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Comparison of new point-of-care troponin assay with high sensitivity troponin in diagnosing myocardial infarction

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ABSTRACT

Objectives: The aim of this study is to compare a new improved point of care cardiac troponin assay (new POC-cTnI) with 1. its predecessor (old POC-cTnI) and 2. a high sensitivity assay (hs-cTnI) for the diagnosis of acute myocardial infarction (AMI) and for major adverse cardiac events (MACE) by 30 days.
Methods: This is a single centre observational study, set in Christchurch Hospital, New Zealand. Patients presenting to the emergency department with non-traumatic chest pain underwent blood sampling at 0 h and 2 h post presentation for analysis with the 3 cTnI assays for the outcome of AMI and for analysis using an accelerated diagnostic protocol (ADP-normal 2 h troponins, normal electrocardiograms and Thrombolysis In Myocardial Infarction (TIMI) score of 0 or ≤1) for 30 day MACE.
Results: Of 962 patients, 220 (22.9%) had AMI. Old POC-cTnI was least sensitive at 70.0% (65.4–73.9%) by 2 h ($p < 0.001$). New POC-cTnI, sensitivity 93.6% (89.9–96.2%) had similar sensitivity to hs-cTnI, sensitivity 95.0% (91.5–97.3%) ($p = 0.508$). There were 231 (24.0%) patients with 30 day MACE. When used as part of the ADP, all assays had 100% (98.0–100%) sensitivity using TIMI = 0. Sensitivities of new POC-cTnI ADP, 98.3% (95.4–99.4%), old POC-cTnI, 96.5% (93.2–98.4%) and hs-cTnI, 98.7% (96.0–99.7%) were similar ($p = 0.063$–0.375) using TIMI ≤ 1.
Conclusions: A new POC-cTnI has improved sensitivity for AMI and MACE compared with its predecessor and comparable sensitivity to a high sensitivity assay. Now that sensitivities of the POC assay are improved, the new assay may be a useful alternative to central laboratory assays when rapid turn-around times are not possible.

1. Introduction

Risk stratification tools for the evaluation of patients presenting with chest pain suspicious of acute coronary syndrome (ACS)/acute myocardial infarction (AMI) have been around for decades. Such tools have previously required patients to remain in hospital for lengthy periods whilst undergoing investigation. However, given that most patients presenting in this way ultimately do not have ACS, the concept of the accelerated diagnostic protocol (ADP) has been developed. Accelerated diagnostic protocols involve using a more rapid investigation pathway for a sub-group of patients with chest pain identified as being at low risk of an ACS [1].

The multinational ASPECT (Asia Pacific Evaluation of Chest pain Trial) [2] study evaluated an ADP comprising early measurement (at presentation and 2 h later) of a point of care (POC) biomarker panel (cardiac troponin [cTn] I/myoglobin/creatine kinase) and electrocardiograms in conjunction with the Thrombolysis In Myocardial Infarction (TIMI) score. Those with an ADP score of 0 (9.8%) were identified as being at very low-risk for 30 day major adverse cardiac events (MACE) (0.9%) and suitable for expedited discharge. Subsequent research including the ADAPT (2-hour Accelerated Diagnostic protocol

Abbreviations: ADAPT, 2-hour Accelerated Diagnostic protocol to Assess Patients with chest pain symptoms using contemporary Troponins; ADP, accelerated diagnostic protocol; AMI, acute myocardial infarction; ASPECT, Asia Pacific Evaluation of Chest Pain Trial; ED, Emergency Department; (hs)-cTn, (high sensitivity) cardiac troponin; MACE, major adverse cardiac events; POC, point of care; TIMI, Thrombolysis In Myocardial Infarction.

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to Assess Patients with chest pain symptoms using contemporary Troponins) trial [3] has shown that more patients can be identified as low risk with no loss of clinical sensitivity for the occurrence of MACE/ACS when cTn (laboratory or POC) is the only biomarker contingent of the ADP (without myoglobin and creatine kinase) [3,4].

