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Review Article

Time to shift from contemporary to high-sensitivity cardiac troponin in diagnosis of acute coronary syndromes

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ABSTRACT

Early rule-in and rule-out of non-ST-segment elevation myocardial infarction (NSTEMI) is a challenge. In patients with inconclusive findings on ECG, cardiac biomarkers play a crucial role in the diagnosis. The introduction of the new high-sensitive cardiac troponin test (hs-TnI assay) has changed the landscape of NSTEMI diagnosis.

The new hs-TnI assay can detect troponin values at a lower level compared with a contemporary cardiac troponin (cTn) assay. The hs-cTnI assay has a coefficient of variation of ≤10%, well below the 99th percentile value. It reduces the time to diagnose acute myocardial infarction from 6 h to 3 h. A recent study has demonstrated that hs-cTnI can further reduce the time to 1 h in 70% of all patients with chest pain.

The European Society of Cardiology 2015 guidelines recommend including a second sample of hs-cTnI within 3 h of presentation This increases the sensitivity of the hs-TnI assay from 82.3% (at admission) to 98.2% and negative predictive value from 94.7% (at admission) to 99.4%. Combining the 99th percentile at admission with serial changes

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in troponin increases the positive predictive value to rule in acute coronary syndrome from 75.1% at admission to 95.8% after 3 h.

The 2015 ESC Guidelines recommend the use of a rapid rule out protocol (0 h and 1 h) when hs-cTnI with a validated 0 to1 h algorithm is available.

Training and displaying the clinical algorithm depicting the role of hs-TnI assay in acute cardiac care units and in EDs are an efficient way to deliver the new standard of care to patients. Compared with contemporary troponin assays, the hs-cTn assay accelerates the diagnostic pathway to 0–1 h, thus reducing the time for diagnosis of NSTEMI and hence, its management.

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1. Challenges in diagnosing NSTEMI

Acute coronary syndrome (ACS), comprising ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina, is the most common cause of mortality in patients with CAD.[1] Studies from India and China have reported that STEMI remains more frequent than NSTEMI.[2–4] According to the CREATE registry, the incidence of STEMI (60.6%) was greater than that of NSTEMI (39.4%) in India, which is in contrast to data from the developed countries.[5] A recent study by Sharma et al.[6] also reported that the incidence of STEMI (63.7%) was higher than that of NSTEMI (11.3%). This study, conducted in ACS patients of south Indian population, noted that ACS occurred 10 years earlier among Indians compared with western population. The discrepancies in the incidence of STEMI and NSTEMI can be partly attributed to factors such as more subtle or atypical symptoms of NSTEMI in older patients and in women and non-availability of more sensitive cardiac biomarkers, thereby reduced the number of NSTEMI cases diagnosed.[7] In this background, cardiac biomarkers have emerged as integral components in the diagnosis of NSTEMI.

2. Implications of early diagnosis of NSTEMI

Despite advances in therapeutic strategies, the rate of acute myocardial infarction (AMI) and consequent mortality remain high in patients with ACS. Therefore, timely diagnosis, especially early ruling in or ruling out of MI is of utmost importance.[7] Early rule-in of AMI prevents the mistaken discharge of patients with AMI with normal findings on initial ECG and also helps in early initiation of effective evidence-based therapy.[8,9] An early rule-out of AMI prevents inadvertent admission of patients without ACS and facilitates early discharge of patients and thereby decreases the unwarranted healthcare burden.[10] Moreover, a delay in rule-in of AMI may increase the risk of complications and mortality, particularly in patients with pre-existing CAD. Similarly, a delay in rule-out of AMI may contribute to prolonged assessments, unnecessary investigations, increased patient anxiety, as well as overcrowding in the emergency department.[11]

3. Role of cardiac biomarkers in patients with nondiagnostic ECGs

Cardiac biomarkers are crucial to establish the diagnosis of ACS, especially in patients with nondiagnostic findings on ECG.[12] Cardiac biomarkers used include creatinine kinase, myoglobin, cardiac troponin (cTn), brain natriuretic peptide, lactate dehydrogenase, aspartate aminotransferases, and heart fatty acid binding protein.[13] Cardiac troponin: Cardiac troponins T and I (cTnT and cTnI) are the most sensitive and cardiac specific biomarkers currently available to diagnose non-STACS,[10,11] owing to the tissue-specific expression of cTnT and cTnI in the myocardium.[14] However, in patients with chronic renal failure, cTnI has greater specificity for myocardial injury than cTnT.[15] A diagnosis of AMI is based on the detection of a rise and/or fall of cTn along with the presence of characteristic symptoms, and/or ECG or imaging evidence of acute myocardial ischemia.[13,16] The cut-off value of cTn to diagnose MI is defined as a concentration exceeding the 99th percentile of a normal reference population (i.e. upper reference limit [URL]) using an assay with an imprecision (coefficient of variation, CV) ≤10% at the URL.[16] However, the contemporary cTn assays cannot measure cTn levels at low concentrations corresponding to the 99th percentile value of a normal reference population.[17] Thus, they lack the precision criteria to diagnose AMI. Consequently, the high-sensitivity cardiac troponin (hs-cTn) assays were developed to meet the requirements of analytical precision and overcome the shortcomings associated with contemporary cTn assays.[18]

