Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 14, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.02.078

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

Louise Cullen, MB, BS,*† Christian Mueller, MD,‡ William A. Parsonage, DM,*§ Karin Wildi, MD,‡ Jaimi H. Greenslade, PhD,*†§ Raphael Twerenbold, MD,‡ Sally Aldous, MB, ChB, MD,‖ Bernadette Meller, MD,‡ Jillian R. Tate, MSc,* Tobias Reichlin, MD,‡¶ Christopher J. Hammett, MB, ChB, MD,* Christa Zellweger, MD,‡ Jacobus P. J. Ungerer, MMed, MB, ChB,* Maria Rubini Gimenez, MD,‡ Richard Troughton, MB, ChB, PhD,# Karsten Murray, MD,‡ Anthony F. T. Brown, MB, ChB,*§ Mira Mueller, MD,‡ Peter George, MB, BS,‖ Tamina Mosimann, MD,‡ Dylan F. Flaws, BA, MSc,§ Miriam Reiter, MD,‡ Arvin Lamanna, MB, BS,* Philip Haaf, MD,‡ Christopher J. Pemberton, PhD,# A. Mark Richards, PhD, MD,# Kevin Chu, MB, BS, MS,*§ Christopher M. Reid, PhD,** William Frank Peacock, MD,†† Allan S. Jaffe, MD,‡‡ Christopher Florkowski, MB, BS,‖ Joanne M. Deely, PhD,§§ Martin Than, MB, BS‖

Herston, Brisbane, and Melbourne, VIC, Australia; Basel, Switzerland; Christchurch, New Zealand; Boston, Massachusetts; Houston, Texas; and Rochester, Minnesota

Objectives The study objective was to validate a new high-sensitivity troponin I (hs-TnI) assay in a clinical protocol for assessing patients who present to the emergency department with chest pain.

Background Protocols using sensitive troponin assays can accelerate the rule out of acute myocardial infarction in patients with low-risk (suspected) acute coronary syndrome (ACS).

Methods This study evaluated 2 prospective cohorts of patients in the emergency department with ACS in an accelerated diagnostic pathway integrating 0- and 2-h hs-TnI results, Thrombolysis In Myocardial Infarction (TIMI) risk scores, and electrocardiography. Strategies to identify low-risk patients incorporated TIMI risk scores = 0 or ≤1. The primary endpoint was a major adverse cardiac event (MACE) within 30 days.

Results In the primary cohort, 1,635 patients were recruited and had 30-day follow-up. A total of 247 patients (15.1%) had a MACE. The finding of no ischemic electrocardiogram and hs-TnI ≤26.2 ng/l with the TIMI = 0 and TIMI ≤1 pathways, respectively, classified 19.6% (n = 320) and 41.5% (n = 678) of these patients as low risk; 0% (n = 0) and 0.8% (n = 2) had a MACE, respectively. In the secondary cohort, 909 patients were recruited. A total of 156 patients (17.2%) had a MACE. The TIMI = 0 and TIMI ≤1 pathways classified 25.3% (n = 230) and 38.6% (n = 351), respectively, of these patients as low risk; 0% (n = 0) and 0.8% (n = 1) had a MACE, respectively. Sensitivity, specificity, and negative predictive value for TIMI = 0 in the primary cohort were 100% (95% confidence interval [CI]: 98.5% to 100%), 23.1% (95% CI: 20.9% to 25.3%), and 100% (95% CI: 98.8% to 100%), respectively. Sensitivity, specificity, and negative predictive value for TIMI ≤1 in the primary cohort were 99.2 (95% CI: 97.1 to 99.8), 48.7 (95% CI: 46.1 to 51.3), and 99.7 (95% CI: 98.9 to 99.9), respectively. Sensitivity, specificity, and negative value for TIMI ≤1 in the secondary cohort were 99.4% (95% CI: 96.5 to 100), 46.5% (95% CI: 42.9 to 50.1), and 99.7% (95% CI: 98.4 to 100), respectively.

Conclusions An early-discharge strategy using an hs-TnI assay and TIMI score ≤1 had similar safety as previously reported, with the potential to decrease the observation periods and admissions for approximately 40% of patients with suspected ACS. (Advantageous Predictors of Acute Coronary Syndromes Evaluation [APACE] Study, NCT00470587; A 2hr Accelerated Diagnostic Protocol to Assess patients with chest Pain symptoms using contemporary Troponins as the only biomarker [ADAPT]: a prospective observational validation study, ACTRN12611001069943) (J Am Coll Cardiol 2013;62:1242–9) © 2013 by the American College of Cardiology Foundation

High-sensitivity troponin (hs-Tn) assays have shown excellent diagnostic performance in the evaluation of patients with possible acute myocardial infarction (AMI) (1–3). However, clinicians worry that because of lower specificity for the diagnosis of AMI (4,5), many patients may require unnecessary investigations because of elevated troponin values. Approximately 75% to 85% of patients who present to emergency departments with chest pain are not finally diagnosed with acute coronary syndrome (ACS) (6). Prolonged assessment of these patients contributes to overcrowding, increased costs, and adverse patient outcomes, including increased mortality. Early-discharge strategies combining electrocardiography (ECG), Thrombolysis In Myocardial Infarction (TIMI) score of 0, and multimarkers or some of the contemporary sensitive troponin assays have classified 10% to 20% of chest pain presentations as low risk (7,8). More patients could be safely classified as low risk by incorporating the new hs-TnI assays into similar strategies that assess patients with possible ACS (9).

