What is the 30-day rate of adverse cardiac events in chest pain patients with ED troponin I assays ≤ 99th centile using a contemporary sensitive assay? An exploratory analysis

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Aim **For nonhigh-risk patients who 'rule out' for acute coronary syndrome, Australasian guidelines recommend further testing to identify coronary artery disease. Testing is usually performed as an outpatient procedure. This recommendation has not changed with the advent of sensitive biomarker assays. We aimed to determine the 30-day rate of adverse cardiac events in emergency department (ED) chest pain patients without known coronary artery disease who had ED troponin I (TnI) assays ≤ 99th centile using a contemporary troponin assay, stratified by the Heart Foundation (HF; Australia) risk group.**

Methods **This study is a substudy of a prospective observational study. Clinical and investigational data were collected. The primary outcome of interest was the proportion of patients with ED TnI assays ≤ 99th centile who suffered a major adverse cardiac event (MACE; myocardial infarction, death, major arrhythmia) within 30 days, stratified by HF risk group. The secondary outcome was the rate of MACE or revascularization in non-HF high-risk patients.**

Results **A total of 460 patients were studied. Among them, 388 had no TnI assay > 99th centile. There was one MACE in this group [0.26%, 95% confidence interval (CI) 0.05–1.5%]: a non-ST segment elevation myocardial infarction in an HF high-risk patient. There were no MACEs among nonhigh-risk patients (0%, 95% CI 0–1.5%), and one patient had revascularization (0.4%; 95% CI 0.7–2.2%).**

Conclusion **Among ED patients presenting with suspected acute coronary syndrome, adverse cardiac events at 30 days are rare in nonhigh-risk patients with contemporary TnI assays < 99th centile. *European Journal of Emergency Medicine* 00:000–000 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Coronary artery disease (CAD) is common, and failure to identify and treat it may result in preventable morbidity or mortality [1]. The main role of an emergency department (ED) is to determine which patient presenting with chest pain has an acute coronary syndrome (ACS). These patients require to be admitted to the hospital for urgent treatment to avoid adverse events. This is done on the basis of clinical risk stratification combined with ECG analysis and troponin assays. In Australasia, the recommended approach to clinical risk stratification is the Heart Foundation (HF; Australia) risk stratification table in the HF guidelines for the management of acute coronary syndromes 2006 (Table 1) [2]. The guidelines recommend that patients classified as high risk be admitted to the hospital for aggressive investigation and treatment and that the remainder undergo a period of observation and serial biomarker and ECG testing. For those without evidence of ACS at the conclusion of the latter process, the guidelines recommend that 'where practicable, (they) undergo provocative testing (e.g. stress test) before discharge. If not immediately available, provocative testing should be arranged at the earliest opportunity, optimally within 72 h of the index episode (grade C recommendation)' [2]. In Australasia, most patients undergo further testing as outpatients. The rationale behind this recommendation is that ED assessments including ECG and biomarkers rule out myocardial infarction (MI) but not CAD; thus, ED chest pain patients should undergo further testing for clinically significant CAD so that an intervention can be performed, if required, to prevent future morbidity and mortality. The grading assigned by the authors of the recommendations acknowledges that the evidence base for this recommendation is not strong. The recommendation has also remained essentially unchanged despite advances in biomarker technology, which have increased detection of small amounts of myocardial necrosis.

It is possible that patients identified as not having ACS at the index ED visit using more sensitive troponin assays have a very low rate of adverse cardiac events and that a blanket recommendation for further testing may generate high rates of additional testing and, potentially,

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Table 1 Heart foundation Australia risk stratification table

Risk group	Characteristics
High	Presentation of clinical features consistent with ACS and any of the following:
	Repetitive or prolonged (>10 min) ongoing chest pain/ discomfort
	Elevation of at least one cardiac biomarker
	Persistent or dynamic ST depression ≥ 0.5 mm or new T-wave inversion ≥ 2 mm
	Transient ST segment elevation ≥ 0.5 mm in more than two contiguous leads
	Haemodynamic compromise: systolic BP<90 mmHg, cool peripheries, diaphoresis, Killip class>1 and/or new onset mitral regurgitation
	Sustained ventricular tachycardia
	Syncope
	LV systolic d=dysfunction (LVEF<40%)
	Prior PCI within 6 months or prior CABG
	Presence of known diabetes (with typical symptoms of ACS)
	Chronic kidney disease: estimated GFR<60 ml/min (with typical symptoms of ACS)
Intermediate	Presentation of clinical features consistent with ACS and any of the following:
	Chest pain or discomfort within the past 48 h, which occurred at rest, or was repetitive or prolonged (but has currently resolved)
	Age>65 years
	Prior CAD: previous MI with LVEF ≤ 40% or known coronary lesion with >50% stenosis
	No high risk ECG changes (see above)
	Two or more of known hypertension, family history, active smoking or hyperlipidaemia
	Presence of known diabetes (with atypical symptoms of ACS)
	Chronic kidney disease: estimated GFR<60 ml/min (with atypical symptoms)
	Prior aspirin use
	No high risk features.
Low	Presentation of clinical features consistent with ACS without any intermediate or high-risk features (e.g. lowering of angina threshold, onset of angina within the last month)

