The utility of presentation and 4-hour high sensitivity troponin I to rule-out acute myocardial infarction in the emergency department

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The utility of presentation and 4-hour high sensitivity troponin I to rule-out acute myocardial infarction in the emergency department.

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Abbreviations

ADP: Accelerated Diagnostic Pathway
AMI: Acute Myocardial Infarction
NSTEMI: Non-ST Elevated Myocardial Infarction
ECG: Electrocardiogram
ESC: European Society of Cardiology
hs-cTnI: high sensitivity cardiac Troponin I
hs-cTnT: high sensitivity cardiac Troponin T
LoD: Limit of Detection
NICE: National Institute for Health Care and Excellence

Abstract

a) Objectives: International guidance recommends that early serial sampling of high sensitivity troponin be used to accurately identify acute myocardial infarction (AMI) in chest pain patients. The background evidence for this approach is limited. We evaluated whether on presentation and 4-hour high-sensitivity troponin I (hs-cTnI) could be used to accurately rule-out AMI.

b) Design and Methods: hs-cTnI was measured on presentation and at 4-hours in adult patients attending an emergency department with possible acute coronary syndrome. We determined the sensitivity for AMI for at least one hs-cTnI above the 99th percentile for a healthy population or alone or in combination with new ischemic ECG changes. Both overall and sex-specific 99th percentiles were assessed.. Patients with negative tests were designated low-risk.

c) Results: 63 (17.1%) of 368 patients had AMI. The median (interquartile range) time from symptom onset to first blood sampling was 4.8 hours (2.8-8.6). The sensitivity of the presentation and 4h hs-cTnI using the overall 99th percentile was 92.1% (95% CI 82.4% to 97.4%) and Negative Predictive Value 95.4% (92.3% to 97.4%) with 78.3% low-risk. Applying the sex-specific 99th percentile did not change the sensitivity. The addition of ECG did not change the sensitivity.

d) Conclusion: Hs-cTnI >99th percentile thresholds measured on presentation and at 4-hours was not a safe strategy to rule-out AMI in this clinical setting irrespective of whether sex-specific 99th percentiles were used, or whether hs-cTnI was combined with ECG results.

Key Words: high sensitivity troponin; acute myocardial infarction; emergency department; emergency room; accelerated diagnostic pathway; acute coronary syndrome; STEMI; NSTEMI

1. Introduction

Twin imperatives drive the assessment of patients presenting with chest pain to Emergency Departments (ED), namely early identification of patients with an acute myocardial infarction (AMI) and early identification of those at very low short-term risk of harm from AMI or ischemic heart disease. The former facilitates earlier planning of treatment and the latter helps avoids unnecessary inpatient admissions. Historically, most patients with symptoms suggestive of AMI undergo prolonged assessment, either in the ED or as hospital in-patients even though three quarters of these patients ultimately do not have a final diagnosis of AMI[1-3].

High sensitivity cardiac troponin assays (hs-cTn) produce analytically reliable results at the 99th percentile of a healthy population which may facilitate identification of patients suitable (i.e. safe) for rapid discharge to outpatient care with potentially major benefits for health services costs and ED and hospital overcrowding[4-7]. A second measurement of hs-cTn from a blood sample drawn two to four-hours after hospital attendance time-point may be useful. Whereas accelerated chest pain pathways incorporating presentation and 2h sampling can identify an increased proportion of low-risk patients[8,9] a presentation and 3h or 4h timeframe is still short enough so that patients could remain in the ED under the care of the original clinicians without transfer to another hospital area or handover to other staff.

The 2011 European Society of Cardiology (ESC) guidelines for management of acute coronary syndrome without persistent ST-segment elevation recommended a rapid rule-out of AMI protocol with only serial sampling of high sensitivity cardiac troponin[10]. A presentation and 3h sampling time was proposed based on two studies, one utilised a small sample size and the other utilised only one sample per patient[11,12]. An earlier generation troponin assay had yielded no

statistical difference in the positivity for AMI using greater than 3h or greater than 6h between samples[1,13,14]. The 2011 guidelines additionally recommended that where both troponin values are less than the 99th percentile of a healthy population that the Global Registry of Coronary Events (GRACE) be applied to confirm low risk. Since publication of the ESC guidelines a study by Keller and colleagues in a cohort of patients presenting with chest pain found that a prototype high sensitivity cardiac Troponin I (hs-cTnI) at a 99th percentile threshold of 30 ng/L had a 98.2% (95.9% to 99.4%) sensitivity for AMI with serial sampling at presentation and 3h[5].

