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Performance of the 2-hour Accelerated Diagnostic Protocol Within the American College of Radiology Imaging Network PA 4005 Cohort

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Abstract

Objectives—The 2-hour accelerated diagnostic protocol (ADAPT) is a decision rule designed to identify emergency department (ED) patients with chest pain for early discharge. Previous studies in the Asia-Pacific region demonstrated high sensitivity (97.9% to 99.7%) for major adverse cardiac events (MACE) at 30 days. The objective of this study was to determine the validity of ADAPT for risk stratification in a cohort of U.S. ED patients with suspected acute coronary syndrome (ACS).

Methods—A secondary analysis of participants enrolled in the American College of Radiology Imaging Network (ACRIN) PA 4005 trial was conducted. This trial enrolled 1,369 patients at least 30 years old with symptoms suggestive of ACS. All data elements were collected prospectively at the time of enrollment. Each patient was classified as low risk or at risk by ADAPT. Early discharge rate and sensitivity for MACE, defined as cardiac death, myocardial infarction (MI), or coronary revascularization at 30 days, were calculated.

Results—Of 1,140 patients with complete biomarker data, MACE occurred in 31 patients (2.7%). Among 551 of the 1,140 (48.3%, 95% confidence interval [CI] = 45.4% to 51.3%), ADAPT identified for early discharge; five of the 551 (0.9%, 95% CI = 0.3% to 2.1%) had MACE at 30 days. ADAPT was 83.9% (95% CI = 66.3% to 94.5%) sensitive, identifying 26 of 31 patients with MACE. Of the five patients identified for early discharge by ADAPT with MACE, there were no deaths, one patient with MI, and five with revascularizations.

Conclusions—In this first North American application of the ADAPT strategy, sensitivity for MACE within 30 days was 83.9%. One missed adverse event was a MI, with the remainder representing coronary revascularizations. The effect of missing revascularization events needs further investigation.

Approximately 8 to 10 million patients complaining of chest pain present to emergency departments (EDs) annually in the United States.¹ In an attempt to avoid missing the diagnosis of acute coronary syndrome (ACS), emergency physicians use liberal testing strategies in patients with acute chest pain. This results in more than 50% of ED patients with acute chest pain receiving comprehensive cardiac evaluations (serial cardiac biomarkers and stress testing or angiography) at an estimated cost of \$10 to \$13 billion annually,^{2–6} yet fewer than 10% of these patients are ultimately diagnosed with ACS.^{6–10}

Current care patterns for patients with acute chest pain fail to focus health system resources on patients likely to benefit. Among low-risk patients who have ACS rates as low as 2%, stress testing and cardiac imaging is associated with a substantial number of false-positive and nondiagnostic tests, which leads to additional unnecessary and often invasive procedures.¹¹ Consensus among health system leaders, clinicians, and educators is building regarding the need to more efficiently evaluate patients with acute chest pain.¹²

The 2-hour accelerated diagnostic protocol (ADAPT),^{13,14} which combines 0- and 2-hour cardiac troponin (cTn) tests, electrocardiograms (ECGs), and an adapted Thrombolysis in Myocardial Infarction (TIMI) score, is a recently developed decision rule designed to identify ED patients safe for early discharge. Previous studies in the Asia-Pacific region have demonstrated that ADAPT can classify 20% of patients with acute chest pain for early discharge while simultaneously achieving high sensitivity (97.9% to 99.7%) for major adverse cardiac events (MACE) at 30 days.^{13,15} Based on these studies, many believe that ADAPT has the potential to more efficiently focus inpatient resources and objective cardiac testing (stress testing or angiography) on patients likely to benefit. However, the performance of ADAPT within a cohort of US ED patients has yet to be examined.

We designed a secondary data analysis of the American College of Radiology Imaging Network (ACRIN) PA 4005 cohort to determine the validity of ADAPT in a group of U.S. ED patients with suspected ACS. Specifically we sought to determine if ADAPT can classify 20% or more patients with acute chest pain as safe for early discharge while maintaining high sensitivity and negative predictive value (NPV) for MACE. While the precise value of an acceptable sensitivity and NPV for MACE is a matter of considerable debate, many believe that a successful chest pain risk stratification strategy must achieve >99% NPV (corresponding with a < 1% missed MACE rate among patients with a low-risk assessment) and approach a 99% sensitivity.¹⁶

METHODS

Study Design

A secondary analysis was conducted of patients prospectively enrolled in the ACRIN PA 4005 trial, clinical trial number NCT00933400.² Participants were enrolled from July 7, 2009, through November 3, 2011, and all gave informed consent at the time of study entry. The institutional review board of each participating institution approved the trial protocol.

