

## Original Investigation

# A 2-Hour Diagnostic Protocol for Possible Cardiac Chest Pain in the Emergency Department

## A Randomized Clinical Trial

Martin Than, MBBS; Sally Aldous, MD; Sarah Jane Lord, MBBS; Stephen Goodacre, PhD; Christopher M. A. Frampton, PhD; Richard Troughton, PhD; Peter George, MBBS; Christopher Michael Florkowski, MD; Michael Ardagh, PhD; David Smyth, MD; David Lewis Jardine, MD; William Frank Peacock, MD; Joanna Young, PhD; Gregory Hamilton, PhD; Joanne M. Deely, PhD; Louise Cullen, MBBS; A. Mark Richards, MD

**IMPORTANCE** Patients with chest pain represent a high health care burden, but it may be possible to identify a patient group with a low short-term risk of adverse cardiac events who are suitable for early discharge.

**OBJECTIVE** To compare the effectiveness of a rapid diagnostic pathway with a standard-care diagnostic pathway for the assessment of patients with possible cardiac chest pain in a usual clinical practice setting.

**DESIGN, SETTING, AND PARTICIPANTS** A single-center, randomized parallel-group trial with blinded outcome assessments was conducted in an academic general and tertiary hospital. Participants included adults with acute chest pain consistent with acute coronary syndrome for whom the attending physician planned further observation and troponin testing. Patient recruitment occurred from October 11, 2010, to July 4, 2012, with a 30-day follow-up.

**INTERVENTIONS** An experimental pathway using an accelerated diagnostic protocol (Thrombolysis in Myocardial Infarction score, 0; electrocardiography; and 0- and 2-hour troponin tests) or a standard-care pathway (troponin test on arrival at hospital, prolonged observation, and a second troponin test 6-12 hours after onset of pain) serving as the control.

**MAIN OUTCOMES AND MEASURES** Discharge from the hospital within 6 hours without a major adverse cardiac event occurring within 30 days.

**RESULTS** Fifty-two of 270 patients in the experimental group were successfully discharged within 6 hours compared with 30 of 272 patients in the control group (19.3% vs 11.0%; odds ratio, 1.92; 95% CI, 1.18-3.13;  $P = .008$ ). It required 20 hours to discharge the same proportion of patients from the control group as achieved in the experimental group within 6 hours. In the experimental group, 35 additional patients (12.9%) were classified as low risk but admitted to an inpatient ward for cardiac investigation. None of the 35 patients received a diagnosis of acute coronary syndrome after inpatient evaluation.

**CONCLUSIONS AND RELEVANCE** Using the accelerated diagnostic protocol in the experimental pathway almost doubled the proportion of patients with chest pain discharged early. Clinicians could discharge approximately 1 of 5 patients with chest pain to outpatient follow-up monitoring in less than 6 hours. This diagnostic strategy could be easily replicated in other centers because no extra resources are required.

**TRIAL REGISTRATION** anzctr.org.au Identifier: ACTRN12610000766011

*JAMA Intern Med.* 2014;174(1):51-58. doi:10.1001/jamainternmed.2013.11362  
Published online October 7, 2013.

← Invited Commentary page 59

+ Supplemental content at  
jamainternalmedicine.com

+ CME Quiz at  
jamanetworkcme.com and  
CME Questions page 172

**Author Affiliations:** Emergency Department, Christchurch Hospital, Christchurch, New Zealand (Than, Aldous, George, Smyth, Jardine, Young); University of Sydney, Sydney, Australia (Lord); University of Sheffield and Northern General Hospital, Sheffield, England (Goodacre); University of Otago, Christchurch, New Zealand (Frampton, Troughton, Ardagh, Richards); Canterbury Health Laboratories, Christchurch, New Zealand (Florkowski); Baylor College of Medicine, Houston, Texas (Peacock); Canterbury District Health Board, Christchurch, New Zealand (Hamilton, Deely); Royal Brisbane and Women's Hospital, Herston, and Queensland University of Technology, Brisbane, Australia (Cullen).

**Corresponding Author:** Martin Than, MBBS, Emergency Department, Christchurch Hospital, Riccarton Ave, Private Bag 4710, Christchurch, New Zealand (martinthan@xtra.co.nz).

Patients with symptoms suggestive of acute coronary syndromes (ACS) compose approximately 5% to 10% of annual presentations to emergency departments (EDs) and up to 25% of hospital admissions.<sup>1</sup> Assessment and safe disposition of these patients is a major challenge for clinicians because a missed diagnosis of ACS can lead to death or other adverse outcomes.<sup>2</sup> International guidelines for the investigation of ACS recommend serial measurements of contemporary (non-high sensitivity) cardiac troponin during 6 to 12 hours from the time of symptom onset or presentation to the ED.<sup>3-7</sup> Consequently, safe patient workup generally requires considerable time, even though less than 25% of patients with chest pain finally receive diagnoses of ACS.<sup>8-10</sup> A combination of the high numbers of patients assessed and prolonged observation contributes to ED overcrowding, which is associated with high costs and adverse patient outcomes, including increased mortality.<sup>11-15</sup> A study<sup>11</sup> of more than 14 million patients showed significantly worse outcomes for patients staying in the ED longer than 6 hours compared with those who remain only 1 hour. A reliable diagnostic strategy is needed using serial troponin testing over a short time frame to identify a low-risk patient group who could avoid prolonged observation.

