

2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker

The ADAPT Trial

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Objectives	The purpose of this study was to determine whether a new accelerated diagnostic protocol (ADP) for possible cardiac chest pain could identify low-risk patients suitable for early discharge (with follow-up shortly after discharge).
Background	Patients presenting with possible acute coronary syndrome (ACS), who have a low short-term risk of adverse cardiac events may be suitable for early discharge and shorter hospital stays.
Methods	This prospective observational study tested an ADP that included pre-test probability scoring by the Thrombolysis In Myocardial Infarction (TIMI) score, electrocardiography, and 0 + 2 h values of laboratory troponin I as the sole biomarker. Patients presenting with chest pain due to suspected ACS were included. The primary endpoint was major adverse cardiac event (MACE) within 30 days.
Results	Of 1,975 patients, 302 (15.3%) had a MACE. The ADP classified 392 patients (20%) as low risk. One (0.25%) of these patients had a MACE, giving the ADP a sensitivity of 99.7% (95% confidence interval [CI]: 98.1% to 99.9%), negative predictive value of 99.7% (95% CI: 98.6% to 100.0%), specificity of 23.4% (95% CI: 21.4% to 25.4%), and positive predictive value of 19.0% (95% CI: 17.2% to 21.0%). Many ADP negative patients had further investigations (74.1%), and therapeutic (18.3%) or procedural (2.0%) interventions during the initial hospital attendance and/or 30-day follow-up.
Conclusions	Using the ADP, a large group of patients was successfully identified as at low short-term risk of a MACE and therefore suitable for rapid discharge from the emergency department with early follow-up. This approach could decrease the observation period required for some patients with chest pain. (An observational study of the diagnostic utility of an accelerated diagnostic protocol using contemporary central laboratory cardiac troponin in the assessment of patients presenting to two Australasian hospitals with chest pain of possible cardiac origin; ACTRN12611001069943) (J Am Coll Cardiol 2012;59:2091-8) © 2012 by the American College of Cardiology Foundation

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**Abbreviations
and Acronyms**

- ACS** = acute coronary syndrome(s)
- ADP** = accelerated diagnostic protocol
- AMI** = acute myocardial infarction
- cTn** = cardiac troponin
- cTnI** = cardiac troponin I
- ECG** = electrocardiography
- ED** = emergency department
- HS-cTn** = highly sensitive cardiac troponin
- MACE** = major adverse cardiac event(s)
- STEMI** = ST-segment elevation myocardial infarction
- TIMI** = Thrombolysis In Myocardial Infarction

A missed diagnosis of acute coronary syndrome (ACS) may lead to further ischemic events and a potentially preventable death or disability. Therefore, patients with symptoms suggestive of ACS often undergo a lengthy assessment in the emergency department (ED) or as hospital inpatients. These patients account for approximately 10% of ED

presentations and 25% of hospital admissions (1), yet up to 85% do not have a final diagnosis of ACS (2-4). Prolonged assessment contributes to duplication of work, high costs, and ED overcrowding, which leads to adverse patient outcomes, including increased mortality (1,5). The need for accurate identification of a low-risk group that may be safely dis-

charged without jeopardy of an adverse event from an ACS is therefore a priority (4).

International guidelines for the investigation of ACS recommend serial measurement of cardiac troponin (cTn) at the onset of symptoms, and many hospitals use the presentation at the ED as time zero for sampling (6-10). A reproducible, reliable, and more timely process for identifying patients presenting with chest pain who have a low short-term risk of adverse cardiac events is needed to support their earlier discharge (4). Only 2 studies have prospectively validated accelerated diagnostic protocols (ADPs) for the early discharge of low-risk patients using serial biomarkers in the first 2 hours after arrival (11,12).

The recent ASPECT (A 2-h Diagnostic Protocol to Assess Patients with Chest Pain Symptoms in the Asia-Pacific region) study used 0- and 2-h biomarker testing with a point-of-care multimer panel, electrocardiography (ECG), and the Thrombolysis In Myocardial Infarction (TIMI) score (11). In that study, the ADP identified 9.8% of patients with suspected ACS who could have been discharged early from the ED, with a sensitivity of 99.3% for 30-day major adverse cardiac events (MACE).

Some studies have shown superiority of point-of-care multimer strategies compared with troponin alone when used for early evaluation of such patients, but studies have been criticized for using relatively insensitive cTn assays. Current laboratory troponins may now be equivalent or superior to point-of-care multimer strategies even at these early time points (13). This might increase the number of patients eligible for early discharge, while maintaining very high sensitivity (>99%).

The purpose of this study was to determine if an ADP using a serial troponin as the only biomarker could identify

ED patients suspected of having ACS who are suitable for safe early discharge. These patients could then have early outpatient or accelerated in-patient follow-up.