Study Setting and Population

Participants were enrolled from five U.S. tertiary care center EDs. Eligibility criteria required that subjects be at least 30 years old, with signs or symptoms consistent with possible ACS, in whom the physician planned objective cardiac testing or admission to rule-out ACS. Eligible patients had initial TIMI scores of 0 to 2 and no evidence of acute ischemia on ECGs at presentation. Patients were excluded if they had symptoms clearly noncardiac in origin, coexisting conditions that required admission, normal findings on coronary computed tomography angiography (CCTA) or invasive angiography within the past year, or contraindications to CCTA. Inclusion criteria for ACRIN PA 4005 differ from those of the ADAPT Trial. The ADAPT Trial enrolled adults at least 18 years old, with at least 5 minutes of symptoms consistent with ACS, in whom the attending physician planned to obtain serial cTn tests.¹³

ACRIN participants were randomized to a CCTA-based risk stratification strategy or a usual care strategy in a 2:1 ratio. Patients randomized to the CCTA arm received CCTA as the first evaluation, while patients randomized to usual care received testing determined by their health care providers. In both groups, decisions regarding disposition, additional diagnostic testing, and treatment were made by the clinical teams. Cardiac testing (CCTA or stress testing) often occurred after observation unit or hospital admission. When stress testing was performed, a graded exercise or pharmacologic stress was used according to protocols at the participating study sites.² Participants from each study arm with complete data needed to risk-stratify patients based on ADAPT (see below) were included in this analysis irrespective of CCTA or stress testing results.

Study Protocol

Structured data collection was performed prospectively in accordance with the standardized reporting guidelines for studies evaluating ED patients with possible ACS and the American College of Cardiology (ACC) key definitions for measuring the management and outcome of ACS.^{17,18} Demographic, history, physical examination, TIMI score, ECG, diagnostic testing, and disposition data were collected prospectively on all trial participants.

Contemporary cTn measurements were obtained during the initial ED evaluations, and serial measurements were obtained at 90 to 180 minutes after ED arrival. Assays used by the study sites included: 1) Access Accu cTnI (Beckman Coulter, Brea, CA), which has a 99th percentile (or upper reference limit [URL]) of 0.04 µg/L and 10% coefficient of variation (CV) of 0.06 µg/L; 2) TnI-Ultra assay using the ADVIA Centaur platform (Siemens, Munich, Germany), which has a URL of 0.04 µg/L and 10% CV of 0.04 µg/L; 3) Triage Cardiac Panel Point-of-Care (Alere, Waltham, MA), which has a URL of 0.4 µg/L and 16.7% CV of 0.4 µg/L; 4) Cobas Elecsys Troponin T STAT (Roche, Basel, Switzerland), which has a URL of 0.01 µg/L and 10% CV of 0.03 µg/L; and 5) I-site Cardiac Troponin Assay (Abbott, Abbott Park, IL), which has a URL of 0.08 µg/L and 10% CV of 0.010 µg/L.

All patients underwent structured record reviews to determine outcomes, diagnostic tests, and treatments received during their index visits. Patients were contacted by phone at least 30 days after presentation to determine if they had MACE within the 30-day follow-up period. Patient self-reported events were confirmed by hospital record review. Patients

unable to be reached using their primary or secondary contact phone numbers underwent record review to evaluate for adverse events. The Social Security Death Master File (www.ssdmf.com) was used for patients for whom follow-up by telephone or record review failed to provide information regarding 30-day events.

ADAPT

The ADAPT decision rule was applied to all of the study participants to risk-stratify patients into low-risk or at-risk groups. ADAPT consists of a TIMI score assessment, ECG, and serial cTn measurement (at 0 and 2 hours). A patient is considered low risk for ACS (appropriate for early discharge) if his or her TIMI score is zero, ECG has no new ischemic changes, and serial cTn's are below the institutional cutoff for an elevated cTn concentration. Ischemic ECG changes were defined as ST-segment depression of at least 0.1 mV, T-wave inversions of at least 0.3 mV, or Q waves >30 msec in at least two contiguous leads.¹⁷ All of the data elements necessary to risk-stratify patients based on ADAPT were collected prospectively from ACRIN PA 4005 participants and the treating physician during the index visit.