Analytical sensitivity (limit of detection) of an assay is defined as the ability of the assay to measure the minimum detectable concentration of an analyte which can be reliably distinguished from the limit of blank (the highest *apparent* analyte concentration expected to be found when replicates of a blank sample containing no analyte are tested) and at which detection is feasible [5]. In order to maintain optimal clinical sensitivity (the chance of testing positive [elevated cTn] amongst those with the condition [AMI]), the analytical sensitivity of an assay must be below the decision cut-point. In the case of cTn, the decision cut-point is recommended at the 99th percentile of a normal population [6]. However, precision, or repeatability, of assay test results, is also important and is expressed using the inter and intra-assay coefficients of variation. Guidelines recommend a coefficient of variation equal or lower than 10% at the 99th percentile [6].

The POC cTnI used in ASPECT has low analytical sensitivity and the recommended precision is not achieved whereas the laboratory cTnIs used in ADAPT have superior analytical sensitivity and achieve near guideline recommended precision. High sensitivity cardiac troponins (hs-cTn) fulfil all recommended criteria.

Further analysis of ADAPT/ASPECT showed that although the POC-cTnI assay performed inferiorly to sensitive and hs-cTn laboratory assays for the diagnosis of AMI, performance of all troponins were comparable when used as part of the ADP with a TIMI score cut-point of 0 [3,4]. However, additional analysis showed that use of an hs-cTnI allowed the ADP to be modified to include a broader low-risk group by including patients with a TIMI score of ≤1 (0 and 1 rather than just 0), classified as low risk (41.5%) whilst maintaining safety against adverse events (30 day MACE rate 0.8%) [7].

The aim of this pre-specified analysis of the data from the New Zealand arm of ASPECT/ADAPT was to compare a new POC cTn assay, that claims to have improved analytical sensitivity, 1. with the POC assay used in the ASPECT and 2. with a central laboratory hs-cTnI assay (the assay currently used in clinical practice at our institution). This analysis assessed both individual performances of assays in the diagnosis of AMI and also for MACE by 30 days when used as part of the ADP.

2. Materials and methods

2.1. Study design

The study design has previously been reported in detail [3]. In brief, patients presenting to the ED between 0530 and 2000 from November 2007 until April 2010 were recruited by research nursing staff. Those with symptoms suggestive of cardiac ischaemia (acute chest, epigastric, neck, jaw or arm pain or discomfort or pressure without an apparent non-cardiac source) were included. Patients were excluded if they were <18 years, unable to provide informed consent, unwilling to participate or would not be available for follow-up. Hospital clinical protocols required laboratory cTnI levels to be measured at presentation (0 h) and again at least 6 h later. Additional sample was taken at 2 h post presentation for study laboratory cTnI measurement, at 0 h and 2 h for immediate analysis on a POC device and freezing for later analysis using other cTn assays. Electrocardiograms were recorded at presentation and ≥6 h later, during episodes of symptoms and if requested by medical staff. Data for the TIMI score were collected by research nurses. The decision to perform stress testing, coronary angiography and other management plans was at the discretion of the attending clinician with knowledge of the clinically utilized cTnI results but without the knowledge of all other cTn assays under investigation or ADP results as a whole.

Patients were followed for 30 days by telephone contact, review of patient notes and search of the National Health Index database (identifies national hospital attendances/deaths using a unique alphanumeric identifier). The research protocol was approved by the Upper South A Regional Ethics Committee of the New Zealand Ministry of Health. All participants gave informed consent.

2.2. Troponin assays

The 99th percentile of a normal population, analytical sensitivity (limit of detection), 10% coefficient of variation and decision cut-point for each assay is shown in Table 1.

The reference test was Architect Troponin I, Abbott Diagnostics, Chicago, Illinois. Blood samples for the hospital clinical pathway were obtained at presentation and 6–12 h after presentation and were sent in tubes coated with lithium heparin.