Methods

Study design and setting. The ADAPT (2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker) trial was a prospective observational validation study designed to assess a predefined ADP that consisted of TIMI score risk assessment, ECG, and 0- and 2-h central laboratory contemporary cardiac troponin I (cTnI) as the only biomarker. The study population was from the Brisbane, Australia and Christchurch, New Zealand, that is, 2 of the 14 sites participating in the ASPECT study. Most participants were recruited as part of the ASPECT trial, but we also included additional patients through ongoing post-ASPECT recruitment at both centers. The process for 2-h blood sampling and central laboratory analysis of cTnI was pre-planned before the start of the ASPECT study, and a priori local ethics committee approval was obtained for this. All participants provided written informed consent. The results of the 2-h cTnI samples were not used as part of routine clinical care (or for reference standard adjudication). This study was subsequently separately registered with the Australia-New Zealand Clinical Trials Registry, ACTRN12611001069943.

Participants. Patients were enrolled consecutively between November 2007 and February 2011, at 2 urban EDs in Brisbane, Australia and in Christchurch, New Zealand. Due to local recruitment logistics, enrollment did not start and finish at the same time in each center. Criteria for enrollment included age ≥ 18 years of age, with at least 5 min of symptoms consistent with ACS, where the attending physician planned to perform serial cTn tests. The American Heart Association case definitions for possible cardiac symptoms were used (i.e., acute chest, epigastric, neck, jaw, or arm pain; or discomfort or pressure without an apparent noncardiac source) (14). Patients were excluded for any of the following: ST-segment elevation myocardial infarction (STEMI), a clear cause other than ACS for the symptoms (e.g., examination findings of varicella zoster), inability to provide informed consent, staff considered recruitment to be inappropriate (e.g., receiving palliative treatment), transfer from another hospital, pregnancy, previous enrollment, or inability to be contacted after discharge. Perceived high risk was not used as an exclusion criterion. Patients were managed according to local hospital protocols, including blood draws for cTnI measurement at presentation, and then 6 to 12 h afterwards in compliance with international guidelines (6,14). Christchurch Hospital used the Abbott ARCHITECT cTnI assay (Abbott, Inc., Chicago, Illinois), which has a detection limit of $<0.01 \mu\text{l}$, 99th percentile of $0.028 \mu\text{l}$, 10% coefficient of variation of $0.032 \mu\text{l}$, and a

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decision cutoff, as per manufacturer, of $>0.030 \mu\text{l}$. Royal Brisbane and Women's Hospital used the DxI Access Accu cTnI assay (Beckman Coulter, Chaska, Minnesota), which has a detection limit of $0.01 \mu\text{l}$, 99th percentile of $0.04 \mu\text{l}$, 10% coefficient of variation of $0.06 \mu\text{l}$, and a decision cutoff, as per manufacturer, of $>0.04 \mu\text{l}$. Following Federal Drug Authority concerns about results consistency between DxI analyzers for measurement of the Beckman assay, a local reassessment was performed in Brisbane that showed only a 5% bias between the 2 local DxI analyzers. Long-term imprecision at the 99th percentile has been 13% to 14%. After assessment of local data, there has been no market withdrawal in Australasia. In both centers, results for clinical use and outcomes adjudication were rounded to 2 decimal places.

Data were collected prospectively using a published data dictionary (15). Nursing staff collected the demographic and clinical data from patients, supervised ECG testing, and drew blood samples for cTnI testing. If a patient was unsure of an answer to a question (e.g., history of hypertension), a response of "No" was recorded. Patients were followed up to determine the occurrence of MACEs within 30 days of presentation, at 45 days, and after 1 year using all of: 1) telephone contact by research staff; 2) review of patients' hospital notes; and 3) a national health events search (which identifies any death). Data were also recorded regarding the use of further testing for ACS (e.g., stress testing or imaging) and interventions (therapeutic or procedural) within 30 days. The Centre for Clinical Research Excellence, Monash University, Melbourne, Australia, independently undertook data coordination, monitoring, analysis, and source verification.

Index test. The predefined ADP under investigation consisted of a TIMI risk score of 0 at presentation (16), no ischemic changes on the initial ECG (i.e., not known to be pre-existing), and central laboratory cTnI concentrations (at 0 and 2 h after arrival) below the institutional cutoff used to indicate troponin elevation (Table 1). For a patient to be identified as low risk, all parameters in the ADP had to be negative.

Patients with ischemic ECG changes and no evidence that they were pre-existing, were defined as high risk. ECG changes were defined as ST-segment depression of at least 0.05 mV in ≥ 2 contiguous leads (including reciprocal changes), T-wave inversion of at least 0.1 mV , or Q waves $>30 \text{ ms}$ in width and $\geq 0.1 \text{ mV}$ in depth in at least 2 contiguous leads (15,17–19). Patients with other abnormal ECG findings (e.g., pacing artifact and left bundle branch block) that were present on pre-existing ECGs were not defined as high risk.