Study Measures

Our primary outcome was the rate of MACE within 30 days of presentation, defined as the composite of cardiac death, myocardial infarction (MI), or coronary revascularization. The definition of MACE and its components were based on the standardized reporting guidelines for studies evaluating risk stratification of ED patients with potential ACS and ACC key data elements and definitions for measuring the clinical management and outcomes of patients with ACS.^{17,18} All deaths were reviewed by an independent adjudication committee to determine cardiac relatedness. MI was defined by an elevated cTn above the threshold for normal at each study site, in the setting of symptoms consistent with ACS, with or without ECG changes. The adjudication committee confirmed that all MI events met the universal definition of MI.¹⁹ Coronary revascularization was defined as coronary artery bypass grafting, stent placement, or other percutaneous coronary intervention.

Secondary outcomes included the rate of patients identified by ADAPT as safe for early discharge, inducible ischemia on stress testing, and obstructive coronary artery disease (>50% stenosis) on CCTA. Consistent with the prior use of ADAPT, patients with low-risk assessments were considered safe for early discharge.^{14,15} Based on ADAPT Trial definitions, patients identified as safe for early discharge could have been discharged without index visit stress testing.¹⁵

Data Analysis

The percentage of patients identified by ADAPT as safe for early discharge (low risk) and the sensitivity, specificity, and positive predictive value (PPV) and NPV of ADAPT for MACE were calculated. Corresponding 95% exact binomial confidence intervals (CIs) were also computed. For purposes of these computations, patients with unknown MACE status (<1%; 10 of 1,140) were counted as MACE-negative. In addition, the sensitivity of serial cTn at 0 and 90 to 180 minutes used alone (not combined with a decision rule) was

calculated to determine the incremental value of the addition of the ADAPT decision rule to serial cTn testing. Statistical analysis was performed using SAS 9.3 and R 2.15.3.

RESULTS

From July 7, 2009, through November 3, 2011, a total of 1,369 low-risk patients with symptoms suggestive of ACS were enrolled. Due to incomplete cTn data, 229 patients were excluded from this analysis, leaving 1,140 patients in this study (Figure 1). Assessment for 30-day MACE was complete for 99% (1,130 of 1,140), with their characteristics and outcomes summarized in Tables 1 and 2. Most patients, 84% (958 of 1,140), received objective cardiac testing, and 62% (703 of 1,140) were admitted. MACE occurred at index visit or within 30 days in 2.7% (31 of 1,140) of the cohort.

ADAPT identified 551 of 1,140 (48.3%, 95% CI = 45.4% to 51.3%) patients as safe for early discharge, of whom five of 551 (0.9%, 95% CI = 0.3% to 2.1%) had MACE at 30 days. ADAPT was 83.9% (95% CI = 66.3% to 94.5%) sensitive for MACE, identifying 26 of the 31 patients with MACE. Serial troponins used alone without a decision rule were 32.3% (95% CI = 16.7% to 51.4%) sensitive for MACE (see Table 3 for the performance characteristics of the ADAPT decision rule and serial troponins). Of the five patients identified for early discharge by ADAPT with MACE, one had an MI and revascularization within the index visit, three others had index visit revascularization, and one had revascularization within the 30-day follow-up period (see Table 4 for a description of the patients with missed MACE). Among the 669 patients in the analysis set imaged with CCTA, 331 (49.5%, 95% CI = 45.6% to 53.3%) were identified as safe for early discharge by ADAPT, of whom 26 of the 331 (7.9%, 95% CI = 5.2% to 11.3%) had 50% coronary stenosis. Stress testing was completed in 351 patients, of whom 146 (41.6%, 95% CI = 36.4% to 46.9%) were identified for early discharge by ADAPT. Among these patients, 10 of 146 (6.8%, 95% CI = 3.3% to 12.2%) had inducible ischemia.

DISCUSSION

In this first North American application of the ADAPT strategy, all data elements were collected prospectively at the time of enrollment and the results demonstrated lower than expected sensitivity for MACE (83.9%). While ADAPT identified a large group of patients (48%) for early discharge, 0.9% of these patients had MACE (with the upper bound of the 95% CI for MACE exceeding 2%). Therefore, we were unable to validate ADAPT in a cohort of low-risk U.S. ED patients with ACS. These findings conflict with prior studies by the creators of ADAPT and suggest that further study of this decision rule may be warranted prior to widespread implementation.