Diagnostic strategies incorporating point-of-care panels or sensitive and highly sensitive troponins have been shown to identify subgroups of low-risk patients with chest pain who may be eligible for early discharge from the hospital with high sensitivities and negative predictive values.<sup>16-21</sup> The observational ADAPT study described a 2-hour accelerated diagnostic protocol (ADP) combining 0- and 2-hour cardiac troponin tests, electrocardiograms (ECGs), and an adaptation of the Thrombolysis in Myocardial Infarction (TIMI) score.<sup>16</sup> The ADP classified 20% of chest pain presentations as low-risk with a subsequent 0.3% rate of short-term adverse events. These low-risk patients might therefore be discharged early to outpatient follow-up investigation or proceed more quickly to further inpatient testing, potentially shortening hospital length of stay. The efficacy of implementing this type of intervention has not been evaluated in a patient population.

Clinicians do not always adhere to clinical pathways or guidelines. For example, a study<sup>22</sup> including 117 EDs found that international guidelines for the investigation of suspected pulmonary embolism were not followed for 47% of patients. It is therefore important to determine whether the ADP will work within a clinical pathway implemented in daily hospital care where the attending clinician has final decision-making authority. We designed a trial using the Consolidated Standards for Reporting of Trials (CONSORT) group pragmatic trials guidance to test for the existence and size of any beneficial effect of using the ADAPT ADP in the conditions in which it usually would be applied. We conducted a randomized clinical trial comparing use of the ADP with conventional diagnostic assessment. We compared the rate of successful ED discharge within 6 hours (defined as without a major adverse cardiac event occurring within 30 days).

## Methods

### Study Design and Participants

This study was a single-center randomized clinical trial (1:1 allocation ratio) designed to compare the effectiveness of 2 investigative pathways for the assessment of patients with possible cardiac chest pain. The trial design was based on the CONSORT extension statement for pragmatic trials,<sup>23</sup> and clinical management therefore was not strictly controlled. Although pathways for the intervention and control arms were provided, the final clinical management decision, based on either subjective or structured risk assessment, as well as on test results, was at the discretion of the attending clinician. Research staff documented, but did not intervene in, clinical decisions. The research protocol received regional ethics committee approval, and informed consent was obtained from all patients.

Recruitment occurred from October 11, 2010, to July 4, 2012, between 8 AM and 10 PM, 7 days a week. Consecutively consenting patients who presented acutely to the Christchurch Hospital ED with possible cardiac chest pain were enrolled. Eligible patients were those aged 18 years or older who had symptoms consistent with ACS and for whom the attending physician planned further observation/admission and troponin testing to investigate for possible acute myocardial infarction. The American Heart Association<sup>24</sup> case definitions for possible cardiac symptoms were used (ie, acute chest, epigastric, neck, jaw, or arm pain, or discomfort or pressure without an apparent noncardiac source). All eligible patients were randomized regardless of their likely final TIMI score, and perceived high risk of ACS was not used as an exclusion criterion. Patients were excluded for any of the following reasons: ST-segment elevation myocardial infarction, an initial clear cause other than ACS for the symptoms (eg, pneumonia), inability to provide informed consent, staff considered recruitment to be inappropriate (eg, receiving palliative treatment), chest pain symptoms began more than 12 hours before presentation, persisting chest pain, transfer from another hospital, pregnancy, previous inclusion in the study, or inability to be contacted after discharge.

### Study Setting

Christchurch Hospital is the general and tertiary hospital for approximately 450 000 people. The ED has approximately 75 000 new patient attendances per year. Patients arriving at the ED with chest pain do so mainly by self-presentation or via a call to ambulance services, or after referral from primary care physicians. Patients who present to the ED with possible cardiac symptoms usually are entered into a special cardiac chest pain clinical pathway containing specific steps and guidance. Clinicians are expected to follow the guidance in the pathway unless they can document good clinical reasons not to. The hospital used a troponin assay that has a manufacturer-specified limit of detection of less than 0.01 ng/mL, 99th percentile of 0.028 ng/mL, and 10% coefficient of variation of 0.032 ng/mL (ARCHITECT troponin I [TnI] assay; Abbott). At Christchurch Hospital, results were rounded to 2 decimal places; results re-

ported as greater than 0.03 ng/mL were classified as positive. (Conversion of TnI to micrograms per liter is 1:1.)

### Randomization and Blinding

A computer-generated block randomization sequence (permuted blocks of 20) was used to populate consecutively numbered sealed envelopes, placed within closed study packs. The recruiting personnel were unaware of this sequence. The 3 senior clinicians (S.A. and R.T.) who adjudicated for the presence of any major adverse cardiac event (MACE) were blinded to study group allocation. Adjudications were entered into a database separate from other trial information. It was not possible to blind the patients or clinical staff.

### Interventions

In the control group of the trial, patients were entered into the hospital's standard-care cardiac chest pain pathway. On arrival, patients received an initial ECG and a blood sample was obtained for the first TnI test. The blood sampling for the second TnI test was timed so that it took place 6 to 12 hours after the onset of the possible cardiac symptoms.<sup>3-7</sup> Standard care usually involved observation/admission under the care of an inpatient team. Plans for follow-up investigations (eg, exercise stress test) were at the discretion of the senior clinician. Discharge advice was provided to patients on recommended lifestyle modifications, and guidance was given on how to respond to any future symptoms. Patients were encouraged to visit their primary care physician within 7 days.