Central laboratory cTnI concentrations (at 0 and 2 h after arrival) above the institutional cutoff were used to indicate cTnI elevation. The same troponin assays and cutoffs were used to indicate cTnI elevation as for standard care at each institution (as described previously).

Reference standard. The primary endpoint was a composite of MACEs that occurred within 30 days after first presentation

Table 1 The ADAPT ADP

All parameters had to be negative for the ADP to be considered negative and for the patient to be identified as low-risk

1. cTnI level at 0 and 2 h below institutional cutoff for an elevated troponin concentration
2. No new ischemic changes on the initial ECG
3. TIMI score = 0 (16)
 - a. Age ≥ 65 yrs
 - b. Three or more risk factors for coronary artery disease: (family history of coronary artery disease, hypertension, hypercholesterolaemia, diabetes, or being a current smoker)
 - c. Use of aspirin in the past 7 days
 - d. Significant coronary stenosis (e.g., previous coronary stenosis $\geq 50\%$)
 - e. Severe angina (e.g., ≥ 2 angina events in past 24 h or persisting discomfort)
 - f. ST-segment deviation of $\geq 0.05 \text{ mV}$ on first ECG
 - g. Increased troponin and/or creatine kinase-MB blood tests (during assessment*)

*The results of the 0-h cardiac troponin-I (cTnI) were used for calculation of the Thrombolysis In Myocardial Infarction (TIMI) score in this study, which is a modification from the original published score. This score parameter and that of ST-segment deviation are effectively redundant in the ADAPT accelerated diagnostic protocol (ADP) because of the broader cTnI and electrocardiographic (ECG) criteria (1 and 2).

(including the initial hospital attendance). An adverse event included: death (unless clearly noncardiac), cardiac arrest, emergency revascularization procedure, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention, and acute myocardial infarction (AMI) (Online Table 1). AMI was classified using the global taskforce recommendations requiring evidence of myocardial necrosis together with clinical evidence of myocardial ischemia (ischemic symptoms, ECG changes, or imaging evidence) (8). Necrosis was diagnosed on the basis of a rising or falling pattern (a delta of $\geq 20\%$ was used) of the laboratory troponin concentrations, with at least 1 value above the decision cutpoint (99th percentile, at a level of assay imprecision near 10%). The cTnI results from blood draws at presentation, and after 6 to 12 h (i.e., from routine care) were used for determination of necrosis. If the cTnI concentration was elevated, but a $<20\%$ rise or fall was recorded, then other causes of a raised troponin concentration were actively pursued by the adjudicators. If no clear alternative cause of the troponin rise was evident, and if the clinical presentation was suggestive of an ACS, an adjudicated diagnosis of AMI was decided.

Statistical analysis. Baseline characteristics of the participants were analyzed with conventional group descriptive statistics. For continuous variables, mean \pm SD were calculated, whereas for categorical data, the proportions in each of the ADP positive and negative groups were reported. The sensitivity, specificity, and positive and negative predictive values for hierarchical primary and secondary events were generated using chi-square analyses for the ADP as a whole and its constituents individually or in combination. Sensitivities were compared using the McNemar test.

