Effectiveness of EDACS Versus ADAPT Accelerated Diagnostic Pathways for Chest Pain: A Pragmatic Randomized Controlled Trial Embedded Within Practice

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Study objective: A 2-hour accelerated diagnostic pathway based on the Thrombolysis in Myocardial Infarction score, ECG, and troponin measures (ADAPT-ADP) increased early discharge of patients with suspected acute myocardial infarction presenting to the emergency department compared with standard care (from 11% to 19.3%). Observational studies suggest that an accelerated diagnostic pathway using the Emergency Department Assessment of Chest Pain Score (EDACS-ADP) may further increase this proportion. This trial tests for the existence and size of any beneficial effect of using the EDACS-ADP in routine clinical care.

Methods: This was a pragmatic randomized controlled trial of adults with suspected acute myocardial infarction, comparing the ADAPT-ADP and the EDACS-ADP. The primary outcome was the proportion of patients discharged to outpatient care within 6 hours of attendance, without subsequent major adverse cardiac event within 30 days.

Results: Five hundred fifty-eight patients were recruited, 279 in each arm. Sixty-six patients (11.8%) had a major adverse cardiac event within 30 days (ADAPT-ADP 29; EDACS-ADP 37); 11.1% more patients (95% confidence interval 2.8% to 19.4%) were identified as low risk in EDACS-ADP (41.6%) than in ADAPT-ADP (30.5%). No low-risk patients had a major adverse cardiac event within 30 days (0.0% [0.0% to 1.9%]). There was no difference in the primary outcome of proportion discharged within 6 hours (EDACS-ADP 32.3%; ADAPT-ADP 34.4%; difference −2.1% [−10.3% to 6.0%], P=.65).

Conclusion: There was no difference in the proportion of patients discharged early despite more patients being classified as low risk by the EDACS-ADP than the ADAPT-ADP. Both accelerated diagnostic pathways are effective strategies for chest pain assessment and resulted in an increased rate of early discharges compared with previously reported rates. [Ann Emerg Med. 2016;68:93-102.]

Please see page 94 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background and Importance

The diagnostic challenge of assessing patients presenting to the emergency department (ED) with symptoms suggestive of cardiac ischemia is to maintain high accuracy for the rule-out of acute myocardial infarction without unnecessary admission.[1] The development of risk assessment aids and accelerated diagnostic pathways has provided new screening tools to improve the rate of early safe discharge to outpatient care of patients with symptoms that suggest acute myocardial infarction. An accelerated diagnostic pathway facilitates faster diagnostic decisions through blood sampling at earlier points for cardiac troponin (cTn) level for some patients stratified into a low-risk category with the pathway (Figure 1). This allows clinicians to rapidly proceed to the same "next step" in clinical management (such as cardiac stress test, imaging, or discharge) as would have occurred with a more prolonged time course for serial troponin level testing to exclude acute myocardial infarction.

Most accelerated diagnostic pathways have been evaluated only in observational studies.[2-4] The findings of observational research may overestimate the effect of

Editor's Capsule Summary

What is already known on this topic

Several accelerated diagnostic protocols using high-sensitivity troponins are challenging the traditional process of ruling out acute myocardial infarction during 8 to 24 hours.

What question this study addressed

This pragmatic clinical trial compared 2 such protocols, the ADAPT-ADP and the EDACS-ADP, to determine the proportion of patients discharged without an adverse event, using each protocol.

What this study adds to our knowledge

The EDACS-ADP identified 11.8% more low-risk patients (95% confidence interval 2.8% to 19.4%) than ADAPT-ADP; however, the proportion of all discharged was not different (32.3% versus 34.4%). No low-risk patients in either group had a major adverse event.

How this is relevant to clinical practice

Regardless of protocol used, the patients considered low risk were unlikely to have an adverse event. The EDACS-ADP identified more patients but had the same discharge rate as the ADAPT-ADP, raising the concern that clinicians might not be acting on this information.

intervention. In contrast, pragmatic randomized controlled trials (without strictly enforced procedures) enable new accelerated diagnostic pathways to be compared with one another or with current practice and provide an indication of clinician acceptance of a new process. They account for the realities of medicine in a complex, busy environment, including potential latency of staff education in achieving acceptance and adoption of a new process.

Since the advent of cTns, only 1 randomized controlled trial has assessed the ability of an accelerated diagnostic pathway to hasten decisionmaking.[5] This trial demonstrated an increased rate of successful discharge to outpatient care within 6 hours of presentation from a local baseline of 11.0% to 19.3% by using an accelerated diagnostic pathway incorporating the Thrombolysis in Myocardial Infarction (TIMI) score. To our knowledge, no randomized controlled trials have incorporated the use of high-sensitivity cardiac troponin assays either within an accelerated diagnostic pathway or as part of the outcomes adjudication.