ACS, acute coronary syndrome; BP, blood pressure; CABG, coronary artery bypass grafts; CAD, coronary artery disease; GFR, glomerular filtration rate; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention. Reproduced with permission from [2].

revascularizations (with cost and adverse-event implications) without having an impact on morbidity or mortality. To further understand this issue, this study aimed to determine the 30-day rate of adverse cardiac events in ED chest pain patients without known CAD who had ED troponin I (TnI) assays ≤ 99th centile using a contemporary troponin assay, stratified by the HF risk group.

Methods

This is a post-hoc substudy of a prospective observational study of consecutive adult patients presenting to the ED of two community teaching hospitals between 19 January 2009 and 30 June 2009 with nontraumatic chest pain (or equivalents) and undergoing evaluation for potential ACS. Patients were not eligible for the study if they had clearly ischaemic ECG features identified by the treating clinician at initial assessment (including ST segment elevation myocardial infarction), they had previously diagnosed CAD, they did not have a troponin assay or ECG performed within 24 h of pain onset, there was a clear non-ACS diagnosis made by the treating clinician at initial assessment, they had a serious arrhythmia before hospital presentation or at ED presentation (including cardiac arrest), there was a language barrier, the lack of a telephone precluded follow-up or they were aged below 18 years. Patients were also excluded if they did not provide consent or were lost to follow-up. The project was approved by the study institution as a quality assurance project under the National Health and Medical Research Council (Australia) Quality Assurance guidelines. Patient consent for data collection from medical records was not required. Participants provided verbal consent to telephonic follow-up.

Historical, clinical and investigational data were collected on a piloted data collection form. Data collected were on demographics, cardiac risk factors, history of CAD or other heart diseases, clinical features at ED presentation, HF risk group classification, medications, results of biochemical analyses using cardiac biomarkers, ECG findings, interventions during hospitalization, clinical course and occurrence of defined major adverse cardiac events (MACEs) at 30 days. Determination of MACEs was by a combination of a review of the medical records and telephonic follow-up. For the two patients lost to follow-up, vital status was confirmed through a death registry search; both patients were alive. MACE included death, MI, cardiac arrest, or significant arrhythmia within 30 days of the index visit.

The primary outcome of interest was the proportion of patients with ED TnI assays ≤ 99th centile who suffered a MACE. The secondary endpoint of MACE or revascularization was analysed separately, recognizing that intervention is subject, to some extent, to decision-making by the cardiologist and local processes, incentives and resources and does not, by itself, necessarily indicate an increased risk of morbidity/mortality.

For the workup to be defined as negative all TnI assays performed in the ED were required to be ≤ 99th centile of the test. Timing of biomarkers was in accordance with the current Australasian guidelines for sensitive troponin assays [3]. Tests were performed at presentation and 3–4 h later, as long as the latter test was performed more than 6 h after symptom onset. If a patient presented more than 6 h after symptom onset, a single assay was deemed sufficient to rule out MI. The decision to admit the patient was at the discretion of the treating doctor, recognizing that unstable angina is a clinical diagnosis and may not have ECG or biomarker evidence. Patients admitted to the cardiology service for further evaluation underwent additional tests at that unit's discretion.

The troponin assay used by the laboratory was TnI-Ultra by Siemens Diagnostics (Erlangen, Germany) performed on an Advia Centaur analyser (Siemens Diagnostics). The test has a reported range of 0.006–50 μg/l. The coefficient of variation is 10% at 0.03 μg/l TnI, 5.3% at 0.08 μg/l TnI and 4.1% at 0.18 μg/l TnI. The 99th percentile is 0.04 μg/l TnI [95% confidence interval (CI) 0.03–0.05 μg/l] (manufacturer's information).