Fresh whole blood samples in ethylenediaminetetraacetic acid tubes were taken at 0 h and 2 h post presentation and immediately analysed on the Triage CardioProfilER (Alere, San Diego, California) for cTnI (old POC-cTnI) then centrifuged. The plasma was stored frozen at −80 °C for later analysis in a blinded fashion in batches for a new POC cTnI (new POC-cTnI, Alere Cardio3, San Diego, California). The new POC-cTnI has not published its limit of detection but has improved limit of blank, as judged by the 95th percentile of twenty replicates per day each of a whole and plasma blank sample each tested for 5 days on three lots of test devices. The 99th percentile was determined using specimens obtained from 989 apparently healthy individuals (cTnI results ranged from <10 ng/L to 65 ng/L). Precision was tested for a high (600 ng/L) and low (60 ng/L) control plasma with 80 replicates for each control, over 40 separate test runs, over 20 days of. Total precision for the high control was 11.0% and of 16.7% for the low control.

Further frozen plasma samples were later analysed in a blinded fashion in batches for a high sensitivity cTnI (hs-cTnI, Architect Troponin I, Abbott Diagnostics, Chicago, Illinois).

2.3. Electrocardiograms

Ischaemic electrocardiogram changes were defined by ST depression of ≥0.5 mm or T-wave inversion of ≥1 mm in ≥two contiguous leads, not known to be old.

2.4. Adjudication

Patient data were recorded according to the American College of Cardiology's key data elements and definitions for measuring the clinical management and outcomes of patients with ACS [8], standardized guidelines for reporting data for patients with ACS [9] and presented as per Comprehensive Standardised Data Definitions for ACS Research in ED Australasia [10]. Diagnoses on admission and at follow-up were independently adjudicated by a Cardiologist and a Cardiology Research Clinician, blinded to the results of the test assays and ADP results. A second Cardiologist was involved in cases of discrepancy.

2.5. Outcome measures

The primary outcome measure was a comparison of the diagnostic performance of the new POC-cTnI with 1. the old POC-cTnI and 2. Hs-cTnI in isolation when measured at 0 h and 2 h after presentation for the diagnosis of AMI. The diagnostic criteria for AMI (as per Universal Definition) were a detection of a rise and/or fall of cTn with at least one value above the 99th percentile in the setting of symptoms of ischaemia, with or without new or presumed new significant ST-segment/T wave changes/new left bundle branch block/development of pathological Q waves or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality [6].

The secondary outcome measure was a comparison of the ADP where the cTn contigent included 0 h and 2 h new POC-cTnI with 1. the ADP using old POC-cTnI and 2. the ADP using hs-cTnI in combination with the TIMI score (both cut-points of 0 and ≤1) and electrocardiogram results for the outcome of a MACE (where MACE was defined as AMI, cardiac death, cardiogenic shock, emergency revascularization, ventricular arrhythmia or high degree heart block requiring treatment) by 30 days post presentation.

2.6. Statistical analysis

Continuous variables are presented as medians/interquartile ranges, and categorical variables as numbers/percentages. We calculated the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of each of the cTn assays for the diagnosis of AMI at 0 h and also by 2 h (i.e. incorporating both 0 h and 2 h results). We then calculated the same parameters for an ADP incorporating values from each of the cTn assays using both cut-points for the TIMI score for the outcome of MACE at 30 days. Sensitivities and specificities were compared using the McNemar test. All statistics were completed using SPSS version 20.

3. Results

There were 1184 patients recruited in the New Zealand arm of the ASPECT/ADAPT study. There were 962 patients with complete results for each of the troponin assays at both 0 h and 2 h. Patient characteristics are shown in Table 2.

There were 220 patients (22.9%) diagnosed with AMI (196 non ST elevation AMI and 24 ST elevation AMI). At both time points all assays were more sensitive ($p < 0.001$ for all pair-wise comparisons) than the old POC-cTnI test which failed to identify 93 patients with AMI at 0 h and 66 patients by 2 h. Both other assays were as sensitive as each other ($p = 0.302$ at 0 h and 0.508 by 2 h). The hs-cTnI failed to identify 22 and new POC-cTnI 27 patients with AMI when measured at 0 h (Table 3) and hs-cTnI failed to identify 11 and new POC-cTnI 14 patients with AMI using both 0 h and 2 h measurements (Table 4). New POC-