Although the TIMI risk score has been successfully adapted for rule-out of acute coronary syndrome,[5,6] it was not designed to identify low-risk patients from a clinically diverse ED population. We therefore developed the Emergency Department Assessment of Chest Pain Score (EDACS) specifically to identify patients presenting to the ED with chest pain who were at low 30-day risk of a major adverse cardiac event.[7] EDACS was developed from 37 candidate variables in a derivation cohort of 1,974 patients in the ED with possible cardiac ischemia. It combines clinical variables identified as independent predictors for major adverse cardiac events to identify a subgroup of patients who are at low risk of such an event within 30 days (Table 1). When combined with ECG and either contemporary or high-sensitivity cTn results, this score forms part of an accelerated diagnostic pathway (EDACS-ADP). In derivation and validation cohorts using contemporary cTn, the EDACS-ADP identified 45% and 51% of patients as low risk, with a sensitivity for 30-day major adverse cardiac event of 99% and 100%, respectively.[7] This performance observed

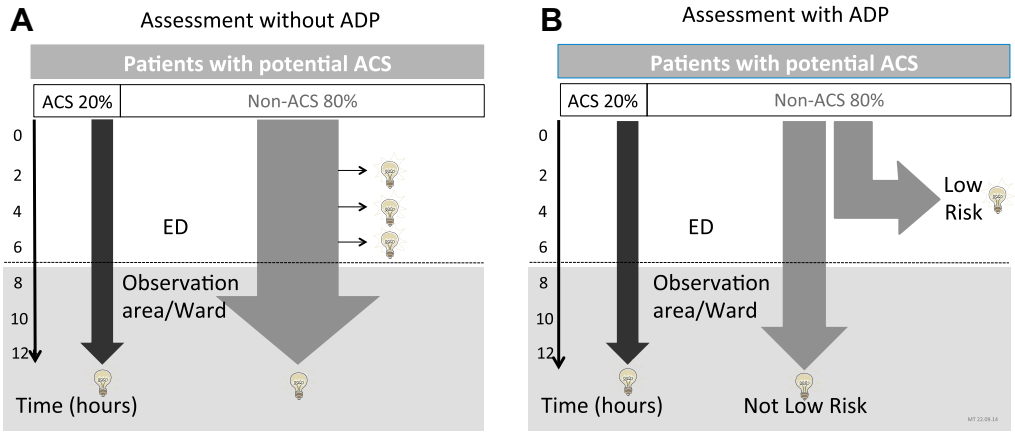

Figure 1. Schematic illustrating earlier decisionmaking through accelerated diagnostic pathways. Light bulbs indicate clinical decision points. *ACS*, Acute coronary syndrome.

Table 1. Accelerated diagnostic pathway criteria for classification patients as low risk.

Control ADP (ADAPT)	Intervention ADP (EDACS)	
No new ischemic ECG changes	No new ischemic ECG changes	
Negative troponin results at 0 and 2 h (hs-cTnI <16 ng/L for women; hs-cTnI <34 ng/L for men)	Negative troponin results at 0 and 2 h (hs-cTnI <16 ng/L for women; hs-cTnI <34 ng/L for men)	
TIMI score=0, where 1 point is given for each of the following criteria (maximum TIMI score=5):	EDACS <16, where points are allocated according to the following:	
(i) Age ≥65 y	(i) Age:	
(ii) ≥3 of the following 5 CAD risk factors: family history of premature CAD (ie, at age <55 y, angina, MI, sudden cardiac death without obvious cause), dyslipidemia, diabetes, hypertension, current smoker	Age range, y	Points
(iii) Known CAD (stenosis ≥50%)	18–45	2
(iv) Acetylsalicylic acid/aspirin use in the last 7 days	46–50	4
(v) Recent severe angina (eg, ≥2 events in last 24 h)	51–55	6
	56–60	8
	61–65	10
	66–70	12
	71–75	14
	76–80	16
	81–85	18
	≥86	20
	(ii) Only if age 18–50 y	
	Known CAD or ≥3 of the following 5 CAD risk factors: family history of premature CAD (ie, at age <55 y, angina, MI, sudden cardiac death without obvious cause), dyslipidemia, diabetes, hypertension, current smoker	4
	(iii) Symptoms	
	Diaphoresis (in association with pain*)	3
	Pain* radiates to arm or shoulder	5
	Pain* occurs or worsened with inspiration (pleuritic in nature)	−4
	Pain* reproduced by palpation	−6
	(iv) Sex	
	Male	6
No red flags (ie, patients with an unstable presentation comprising abnormal vital signs or pain that is ongoing or in a crescendo pattern should not be considered for the low-risk pathway)	No red flags (ie, patients with an unstable presentation comprising abnormal vital signs or pain that is ongoing or in a crescendo pattern should not be considered for the low-risk pathway)	

ADP, Accelerated diagnostic pathway; *CAD*, coronary artery disease.
*Pain that caused presentation to hospital.
Web calculators for the EDACS score available at: http://edaculator.adelaideemergencyphysicians.com and http://www.mdcalc.com/emergency-department-assessment-chest-pain-score-edacs/

in the observational cohort required testing in a routine clinical setting, using a prospective pragmatic randomized controlled trial.

Goals of This Investigation

Clinicians do not always adhere to clinical pathways or guidelines as expected, and it is important to determine whether the EDACS-ADP would work within a clinical pathway implemented into daily hospital care when the attending clinician has final decisionmaking authority. We therefore designed a trial to test for the existence and size of any beneficial effect of using the EDACS-ADP in routine clinical care. We tested the null hypothesis that there was no difference in using the EDACS-ADP to classify patients to low-risk category and early discharge from the ED than using the modified ADAPT-ADP.

