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ORIGINAL ARTICLE

Performance of Risk Stratification for Acute Coronary Syndrome with Two-hour Sensitive Troponin Assay Results

Louise Cullen, MBBS[a,b,c*], Jaimi Greenslade, PhD[a,b], Martin Than, MBBS[e], Jillian Tate, MSc[f], Jacobus P.J. Ungerer, MBChB, MMed[f], Carel Pretorius, MBChB[f], Christopher J. Hammett, MBChB, MD[c,d], Arvin Lamanna, MBBS[d], Kevin Chu, MBBS MSc[a,c], Anthony F.T. Brown, MBChB[a,c], William A. Parsonage, DM[c,d]

[a]Department of Emergency Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia
[b]School of Public Health, Queensland University of Technology, Brisbane, Australia
[c]School of Medicine, The University of Queensland, Brisbane, Australia
[d]Department of Cardiology, Royal Brisbane and Women's Hospital, Brisbane, Australia
[e]Department of Emergency Medicine, Christchurch Hospital, New Zealand
[f]Pathology Queensland, Brisbane, Australia

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Background Risk stratification processes for patients with possible acute coronary syndrome (ACS) recommend the use of serial sensitive troponin testing over at least 6 h. Troponin assays vary in their analytical performance. Utility in accurate risk stratification at 2 h post-presentation is unknown.

Methods A diagnostic accuracy study of patients presenting to the emergency department (ED) with symptoms of ACS was performed. Troponin was measured at 0, 2 and 6 h post-presentation. Acute myocardial infarction (AMI) was adjudicated by cardiologists and incorporated the 0 and 6 h troponin values measured by a sensitive troponin assay. Results were described using standard measures of test accuracy.

Results Of the 685 patients, 51 (7.4%) had 30-day AMI or cardiac death, and 76 (11.1%) had secondary outcomes (all cause death, ACS and revascularisation procedures). There was no significant difference in the diagnostic accuracy of early versus late biomarker strategies when used with the current risk stratification processes. Incorporation of a significant delta did not improve the stratification at 2 h post-presentation.

Conclusions Accelerated risk stratification of patients with ACS symptoms may occur at 2 h post-presentation using troponin results measured by a sensitive assay. Incorporation of such a strategy could support improvements in patient flow within EDs.

Keywords Troponin • Emergency Service • Hospital • Acute coronary syndrome • Risk stratification

Introduction

Acute coronary syndromes (ACS) are the most common serious conditions in patients presenting to the Emergency Department (ED) with chest pain. The diagnosis of the spectrum of ACS, from the biomarker-negative condition of unstable angina pectoris to acute myocardial infarction (AMI), can be challenging. Many different risk stratification rules may be employed to assess the likelihood of acute coronary syndromes in patients with chest pain presenting

*Corresponding author at: Department of Emergency Medicine, Royal Brisbane and Women's Hospital, Herston, QLD 4029, Australia.
Tel.: +61 7 3646 7901; fax: +61 7 3646 1643., Email: louise_cullen@health.qld.gov.au

to the ED. Within Australia, the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand (NHFA/CSANZ) guidelines are most frequently used for this purpose (Supplementary Table) [1]. Using sensitive troponin assays, these guidelines recommend serial troponin testing over 6–8 h [2,3]; however, fewer than 20% of the ED patients tested for ACS have a final diagnosis of any serious acute cardiac conditions including AMI [4,5]. This lengthy assessment process contributes to ED overcrowding and high admission rates for this cohort, and delays further objective investigations for underlying coronary artery disease.

Serial testing using recently developed troponin assays within 2–3 h of presentation to hospital may allow early rule-in and rule-out of AMI [6–8], with determination of changing patterns of troponin concentration over time (delta cTn) providing important methods to distinguish acute from chronic causes of cTn elevation (e.g. AMI versus chronic heart failure). Definition of a significant delta cTn may improve the diagnostic accuracy for troponin testing for AMI [9], with both relative change (expressed as a percentage) [10,11] and absolute changes between a baseline and follow-up sample having clinical utility [8]. Guidance on the precise utility of this method is evolving [12], with differences in the analytical characteristics of troponin assays mandating individual assessment of assays to define the optimum metrics applicable in clinical context.