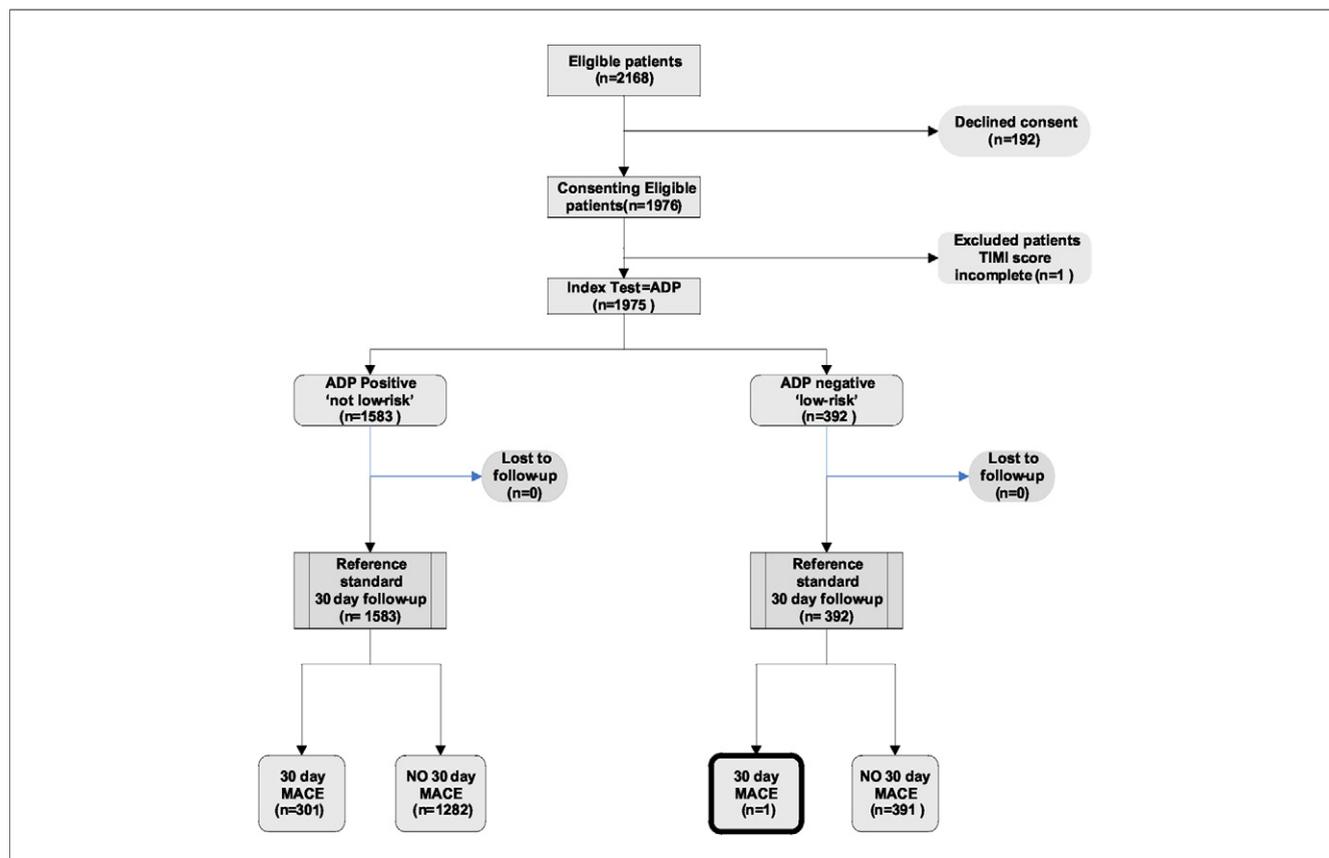


Figure 1. Participant Recruitment Flowchart

The 193 patients eligible, but not recruited, were similar in age, gender, and risk factors ($p > 0.05$ for all). The 30-day follow-up included initial hospital attendance, and no patients were lost to follow-up. ADP = accelerated diagnostic protocol; MACE = major adverse coronary event(s); TIMI = Thrombolysis In Myocardial Infarction.

Results

Patient characteristics. There were 1,975 consenting, eligible patients suitable for analysis (Fig. 1). No patients were lost to 30-day follow-up. Participants were predominantly Caucasian, older men who commonly had risk factors for coronary artery disease; the cohort had a significant rate of known coronary artery disease (Table 2).

A total of 302 patients (15.3%) had a primary outcome event within 30 days, with most occurring within the first 10 days. The majority of these events (15.1%) were myocardial infarctions (Table 3). The ADP identified 392 patients (20%) as low risk of a MACE within 30 days (Table 4).

Diagnostic accuracy. Table 5 presents the statistical analysis of the ADP and its parameters for predicting MACEs within 30 days. Only 1 (0.25%) patient, classified as low risk by the ADP, had a MACE during initial hospital attendance and follow-up. This patient was a 52-year-old Caucasian male who presented after 3.5 h of chest pain. He was previously healthy, with no risk factors for ischemic heart disease. He had a normal ECG and his Abbott troponin I was $<0.01 \mu\text{g/l}$ at 0 h, $0.03 \mu\text{g/l}$ at 2 h, and $16.8 \mu\text{g/l}$ after 12 h. He underwent

angiography and stenting for right coronary and circumflex artery stenosis. The patient had no further cardiac problems during 1 year of follow-up.

A secondary analysis using a TIMI score of 0 or 1 (as opposed to TIMI 0) in the ADP resulted in 38.4% of patients being categorized as low risk, but with 9 false negative results for the primary outcome, giving a sensitivity of 97.0%, negative predictive value of 98.8%, specificity of 44.8%, and positive predictive value of 24.1%.

Individual diagnostic parameters were not as effective at identifying patients who had a MACE compared with when these parameters were used together (Tables 4 and 5). The combination of TIMI score and ECG without 0- and 2-h troponin failed to identify 5 patients with a MACE at 30 days. Using the ADP, 4 of these 5 patients were correctly identified with a reduction in the number of false negatives to 1 (Fig. 2). The ADP identified a larger proportion of patients as low risk in participants presenting early after the onset of symptoms (0 to 3 h) than among those presenting later (Online Table 1).