MATERIALS AND METHODS

This study was a single-center, pragmatic, randomized, clinical trial[8] to compare the effectiveness of 2 accelerated diagnostic pathways for the assessment of patients presenting to the ED with possible cardiac ischemia. It compared a control accelerated diagnostic pathway (ADAPT-ADP[5,9]) and a novel accelerated diagnostic pathway (EDACS-ADP[7]). The trial design was based on the Consolidated Standards of Reporting Trials (CONSORT) extension statement for pragmatic trials,[8] and therefore the interventions allocated by randomization were not strictly enforced. Although pathways for the intervention and control arms were provided, the final clinical management decision was at the discretion of the treating clinician. Research staff documented clinical decisions but did not attempt to influence or intervene in them. The research protocol was approved by the New Zealand Health and Disability Ethics Committee. Informed consent was obtained from all patients.

Setting

Christchurch Hospital is an academic general hospital and tertiary referral center servicing a regional population

of more than 500,000. The ED has 85,000 patient attendances per year. Patients self-present from the community (by ambulance or own transport), but there are also many referrals from primary care physicians. Local guidelines for patients with possible acute myocardial infarction require assessment by ED staff, including an ECG, within 10 minutes of arrival to detect and fast-track the management of patients with ST-segment elevation myocardial infarction. The clinical experience of the physicians ranges from intern through attending specialists.

Selection of Participants

Eligible patients were aged 18 years or older and presenting acutely from the community to the ED with possible cardiac symptoms suggestive of acute myocardial infarction for which the attending clinician(s) intended to perform serial troponin analysis to investigate for possible acute myocardial infarction. In accordance with American Heart Association case definitions, possible cardiac symptoms included the presence of acute chest, epigastric, neck, jaw, or arm pain or discomfort or pressure without apparent noncardiac source.[10] Patients were excluded if any of the following conditions were satisfied: diagnosed ST-segment elevation myocardial infarction on arrival; proven or likely noncoronary pathology as the cause of symptoms; need for admission because of, or for further investigation of, other medical conditions regardless of a negative cTn result; previously enrolled in this study; anticipated problem with follow-up (eg, resident outside New Zealand); and unable to provide informed consent. Enrollment was consecutive during the hours of the available research nurse (normally 8 AM to 11 PM, 7 days a week).

The troponin assay used was the Abbott Architect high-sensitivity troponin I (hs-cTnI; Abbot Diagnostics, Chicago, IL). The 99th percentile is 16 ng/L for women and 34 ng/L for men, and the coefficient of variation is less than 10% at 4.7 ng/L (per manufacturer's package insert). For local clinical patient management, troponin values above these sex-specific 99th percentiles were reported as positive results.

Research nurses identified potential cases with both the ED attendance screen and direct presence at the triage desk. After consenting, randomization (1:1 allocation ratio) used a sequential sealed envelope process. Study packs were kept in a locked filing cabinet. The numbered opaque envelope containing the randomization allocation included a number matched to the study packs. After consent, the research nurse opened the next randomization envelope and informed the patient's clinician to which pathway the patient was allocated. The randomization envelope contained a paper copy of the allocated score, which, when completed by the clinician (without influence from the research staff), became part of the official patient record. The randomization sequence arranged in permuted blocks was generated by a statistician independent of patient recruitment or outcome adjudication. Clinicians were educated about the scores and background evidence for the study, but not about the 6-hour primary outcome.

Interventions

In the control arm, patients followed the hospital's standard-care cardiac chest pain pathway incorporating the ADAPT-ADP. On arrival, patients received an initial ECG, and a blood sample was obtained for the first hs-cTnI test. Risk factors and symptoms were recorded and a modified TIMI score was calculated by the clinician. If the initial hs-cTnI test result was negative, there was no new ischemia observed by the attending clinician(s) on the first ECG, and the modified TIMI score was 0, patients were moved to an ED or inpatient ward observation area without ECG monitoring. New ECG 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 ms in width and 0.1 mV or greater in depth in at least 2 contiguous leads. Changes that were present on available preexisting ECGs were not defined as new ischemia. At 2 hours after the initial tests, blood was drawn for a second hs-cTnI test. If all test results were negative, patients were classified as low risk. These patients were then discharged and scheduled for an outpatient stress test (typically exercise treadmill test) unless the clinician decided that this was not clinically indicated (eg, further cardiac testing was considered inappropriate or had been recently performed). If any diagnostic parameter was positive or the TIMI score was greater than or equal to 1, patients were classified as not low risk and were then admitted and managed according to the usual clinical pathway.

In the experimental arm, patients received an initial ECG, and a blood sample was obtained for the first hs-cTnI test. Risk factors and symptoms were recorded and the clinician calculated the EDACS. If the initial hs-cTnI test result was below the 99th percentile, there was no new ischemia (as defined above) observed on the first ECG, and EDACS was less than 16, patients were moved to an ED or ward observation chair without ECG monitoring. At 2 hours after the initial tests, blood was drawn for a second hs-cTnI test. If all test results were negative, patients were classified as low risk, scheduled for an outpatient stress test (normally exercise treadmill test), and discharged. If any diagnostic factor was positive or the EDACS was greater than or equal to 16, patients were not classified as low risk and their care was managed according to the standard clinical pathway.

At Christchurch ED, clinical pathway forms exist to standardize care in accordance with best practice. These

forms are part of the patient record, and clinicians are expected to follow the pathway unless they can document good clinical reasons not to. Patients presenting with possible cardiac ischemia are entered onto a dedicated "cardiac chest pain clinical pathway" (Canterbury District Health Board official document C240005). This pathway advises clinicians to identify patients at low risk and suitable for early discharge, using the designated accelerated diagnostic pathway (ADAPT or EDACS).