In prior publications by Than and colleagues,^{13,15} ADAPT identified approximately 20% of patients with acute chest pain as safe for early discharge while maintaining high sensitivity for MACE. The reported sensitivities of ADAPT for MACE in the Asia-Pacific region are 99.7,¹³ 99.6,²⁰ and 97.9%,¹⁵ all much higher than the 83.9% (95% CI = 66.3% to 94.5%) sensitivity within the ACRIN PA 4005 cohort. Our results also differ from an analysis that reported 100% sensitivity for MACE using a modified application of ADAPT (using high-

sensitivity cTn rather than contemporary cTn) within the APACE cohort of 909 patients with acute chest pain from Italy, Switzerland, and Spain.²¹

The lower sensitivity of ADAPT in our study may be explained in part by differences in our patient population compared to prior validation studies. The ACRIN PA 4005 trial study procedures made it unlikely that patients with positive initial cTn levels would be enrolled. This differs from the ADAPT validation studies, which included patients with non-ST-segment elevation myocardial infarction (NSTEMI) at initial ED presentation. In fact, these index NSTEMIs account for most of the MACE events within the ADAPT validation studies. For example, in the most recent randomized controlled trial by Than et al., 94% (77 of 82) of patients with MACE had index NSTEMIs.¹⁵ Since cTn is a component of the ADAPT decision rule, by definition all of the patients with index NSTEMIs apparent on the initial two cTn measures were identified as “at risk” by ADAPT, thereby boosting sensitivity. High sensitivity produced from identifying index NSTEMI patients may be somewhat misleading, because these events were likely to be identified with or without the use of ADAPT.

Another factor that may be contributing to the decreased sensitivity of ADAPT in this analysis is a variation in the number of revascularization events in ACRIN PA 4005 versus the ADAPT cohorts. Among the patients in our analysis with MACE who were identified for early discharge by ADAPT, only one patient had an NSTEMI, with the remaining events representing revascularization procedures without MI. The Asia-Pacific validations of ADAPT included coronary revascularization as part of their MACE composite endpoint. However, revascularization events accounted for only 8.3% (26 of 302) of MACE events in the ADAPT trial, and 1.2% (1 out of 82) of MACE events in their recent randomized trial. This differs from our cohort, in which 96.8% (30 of the 31) of patients with MACE underwent revascularization. It is well documented that revascularization procedures are much more common in the U.S. compared to other developed countries.^{22,23} Therefore, health system differences may explain differences in revascularization rates. These differences highlight the difficulty in generalizing results of chest pain risk stratification studies conducted in other health care systems to U.S. patient populations. In addition, more frequent use of CCTA in this cohort may have resulted in a higher revascularization rate. Recent meta-analyses comparing CCTA to usual care have demonstrated higher revascularization rates among patients receiving CCTA.^{24,25}

The importance of revascularization events among patients identified as safe for early discharge is unclear. While revascularization procedures improve mortality and reinfarction rates among patients with acute or prior MIs, recent studies have questioned the role of revascularization in patients without acute cTn elevations.²⁶ The COURAGE trial and recent systematic reviews failed to show a difference in risk of MI or death among patients with stable coronary artery disease receiving percutaneous coronary intervention when compared to medical management.^{27–30} In individual patients it is often difficult to adjudicate if revascularizations are “appropriate” and impossible to determine the relationship between the procedure and the occurrence or lack of occurrence of downstream MACE. To better understand the utility and safety of clinical decision rules such as ADAPT, further study is

needed to determine the importance of identifying patients for early discharge who would have otherwise undergone revascularization.

Patients identified as low risk (safe for early discharge) by ADAPT also had high rates of significant coronary artery disease on CCTA (7.9%) and inducible ischemia on stress testing (6.8%). Although ADAPT was not designed to identify the presence or absence of coronary artery disease, high rates of coronary stenosis and inducible ischemia among patients identified as low risk could indicate risk misclassification. Furthermore, identifying these patients for early discharge from the ED without cardiac imaging or stress testing may be a missed opportunity to initiate needed medical or invasive therapy.

Specificity and early discharge rates of ADAPT for MACE were higher in our cohort compared to previous studies. The ADAPT trial demonstrated a specificity of 23.4% and early discharge rate of 20%. In our analysis, the specificity and early discharge rates were 49.2% and 48.3%, respectively. These differences are likely explained by the ACS risk profile of our cohort compared to the ADAPT trial. The ADAPT trial included patients at higher risk than the ACRIN PA 4005 cohort, including patients with positive initial cTn levels. This is evident when comparing MACE rates of the ADAPT trial to our cohort (15.3% vs. 2.7%). Therefore, it is not surprising that within our cohort, more patients without MACE were identified by ADAPT as low risk, thus improving specificity and early discharge rate.

Based on the strength of their prior studies, many physicians and some health systems within the U.S. have begun to incorporate ADAPT into their clinical practices, with the hope of safely increasing early discharge rates and more efficiently focusing inpatient resources. The results of this study suggest that these actions may be premature. The results of our analysis do not invalidate the prior studies of ADAPT in the Asia-Pacific region. However, they do raise important questions that require further investigation before widespread adoption of ADAPT within the U.S. can be endorsed.

