Application of the TIMI Risk Score for Unstable Angina and Non-ST Elevation Acute Coronary Syndrome to an Unselected Emergency Department Chest Pain Population

Charles V. Pollack Jr., MA, MD, Frank D. Sites, RN, Frances S. Shofer, PhD, Keara L. Sease, MAEd, Judd E. Hollander, MD

Abstract

Objectives: Patients presenting with chest pain or related symptoms suggestive of myocardial ischemia, without ST-segment elevation (NSTE) on their presenting electrocardiograms, often present a diagnostic challenge in the emergency department (ED). Prompt and accurate risk stratification to identify those patients with NSTE chest pain who are at highest risk for adverse events is essential, however, to optimal management. Although validated and used frequently in patients already enrolled in acute coronary syndrome trials, the Thrombolysis in Myocardial Infarction (TIMI) risk score never has been examined for its value in risk stratification in an all-comers, non–trial-based ED chest pain population.

Methods: An analysis of an ED-based prospective observational cohort study was conducted in 3,929 adult patients presenting with chest pain syndrome and warranting evaluation with an electrocardiogram. These patients had TIMI risk scores determined at ED presentation. The main outcome was the composite of death, acute myocardial infarction (MI), and revascularization within 30 days.

Results: The TIMI risk score at ED presentation successfully risk-stratified this unselected cohort of chest pain patients with respect to 30-day adverse outcome, with a range from 2.1%, with a score of 0, to 100%, with a score of 7. The highest correlation of an individual TIMI risk indicator to adverse outcome was for elevated cardiac biomarker at admission. Overall, the score had similar performance characteristics to that seen when applied to other databases of patients enrolled in clinical trials and registries using a 14-day end point.

Conclusions: The TIMI risk score may be a useful tool for risk stratification of ED patients with chest pain syndrome.

ACADEMIC EMERGENCY MEDICINE 2006; 13:13–18 © 2006 by the Society for Academic Emergency Medicine

Keywords: acute coronary syndrome, complications, risk stratification, emergency department, TIMI risk score, chest pain

Risk stratification for patients who present to the emergency department (ED) with chest pain syndromes, in the absence of diagnostic electrocardiographic (ECG) findings, remains an inexact science. Clinical acumen, ECG results, and biomarker assays generally may be helpful, but in the ED, 2% to 5% of patients with myocardial infarction (MI) still go undetected.[1] Quick and accurate risk stratification of chest pain patients in the ED is essential to evidence-based initiation of early, aggressive medical and interventional management of non–ST-segment-elevation (NSTE) acute coronary syndrome (ACS).[2]

Across populations of patients, risk in patients presenting with unstable angina and NSTEMI has been assessed by using multivariable regression techniques in several large clinical trials. These models have not yet been validated in large prospective studies of NSTE ACS patients. Boersma et al.[3] analyzed the connection between baseline characteristics and the incidence of death and death-plus-myocardial (re)infarction at 30 days. The

From the Department of Emergency Medicine, Pennsylvania Hospital and Hospital of the University of Pennsylvania, University of Pennsylvania Health System (CVP, FDS, FSS, KLS, JEH), Philadelphia, PA.

Received November 9, 2004; revision received April 25, 2005; accepted June 3, 2005.

Address for correspondence and reprints: Charles V. Pollack, Jr., MD, Chairman, Department of Emergency Medicine, Pennsylvania Hospital, 800 Spruce Street, Philadelphia, PA 19107. Fax: 215-829-8044; e-mail: pollackc@pahosp.com.

doi: 10.1197/j.aem.2005.06.031
ISSN 1069-6563
PII ISSN 1069-6563583

most important baseline features associated with death in that analysis were age, heart rate, systolic blood pressure, ST-segment depression, signs of pump failure, and elevated levels of biomarkers. A risk estimation score was developed from this analysis, but its complexity renders it largely unsuitable for bedside use in the ED.