In summary, the only difference between the 2 study arms was the tool used for risk scoring: modified TIMI versus EDACS. In both pathways, sentinel findings indicative of potential clinical instability and were described as red flags. These were either chest discomfort (thought to be possibly cardiac in origin) that was ongoing or in a crescendo pattern, or the presence of abnormal vital signs. The presence of a red flag meant that patients were classified as not low risk irrespective of the risk assessment score.

Outcome Measures

The primary objective was to compare the effectiveness, when applied to clinical practice, of an accelerated diagnostic pathway within a clinical pathway that uses EDACS against the standard accelerated diagnostic pathway, which incorporates the TIMI score. The primary outcome was successful discharge, defined as discharge from the hospital within 6 hours of ED arrival and without major adverse cardiac event within 30 days. Major adverse cardiac event was defined as death (unless clearly noncardiac, eg, from trauma), cardiac arrest, emergency revascularization procedure, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention, and acute myocardial infarction. All patients were followed up with all 3 of the following approaches: telephone contact, review of patient hospital notes, and national death and health events search. (Patients in New Zealand have a unique alphanumeric identifier for tracking all hospital inpatient and outpatient events within the nation's health system.) Senior clinicians adjudicated for the presence of any major adverse cardiac event and were blinded to study group allocation. Adjudications were entered into a separate database independent of all other trial data. The proportion of patients identified as low risk was also compared.

Preliminary research predicted a 17% discharge rate at 6 hours in the control arm (experimental arm of the former randomized controlled trial).[5] It was considered that if in the experimental arm at least 30% of patients were successfully discharged, then this proportion would represent a meaningful effect on clinical practice. This study was powered to detect a 13% difference between the successful early discharge rates, with a β=.10 (90% power) and a 2-tailed α=.05. This required recruitment of 265 patients in each arm and 530 patients in total. Blinding of patients and clinical staff was not clinically possible.

Primary Data Analysis

The unit of analysis was patient and the primary outcome compared randomized groups with a χ^2 test. An adjusted comparison of the primary outcome was also undertaken, which included any baseline measure, not part of the modified TIMI or EDACS scores, in which there was baseline imbalance between control and experimental groups. The analysis used a multiple logistic regression and the results are presented as adjusted odds ratios with the 95% confidence intervals. The primary analysis was undertaken on an intention-to-treat basis. All statistical analysis was performed in R (version 3.1.0).[11]

RESULTS

Characteristics of Study Subjects

We randomized 560 patients from June 26, 2013, to July 30, 2014. Two patients later withdrew consent, leaving 558 for the intention-to-treat analysis (Figure 2). There were 279 patients in each arm. The cohort was largely men (61%), of New Zealand European ethnicity (76%), and with a mean age of 58.7 years (Table 2). Patients presented at a median of 3.0 hours (interquartile range 1.5 to 7.8 hours) after symptom onset. Sixty-six of 558 patients (11.8%) had a major adverse cardiac event within 30 days (Table 3). All mortality events and all hospital admission events were available for review for all patients within the 30-day follow-up period from Christchurch hospital inpatient data and the national health event tracking system, which tracks all health events within New Zealand. Additionally, 516 participants (97.7%) were contacted by telephone or returned a questionnaire.

The EDACS-ADP classified 15.4% more patients as low risk than the ADAPT-ADP (47.7% [n=133] versus 32.3% [n=90]; difference 15.4% [95% confidence interval 7.0% to 23.8%]). After reassignment of some patients to "not low risk" because of the presence of clinical red flags, 11.1% more patients (95% confidence interval 2.8% to 19.4%) were classified as low risk by the experimental accelerated diagnostic pathway (41.6%; n=116) than by the control accelerated diagnostic pathway (30.5%; n=85) (see also Figure E1, available online at http://www.annemergmed.com). Eighty-five percent of low-risk patients had a stress test within 3 days of ED presentation.

Main Results

There was no difference in the overall proportion of patients successfully discharged (without major

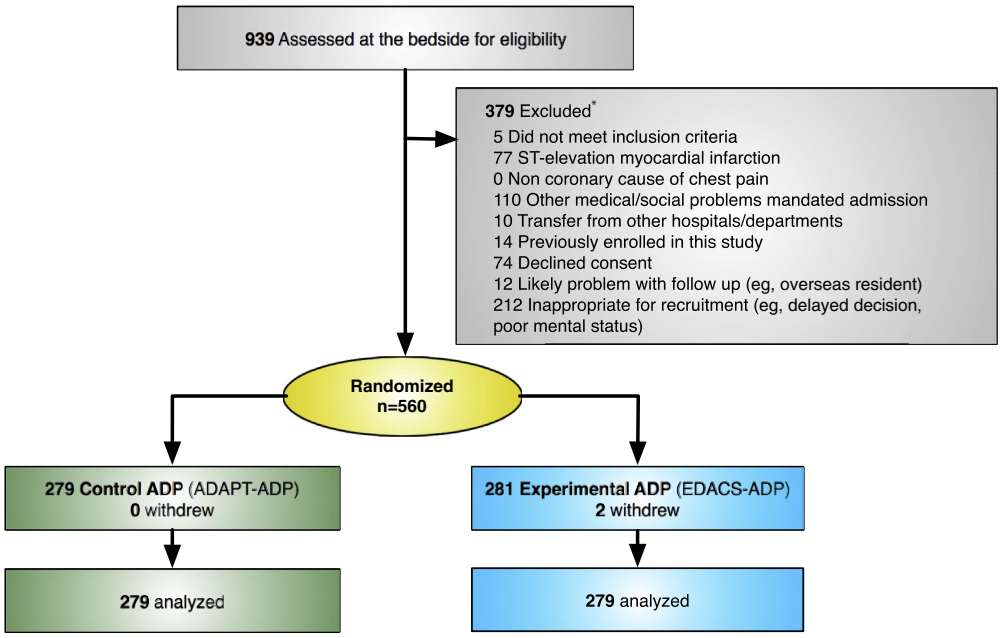

Figure 2. CONSORT diagram of patient flow and numbers. *Some patients met multiple exclusion criteria.