See page 1250

Troponin testing alone cannot identify all patients at risk for AMI or other serious cardiac conditions, and it seems that biomarker-negative unstable angina pectoris can still be present. Therefore, troponin testing alone is unable to identify patients who are safe for early discharge. Previous research on hs-Tn assays has focused on their use in the early exclusion (rule out) of AMI (1–3) but has not focused on the low-risk group or defined the optimal methods of integrating assays into emergency department clinical practice pathways in the diverse group of patients with chest pain, data that are critically needed (10).

Evidence of how to integrate new high-sensitivity assays into clinical practice protocols is required to guide clinicians on their optimal use (10). The TIMI score was established for the risk stratification of patients with ACS and divides patients into prognostic categories that enable targeted management according to the level of risk (11). Serial contemporary troponin assay results used in association with a TIMI score = 0 enables identification of low-risk cohorts of approximately 20% of patients who are suitable for early discharge from the emergency department with few false-negative results (7,12). High-sensitivity assays may make it possible to increase the proportion of patients identified as low risk by including patients with a higher pre-test probability of ACS, that is, both TIMI = 0 and 1.

This study aimed to internally and externally validate the first commercially available hs-TnI assay within an accelerated diagnostic protocol (ADP) for patients with possible ACS. Two multicenter emergency department cohorts were investigated. The aim was to optimize the proportion of

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
ADP = accelerated diagnostic protocol
AMI = acute myocardial infarction
CI = confidence interval
ECG = electrocardiography
hs-TnI = high-sensitivity troponin I
MACE = major adverse cardiac event(s)
TIMI = Thrombolysis In Myocardial Infarction

From the *Royal Brisbane and Women's Hospital, Herston, Australia; †Queensland University of Technology, Brisbane, Australia; ‡University Hospital Basel, Basel, Switzerland; §University of Queensland, Brisbane, Australia; ||Christchurch Hospital, Christchurch, New Zealand; ¶Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; #University of Otago, Christchurch, New Zealand; **Monash University, Melbourne, VIC, Australia; ††Baylor College of Medicine, Houston, Texas; ‡‡Mayo Clinic, Rochester, Minnesota; and the §§Canterbury District Health Board, Christchurch, New Zealand. Funded by Queensland Emergency Medicine Research Foundation, Christchurch Heart Institute and Health Research Council and Heart Foundation of New Zealand, Christchurch Emergency Care Foundation, Abbott Diagnostics, Alere, Swiss National Science Foundation, University Basel, Swiss Heart Foundation, Roche, Siemens, and University Hospital Basel. Dr. Cullen has received funding from the Queensland Emergency Medical Research Foundation for chest pain clinical trials; from Abbott Diagnostics, Roche, Alere, Siemens, and Radiometer Pacific for clinical trials; and from Alere, Boehringer-Ingelheim, Pfizer, AstraZeneca, Abbott Diagnostics, and Radiometer Pacific for speaking and education. Prof. Mueller has received research grants from the Swiss National Science Foundation, University Basel, Swiss Heart Foundation, Stiftung für kardiovaskuläre Forschung Basel, 8sense, Abbott, Alere, Brahms, Critical Diagnostics, Nanosphere, Roche, Siemens, and the Department of Internal Medicine; and honoraria to speak from Abbott, Alere, Brahms, Novartis, Roche, and Siemens. Dr. Parsonage has received funding from the Queensland Emergency Medicine Research Foundation, Abbott Diagnostics, Roche, Alere, and Beckmann Coulter for research on diagnostic protocols; and honoraria, travel expenses, and consultancy fees from Abbott, AstraZeneca, Hospira, and Sanofi-Aventis. Dr. Aldous has received funding from the National Heart Foundation (New Zealand) for cardiac research. Dr. Reichlin has received research grants from the Swiss National Science Foundation (PASMP3-136995), Swiss Heart Foundation, University of Basel, Professor Max Cloetta Foundation, and the Department of Internal Medicine, University Hospital Basel; and honoraria to speak from Brahms and Roche. Dr. Hammett has received consultancy fees from Lilly and Bayer; speaker fees from AstraZeneca, Lilly, Bayer, and Boehringer-Ingelheim; and travel grants from Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Boston Scientific, Cordis, Lilly, Medtronic, Pfizer, Sanofi, and Schering-Plough. Dr. Ungerer has received funding from Pathology Queensland Study, Research and Education Trust Fund for unrelated research. Dr. Brown has received funding from AstraZeneca, Boehringer-Ingelheim, Aventis, and Roche to attend educational meetings; honoraria from Boehringer-Ingelheim and Roche for educational material; is on the Board of the Queensland Emergency Medical Research Foundation and received funding from this body as a co-investigator; and has been an Expert Medical Witness by the Queensland, Victorian, NT Coroner, and various legal companies. Peter George has received funding from Abbott, Beckman Coulter, and Roche for speaking. Dr. Flaws has received support from Alere to travel to meetings. Dr. Pemberton has received funding from the Health Research Council of New Zealand for studies investigating novel diagnostic markers of acute coronary syndromes. Dr. Richards has received speaker honoraria and funds from Roche Diagnostics and Alere for research support. Dr. Chu has received funding from the Queensland Emergency Medicine Research Foundation for unrelated research. Dr. Reid has received funding from the National Health & Medical Research Council (Australia) for Cardiovascular 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, and The Medicines Company; and has been a speaker for Bureau Abbott, and Alere. Dr. Deely has received funding from the Emergency Care Foundation for medical writing and Health Research Council (New Zealand) for unrelated research. Dr. Than has received funding from the Health Research Council (New Zealand) for two chest pain random clinical trials, the New Zealand National Heart Foundation for analysis of blood troponins from a chest pain clinical trial, and the Canterbury Community Trust for a diagnostic for unrelated research, and is Chair of the Emergency Care Foundation. All other authors have reported they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 3, 2012; revised manuscript received February 5, 2013, accepted February 25, 2013.