A simpler approach, more amenable to typical ED practice, recently was published by Antman et al.[4] The Thrombolysis In Myocardial Infarction (TIMI) Investigators developed a seven-point risk score (Table 1) that was validated as being predictive of the risk of developing an adverse cardiac outcome (death, [re]infarction, or recurrent severe ischemia requiring revascularization) within 14 days of presentation for patients with unstable angina or NSTEMI. The *TIMI risk score,* defined as the number (zero to seven) of positive individual variables, relates to a risk of adverse outcomes ranging from approximately 5% to 41% when applied retrospectively to patients studied in large NSTE ACS trials.[4] The score was derived from data in the TIMI 11B trial[5] and has been validated in retrospective analyses of five additional large registries and trials: ESSENCE,[6,7] TACTICS-TIMI 18,[8] PRISM-PLUS,[9,10] TIMI-III,[11,12] and CURE.[13,14] The TIMI risk score is of potential interest even beyond simple prognostication of outcomes because it also appears to be predictive of increasing benefit from specific therapies as risk increases.[4,8,10] It was developed from the retrospective analysis of a relatively high-risk NSTE ACS randomized clinical trial and therefore may not be appropriate for use in screening an unselected ED chest pain population, in which the aggregate cardiac risk would be expected to be significantly lower. Despite this concern, the score has been recommended as a potential screening tool in just such a population.[2,15] We therefore sought to determine the applicability of this instrument to an unselected ED chest pain population, in terms not only of predicting adverse events over the ensuing 30 days but also of predicting the benefit of specific management strategies. If it could accurately risk-stratify patients at the time of initial ED evaluation, it potentially could be used as a tool to assist triage or disposition decisions.

Table 1
The TIMI Risk Score Uses Patient Data Typically Available in the ED to Determine Relative Risk

Age > 65 yr
Documented prior coronary artery stenosis > 50%*
Prior cardiac catheterization with known disease
Prior angioplasty or stent
Prior bypass (CABG)
Documented prior myocardial infarction
Three or more conventional cardiac risk factors
Hypertension
Diabetes
Cholesterol elevation
Family history CAD/MI
History of tobacco use
Use of aspirin in the preceding 7 days
Two or more anginal events in the past 24 hours†
ST-segment elevation or depression > 1 mm
Elevated cardiac biomarkers

Derived[4] from the TIMI-11B study,[5] the score is additive without weighting (0–7).
* This parameter was expanded to be useful in the ED by applying the listed proxies, because actual cardiac catheterization results are usually not available in the study ED.
† The TIMI 11B study defined one form of severe angina as two or more anginal events in the past 24 hours. We had not begun data collection with this discrete data point; therefore we also used a difference in duration of time of the most recent episode of chest pain and the time from onset of first episode of chest pain to ED presentation as meeting this criteria. Differences suggest that more than one episode of chest pain occurred.

METHODS

Study Design

This was a secondary analysis of a prospective observational cohort study that was designed to evaluate several risk stratification algorithms and biochemical tests for ED chest pain patients. The University of Pennsylvania Committee on Research Involving Human Subjects approved the study.

Study Setting and Population

The study setting was the ED of an urban tertiary care center with an annual adult patient visit census of approximately 51,000. There is no chest pain evaluation center at this institution. The institution sponsors an accredited emergency medicine residency (PGY 1–4) with a current resident complement of nine per year. Every patient in the department is evaluated by an attending emergency physician before disposition.

A convenience sample of patients older than 24 years of age who presented to the ED between July 9, 1999 and March 31, 2002 with chest pain syndrome and who received an electrocardiogram (ECG) were included. Patients younger than 24 years of age were included only if they had used cocaine in the week before presentation. ECGs and serum biomarkers were obtained in an assessment for possible myocardial ischemia at the discretion of the treating physician independent of and before study enrollment. Patients with ischemic ST segment elevation that was not known to be old were excluded, because the TIMI risk score was not designed for use in this population and these patients readily are identified as high risk during their initial evaluation. Eligible patients were identified by trained research assistants, who were present in the ED 16 hours per day, seven days per week. During these hours, patients were enrolled consecutively.

Measurements

Patients underwent a structured history and physical examination at the time of initial presentation to the ED. The treating physician recorded these clinical data on a data collection instrument that included the components of the TIMI risk score at presentation (Table 1). An initial ECG was obtained at the time of presentation. The treating emergency physician determined patient disposition. In lieu of retrospective medical record review to obtain clinical course information, admitted patients were followed daily throughout their hospital course by a member of the investigative team. All patients were contacted 30 days after presentation for follow-up. Patients or their proxies were queried about death, MI, and revascularization during the 30-day period.

Main Outcomes

The main outcome was the composite of death, MI, and coronary revascularization (percutaneous coronary intervention [PCI] and coronary artery bypass surgery [CABG]) within 30 days of the index ED presentation. The final diagnosis of in-hospital MI was based on the clinical presentation, serial ECGs, and serial biomarker analysis (CK-MB and cardiac troponin I) in the hospital's clinical laboratory according to European Society of Cardiology–American College of Cardiology criteria.[16]

Data Analysis

Data were entered into a Microsoft Access 97 database (Microsoft, Redmond, WA) and were imported into SAS 9.0 (SAS Institute, Cary, NC) for statistical analysis. Continuous data are presented either as means with SDs or as medians, based on the distribution of the data. Categorical data are presented as the percentage frequency occurrence. The relationship between TIMI risk score and the triple composite outcome was analyzed by using chi-square testing and the Cochran-Armitage trend test.