The more recent National Institute for Health Care and Excellence (NICE) diagnostics guidance for hs-cTn assays recommending that "the assays are recommended for use with early rule-out protocols, which typically include a blood sample for cardiac troponin I or T taken at initial assessment in an emergency department and a second blood sample taken *after* 3 hours". Also recommended is that the high sensitivity troponin be used in conjunction with electrocardiogram (ECG) for diagnosis of NSTEMI[15].

We aimed to prospectively validate that plasma troponin levels analysed with a hs-cTn assay at presentation (0h) and 4h from hospital presentation can rule-out AMI in patients presenting acutely to Emergency Departments with chest discomfort that might be due to an AMI. We assessed both the troponin alone (ESC) and troponin plus ECG (NICE) strategies. For each strategy we also compared the performance of overall 99th percentile to the sex-specific percentiles. Additionally, we assessed the sensitivity for AMI and the proportion of patients who could be designated as low risk for AMI when the threshold used was the limit of detection of the high sensitive troponin.

2. Methods

An observational cohort study design was used. Patients were recruited in conjunction with a randomised controlled trial comparing an 'accelerated' (2 hour) chest pain diagnostic pathway against the standard investigative process at Christchurch Hospital. This trial has been described in detail elsewhere[8] and was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, received regional ethics approval and was registered on anzctr.org.au as ACTRN12610000766011. Briefly, eligible patients were aged ≥18 years, presenting acutely from the community to the ED with symptoms suggestive of AMI for whom, following initial clinical assessment the attending physician(s) planned to investigate for AMI with serial biomarker tests. In accordance with American Heart Association case definitions, possible cardiac symptoms included: the presence of acute chest, epigastric, neck, jaw or arm pain or discomfort or pressure without apparent non-cardiac source[2]. Patients were excluded if any of the following conditions were satisfied: ST Segment Elevation Myocardial Infarction (STEMI) as demonstrated by an ST elevation on any electrocardiograph (ECG) at presentation (Note: patients with all other ECG changes, including ST depression, were included); chest pain episode began >12 hours prior to assessment, proven or suspected non-coronary pathology as the cause of chest pain; need for admission regardless of a cTn <99th percentile, due to other medical conditions, or need for other investigations; previously enrolled in this study; anticipated problem with follow-up (e.g. resident outside New Zealand or terminal illness); or unable or unwilling to provide informed consent. Enrolment was consecutive during the hours of available research nurse (normally 0800 to 2300, 7 days a week). This analysis was limited to patients with sufficient stored plasma sample available for hs-cTnI assay at both presentation and 4 hours.

2.1 Reference standard

Classification of AMI was based upon global taskforce recommendations requiring evidence of myocardial necrosis together with evidence of myocardial ischaemia (ischaemic symptoms, ECG changes or imaging evidence)[4] Necrosis was diagnosed on the basis of a rising or falling pattern of the laboratory cardiac troponin (ARCHITECT troponin I [TnI] assay; Abbott) level, with at least one value above the 99th percentile (28 ng/L). The manufacturer-specified LOD for the assay was 10 ng/mL, and 10% coefficient of variation was at 32 ng/L. Outcomes and investigations were reported using predefined standardised reporting guidelines[16]. The presence of AMI was adjudicated independently by local cardiologists using these reporting guidelines and blinded to the results of the hs-cTnI (index test). If the reference troponin was above the reference range, but there was no rise or fall, other causes of a raised troponin were considered. If no clear alternative cause of the troponin rise was apparent then, if the clinical presentation was suggestive of ACS, an adjudicated diagnosis of AMI was made. A panel of two cardiologists performed the adjudication independent of each other with a third cardiologist making an independent adjudication in cases of disagreement.