The majority of ADP negative patients (316 of 392 [74.1%]) had further investigations within 30 days, and most of

Table 2 Demographics: Participant Characteristics

Characteristics	Total (N=1,975)	ADP Positive	ADP Negative
Demographics			
Age, yrs	60.4 ± 14.9	63.2 ± 14.8	49.4 ± 9.2
Sex (% male)	60.0 (1,185)	60.1 (951)	59.7 (234)
Ethnicity*			
Caucasian	89.8 (1,748)	90.3 (1,411)	87.5 (337)
Maori	1.7 (34)	1.9 (30)	1.0 (4)
Aboriginal	0.8 (16)	0.8 (13)	0.8 (3)
Indian	0.9 (17)	0.8 (13)	1.0 (4)
Chinese	0.2 (3)	0.2 (3)	0 (0)
Other	6.8 (129)	6.0 (92)	9.6 (37)
Risk factors			
Hypertension	52.1 (1,029)	59.0 (934)	24.2 (95)
Diabetes	14.4 (285)	17.4 (276)	2.3 (9)
Dyslipidemia	51.1 (1,009)	57.5 (907)	26.1 (102)
Smoking			
Previous smoker	41.7 (823)	43.5 (688)	34.5 (135)
Current smoker	18.9 (374)	18.3 (289)	21.7 (85)
Family history of coronary artery disease	53.5 (1,056)	55.4 (874)	46.4 (182)
Medical history			
Angina	33.8 (668)	41.5 (657)	2.8 (11)
Coronary artery disease	21.0 (415)	26.2 (414)	0.3 (1)
Acute myocardial infarction	23.3 (461)	29.1 (461)	0 (0)
Revascularization	17.3 (341)	21.7 (341)	0 (0)
Congestive heart failure	7.9 (157)	9.8 (155)	0.5 (2)
Stroke	9.6 (190)	11.6 (183)	1.8 (7)
Coronary artery bypass graft	8.7 (172)	10.9 (172)	0 (0)
Arrhythmia	6.1 (121)	7.4 (116)	1.3 (5)
Length of initial hospital attendance (h)			
Median	31.3 (24–96)	48.0 (24–120)	24.1 (11.3–28.1)
Mean	81.8 ± 245.2	93.1 ± 270.8	34.8 ± 48.2

Values are mean ± SD, % (n), or median (interquartile range [IQR]). *Data missing in 28 patients. Values >100% due to multiple factors reported by patients.

these investigations were stress tests (81.1%) and occurred during the initial hospital attendance (88.0%). Investigations generally occurred within a median timeframe of approximately 7 days (Online Table 2a). Therapeutic and procedural interventions occurred in 18.3% and 2.0% of ADP negative patients, respectively (Online Table 2b).

Discussion

This large 2-center Australasian study prospectively validated a 2-h ADP incorporating ECG, TIMI score, and cTnI. With use of this ADP, a large group (20%) of patients presenting with possible ACSs was identified as low risk

Table 3 Frequency and Type of Major Adverse Cardiac Event During Initial Hospital Attendance or 30-Day Follow-Up

Major Adverse Cardiac Event	No. of Events (n = 350)	Percentage of Patients Who Had Event Type (n = 302)	Percentage Frequency of Event Type of Total Patients (N = 1,975)
Non-STEMI	273	90.40	13.82
STEMI	25	8.28	1.27
Emergency revascularization	26	8.61	1.32
Cardiovascular death	8	2.65	0.41
Ventricular arrhythmia	6	1.99	0.30
Cardiac arrest	3	0.99	0.15
Cardiogenic shock	4	1.32	0.20
High atrioventricular block	5	1.66	0.25

ST-segment elevation myocardial infarction (STEMI) occurred after initial recruitment. *350 events occurred in 302 patients during initial hospital attendance or 30-day follow-up.

Table 4 Test Parameter Performance: Occurrence of Major Adverse Cardiac Events During Initial Hospital Attendance or 30-Day Follow-Up According to the Results of Individual and Combination of the Accelerated Diagnostic Protocol Test Parameters

Test	Outcome			Test	Outcome		
	MACE	No MACE	Total		MACE	No MACE	Total
ECG*				Troponin†			
Positive	74	193	267	Positive	264	124	388
Negative	228‡	1,480	1,708	Negative	38‡	1,549	1,587
Total	302	1,673	1,975	Total	302	1,673	1,975
TIMI§				ECG + troponin			
Positive	293	1,238	1,531	Positive	269	291	560
Negative	9‡	435	444	Negative	33‡	1,382	1,415
Total	302	1,673	1,975	Total	302	1,673	1,975
ECG + TIMI¶				ADP (ECG + TIMI* + troponin)#			
Positive	297	1,280	1,577	Positive	301	1,282	1,583
Negative	5‡	393	398	Negative	1‡	391	392
Total	302	1,673	1,975	Total	302	1,673	1,975

