A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study

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Summary

Background Patients with chest pain contribute substantially to emergency department attendances, lengthy hospital stay, and inpatient admissions. A reliable, reproducible, and fast process to identify patients presenting with chest pain who have a low short-term risk of a major adverse cardiac event is needed to facilitate early discharge. We aimed to prospectively validate the safety of a predefined 2-h accelerated diagnostic protocol (ADP) to assess patients presenting to the emergency department with chest pain symptoms suggestive of acute coronary syndrome.

Methods This observational study was undertaken in 14 emergency departments in nine countries in the Asia-Pacific region, in patients aged 18 years and older with at least 5 min of chest pain. The ADP included use of a structured pre-test probability scoring method (Thrombolysis in Myocardial Infarction [TIMI] score), electrocardiograph, and point-of-care biomarker panel of troponin, creatine kinase MB, and myoglobin. The primary endpoint was major adverse cardiac events within 30 days after initial presentation (including initial hospital attendance). This trial is registered with the Australia-New Zealand Clinical Trials Registry, number ACTRN12609000283279.

Findings 3582 consecutive patients were recruited and completed 30-day follow-up. 421 (11·8%) patients had a major adverse cardiac event. The ADP classified 352 (9·8%) patients as low risk and potentially suitable for early discharge. A major adverse cardiac event occurred in three (0·9%) of these patients, giving the ADP a sensitivity of 99·3% (95% CI 97·9–99·8), a negative predictive value of 99·1% (97·3–99·8), and a specificity of 11·0% (10·0–12·2).

Interpretation This novel ADP identifies patients at very low risk of a short-term major adverse cardiac event who might be suitable for early discharge. Such an approach could be used to decrease the overall observation periods and admissions for chest pain. The components needed for the implementation of this strategy are widely available. The ADP has the potential to affect health-service delivery worldwide.

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Introduction Every year, an estimated 5–10% of presentations to emergency departments, and up to a quarter of hospital admissions are attributable to symptoms suggestive of acute coronary syndromes. Patients with a missed diagnosis of acute myocardial infarction are at increased risk of a major adverse cardiac event. The need for safe discharge without a substantial risk of a major adverse cardiac event is a priority and a driver of clinician behaviour. Consequently, most patients with symptoms suggestive of acute coronary syndromes undergo lengthy assessment, either in the emergency department or as hospital inpatients, even though 75–85% of these patients ultimately do not have a final diagnosis of acute coronary syndromes. The assessment processes vary between institutions, with no one process being ideal. Present recommendations are for serial sampling of cardiac troponin over at least 6 h from the onset of symptoms. Concerns about accuracy of patients’ recall of events has led many centres to time troponin sampling from the moment of presentation to the emergency department. Prolonged assessment contributes to overcrowding in the hospital or department, physician duplication of effort, and clinical risk as patients are treated by different clinical staff. Emergency department overcrowding is associated with increased costs and adverse patient outcomes, including increased mortality.

A reliable, reproducible, and more timely process for the identification of chest pain presentations that have a low short-term risk of a major adverse cardiac event is needed to facilitate earlier discharge. Accelerated diagnostic
protocols (ADPs), clinical decision rules, and prediction rules are terms for processes or methods intended to help clinicians to make bedside diagnostic and therapeutic decisions. They involve variables from the patient’s history and examination, and often incorporate the results of diagnostic tests. ADPs for chest pain are well established but emphasise the need to assess the patient for at least 6 h after the onset of symptoms. Some studies have safely investigated patients with serial biomarkers during 1·5–3 h in a low-risk patient group, but have not defined a reproducible method to identify this low-risk group.