RESULTS

During the study period, 3,326 eligible patients presented to the ED for a total of 3,929 visits. Patients' mean (± SD) age was 51.6 (± 15.9) years; 60% were female, and 69% were African American. Patients presented a median of 300 minutes (interquartile range [IQR], 60–1,440 minutes) after symptom onset, and the total duration of symptoms was a median of 120 minutes (IQR, 15–720 minutes). The majority of patients (2,391 [60.9%]) presented with chest pain as their chief complaint. Selected chest pain characteristics, associated symptoms, cardiac risk factors, and medical history are shown in Table 2.

Per the study's inclusion criteria, each patient had at least one ECG. Initial ECGs for the study cohort included ST elevation (deemed not acutely ischemic by the treating physician) in 109 (3%) patients who ultimately did not prove to have STEMI but whose conditions instead were attributed to acute pericarditis or to benign early ventricular repolarization; ST segment depression deemed consistent with acute ischemia in 265 patients (7%); abnormal T-wave inversions in 724 patients (18%); pathological q-waves in 209 patients (5%); left bundle branch block in 72 patients (2%); and right bundle branch block in 104 patients (3%). Presentation ECGs were used to calculate the TIMI risk score.

Of the 3,929 visits analyzed in this study, 2,787 included at least one cardiac biomarker assay. When biomarkers were not obtained, they were assumed to be negative, in keeping with routine clinical practice. Presentation (or the earliest) biomarker results were used to calculate the TIMI risk score.

There were 2,425 patients (56.6%) for whom the disposition was admission to the hospital. The admission location was as follows: ICU, 365 (9%); non-ICU monitored bed, 1,905 (48%); unmonitored bed, 124 (5%); transferred to another institution, 9 (0.2%); directly to cardiac catheterization from the ED, 7 (0.2%); and 2 patients died in the ED. Twelve patients (0.3%) left against medical advice. There were 1,504 patients (38%) discharged to home from the ED.

Table 2
Presenting Characteristics of Patients

Patient Characteristics	*n* (%)
Location of chest pain	
Mid-chest	1,527 (39)
Left chest	1,576 (40)
Other	826 (21)
Associated symptoms	
Dyspnea	1,896 (48)
Diaphoresis	782 (20)
Nausea and vomiting	838 (21)
Dizziness	514 (13)
Weakness	394 (10)
Palpitations	392 (10)
Cardiac risk factors	
Hypertension	1,913 (49)
Diabetes mellitus	705 (18)
Hypercholesterolemia	703 (18)
Tobacco use	1,454 (37)
Cocaine use	85 (2)
Family history	800 (20)
Medical history	
Myocardial infarction	432 (11)
Angina	502 (13)
Congestive heart failure	388 (10)
CAD	761 (19)

During index hospitalization, there were 21 deaths (0.5%), 225 patients with confirmed MI (5.7%), 471 patients diagnosed with unstable angina (12%), and 3,233 without documented ACS (82%).

Thirty day follow-up was available for 98% of the patients in the study. At 30-day follow-up, there were 43 patients who had died. Fifteen patients sustained MI after hospital discharge, 14 patients reported having had PCI after hospital discharge, and 10 patients had undergone CABG after index hospitalization.

The TIMI risk score calculated at the time of ED presentation correlated to the likelihood of adverse outcomes within 30 days (Table 3; chi-square, $p < 0.001$ and Cochran-Armitage trend test, $p < 0.001$). The TIMI risk score also was related to adverse events at shorter time periods, such as in hospital and at 14-day follow-up (data not shown). Table 4 shows the frequency of each individual component of the TIMI risk score, as well the odds ratios (OR) for predicting death, acute myocardial infarction, and revascularization. The OR was greatest for elevated biomarkers (17.9) and for prior revascularization (4.0).

