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Identifying Patients for Early Discharge: Performance of Decision Rules Among Patients with Acute Chest Pain

Simon A. Mahler¹, Chadwick D. Miller², Judd E. Hollander³, John T. Nagurney⁴, Robert Birkhahn⁵, Adam J. Singer⁶, Nathan I. Shapiro⁷, Ted Glynn⁸, Richard Nowak⁹, Basma Safdar¹⁰, Mary Peberdy¹¹, Francis L. Counselman¹², Abhinav Chandra¹³, Joshua Kosowsky¹⁴, James Neuenschwander¹⁵, Jon W. Schrock¹⁶, Stephen Plantholt¹⁷, Deborah B. Diercks¹⁸, and W. Frank Peacock¹⁹

¹Wake Forest School of Medicine, Winston-Salem, NC. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

²Wake Forest School of Medicine, Winston-Salem, NC. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

³University of Pennsylvania, Philadelphia, PA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

⁴Massachusetts General Hospital, Boston, MA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

⁵New York Methodist Hospital, Brooklyn, NY. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

⁶Stony Brook University, Stony Brook, NY. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

⁷Beth Israel Deaconess Medical Center, Boston, MA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

⁸Ingham Regional Medical Center, Lansing, MI. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

⁹Henry Ford Health System, Detroit, MI. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

¹⁰Yale University, New Haven, CT. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Address for correspondence: Simon A. Mahler, M.D., Departments of Epidemiology and Prevention, and Emergency Medicine, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157 USA, Phone: 336-716-2189 Fax: 336-716-1705, smahler@wakehealth.edu.

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¹¹Virginia Commonwealth University, Richmond, VA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

¹²Eastern Virginia Medical School, Norfolk, VA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

¹³Duke University, Durham, NC. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

¹⁴Brigham and Women's Hospital, Boston, MA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

¹⁵Ohio State University Medical Center, Columbus, OH. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

¹⁶Metro Health Medical Center, Cleveland, OH. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

¹⁷St. Agnes Hospital, Baltimore, MA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

¹⁸University of California, Davis, Sacramento, CA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

¹⁹Cleveland Clinic Foundation, Cleveland, OH. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Abstract

Background—The HEART score and North American Chest Pain Rule (NACPR) are decision rules designed to identify acute chest pain patients for early discharge without stress testing or cardiac imaging. This study compares the clinical utility of these decision rules combined with serial troponin determinations.

Methods and Results—A secondary analysis was conducted of 1005 participants in the Myeloperoxidase In the Diagnosis of Acute coronary syndromes Study (MIDAS). MIDAS is a prospective observational cohort of Emergency Department (ED) patients enrolled from 18 US sites with symptoms suggestive of acute coronary syndrome (ACS). The ability to identify participants for early discharge and the sensitivity for ACS at 30 days were compared among an unstructured assessment, NACPR, and HEART score, each combined with troponin measures at 0 and 3 hours. ACS, defined as cardiac death, acute myocardial infarction, or unstable angina, occurred in 22% of the cohort. The unstructured assessment identified 13.5% (95% CI 11.5-16%) of participants for early discharge with 98% (95% CI 95-99%) sensitivity for ACS. The NACPR identified 4.4% (95% CI 3-6%) for early discharge with 100% (95% CI 98-100%) sensitivity for ACS. The HEART score identified 20% (95% CI 18-23%) for early discharge with 99% (95% CI 97-100%) sensitivity for ACS. The HEART score had a net reclassification improvement of 10% (95% CI 8-12%) versus unstructured assessment and 19% (95% CI 17-21%) versus NACPR.

Conclusions—The HEART score with 0 and 3 hour serial troponin measures identifies a substantial number of patients for early discharge while maintaining high sensitivity for ACS.

Keywords

chest pain; risk stratification; clinical decision rules; acute coronary syndrome

Although patients frequently present with symptoms of suspected acute coronary syndrome (ACS), risk stratification remains challenging and inefficient. Although the Thrombolysis in Myocardial Infarction (TIMI) risk score and Global Registry of Acute Coronary Events (GRACE) score are recommended to aid risk stratification, they are not sensitive enough to avoid objective testing or inpatient care [1-4]. Emergency Department (ED) patients with low-risk TIMI and GRACE scores have ACS rates above the acceptable miss rate of 1% [3, 5]. More sensitive rules have been reported, but they identify fewer than 20% of acute chest pain patients for early discharge [6, 7].

The HEART score and North American Chest Pain Rule (NACPR) are recently developed decision rules designed to identify ED patients with symptoms suggestive of ACS for early discharge without objective cardiac testing (stress testing or cardiac imaging). However, both require further validation before prospective implementation [7, 8]. In addition, there is little evidence comparing the clinical utility of these decision rules to each other or to an unstructured clinical evaluation (a clinical assessment based on physician gestalt without the use of a clinical decision rule).