Descriptive analyses were carried out. Comparisons of proportions between high-risk and nonhigh-risk groups were made using the χ^2-test or Fisher's test (as appropriate), and the Mann–Whitney *U*-test was used to compare continuous data. As this was an exploratory analysis of a substudy, no a-priori sample size calculation was performed. For the comparison of the combined outcome of MACE or revascularization between the HF high-risk group and the nonhigh-risk group, a post-hoc power estimation of 0.75 was obtained using a sample size of 130/group (the smaller of the samples), an α-value of 0.05 and an effect size of 3.6% (4 vs. 0.4%).

Results

A total of 460 patients were studied. Sample derivation is shown in Fig. 1 and characteristics of the sample are shown in Table 2.

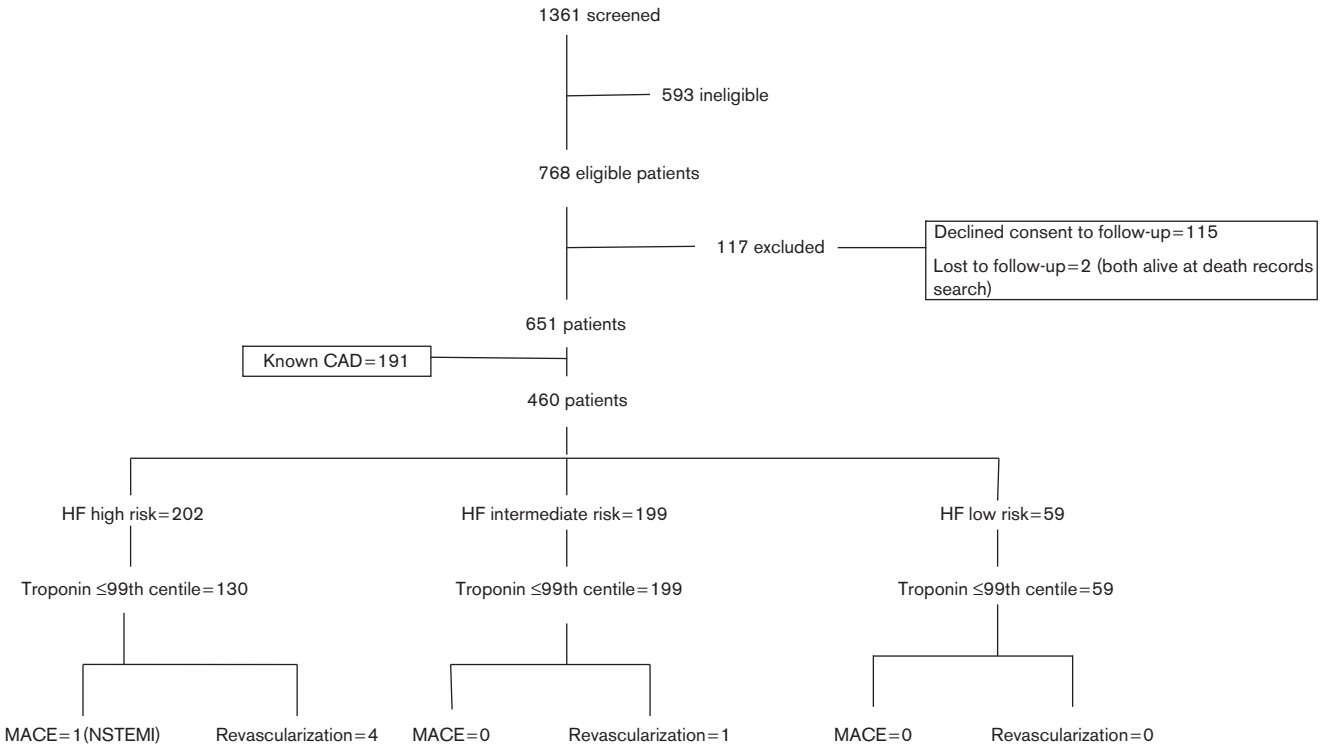
Of the patients, 388 had all TnI assays $\leq$ 99th centile. There was one MACE (a non-ST segment elevation myocardial infarction with revascularization) in this group (0.26%, 95% CI 0.05–1.5%) and five additional revascularizations within 30 days (1.3%; 95% CI 0.6–3%). Details of patients with defined outcomes are shown in Table 3. All patients except one belonged to the HF high-risk group and were admitted to the hospital at the index ED presentation. The lone nonhigh-risk patient, who was discharged from the ED at the index visit, experienced recurrent chest pain and re-presented to the ED of another hospital at which time he was admitted and underwent angioplasty.

On comparing the HF high-risk group with the nonhigh-risk group, the rate of MACE was found to be similar (0.2 vs. 0%; $P = 0.34$); however, the rate of revascularization was higher in the HF high-risk group (3 vs. 0.4%; $P = 0.045$) as was combined MACE or revascularization (3.9 vs. 0.4%; $P = 0.018$).