JACC Vol. 62, No. 14, 2013
October 1, 2013:1242–9

patients identified as low risk for serious 30-day major adverse cardiac events (MACE).

Methods

Participants. The ADP was investigated as 2 substudies; the primary, internal cohort was ADAPT (Accelerated Diagnostic protocol to Assess Patients with chest pain symptoms using contemporary Troponin as the only biomarker) (8), and the secondary external cohort was APACE (Advantageous Predictors of Acute Coronary Syndromes Evaluation) (3,13). In the ADAPT cohort, patients were consecutively recruited at 2 urban emergency departments in Brisbane, Australia, and Christchurch, New Zealand. Patients in the ADAPT cohort were prospectively recruited adults with at least 5 min of possible cardiac symptoms in accordance with the American Heart Association case definitions (acute chest, epigastric, neck, jaw, or arm pain; or discomfort or pressure without a clear noncardiac source) (14). Recruitment occurred between November 2007 and February 2011, but local logistics resulted in different enrollment periods in each center (8). Exclusion criteria included pregnancy, age <18 years, unable or unwilling to consent, recruitment inappropriate (e.g., terminal illness), transfer from another hospital, and patients in whom follow-up was considered impossible (e.g., homeless) (8). Data were prospectively collected on standardized collection forms using a published data dictionary (8,15). Research staff collected the demographic and clinical data from patients, supervised ECG testing, and drew blood samples for troponin testing (8). If a patient was unsure of an answer to a question (e.g., history of diabetes), a response of "no" was recorded (8). In the APACE cohort, consecutive adult patients were prospectively recruited who presented to the emergency departments in a multinational, multicenter study with symptoms suggestive of AMI with onset or peak symptoms within the previous 12 h (3). Patients were excluded who had end-stage renal failure treated with dialysis (3,13). The ADAPT substudy was performed in accordance with details registered with the ACTRN12611001069943 (8) and APACE (NCT00470587) (3,13).

In both cohorts, patients received usual care according to local hospital protocols, including blood draws for troponin measurement at presentation and then 6 to 9 h later in compliance with international guidelines (16) or as long as clinically appropriate in the APACE cohort, with timing left to the discretion of the attending physician. Additional blood samples from consenting patients were stored for preplanned analysis with hs-Tn assays. In both cohorts, usual care included further assessment by exercise tolerance testing, nuclear myocardial perfusion scanning, coronary computed tomography angiography, stress echocardiography, and/or invasive coronary angiography for all patients with elevated troponin results and/or ECG findings of ischemia. The clinical context of the presentation occasionally precluded further investigation (3,8).

Patients in both studies were followed up for MACE within 30 days using telephone follow-up and a national health-events search (which identifies any death) at least 6 months after the follow-up period. When patients reported further medical contact in the 30-day period, their hospital notes and documentation from subsequent medical contact and cardiac investigations were reviewed (8). The Centre for Clinical Research Excellence, Monash University, Melbourne, Australia, independently undertook data coordination, monitoring, and source data verification for the ADAPT study (8). The University Hospital, Basel, Switzerland, undertook data coordination, monitoring, and source data verification for the APACE study. Approval from local ethics committees was obtained, and all patients had provided written informed consent.

Procedures. The primary endpoint was MACE within 30 days after initial presentation (including initial hospital attendance). The criteria for a MACE included any of the following: death (excluding clearly noncardiac), cardiac arrest, AMI, emergency revascularization procedure, cardiogenic shock, ventricular arrhythmia requiring intervention, and high-degree atrioventricular block requiring intervention.

Outcomes and investigations were reported with predefined, structured reporting guidelines (15). The presence of a 30-day MACE was adjudicated independently using these reporting guidelines. Adjudication of all cardiac endpoints was performed by 2 cardiologists with a third cardiologist in cases of disagreement. Cardiologists were masked to results of the index-test biomarkers under investigation, but they had knowledge of the clinical record, ECG, and serial troponin results from routine care.

In accordance with international guidelines, blood was drawn on presentation and at least 6 h later or as long as clinically indicated for troponin results that were used to determine the presence of myocardial necrosis (14,17). These samples were analyzed at the recruitment site laboratories (Online Appendix 1) and were the only troponin values used in patient management. The diagnosis of AMI was based on evidence of myocardial necrosis together with clinical evidence of myocardial ischemia (ischemic symptoms, ECG changes, or imaging evidence) in accordance with current guidelines (17). Additional details of the criteria for adjudication are provided in Online Appendix 2.