Decision rules attempting to identify patients for early discharge based a single troponin measurement have had varying success, highlighting the importance of serial troponin measurements to increase sensitivity [9, 10]. Recently, we reported that adding a second troponin measurement to the HEART score improved sensitivity for major adverse cardiac events from 58% to 100% in a low-risk cohort designated for observation unit care [9]. Therefore, the objective of this study was to determine the ability of three risk stratification strategies – an unstructured clinician assessment, NACPR, and HEART score, each combined with serial troponin measures – to identify patients for early discharge while maintaining an acceptable ACS miss rate (below 1%).

Methods

Study Design

A secondary analysis was conducted of patients prospectively enrolled in the Myeloperoxidase In the Diagnosis of Acute coronary syndromes Study (MIDAS), clinical trial number NCT00415948. Participants were enrolled from May 2006 to September 2007, and all gave informed consent at the time of study entry. Details of the MIDAS trial have been previously described.[11] The MIDAS protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the Institutional Review Board of each participating institution.

Participants

Participants were enrolled from 18 US tertiary care center EDs. Eligibility criteria required subjects be at least 18 years old, with symptoms of suspected ACS, starting within 6 hours of presentation and lasting at least 30 minutes, in whom the physician planned objective cardiac testing. Acceptable objective cardiac testing was defined as: invasive coronary angiography, computed tomography coronary angiography, or stress testing with electrocardiography, nuclear imaging, cardiac magnetic resonance imaging, or echocardiography. Patients were excluded if they were unable or unwilling to consent to serial blood draws and a 30-day follow-up phone interview. All patients received medical care consistent with local practice, including local biomarker ordering and interpretation, which was unaffected by enrollment in MIDAS.

Risk Stratification Strategies

The unstructured assessment consisted of a 5-point Likert scale of ACS probability completed by the physician at subject enrollment. Low-risk was defined by an ACS probability score of 1 and negative troponin results at 0 and 3 hours. High risk was defined by a Likert score of >2 , or a troponin level >0.05 ng/ml at 0 or 3 hours. Timepoints of 0 and 3 hours were used because contemporary troponin assays identify most patients with acute myocardial infarction within 3 hours of ED arrival.[10, 12, 13]

While all five elements of the NACPR were collected in MIDAS (Figure 1), adaptations were required to calculate the NACPR for this study. In MIDAS, ECG interpretation was determined by the site investigator as “consistent with ACS”, “not consistent with ACS”, or “unchanged from prior.” The NACPR ECG variable “acute ischemic ECG changes” was defined from MIDAS as an investigator determination of an ECG “consistent with ACS.” A “history consistent with ACS” was defined as an ACS probability Likert score of >2 . In MIDAS, known coronary disease was determined by the site investigator through record review or patient self-report. As in the NACPR derivation study, we used age >50 years as a cut-point [7]. We considered, patients with any high risk category in the NACPR, including a troponin level >0.05 ng/ml at 0 or 3 hours, as high risk. Our serial troponin measurements differed from the NACPR derivation study, which used 0 and 6 hour timepoints. A sensitivity analysis was performed adding a 6-hour serial troponin measure [7].

Elements of the HEART score also were collected in MIDAS (Figure 1), but again adaptations were required. To determine the history component, a MIDAS ACS probability Likert score of 1 was defined as slightly suspicious (0 points for the HEART score), 2 as moderately suspicious (1 point), and >3 as highly suspicious (2 points). An ECG interpretation “consistent with ACS” by a MIDAS investigator was given 2 points for the HEART score ECG component, while a MIDAS interpretation of “unchanged from prior” or “not consistent with ACS” was given 0 points. Risk factors included in the HEART score were available from MIDAS data, except for family history. HEART scores were calculated for each study participant. Low-risk was defined as a HEART score of 0 to 3 with negative 0 and 3 hour troponin measures; high risk was defined as a HEART score of >4 , or any positive troponin result [8, 14]. Risk stratification definitions described above were determined *a priori* and scores were determined blinded to patient outcomes.

Venous blood samples were collected, as part of MIDAS, in ethylene diamine tetraacetic acid and the plasma stored at -80 C within 1 hour of collection. Troponin measures for the risk stratification strategies were performed centrally using the Triage Cardio3 TnI point of care platform (Alere, Waltham, MA) [15]. The reference value for this assay was determined using banked plasma samples from healthy controls. The 99th percentile TnI reference value for the Cardio3 TnI assay is <0.05 ng/ml, and has a coefficient of variation of 16.7% at this cutpoint [16]. A negative troponin result was defined as <0.05 ng/ml, and positive as ≥ 0.05 ng/ml. Local investigators were blinded to these troponin results and they were not used to determine clinical outcomes.