2.2 Index Tests

Hs-cTnI sampling was on presentation to the ED and 4 hours later. Blood was drawn into 1x4mL Lithium heparin tubes, spun at 3220 RCF at 4°C for 10 minutes, 1ml of plasma was then transferred to one or two 1.5mL tubes and immediately stored at -80°C for later thawing and assay. Samples were assayed 12 to 36 months following collection. An ischaemic ECG was defined as ST-segment depression of at least 0.05 mV in 2 or more contiguous leads (including reciprocal changes), T-wave inversion of at least 0.1 mV, or Q-waves >30 ms in width and greater than or equal to 0.1 mV in depth in at least 2 contiguous leads. Patients with other

abnormal ECG findings (eg, pacing artefact and left bundle-branch block) that were present on pre-existing ECGs were not defined as high risk. The troponin assay used for the index test was the Abbott Architect *Stat* high sensitivity troponin I (hs-cTnI). It has a limit of detection (LOD) of 2 ng/L, 10% CV at 5 ng/L (Limit of Quantitation LoQ), sex-specific 99th percentile of 16 ng/L for women and 34 ng/L for men, and overall 99th percentile of 26 ng/L (Manufacturer provided thresholds). Assessment of five risk stratification strategies was performed where low-risk was defined as:

(i) presentation and 4h hs-cTnI values less than the overall 99th percentile,

(ii) presentation and 4h hs-cTnI values less than the sex-specific 99th percentiles,

(iii) no ischemic changes on ECG and presentation and 4h hs-cTnI values less than the overall 99th percentile,

(iv) no ischemic changes on ECG and presentation and 4h hs-cTnI values less than the sex-specific 99th percentiles, and

(v) no ischemic changes on ECG and presentation (only) hs-cTnI less than the LOD.

Demographics of the sample were reported using standard descriptive statistics. For each strategy, the sensitivity, specificity, negative predictive value, and positive predictive value were reported for AMI. For each strategy we determined the proportion of patients identified as low risk for AMI. We further calculated the GRACE score for false negatives and took a score <140 to confirm the classification as low-risk according with the ESC guidelines. All confidence intervals presented are exact binomial 95% confidence intervals. All calculations were made in R[17].

3. Results

There were 368 patients. The first blood sample was taken a median (interquartile range) 4.8 (2.8-8.6) hours after onset of symptoms. The median time difference between the presentation and the 4h sample was 4.4 h (4.25 to 4.63). Sixty-three (17.1%) were diagnosed with AMI. Demographics are given in table 1.

Table 1: Cohort characteristics

Variable	Value
Age (years)	61±13
Female	35% (129)
Weight (kg)	85±19
Ethnicity (self identified)	
Maori	9
New Zealander/ New Zealand European	329
Other	30
Risk Factors and History (patient reported)	
Hypertension	36.8% (174)
Dyslipidaemia	53.8% (198)
Diabetes	16.0% (57)
Current smoker	18.5% (68)
Family history of Ischemic Heart Disease	60.3% (222)
Prior:	
Myocardial Infarction	26.6% (98)
Angina	37.0% (136)
Ventricular Tachycardia	4.6% (17)
CAD	44.0% (162)
Atrial Arrhythmia	9.5% (35)
Congestive Heart Failure	4.3% (16)
Stroke or Transient Ischemic Attack	11.1% (41)
Peripheral Arterial Disease	4.6% (17)
Coronary Artery Bybass Graft	7.6% (28)
Coronary Angioplasty	27.7% (102)
Rheumatoid Arthritis	2.2% (8)
Outcomes	
ECG positive	5.4% (20)
STEMI	1 (0.3%)
NSTEMI	62 (16.8%)
Hospital length of stay (Days)	1.2 (0.9-3.1)

Data presents as n (%) or mean±SD or median (lower quartile - upper quartile)

The sensitivity for AMI of presentation and 4h hs-cTnI only using the overall 99th percentile was 92.1% (95% CI: 82.4% to 97.4%) with 78.3% identified as low risk. The Negative Predictive Value (NPV) was 98.3% (96.0% to 99.4%); Table 2. The five false negatives were all male. Their GRACE score was <140 in all cases confirming they were considered low-risk by this algorithm. Three showed increase in hs-cTnI of >10 ng/L between samples; symptom onset time was more than 3 hours prior to the first blood sample in three cases, Table 3.