For an assessment of possible acute coronary syndromes, a maximum of 60 min is recommended for the availability of troponin results. Many central laboratories have difficulty in meeting this standard. Point-of-care biomarkers represent a possible solution to meeting this target. The Thrombolysis In Myocardial Infarction (TIMI) score for unstable angina or non-ST elevation myocardial infarction is an externally validated and widely used structured risk assessment method. Its use in conjunction with serial 0–2 h biomarker testing

![Figure 1](https://www.thelancet.com/Vol_377_March_26_2011)

**Figure 1:** Trial profile of participant recruitment and outcomes according to ADP classification

3853 eligible patients

- 202 declined consent
- 3651 consenting eligible patients
- 3630 had ADP index test

**Panel 1: The TIMI score for unstable angina or non-ST elevation myocardial infarction**

(1) Age 65 years or older
(2) Three or more risk factors for coronary artery disease (family history of coronary artery disease, hypertension, hypercholesterolaemia, diabetes, or being a current smoker)
(3) Use of aspirin in the past 7 days
(4) Significant coronary stenosis (eg, previous coronary stenosis ≥50%)
(5) Severe angina (eg, two or more angina events in past 24 h or persisting discomfort)
(6) ST-segment deviation of 0·05 mV or more on first electrocardiograph
(7) Increased troponin and/or creatine kinase MB on initial blood tests*

The TIMI score had to be zero for the sum of its seven parameters to be categorised as 0. TIMI=Thrombolysis In Myocardial Infarction. *Point-of-care values were used for TIMI score calculation.
Methods

Participants

Enrolment occurred at 14 urban emergency departments in nine countries in the Asia-Pacific region (Australia, China [including Hong Kong], India, Indonesia, New Zealand, Singapore, South Korea, Taiwan, and Thailand). Patients were included if they were at least 18 years old and had at least 5 min of chest pain (or discomfort) suggestive of acute coronary syndromes for whom the attending physician planned to investigate for these syndromes with serial biomarker tests. In accordance with American Heart Association case definitions,16 possible cardiac symptoms included acute chest; epigastric, neck, jaw, or arm pain; or discomfort or pressure without an apparent non-cardiac source. Generally, atypical symptoms (fatigue, nausea, vomiting, diaphoresis, faintness, and back pain) were not used as inclusion criteria in the absence of chest pain.

Patients were excluded if they had an ST-segment elevation acute myocardial infarction, there was a clear cause other than acute coronary syndromes for the symptoms (eg, clinical findings of pneumonia), they were unable or unwilling to provide informed consent, staff considered recruitment to be inappropriate (eg, terminal illness), they were transferred from another hospital, they were pregnant, they were recruited on previous presentation, or they were unable to be contacted after discharge. Perceived high risk was not regarded as an exclusion criterion. Recruitment included consecutive eligible cases at each site. Overall enrolment occurred between November, 2007, and July, 2010, but individual sites started and finished at different times according to local logistics. Patients were managed according to local protocols.

All data collection occurred prospectively and the data dictionary has been published previously.15 Research nursing staff collected the demographic and risk data from each patient, supervised ECG testing, and drew blood samples for biomarker testing. If a patient was unsure of an answer (eg, family history) a response of no was recorded. Patients were tracked for adverse events at 30 days from initial attendance with hospital records and telephone follow-up. Data coordination, monitoring and analysis, and source verification was done through an independent university clinical research organisation at a non-recruitment location in Australia (Centre for Clinical Research Excellence, Monash University, Melbourne). Approval from local ethics committees was obtained, and all patients provided written informed consent.

Procedures

The primary endpoint was major adverse cardiac events within 30 days after initial presentation (including initial hospital attendance). The criteria for major adverse cardiac event included any of the following: death (not clearly non-cardiac), cardiac arrest, an emergency revascularisation procedure, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention,