Outcomes

Results from clinical care, record review, and follow-up (e.g. ECG, local biomarker, objective cardiac testing, or cardiac catheterization results) were used by site investigators to determine gold standard clinical outcomes. Our primary outcome was rate of ACS within 30 days of presentation, defined as the composite of cardiac death, acute myocardial infarction (AMI), and unstable angina (UA). The definition of ACS and its components were based on the standardized reporting guidelines for studies evaluating risk stratification of Emergency Department patients with potential acute coronary syndromes [5]. In MIDAS, AMI was

determined by site-adjudicated diagnosis performed locally by study investigators based on cardiac diagnostics and troponins performed as routine care. The number of troponins obtained for the site-adjudicated diagnosis was based on the local standard of care. Central biomarker testing was not used by site investigators in outcome adjudication. The protocol-specified definition of AMI was a typical rise and gradual fall of troponin with at least one of the following: ischemic symptoms, development of pathological ECG Q waves, ECG changes indicative of ischemia, or coronary revascularization. An *a priori* decision was made to include all patients with an adjudicated diagnosis of AMI in this analysis regardless of type: ST-segment elevation AMI (STEMI) or non-ST-segment elevation AMI (NSTEMI). Although most patients with a STEMI do not provide a diagnostic or disposition dilemma to emergency physicians, we decided to include patients with STEMI, because some present atypically or without ST-elevation on the initial ECG.

UA was defined by ischemia confirmed by ECG ST-segment changes with recurrent symptoms or a troponin elevation that did not meet AMI criteria and required either >70% coronary stenosis on coronary angiography, or inducible ischemia with stress testing if cardiac catheterization was not performed. This definition of UA is compliant with the standardized reporting guidelines [5]. Determination of the primary outcome was performed locally by hospital record review and structured telephone interviews occurring at 30 days following the index visit +2 days, consistent with standardized reporting guidelines for ED ACS risk stratification studies [5]. A patient was identified for early discharge if they were low-risk by a decision rule and had negative troponins at 0 and 3 hours. This identified a population for each clinical decision rule that could have been discharged from the ED or Observation Unit without objective cardiac testing.

Statistical Methods

Univariate logistic regression was used to model the relationship between risk stratification strategy and ACS at 30 days. The percentage of patients identified for early discharge and sensitivity for ACS was calculated for each strategy. The sensitivity of serial troponin results at 0 and 3 hours used alone (without a decision rule) was calculated to determine the incremental value of a clinical decision rule when added to serial troponin testing. C-statistics were used to evaluate and compare the clinical utility of each strategy using the method of Hanley and McNeil [17, 18].

Net Reclassification Improvement (NRI) was calculated for each pairwise comparison of risk stratification strategies. Results from each risk stratification strategy were used to classify patients as high or low-risk. The NRI was calculated based on each rule's ability to increase the proportion of high-risk patients experiencing ACS and decrease the proportion of low-risk patients experiencing ACS [18, 19].

Sensitivity analyses were performed to assess the impact of changing the definition of a low-risk ACS probability Likert score, missing data, and adding a serial 6-hour troponin measure. In the first sensitivity analysis, low-risk for the unstructured assessment and the history component of the NACPR were changed from a Likert score of 1 to a score of <2. A slightly suspicious HEART score history (0 points) was modified (from a Likert score of 1) to a score of <2, a moderately suspicious history (1 point) was changed to a score of 3, and a highly suspicious history (2 points) was changed to a score of >4. The impact of missing data was assessed using simple random selection imputation based on variable frequencies in the complete data set. For example, assessment for diabetes was incomplete in 33 patients and the rate of diabetes in the complete data set was 27%, therefore diabetes was randomly assigned to 9 of the 33 patients with missing data. Family history was imputed with simple random selection using a 30% positive family history rate, due to similar rates in the literature [8]. The impact of combining serial troponins at 0, 3, and 6 hours with each

decision rule was assessed by classifying patients as high risk if they had a positive troponin at any serial measurement or were high risk by a decision rule. Statistical analysis was performed using SAS 9.2 (Cary, North Carolina).

Results

From 12/2006-9/2007, 1107 patients with symptoms of suspected ACS were enrolled. Due to incomplete troponin data, 102 were excluded, leaving 1005 patients for analysis (Figure 2). Assessment for 30 day ACS was complete for 98% (988/1005) with their characteristics and outcomes summarized in Table 1. Most patients, 89.5% (899/1005), were admitted or received objective cardiac testing. Discharge from the ED without objective cardiac testing occurred in only 7.2% (72/1005) of the cohort. An ACS event at index visit or within 30 days occurred in 22% (222/1005) of the cohort.