The sensitivity for AMI and other metrics were the same for the sex-specific 99th percentile thresholds. The addition of ECG did not change the sensitivity for the test. The sensitivity was 100% (91.6% to 100%) for the LoD as threshold, with 11.4% identified as low-risk.

Table 2: Diagnostic metrics for each index test

Tests		AMI	Not AMI	Proportion Low Risk (%)	Sensitivity (%)	Specificity (%)	Negative Predictive Value (%)	Positive Predictive Value (%)
(i) Presentation and 4h hs-cTnI > overall 99th Percentile	Test positive	58	22	78.3	92.1 (82.4 to 97.4)	92.8 (89.3 to 95.4)	95.4 (92.3 to 97.4)	74.2 (62.0 to 84.2)
	Test negative	5	283					
(ii) Presentation and 4h hs-cTnI > sex specific 99th Percentile	Test positive	58	22	78.3	92.1 (82.4 to 97.4)	92.8 (89.3 to 95.4)	95.4 (92.3 to 97.4)	74.2 (62.0 to 84.2)
	Test negative	5	283					
(iii) ECG + Presentation and 4h hs-cTnI > overall 99th Percentile	Test positive	58	25	77.4	92.1 (82.4 to 97.4)	91.8 (88.1 to 94.6)	98.2 (96.0 to 99.4)	69.9 (58.8 to 79.5)
	Test negative	5	280					
(iv) ECG + Presentation and 4h hs-cTnI > sex specific 99th Percentile	Test positive	58	25	77.4	92.1 (82.4 to 97.4)	91.8 (88.1 to 94.6)	98.2 (96.0 to 99.4)	69.9 (58.8 to 79.5)
	Test negative	5	280					
(v) ECG + Presentation hs-cTnI >Limit of Detection (2 ng/L)	Test positive	63	263	11.4	100 (91.6 to 100)	13.8 (10.1 to 18.2)	100 (87.7 to 100)	19.3 (15.2 to 24.0)
	Test negative	0	42					

Table 3: Details of the False Negatives for index test (i) Presentation and 4h hs-cTnI > overall 99th Percentile

Study ID	CP150	CP157	CP170	CP464	CP530
sex	M	M	M	M	M
age	47	73	84	72	69
Hs-cTnI at presentation (ng/L)	7.2	13.8	6.5	7.1	7
Hs-cTnI at 4h (ng/L)	17.9	24.1	23	8.3	8.3
cTnI (ng/L) at presentation	<10	<10	<10	10	20
First cTnI (ng/L) at >6h	60	120	30	20‡	40
ECG	Negative	Negative	Negative	Negative	Negative
Relative difference (%)	148.6	74.6	253.8	16.9	18.6
Absolute difference (ng/L)	10.7	10.3	16.5	1.2	1.3
Time from symptom onset to presentation sample (h)	2.58	4.83	2.83	3.75	5.92
Heart rate (bpm)	82	58	60	70	70
Systolic blood pressure	121	126	160	124	190
Creatinine (µmol/L)	130*	81	91	148**	65
Killip Class	NA	1	2	1	NA
GRACE score (Death or MI in hospital)	<133†	101	124	113	<132†
Pain					
Pleuritic	No	No	No	No	Yes
On palpitation	No	No	No	No	No
Radiates to arm	No	No	Yes	Yes	No
Diaphoresis	Yes	Yes	Yes	Yes	No
Risk Factors and History (patient reported)					
Hypertension	Yes	Yes	Yes	No	No
Dyslipidaemia	Yes	Yes	Yes	Yes	No
Diabetes	No	Yes	No	No	No
Current smoker	No	No	No	No	No
Family history of Ischemic Heart Disease	Yes	Yes	Yes	Yes	No
Use of Aspirin in last 7 days	No	No	No	Yes	No
Prior:					
Myocardial Infarction	No	No	Yes	Yes	No
Angina	No	Yes	Yes	Yes	No
Ventricular Tachycardia	No	No	No	No	No
CAD	No	Yes	Yes	Yes	No
Atrial Arrhythmia	No	No	No	Yes	No
Congestive Heart Failure	No	No	No	No	No
Stroke or Transient Ischemic Attack	No	No	Yes	Yes	No
Peripheral Arterial Disease	No	Yes	No	No	No
Coronary Artery Bybass Graft	No	No	No	No	No
Coronary Angioplasty	No	No	Yes	Yes	No
Rheumatoid Arthritis	No	No	No	No	No
Modified TIMI risk score††	0	3	3	3	1
Investigations and Treatments					
Revascularisation	Urgent PCI at 3 days	Urgent CABG at 12 days	No	No	Urgent PCI at 6 days
Angiostenosis	Yes	None	None	Yes	Yes
Echocardiogram ejection fraction	NA	62	36	62	65
EMRA	NA	No	Yes	No	Yes

