assay. There are no analytical data to evaluate the cTnI assay, but it appears similar to contemporary cTnI assays at best. The new hs-cTnT assay (2) is a novel high-sensitivity assay. Although there are no published analytical studies of the assay, there are several clinical publications. The hs-cTnT assay appears more analytically sensitive (4) than the others (see “What Does the Future Hold?” below). Despite that, the hs-cTnT assay was not statistically better clinically than the other assays for detection of acute myocardial infarction (AMI) (1).

How Novel Are the Findings?

They are not novel. The findings are more robust because larger patient groups were used. But the concept is not new that if one uses (a) sensitive contemporary assays as opposed to many presently available insensitive assays and (b) the 99th percentile cutoff recommended by guidelines groups, then early diagnosis occurs frequently. It is the use of the 99th percentile value as a decision cutoff that is key for early diagnosis. Similar findings were reported in 2006 and confirmed. The *New England Journal of Medicine* results (1, 2) are impressive, which likely reflects differences in the populations studied. Hopefully, the publicity associated with *The New England Journal of Medicine* will stimulate clinicians to use the 99th percentile values as decision cutoffs for diagnosis. The lack of benefit of rapidly rising markers (other than cTn), as described in the Keller et al. article (1), also has been shown in multiple previous reports.

Since Some of These Assays Are Currently in Use in the US and Most Are in Use in Europe, Is This the Approach Clinicians Use?

No. Many places do not use the 99th percentile cutoff value. Many hospitals using these assays use cutoff values higher than the 99th percentile, which diminishes clinical sensitivity. Using the 99th percentile value identifies not only patients with coronary disease but many in whom the etiology of cardiac injury is unclear. Patients with cardiovascular comorbidities have chronic cTn increases, and many other acute diseases, such as pulmonary embolism or myocarditis, produce acute increases. In the future, there will be new etiologies of cardiac injury discovered as we develop more analytically sensitive assays that unmask new pathologies. Admittedly, this situation can lead to extensive—some would say unnecessary—testing and concern on the part of physicians and patients. Nonetheless, we are unaware of cutoff values that aid in distinguishing patients with coronary artery disease from patients with other conditions, so sorting out the correct diagnosis becomes a clinical challenge, not a reason to use higher cutoffs.

How Did These Studies Deal with the Problem of Increased cTn Concentrations Produced by These Other Disease Processes?

Not very well. For the most part, the authors of these articles used a cTn concentration above the cutoff value as the sole criterion for the diagnosis of acute coronary syndrome (ACS). Thus most patients who had increased cTn because of non-ACS conditions were cat-
Categorization as ACS. The Keller et al. study (1) did address this issue to some extent. Morrow (3) noted that doing so diminished the specificity of an increased cTn value for coronary artery disease from 97% to 90%. For every 100 patients with increased cTn, only 77 had AMI, resulting in a predictive value of 50% (3).

In other parts of their articles, the investigators avoided the issue of noncoronary conditions that increase cTn. Some of the cTn increases detected probably reflected chronic cardiovascular comorbidities. Such increases occur in roughly 0.7% of the general population (5) and are probably even more frequent in hospital and emergency department populations. Increased results in such patients in most of the analyses in these articles were called true positives, inflating rather than diminishing the estimation of the diagnostic accuracy of the tests. The presence of a changing (rising and/or falling) pattern, which is an essential part of the criteria for the diagnosis of AMI in all the guidelines, was used in only a subset of patients in the Reichlin et al. article (2) as an exploratory analysis. Some of the more chronic increases may have been caught in the Keller et al. analysis (1) of clinical specificity. But if the chronic disease leading to the increase was stable coronary heart disease, these patients probably were counted as having non-ST-elevated myocardial infarction (non-STEMI). Thus, the lack of using a change between 2 timed specimens (8) helped the cTn assays look better.

In both studies (1, 2), there was a higher prevalence of coronary disease than is seen in US studies. This is because they included all patients, including those with STEMI. This issue was inadequately discussed. This inclusion increases the frequency of positive results, i.e., it increases the pretest probability that increases will be due to acute coronary artery disease. In the Reichlin et al. study (2), 46% of patients had acute coronary disease. In the Keller et al. study (1), 35% of patients had either AMI or unstable angina.

This is typical of European studies, but US studies have an incidence of ACS of 20%–25% at most in all comers. In the ROMICAT (Rule Out Myocardial Infarction Using Computer-Assisted Tomography) study of US patients with intermediate to low risk, in whom biomarkers are determinative, the incidence of coronary artery disease was only 8%. These differences have a huge effect on the apparent diagnostic accuracy of a cTn assay for ACS. The intermediate- to low-risk group is critical and was not discussed (1, 2).

Can Such a Large Number of Patients Be Diagnosed as Early as Claimed?

The concept is correct but some interpretations of the data are overstated. The gold standard for the diagnosis of AMI in these studies was either a less sensitive conventional assay or assays that, though equally sensitive, were used at higher cutoff values than the assays studied. This is not stated but is likely, because many of the assays used were the ones being studied or ones with equivalent sensitivity (4). Thus, it is likely that the cutoff value used for these comparisons was not the 99th percentile value. It is not surprising that, when one superimposes a more-sensitive approach on a less-sensitive standard, early diagnosis is increased. However, the more-sensitive assays also increase detection of disease, and analyses defining the timing of diagnosis should use the more-sensitive assay data. Most of the analyses did not.

Unfortunately, these articles did not define how many patients ruled in late with the sensitive assays. Thus how long one must wait to rule out AMI is unclear. This is a critical issue, especially when a low proportion of patients have ACS.

What Are the Important Take-Home Points?

1. The rapid diagnosis of AMI is feasible using contemporary assays and the 99th percentile cutoff.
2. We still are not sure how long it takes to rule out AMI. Until additional data are available, we advocate a 6-h process.
3. Unstable angina is still a diagnosis that should be considered using contemporary assays.
4. A rising and/or falling cTn pattern is key to improving the specificity of diagnosis of ACS. This issue is underemphasized. Studies need to be done with ROC curve analysis (4) to determine, for each assay, the optimal change value. It is unclear whether one should rely on a reference change value based on analytical and biological variability or clinical optimization.
5. Using the strategy used in these articles will reduce the specificity of an increased cTn for coronary artery disease and detect more patients with other reasons for increases.
6. The only hs assay studied was the hs-cTnT, and readers should understand that the other assays are those in routine use today.

What Does the Future Hold?

Novel high-sensitivity cTnI assays with lower limits of quantification have been described (Roche, Beckman Coulter, Nanosphere, Singulex). These new assays will further improve the rapidity of diagnosis and also increase the frequency of increases that are not related to ACS. The Roche hs-cTnT assay studied (2) is an example; it measures cTnT in >90% of healthy people. When these new high-sensitivity assays arrive for use, the application of change criteria will be key. The proper use of these assays also will require an awareness of the relevant analytical and preanalytical specifications.
which, given the increased sensitivity of these assays, will have the potential to markedly influence results.

The issues highlighted are key to understanding what the field needs to progress. There is promise. Hopefully these articles, by emphasizing the need to use the 99th percentile cutoff value, will help. Further progress depends on clinicians learning about analytical issues and laboratorians understanding the challenges that new high-sensitivity assays pose. This will require improved interactions between disciplines.

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References