Strengths of this analysis include prospective data collection for all ADAPT decision rule variables and robust follow-up for 30-day MACE events. Multisite enrollment and the variety of contemporary cTn assays used in the ACRIN PA 4005 cohort enhance the generalizability of this analysis. In addition, missed MACE in the five patients identified for early discharge by ADAPT was not isolated to a particular study site or cTn assay—this finding increases generalizability. Also, our study is strengthened by CCTA and stress imaging data, which provide valuable risk-stratification information for this cohort.

LIMITATIONS

This cohort consisted of low-risk ED patients at US tertiary care centers with signs or symptoms consistent with ACS and planned objective cardiac testing, but without obvious ACS at presentation. As such, this cohort differs from the cohort in which ADAPT was derived and validated. Specifically, our cohort was lower risk than the patient population studied in the ADAPT trial. However, because ADAPT is unlikely to be used by U.S. providers in patients with obvious ACS on initial ED presentation or known coronary artery disease, conducting this study within a lower-risk cohort may add external validity to our

findings. Furthermore, ADAPT was expected to have high sensitivity within a low-risk cohort. In addition, given the selected nature of this cohort, the results of this study may not be generalizable to all U.S. hospital settings. Also, the primary objective of the ACRIN PA 4005 cohort was to compare CCTA to traditional care, not the evaluation of clinical decision rules. However, all of the data elements required to risk stratify patients using ADAPT were collected a priori from the treating ED physicians. Furthermore, it is our view that the ACRIN PA 4005 cohort provides an ideal population for testing a clinical decision rule due to its inclusion of U.S. patients with acute chest pain and diagnostic uncertainty.

Another potential limitation of this analysis is subtle differences in the definitions used by the ACRIN PA 4005 cohort compared to the ADAPT trial. For example, ACRIN PA 4005 defined ischemic ECG changes based on the standardized reporting guidelines for studies evaluating risk stratification of ED patients with potential ACS.¹⁷ This definition differs slightly from what was used to classify ECGs as ischemic in the ADAPT trial. In addition, variability in the timing of the second troponin measure within the ACRIN PA 4005 cohort is a potential limitation. The second troponin was often measured beyond the 90- to 180-minute window, which differs from the ADAPT analysis (using 0- and 2-hour troponins). However, a second measure of troponin at >2 hours should not harm the sensitivity of the ADAPT decision rule.^{31,32} An additional limitation of the ACRIN PA 4005 data set was the lack of data necessary to accurately calculate other clinical decision rules such as the North American Chest Pain Rule and the HEART Pathway.^{33–35} Finally, patients were enrolled in ACRIN PA 4005 before widespread adoption of high-sensitivity cTn assays (not currently available within the United States); thus, occurrence of MI is based on contemporary cTn assay results (10% coefficient of variation at the 99th percentile URL). Thus, smaller cTn elevations, not detected by current assays, would not have been identified as MIs. The performance of ADAPT combined with the highest sensitivity cTn assays may have increased sensitivity for MACE. However, in a recent study by Keller et al.,⁶ use of serial contemporary troponin assays at 0 and 3 hours was as sensitive for detection of MI as newer high-sensitivity assays. Furthermore, high-sensitivity assays were not used in the Asia-Pacific validation of ADAPT, and given the limited availability of high-sensitivity assays, use of contemporary troponin assays increases the generalizability of our results.

CONCLUSIONS

Within a cohort of U.S. ED patients at low risk for acute coronary syndrome, the 2-hour accelerated diagnostic protocol had lower than expected sensitivity for major adverse cardiac events (83.9%), and 0.9% of patients identified for early discharge by the 2-hour accelerated diagnostic protocol had missed major adverse cardiac events. Discrepancies in the performance of the 2-hour accelerated diagnostic protocol in the American College of Radiology Imaging Network PA 4005 compared to prior validation cohorts may be explained by differences in our patient populations and health care systems. While the lower sensitivity of the 2-hour accelerated diagnostic protocol reported in this analysis does not invalidate prior studies of the 2-hour accelerated diagnostic protocol, it should provide impetus for future examination. Furthermore, the importance of missing revascularization events among patients identified for early discharge needs additional investigation.