In addition to sampling for routine clinical care, blood was drawn on presentation and 2 h later for both the ADAPT and APACE cohorts. Samples were immediately centrifuged. Serum and ethylenediaminetetraacetic plasma were separated and stored frozen at −70°C, within 2 h, for later analysis using hs-cardiac Tn assays. During March and April 2012 in Australia and New Zealand, and June and September 2012 in Switzerland, previously unthawed samples were tested with the final pre-commercial release

version of the ARCHITECT High Sensitive *STAT* Troponin-I assay (Abbott Laboratories, Abbott Park, Illinois). Laboratory technicians were blinded to patient data. Samples were thawed, mixed, and centrifuged (for 30 min at 3,000 relative centrifugal force and 4°C for serum samples or 10 min, twice, at 3,000 relative centrifugal force for plasma samples) before analysis and according to the manufacturer's instructions. The hs-TnI assay has a 99th percentile concentration of 26.2 ng/l with a corresponding coefficient of variation of <5% and a limit of detection of 1.2 ng/l (18). Long-term stability of TnI has been demonstrated (19). Good correlation between plasma and serum has been demonstrated (20). Total imprecision (coefficient of variation) for the manufacturer's quality controls measured over 11 days of specimen analysis ranged from 3.53% at 19.90 ng/l to 2.20% at 14,604 ng/l cardiac TnI (n = 31 to 33) at the Australian site.

The pre-defined diagnostic protocols under investigation included a combination of: 1) TIMI risk score; 2) ECG; and 3) hs-TnI sampling at 0 and 2 h. The first ADP defined low risk as patients with a TIMI score of 0 plus no new ischemic changes on ECG and 0- and 2-h hs-TnI concentrations ≤26.2 ng/l (Online Appendix 3). The second ADP defined low risk as those with a TIMI score of ≤1 (i.e., 0 or 1) plus no new ischemic changes on ECG and 0- and 2-h hs-TnI concentrations ≤26.2 ng/l (Online Appendix 3).

The TIMI risk score for unstable angina or non–ST-segment elevation myocardial infarction uses 7 predictors with a value of 1 point assigned for each positive finding (11). When the TIMI score was used within the ADP (Online Appendix 3), the original criteria on ECG and biomarkers were unnecessary because of the broader criteria required. These 2 original TIMI parameters were incorporated within ECG findings of new ischemic changes and increased hs-TnI results on 0- or 2-h blood tests. Abnormal ECG criteria are outlined in Online Appendix 4. The cutoff value for an elevated hs-TnI was the 99th percentile (26.2 ng/l).

Statistical analysis. Baseline characteristics of the participants were calculated. For continuous variables, mean ± SD and median ± interquartile range were calculated. For categoric data, the proportions in each of the ADP-positive and -negative groups were reported. The sensitivity, specificity, and positive and negative predictive values for hierarchical primary and secondary events were generated using chi-square analyses for the ADP as a whole and its constituents individually or in combination. Correlated proportions and sensitivities were compared using the McNemar test. Analyses were done with the Statistical Package for the Social Sciences (version 19.0, SPSS Inc., Chicago, Illinois).

Results

Integrating hs-TnI with a TIMI score ≤1 within the protocol classified 41.5% (678 of 1,635; p < 0.01) and 38.6% (351 of 909) of patients as low risk (ADAPT and APACE, respectively; Table 1), while maintaining excellent diagnostic statistics (Table 2). Only 0.8% and 0.6% of the patients who had a 30-day adverse event in ADAPT and APACE, respectively, were classified in this group. Fewer patients were classified as low risk (19.6% [320 of 1,635] and 25.3% [230 of 909], ADAPT and APACE, respectively) with the use of a TIMI risk score of 0 within the ADP.

Table 1 Occurrence of Major Adverse Cardiac Events During Initial Hospital Attendance or 30-Day Follow-Up According to Individual and Combinations of the ADP Test Parameters in the ADAPT and APACE Cohorts

ADAPT	MACE (n = 247)	No MACE (n = 1,388)	Total (n = 1,635)
ECG*			
Positive	46 (18.6)	58 (4.2)	104 (6.4)
Negative	201 (81.4)†	1,330 (95.8)	1,531 (93.6)
TIMI = 0‡			
Positive	243 (98.4)	1,065 (76.7)	1,308 (80)
Negative	4 (1.6)†	323 (23.3)	327 (20)
TIMI ≤1§			
Positive	210 (85.0)	693 (49.9)	903 (55.2)
Negative	37 (15.0)†	695 (50.1)	732 (44.8)
hs-TnI‖			
Positive	227 (91.9)	96 (6.9)	323 (19.8)
Negative	20 (8.1)†	1,292 (93.1)	1,312 (80.2)
TIMI = 0 or hs-TnI or ECG¶			
Positive	247 (100)	1,068 (76.9)	1,315 (80.4)
Negative	0 (0)†	320 (23.1)	320 (19.6)
TIMI ≤1 or hs-TnI or ECG#			
Positive	245 (99.2)	712 (51.3)	957 (58.5)
Negative	2 (0.8)†	676 (48.7)	678 (41.5)
APACE	**MACE (n = 156)**	**No MACE (n = 753)**	**Total (n = 909)**
ECG*			
Positive	81 (51.9)	165 (21.9)	246 (27.1)
Negative	75 (48.1)†	588 (78.1)	663 (72.9)
TIMI = 0‡			
Positive	155 (99.4)	504 (66.9)	659 (72.5)
Negative	1 (0.6)†	249 (33.1)	250 (27.5)
TIMI ≤1§			
Positive	144 (92.3)	344 (45.7)	488 (53.7)
Negative	12 (7.7)†	409 (54.3)	421 (46.3)
hs-TnI‖			
Positive	129 (82.7)	62 (8.2)	191 (21.0)
Negative	27 (17.3)†	691 (91.8)	718 (79.0)
TIMI = 0 or hs-TnI or ECG¶			
Positive	156 (100)	523 (69.5)	679 (74.7)
Negative	0 (0)†	230 (30.5)	230 (25.3)
TIMI ≤1 or hs-TnI or ECG#			
Positive	155 (99.4)	403 (53.5)	558 (61.4)
Negative	1 (0.6)†	350 (46.5)	351 (38.6)