4. Entry of high-sensitive cardiac troponin has changed the landscape of NSTEMI

According to the International Federation of Clinical Chemistry (IFCC) Task Force Recommendation on Analytical Characteristics, an assay is considered high sensitive if the total imprecision (i.e. CV) at the 99th percentile value is ≤10%, and measurable concentrations below the 99th percentile can be attained at a concentration value above the assay's limit of detection (LOD) in at least 50% (and ideally >95%) of healthy individuals.[19] The hs-cTn assays are capable of measuring cTn in single digit ranges of nanograms per liter; some research

Table 1 – Characteristics of the Abbott ARCHITECT hs-cTnI and Roche Elecsys hs-cTnT assay.

Company/platform/assay	Cardiac troponin concentration at		
	LOD (ng/L)	99th percentile ng/L (CV)	10% CV concentration (ng/L)
Abbott ARCHITECT hs-cTnI assay	1.2	16 (5.6%)	3
Roche Elecsys hs-cTnT assay	5.0	14 (8%)	13

LOD: limit of detection; CV: coefficient of variation.

assays facilitate detection of cTn at concentrations even lower than 1 ng/L. Thus, with the use of hs-cTn assays, the 99th percentile of cTn levels can be calculated more precisely in the reference population, which is the recommended URL. Additionally, the hs-cTn assays measure the URL with a CV of <10%. Small differences in cTn levels over time can be detected more easily due to the high precision of hs-cTn assays.[20]

In a recent publication by Love et al. the two high-sensitivity assays are discussed, one by Abbott Diagnostics and the other by Roche Diagnostics, an overview of which is presented in Table 1.[21] The hs-cTn assays are advantageous when compared with contemporary cTn assays in that they are associated with increased sensitivity, higher diagnostic accuracy for early diagnosis. Several hs-cTn assays with different values for the 99th percentile URL as defined by the manufacturer are currently available in the market.[22] According to the manufacturer's specifications, the Abbott ARCHITECT STAT hs-cTnI assay can detect troponin I in 96% of the reference population and has a turnaround time (TAT) of 16 min.[3] The Roche Elecsys high-sensitive troponin T assay can detect troponin T in 25% of the reference population and has an estimated TAT of 18 min.[23,13] It is also available as a STAT version, which has a short TAT of 9 min. Since the 99th percentile value and the rate of detection of cardiac troponin in reference population differ for each assay, the name of the test kit or the assay instrument used should be mentioned as assay references.

A prospective multicenter study by Gimenez et al. has demonstrated that the ARCHITECT STAT hs-cTnI assay has a significantly higher diagnostic accuracy for NSTEMI, when compared with Roche hs-cTnT assay among patients presenting to the ED within 3 h of chest pain onset. Among early presenters (representing 25% of overall study cohort), the area under the curve (AUC) at presentation for hs-cTnI was 0.92; 95% confidence interval (CI): 0.89–0.94 when compared with the AUC for hs-cTnT of 0.89; 95% CI: 0.86–0.91 ($p = 0.019$).[24]

Evidence indicates major differences in the diagnosis, management and treatment outcomes of ACS between men and women, with early and late mortality due to ACS being reported to be higher in women than in men. The under diagnosis of MI in women and the inequalities in treatment and outcomes might be attributed to the use of a single diagnostic cut off with contemporary cTn assays. The ARCHITECT STAT hs-cTnI is the only assay that identifies potentially important differences in the reference range for troponin between men and women.[22,25] In a prospective cohort study by Shah et al., the use of new hs-cTnI assay with a sex-specific diagnostic threshold (for women: 16 ng/L) led to an increase in the number of women diagnosed with type 1 MI from 16% (with the generic threshold of 26 ng/L) to 22%. This may change the landscape of ACS therapy in women, who so far are less likely to receive evidence-based therapy due to under diagnosis.[26]

The ESC 2015 guidelines for the management of ACS recommend including a second sample within 3 h of presentation, as with the use of a second sample, the sensitivity of hs-cTn assays for MI approaches 100%.[18] In a study by Keller et al., inclusion of a second sample at 3 h after admission increased the sensitivity of the hs-cTnI assay from 82.3% (at admission) to 98.2% and negative predictive value from 94.7% (at admission) to 99.4%. Additionally, when the 99th percentile at admission was combined with serial changes in troponin concentrations within 3 h, the positive predictive value of hs-cTnI assay to rule in AMI increased from 75.1% at admission to 95.8% after 3 h.[27]