In the experimental group of the trial, patients received an initial ECG and a blood sample was obtained for TnI on their arrival at the hospital, and their modified TIMI score<sup>25</sup> was calculated (Table 1). If there was no new ischemia observed on the first ECG, the initial TnI test result was normal, and the TIMI score was 0, patients were moved to an ED observation bed without ECG monitoring. At 2 hours after the initial tests (approximately 2 hours after presentation to the ED), another ECG was obtained and blood was drawn for a second TnI test. If all test results were negative, patients were classified as low risk and discharged. All patients who were discharged early on the basis of the ADP were scheduled to return to the hospital within 72 hours as outpatients for a stress test (usually an exercise treadmill test) using the same slot they would have been allocated as an inpatient. If any diagnostic factor was positive or the TIMI score was 1 or more, patients were not classified as low risk and their care was managed according to the standard cardiac chest-pain clinical pathway with a TnI test performed 6 to 12 hours after symptom onset (Supplement [eFigure]). Discharge arrangements were otherwise the same as for the control group.

### Outcome Measures

The primary end point of the study was successful discharge, defined as discharge from the hospital within 6 hours of ED arrival and without a subsequent MACE within 30 days. A time point was chosen for the primary outcome rather than admission/discharge rate because hospital admission is defined differently in different locations/countries. Six hours was selected as the time point for the primary outcome because it is

Table 1. ADP Criteria for Patient Classification as Low Risk<sup>16</sup>

Criteria
All factors had to be negative for the patient to be classified as low risk and suitable for early discharge with outpatient stress test.
1. Modified TIMI score, 0 (ie, all 7 criteria absent) <sup>a</sup>
a. Age $\geq 65$ y
b. $\geq 3$ Risk factors for coronary artery disease: family history of coronary disease, hypertension, hypercholesterolemia, diabetes mellitus, or current smoker
c. Use of aspirin in the past 7 d
d. Significant coronary stenosis (eg, previous coronary stenosis $\geq 50\%$ )
e. Severe angina (eg, $\geq 2$ angina events in past 24 h or persisting discomfort)
f. ST-segment deviation of $\geq 0.05$ mV on first ECG
g. Increased initial troponin level <sup>b</sup>
2. Negative troponin test result at 0 and 2 h <sup>b</sup>
3. No new ischemic ECG changes <sup>c</sup>
If a patient's pain returned or there were abnormal vital signs <sup>d</sup> the patient was considered not at low risk. The ADP is the first step in the experimental pathway, which includes further testing (eg, stress testing).

Abbreviations: ADP, accelerated diagnostic protocol; ECG, electrocardiogram; TIMI, Thrombolysis in Myocardial Infarction.

<sup>a</sup> Assessment of the modified TIMI score for unstable angina and non-ST elevation acute coronary syndrome and ECG was done by the attending clinician. With the TIMI score, 1 point is given for each criterion from a to g. If any criterion is positive, the score is greater than 0 and the patient is not considered low risk.

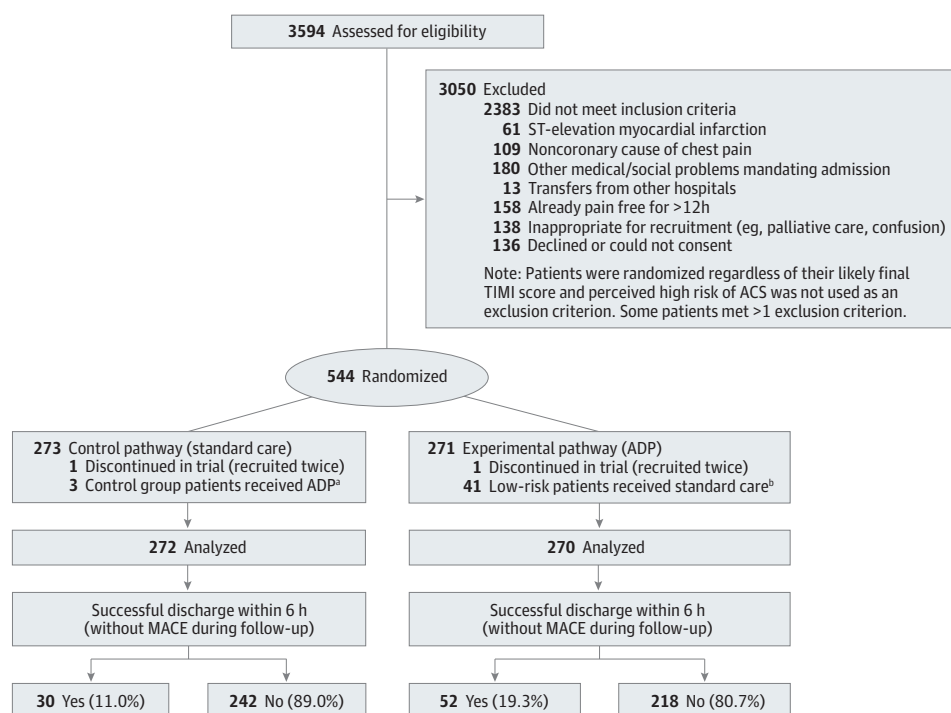
<sup>b</sup> Troponin test result was classified as positive if above the institutional cutoff and negative if equal to or below cutoff. The results of the 0-hour troponin I testing were used for calculation of the TIMI score in this study. The score criteria for points 1f and 1g are effectively redundant in the ADP because of the broader troponin and ECG criteria in points 2 and 3.