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References

- Owens PL, Barrett ML, Gibson TB, Andrews RM, Weinick RM, Mutter RL. Emergency department care in the United States: a profile of national data sources. *Ann Emerg Med*. 2010; 56:150–65. [PubMed: 20074834]
- Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. *N Engl J Med*. 2012; 366:1393–403. [PubMed: 22449295]
- Heller GV, Stowers SA, Hendel RC, et al. Clinical value of acute rest technetium-99 m tetrofosmin tomographic myocardial perfusion imaging in patients with acute chest pain and nondiagnostic electrocardiograms. *J Am Coll Cardiol*. 1998; 31:1011–7. [PubMed: 9562001]
- Roberts R, Kleiman NS. Earlier diagnosis and treatment of acute myocardial infarction necessitates the need for a 'new diagnostic mind-set'. *Circulation*. 1994; 89:872–81. [PubMed: 8313577]
- Hoffmann U, Nagurny JT, Moselewski F, et al. Coronary multidetector computed tomography in the assessment of patients with acute chest pain. *Circulation*. 2006; 114:2251–60. [PubMed: 17075011]
- Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation*. 2011; 123:e18–209. [PubMed: 21160056]
- Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med*. 2000; 342:1163–70. [PubMed: 10770981]
- Pines JM, Isserman JA, Szyld D, Dean AJ, McCusker CM, Hollander JE. The effect of physician risk tolerance and the presence of an observation unit on decision making for ED patients with chest pain. *Am J Emerg Med*. 2010; 28:771–9. [PubMed: 20837253]
- Fleischmann KE, Goldman L, Johnson PA, et al. Critical pathways for patients with acute chest pain at low risk. *J Thromb Thrombol*. 2002; 13:89–96.
- Gomez MA, Anderson JL, Karagounis LA, Muhlestein JB, Mooers FB. An emergency department-based protocol for rapidly ruling out myocardial ischemia reduces hospital time and expense: results of a randomized study (ROMIO). *J Am Coll Cardiol*. 1996; 28:25–33. [PubMed: 8752791]
- Hermann LK, Weingart SD, Duvall WL, Henzlova MJ. The limited utility of routine cardiac stress testing in emergency department chest pain patients younger than 40 years. *Ann Emerg Med*. 2009; 54:12–6. [PubMed: 19231025]
- Redberg RF. Coronary CT angiography for acute chest pain. *N Engl J Med*. 2012; 367:375–6. [PubMed: 22830468]
- 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; 59:2091–8. [PubMed: 22578923]
- 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. [PubMed: 21435709]
- Than M, 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; 174:51–8. [PubMed: 24100783]
- Than M, 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; 166:752–4. [PubMed: 23084108]

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. [PubMed: 15576525]
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. A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). *J Am Coll Cardiol*. 2001; 38:2114–30. [PubMed: 11738323]
19. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation*. 2007; 116:2634–53. [PubMed: 17951284]
20. 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; 19:510–6. [PubMed: 22594354]
21. Cullen L, Mueller C, Parsonage WA, et al. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol*. 2013; 62:1242–9. [PubMed: 23583250]
22. Kaul P, Chang WC, Lincoff AM, et al. Optimizing use of revascularization and clinical outcomes in ST-elevation myocardial infarction: insights from the GUSTO-V trial. *Eur Heart J*. 2006; 27:1198–206. [PubMed: 16608859]
23. Fu Y, Chang WC, Mark D, et al. Canadian-American differences in the management of acute coronary syndromes in the GUSTO IIb trial: one-year follow-up of patients without ST-segment elevation. Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) II Investigators. *Circulation*. 2000; 102:1375–81. [PubMed: 10993855]
24. D'Ascenzo F, Cerrato E, Biondi-Zoccai G, et al. Coronary computed tomographic angiography for detection of coronary artery disease in patients presenting to the emergency department with chest pain: a meta-analysis of randomized clinical trials. *Eur Heart J Cardiovasc Imag*. 2013; 14:782–9.
25. Hulten E, Pickett C, Bittencourt MS, et al. Outcomes after coronary computed tomography angiography in the emergency department: a systematic review and meta-analysis of randomized, controlled trials. *J Am Coll Cardiol*. 2013; 61:880–92. [PubMed: 23395069]
26. Simoons ML, Windecker S. Controversies in cardiovascular medicine: chronic stable coronary artery disease: drugs vs. revascularization. *Eur Heart J*. 2010; 31:530–41. [PubMed: 20106842]
27. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007; 356:1503–16. [PubMed: 17387127]
28. Katritsis DG, Ioannidis JP. PCI for stable coronary disease. *N Engl J Med*. 2007; 357:414–5. [PubMed: 17652659]
29. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in non-acute coronary artery disease: a meta-analysis. *Circulation*. 2005; 111:2906–12. [PubMed: 15927966]
30. Bucher HC, Hengstler P, Schindler C, Guyatt GH. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials. *BMJ*. 2000; 321:73–7. [PubMed: 10884254]
31. Storrow AB, Nowak RM, Diercks DB, et al. Absolute and relative changes (delta) in troponin I for early diagnosis of myocardial infarction: results of a prospective multicenter trial. *Clin Biochem*. 2014 doi:10.1016/j.clinbiochem.2014.09.012.
32. Storrow AB, Christenson RH, Nowak RM, et al. Diagnostic performance of cardiac Troponin I for early rule-in and rule-out of acute myocardial infarction: results of a prospective multicenter trial. *Clin Biochem*. 2014 doi:10.1016/j.clinbiochem.2014.08.018.
33. 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. [PubMed: 21885156]
34. Mahler SA, Hiestand BC, Goff DC, et al. Can the heart score safely reduce stress testing and cardiac imaging in patients at low risk for major adverse cardiac events? *Crit Pathw Cardiol*. 2011; 10:128–133. [PubMed: 21989033]