<table>
<thead>
<tr>
<th>Low risk (n=352)</th>
<th>High risk (n=3230)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>49.8 (9.2)</td>
<td>62.8 (14.0)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>190 (56.4%)</td>
<td>1281 (40.5%)</td>
</tr>
<tr>
<td>Chinese</td>
<td>66 (19.6%)</td>
<td>1108 (35.1%)</td>
</tr>
<tr>
<td>Korean</td>
<td>26 (7.7%)</td>
<td>194 (6.1%)</td>
</tr>
<tr>
<td>Indonesian</td>
<td>10 (3.0%)</td>
<td>200 (6.3%)</td>
</tr>
<tr>
<td>Indian</td>
<td>9 (2.7%)</td>
<td>122 (3.9%)</td>
</tr>
<tr>
<td>Thai</td>
<td>0</td>
<td>70 (2.2%)</td>
</tr>
<tr>
<td>Malay</td>
<td>2 (0.6%)</td>
<td>46 (1.5%)</td>
</tr>
<tr>
<td>Maori</td>
<td>3 (0.9%)</td>
<td>30 (0.9%)</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>1 (0.3%)</td>
<td>8 (0.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>30 (8.9%)</td>
<td>102 (3.2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (4.2%)</td>
<td>69 (2.1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65 (19.9%)</td>
<td>1921 (60.4%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>76 (24.0%)</td>
<td>1505 (48.3%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>18 (8.6%)</td>
<td>1120 (44.0%)</td>
</tr>
<tr>
<td>CAD</td>
<td>4 (1.9%)</td>
<td>735 (28.9%)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0</td>
<td>625 (24.5%)</td>
</tr>
<tr>
<td>Revascularisation</td>
<td>0</td>
<td>541 (21.3%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2 (1.0%)</td>
<td>281 (11.0%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (1.4%)</td>
<td>278 (10.9%)</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>200 (7.8%)</td>
</tr>
<tr>
<td>Arhythmia</td>
<td>5 (2.0%)</td>
<td>158 (6.2%)</td>
</tr>
<tr>
<td>Length of initial hospital attendance (h)</td>
<td>26.0 (9.9–37.0)</td>
<td>50.1 (12.6–123.3)</td>
</tr>
</tbody>
</table>

Data are mean (SD), number (%), or median (IQR). Data were missing for each category as follows: ethnic origin (84), hypertension (75), dyslipidaemia (148), family history of CAD (118), smoking (54), previous medical history (824), and time in hospital (196). ADP=accelerated diagnostic protocol. CAD=coronary artery disease. CABG=coronary artery bypass graft.

Table 1: Characteristics for low-risk (ADP negative) and high-risk (ADP positive) participants in the ASPECT study (n=3582)
and prevalent (ie, being the cause for the patient’s initial presentation) and incident (ie, occurring during the 30-day follow-up) acute myocardial infarction. Outcomes and investigations were reported with minimum subjectivity with predefined standardised reporting guidelines (webappendix p 1). The presence of a major adverse cardiac event was adjudicated independently by local cardiologists with these reporting guidelines. Cardiologists were masked to results of the index test biomarkers under investigation and derived guidelines. Cardiologists were masked to results of the index tests, with only central laboratory measurements part of normal care and were analysed at the recruitment site central hospital laboratory. Webappendix p 2 provides a summary of the characteristics of the laboratory troponins used at each hospital site. Treating clinicians were masked to the results of the index tests with only central laboratory troponin results used in patient management. Classification of acute myocardial infarction was based on global taskforce recommendations requiring evidence of myocardial necrosis together with evidence of myocardial ischaemia (ischaemic symptoms, ECG changes, or imaging evidence). Necrosis was diagnosed on the basis of a rising or falling pattern of the laboratory cardiac troponin concentrations, with at least one value above the 99th percentile, at a level of assay imprecision near to 10%. If the troponin concentration was greater than the reference range, but no rise or fall was recorded, other causes of a raised troponin concentration were considered by the adjudicating cardiologist. If no clear alternative cause of the troponin rise was apparent, and if the clinical presentation was suggestive of acute coronary syndromes, an adjudicated diagnosis of acute myocardial infarction was made.

The predefined ADP under investigation was a combination of TIMI risk score of 0, no new ischaemic changes on the initial ECG, and normal point-of-care biomarker panel (at 0–2 h after arrival). All parameters had to be negative for the ADP to be considered negative (and thus for the patient to be identified as low risk). The TIMI score (panel 1) for unstable angina or non-ST-elevation myocardial infarction. POC-point of care. ADP-accelerated diagnostic protocol. ECG-alone; any new ischaemia was positive. Numbers of patients who were identified as low risk by the diagnostic parameter(s) but had a MACE (ie, false-negative cases).