Apart from AMI, several other conditions such as congestive heart failure, renal disease, myocarditis, severe infection and musculoskeletal conditions may also be associated with elevated cTn levels. Along with careful clinical assessment, serial sampling is essential to differentiate AMI from these conditions.[3] The hs-cTn assays are also capable of being detected in 50% of apparently disease-free individuals, with some hs-cTnI assays being able to do so in as high as 90% of this population.[26]

5. Protocol for early rule-out of AMI using hs-cTnI assay

The 2015 ESC guidelines recommend the use of a rapid rule out protocol (0 h and 1 h or 0 and 3 h) when high-sensitive cardiac troponin test (hs-cTnI) with a validated 0 h/1 h algorithm is available.[18,28] Abbott Diagnostics has proposed an algorithm for the early rule out of AMI (Fig. 1). The algorithm highlights that if a patient presents to the ED with chest pain of >6 h of onset and the hs-TnI value is below the LOD, TIMI is ≤1 and GRACE score below 140, the patient can be ruled out for AMI.

If the pain is <6 h of onset and the hs-TnI value is below the 99th percentile gender-specific cutoffs, a repeat sample is recommended 3 h later. If the second value is greater than 50% relative change value (RCV), then the patient should be admitted for intervention. If the first hs-TnI value is above the gender specific cutoffs, a second sample is recommended at 3 h. If the second hs-TnI value is also above the gender-specific cutoffs, but without significant RCV (RCV <50%) then AMI can be ruled out. If the first troponin value is 10 times the gender-specific cutoffs, then the patient should be admitted for intervention.

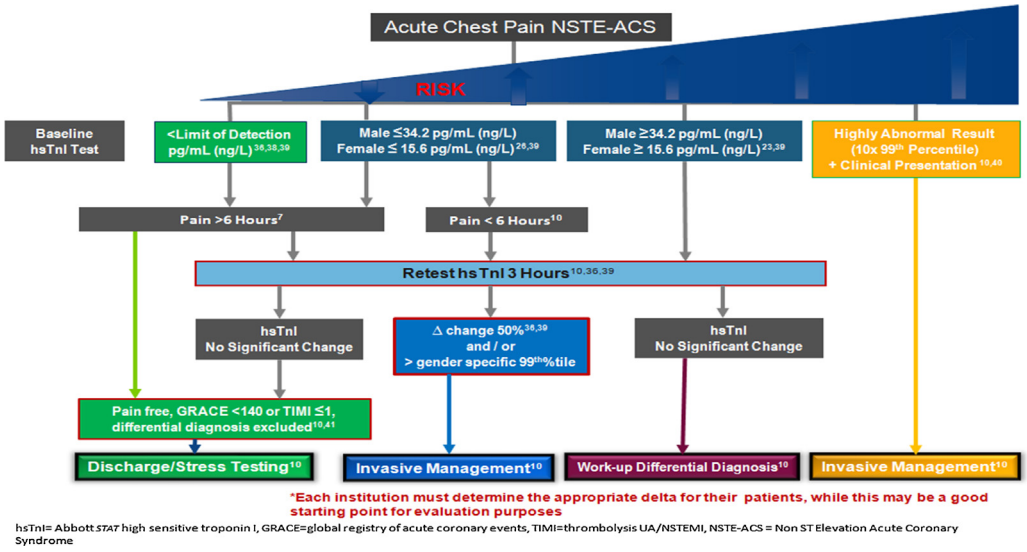

Fig. 1 – Abbott proposed algorithm for triage of NSTE-ACS (Non-ST-segment elevation acute coronary syndrome) patients based on hs-cTn I results.

6. Conclusion

The hs-cTn assay is associated with improved sensitivity and precision in the diagnosis of ACS. It helps to detect changes early, and rule out NSTEMI within 3 h. Obtaining a second sample within 3 h of presentation improves the sensitivity to nearly 100%. According to Gimenez et al.,[24] hs-cTnI has significantly higher diagnostic accuracy compared to hs-cTnT. Additionally, it is important to use only assays with gender-specific cut off rates and thus facilitate improved diagnosis of NSTEMI in women. As the 99th percentile value and the rate of detection of cardiac troponin in reference population differs for each assay, the name of the test kit or the assay instrument used should be mentioned as assay references. Among the hs-cTn assays available, the ARCHITECT STAT hs-cTnI assay has a CV of 5.6% at the 99th percentile, can detect troponin I in 96% of the reference population and has gender-specific cut off rates.[18] The enhanced sensitivity of the new hs-cTn assays could translate into earlier intervention for patients with confirmed NSTEMI and shorter inpatient hospital stay for patients without elevated troponin levels. The increased use of newer hs-cTnI assay could lead to a paradigm shift in the management of patients with NSTEMI.

Conflicts of interest

The authors have none to declare.

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