adverse cardiac event within 30 days) within 6 hours (EDACS-ADP arm 90 [32.3%] versus ADAPT-ADP arm 96 [34.4%]; difference −2.1% [−10.3% to 6.0%], *P*=.65) (Table 3).

There was no difference in the proportion of patients classified as low risk and successfully discharged within 6 hours (EDACS-ADP arm 73 [26.2%] versus ADAPT-ADP arm 64 [22.9%]) (Table 3). Of the 43 of 279 low-risk

Table 2. Baseline characteristics.*

Variable	Total Cohort (n=558)	Control ADP (ADAPT) (n=279)	Experimental ADP (EDACS) (n=279)
Age, y	58.7 (11.9)	57.8 (12.0)	59.6 (11.8)
Women	218 (39.1)	105 (37.8)	113 (40.4)
Weight, kg	86.3 (18.7)	86.2 (18.8)	86.3 (18.6)
Body mass index, kg/m^2	29.0 (5.6)	29.1 (5.4)	29.0 (5.9)
Ethnicity			
Asian	14 (2.5)	9 (3.2)	5 (1.8)
Maori	21 (3.8)	13 (4.7)	8 (2.9)
New Zealand European	423 (75.8)	210 (75.5)	213 (76.3)
New Zealand European and Maori	1 (0.2)	1 (0.4)	0
Pacific Islander	9 (1.6)	2 (0.7)	7 (2.5)
Other European	46 (8.2)	16 (5.7)	30 (10.8)
Other	34 (6.1)	20 (7.2)	11 (3.9)
Not stated	12 (2.2)	7 (2.5)	5 (1.8)
Risk factors and history			
Hypertension	290 (52.0)	143 (51.4)	147 (52.5)
Dyslipidemia	284 (50.9)	145 (52.2)	139 (49.6)
Diabetes	78 (14.0)	34 (12.2)	44 (15.7)
Current smoker	84 (15.1)	41 (14.7)	43 (15.4)
Family history of ischemic heart disease	199 (35.7)	103 (37.1)	96 (34.3)
Previous angina	160 (28.7)	75 (27.0)	85 (30.4)
Previous myocardial infarction	130 (23.3)	55 (19.8)	75 (26.8)
Previous peripheral vascular disease	32 (5.7)	13 (4.7)	19 (6.8)
Previous percutaneous coronary intervention or coronary artery bypass graft	153 (27.4)	68 (24.5)	85 (30.4)
Previous ischemic heart disease	236 (42.3)	120 (43.2)	116 (41.4)
Previous cardiovascular disease or transient ischemic attack	33 (5.9)	20 (7.2)	13 (4.6)

*Data are presented as No. (%) or mean (SD) or median (lower quartile–upper quartile).

Table 3. Outcomes.

Outcome	Total Cohort (n=558) (%)	Control ADP (ADAPT) (n=279) (%)	Experimental ADP (EDACS) (n=279) (%)	Difference, % (95% CI)
Negative ECG and troponin results, and either TIMI score 0 or EDACS <16	223 (38.6)	90 (32.3)	133 (47.7)	15.4 (7.0 to 23.8)
Negative ECG and troponin results, and TIMI score 0 or EDACS <16 and no red flag (low risk)	201 (34.8)	85 (30.5)	116 (41.6)	11.1 (2.8 to 19.4)
Low-risk patients successfully discharged within 6 h*	137 (24.6)	64 (22.9)	73 (26.2)	3.2 (−4.3 to 10.7)
Primary outcome: patients successfully discharged within 6 h†	186 (33.3)	96 (34.4)	90 (32.3)	−2.1 (−10.3 to 6.0) *P*=.65
Diagnoses during initial presentation (all in non–low-risk patients)				
STEMI‡	5 (0.9)	3 (1.1)	2 (0.7)	−0.4 (−1.6 to 2.3)
NSTEMI	60 (10.8)	26 (9.3)	34 (12.2)	2.9 (−8.4 to 2.6)
Unstable angina	32 (5.7)	12 (4.3)	20 (7.2)	2.9 (−7.1 to 1.3)
Total patients with ACS diagnosis	97 (17.4)	41 (14.7)	56 (20.1)	5.4 (−12 to 1.3)
Emergency revascularization	3 (0.5)	2 (0.7)	1 (0.4)	−0.4 (−1.2 to 1.9)
Death	1 (0.2)	1 (0.4)	0	−0.4 (−0.7 to 1.4)
Total patients with a MACE	65 (11.6)	29 (10.4)	36 (12.9)	2.5 (−8.2 to 3.2)
Additional diagnoses during readmissions during 30 days after index presentation (all in non–low-risk patients)				
STEMI	1 (0.2)	1 (0.4)	0	−0.4 (−0.7 to 1.4)
NSTEMI	2 (0.4)	0	2 (0.7)	0.7 (−2.1 to 0.6)
Total patients with a MACE	3 (0.5)	1 (0.4)	2 (0.7)	0.4 (−1.9 to 1.2)
Total patients with a MACE within 30 days of presentation (from index presentation or readmission)	66 (11.8)	29 (10.4)	37 (13.3)	2.9 (−8.6 to 2.8)