Table 2: Frequency and type of major adverse cardiac event during initial hospital attendance or 30-day follow-up

<table>
<thead>
<tr>
<th>MACE</th>
<th>No MACE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG*</td>
<td>Positive 148 (4.1%)</td>
<td>879 (24.5%)</td>
</tr>
<tr>
<td></td>
<td>Negative 273 (7.6%)</td>
<td>2282 (63.7%)</td>
</tr>
<tr>
<td></td>
<td>Total 421 (11.8%)</td>
<td>3161 (88.2%)</td>
</tr>
<tr>
<td>TIMI‡</td>
<td>Positive 407 (11.4%)</td>
<td>2606 (72.8%)</td>
</tr>
<tr>
<td></td>
<td>Negative 14 (0.4%)</td>
<td>555 (15.4%)</td>
</tr>
<tr>
<td></td>
<td>Total 421 (11.8%)</td>
<td>3161 (88.2%)</td>
</tr>
<tr>
<td>ECG and TIMI§</td>
<td>Positive 413 (11.6%)</td>
<td>2701 (75.4%)</td>
</tr>
<tr>
<td></td>
<td>Negative 8 (0.2%)</td>
<td>460 (12.8%)</td>
</tr>
<tr>
<td></td>
<td>Total 421 (11.8%)</td>
<td>3161 (88.2%)</td>
</tr>
<tr>
<td>POC biomarkers¶</td>
<td>Positive 349 (9.7%)</td>
<td>1391 (38.8%)</td>
</tr>
<tr>
<td></td>
<td>Negative 72 (2.0%)</td>
<td>1770 (49.4%)</td>
</tr>
<tr>
<td></td>
<td>Total 421 (11.8%)</td>
<td>3161 (88.2%)</td>
</tr>
<tr>
<td>ECG and POC biomarkers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive 374 (10.4%)</td>
<td>1803 (50.3%)</td>
</tr>
<tr>
<td></td>
<td>Negative 47 (1.3%)</td>
<td>1358 (37.9%)</td>
</tr>
<tr>
<td></td>
<td>Total 421 (11.8%)</td>
<td>3161 (88.2%)</td>
</tr>
<tr>
<td>ADP**</td>
<td>Positive 418 (11.7%)</td>
<td>2812 (78.5%)</td>
</tr>
<tr>
<td></td>
<td>Negative 3 (0.08%)†</td>
<td>349 (9.7%)</td>
</tr>
<tr>
<td></td>
<td>Total 421 (11.8%)</td>
<td>3161 (88.2%)</td>
</tr>
</tbody>
</table>

MACE=major adverse cardiac event. ECG=electrocardiograph. TIMI=Thrombolysis In Myocardial Infarction score for unstable angina or non-ST-elevation myocardial infarction. POC-point of care. ADP-accelerated diagnostic protocol. ECG-alone; any new ischaemia was positive. Numbers of patients who were identified as low risk by the diagnostic parameter(s) but had a MACE (ie, false-negative cases).

Table 3: Occurrence of MACE during initial hospital attendance or 30-day follow-up according to results of individual and combinations of the ADP test parameters

See Online for webappendix
least 0.1 mV, or Q-waves greater than 30 ms in width and 0.1 mV or greater in depth in at least two contiguous leads.\textsuperscript{17,18,20} Patients with abnormal ECG findings (eg, pacing, left ventricular hypertrophy, and left bundle branch block) that were proven to be pre-existing on previous ECGs were defined as low risk.