The unstructured assessment identified 13.5% (95%CI 11.5-16%) of patients for early discharge without objective cardiac testing. In comparison, the NACPR identified 4% (95% CI 3-6%) and the HEART score identified 20% (95% CI 18-23%) for early discharge. All three risk stratification strategies had high sensitivities with point estimates missing less than 1% of ACS events. The 95% confidence interval for missed ACS rate remained below 1% for the NACPR and HEART score strategies, but exceeded 1% for the unstructured assessment. The sensitivity for the unstructured assessment was 98% (95%CI 95-99%) compared to 100% (95%CI 98-100%) for the NACPR and 99% (95%CI 97-100%) for the HEART score. The sensitivity of serial troponins used alone, without a decision rule, was only 56% (95%CI 49-62%). The initial troponin was positive in 34% (75/222) of the patients with 30 day ACS events. The 3 hour troponin picked up an additional 49 patients for a total of 56% (124/222) of ACS patients. The addition of a serial 3 hour troponin to the unstructured assessment and HEART score resulted in the identification of 1 patient with ACS that would have been missed using the decision rules with a single troponin measurement. See Table 2 for the performance characteristics of each risk stratification strategy. Frequencies for the determinants of each risk stratification strategy are presented in the Table 3.

Comparing the HEART score strategy to the unstructured or NACPR strategies resulted in a net reclassification improvement (NRI) of 10% (95% CI 8-12%) and 19% (95% CI 17-21%) respectively. The NACPR compared to the unstructured assessment resulted in an NRI of -9% (95% CI -10, -8%). A summary of c-statistics and net reclassification improvement for the various risk stratification strategies is presented in Table 4. A summary of missed events is presented in Table 5 and Figure 3.

The sensitivity analysis changing the low-risk ACS probability definition from a Likert score of 1 to <2 increased the number of patients identified for early discharge by the NACPR (8.5%, 95% CI 7-10%) and HEART score (30%, 95% CI 27-33%) while decreasing sensitivity (99.6%, 95% CI 97.5-100% and 98%, 95% CI 95-99%, respectively). The sensitivity analysis for missing data demonstrated that absent data had little impact on the performance of the risk stratification strategies (Appendix 1). Adding a 6-hour serial troponin measure to the risk stratification strategies resulted in the identification of one additional ACS event at 30 days for the unstructured assessments and the HEART score (Appendix 2).

Discussion

This analysis suggests that an unstructured assessment, NACPR, and HEART score, combined with 0 and 3 hour troponin measurements, can identify ED patients with acute

chest pain for early discharge while retaining an acceptable ACS miss rate (below 1%). These findings have added impact as these rules were applied to a cohort identified by their physicians as requiring objective cardiac testing. In fact, nearly 90% of this cohort were either admitted or received objective cardiac testing prior to discharge. While all risk stratification strategies would have resulted in a 30 day adverse event rate of less than 1%, the unstructured assessment had an upper bound of the 95% confidence interval exceeding 1%, suggesting that the HEART score and NACPR may provide greater safety.

Combining clinical decision rules with serial troponin measurement appears to be a key to successful risk stratification. Prior attempts to define a very low-risk cohort based on a single troponin measurement have had varying success highlighting the importance of serial measurements to maximize sensitivity [9, 20]. Recently the ASia-Pacific Evaluation of Chest pain Trial (ASPECT) demonstrated that with serial cardiac biomarkers, a very low adverse event rate can be achieved [6]. Similarly, we reported that adding a second troponin measurement to the HEART score resulted in a 0% miss rate in a low-risk cohort designated for observation unit care [9]. Findings from this MIDAS analysis are consistent with these previous studies. Furthermore, this analysis demonstrates the value of adding a clinical decision rule to serial troponins. Serial troponins at 0 and 3 hours had a sensitivity of 56% and would have missed 98 patients with ACS at 30 days. The addition of a decision rule resulted in an absolute increase in sensitivity of 42-44% for 30 day ACS.

High sensitivities for ED chest pain risk stratification strategies often comes at the expense of identifying patients for early discharge. Maximizing sensitivity results in many false-positive cases (patients identified as high risk without an event at 30 days) and low numbers of true negatives (patients identified as low-risk without an event at 30 days). For example, ASPECT reported sensitivity above 99%, but identified fewer than 10% of patients for early discharge without objective cardiac testing [6]. The derivation study of the NACPR reported a sensitivity of 100% and identified 18% for early discharge [7]. The results are less impressive when considering that NACPR and ASPECT enrolled patients at all risk levels, including those at very-low-risk for ACS, who would have been identified for discharge with or without the use of a decision rule. In contrast, MIDAS eligibility criteria required patients identified by their providers as needing objective cardiac testing. As a result, most very-low-risk patients were not included (22% event rate). Previous ED risk stratification studies have reported rates of 5-18% [6-8, 20, 21].