Values are n (%). *ECG alone; any new ischemia at 0 or 2 h is positive. †Numbers of patients who were identified as low risk by the diagnostic parameter(s) but had a MACE (i.e., false-negative cases). ‡TIMI score ≥1 is positive. The 0-h hs-TnI result was part of the TIMI score. §TIMI score ≥2 is positive. ‖hs-TnI at 0 or 2 h >26.2 ng/l is positive. ¶Any new ischemia at 0 or 2 h or 0- or 2-h hs-TnI >26.2 ng/l or TIMI ≥1 is positive. #Any new ischemia at 0 or 2 h or 0- or 2-h hs-TnI >26.2 ng/l or TIMI ≥2 is positive.

ADP = accelerated diagnostic protocol; ECG = electrocardiography; hs-TnI = high-sensitivity troponin I; MACE = major adverse cardiac event(s); TIMI = Thrombolysis In Myocardial Infarction.

Table 2 Accuracy (95% CI) of ECG, hs-TnI, TIMI, and ADP for Exclusion of MACE

		ECG*	hs-TnI†	TIMI = 0	TIMI ≤1	TIMI = 0 and ECG* and hs-TnI†	TIMI ≤1 and ECG* and hs-TnI†
Sensitivity	ADAPT cohort	18.6 (14.3–23.9)	91.9 (87.8–94.6)	98.4 (95.9–99.4)	85.0 (80.0–88.9)	100 (98.5–100)	99.2 (97.1–99.8)
	APACE cohort	51.9 (43.8–60.0)	82.7 (75.8–88.3)	99.4 (96.5–100)	92.3 (87.0–96.0)	100 (97.7–100)	99.4 (96.5–100)
Negative predictive value	ADAPT cohort	86.9 (85.1–88.5)	98.5 (97.7–99.0)	98.8 (96.9–99.5)	94.9 (93.1–96.3)	100 (98.8–100)	99.7 (98.9–99.9)
	APACE cohort	87.7 (86.0–91.0)	96.3 (94.6–97.5)	99.6 (97.8–100)	97.2 (95.1–98.5)	100 (98.4–100)	99.7 (98.4–100)
Specificity	ADAPT cohort	95.8 (94.6–96.8)	93.1 (91.6–94.3)	23.3 (21.1–25.6)	50.1 (47.4–52.7)	23.1 (20.9–25.3)	48.7 (46.1–51.3)
	APACE cohort	78.1 (75.0–81.0)	91.8 (89.6–93.6)	33.1 (29.7–36.6)	54.3 (50.7–57.9)	30.5 (27.3–34.0)	46.5 (42.9–50.1)
Positive predictive value	ADAPT cohort	44.2 (35.1–53.8)	70.3 (65.1–75.0)	18.6 (16.6–20.8)	23.3 (20.6–26.1)	18.8 (16.8–21.0)	25.6 (22.9–28.5)
	APACE cohort	32.9 (27.1–39.2)	67.5 (60.4–74.1)	23.5 (20.3–27.0)	29.5 (25.5–33.8)	23.0 (19.9–26.3)	27.8 (24.1–31.7)

*ECG alone; any new ischemia at 0 or 2 h is positive. †hs-TnI at 0 and 2 h ≤26.2 ng/l.
ADP = accelerated diagnostic protocol; CI = confidence interval; other abbreviations as in Table 1.

There were 1,976 consenting patients recruited in the ADAPT cohort, of whom 1,635 had stored samples available for the primary analysis (Fig. 1). No patients were lost to 30-day follow-up. The APACE cohort included 909 patients with stored samples for analysis (Fig. 1). Baseline characteristics of the 2 cohorts are shown in Table 3. In the ADAPT cohort, 247 of 1,635 patients (15.1%) had a total of 280 adverse cardiac events within 30 days of presentation; 242 events were myocardial infarction (Table 4). In the APACE cohort, 156 of 909 patients (17.2%) had a total of 261 adverse cardiac events within 30 days of presentation; 153 events were myocardial infarction. Contribution of the individual parameters of the ADP and combinations of these are shown in Online Appendix 5.

In the ADAPT and APACE cohorts, 94.9% and 96.0% of patients, respectively, had an hs-TnI value on presentation above the limit of detection (1.2 ng/l) for the hs-TnI assay (Table 5).

Further objective investigations within the 30-day period, including exercise stress testing, echocardiography, computed tomography coronary angiography, and angiography, were performed in 246 patients (76.9 %) and 519 patients (76.5%) in the ADAPT low-risk cohorts analyzed using TIMI = 0 and TIMI ≤1, respectively, and 51 patients (22.2 %) and 94 patients (26.8%) in the APACE low-risk cohort analyzed using TIMI = 0 and TIMI ≤1, respectively (Table 3).

