Validation of the No Objective Testing Rule and Comparison to the HEART Pathway

Jason P. Stopyra MD, Chadwick D. Miller MD MS, Brian C. Hiestand MD, MPH, Cedric W. Lefebvre MD, Bret A. Nicks MD, David M. Cline MD, Kim L. Askew MD, Robert F. Riley MD, MS, Gregory B. Russell MS, and James W. Hoekstra MD
Simon A. Mahler MD MS

ABSTRACT

Background: The no objective testing rule (NOTR) is a decision aid designed to safely identify emergency department (ED) patients with chest pain who do not require objective testing for coronary artery disease.

Objectives: The objective was to validate the NOTR in a cohort of U.S. ED patients with acute chest pain and compare its performance to the HEART Pathway.

Methods: A secondary analysis of 282 participants enrolled in the HEART Pathway randomized controlled trial was conducted. Each patient was classified as low risk or at risk by the NOTR. Sensitivity for major adverse cardiac events (MACE) at 30 days was calculated in the entire study population. NOTR and HEART Pathways were compared among patients randomized to the HEART Pathway in the parent trial using McNemar's test and the net reclassification improvement (NRI).

Results: Major adverse cardiac events occurred in 22/282 (7.8%) participants, including no deaths, 16/282 (5.6%) with myocardial infarction (MI), and 6/282 (2.1%) with coronary revascularization without MI. NOTR was 100% (95% confidence interval [CI] = 84.6%–100%) sensitive for MACE and identified 78/282 patients (27.7%, 95% = CI 22.5–33.3%) as low risk. In the HEART Pathway arm (n = 141), both NOTR and HEART Pathway identified all patients with MACE as at risk. Compared to NOTR, the HEART Pathway was able to correctly reclassify 27 patients without MACE as low risk, yielding a NRI of 20.8% (95% CI = 11.3%–30.2%).

Conclusions: Within a U.S. cohort of ED patients with chest pain, the NOTR and HEART Pathway were 100% sensitive for MACE at 30 days. However, the HEART Pathway identified more patients suitable for early discharge than the NOTR.

Health care assets such as stress testing and hospitalization are inefficiently utilized on patients who present to emergency departments (ED) with acute chest pain. Overtesting leads to a significant number of false-positive and nondiagnostic tests, additional unnecessary and often invasive procedures, and radiation exposure, as well as ED and inpatient crowding.[1] Healthcare leaders agree that there is a need to more efficiently evaluate the 10 million patients who present to U.S. ED annually complaining of chest pain.[2]

From the Department of Emergency Medicine (JPS, CDM, BCH, CWL, BAN, DMC, KLA, JWH, SAM) and the Department of Biostatistical Sciences (GBR), Wake Forest School of Medicine, Winston-Salem, NC; and the Division of Cardiology, University of Washington (RFR), Seattle, WA.
Received November 18, 2016; revision received January 26, 2017; accepted February 6, 2017.
This study was funded by the American Heart Association (12CRP12000001). Dr. Mahler received funding from the Donaghue Foundation, Duke Endowment, Abbott Point of Care, and NHLBI (1 R01 HL118263-01, L30 HL120008). He was also an active investigator and on an advisory board for Roche and Chief Medical Officer for Impathiq Inc. Dr. Miller is a consultant for Abbott and Siemens. Dr. Stopyra received funding from Abbott Point of Care.
The authors have no potential conflicts to disclose.
Supervising Editor: Shahriar Zehtabchi, MD.
Address for correspondence and reprints: Jason P. Stopyra, MD; e-mail: jstopyra@wakehealth.edu.
ACADEMIC EMERGENCY MEDICINE 2017;24:1165–1168.

doi: 10.1111/acem.13221
ISSN 1069-6563
PII ISSN 1069-6563583

Accelerated diagnostic protocols (ADPs) have been developed to more accurately risk stratify ED patients with acute chest pain and avoid unnecessary testing.[3] The no objective testing rule (NOTR) is an easy-to-use ADP, which does not depend on subjective criterion. In a prior study, the NOTR identified 31% of patients as low risk, who could forego objective cardiac testing while achieving a sensitivity of 97.6% for acute coronary syndrome (ACS).[4] However, NOTR has yet to be validated in U.S. ED patients or compared to another ADP. The objectives of this analysis were to determine if NOTR meets the standard of a useful decision aid (safely identifying 20% or more patients for early discharge) and to compare its sensitivity and early discharge rates to those of the HEART Pathway in a cohort of U.S. ED patients.[5]

METHODS

Study Design

A retrospective analysis of participants enrolled in the HEART Pathway randomized controlled trial (RCT) was conducted. Participants were enrolled from September 2012 through February 2014, and all gave written informed consent at the time of study entry. The HEART Pathway trial was approved by the internal review board of the sponsoring organization and was registered with ClinicalTrials.gov (clinical trial number NCT01665521) prior to enrollment. Methods of the HEART Pathway trial have been previously described.[3]

Study Setting and Population

Participants were enrolled from the ED of (withheld for review) an academic tertiary care center. ED patient volume during the enrollment period consisted of approximately 104,000 encounters per year. Contemporary serum troponin measurements were performed using the ADVIA Centaur TnI-UltraTM assay (Siemens), which has a 99th percentile upper reference limit (URL) and 10% coefficient of variance at 0.04 μg/L.