<sup>c</sup> Ischemic ECG changes with no evidence that they were preexisting. Electrocardiographic changes were defined as ST-segment depression of at least 0.05 mV in 2 or more contiguous leads (including reciprocal changes), T-wave inversion of at least 0.1 mV, or Q-waves greater than 30 milliseconds in width and 0.1 mV or greater in depth in at least 2 contiguous leads.<sup>26-28</sup> Patients with other abnormal ECG findings (eg, pacing artifact and left bundle-branch block) that were present on preexisting ECGs were not defined as high risk.

<sup>d</sup> Abnormal vital signs were classified as pulse rate less than 50 or greater than 100 bpm, systolic blood pressure less than 100 or greater than 200 mm Hg, and respiratory rate greater than 30 per minute.

an upper limit of time that a patient can remain in the ED without an effect on overcrowding and adverse patient outcomes.<sup>11</sup> For all patients in the study, MACE was reported if any of the following 7 predefined published ACS-related diagnoses<sup>26</sup> were made during the initial hospital admission or during the 30-day follow-up period: (1) death (unless clearly noncardiac), (2) cardiac arrest, (3) emergency revascularization procedure, (4) cardiogenic shock, (5) ventricular arrhythmia needing intervention, (6) high-degree atrioventricular block needing intervention, and (7) acute myocardial infarction.<sup>5,26</sup> Patients were followed up to determine the occurrence of MACE within 30 days after presentation using all of the following methods: telephone contact, review of patient medical records, and a national death and health events search. Patients in New Zealand have a unique alphanumeric identifier for tracking of all hospital inpatient and outpatient events within the nation's health system.

Figure 1. Trial Profile



Accelerated diagnostic protocol (ADP) included Thrombolysis in Myocardial Infarction (TIMI) score for unstable angina and non-ST elevation acute coronary syndrome of 0, electrocardiogram, and 0- and 2-hour troponin testing.<sup>25</sup>  
<sup>a</sup>Three patients assigned to the control pathway received treatment via the experimental pathway and were discharged early.  
<sup>b</sup>Forty-one patients assigned to the experimental pathway and classified as

low-risk received standard care. These patients were admitted for further inpatient investigation for acute coronary syndrome (n = 35) or because an alternative diagnosis requiring admission had become apparent (n = 6). None of these patients had an acute coronary syndrome. No study patients were lost to follow-up or excluded from the analysis.

### Sample Size

We estimated a 5% early discharge rate in the control group and a 17% early discharge rate in the experimental group (95% CI lower boundary, 14%). The study was powered to detect a 9% difference between the randomized groups in the primary outcome of early discharge rate with 90% power and a 2-tailed  $\alpha = .05$ , requiring 250 patients per group.

### Statistical Analysis

Successful discharge and occurrence of MACE were compared between study groups using the  $\chi^2$  test or Fisher exact test and the odds ratio with 95% CI. The primary analysis was undertaken on an intention-to-treat basis.

## Results

### Study Patients

Of the 544 patients who underwent randomization, 2 were removed from the trial because they were included twice. All remaining 542 patients were successfully monitored for 30 days (Figure 1). Participants were predominantly older men of New Zealand European origin (white) and commonly had cardiovascular risk factors and prior cardiovascular disease (Table 2).<sup>25</sup> There were no significant differences in characteristics at base-

line between treatment groups. Investigations and cardiac interventions were similar between the study groups (Supplement [eTable 1]).

### Early Discharge

Significantly more patients were successfully discharged within 6 hours of arrival using the experimental pathway (52 of 270 [19.3%]) than using the standard-care pathway (30 of 272 [11.0%]) (Table 3). The difference of 8.3% was statistically significant (95% CI, 1.8-14.0; odds ratio, 1.92; 95% CI, 1.18-3.13; number needed to treat, 13). With use of the standard-care pathway, 20 hours was required to discharge the same proportion of patients discharged in 6 hours with use of the experimental pathway (Figure 2). Thirty-five patients (13.0%) in the experimental group who were classified as low risk were admitted to an inpatient ward for further investigation for possible ACS; none received that diagnosis.

### Secondary Outcomes

There were no significant differences in numbers of MACEs experienced by the patients assigned to either diagnostic pathway (Table 3). Eighty-one of the 542 patients (14.9%) had at least 1 of the 7 diagnoses related to MACE during their initial hospital attendance. One of the 542 patients (0.2%) experienced a MACE during the 30-day follow-up period. This patient was

among those in the experimental group discharged within 6 hours and therefore was not regarded as having a successful discharge. The patient was a 63-year-old man who arrived at the ED 6.5 hours after chest pain onset. The morning following discharge, he had an exercise treadmill test, and the results were misinterpreted. The test was terminated after 3 minutes when the patient experienced anginal chest pain and an ECG showed early ischemic changes. The test was reported as normal by a junior resident and the patient was released without follow-up; he returned 7 days later with an ST-segment elevation myocardial infarction. No adverse events occurred in patients discharged within 6 hours in the control group. There were no adverse events in either group between the time of discharge and the time of the exercise stress testing, which occurred within 72 hours for 99% of the patients in both groups.