Two patients in the ADAPT cohort and 1 patient in the APACE cohort were determined as low risk and had a 30-day event (Online Appendix 6). The adjudicated diagnosis for all 3 of these patients was non–ST-segment myocardial infarction.

Discussion

Two large, international, multicentered emergency department cohorts have validated the integration of hs-TnI

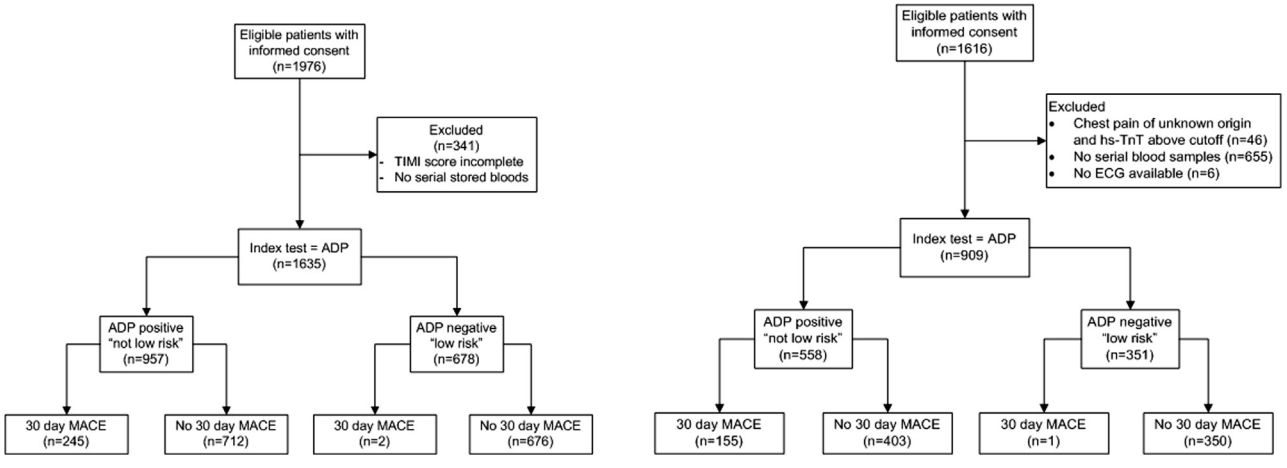

Figure 1 ADAPT and APACE Cohort-Participant Flow Diagrams for the Accelerated Diagnostic Protocol Incorporating hs-TnI and TIMI 1

Shown are the ADAPT (Accelerated Diagnostic protocol to Assess Patients with chest Pain symptoms using contemporary troponin as the only biomarker) **(left)** and APACE (Advantageous Predictors of Acute Coronary Syndromes Evaluation) **(right)** flow diagrams. ADP = accelerated diagnostic protocol; ECG = electrocardiogram; hs-TnT = high-sensitivity troponin T; MACE = major adverse cardiac event(s); TIMI = Thrombolysis In Myocardial Infarction.

Table 3 Characteristics for Low-Risk and High-Risk Participants in the ADAPT and APACE Cohorts

Characteristics	ADAPT Cohort (n = 1,635)		APACE Cohort (n = 909)	
	Low Risk (TIMI ≤1, Normal ECG and Normal hs-TnI) (n = 678)	High Risk (TIMI >1 or Abnormal ECG or Increased hs-TnI) (n = 957)	Low Risk (TIMI ≤1, Normal ECG and Normal hs-TnI) (n = 351)	High Risk (TIMI >1 or Abnormal ECG or Increased hs-TnI) (n = 558)
Age, yrs	51.3 (11.9)	67.0 (13.5)	53.5 (14.6)	66.4 (13.8)
Male, %	399 (58.8)	577 (60.3)	238 (67.8)	397 (71.1)
Risk factors				
Hypertension	197 (29.1)	655 (68.4)	139 (39.6)	437 (78.3)
Dyslipidemia	236 (34.8)	689 (72)	72 (20.5)	345 (61.8)
Diabetes	40 (5.9)	203 (21.2)	26 (7.4)	131 (23.5)
Family history of coronary artery disease	312 (46)	617 (64.5)	58 (16.5)	142 (25.4)
Smoking (current)	156 (23)	143 (14.9)	124 (35.3)	111 (19.9)
Medical history				
Angina	46 (6.8)	543 (56.7)	Not recorded	Not recorded
AMI	6 (0.9)	380 (39.7)	3 (0.9)	215 (38.5)
Angiography	2 (0.3)	282 (29.5)	3 (0.9)	230 (41.2)
Congestive heart failure	6 (0.9)	120 (12.5)	17 (4.8)	96 (17.2)
Cerebrovascular event	29 (4.3)	154 (16.1)	8 (2.3)	37 (6.6)
CABG	1 (0.1)	138 (14.4)	1 (0.3)	83 (14.9)
Time of symptom onset to presentation (h)				
Mean (SD)	21.1 ± 58.5	23.4 ± 62.5	13.5 ± 21.9	14.1 ± 21.4
Median (IQR)	4.6 (1.7–14.9)	6.2 (2.4–16.6)	4 (2–11)	5 (3–12)
Length of initial hospital attendance (h)				
Mean (SD)	39.7 ± 59.6	104.4 ± 151.5	29.7 ± 65.9	115.8 ± 200.0
Median (IQR)	26.3 (10.4–31.4)	65.9 (28.5–124.8)	7.2 (5–21.8)	47.9 (8.2–169.2)
Investigations within 30 days				
Stress ECG	446 (65.8)	206 (21.5)	64 (18.2)	76 (13.6)
Stress radionuclide imaging	42 (6.2)	50 (5.2)	22 (6.3)	80 (14.3)
Stress echocardiogram	8 (1.2)	20 (2.1)	Not recorded	Not recorded
Non-stress echocardiogram	48 (7.1)	130 (13.6)	Not recorded	Not recorded
Angiography	57 (8.4)	317 (33.1)	12 (3.4)	194 (34.8)

