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Transitioning high sensitivity cardiac troponin I (hs-cTnI) into routine diagnostic use: More than just a sensitivity issue

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ABSTRACT

Objectives: High sensitivity cardiac troponin T and I (hs-cTnT and hs-cTnI) assays show analytical, diagnostic and prognostic improvement over contemporary sensitive cTn assays. However, given the importance of troponin in the diagnosis of myocardial infarction, implementing this test requires rigorous analytical and clinical verification across the total testing pathway. This was the aim of this study.

Design and methods: Analytical verification included assessment of critical outlier frequency, for hs-cTnI and cTnI assays. Concordance for paired cTnI and hs-cTnI measurements ($n=1096$) was verified using 99th percentiles for both genders (cTnI: 30 ng/L, hs-cTnI: 25 ng/L) and for men and women separately (hs-cTnI: M: 34;F: 16 ng/L). Discordant data was correlated with clinical and laboratory information. Diagnosis of Acute Coronary Syndrome (ACS) or Non-ACS was adjudicated by two cardiologists independently.

Results: The hs-cTnI assay showed a lower (10-fold) critical outlier rate (0.091%) and more detectable results above the limit of detection (LOD) (23.4%) and 99th percentile (2.4%), compared to cTnI. Analytical concordance between the two assays was high (94.5%) but decreased (91.7%) when gender-specific hs-cTnI cut-offs were used. The hs-cTnI assay gave fewer false negatives (up to 1.0%) but disproportionately more false positives (up to 6.7%) overall, which improved (3.9%) for serial measurements.

Conclusions: Laboratories should analytically and clinically verify hs-cTn assays before use, with attention to performance and the clinical and diagnostic algorithms that support appropriate testing and result interpretation. Work in the pre- and post-analytical phases is necessary to augment the analytical improvement in the new era of troponin testing.

1. Introduction

Over the past 10 years cardiac troponins T and I (cTnT and cTnI) have emerged as the cardiac biomarkers of choice for the diagnosis of Acute Myocardial Infarction (AMI), which is defined biochemically by a rise and/or fall in biomarker concentration

Abbreviations: ; ACS, Acute Coronary Syndrome; AMI, Acute Myocardial Infarction; CABG, Coronary Artery Bypass Graft; CD, Critical Difference; CV, Coefficient of Variation; CI, Confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; cTn, Cardiac troponin; hs-cTn, High sensitivity cardiac troponin; LOD, Limit of Detection; IQR, Inter-quartile range; FN, False Negative; FP, False Positive; NSTEMI, Non-ST-segment Elevation Myocardial Infarction; TN, True Negative; TP, True Positive; TTP, Total Testing Pathway.

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with at least one value above the 99th percentile [1]. During this time analytical developments have also resulted in the emergence of high-sensitivity Troponin (hs-cTn) assays into diagnostic use [2,3] which allow earlier detection of myocardial injury and show improved accuracy over established sensitive assays for diagnosis of AMI [4,5]. Improved imprecision at concentrations below the 99th percentile of the normal population has permitted measurement of troponin in a greater proportion of healthy individuals [2] and identification of patients with detectable troponin concentrations, less than the 99th percentile, who are at intermediate risk of major adverse cardiac events (MACE) [6]. A possible paradigm shift for troponin use in prognosis, screening and sub-clinical monitoring of myocardial remodelling has therefore emerged [7,8] and further emphasises the need for laboratories to fully evaluate this test both analytically and clinically.

Although hs-cTn assays are now almost commonplace, with improved diagnostic and prognostic capabilities, much work remains to be done throughout the total testing pathway (TTP). Reports of critical outliers are currently an unexplained feature of high-sensitivity (and contemporary sensitive) assays [9,10] which may require further analytical improvements for understanding of pre-analytical factors. Assay standardisation for cTnI is also ongoing [11]. There are also post-analytical challenges, including the need to accurately differentiate acute, chronic, cardiac and non-cardiac causes of troponin increases by obtaining serial troponin measurements [12]. A significant troponin change, consistent with an ACS, may be expressed as the absolute (Δ, ng/L) or relative (%) change (delta,δ), where the former shows diagnostic advantage [13,14], by evaluations against the Reference Change Value (RCV, %) [15] or by using a probability (z-scores) based approach [16]. To enable accurate interpretation of baseline troponin measurements, work continues to establish appropriate troponin reference ranges, accounting for age, race and gender [17]. There are also issues around the appropriateness of troponin requests in specific situations, which may be explained by a knowledge gap in understanding both the utility and limitations of this test by clinical users.

In view of the current challenges that exist for hs-cTn assays, we report our approach, involving analytical and clinical verification, to help transition from the sensitive cTnI in current use to the new hs-cTnI assay on the Abbott Architect and our attempts to addressing the challenges that remain across the TTP.

Table 1
Demographics, clinical presentation and previous clinical background of patients with cTnI/hs-cTnI data pairs ($n=94$). Most patients within this discordant cohort had a known cardiac background involving any one or more of: Atrial Fibrillation, Angina, Myocardial Infarction (MI), Congestive Cardiac Failure or previous cardiac procedure (Coronary Artery Bypass Graft ([CABG], Percutaneous Coronary Intervention [PCI], Intra-Cardiac Device [ICD], cardiac transplant or valve repair). For patients with a non-cardiac background, most had respiratory disease. ns=Non-Significant difference in age between males and females.

Gender	54 Women/40 Men
Age (Median [IQR])	Women: 82 [70–87] years Men: 79 [68–84] years (ns)
eGFR ml/min/1.73 m^2:	
Median [IQR]	55.5 [31.5–60]
% of patients with eGFR:	
≥ 60	45%
30–59	33%
15–29	19%
< 15	3%
CRP concentration (Median[IQR], mg/L)	38.5 [15–90]
% of patients with CRP > 7 mg/L	82%
Presenting symptoms	
Chest pain	[a]20 (Cardiac: 5, Pleuritic: 1)
Shortness of breath	39
Palpitations	3
ECG abnormalities (ST elevation/LBBB/T wave inversion)	1/2/1
Patients with Cardiac background	74
Atria fibrillation	22
Angina	13
MI (STEMI)	15(3)
Congestive cardiac failure	2
Cardiac procedure: CABG/PCI/ICD/Transplant/Valve repair	23 (9/9/3/1/1)
Patients without Non-Cardiac background	20
Respiratory disease (COPD, Pulmonary Fibrosis)	6
Cerbrovascular disease	3
Gastro-intestinal disease	3

[a] Type of Chest pain not specified in 14/20 patients. LBBB=Left Bundle Branch Block. STEMI=ST elevation Myocardia Infarction. COPD=Chronic Obstructive Pulmonary Disease.