DISCUSSION

Chest pain or anginal equivalent associated with ST-segment elevation on presentation to the ED is readily diagnosed, and hospitals typically have standardized and proscriptive pathways for the management of STEMI patients. Patients with symptoms potentially referable to coronary insufficiency and no evidence of ST-segment elevation on ECG may be more problematic for the emergency physician, who is faced with two important tasks: first, to determine whether or not the symptomatology is truly a result of coronary artery disease and second, if so, to determine the risk of adverse outcomes faced

Table 3
Rates of Mortality, Myocardial Infarction, and Revascularization within 30 Days of Presentation Related to the Number of TIMI Risk Factors

No. of TIMI risk factors	0	1	2	3	4	5	6	7
N	1,388	1,133	607	447	231	102	20	1
30-day death/myocardial infarction/revascularization	29 (2.1%)	57 (5%)	61 (10.1%)	87 (19.5%)	51 (22.1%)	40 (39.2%)	9 (45%)	1 (100%)
95% CI	1.4%-2.8%	3.8%-6.2%	7.8%-12.4%	15.8%-23.2%	16.8%-27.4%	29.7%-48.7%	20.9%-69.1%	NA
Chi-square $p < 0.001$, and Cochran-Armitage trend test $p < 0.001$.								

by that patient over the short term, so that therapy tailored to that level of risk may be initiated promptly and properly.[2] A number of investigators have sought to establish a gradient of risk among patients with NSTE ACS, but the heterogeneous nature of the disease and the wide spectrum of risk for death and cardiac ischemic events reported in studies have limited their success.[17–22] The recent development of evidence-based guidelines for risk-oriented management of NSTE ACS patients actually may cause frustration for clinicians who find risk stratification to be inexact and difficult to protocolize.[2,15]

This frustration may be further compounded for emergency physicians by the absence of a simple risk-stratification instrument amenable to ED practice, where knowledge of patient history may be limited, diagnostic resources may be less accessible than in inpatient settings, and pressure for a rapid and error-free diagnosis and disposition is always present. The TIMI risk score potentially offers an easily applied and objective means of adding quantification to the risk stratification process, of giving emergency physicians, cardiologists, and primary care providers a common language of risk assessment, and of helping direct and focus the intensity of therapy within an ED or hospital protocol for NSTE chest pain care. The TIMI score was developed and validated, however, in a clinical trial population of patients with definite NSTE ACS. Our data show that the TIMI risk score also can be used to risk-stratify a broad ED chest pain patient population. The risk of 30-day adverse events ranged from 2.1%, for patients with a TIMI risk score of 0 or 1, to 45% to 100% for patients with a TIMI risk score of six or seven. The simple application of the scale to clinical factors that routinely are elicited early in the ED evaluation of chest pain patients increases its utility.

Table 4
Odds Ratios for Predicting the 30-Day Triple Composite End Point of Death, Acute Myocardial Infarction, and Revascularization for the Individual Components of the TIMI Risk Score

TIMI Risk Characteristic	*n* (%)	Odds Ratio (95% CI)
Age > 65 yr	901 (23)	3.0 (2.4, 3.8)
Prior stenosis > 50%	860 (22)	4.0 (3.2, 5.1)
≥3 Cardiac risk factors	708 (18)	1.9 (1.5, 2.5)
Aspirin use	923 (23)	2.3 (1.8, 3.0)
≥2 Anginal events every 24 h	1,106 (28)	0.95 (0.73, 1.23)
ST-segment deviation	349 (9)	4.9 (3.7, 6.5)
Elevated biomarkers	402 (10)	17.9 (13.8, 23.3)

It should be noted that the likelihood of an adverse outcome in patients with a TIMI risk score of zero is *not* zero, meaning that disposition and treatment decisions made simply on that basis would not be well advised from the perspective of risk management and sound clinical practice. The TIMI risk score therefore should be used in conjunction with clinical judgment for ED chest pain patient risk stratification. Likewise, as already noted, individual components of the TIMI score carry significant predictive ability on their own; biomarker levels and documented ST-segment changes have very strong prognostic implications independently.[16–22]

LIMITATIONS

Possible limitations in the study include selection and misclassification bias. To reduce the risk of selection bias, the research assistants were present in the ED 16 hours per day, seven days per week, during the study period. Together with the ED staff, they screened all ED patients to identify those being evaluated for potential ACS. Also, all patients with chest pain or similar symptomatology, who had an ECG as part of their ED evaluation, were included in the study. Misclassification bias of important adverse end points was reduced by prospectively following all hospitalized study patients on a daily basis, rather than relying on postdischarge medical record review.

There also is a concern that workup bias may be present. Certain elements of the TIMI risk score do not function independently of clinical decision making. A positive ECG or a positive troponin, for example, may supersede other clinical data in directing a patient toward diagnostic coronary angiography. These elements were part of the instrument that we were evaluating, and this limitation applies to the earlier derivation and validation studies of the TIMI risk score and other risk stratification approaches, as well.