Values are n (%) except for age, time of symptom onset, and length of initial hospital attendance. Data were missing for time of symptom onset to presentation (7 in ADAPT and 12 in APACE). Length of hospital attendance was 59h in ADAPT and 29h in APACE.

ADP = accelerated diagnostic protocol; AMI = acute myocardial infarction; ADAPT = Accelerated Diagnostic protocol to Assess Patients with chest Pain symptoms using contemporary troponin as the only biomarker; APACE = Advantageous Predictors of Acute Coronary Syndromes Evaluation; CABG = coronary artery bypass grafting; other abbreviations as in Table 1.

results in a 2-h investigative pathway for the assessment of patients with possible ACS. The strategy using TIMI = 0 classified similar numbers of patients as low risk as previously reported using currently available troponin assays (8,21), while maintaining a sensitivity of >99% in both cohorts. The strategy incorporating a TIMI risk score ≤1 doubled the proportion of patients in the emergency department who are classified as low risk while maintaining >99% sensitivity and negative predictive value for adverse events in both cohorts. This finding suggests that approximately 40% of patients presenting to emergency departments with possible cardiac chest pain could rapidly and safely progress to early discharge for outpatient management (22). The increase in the proportion of patients identified as low risk incorporating TIMI ≤1 in the strategy has the potential to have a considerable impact on reducing hospital admission rates and emergency department overcrowding.

Incorporating hs-TnI results in clinical practice pathways will improve the management of patients presenting with chest pain to emergency departments. The strategy integrating hs-TnI with TIMI ≤1 resulted in an improved specificity of >45% for risk of 30-day cardiac events. This finding is in contrast to previous studies that have found that the improvements in analytic performance of hs-Tn assays have led to increased rates of elevated troponin and decreased specificity for AMI (4).

This is the first paper to validate the clinical integration of hs-TnI into a pragmatic and useful algorithm for medical decision-making in real-life practice. Until now, there has been no literature to provide guidance on how to use hs-TnI in clinical care. Guideline bodies have recommended that the 99th percentile (and not other cutoff levels) be used in clinical practice irrespective of the troponin assay (23,24). This study demonstrates the effectiveness of this cutoff value in combination with the TIMI risk score and ECG findings in clinically useful algorithms for patients with possible ACS in the emergency department.

Some techniques optimize the use of hs-Tn assays using alternative cutoff values (other than the 99th percentile) and change metrics (deltas) (1,2). The details of these techniques need to be individualized for each new assay (10). The value

JACC Vol. 62, No. 14, 2013
October 1, 2013:1242–9

Table 4 Frequency of Major Adverse Cardiac Events During Initial Hospital Attendance or 30-Day Follow-Up Period in the ADAPT and APACE Cohorts

	ADAPT Cohort* (n = 1,635)		APACE Cohort† (n = 909)	
	No. of Events	Frequency of Event Type (%)	No. of Events	Frequency of Event Type (%)
NSTEMI	225	13.8	142	15.6
Emergency revascularization	19	1.2	83‡	9.1‡
STEMI	17	1.0	11	1.2
Cardiovascular death	5	0.3	11	1.2
Ventricular arrhythmia	5	0.3	3	0.3
High atrioventricular block	5	0.3	7	0.8
Cardiogenic shock	3	0.2	2	0.2
Cardiac arrest	1	0.1	2	0.2

*A total of 247 of 1,635 patients (15.1%) in the ADAPT cohort had 280 events. †A total of 156 of 909 patients (17.2%) in the APACE cohort had 261 events. ‡Revascularization within 24 h.

ADAPT = Accelerated Diagnostic protocol to Assess Patients with chest Pain symptoms using contemporary troponin as the only biomarker; APACE = Advantageous Predictors of Acute Coronary Syndromes Evaluation; NSTEMI = non–ST-segment myocardial infarction; STEMI = ST-segment elevation myocardial infarction (occurring after initial recruitment).

of serial changes (deltas) was not assessed in this study. The limit of detection for hs-TnT has been suggested to be clinically useful as a cutoff value. An unrecordable hs-TnT value was found in up to 30% of patients on initial presentation, supporting this cutoff value for the early rule out of AMI when using this assay (1). We cannot recommend the use of the limit of detection as a cutoff value for this assay because of the improved ability of hs-TnI assays to detect troponin concentrations in the normal range, supported by our finding that the majority of patients (>95%) had defined troponin values on presentation.

Three patients in the low-risk group were diagnosed with 30-day events. It is possible that these were cases of false-negative results with hs-TnI (25). However, it is also possible that the apparent troponin elevation identified with the troponin assay in clinical use at the time of recruitment may have been a false-positive result, and the adjudicated outcomes were incorrect (26) (Online Appendix 6).