Index test point-of-care biomarkers were measured with whole blood drawn at presentation and 2 h afterwards. Blood was immediately tested for troponin I, creatine kinase MB, and myoglobin. Results were available (to research staff only) within 15 min with the TRIAGE platform or CardioProfi lER assay panels (both Alere, San Diego, CA, USA). The following assay results were predefined to be positive on either blood draw: troponin I 0.05 μg/L or greater, creatine kinase MB 4–3 μg/L or greater, or an increase of 1–6 μg/L or more within 2 h; and myoglobin concentration of 108 μg/L or greater or an increase of 25% or more within 2 h. The point cutoffs were based on manufacturer recommendations, with an elevated troponin defined as any detectable concentration of troponin. The levels of change were based on a previous publication\textsuperscript{15} and peer-group consensus.

### Statistical analysis

Data were collected with the web-based OpenClinica data capture system. Baseline characteristics of the study population were analysed with conventional group descriptive statistics. \( \chi^2 \) analyses were used to generate two-by-two tables for the calculation of sensitivity, specificity, and positive and negative predictive values. All analyses were done with SPSS (version 18.0.0).

The trial is registered with the Australia-New Zealand Clinical Trials Registry, number ACTRN12609000283279.

### Role of the funding source

The sponsors of this study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

3651 consenting eligible patients were enrolled, of whom 3582 completed 30-day follow-up (figure 1). Webappendix p 3 shows the countries and hospitals that recruited patients. Study participants were mostly older men, either white or Chinese, and commonly had cardiovascular risk factors and background cardiovascular past medical history (table 1). A major adverse cardiac event occurred within 30 days in 421 (11.8%) patients. Non-ST-segment acute myocardial infarction (NSTEMI) was the most frequently occurring major adverse cardiac event (table 2).

The ADP identified 9.8% (352/3582) of patients as being at low risk of a major adverse cardiac event within 30 days (all ADP parameters were negative). Three (0.9%) of these patients had an event during initial hospital attendance and follow-up (figure 1). Webappendix p 4 outlines the clinical details of these false negatives.

The combinations of parameters of the ADP were more effective at identifying patients who had a major adverse cardiac event than were the individual parameters themselves (table 3). The combination of the biomarkers and ECG without the TIMI score did not identify
47 patients with a major adverse cardiac event at day 30. With use of the ADP including TIMI score, 44 additional patients were correctly identified, which reduced the number of false negatives to three (figure 2).

Table 4 shows the statistical analysis of the ADP and its parameters for the prediction of a major adverse cardiac event by day 30. The ADP had a very high sensitivity and negative predictive value (table 4).

Secondary analysis showed that patients identified as low risk by negative ADP were associated with a median initial hospital attendance of 26·0 h (IQR 9·9–37·0) and a mean of 43·2 h (95% CI 36·2–51·2), representing 1–2 hospital bed-days.

Discussion
Findings from this large, multinational study have prospectively validated that a 2-h accelerated diagnostic protocol, with use of point-of-care biomarkers, ECG, and TIMI score, can safely identify patients at very low short-term risk of a major adverse cardiac event (panel 2). These patients could potentially be discharged several hours earlier to outpatient follow-up and further investigations than with present practices.

The near 10% possible reduction in patients needing prolonged assessment in this large patient group could reduce overcrowding in hospitals and emergency departments and provide earlier reassurance and greater convenience for patients. The potential reduction in initial length of stay accords with the findings of a six centre study in the UK.22 These findings together with those from countries included in our study represent 42% of the world’s population. Extrapolation is difficult, but on the basis of incidence rates of chest pain in the USA of 2·21%, there might be 64 million presentations of chest pain per year across these study nations. If the true incidence was half of this rate, then earlier discharge of 10% of patients could affect 3·2 million presentations. Patients in this study who were identified as low risk had an initial hospital attendance of about 1–2 days; these patients could potentially be discharged within 3–4 h of arrival if follow-up investigations could be arranged as an outpatient. Increasing demand for acute hospital beds is a key challenge for modern health services.

The study shows that each of the components of the ADP is essential when used within such an early timeframe after presentation (figure 2, table 3). The use of the TIMI score within the ADP resulted in a lower and more acceptable false negative rate than when only biomarkers and ECG were used for the prediction of 30-day major adverse cardiac event (0·7% vs 11·2%).