* Possibly Acute Kidney Injury; **Probably a chronic elevation given the patient creatinine history.

† Assumes a maximum Killip class of 3 because class 4 is cardiogenic shock and this was not recorded in any case.

†† modified because the score for the troponin and ECG are not included.

‡ a subsequent troponin on the next morning (13 hours later) was 40 ng/L (ie positive).

NA: Not Available; PCI: Percutaneous Coronary Intervention; MI: Myocardial Infarction; EMRA: Echocardiograph regional wall motion abnormality

4. Discussion

The sensitivity for AMI of either presentation and 4h hs-cTnI at the 99th percentile on its own or in combination with ECG on presentation to rule-out AMI was considerably less than 99%, a threshold considered optimal by ED physicians[18]. Even at the best sensitivity for AMI the upper confidence interval of 97.4% was below this level. Notably this is less than the 98.2% (95.9% to 99.4%) found by Keller and colleagues for presentation and 3h hs-cTnI above the 99th percentile for a prototype hs-cTnI assay and without the inclusion of ECG in the test (the inclusion of which should only increase sensitivity). This and the false negatives we observed highlights the dangers of a biomarker only approach, especially where a relatively high threshold (99th percentile of a healthy population) is applied and that findings during clinical assessment must be incorporated into the assessment in a Baysean manner together with biochemical markers. Previously, we have demonstrated in the primary trial that a minimum level of 99% sensitivity for AMI may be reached with risk stratification using the Thrombolysis in Myocardial Infarction (TIMI) risk score in addition to a presentation ECG and presentation and 2 hour contemporary cardiac troponin[8]. The TIMI score incorporates age, risk factors including family history of coronary artery disease, and history. Other risk scoring strategies that may also improve identification of a low-risk cohort, for example the EDACS, HEART, Modified Goldman and Vancouver Chest Pain rule, include the same class of factors with different weightings and variation in the components that make up the history and risk factor scores in particular[9,19-21]. EDACS also includes sex. An EDACS-ADP may classify with high sensitivity over 40% of patients[9].

We also noted that in three of the false negatives there was a small, but measureable change in hs-cTnI of greater than 10 ng/L between samples. Although both samples remained below the

99th percentile, a cautious clinician may not wish to classify these patients as low risk. Further work is needed to decide on the role of deltas below the 99th percentile.

The ESC guideline recommendation of a presentation and typically after 3h high sensitivity troponin samples to rule out AMI are based on only two studies. The first assessed the performance of hs-cTnT with a threshold of 14 ng/L in a population of 57 patients without impaired renal function and with retrospectively confirmed unstable angina and evolving NSTEMI[11]. A sensitivity of 100% for diagnosis of NSTEMI with a wide confidence interval (95% confidence interval: 75.1% to 100%) was achieved for serial sampling on admission and a second sample within 3 hours. The second study was comprised of two cohorts where the performance of a single hs-cTnT measure within a median 3 hours (range 0 to 7 hours) was assessed. Only in one cohort, the Bad Nauheim ACS registry comprising 1023 patients who had been referred for coronary angiography or percutaneous coronary intervention (because of ACS within the previous 48 hours), was the performance of hs-cTnT assessed for diagnosis of AMI[12]. The sensitivity for AMI was 96% and negative predictive value 80%. Both these studies were published at a time when they may have been affected by the calibration issues leading to inaccurate reporting of numerical results for hs-cTnT[22,23].

The NICE guidelines were based on a systematic review of the literature which was dominated by hs-cTnT rather than hs-cTnI studies[24] and only 6 studies which reported multiple testing. The recommendation of a second hs-cTn test ‘typically’ at 3-hour time point was based on consideration of the possibility of ruling in AMI with a suitable delta.