*Electrocardiography (ECG) alone: any new ischemia was positive. †Any cardiac troponin-I (cTnI) greater than the cutoff was positive. ‡Accelerated diagnostic protocol (ADP) false negative cases. §Thrombolysis In Myocardial Infarction (TIMI) score of ≥ 1 was positive. TIMI used contemporary cTnI and ECG result at 0 h. ||cTnI more than the cutoff or any new ischemia on ECG was positive. ¶Any new ischemia on ECG or TIMI score ≥ 1 was positive. #ADP was negative if TIMI score was 0 and ECG and cTnI were all negative. If TIMI score was ≥ 1 or any other parameter was positive, then ADP was positive. MACE = major adverse cardiac event.

and suitable for outpatient care at a risk of 0.25% for a short-term MACE. These patients could have been safely discharged to outpatient follow-up many hours earlier than what usually occurs in current practice. The reduction in time required for observation for some patients through application of this ADP could have significant benefits for health services, even in those centers with chest pain observation units. In the United States alone, >6 million ED visits a year involve patients presenting with chest pain (20). In centers with lower disease prevalence, such as in the United States, it is likely that even more patients would be suitable for discharge to outpatient care with this ADP, which could potentially reduce extended observation in millions of patients annually. In patients unsuitable for outpatient follow-up, a negative ADP result could allow earlier in-patient investigation and still reduce length of stay in the hospital.

The new ADP has a very high sensitivity and negative predictive value, and using a contemporary cTnI as the single biomarker in the ADP doubled the proportion of patients classified as low risk in comparison to the ASPECT study (20% vs. 9.8%) (11). If the cutoff used to define an elevated troponin had been the internationally recom-

mended value of greater than the 99th percentile (rather than using the local institution's cutoff rounded to 2 decimal places), the sensitivity of this ADP would have been unchanged (99.7%). Using such a cutoff would have identified 3 less patients (n = 389; 19.7%) as low risk (Online Table 3).

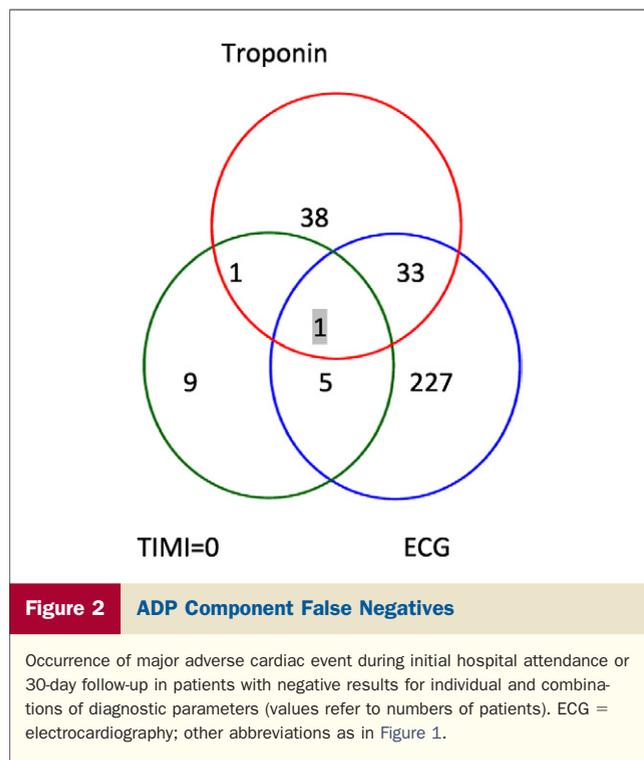
This study confirms that each of the components of the ADP, including troponin, is needed to achieve sufficient sensitivity to be used at an early timeframe after presentation (Table 4). A TIMI score equaling 0 within the ADP resulted in a lower and more acceptable false negative rate than when only troponins and ECG were used for the prediction of 30-day MACEs (0.25% vs. 3.2%).

This study also demonstrates that central laboratory troponin assays currently in use have sufficient sensitivity at an early time point to negate the need for additional biomarkers (such as myoglobin and creatine kinase-MB) as components of the ADP. These other biomarkers do not improve the sensitivity, and reduce the proportion of patients defined as low risk (due to a greater number of patients with a positive biomarker result), as was shown in the ASPECT study (11).