This study had two major aims. The first was to compare the diagnostic accuracy of early biomarker strategies with the NHFA/CSANZ risk stratification processes to the recommended later biomarker testing (>6 h) using sensitive troponin assays. The second was to determine a significant two hour delta for the Siemens Dimension EXL® TnI and assess whether including this delta within the NHFA/CSANZ guidelines would improve risk stratification for ACS.

Methods and Materials

Setting and Selection of Participants

This was a planned secondary analysis of a prospective study of adults presenting to an ED from November 2008 to December 2010 with symptoms requiring evaluation of possible ACS, conducted in an inner city tertiary-referral teaching hospital in Australia with an annual ED census of over 70,000 [5]. The methods have been described in detail previously [5]. In brief, patients were eligible for inclusion if they presented with at least 5 min of chest pain suggestive of ACS. In accordance with the American Heart Association guidelines, this included the presence of acute chest, epigastric, neck, jaw or arm pain or discomfort or pressure or breathlessness, without apparent non-cardiac source [13]. Research assistants obtained informed consent and enrolled eligible patients between the hours of 0800 and 1700 Monday to Friday. Exclusion criteria included pregnancy, patients under the age of 18 years, those unable or unwilling to consent and patients in whom follow-up was considered impossible (homeless or itinerant). The original study was registered with the Australian and New Zealand clinical trials registry ACTRN12610000052033. The protocol was approved by the Royal Brisbane and Women's Human Research and Ethics Committee. All work conformed to the 'Statement on Human Experimentation' by the National Health and Medical Research Council of Australia. Queensland Emergency Medical Research Foundation and Siemens supported this research but had no role in the design or implementation of the study, nor in the decision to publish.

Methods of Measurement

Trained research staff documented clinical features including risk factors using a standardised data collection sheet [14]. Electrocardiographs (ECGs) were acquired at 0, 2 and 6 h post-presentation. Blood was drawn for serum cTnI at 0 and 6 h for analysis in the central laboratory. Patients were managed according to guidelines based on the 2006 NHFA/CSANZ recommendations [15].

Outcome Measures

The primary outcome for risk stratification was cardiac death or AMI within 30 days of presentation, and the secondary outcomes included in addition, all cause death, unstable angina pectoris and revascularisation procedures. Adjudication of all cardiac endpoints was performed by two cardiologists with a third cardiologist in cases of disagreement. Cardiologists were masked to results of the index test biomarkers under investigation, but had knowledge of all other clinical information during the follow up period including the ECGs and serial troponin results from usual care. The reference standard for the diagnosis of AMI required the detection of a rise and/or fall of the reference cTn concentration with at least one value >99th percentile value of the normal reference population, together with evidence of myocardial ischaemia in accordance with international guidelines. Results of additional investigations including stress tests, echocardiography and angiography were incorporated where performed. UAP was adjudicated as patients with negative serial troponin results with ischaemic symptoms and objective evidence of ischaemia on the exercise stress testing (ST depression $\geq$2 mm or $\geq$1 mm in the presence of ischaemic symptoms), stress echocardiography, myocardial perfusion scanning, coronary computed tomography angiography or significant findings on coronary angiography.

Reference Standard

Blood samples were taken on presentation (0 h) and $\geq$6 h with cTnI measured using the Beckman Coulter 2nd generation AccuTnI assay. The 99th percentile of this assay and the cut-off value used to identify an elevated cTnI is 0.04 µg/L, with the limit of detection (LoD) of 0.01 µg/L. The manufacturer's reported coefficient of variation (CV) is 10% at 0.06 µg/L.

Index Test

In addition to sampling for routine clinical care, blood was drawn on presentation and 2 h later and immediately