CI, Confidence interval; *STEMI*, ST-segment elevation myocardial infarction; *MACE*, major adverse cardiac event.
*Negative index test result (negative ECG result, negative 0- and 2-h troponin result, score <threshold, no red flags) and no MACE event within 30 days of presentation, and medical decision to discharge home made within 6 hours of ED presentation.
†Negative index test result (negative ECG result, negative 0- and 2-h troponin result) and no MACE event within 30 days of presentation, and medical decision to discharge home made within 6 hours of ED presentation.
‡Diagnosed after initial assessment on presentation in which patients with initial STEMI were excluded.

patients (15.4%) in the experimental accelerated diagnostic pathway not discharged within 6 hours, most (28 of 43; 65.1%) had TIMI scores greater than or equal to 1, with 15 subsequently discharged within 12 hours and no major adverse cardiac event occurring within 30 days. Among patients classified as low risk with the EDACS-ADP who were not discharged within 6 hours, 17 of 43 (39.5%) had a previous acute myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft, whereas only 5 of 73 (6.85%) of those discharged within 6 hours had had either of those conditions ($P<.001$). Of the 21 of 279 low-risk patients (7.5%) in the ADAPT-ADP arm not successfully discharged within 6 hours, 11 were discharged within 12 hours, with no major adverse cardiac event within 30 days. Overall, no patients classified as low risk in either arm had a major adverse cardiac event within 30 days (0.0% [0.0% to 1.9%]).

DISCUSSION

To our knowledge, this pragmatic randomized controlled trial is the first evaluating 2 accelerated diagnostic pathways designed to facilitate the speed of discharge decisions. It directly compared the ADAPT-ADP, which is based on a risk model developed for use in high-risk populations, with the EDACS-ADP, specifically developed to improve the identification of ED patients at low risk of short-term adverse events. Consistent with the results of the previous development and validation studies for the EDACS-ADP,[7] our study found that a clinically important, larger proportion of patients were categorized as low risk by the EDACS-ADP than the control ADAPT-ADP. However, the primary outcome of the rate of safe discharge to outpatient care within 6 hours was similar in both arms.

A possible contributor to the null result of this randomized controlled trial is that the proportion of patients discharged within 6 hours in the ADAPT-ADP (34.4%) arm was much greater than in the ADAPT arm of a previous randomized controlled trial at the same hospital (18.3%) on which the power calculations had been based, despite a similar proportion of patients being classified as low risk with the ADAPT-ADP in the current and previous trials (32.3% versus 35.0%). Another contributor

may have been the reluctance of physicians to discharge early patients with known coronary artery disease (ie, previous acute myocardial infarction or revascularization procedure); such patients represented 39.5% of cases designated as low risk but not discharged early in the EDACS-ADP arm.

Both the EDACS-ADP and ADAPT-ADP safe discharge rates were greater than in the previous randomized controlled trial.[5] The 15.1% absolute increase in early discharge in the ADAPT-ADP arms between studies partly resulted from improved clinician adherence to the ADAPT-ADP and suggested that clinicians take time to adjust to using a new diagnostic pathway. In the first randomized controlled trial, a large proportion (13%) of patients (in the then-experimental ADAPT-ADP arm) were classified as low risk but still admitted to the hospital (without subsequent ACS). In this study, only 7.5% of patients in the ADAPT-ADP arm were classified as low risk and admitted to the hospital, demonstrating improved compliance, whereas the equivalent rate for the EDACS-ADP was 15%. The early discharge rates in this study demonstrate a noticeable change from the baseline rate determined from analysis of the Christchurch cohort of the original ADAPT observational study, which was 5.4%.[12] This demonstrates that there has been a striking change in clinical practice. The EDACS-ADP was implemented locally within 3 months of completion of this trial (and the release of the preliminary safety analysis) at the request of clinical staff (current pathway, Appendix E1, available online at http://www.annemergmed.com). This was straightforward because the embedding of the research into the patient record meant that the only change required was the removal of the TIMI score. The pathways have now been implemented in 25 of 26 health regions in New Zealand and also widely in Australia.

To our knowledge, this study provides the first evidence of the effective use of the EDACS-ADP in a clinical setting. The trial was conducted without enforcement of the allocated study protocol so that a realistic measurement of the effect of introducing the pathway could be obtained. The EDACS-ADP identified considerably more patients as low risk than the ADAPT-ADP, consistent with the results from observational research.[1,7] Although it may be expected that classifying more patients as low risk with the EDACS-ADP would lead to increased early discharge, clinicians do not always follow pathways or act as expected. For example, a study of 117 EDs found that international evidence-based guidelines for the investigation of pulmonary embolism were not followed for 47% of patients.[13] This phenomenon likely affected the primary outcome. It is possible that over time, with greater clinician acceptance of the protocol and robust clinical education, a higher early-discharge rate may be achieved with the EDACS-ADP. This also emphasizes the point that benefits of diagnostic strategies predicted by observational studies are often not fully achieved when implemented into practice.