Troponin assays with lower and more reliable levels of detection have been developed since this study started, but the assay we used was effective in this ADP. The focus of this study was the safety of the ADP when used as a whole; any contemporary troponin could be used either via the central laboratory or point of care as part of the ADP. Newer assays, which typically have lower detection limits and higher analytical precision, would probably improve the sensitivity of this ADP for the prediction of a major adverse cardiac event; however, their use as part of an ADP has not been reported.22,23

The ADP might be expanded to a broader subset by development of a more specific risk score. The TIMI score was developed from a relatively high-risk population with acute coronary syndromes, but it has been externally validated in more general emergency department populations.6,12 A modified TIMI risk score has been derived and validated in an emergency department population previously with laboratory-based troponins,9,20 with a sensitivity of 96·6% reported in the validation of the ADP. Newer assays, which typically have lower detection limits and higher analytical precision, would probably improve the sensitivity of this ADP for the prediction of a major adverse cardiac event; however, their use as part of an ADP has not been reported.22,23

We searched Medline from March, 1995, to December, 2010, for full reports of original research and review articles with the terms “acute coronary syndrome”, “chest pain”, “emergency department”, “risk stratification tools”, “point of care”, and “clinical decision rule”. We identified 114 articles. Abstracts were downloaded for all titles of potential relevance. Full papers were downloaded when the abstract was also deemed relevant. To be included in the final analysis, studies had to be prospective, have a large population, and have clearly described their methods and results. The methodology must have allowed the conclusions to be generalised to the emergency department population.

Interpretation
Together, the results of these studies show that the identification of patients at low risk for major adverse cardiac events is challenging. Increasing research is emerging into the use of accelerated diagnostic protocols (ADP). These protocols typically include the use of a risk stratification method, serial biomarkers, and electrocardiographs, and usually require an assessment period of 6–12 h. The results of our study indicate that a new ADP incorporating a risk stratification method (TIMI score), electrocardiograph, and point-of-care biomarker testing can identify patients at low risk of 30-day major cardiac event at 2 h.

Panel 2: Research in context
Systematic review
We searched Medline from March, 1995, to December, 2010, for full reports of original research and review articles with the terms “acute coronary syndrome”, “chest pain”, “emergency department”, “risk stratification tools”, “point of care”, and “clinical decision rule”. We identified 114 articles. Abstracts were downloaded for all titles of potential relevance. Full papers were downloaded when the abstract was also deemed relevant. To be included in the final analysis, studies had to be prospective, have a large population, and have clearly described their methods and results. The methodology must have allowed the conclusions to be generalised to the emergency department population.
study. There is no universally accepted definition of a low-risk patient for acute coronary syndromes. This lack of consensus is a serious concern, because according to Bayesian decision making, interpretation of post-test probability after a particular test result is dependent on knowledge of the pre-test probability. The use of a structured and reproducible method is important.\textsuperscript{10–11} Subjective pre-test probability estimation has much lower inter-rater agreement between clinicians than do structured methods.\textsuperscript{14} Furthermore, patients presenting to an emergency department are often initially assessed by junior staff, and evidence shows that traditionally taught clinical variables and risk factors are poor predictors of acute coronary syndromes in an un-differentiated population in these clinics.\textsuperscript{15–17}

Patients without chest pain but who presented with atypical symptoms (fatigue, nausea, vomiting, diaphoresis, faintness, and back pain) were not included in this trial, and we were unable to quantify the number of patients presenting with these symptoms. Thus the applicability of the ADP is limited to the selected cohort of patients with chest pain (or discomfort) suggestive of acute coronary syndromes for whom the attending physician planned to investigate for these syndromes. Another limitation of this study is that this was an observational, not an intervention study. Ideally, a management study of the diagnostic protocol would now occur; however, in practice, such studies are rare.