We identified fewer patients for early discharge by the NACPR rule than in its derivation publication. This difference may be explained by inclusion of very-low-risk patients in the earlier study, or differences in primary outcome measures. The NACPR derivation study's primary outcome was major adverse cardiac events (MACE) at 30 days; a composite endpoint of death, AMI, and coronary revascularization. In this analysis, the primary outcome was ACS at 30 days, defined by cardiac death, AMI, or UA. Including UA as an outcome reflects the concept that failure to identify those at high risk for future events is a lost opportunity to initiate therapy [22].

In this analysis, the HEART score identified a much larger group of patients for early discharge than the NACPR or unstructured assessment. The ability of the HEART score to identify 20% of patients for early discharge would reduce costs, radiation exposure, and decrease false positive and non-diagnostic testing [1]. In addition, the HEART score combined with two troponin assays has now demonstrated a miss rate of 0% and 0.2% in two separate analyses with over 2000 patients [9]. Considering these findings with results of the HEART score derivation and validations performed in Europe using a single troponin assessment, the HEART score appears sufficiently safe and effective to warrant prospective validation.

Study Limitations

This cohort consists of ED patients from tertiary referral centers with a planned objective cardiac evaluation, and represents a higher risk group than an undifferentiated chest pain population. However, patients at lower risk than these probably would have even fewer adverse events, suggesting that our protocol would safely identify more ED patients for early discharge, as found in a previous analysis [9]. The NACPR and HEART score were not tested exactly as originally derived due to limitations of available data; however, our sensitivity analyses suggest that this had little impact on our findings. Limited data also prevented inclusion of TIMI and ADAPT in this analysis. The central troponin assay used in the clinical decision rules was not a high sensitivity assay. Nonetheless, clinical decision rules used with serial troponin measures achieved high sensitivity for detection of ACS at 30 days. MIDAS was conducted before widespread adoption of high-sensitivity troponin assays; thus, occurrence of AMI in MIDAS is based on conventional troponin assay results. Smaller troponin elevations probably were not identified as AMI. However, because nearly the entire cohort received objective cardiac testing, many of these patients likely were diagnosed with UA and still considered to have ACS. The performance of these decision rules combined with the highest sensitivity troponin assays would likely maintain a high sensitivity for ACS, but the impact on the identification of patients for early discharge is unknown. Finally, our primary outcome measure, ACS during index visit or within 30 days, was adjudicated at each site, so inconsistencies may have occurred. Variability was minimized by using objective definitions of outcomes and site monitoring visits.

Performance of local adjudication of cardiovascular events was comparable to central adjudication in an earlier report [23]. Furthermore, local adjudication to determine clinical outcomes at multiple sites using local data such as ECGs, biomarkers, and objective cardiac testing adds external validity to the results.

Conclusions

The HEART score combined with serial troponins identified a substantial number of patients for early discharge with a low missed ACS rate. Use of a structured clinical ACS risk assessment combined with two troponin results is highly sensitive for the detection of ACS. The HEART score plus serial troponins could improve efficiency and quality of chest pain care in the ED. A prospective study of the implementation of the HEART score and serial troponins is warranted.

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APPENDIX 1

Sensitivity Analyses 1 & 2.

Analysis	Risk Stratification Strategy	Early Discharge (95% CI)	Sensitivity (95% CI**)	-LR (95% CI)	AUC (95% CI)	NRI (95% CI)	NRI (95% CI)	Missed ACS Rate (95% CI)
Primary	Unstructured	13.5% (11.5-15.8%)	97.7% (94.7-99.2%)	0.14 (0.06-0.33)	0.57 (0.56-0.59)	Reference	-8.8% (-10.7,-7.2%)	0.5% (0.2-1.2%)
	NACPR	4.4% (3.3-5.7%)	100% (98.0-100%)	0 (0-0.55)	0.53 (0.52-0.54)	-8.8% (-10.7,-7.2%)	Reference	0.0% (0-0.5%)