Overall, for the group, the negative predictive value (NPV) for MACE was 99.7% (95% CI 98.3–100%). The NPV for MACE or revascularization was 98.4% (95% CI 96.5–99.4%). The negative likelihood ratio (LR) for MACE for TnI assays $\leq$ 99th centile (weighted for prevalence) was 0.003 (95% CI 0.0004–0.18). The corresponding negative LR for MACE or revascularization was 0.016 (95% CI 0.007–0.035).

For the nonhigh-risk group, the NPV for MACE was 100% (95% CI 98.2–100%) and the NPV for MACE or revascularization was 99.6% (95% CI 97.5–100%). The negative LR for MACE for TnI assays $\leq$ 99th centile (weighted for prevalence) was 0 with the corresponding

Fig. 1



Sample derivation and outcomes. CAD, coronary artery disease; HF, Heart Foundation Australia; MACE, major adverse cardiac event; NSTEMI, non-ST segment elevation myocardial infarction.

Table 2 Sample characteristics

Variables	Overall cohort ($n=388$)	HF high risk ($n=130$)	HF low or intermediate risk ($n=258$)	Significance (P-value)
Sex (n male, %, 95% CI)	203, 52%, 47–57%	75, 58%, 49–66%	128, 50%, 44–56%	0.13
Age (years; median, IQR)	51, 40–62	58, 49–67	46, 37–59	<0.0001
Ambulance arrival (n, %, 95% CI)	156, 40%, 35–45%	62, 48%, 39–56%	94, 36%, 30–42%	0.26
Risk factors				
Hypertension (n, %, 95% CI)	150, 39%, 34–44%	78, 60%, 51–68%	72, 28%, 23–34%	<0.0001
Diabetes (n, %, 95% CI)	60, 16%, 12–19%	51, 39%, 31–48%	9, 4%, 1.9–6.5%	<0.0001
Current smoker (n, %, 95% CI)	173, 45%, 40–50%	74, 57%, 48–65%	99, 38%, 33–44%	0.0005
Known renal impairment (n, %, 95% CI)	3, 0.8%, 0.3–2.2%	2, 1.5%, 0.4–5.4%	1, 0.4%, 0.07–2.2%	0.52
Family history (n, %, 95% CI)	110, 28%, 24–33%	52, 40%, 32–49%	58, 23%, 18–28%	0.0003
Hypercholesterolaemia (n, %, 95% CI)	131, 34%, 29–39%	69, 53%, 45–61%	62, 24%, 19–30%	<0.0001
Risk scores				
TIMI (median, IQR, range)	0, 0–1, 1–5	1, 1–2, 0–5	0, 0–1, 0–3	<0.0001
GRACE risk score (median, IQR, range)	73, 56–91, 13–165	85, 70–107, 38–165	68, 52–85, 13–155	<0.0001
Number of troponin assays in ED (multiple, n, %, 95% CI)	244, 63%, 58–68%	104, 80%, 72–86%	140, 54%, 48–60%	<0.0001
Disposition (admit to hospital, n, %, 95% CI)	73, 19%, 15–23%	52, 40%, 32–49%	21, 8%, 5.4–12%	<0.0001
Discharge diagnosis MI (n, %, 95% CI)	2, 0.5%, 0.1–1.9%	2, 1.6%, 0.4–5.4%	0, 0%, 0–1.5%	0.11
Outcome at 30 days				
MACE (n, %, 95% CI)	1, 0.3%, 0.05–1.4%	1, 0.7%, 0.1–4.2%	0, 0%, 0–1.5%	0.34
Revascularization without MACE (n, %, 95% CI)	5, 1.3%, 0.6–3%	4, 3%, 1.2–7.7%	1, 0.4%, 0.07–2.2%	0.045
Combined MACE and revascularization (n, %, 95% CI)	6, 1.6%, 0.7–3.3%	5, 3.9%, 1.6–8.7%	1, 0.4%, 0.07–2.2%	0.018

CI, confidence interval; GRACE, global registry of acute coronary events; HF, Heart Foundation Australia; IQR, interquartile range; MACE, major adverse cardiac event; MI, myocardial infarction; TIMI, thrombolysis in myocardial infraction.