The absence of adverse cardiac events among patients categorized as low risk in either pathway offers some reassurance about the safety of these investigative approaches when implemented into actual patient management. In comparison to observational studies of other pathways, a validation of the New Vancouver Chest Pain Rule, using high-sensitivity troponin as the only biomarker, reported 99.1% sensitivity for ACS in 13.0% of patients identified as low risk.[14] In 3 recent validation studies of the HEART (History, ECG, Age, Risk factors and Troponin) score, the proportion of low-risk patients (score 0 to 3) was 20.1% to 36.4%, with a sensitivity of 96.3% to 99.1%. A validation of the North American Chest Pain Rule classified 4.4% of patients as low risk, with a sensitivity of 100%.[15] It remains unclear how these strategies will perform in actual clinical practice.

To our knowledge, this is the first randomized controlled trial that uses only a high-sensitivity cardiac troponin assay and also sex-specific cutoffs within a clinical pathway. It appears that neither change has had an adverse effect on the proportion of patients categorized as low risk. This is consistent with our experience of using this particular hs-cTnI assay in our institution for almost 3 years, during which time there has not been any noticeable increase in troponin I positivity rate (in >20,000 cases) compared with that for the previously used contemporary assay. This is important because, based on experience with high-sensitivity troponin T, concern has been raised that the use of hs-cTnI will also lead to increased positive troponin results, which would lead to a lower proportion of low-risk patients than predicted from previous studies.[16,17] A recent prospective cohort study also suggested that increased positivity may not occur with this hs-cTnI assay.[18] EDACS was developed with 2 contemporary (nonhigh sensitivity) assays and was then also validated with these assays. Thus, the ADAPT and EDACS accelerated diagnostic pathways have now been shown to work effectively with both contemporary and high-sensitivity troponin assays. Lower cutoffs for women might have had a similar effect.[19] The proportion of patients classified here as low risk either with or without incorporating red flags (41.6% and 47.7%, respectively) is similar to that reported in the EDACS-ADP derivation and validation cohorts (42.2% and 51.3%, respectively) using contemporary nonhigh-sensitivity troponin assays. The incorporation of high-sensitivity cardiac troponin within the outcome adjudication in this and future trials is

important because it may lead to the identification of extra, possibly true-positive cases otherwise missed with contemporary troponin assays. This would be reflected in a lower estimated sensitivity and negative predictive value for the accelerated diagnostic pathway.

This was a single-center trial, which may limit the generalizability of the findings. Comparing the EDACS-ADP with an existing accelerated diagnostic pathway made demonstrating a difference between arms harder to achieve (than a comparison with no accelerated diagnostic pathway). However, because the purpose of this trial was to determine whether it was possible to improve on an existing risk model with a "fit-for-purpose" improved risk model, we believe this comparison is appropriate. We chose a pragmatic trial design to help clinicians and health policymakers to judge the effectiveness of the EDACS-ADP in actual clinical care. Therefore, selection criteria were broad and reflected routine clinical practice.[8] The interventional nature of the trial meant that some late acute myocardial infarctions may have been missed despite follow-up because there was no delayed measurement of troponin in some patients. Overall, only 3 patients had a prevalent major adverse cardiac event during follow-up, and although there were no occurrences of major adverse cardiac event in patients discharged early, this study was not powered to compare safety between the intervention and control groups because the numbers of patients required to prove noninferiority for safety compared with an existing diagnostic strategy are very large, and this is particularly true in this setting with a predicted adverse event rate of 0% to 1%. We calculated that to power the study for safety would require a sample size of more than 7,500. We believed that such a large trial was not merited with such a low expectation of detecting a difference. The pragmatic trial design may have also influenced the primary outcome because there was no enforcement to randomization allocation or risk categorization. Clinicians may have been influenced by participation in the trial situation, which may have affected their decisions for either, or both, study groups. In the future, additional insights about accelerated diagnostic pathway pathways may be provided by other study designs (eg, a stepped-wedge cluster randomized controlled trial).

In summary, this trial confirmed that the EDACS-ADP classifies a larger proportion of patients presenting with symptoms suggestive of cardiac ischemia as low risk and eligible for early discharge than the modified TIMI accelerated diagnostic pathway. This did not translate into more early discharges, which may reflect delay in achieving full clinician familiarity and adherence to the pathway. Our finding that both accelerated diagnostic pathways facilitated more early discharges than the previous nonaccelerated pathway demonstrates that accelerated diagnostic pathways can be effective strategies for patient assessment and supports wider implementation.

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REFERENCES

1. Than MP, Herbert M, Flaws D, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the emergency department? a clinical survey. *Int J Cardiol*. 2013;166:752-754.
2. Hess EP, Brison RJ, Perry JJ, et al. Development of a clinical prediction rule for 30-day cardiac events in emergency department patients with chest pain and possible acute coronary syndrome. *Ann Emerg Med*. 2012;59:115-125.e1.
3. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. *Neth Heart J*. 2008;16:191-196.