Analysis	Risk Stratification Strategy	Early Discharge (95% CI)	Sensitivity (95% CI**)	-LR (95% CI)	AUC (95% CI)	NRI (95% CI)	NRI (95% CI)	Missed ACS Rate (95% CI)
	HEART	20.2% (17.8-22.8%)	99.1% (96.5-100%)	0.04 (0.01-0.14)	0.62 (0.61-0.64)	9.6% (7.9,11.6%)	18.9% (16.4, 21.2%)	0.2% (0-0.8%)
Low-risk ACS Probability Likert Score changed to 2 or less	Unstructured	29.6% (26.8-32.5%)	94.6% (90.7-96.7%)	0.15 (0.09-0.26)	0.66 (0.64-0.68)	Reference	-20.8% (18.2,23.2%)	1.2% (0.7-2.1%)
	NACPR	8.5% (6.9-10.4%)	99.6% (97.5-100%)	0.04 (0.01-0.30)	0.55 (0.54-0.56)	-20.8% (18.2,23.2%)	Reference	0.1% (0-0.6%)
	HEART	30.1% (27.3-33.0%)	98.2% (95.4-99.3%)	0.05 (0.02-0.13)	0.68 (0.66-0.70)	4.3% (3.25.8%)	25.7% (23.1,28.5%)	0.4% (0.1-1.1%)
Simple Random Selection Imputation	Unstructured	13.5% (11.5-15.8%)	97.8% (94.8-99.0%)	0.14 (0.06-0.33)	0.57 (0.56-0.59)	Reference	-8.8% (-10.7,-7.2%)	0.5% (0.2-1.2%)
	NACPR	4.4% (3.3-5.7%)	100% (98.0-100%)	0 (0-0.55)	0.53 (0.52-0.54)	-8.8% (-10.7,-7.2%)	Reference	0.0% (0-0.5%)
	HEART	19.3% (16.9-22.9%)	99.1% (96.8-100%)	0.04 (0.01-0.14)	0.62 (0.60-0.64)	8.7% (7.1,10.6%)	17.9% (15.6,20.4%)	0.2% (0-0.8%)

Changing the low-risk ACS probability Likert score to 2 or less and imputation of missing data using simple random selection. ACS=acute coronary syndrome, -LR=negative likelihood ratio, AUC=area under the curve (c-statistic), NRI=Net Reclassification Improvement, CI=confidence interval, NACPR=North American Chest Pain Rule.

APPENDIX 2

Sensitivity Analysis 3.

Analysis	Risk Stratification Strategy	Early Discharge (95% CI)	Sensitivity (95% CI**)	-LR (95% CI)	NRI (95% CI)	Missed ACS Rate (95% CI)
Primary	Unstructured	13.5% (11.5-15.8%)	97.7% (94.7-99.2%)	0.14 (0.06-0.33)	Reference	0.5% (0.2-1.2%)
6 hour troponin added	Unstructured	9.4% (7.7-11.4%)	98.2% (95.3-99.5%)	0.16 (0.06-0.42)	-4.7% (-6.2,-3.5)	0.4% (0.1-1.1%)
Primary	NACPR	4.4% (3.3-5.7%)	100% (98.0-100%)	0 (0-0.55)	Reference	0.0% (0-0.5%)
6 hour troponin added	NACPR	3.2% (2.3-4.5%)	100% (98.0-100%)	0 (0-0.77)	-1.5% (-2.5,-1.0)	0.0% (0-0.5%)
Primary	HEART	20.2% (17.8-22.8%)	99.1% (96.5-100%)	0.04 (0.01-0.14)	Reference	0.2% (0-0.8%)
6 hour troponin added	HEART	14.5% (12.4-16.8%)	99.6% (97.2-100%)	0.03 (0.0-0.18)	-6.7% (-8.5,-5.4%)	0.1% (0.0-0.6%)

Comparison of decision rules combined with 0 and 3 hour serial troponins versus 0, 3, and 6 hour serial troponins. ACS= acute coronary syndrome, -LR= negative likelihood ratio, NRI= Net Reclassification Improvement, CI=confidence interval, NACPR= North American Chest Pain Rule.

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HEART Score		Points
History	Highly Suspicious	2
	Moderately Suspicious	1
	Slightly Suspicious	0
ECG	Significant ST-depression	2
	Non-specific repolarization abnormality	1
	Normal	0
Age	≥ 65	2
	45-65	1
	< 45	0
Risk factors	3 or more risk factors	2
	1-2 risk factors	1
	No risk factors	0
Troponin	≥ 3x normal limit	2
	1-3x normal limit	1
	≤ normal limit	0
Total		

North American Chest Pain Rule		
High risk criteria	Yes	No
Age ≥ 50		
Acute ischemic ECG changes		
Known coronary disease		
Pain typical for ACS		
Any troponin > 99 th percentile		

Figure 1.

The North American Chest Pain Rule (NACPR) and the HEART score. NACPR: a patient is considered low-risk if they have none of the high risk criteria. The HEART score: Low-risk= 0-3, High risk= 4 or greater. Risk factors include currently treated diabetes mellitus, current or recent (<90 days) smoker, diagnosed and/or treated hypertension, diagnosed hypercholesterolemia, family history of coronary artery disease, obesity (body mass index >30), or a history of significant atherosclerosis (coronary revascularization, myocardial infarction, stroke, or peripheral arterial disease). ECG = electrocardiogram, ACS = acute coronary syndrome.