Patients ≥ 21 years old presenting with symptoms suggestive of ACS were screened. Eligibility criteria included the provider ordering an electrocardiogram (ECG) and troponin for ACS evaluation. Patients were excluded for new ST-segment elevation ≥ 1 mm; hypotension; life expectancy < 1 year; a noncardiac medical, surgical, or psychiatric illness determined by the provider to require admission; prior enrollment; non–English speaking; and incapacity/unwillingness to consent.

Data Collection

Data elements from the electronic medical record (EMR) were collected prospectively in accordance with standards of good clinical practice, standardized reporting guidelines,[6] and key data elements and definitions.

At 30 days, a structured record review and telephone interview were conducted to identify events since discharge. In an effort to prevent recall bias, events reported at other healthcare facilities were confirmed using structured review of outside medical records. Incomplete follow-up was handled using the following algorithm: participants with ongoing visits in the EMR were considered to have complete information and were classified based on data available; participants without ongoing visits were considered lost to follow-up. The Social Security Death Master File was searched for participants unable to be contacted.

NOTR

The NOTR decision rule was retrospectively applied to all study participants. NOTR uses cardiac risk factors, history of myocardial infarction (MI) or coronary artery disease, age, serial troponin measures, and a nonischemic ECG (no ST-depression or T-wave inversion in > 1 contiguous lead) to risk stratify patients. All of the data elements needed for NOTR were collected prospectively at the time of enrollment in the HEART Pathway RCT.

Heart Pathway

Trial participants were randomized to the HEART Pathway or usual care using random permuted blocks. In the HEART Pathway arm (n = 141), patients were risk stratified by attending ED providers using the HEART score,[7,8] and serial cardiac troponin measures at 0 and 3 hours. Patients were considered low risk if HEART scores were 0–3 and both serial troponin results were below the URL. Patients with a HEART score of >4 or a troponin measure above the URL were considered at risk.

Study Measures

Our primary outcome was the rate of major adverse cardiac events (MACE) within 30 days of presentation (the composite of death, MI, or coronary revascularization). A consensus of two reviewers (CDM, BCH),

blinded to NOTR and HEART Pathway risk assessment, adjudicated elements required to measure the occurrence of MACE. To make these assessments, reviewers were provided participant's index and discharge records, follow-up call information, records from follow-up, and study definitions. Disagreements were settled by consensus between two reviewers or involvement of a third blinded reviewer.

Data Analysis

The percentage of patients identified by NOTR as low risk, the sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values (PPV, NPV) of NOTR for MACE were calculated within the entire cohort (n = 282). Within the HEART Pathway arm (n = 141) these test characteristics were calculated for NOTR and HEART Pathway. Patients with incomplete follow-up (<4%, 10/282) were considered free of 30-day MACE events. ADP performance was compared using McNemar's test and net reclassification improvement (NRI). Statistical analysis was performed using SAS 9.4 (SAS Institute).

RESULTS

From September 2012 to February 2014, a total of 282 patients with symptoms suggestive of ACS were enrolled in the HEART Pathway RCT. Data needed to determine risk by NOTR were available on all 282 participants. MACE occurred in 22/282 (7.8%): there were no deaths, 16 patients had MI, and six patients had coronary revascularization without MI.

NOTR identified 78/282 patients (27.7%, 95% confidence interval [CI] = 22.5%–33.3%) as low risk. Of these, none had MACE at 30 days. NOTR was 100% (95% CI = 84.6%–100%) sensitive for MACE, identifying 22/22 patients with MACE. Specificity was 30.0% (95% CI = 24.5%–36.0%), PPV was 10.8% (95% CI = 6.9%–15.9%), and NPV was 100% (95% CI = 95.4%–100%).

Within the HEART Pathway arm, MACE occurred in 11/141 (7.8%): there were no deaths, seven patients had MI, and four patients had coronary revascularization without MI. NOTR and HEART Pathway identified all patients with MACE as at risk (11/11); yielding a sensitivity of 100% (95% CI = 71.5%–100%) for both. NOTR identified 39/141 patients (27.7%, 95% CI = 20.5%–35.8%) as low risk, while the HEART Pathway identified 66/141 patients (46.8%, 95% CI = 38.3%–55.4%) as low risk, an absolute difference of 19.1% (95% CI = 13.0%–26.6%; $p < 0.001$). Test characteristics of NOTR and HEART Pathway are summarized in Table 1. Compared to NOTR, the HEART Pathway had a net gain of 27 patients without MACE as low risk, yielding a NRI of 20.8% (95% CI = 11.3%–30.2%), calculated by using an add-on macro in SAS.[9] The HEART Pathway incorrectly moved nine patients up to a higher risk level, a net proportion of events of 0.069, while correctly moving 36 patients down to a nonevent, which yields a net proportion of non-events of 0.277.