Further, this study was not a strict validation of the TIMI risk score in the manner in which it was derived. Although the instrument has been validated as predictive for 14-day outcomes,[4] we tracked 30-day outcomes, deeming these more important. In fact, we find it reassuring that the test performed well with an extended end point period. It also should be noted that our study was not established for the purpose of validating the TIMI risk score, yet the ease with which we were able to calculate scores at ED presentation confirms the premise that the gathering of information on the individual

components of the TIMI risk score is consistent with sound clinical practice.

Our study population was composed of proportionately more black and female patients than were present in the population on whom the TIMI risk score has been validated. Other studies suggest that these patients are less likely to undergo coronary intervention than white males, which would bias against effective risk stratification for outcomes in our population. Despite this concern, the score did indeed perform well.

CONCLUSIONS

For those patients thought to have a potential ACS, our data suggest that the TIMI risk score may be useful in assessing the likelihood of short-term adverse outcomes in ED patients with chest pain. Likewise, its use may help direct intensity of antithrombotic, antiplatelet, and interventional management for those patients.[2,15] Further work is needed to determine the incremental value of the TIMI score over, or in addition to, clinical judgment in the ED population.

References

1. Dagnone E, Collier C, Pickett W, et al. Chest pain with nondiagnostic electrocardiogram in the emergency department: a randomized controlled trial of two cardiac marker regimens. CMAJ. 2000; 162:1561–6.
2. Pollack CV, Roe MT, Peterson ED. 2002 Update to the ACC/AHA Guidelines for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction: implications for emergency department practice. Ann Emerg Med. 2003; 41:355–69.
3. Boersma E, Pieper KS, Steyerberg EW, et al. The PURSUIT Investigators. Predictors of outcomes in patients with acute coronary syndromes without persistent ST-segment elevation: results for an international trial of 9461 patients. Circulation. 2000; 101:2557–67.
4. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000; 284:835–42.
5. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non–Q-wave myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI) 11B trial. Circulation. 1999; 100:1593–601.
6. Cohen M, Demers C, Gurfinkel EP, et al., for the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events Study Group. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. N Engl J Med. 1997; 337:447–52.
7. Sabatine MS, McCabe CH, Morrow DA, et al. Identification of patients at high risk for death and cardiac ischemic events after hospital discharge. Am Heart J. 2002; 143:966–70.
8. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med. 2001; 344:1879–87.
9. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. N Engl J Med. 1998; 338: 1488–97.
10. Morrow DA, Antman EM, Snapinn S, McCabe CH, Theroux P, Braunwald E. An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes: application of the TIMI risk score for UA/NSTEMI in PRISM-PLUS. Eur Heart J. 2002; 23:223–9.
11. Stone PH, Thompson B, Anderson HV, et al. Influence of race, sex, and age on management of unstable angina and non-Q-wave myocardial infarction: the TIMI III registry. JAMA. 1996; 275:1104–12.
12. Scirica BM, Cannon CP, Antman EM, et al. Validation of the Thrombolysis In Myocardial Infarction (TIMI) Risk Score for unstable angina pectoris and non-ST-segment-elevation myocardial infarction in the TIMI III registry. Am J Cardiol. 2002; 90: 303–5.
13. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001; 345:494–502.
14. Budaj A, Yusuf S, Mehta SR, et al. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. Circulation. 2002; 106:1622–6.
15. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction—2002: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). Circulation. 2002; 106:1893–900.
16. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol. 2000; 36:959–69.
17. Cohen M, Hawkins L, Greenberg S, Fuster V. Usefulness of ST-segment changes in greater than or equal to 2 leads on the emergency room electrocardiogram in either unstable angina pectoris or non-Q-wave myocardial infarction in predicting outcome. Am J Cardiol. 1991; 67:1368–73.
18. Nyman I, Areskog M, Areskog NH, Swahn E, Wallentin L. Very early risk stratification by electrocardiogram at rest in men with suspected unstable coronary heart disease. J Intern Med. 1993; 234: 293–301.
19. Selker HP, Beshansky JR, Griffith JL, et al. Use of the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) to assist with triage of patients with chest pain or other symptoms suggestive of acute cardiac ischemia: a multicenter, controlled clinical trial. Ann Intern Med. 1998; 129: 845–55.

20. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med. 1996; 335:1342–9.
21. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. N Engl J Med. 1996; 335:1333–41.
22. Luscher MS, Thygesen K, Ravkilde J, Heickendorff L, for the TRIM Study Group. Applicability of cardiac troponin T and I for early risk stratification in unstable coronary artery disease. Circulation. 1997; 96:2578–85.