35. 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. [PubMed: 23117012]
36. Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *JAMA.* 2011; 306:2684–93. [PubMed: 22203537]

Figure 1.

Study flow diagram: number of patients enrolled, excluded, and with complete data. ACRIN = American College of Radiology Imaging Network; ADAPT = 2-hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker.

Table 1

ACRIN PA 4005 Patient Characteristics and 30-day Outcomes

Patient Characteristics	ADAPT		Patient Included in Analysis (n = 1,140)	Total ACRIN PA 4005 Cohort (n = 1,369)
	Low Risk (n = 551)	At Risk (n = 589)		
Age (yr), mean $\pm$ SD	47 $\pm$ 8	51 $\pm$ 10	49 $\pm$ 9	49 $\pm$ 9
Sex				
Male	254 (46.1)	284 (48.2)	538 (47.2)	645 (47.1)
Female	297 (53.9)	305 (51.8)	602 (52.8)	724 (52.9)
Race *				
White	217 (39.4)	238 (40.4)	455 (39.9)	523 (38.2)
African American	324 (58.8)	336 (57.0)	660 (57.9)	812 (59.3)
Asian	7 (1.3)	8 (1.4)	15 (1.3)	18 (1.3)
Other/unknown	7 (1.3)	11 (1.9)	18 (1.6)	26 (1.9)
Ethnicity				
Hispanic	10 (1.8)	16 (2.7)	26 (2.3)	32 (2.3)
Not Hispanic	531 (96.4)	556 (94.4)	1087 (95.4)	1305 (95.3)
Unknown	10 (1.8)	17 (2.9)	27 (2.4)	32 (2.3)
Risk factors				
Hypertension	214 (38.8)	377 (64.0)	591 (51.8)	694 (50.7)
Smoking	163 (29.6)	205 (34.8)	368 (32.3)	446 (32.6)
Hyperlipidemia	84 (15.2)	230 (39.0)	314 (27.5)	367 (26.8)
Diabetes	36 (6.5)	126 (21.4)	162 (14.2)	194 (14.2)
Family history of coronary disease	135 (24.5)	195 (33.1)	330 (28.9)	394 (28.8)
Index objective cardiac testing				
CCTA	331 (60.1)	338 (57.4)	669 (58.7)	793 (57.9)
50% coronary stenosis	26 (7.9)	54 (16.0)	80 (12.0)	84 (10.6)
<50% coronary stenosis	66 (19.9)	78 (23.1)	144 (21.5)	157 (19.8)
No coronary stenosis	218 (65.9)	186 (55.0)	404 (60.4)	503 (63.4)
Indeterminate	21 (6.3)	20 (5.9)	41 (6.1)	49 (6.2)
Nuclear imaging	69 (12.5)	100 (17.0)	169 (14.8)	200 (14.6)
Exercise ECG	6 (1.1)	5 (0.8)	11 (1.0)	12 (0.9)
Exercise stress echocardiogram	66 (12.0)	76 (12.9)	142 (12.5)	150 (11.0)
Dobutamine stress echocardiogram	5 (0.9)	22 (3.7)	27 (2.4)	28 (2.0)
CMR	1 (0.2)	3 (0.5)	4 (0.4)	4 (0.3)
Angiography	14 (2.5)	37 (6.3)	51 (4.5)	55 (4.0)
Disposition				
Admitted	338 (61.3)	365 (62.0)	703 (61.7)	789 (57.6)
Discharged	207 (37.6)	220 (37.4)	427 (37.5)	555 (40.5)
Left AMA	6 (1.1)	4 (0.7)	10 (0.9)	25 (1.8)
Outcomes at 30 days				
MACE	5 (0.9)	26 (4.4)	31 (2.7)	32 (2.3)