This present study aimed to employ a 4-hour time period between presentation and the second sample. This was deliberate because the primary study already had presentation and 2 hour time points, 4 hours was still short enough to enable discharge from ED to outpatient care within the national 6 hour ED target stay, and was only likely to enhance sensitivity and specificity for AMI over a 3 hour sampling. The study was limited by its size meaning the confidence intervals are broad.

Eggers and colleagues have previously considered the use of the 99th percentile for consecutive presentation and 2-hour hs-cTnI samples in combination with ECG to rule-out NSTEMI[25]. They found the sensitivity for NSTEMI to be 96.9%; as with the current study, too low to be clinically useful. When the authors considered the lower 97.5% threshold (15.5 ng/L) the sensitivity for NSTEMI improved to 98.2% with 54.4% ruled-out by this strategy. Similarly the TRAPID AMI protocol employing an hs-cTnT threshold less than the 99th threshold (ie 12 ng/L) along with a delta of <3 ng/L in 1 hour ruled out 60% of patients with 100% sensitivity in a derivation cohort[26] and 59.5% of patients with 99.6% sensitivity in a validation cohort[27]. Cullen and colleagues assessed the sensitivity for 30-d AMI or cardiac death of a Siemens contemporary troponin I at the 99th percentile (56 ng/L) at 0 and 2h and found a sensitivity of 92.2% [28]. Druey and colleagues also recently assessed the use of contemporary troponin I to rule-out AMI using a 0 and 2h algorithm with a lower threshold of 10ng/L[29]. This ruled-out 44% of patients with a sensitivity of 98.4% in a derivation cohort and 62% of patients with a sensitivity of 94.5% in a validation cohort. The present study was not powered to discover an optimal threshold for rule-out. Nevertheless, we could rule-out 58% of patients with 100% sensitivity (95%CI: 91.6% to 100%) for AMI with a threshold of 8 ng/L. The differences are probably due to differences in cohort characteristics and because the current study had only 63

AMI resulting in broad confidence intervals. Nevertheless, the Eggers analysis and the present study suggest that a threshold between the limit of detection and 99th percentile may be used with serial samples and in combination with ECG to rule-out a significant proportion of patients. We recommend that such strategies be compared in the same cohort with those which also utilise a risk stratification score.

The use of an undetectable hs-cTnT [30,31] or hs-cTnI [5,32] in conjunction with a negative ECG has recently been demonstrated to rule-out AMI on presentation with excellent sensitivity. This study supports those findings with a sensitivity for AMI of 100% allowing 11.4% of patients to be ruled out of having an AMI shortly after presentation to ED. In a cohort of patients with identical exclusion and inclusion criteria Greenslade and colleagues also had 100% sensitivity for AMI for undetectable hs-cTnI and found 17.8% of patients were low risk[15,32]. Similarly Keller and colleagues had a 100% sensitivity with 27.4% low risk[5,15]. On the other hand Body and colleagues found AMI could not be excluded by this method (sensitivity: 97.1%) and recommended further work on serial sampling to improve sensitivity[33]. Although the sensitivity for AMI in our study was 100%, the study size was limited and the lower limit 95% confidence intervals was only 91.6%. Therefore, we too recommend further work.

A limitation of our study potentially affecting our conclusion that performance did not differ with sex-specific thresholds was that the diagnosis of AMI was based on overall (not sex-specific) values. This may have biased against females with low, but abnormal troponin elevations using sex-specific cut points.

5. Conclusion

The sensitivity for AMI of hs-cTnI <99th percentile at presentation and 4 hours alone or in combination of a non-ischaemic ECG was too low to be reliably clinically useful for rule out when used without reference to clinical indicators. The proposed use of classifying patients with hs-cTnI less than the limit of detection on presentation also had good sensitivity and would enable approximately 10% of patients to be classified as low-risk as soon as the first blood results became available.

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Highlights

- AMI can not be ruled out by serial hs-cTnI <99th percentile within the ED
- Sex-specific 99th percentile thresholds do not improve sensitivity
- The addition of negative ECG does not improve sensitivity
- 11% may be ruled out with hs-cTnI <LoD and negative ECG