### Additional Observations

Three patients (1.1%) who were assigned to the standard-care pathway underwent the ADP and were discharged early; none of these patients had a MACE. Two patients (0.7%) in the experimental group were discharged from the ED between 6.6 and 8.2 hours after arrival resulting from delays in clinician review. Six patients (2.2%) in the experimental group classified as low risk were admitted because an alternative diagnosis requiring admission had become apparent (Supplement [eTables 2 and 3]).

## Discussion

In this randomized trial, almost twice as many patients with chest pain were discharged early when clinicians used the experimental pathway rather than the standard-care pathway. To our knowledge, this is the first randomized trial incorporating troponin as the sole biomarker in an ADP within a clinical pathway. The findings are consistent with those of the large observational ADAPT study,<sup>16</sup> in which the same ADP applied post hoc classified 20% of 1975 patients as low risk. Increased early discharge was also shown by the Randomised Assessment of Treatment Using Panel Assay of Cardiac Markers trial,<sup>20</sup> which investigated the impact of point-of-care blood tests in a population with 5 times lower prevalence of MACE than in the present study (2.8% vs 15.1%). The rate of MACE in our cohort was higher than that recorded by other centers.<sup>9,20</sup> Introducing the experimental pathway in locations where the risk of ACS is lower might be expected to achieve higher early discharge rates.

The trial finding has important health resource implications. From a clinical perspective, increasing early discharge rates can help to decrease overcrowding in EDs and hospitals and avoid duplication of staff time. Reducing the time that patients with chest pain spend in the hospital will lessen the pressure on resources and finances. Such savings could have an immense impact in a country such as the United States, where more than 6 million patients present to EDs with chest pain annually.<sup>29</sup>

This study provides the first evidence of the effective use of the experimental pathway in a real-life setting. It was con-

Table 2. Patient Demographics and Risk Characteristics

Characteristic	Pathway, No. (%)	
	Control (Standard Care) (n = 272)	Experimental (Incorporating ADP) (n = 270)
Age, mean (SD), y	60.5 (13.0)	60.5 (12.6)
Sex		
Male	166 (61.0)	171 (63.3)
Female	106 (39.0)	99 (36.7)
Ethnic origin		
New Zealand European	249 (91.5)	251 (93.0)
New Zealand Maori	7 (2.6)	11 (4.1)
Pacific island	3 (1.1)	3 (1.1)
Asian	2 (0.7)	3 (1.1)
Other or not stated	11 (4.0)	2 (0.7)
History of cardiovascular disease		
Coronary artery disease	121 (44.5)	116 (43.0)
Acute myocardial infarction	67 (24.6)	68 (25.2)
Congestive heart failure	14 (5.1)	10 (3.7)
Stroke or transient ischemic attack	27 (9.9)	27 (10.0)
Peripheral arterial disease	11 (4.0)	15 (5.6)
Coronary artery bypass grafting	18 (6.6)	24 (8.9)
Coronary angioplasty	79 (29.0)	73 (27.0)
Ventricular tachycardia	12 (4.4)	12 (4.4)
Atrial arrhythmia	24 (8.8)	26 (9.6)
Other	45 (16.5)	54 (20.0)
Risk factor		
Hypertension	124 (45.6)	120 (44.4)
Diabetes mellitus	38 (14.0)	43 (15.9)
Dyslipidemia	145 (53.3)	134 (49.6)
Family history of coronary artery disease	169 (62.1)	162 (60.0)
Current smoker	51 (18.8)	42 (15.6)
Recent ex-smoker (>1 mo to 1 y)	8 (2.9)	8 (3.0)
Ex-smoker (>1 y)	102 (37.5)	107 (39.6)
TIMI score, 0	89	87
Onset of symptoms to first Tnl sample collection, median (IQR), h	3.08 (2.00-5.81)	3.42 (1.96-7.15)

Abbreviations: ADP, accelerated diagnostic protocol; IQR, interquartile range; TIMI score, Thrombolysis in Myocardial Infarction<sup>25</sup>; Tnl, troponin I.

ducted without enforcement of the allocated study protocol so that a realistic measurement of the impact of introducing the experimental pathway could be obtained. It may seem logical that provision for earlier troponin testing will lead to earlier discharge. However, clinicians may not follow such an approach with sufficient numbers of patients to make implementation of the experimental pathway worthwhile. This effect was illustrated by the high number of patients (in the experimental group) classified as low risk but still admitted to the hospital (without subsequent diagnosis of ACS). This had an important effect on the difference between primary outcomes for each group and suggests that a higher early discharge rate might be achievable with greater acceptance of the protocol by clinicians.

Table 3. Initial In-Hospital Cardiac End Points, Primary Outcome, and Follow-up Adverse Cardiac Events

Characteristic	Pathway, No. (%) <sup>a</sup>		Odds Ratio (95% CI)	P Value <sup>b</sup>
	Control (Standard Care) (n = 272)	Experimental (Incorporating ADP) (n = 270)		
ACS-related diagnoses as part of initial hospital presentation				
Total patients	35 (12.9)	46 (17.0)	1.39 (0.86-2.90)	.17
NSTEMI	33 (12.1)	44 (16.3)	1.41 (0.87-2.29)	.17
STEMI (after initial arrival and assessment) <sup>c</sup>	2 (0.7)	1 (0.4)	0.50 (0.05-5.57)	
Emergency revascularization	1 (0.4)	0		
Ventricular arrhythmia	1 (0.4)	0		
High atrioventricular block	0	3 (1.1)		
Cardiac arrest	0	0		
Cardiogenic shock	0	0		
Cardiovascular death	0	0		
Comparison of study end points during 30-day follow-up for patients discharged within 6 h (excludes events from initial hospital visit)				
Patients successfully discharged	30 (11.0)	52 (19.3)	1.89 (1.16-3.10)	.009
Patients who had a MACE during follow-up (not including initial hospital visit)	0	1 (0.4) <sup>d</sup>		
Patients with a second ACS-related hospital visit (including 1 MACE in row above)	0	1 (0.4) <sup>d</sup>		
ACS-related second visit (excluding MACE)	0	0		