4. Six AJ, Cullen L, Backus BE, et al. The HEART score for the assessment of patients with chest pain in the emergency department. *Crit Pathw Cardiol*. 2013;12:121-126.
5. Than MP, Aldous S, Lord SJ, et al. A 2-hour diagnostic protocol for possible cardiac chest pain in the emergency department: a randomized clinical trial. *JAMA Intern Med*. 2014;174:51-58.
6. Kelly A-M, Klim S. Prospective external validation of an accelerated (2-h) acute coronary syndrome rule-out process using a contemporary troponin assay. *Int J Emerg Med*. 2014;7:42.
7. Than MP, Flaws D, Sanders S, et al. Development and validation of the Emergency Department Assessment of Chest Pain Score and 2 h accelerated diagnostic protocol. *Emerg Med Australas*. 2014;26:34-44.
8. Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ*. 2008;337:a2390.
9. 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;284:835-842.
10. Luepker RV, Apple FS, Christenson RH, et al. 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;108:2543-2549.
11. R Core Team. R: a language and environment for statistical computing. April 2014. Available at: http://www.R-project.org/. Accessed August 14, 2015.
12. Than MP, 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;59:2091-2098.
13. Roy P-M, Meyer G, Vielle B, et al. Appropriateness of diagnostic management and outcomes of suspected pulmonary embolism. *Ann Intern Med*. 2006;144:157-164.
14. Cullen L, Greenslade JH, Than MP, et al. The new Vancouver Chest Pain Rule using troponin as the only biomarker: an external validation study. *Am J Emerg Med*. 2014;32:129-134.
15. Mahler SA, Miller CD, Hollander JE, et al. Identifying patients for early discharge: performance of decision rules among patients with acute chest pain. *Int J Cardiol*. 2013;168:795-802.
16. de Lemos JA. Increasingly sensitive assays for cardiac troponins: a review. *JAMA*. 2013;309:2262-2269.
17. Korley FK, Jaffe AS. Preparing the United States for high-sensitivity cardiac troponin assays. *J Am Coll Cardiol*. 2013;61:1753-1758.
18. Sandoval Y, Smith SW, Schulz KM, et al. Diagnosis of type 1 and type 2 myocardial infarction using a high-sensitivity cardiac troponin I assay with sex-specific 99th percentiles based on the third universal definition of myocardial infarction classification system. *Clin Chem*. 2015;61:657-663.
19. Shah ASV, Griffiths M, Lee KK, et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ*. 2015;350:g7873.

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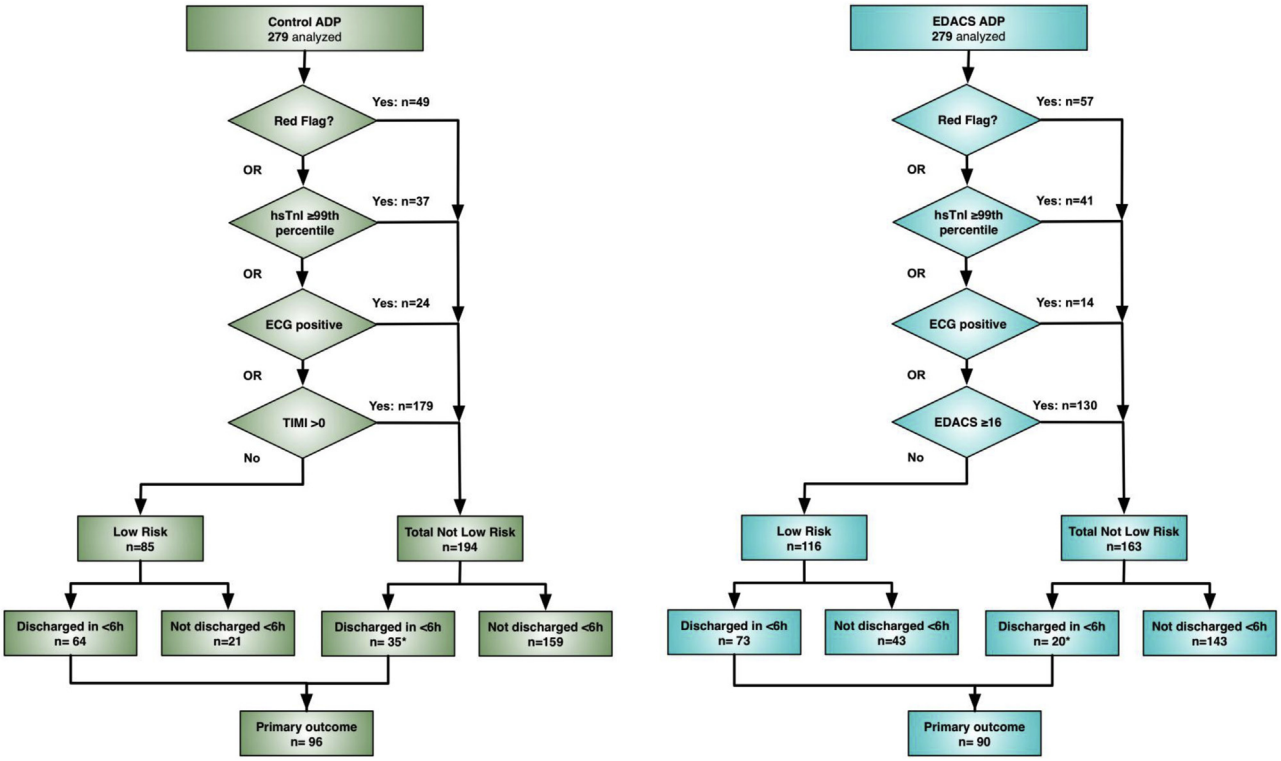

Figure E1. Flowcharts of pathways followed by patients in each arm of the study. *Three Control-ADP patients had positive ECG results and 2 EDACS-ADP patients had positive ECG results (1 with an increased troponin level), and therefore they did not meet the successful discharge criteria. They were discharged on the discretion of the attending physician.