Figure 2.
Study flow diagram: numbers of patients enrolled, excluded, and with complete data.
MIDAS= Myeloperoxidase In the Diagnosis of Acute coronary syndromes Study,
NACPR=North American Chest Pain Rule.

Figure 3. Number of ACS events at 30 days. AMI, unstable angina, and cardiac deaths, missed by each risk stratification strategy. ACS = acute coronary syndrome, AMI= acute myocardial infarction.

Table 1

MIDAS patient characteristics and 30-day outcomes.

Patient Characteristics	Number (n = 1005)	Percent
<u>Age</u> —mean $\pm$ SD	58.1 $\pm$ 13.4	
<u>Gender</u>		
Male	545	54.2%
Female	460	45.8%
<u>Ethnicity</u>		
Caucasian	676	67.3%
African American	256	25.5%
Hispanic	55	5.5%
Other	18	1.8%
<u>Risk Factors</u>		
Hypertension	678	67.5%
Smoking	282	28.1%
Hyperlipidemia	574	57.1%
Diabetes	270	26.9%
Obesity (BMI>30)	425	42.3%
Known coronary disease	429	42.7%
<u>Objective Cardiac Testing</u>		
Nuclear imaging	302	30.0%
Exercise ECG	156	15.5%
Dobutamine stress echocardiogram	81	8.1%
CMR	11	1.1%
CCTA	47	4.7%
Angiography	258	25.6%
<u>Disposition</u>		
Hospital admission	660	65.7%
Discharged	311	30.9%
Discharged without objective testing	72	7.2%
Discharged after objective testing	239	23.8%
AMA/ Unknown/Other	34	3.4%
<u>Outcomes at 30 Days</u>		
Non-Cardiac chest pain	731	72.7%
Pulmonary Embolism	6	0.6%
Aortic Dissection	2	0.2%
Stable Angina	43	4.3%
PCI (without AMI or UA)	3	0.3%
Non-Cardiac death	1	0.1%
Acute Coronary Syndrome	222	22.1%
Cardiac death	6	0.6%
AMI	107	10.6%

Patient Characteristics	Number (n = 1005)	Percent
STEMI	28	2.7%
NSTEMI	79	7.9%
With revascularization	54	5.4%
PCI	42	4.2%
CABG	12	1.2%
Unstable Angina	109	10.8%
With revascularization	57	5.7%
PCI	45	4.5%
CABG	11	1.1%
70% coronary stenosis on angiography	81	8.1%
Inducible ischemia nuclear imaging	23	2.3%
Inducible ischemia dobutamine stress echocardiogram	2	0.2%
Inducible ischemia exercise ECG	3	0.3%

SD= standard deviation, BMI= body mass index, ECG = electrocardiogram, CMR= cardiac magnetic resonance imaging, CCTA= coronary computed tomography angiography, AMA = against medical advice, AMI= acute myocardial infarction, PCI = percutaneous coronary intervention, CABG= coronary artery bypass graft.

Table 2

Test characteristics of the risk stratification strategies for detection of acute coronary syndrome (ACS) at 30 days.

Risk Stratification Strategy	30 Day ACS		Total (n)		
	Yes (n)	No (n)			
Unstructured High Risk	217	648	865		
Unstructured Low-risk	5	130	135		
Total (n)	222	778	1000		
NACPR High Risk	222	736	958		
NACPR Low-risk	0	44	44		
Total (n)	222	780	1002		
HEART High Risk	218	573	791		
HEART Low-risk	2	198	200		
Total (n)	220	771	991		
Risk Stratification Strategy	Early Discharge (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	-LR (95% CI)	AUC (95% CI)
Unstructured	13.5% (11.5-15.8%)	97.7% (94.7-99.2%)	16.7% (14.3-19.5%)	0.14 (0.06-0.33)	0.57 (0.56-0.59)
NACPR	4.4% (3.3-5.7%)	100% (98.0-100%)	5.6% (4.2-7.5%)	0 (0-0.55)	0.53 (0.52-0.54)
HEART	20.2% (17.8-22.8%)	99.1% (96.5-100%)	25.7% (22.7-28.9%)	0.04 (0.01-0.14)	0.62 (0.61-0.64)

The number of patients with and without ACS identified as high and low-risk by the risk stratification strategies, the percentage identified for early discharge, sensitivity, specificity, negative likelihood ratio, and area under the curve. n= number, -LR= negative likelihood ratio, AUC= area under the curve (c-statistic). NACPR= North American Chest Pain Rule.