The low specificity (11%) of our approach might be regarded as a limitation, but the ADP was used as an exclusion method to predict safety of early discharge of patients and not to establish inpatient management. These patients would otherwise have had extended observation or admission. The low specificity accords with other diagnostic instruments to exclude acute coronary syndromes.\textsuperscript{18} The goal of a more specific test is to rule-in a diagnosis if positive with sufficient certainty to initiate a change in management. In the setting that we studied, a positive protocol result merely classified patients as requiring management as usual. The patients would otherwise have had extended observation or admission. The low specificity accords with other diagnostic instruments to exclude acute coronary syndromes.\textsuperscript{18} The goal of a more specific test is to rule-in a diagnosis if positive with sufficient certainty to initiate a change in management. In the setting that we studied, a positive protocol result merely classified patients as requiring management as usual. The patients would otherwise have had extended observation or admission.

Conflicts of interest

MT, MB, SHL, RRK, and LC received grants and supplies by Alere Medical. MT, AMR, and LC received honoraria for previous speaking and lecturing from Alere Medical. MT, MB, AMR, SHL, RRK, LC, and W-KC received support for travel to meetings from Alere Medical. HFH and HFK received grants from Science International Corporation. HFH received support for travel from Science International Corporation. MWA received unrelated grants from HRCNZ. LC received grants from the Queensland Emergency Research Foundation (QEMRF). SA received grants from the National Heart Foundation of New Zealand, and support for travel to meetings from the Christchurch Cardio-Endocrine Research Group. CMR received grants from the National Health and Medical Research Council. WAP has received grants from the QEMRF. He is a board member of Sanofi-Aventis, is a consultant for Hospira, and has been paid to give lectures for Sanofi-Aventis and Roche, all unrelated to this project. WFP has received consultancy payments from Alere for unrelated projects. SS received grants, support for travel to meetings, and fees for participation in review activities from Medquest Jaya Global. DH, RD, QH, KS-M, DFF, RS-L, SS, and PS received support from Alere to travel to meetings. T-FC, K-CT, F-YC, and W-HC received grants for nurses and support for travel from Progressive Group (Taiwan). PMG has received unrelated grants from the Health Research Council (New Zealand), National Heart Foundation New Zealand, and National Health and Medical Research Council; and unrelated honoraria from Roche, AstraZeneca, and Abbott Laboratories.

Acknowledgments

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References

Acute MI: triple-markers resurrected or Bayesian dice?

Acute coronary syndromes are the acute manifestations of a disease that will ultimately kill around one in six people,¹ a disease that has been feared for centuries and is still revered by physicians. The disease can kill instantly, yet the symptoms and signs alone simply cannot be relied on to differentiate an acute coronary syndrome from much less threatening disorders.² Even William Osler, one of the most esteemed diagnosticians in history, said: “One must be a professional Ulysses in craft and wisdom not sometimes to err in estimating the nature of an attack of severe heart pain. There is no group of cases so calculated to keep one in a condition of wholesome humility.”³

Most people who seek emergency medical attention for symptoms compatible with an acute coronary syndrome do not actually have the syndrome. We do, however, invest substantial time and money establishing that through diagnostic investigations. These investigations usually mandate hospital admission, meaning that such patients account for over a quarter of all acute medical admissions.⁴ The need for an effective rapid rule-out strategy to facilitate early discharge from the emergency department has been appreciated for over 20 years. Despite extensive research, however, none has been widely adopted.

One potential strategy that has gained considerable interest over the past decade is triple-marker testing. Creatine kinase-MB fraction and myoglobin rise early after the onset of infarction, while the rise in troponin is late and sustained. In theory, the strategy should detect infarction in patients who present both early and late after symptom onset. However, some of the studies reporting high sensitivities and negative predictive values had important verification bias,⁵ while other studies had inadequate sensitivity.⁶

In The Lancet, Martin Than and colleagues⁷ report the ASia-Pacific Evaluation of Chest pain Trial (ASPECT), a multinational prospective diagnostic cohort study. The study, which included 3582 patients, investigated the diagnostic accuracy of an accelerated diagnostic protocol that would enable early discharge for patients who met the predefined criteria of a Thrombolysis In Myocardial Infarction (TIMI) risk score of 0 (out of 7), no ischaemic ECG changes, and normal point-of-care triple-marker panels at presentation and 2 h later. This strategy would have identified 9·8% of patients as eligible for early discharge, 0·9% of whom went on to have a major adverse cardiac event within 30 days. Use of the protocol could potentially have saved 1–2 hospital bed-days per low-risk patient.