Table 5 Diagnostic Accuracy: Accuracy of cTnI, ECG, TIMI, and ADP for Prediction of MACE

ECG	ECG*	Troponin†	Troponin and ECG‡	TIMI and ECG§	ADP (ECG+ TIMI + Troponin)
Sensitivity	24.5 (20.0-29.7)	87.4 (83.2-90.7)	89.1 (85.1-92.1)	98.3 (96.2-99.3)	99.7 (98.1-99.9)
Negative predictive value	86.7 (85.0-88.2)	97.6 (96.7-98.3)	97.7 (96.7-98.3)	98.7 (97.1-99.5)	99.7 (98.6-100.0)
Specificity	88.5 (86.8-89.9)	92.6 (91.2-93.7)	82.6 (80.7-84.3)	23.5 (21.5-25.6)	23.4 (21.4-25.5)
Positive predictive value	27.7 (22.7-33.4)	68.0 (63.2-72.5)	48.0 (43.9-52.2)	18.8 (17.0-20.8)	19.0 (17.2-21.0)
Negative likelihood ratio	0.85 (0.80-0.91)	0.14 (0.10-0.18)	0.13 (0.10-0.18)	0.07 (0.03-0.17)	0.01 (0.002-0.10)
Positive likelihood ratio	2.12 (1.67-2.70)	11.79 (9.90-14.05)	5.12 (4.58-5.72)	1.29 (1.25-1.33)	1.30 (1.27-1.34)

*ECG alone: any new ischemia was positive. †cTnI more than cutoff for an elevated troponin was positive. ‡Troponin and ECG: cTnI more than cutoff value for an elevated troponin and/or any new ischemia on ECG was positive. §TIMI and ECG: TIMI score of ≥ 1 was positive and/or any new ischemia on ECG was positive. ||ADP was negative if TIMI score was 0 and ECG and troponin were all negative. If TIMI score was ≥ 1 or any other parameter was positive, then ADP was positive. Abbreviations as in Table 4.



The results show that the ADP is sensitive for both early and late presenters, identifying a greater proportion of patients as low risk in early presenters. Thus, the ADP could have the greatest impact in patients presenting within 3 h of symptom onset, the group in which the second troponin sampling time point is usually most delayed.

Body et al. (21) described how a highly sensitive cTn (HS-cTn) assay may allow early “rule-out” of AMI using a blood test only on arrival. Their study utilized the assay level of detection rather than the 99th percentile. Highly sensitive assays are not yet widely available, but if prospectively validated, then this approach may be important. However, when early results are used in conjunction with the TIMI risk score and ECG, sensitivity may not be significantly improved and specificity may be reduced. It is not yet clear how early after presentation we can rely on negative highly sensitive troponin results alone without requiring other clinical data such as the TIMI score. Further work is also needed to guide the interpretation and management of the increased number of patients with a positive troponin result that occur using highly sensitive troponin assays. Other biomarkers, such as copeptin and heart fatty acid binding protein, may improve the baseline sensitivity for AMI; however, their use as part of an ADP has not been reported (22,23). The early identification of patients with AMI is important, but identifying a true low-risk cohort must involve the detection of those at risk of a broader group of adverse events, in addition to AMI.

Study limitations. The applicability of the ADP is restricted to the selected cohort of patients with chest discomfort suggestive of ACSs that the attending physician

planned to investigate. In particular, the inclusion of predominantly Caucasian patients may restrict the international generalizability of these findings. Patients who presented with atypical symptoms without chest pain were not included in this trial, and deciding when to investigate these for an ACS remains a challenge.

The study was an observational study and not an intervention study. Ideally, a randomized controlled trial of the diagnostic protocol would now occur. However, in practice, such studies are rare. As a result of the observational design, most ADP negative patients had further investigations and some treatments as in-patients (Online Tables 2a and 2b). Hospital admission, investigation, and subsequent treatment (e.g., revascularization, antiplatelet, or antithrombotic therapy) were common and possibly secured better outcomes. Thus, patients who are ADP negative require further nonurgent follow-up investigations and possibly treatment. In some health systems, it will be possible for these investigations to occur rapidly on an outpatient basis, and where this is not possible, a negative ADP result could allow earlier progression to in-patient investigation and still reduce length of stay in the hospital.

The sensitivity of the ADP appears to be high. HS-cTn assays appear to detect and predict additional adverse outcomes compared with conventional assays. It is possible that if an HS-cTn assay was used as the reference standard troponin at arrival and after 6+ h, then this would lead to a greater number of patients being classified as having a non-STEMI and, therefore, maybe a lower sensitivity. This potential limitation is always a possibility when changing technology creates a more sensitive reference standard. It is also possible that by using HS-cTn assays, some patients with negative results may be able to avoid, or have less extensive follow-up investigations after ED assessment than occurred in this cohort of patients. This requires further evaluation. The purpose of this study was to show that an ADP could use the same 2 troponin assays as currently used at our hospitals to identify a group of patients as very low risk at an earlier time point than usual. The specificity (23.5%) of our method might be regarded as a limitation, but as a “rule-out” rather than a “rule-in” tool, this specificity is a significant improvement compared with other pathways (11). Patients who are not low risk according to the ADP should continue to be managed with existing clinical care that involves extended observation or admission. A process yielding a higher specificity could discharge a larger number of patients, but at the cost of an unacceptable drop in sensitivity. This is demonstrated by the improved low-risk eligibility, but increase in false negative cases that would occur by using a TIMI score of 0 or 1 within this ADP. The TIMI score was derived from a high-risk in-patient population to predict the likelihood of a MACE and to guide therapy, and not for this “rule-out” purpose in a low-risk ED population. Yet to date, it is one of the most validated ACS risk tools available.