Table 1
Performance Characteristics of the NOTR and the HEART Pathway Within the HEART Pathway Arm

Risk Stratification Strategy	30-day MACE		Total (n)
	Yes (n)	No (n)	
NOTR			
At risk	11	91	102
Low risk	0	39	39
Total (n)	11	130	141
HEART			
At risk	11	64	75
Low risk	0	66	66
Total (n)	11	130	141

	% Low Risk (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
NOTR	27.7% (20.5–35.8)	100% (71.5–100)	30.0% (24.5–36.0)	10.8% (6.9–15.9)	100% (91.0–100)	1.43 (1.28–1.60)	0.00
HEART	46.8% (38.3–55.4)	100% (71.5–100)	50.8% (41.9–59.6)	14.7% (7.6–24.7)	100% (94.6–100)	2.03 (1.71–2.42)	0.00

MACE = major adverse cardiac events; NOTR = no objective testing rule; NLR = negative likelihood ratio; NPV = negative predictive value; PLR = positive likelihood ratio; PPV = positive predictive value.

DISCUSSION

The primary finding of this analysis is that NOTR is highly sensitive for MACE, but does not identify as many patients for early discharge as the HEART Pathway. The performance of NOTR in our study is consistent with results from Greenslade and colleagues,[4] who identified 31% of patients with chest pain as low risk while achieving a sensitivity of 97.6% for ACS.

The high sensitivity required of chest pain risk stratification ADPs often comes at the expense of identifying fewer patients for early discharge. Attempts to maximize sensitivity result in an increase in false-positive cases and lower numbers of true negatives. In our comparison of NOTR to the HEART Pathway, the HEART Pathway was better than NOTR in achieving a balance between the need for high sensitivity and limiting the number of false-positive patients. The HEART Pathway identified nearly 20% more patients for early discharge than NOTR while maintaining 100% sensitivity for MACE.

As the U.S. healthcare system transitions to a value-based healthcare delivery model, tools that avoid unnecessary cardiac testing and hospital admissions will be increasingly important. Our data suggest that the HEART Pathway is superior to NOTR in providing value. New ADPs or modifications to the HEART Pathway should seek to maintain a high sensitivity (>99%) while increasing the percentage of low-risk patients identified for early discharge.

LIMITATIONS

Our small sample size and small number with MACE produced wide CIs, which limits the ability to draw definitive conclusions. Enrollment from a single academic medical center may limit generalizability. Our cohort differs from the cohort used to derive and validate NOTR as our cohort includes patients with initial elevated troponins and ischemic ECGs. Follow-up was incomplete on 10 patients (3.5% of participants), which may have caused misclassification and underestimation of MACE. In the HEART Pathway RCT serial troponins were obtained at 0 and 3 hours after arrival rather than at 0 and 2 hours as required by NOTR. However, a second measure of troponin at >2 hours should enhance sensitivity without substantively decreasing early discharges.[10]

CONCLUSIONS

Within a U.S. cohort of ED patients with symptoms concerning for acute coronary syndrome, the no objective testing rule was 100% sensitive for 30-day major adverse cardiac events and identified 28% as low risk. However, the HEART Pathway has improved specificity and outperformed no objective testing rule by correctly identifying 19% more patients as low risk and safe for early discharge.

References

1. 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.
2. 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.
3. Mahler SA, Riley RF, Hiestand BC, et al. The HEART Pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. Circ Cardiovasc Qual Outcomes 2015;8:195–203.
4. Greenslade JH, Parsonage W, Than M, et al. A clinical decision rule to identify emergency department patients at low risk for acute coronary syndrome who do not need objective coronary artery disease testing: the no objective testing rule. Ann Emerg Med 2016;67:478–89. e2.
5. Mahler SA, Miller CD, Hollander JE, et al. Identifying patients for early discharhge: performance of decision rules among patients with acute chest pain. Int J Cardiol 2013;168:795–802.
6. Hollander JE, Blomkalns AL, Brogan GX, et al. Standardized reporting guidelines for studies evaluating risk stratification of emergency department patients with potential acute coronary syndromes. Ann Emerg Med 2004;44:589–98.
7. Backus BE, Six AJ, Kelder JC, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol 2013;168:2153–8.
8. Six AJ, Cullen L, Backus BE, et al. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. Crit Pathw Cardiol 2013;12:121–6.
9. Kennedy KF, Pencina MJ. A SAS® Macro to Compute Added Predictive Ability of New Markers Predicting a Dichotomous Outcome. Southeast SAS® Users Group (Proceedings), Boston, MA, 2010.
10. 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 2015;48:254–9.