Table 3

Frequency of risk stratification strategy determinants in the MIDAS cohort.

Risk Stratification Strategy	Number (n = 1005)	Percent
<u>Unstructured Assessment</u>		
ACS probability		
1 lowest probability	176	17.5%
2	211	21.0%
3	285	28.3%
4	198	19.7%
5 highest probability	128	12.7%
Missing	7	0.7%
Unstructured & Serial Troponin		
Low-risk	135	13.4%
High risk	865	86.1%
Incomplete	5	0.5%
<u>North American Chest Pain Rule</u>		
Age >50	709	70.6%
ECG changes consistent with ACS	218	21.7%
Known Coronary Disease	429	42.7%
History Consistent with ACS	822	81.8%
Positive Serial Troponin	290	28.9%
Total NACPR		
Low-risk	44	4.4%
High Risk	957	95.3%
Incomplete	3	0.3%
<u>HEART Score</u>		
History		
Slightly Suspicious	176	17.5%
Moderately Suspicious	211	21.0%
Highly Suspicious	611	60.8%
Age		
65	305	30.4%
45-65	514	51.1%
45	186	18.5%
ECG changes consistent with ACS	218	21.7%
Number of Risk Factors		
0	82	8.2%
1-2	320	31.8%
3 or more	603	60.0%
Initial troponin		
Negative	900	89.6%
1-3 x normal limit	32	3.2%

Risk Stratification Strategy	Number (n = 1005)	Percent
>3 x normal limit	73	7.3%
Total HEART Score		
0	4	0.4%
1	48	4.8%
2	83	8.3%
3	111	11.0%
4	197	19.6%
5	239	23.8%
6 or greater	306	30.4%
Incomplete	17	1.7%
HEART Score & Serial Troponin		
Low risk	200	19.9%
High risk	791	78.7%
Incomplete	14	1.4%

ACS=acute coronary syndrome, ECG=electrocardiogram, NACPR= North American Chest Pain Rule

Table 4

Net Reclassification Improvement (NRI) and comparison of each strategy's receiver operator characteristics (ROC) for 30 day ACS.

Risk Stratification Strategy	Reclassification of true positive ACS; n (%)	Reclassification of true negative ACS; n (%)	NRI (95% CI)	p value	Change in C-Statistic (95% CI)	p value
Unstructured (reference)	-----	-----	-----	-----	-----	-----
NACPR	5 (2.3%)	-86 (-11.1%)	-8.8% (-10.7, -7.2%)	<0.0001	-0.05 (-0.06, -0.03)	<0.0001
HEART	2 (0.9%)	67 (8.7%)	9.63% (7.9, 11.6%)	<0.0001	0.05 (0.03, 0.07)	<0.0001
Risk Stratification Strategy						
NACPR (reference)	-----	-----	-----	-----	-----	-----
HEART	-2 (-0.9%)	152 (19.8%)	18.86% (16.4, 21.2%)	<0.0001	0.09 (0.08, 0.11)	<0.0001

A comparison of each risk stratification strategy using net reclassification improvement and c-statistic change. n= number, NRI=net reclassification improvement, ACS= acute coronary syndrome, NACPR= North American Chest Pain Rule.

Table 5

Characteristics of patients with missed ACS.

Missed ACS	Age	Sex	Race	CAD history	0 hour troponin	3 hour troponin	Objective Cardiac Testing	ACS
Unstructured Assessment	91	Male	Caucasian	CABG	0.02	0.02	None	NSTEMI
	46	Male	Caucasian	4 Stents, AMI	0.0	0.0	Positive nuclear stress test	UA
	82	Female	Caucasian	AMI	0.0	0.0	Positive adenosine stress test	UA
	66	Male	Caucasian	None	0.0	0.0	Positive dobutamine stress test	UA
	50	Male	Caucasian	AMI	0.0	0.0	Positive nuclear stress test	UA
HEART score	46	Male	Caucasian	None	0.0	0.0	Negative exercise ECG stress test at index visit. 100% occlusion of OMI on coronary angiogram during rehospitalization.	STEMI, V-fib arrest, PCI in 30 day follow-up period.
	42	Male	Caucasian	None	0.0	0.0	Positive exercise ECG stress test. Patient refused index coronary angiogram.	UA

Characteristics of the 5 patients with missed ACS by the unstructured assessment and the 2 patients with missed ACS by the HEART score. ACS=acute coronary syndrome, CAD= coronary artery disease, CABG= coronary artery bypass graft, NSTEMI=Non ST-elevation Myocardial Infarction, AMI= acute myocardial infarction, PCI = percutaneous coronary intervention, CABG= coronary artery bypass graft, UA= unstable angina, STEMI= ST-elevation myocardial infarction, ECG = electrocardiogram