Conclusions

A 2-h ADP using a central laboratory troponin as the sole biomarker in conjunction with ECG and the TIMI risk score identified a large group of patients suitable for safe early discharge. These patients are at low risk of a short-term MACE. They could therefore have rapid discharge with early outpatient follow-up or proceed more quickly to further in-patients tests, potentially shortening hospital length of stay. The components required for this strategy are already widely available; therefore, rapid uptake of the ADP is possible by most hospitals with the potential for immediate health service benefit.

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REFERENCES

1. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. *Heart* 2005;91:229-30.
2. Pollack CV Jr., Sites FD, Shofer FS, Sease KL, Hollander JE. Application of the TIMI risk score for unstable angina and non-ST elevation acute coronary syndrome to an unselected emergency department chest pain population. *Acad Emerg Med* 2006;13:13-8.
3. Chase M, Robey JL, Zogby KE, Sease KL, Shofer FS, Hollander JE. Prospective validation of the Thrombolysis in Myocardial Infarction Risk Score in the emergency department chest pain population. *Ann Emerg Med* 2006;48:252-9.
4. Hollander JE. The continuing search to identify the very-low-risk chest pain patient. *Acad Emerg Med* 1999;6:979-81.
5. Bernstein SL, Aronsky D, Duseja R, et al. The effect of emergency department crowding on clinically oriented outcomes. *Acad Emerg Med* 2009;16:1-10.
6. Pollack CV Jr., Antman EM, Hollander JE. 2007 focused update to the ACC/AHA guidelines for the management of patients with ST-segment elevation myocardial infarction: implications for emergency department practice. *Ann Emerg Med* 2008;52:344-55.
7. Amsterdam EA, Kirk JD, Bluemke DA, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation* 2010;122:1756-76.
8. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation* 2007;116:2634-53.
9. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. *J Am Coll Cardiol* 2007;50:652-726.
10. Aroney CN, Dunlevie HL, Bett JH. Use of an accelerated chest pain assessment protocol in patients at intermediate risk of adverse cardiac events. *Med J Aust* 2003;178:370-4.
11. Than M, Cullen L, Reid CM, et al. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. *Lancet* 2011;377:1077-84.
12. Goodacre SW, Bradburn M, Cross E, Collinson P, Gray A, Hall AS. The Randomised Assessment of Treatment using Panel Assay of Cardiac Markers (RATPAC) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. *Heart* 2011;97:190-6.
13. Lee-Lewandrowski E, Januzzi JL Jr., Grisson R, Mohammed AA, Lewandrowski G, Lewandrowski K. Evaluation of first-draw whole blood, point-of-care cardiac markers in the context of the universal definition of myocardial infarction: a comparison of a multimarker panel to troponin alone and to testing in the central laboratory. *Arch Pathol Lab Med* 2011;135:459-63.
14. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies. *Circulation* 2003;108:2543-9.
15. Cullen L, Than M, Brown AF, et al. Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments in Australasia. *Emerg Med Australas* 2010;22:35-55.
16. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835-42.
17. Hollander JE, Blomkalns AL, Brogan GX, et al. Standardized reporting guidelines for studies evaluating risk stratification of ED patients with potential acute coronary syndromes. *Acad Emerg Med* 2004;11:1331-40.
18. Cannon CP, Battler A, Brindis RG, et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. *J Am Coll Cardiol* 2001;38:2114-30.
19. Forest RS, Shofer FS, Sease KL, Hollander JE. Assessment of the standardized reporting guidelines ECG classification system: the presenting ECG predicts 30-day outcomes. *Ann Emerg Med* 2004;44:206-12.
20. Pitts SR, Niska RW, Xu J. National Hospital Ambulatory Medical Care Survey: 2006 Emergency Department Summary: Division of Health Care Statistics 2008. Available at: <http://www.cdc.gov/nchs/data/nhsr/nhsr007.pdf>. Accessed November 12, 2010.
21. Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol* 2011;58:1332-9.
22. Reichlin T, Hochholzer W, Stelzig C, et al. Incremental value of copeptin for rapid rule out of acute myocardial infarction. *J Am Coll Cardiol* 2009;54:60-8.
23. Valle HA, Riesgo LG, Bel MS, Gonzalo FE, Sanchez MS, Oliva LI. Clinical assessment of heart-type fatty acid binding protein in early diagnosis of acute coronary syndrome. *Eur J Emerg Med* 2008;15:140-4.

Key Words: acute coronary syndromes ■ acute myocardial infarction ■ emergency department ■ sensitivity and specificity ■ troponins.

APPENDIX

For the supplemental tables, please see the online version of this article.