Abbreviations: ACS, acute coronary syndrome; MACE, major adverse cardiac event; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

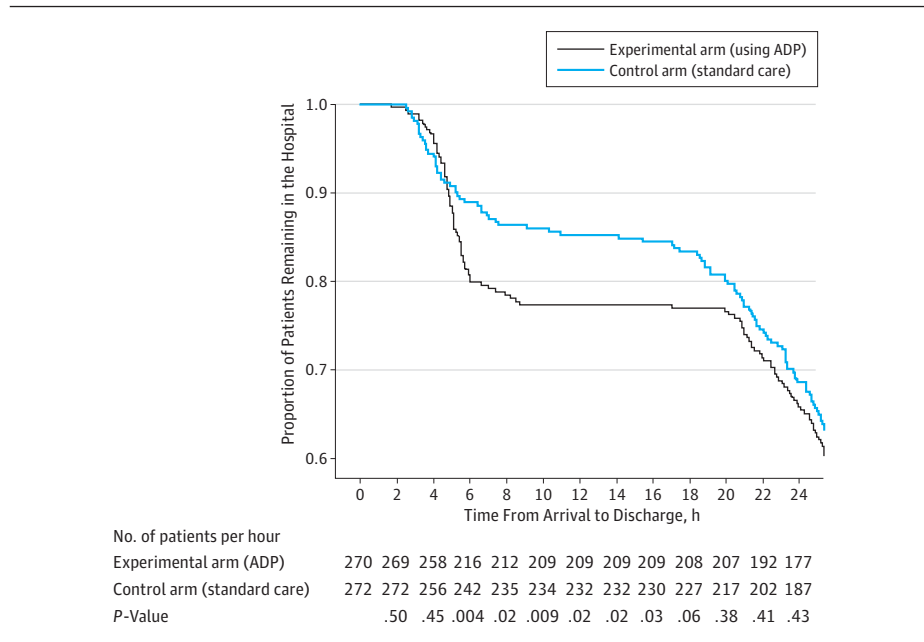
<sup>a</sup> Of 270 patients, 47 (17.4%) from the experimental pathway had a total of 49 ACS-related diagnoses or events during initial hospital visit (46 patients) or 30-day follow-up (1 patient); 35 of 272 patients (12.9%) in the standard-care pathway had a total of 37 ACS-related diagnoses or events during the initial hospital visit (35 patients) or 30-day follow-up (0 patients).

<sup>b</sup> P values were calculated using  $\chi^2$  or Fisher exact test.

<sup>c</sup> STEMI documented after initial recruitment.

<sup>d</sup> A single patient had a MACE and therefore an ACS-related second presentation during 30-day follow-up. This patient was not classified as a successful discharge.

Figure 2. Hospitalization Times for Patients Randomized to Each Diagnostic Pathway



ADP indicates accelerated diagnostic protocol.

In addition, to make the experimental pathway more reproducible, there was no provision of extra staff, bed, or capital resources to the experimental group. It is therefore possible that logistical constraints (eg, availability of medical staff to review patients) might have prevented timely discharge of many low-risk patients, but this occurred only twice. All the components needed for implementation of the experimental pathway are widely available internationally. Consequently, it

could provide a screening process that could be integrated with existing chest-pain assessment processes at other hospitals to create significant benefits without financial investment.

Many centers have or will soon have high-sensitivity cardiac troponin (HS-cTn) assays instead of the TnI assay used in the present trial. If HS-cTn were incorporated into the ADP, fewer patients might be identified as low risk because of the potential for increased numbers of positive results with HS-cTn

compared with assays that are not highly sensitive. Evidence is now available that this ADP also works when used with HS-cTnI or HS-cTnT assays. In recent studies<sup>30</sup> using HS-cTnT, 15.3% of patients were identified as low risk, with a negative predictive value of 99.3% for acute myocardial infarction. Using HS-cTnI, 19.6% to 25.3% of patients were identified as low risk with a negative predictive value for MACE of 100%.<sup>31</sup>

There are some limitations of the present study. This was a single-center trial, which may limit the generalizability of the findings. The single-center design also limited the sample size, so it was not possible to make subgroup comparisons. Although the rates of MACE did not differ significantly between the study groups, we cannot exclude a small difference in the risk of MACE following early discharge because our study was not powered to compare rates of MACE between the intervention and control groups. However, the safety of the ADP was demonstrated in the 1975 patients participating in the ADAPT observational study<sup>16</sup> and has been confirmed using HS-TnI in 909 patients from the Advantageous Predictors of Acute Coronary Syndromes Evaluation cohort in Germany and Switzerland.<sup>31</sup> Although larger observational studies need to further evaluate the safety of the ADP when fully implemented, our study is an important first step in proving that its use is feasible and will facilitate early discharge from the ED. This experimental pathway has been successfully implemented at Christchurch Hospital and Nambour Hospital, Australia, and