Study limitations. The applicability of this risk-stratification process is limited to patients with chest pain or discomfort. Patients with ACS and other serious conditions may present with atypical symptoms, such as fatigue or nausea without associated chest discomfort. Most patients recruited were Caucasian, limiting the generalizability of the results to other populations; however, the studies were conducted in 2 geographically distinct regions. During these observational studies, at least 77% of patients in the ADAPT and 27% of patients in the APACE low-risk cohorts received further treatment and/or investigations during the index presentation. In low-risk patients, we would argue such studies can be safely accomplished on an outpatient basis (27,28), but further studies (ideally in a randomized controlled trial) are required to determine whether further investigation (including outpatient testing) is required in the low-risk cohort to prevent longer-term, adverse outcomes.

Table 5 Participants With Detectable Troponin Values (>1.2 ng/l) on Presentation

	n	%
ADAPT cohort	1,551	94.9
APACE cohort	873	96.0

ADAPT = Accelerated Diagnostic protocol to Assess Patients with chest Pain symptoms using contemporary troponin as the only biomarker; APACE = Advantageous Predictors of Acute Coronary Syndromes Evaluation.

Conclusions

An early-discharge strategy using an hs-TnI assay and TIMI score ≤1 had similar safety as previously reported, with the potential to decrease the observation periods and admissions for approximately 40% of patients with suspected ACS.

Acknowledgments

The authors thank the patients who participated in the study, the research staff, the emergency department staff, and the laboratory technicians of all participating sites for valuable efforts.

Reprint requests and correspondence: Dr. Louise Cullen, Department of Emergency Medicine, Royal Brisbane and Women's Hospital, Herston, Brisbane, Queensland, Australia 4029. E-mail: louise_cullen@health.qld.gov.au.

REFERENCES

1. Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. J Am Coll Cardiol 2011;58:1332–9.
2. 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.
3. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858–67.
4. Jairam S, Jones P, Samaraie L, Chataline A, Davidson J, Stewart R. Clinical diagnosis and outcomes for Troponin T 'positive' patients assessed by a high sensitivity compared with a 4th generation assay. Emerg Med Australas 2011;23:490–501.
5. De Lemos JA, Morrow DA, de Filippi CR. Highly sensitive troponin assays and the cardiology community: a love/hate relationship? Clin Chem 2011;57:826–9.
6. Chase M, Robey J, Zogby K, Sease K, Shofer F, Hollander J. Prospective validation of the Thrombolysis in Myocardial Infarction risk score in the emergency department chest pain population. Ann Emerg Med 2006;48:252–9.
7. 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.
8. 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.
9. Twerenbold R, Jaffe A, Reichlin T, Reiter M, Mueller C. High-sensitive troponin T measurements: what do we gain and what are the challenges? Eur Heart J 2012;33:579–86.
10. Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J 2012;33:2252–7.

11. Antman EM. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835–42.
12. Goodacre SW, Bradburn M, Cross E, et al. The Randomised Assessment of Treatment using Panel Assay of Cardiac Markers (RATPAC) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. Heart 2011;97:190–6.
13. Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011;124:136–45.
14. 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;108:2543–9.
15. Cullen L, Than M, Brown AF, et al. Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments in Australasia. Emerg Med Australas 2010;22:35–55.
16. Amsterdam EA, Kirk JD, Bluemke DA, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. Circulation 2010;122:1756–76.
17. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634–53.
18. Apple FS, Collinson PO. Analytical characteristics of high-sensitivity cardiac troponin assays. Clin Chem 2012;58:54–61.
19. Kavsak PA, MacRae AR, Yerna MJ, Jaffe AS. Analytic and clinical utility of a next-generation, highly sensitive cardiac troponin I assay for early detection of myocardial injury. Clin Chem 2009;55:573–7.
20. Koerbin G, Tate J, Potter JM, Cavanaugh J, Glasgow N, Hickman PE. Characterisation of a highly sensitive troponin I assay and its application to a cardio-healthy population. Clin Chem Lab Med 2012;50:871–8.
21. 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.
22. Scheuermeyer FX, Christenson J, Innes G, Boychuk B, Yu E, Grafstein E. Safety of assessment of patients with potential ischemic chest pain in an emergency department waiting room: a prospective comparative cohort study. Ann Emerg Med 2010;56:455–62.
23. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634–53.
24. Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J 2012;33:2252–7.
25. Eriksson S, Halenius H, Pulkki K, Hellman J, Pettersson K. Negative interference in cardiac troponin I immunoassays by circulating troponin autoantibodies. Clin Chem 2005;51:839–47.
26. Panteghini M. A critical appraisal of experimental factors influencing the definition of the 99th percentile limit for cardiac troponins. Clin Chem Lab Med 2009;47:1179–82.
27. Meune C, Reichlin T, Irfan A, et al. How safe is the outpatient management of patients with acute chest pain and mildly increased cardiac troponin concentrations? Clin Chem 2012;58:916–24.
28. Meyer MC, Mooney RP, Sekera AK. A critical pathway for patients with acute chest pain and low risk for short-term adverse cardiac events: role of outpatient stress testing. Ann Emerg Med 2006;47:435.e1–3.

Key Words: acute myocardial infarction ▪ ADAPT ▪ APACE ▪ chest pain ▪ high-sensitivity troponin I ▪ TIMI.

APPENDIX

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