Table 3 Characteristics of patients with a major adverse cardiac event or revascularization

Patient	Age	Sex	HF risk group	TIMI score	GRACE risk score	No. TnI in ED ≤ 0.04	Peak troponin	Disposition from ED	Outcome
A	69	Male	High	2	89	2	0.42	Admit	NSTEMI + revascularization
B	68	Male	High	2	117	2	0.02	Admit	Revascularization
C	65	Female	High	3	96	2	0.02	Admit	Revascularization
D	79	Male	High	2	86	2	0.02	Admit	Revascularization
E	65	Male	High	4	104	1	0.02	Admit	Revascularization
F	46	Male	Intermediate	0	64	1	0.02	Discharged	Revascularization

ED, emergency department; GRACE, global registry of acute coronary events; HF, Heart Foundation Australia; NSTEMI, non-ST segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infraction; TnI, troponin I.

negative LR for MACE or revascularization being 0.004 (95% CI 0.0006–0.028).

Discussion

This study suggests that the 30-day rate of MACE is very small in patients without known CAD for whom MI had been ruled out with TnI assays ≤ 99th centile in the ED. No MACE was identified in patients classified as non-high-risk when clinical assessment was performed in addition to biomarker assays. This is in accordance with other published data. In the ACRIN-PA trial [4], although the specific troponin assay used is not stated, only two of 1356 (0.15%; 95% CI 0.03–0.6%) patients who did not have MI at the index visit had an MI at the 28-day follow-up; there were no deaths. In the ROMICAT II study [5], five of 964 patients without the diagnosis of MI at the index visit and without known CAD had an MI within 28 days (0.05%; 95% CI 0.5–1.3%). Again, there were no deaths. Taken together, these data represent growing evidence that patients with TnI assays ≤ 99th centile, especially those with non-high-risk clinical assessment, have very low rates of adverse cardiac events in the medium term. This challenges the recommendation that all of these patients should undergo further testing to rule out CAD.

Testing strategies to rule out CAD include exercise stress tests, nuclear medicine studies and computed tomography coronary angiography (CTCA). They have varying sensitivities for detection of CAD, but all report good NPVs [6–8]. They are however associated with varying levels of adverse events related to the tests themselves. For nuclear medicine studies and CTCA these include radiation exposure and subsequent risk of cancer. There is also some evidence that CTCA results in higher rates of angiography and revascularization compared with other approaches, without mortality benefit [9]. Evidence showing improved patient outcome as a result of testing is minimal. For many low-risk patients the risk of additional testing and its consequences may outweigh the risk of undetected CAD.

It is possible that a selective approach to further testing would better balance the risks and costs. A selective approach might be adopted by using risk factors such as diabetes, metabolic syndrome or a strong family history. There is some research to suggest that risk factors such as

these identify more patients with clinically significant CAD [10]. Our data suggest that the HF risk stratification table might also prove to be a useful tool, with excellent NPVs in nonhigh-risk patients.

Other approaches to risk stratification of ED chest pain patients with respect to 30-day adverse events have been proposed. These include the HEART score [11] and the North American Chest Pain rule [12]. There have also been a number of papers describing the safety of accelerated diagnostic pathways using Thrombolysis in Myocardial Infarction (TIMI) scores and serial biomarker assays at 0 and 3 h [13–15]. Although these studies have investigated adverse events at 30 days, none have advocated not conducting follow-up testing after ED assessment for ACS and none have focused on the subgroup of patients without known CAD. It is possible that one of these approaches would result in better classification accuracy than that of the HF risk stratification table. This is worthy of future research.

There are some limitations to this study, which should be considered when interpreting its results. Although patients were identified prospectively, some data were collected from medical records, which was associated with the inherent weaknesses of this method of data collection. Follow-up was completed for 84% of eligible patients, mainly because of refusal of consent. If patients who did not participate had a higher rate of MACE the results would have been different. The study was conducted at a single site and thus the results may not be generalizable to other settings. Determination of risk factors and previous history was by patient self-report. No attempt was made to confirm the information provided, reflecting the 'real world' ED setting. We did not collect data on rates of compliance with testing for CAD or their impact on outcome. Clearly, a positive test would be a powerful driver for intervention. It was not possible to determine the drivers of revascularization procedures. If some were emergent because of recurrent symptoms with strong evidence of myocardial ischaemia, it might alter the analysis. It is also possible that there were some cases in which the diagnosis of MI was missed, principally because of atypical presentations, particularly the lack of chest pain.

Conclusion

Among ED patients presenting with suspected ACS, adverse cardiac events at 30 days are rare in nonhigh-risk patients with contemporary TnI assays < 99th centile. The recommendation of routine testing for CAD in this group should be reconsidered.

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Conflicts of interest

A.-M.K. is a coauthor of the National Heart Foundation guidelines for the management of ACS (Australia) and their addenda.

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