Queen Elizabeth II Hospital in Hong Kong and has been running for almost a year without adverse events.<sup>32</sup>

In the ADAPT<sup>16</sup> and APACE<sup>31</sup> groups, the negative predictive values of the ADP were 99.7% and 100%, respectively. In the experimental arm of our trial, of 94 patients classified as low risk, 1 had a MACE on follow-up, giving a similar negative predictive value at 98.9%. An attempt to achieve a zero rate of missed MACE may be very difficult without creating a considerable increase in health system costs. For the single patient with MACE in our study, the event occurred following clinician error that could have happened in either pathway. The second TnI was performed 8.5 hours after symptom onset, making the same outcome likely had randomization of that patient been to the control group. Local procedures were modified for both pathways so that senior clinicians now interpret stress tests. This case emphasizes that there is still a need for a follow-up test for ischemic heart disease, such as a stress test, after the ADP is completed.

This trial demonstrated that the experimental pathway is an effective and practical strategy to improve early discharge rates for some patients with chest pain. The strategy can easily be replicated. Use in the clinical setting would allow discharge of more patients with chest pain to outpatient follow-up within 6 hours of presentation. The reduction in time required to assess some patients could have significant benefits in terms of reduced consumption of health resources, costs, and patient anxiety and inconvenience.

#### ARTICLE INFORMATION

**Accepted for Publication:** August 1, 2013.

**Published Online:** October 7, 2013.

doi:10.1001/jamainternmed.2013.11362.

**Author Contributions:** Dr Than had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Than, Aldous, Goodacre, Frampton, George, Ardagh, Jardine, Cullen, Richards, Hamilton, Deely.

**Acquisition of data:** Than, Aldous, Troughton, George, Florkowski, Smyth, Richards.

**Analysis and interpretation of data:** Than, Lord, Goodacre, Troughton, George, Ardagh, Peacock, Young, Deely, Cullen, Richards.

**Drafting of the manuscript:** Than, Lord, Young, Deely, Cullen.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Lord, Frampton.

**Obtained funding:** Than, Goodacre, Troughton, Hamilton, Richards.

**Administrative, technical, and material support:** Than, Aldous, Troughton, George, Florkowski, Ardagh, Smyth, Jardine, Deely, Richards.

**Study supervision:** Troughton, George, Ardagh, Jardine, Cullen.

**Conflict of Interest Disclosures:** Dr Than has received funding from Alere, Abbott, Beckman, and Roche for speaking and support for other research. Dr Goodacre has received funding from the UK National Institute for Health Research for chest pain trials. Dr George receives funding from Abbott, Beckman Coulter, and Roche for speaking. Dr Ardagh has received funding from the Health

Research Council, New Zealand (HRCNZ) for unrelated research. Dr Peacock has received research grants from Abbott, Alere, Brahms, Novartis, Roche, and The Medicines Company; has been a consultant for Abbott, Alere, Lily, The Medicines Company; has been a speaker for Bureau Abbott, Alere, and EKjmr; and had ownership interest in Comprehensive Research Associates LLC, Vital Sensors, and Emergencies in Medicine LLC. Dr Deely receives funding from the Emergency Care Foundation for medical writing and HRCNZ for unrelated research. Dr Cullen has received funding from Abbott Diagnostics, Roche, Alere, Siemens, and Radiometer Pacific for clinical trials, and from Alere, Boehringer Ingelheim, Pfizer, AstraZenica, Abbott Diagnostics, and Radiometer Pacific for speaking and education. Dr Richards receives speaker honoraria from Roche Dx and Alere. No other disclosures were reported.

**Funding/Support:** Financial support for this study was provided by the Health Research Council of New Zealand and Canterbury District Health Board.

**Role of the Sponsor:** The HRCNZ and Canterbury District Health Board had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Additional Contributions:** The following Canterbury District Health Board staff contributed to the study. Coordination support: Lorraine Skelton, RN, Viki Robinson, BA, RComp N, and Deidre Krause, RN. Data management: Barabara Neame, BTEch and Nick Davis, Equipment coordination: Kay Ratahi. Recruitment,

phlebotomy, and telephone follow-up: Becky Hayston, BNurs, Carol Groves, RGON, Cindy Dorset, Jackie Hughs, RN, Joanne Davies, RN, MSc, Judy Heslop, NZCS, Debra Latimer, BA, PGCCPC, BN, RN, DipParamedSci, Deidre Krause, RN, Nikki Ross, RN, Sara Raudsepp, PGDipHealSci, Felicity Turner, NZRN, Jane Byrne, BSC Hons, Marlene Batchelor, BA, Mike O'Callaghan, RN, Ruth Jardine, RGON, BN, and Susan O'Brien, BA. ECG and diagnosis adjudication: Mark Baily, MBChB, PGDipMSM. Protocol development: Helen Kleindienst, BSc. Senior management support: Anne Esson, RGON, ADipN, BA, Carolyn Gullery, BSc, and David Meates, BAgSci. As staff, all received salary support but no additional payment from the authors.

#### REFERENCES

- Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. *Heart*. 2005;91(2):229-230.
- Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med*. 2000;342(16):1163-1170.
- Cooper A, Calvert N, Skinner J, et al. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE clinical guidelines. Published March 2010. <http://publications.nice.org.uk/chest-pain-of-recent-onset-cg95>. Accessed March 15, 2011.
- Amsterdam EA, Kirk JD, Bluemke DA, et al; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Cardiovascular Nursing, and Interdisciplinary Council on Quality of Care and Outcomes Research.

- Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation*. 2010;122(17):1756-1776.
5. Thygesen K, Alpert JS, White HD, et al; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation*. 2007;116(22):2634-2653.
  6. Anderson JL, Adams CD, Antman EM, et al; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction); American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association of Cardiovascular and Pulmonary Rehabilitation; Society for Academic Emergency Medicine. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons; endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine [published correction appears in *Circulation*. 2008;117(9):e180]. *Circulation*. 2007;116(7):e148-e304. doi:10.1161/CIRCULATIONAHA.107.181940.
  7. Thygesen K, Mair J, Katus H, et al; Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J*. 2010;31(18):2197-2204.
  8. 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(1):13-18.
  9. Diercks DB, Peacock WF 4th, Hollander JE, et al. Diagnostic accuracy of a point-of-care troponin I assay for acute myocardial infarction within 3 hours after presentation in early presenters to the emergency department with chest pain. *Am Heart J*. 2012;163(1):74-80.e4. doi:10.1016/j.ahj.2011.09.028.
  10. Hollander JE. The continuing search to identify the very-low-risk chest pain patient. *Acad Emerg Med*. 1999;6(10):979-981.
  11. Guttman A, Schull MJ, Vermeulen MJ, Stukel TA. Association between waiting times and short term mortality and hospital admission after departure from emergency department: population based cohort study from Ontario, Canada. *BMJ*. 2011;342:d2983.
  12. Sprivilis PC, Da Silva JA, Jacobs IG, Frazer AR, Jelinek GA. The association between hospital overcrowding and mortality among patients admitted via Western Australian emergency departments. *Med J Aust*. 2006;184(5):208-212.
  13. Diercks DB, Roe MT, Chen AY, et al. Prolonged emergency department stays of non-ST-segment-elevation myocardial infarction patients are associated with worse adherence to the American College of Cardiology/American Heart Association guidelines for management and increased adverse events. *Ann Emerg Med*. 2007;50(5):489-496.
  14. Pines JM, Hollander JE. Emergency department crowding is associated with poor care for patients with severe pain. *Ann Emerg Med*. 2008;51(1):1-5.
  15. Pines JM, Iyer S, Disbot M, Hollander JE, Shofer FS, Datner EM. The effect of emergency department crowding on patient satisfaction for admitted patients. *Acad Emerg Med*. 2008;15(9):825-831.
  16. Than M, Cullen L, Aldous S, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. *J Am Coll Cardiol*. 2012;59(23):2091-2098.
  17. 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(9771):1077-1084.
  18. McCord J, Nowak RM, McCullough PA, et al. Ninety-minute exclusion of acute myocardial infarction by use of quantitative point-of-care testing of myoglobin and troponin I. *Circulation*. 2001;104(13):1483-1488.
  19. 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(13):1332-1339.
  20. Goodacre SW, Bradburn M, Cross E, Collinson P, Gray A, Hall AS; RATPAC Research Team. 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(3):190-196.
  21. Aldous SJ, Richards M, Cullen L, Troughton R, Than M. A 2-hour Thrombolysis in Myocardial Infarction score outperforms other risk stratification tools in patients presenting with possible acute coronary syndromes: comparison of chest pain risk stratification tools. *Am Heart J*. 2012;164(4):516-523.
  22. Roy PM, Meyer G, Vielle B, et al; EMDEPU Study Group. Appropriateness of diagnostic management and outcomes of suspected pulmonary embolism. *Ann Intern Med*. 2006;144(3):157-164.
  23. Zwarenstein M, Treweek S, Gagnier JJ, et al; CONSORT group; Pragmatic Trials in Healthcare (Practihc) group. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ*. 2008;337:a2390. doi:10.1136/bmj.a2390.
  24. Luepker RV, Apple FS, Christenson RH, et al; AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; National Heart, Lung, and Blood Institute. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation*. 2003;108(20):2543-2549.
  25. 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(7):835-842.
  26. 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(1):35-55.
  27. Hollander JE, Blomkalns AL, Brogan GX, et al; Multidisciplinary Standardized Reporting Criteria Task Force. Standardized reporting guidelines for studies evaluating risk stratification of ED patients with potential acute coronary syndromes. *Acad Emerg Med*. 2004;11(12):1331-1340.
  28. 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(3):206-212.
  29. Pitts SR, Niska RW, Xu J, Burt CW. National Hospital Ambulatory Medical Care Survey: 2006 emergency department summary. *Natl Health Stat Report*. 2008;(7):1-38.
  30. Aldous SJ, Richards MA, Cullen L, Troughton R, Than M. A new improved accelerated diagnostic protocol safely identifies low-risk patients with chest pain in the emergency department. *Acad Emerg Med*. 2012;19(5):510-516.
  31. Cullen L, Müller C, Parsonage WA, et al. Validation of high-sensitivity troponin I in a 2-h diagnostic strategy to assess 30-day outcomes in emergency-department patients with possible acute coronary syndrome [published online April 10, 2013]. *J Am Coll Cardiol*. doi:10.1016/j.jacc.2013.02.078.
  32. George T, Ashover S, Cullen L, et al. Introduction of an accelerated diagnostic protocol in the assessment of emergency department patients with possible acute coronary syndrome: the Nambour Short Low-Intermediate Chest Pain Project. *Emerg Med Australas*. 2013;25(4):340-344.