ASPECT was well designed to achieve its objectives, and shows that it is possible to achieve an acceptably high sensitivity when triple-marker testing is used in the appropriate population. However, that selection of the appropriate population was pivotal to the success of the accelerated discharge protocol. Triple-marker testing alone had a relatively low sensitivity, at just 82·9%. The overall sensitivity of the protocol increased to an acceptable level because of the application of Bayesian principles, with biomarker testing only in patients with a low pretest probability of disease (ie, patients with a TIMI risk score of 0 and a normal ECG). Thus, predicting just over 80% of major adverse cardiac events in an already low-risk population yields an even lower net risk.

Most people will probably consider this net risk to be statistically acceptable. However, if properly informed, low-risk patients might feel differently about the relative merits of waiting for definitive 6-h laboratory-based troponin testing or going home after 2 h on the basis of results from a test that correctly identifies serious coronary disease, when present, in just over eight of ten occasions. This issue is particularly pertinent in view of the recent development of highly

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sensitive troponin assays, some of which can have a sensitivity of around 90% (for acute myocardial infarction) at the time of presentation and possibly up to 100% within 3 h,1,8 and by research into other promising biomarkers such as heart fatty acid binding protein and copeptin.10,11 It therefore remains important that triple-marker testing is compared with some of these more recent alternatives. Now, more than ever, it will also be important to compare the relative merits of point-of-care testing with laboratory-based assays that have much higher analytical sensitivity and precision.

Finally, the recent Randomised Assessment of Triage with Panel Assay of Cardiac markers (RATPAC) trial12 showed that, although triple-marker testing increased the proportion of patients successfully discharged from the emergency department and reduced the median length of initial hospital stay, such testing was also associated with increased mean length of hospital stay and greater use of coronary care, which might be a function of the low specificity and positive predictive value of the biomarker panel. The findings of a cost-effectiveness analysis are expected shortly.13

In the ASPECT trial, the biomarkers alone had a positive predictive value of only 20-1%. Although it is not imperative that the overall specificity of the accelerated diagnostic protocol is high (ultimately, the specificity of 10% still potentially means that 10% of “healthy” patients are eligible for early discharge when they would otherwise have been admitted), the low specificity of the biomarker panel (56% in ASPECT) might be more of a problem. It could be harder for clinicians to ignore increases in biomarkers that supposedly indicate myocardial necrosis, thus prompting over-treatment and over-investigation.

Ultimately, ASPECT has successfully established that an accelerated diagnostic protocol incorporating triple-marker testing successfully identifies a group of patients at very low risk of major adverse cardiac events who could reasonably be considered for early discharge. The field must now ask whether the strategy defined is indeed optimal, whether more sensitive and specific assays might improve performance, and whether these promising data will stand up to subsequent analyses of cost-effectiveness and patients’ preference.

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I have attended two advisory group meetings for Roche Diagnostics (no fees were paid and travel expenses were not claimed). I have done research supported by collaborative agreements with Alere Diagnostics (including free transport and testing of samples), Roche Diagnostics (including donation of reagents for serum testing), and Randox Diagnostics (involving loan of equipment and donation of reagents to test plasma samples). Siemens Diagnostics will donate reagents for a research project I am leading. I have received honoraria for speaking engagements with Bristol-Myers Squibb and PASTEST, and have spoken at meetings sponsored by Roche Diagnostics and Randox Diagnostics (no honoraria). I received an honorarium for assisting Bristol-Myers Squibb to prepare educational presentations. Roche Diagnostics and Randox Diagnostics have arranged travel and accommodation for presentations at company-sponsored symposia in Europe (with Randox Diagnostics, this is still pending). I attended a lecture and subsequent meal sponsored by Brahms Diagnostics.