Patient Characteristics	ADAPT		Patient Included in Analysis (<i>n</i> = 1,140)	Total ACRIN PA 4005 Cohort (<i>n</i> = 1,369)
	Low Risk (<i>n</i> = 551)	At Risk (<i>n</i> = 589)		
Cardiovascular death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MI	1 (0.2)	13 (2.2)	14 (1.2)	15 (1.1)
With revascularization	1 (0.2)	12 (2.0)	13 (1.1)	13 (0.9)
PCI	1 (100.0)	12 (100.0)	13 (100.0)	13 (100.0)
CABG	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Revascularization without MI	4 (0.7)	13 (2.2)	17 (1.5)	17 (1.2)
PCI	4 (100.0)	10 (76.9)	14 (82.4)	14 (82.4)
CABG	0 (0.0)	3 (23.1)	3 (17.6)	3 (17.6)

Data are reported as *n* (%).

ACRIN = American College of Radiology Imaging Network; AMA = against medical advice; CABG = coronary artery bypass graft; CMR = cardiac magnetic resonance imaging; CCTA = coronary computed tomography angiography; ECG = electrocardiogram; MI = myocardial infarction; PCI = percutaneous coronary intervention.

* Participants could endorse more than one race.

Table 2

Frequency of ADAPT Risk Stratification Determinants

Risk Stratification Strategy	Number	Percent
TIMI score < 0	574	50.4
Age ≥ 65 yr	69	6.1
At least three cardiac risk factors	236	20.7
Aspirin use (prescribed) in past 7 days	163	14.3
Documented prior coronary stenosis (≥ 50%)	7	0.6
At least two episodes of chest pain in 24 hours	250	21.9
ST elevation or depression	6	0.5
Elevated troponin	1	0.1
Ischemic ECG changes	18	1.6
Positive serial troponin	26	2.3
Total ADAPT		
Low risk	551	48.3
At risk	589	51.7

ADAPT = 2-hour accelerated diagnostic protocol; ECG = electrocardiogram; TIMI = Thrombolysis in Myocardial Infarction.

Table 3

Test Characteristics of ADAPT for Detection of MACE at 30 Days.

Risk Stratification Strategy	30-Day MACE		Total (n)
	Yes (n)	No (n)	
ADAPT at-risk	26	563	589
ADAPT low-risk	5	546	551
Total (n)	31	1,109	1,140

	Early Discharge % (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV (95% CI)	NPV (95% CI)
Serial troponins, (0–2 hours)	97.7 (96.7–98.5)	32.3 (16.7–51.4)	98.6 (97.7–99.2)	38.5 (20.2–59.4)	98.1 (97.1–98.8)
ADAPT	48.3 (45.4–51.3)	83.9 (66.3–94.5)	49.2 (46.3–52.2)	4.4 (2.9–6.4)	99.1 (97.9–99.7)

ADAPT = 2-hour Accelerated Diagnostic protocol; PPV = positive predictive value; NPV = negative predictive value.

Table 4

Characteristics of the Five Patients With Missed MACE by ADAPT

Age (yr)	Sex	Race	CAD history	0-hour Troponin (99th Percentile)	2-hour Troponin (99th Percentile)	Objective Cardiac Testing	MACE
56	Male	African American	None	<0.05 (0.4)	0.08 (0.4)	Peak troponin of 8.69 micrograms/L; 70% stenosis on CCTA; 100% stenosis of the circumflex on coronary angiogram.	NSTEMI and PCI
48	Male	White	None	0.00 (0.08)	0.00 (0.08)	Positive exercise stress echocardiogram; 60% stenosis of the LAD on coronary angiogram; positive nuclear stress test during 30-day follow-up (3 days prior to PCI)	PCI during 30-day follow-up
48	Female	African American	None	<0.05 (0.4)	<0.05 (0.4)	50%–69% stenosis on CCTA; 75% stenosis of the LAD on coronary angiogram	PCI
54	Male	African American	None	<0.05 (0.4)	<0.05 (0.4)	70% stenosis on CCTA; 85% stenosis of the RCA/PDA on coronary angiogram.	PCI
51	Male	White	None	<0.05 (0.4)	<0.01 (0.01)	70% stenosis on CCTA; positive nuclear stress test; 99% stenosis of the RCA/PDA on coronary angiogram.	PCI

CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ECG = electrocardiogram; MACE = major adverse cardiac events; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PDA = posterior descending artery; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.