Published in final edited form as:

Medicine (Baltimore). 2009 September ; 88(5): . doi:10.1097/MD.0b013e3181b98782.

Clinical Risk Stratification in the Emergency Department Predicts Long-Term Cardiovascular Outcomes in a Population-Based Cohort Presenting with Acute Chest Pain: Primary Results of the Olmsted County Chest Pain Study

Michael E. Farkouh, MD, MSc, Ashish Aneja, MD, Guy S. Reeder, MD, Peter A. Smars, MD, Sameer Bansilal, MD, MSc, Ryan J. Lennon, MS, Heather J. Wiste, BA, Louai Razzouk, MD, Kay Traverse, RN, David R. Holmes Jr., MD, and Verghese Mathew, MD

Division of Cardiovascular Diseases and Internal Medicine (GSR, DRH, VM), the Division of Emergency Medical Services and Internal Medicine (PAS), the Division of Biomedical Statistics and Informatics (RJL, HJW) and the Section of Health Services Evaluation (KT), Mayo Clinic College of Medicine, Mayo Clinic and Foundation, Rochester MN, and the Mount Sinai School of Medicine Cardiovascular Institute (MEF, AA, SB, LR).

Abstract

The long-term cardiovascular outcomes of a population-based cohort presenting to the emergency department (ED) with chest pain and classified with a clinical risk stratification algorithm are not well documented. The Olmsted County Chest Pain Study is a community-based study that included all consecutive patients presenting with chest pain consistent with unstable angina presenting to all Olmsted County EDs. Patients were classified according to the Agency for Health Care Policy and Research (AHCPR) criteria. Patients with ST elevation myocardial infarction and chest pain of non-cardiac origin were excluded. Main outcome measures were major adverse cardiovascular and cerebrovascular events (MACCE) at 30 days and a median follow up of 7.3 years, and mortality through a median of 16.6 years. The 2271 patients were classified: 436 (19.2%) as high-, 1,557 (68.6%) as intermediate- and 278 (12.2%) as low-risk. Thirty-day MACCE occurred in 11.5% in high-risk, 6.2% in intermediate-risk, and 2.5% in the lowrisk group ($p < 0.001$). At 7.3 years, significantly more MACCE were recorded in the intermediate (HR 1.91; 95% CI 1.33–2.75) and high-risk groups (HR 2.45; 95% CI 1.67–3.58). Intermediate- and high-risk patients demonstrated a 1.38 fold (95% CI 0.95–2.01, $p = 0.09$) and a 1.68 fold (95% CI 1.13–2.50, $p = 0.011$) higher mortality compared to lowrisk patients at 16.6 years. At 7.3 and 16.6 years of follow-up, biomarkers were not incrementally predictive of cardiovascular risk. In conclusion, a widely-applicable rapid clinical algorithm using AHCPR criteria can reliably predict long-term mortality and cardiovascular outcomes. This algorithm, when applied in the ED, affords an excellent opportunity to identify patients who might benefit from optimization of their cardiovascular risk management.

Address reprint requests to: Michael E. Farkouh, MD, MSc, Mount Sinai Cardiovascular Institute, Mount Sinai Medical Center, Box 1074, One Gustave L. Levy Place, New York, NY 10029, michael.farkouh@mssm.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

Acute chest pain in the emergency department (ED) is an important public health problem. It accounts annually for approximately 5 million patient visits, leading to 1.5 million hospitalizations for acute coronary syndromes (ACS) in the United States alone (23, 6). In 1994, the Agency for Health Care Policy and Research (AHCPR) published definitive guidelines for the diagnosis and management of unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) (6). The Braunwald classification (7), the foundation for the AHCPR guidelines, has been prospectively validated to predict in-hospital cardiac complications (9), and forms the basis for predicting the short-term risk of death or non-fatal myocardial infarction (MI) in the 2007 ACC/AHA Guideline for the management of patients with UA/NSTEMI (4). Based upon the Braunwald classification and the current ACC/AHA guideline, it is widely recommended that high-risk patients be admitted to the hospital, and the majority of low-risk patients can be discharged to follow up with their Primary Care Physician or Cardiologist following stress testing. In the absence of contraindications, intermediate-risk patients are recommended to undergo evaluation over 6–12 hours, including stress testing, thereby further sub-stratifying these patients into a high-risk group for admission or a lower risk group for outpatient care (14). However, the AHCPR classification for chest pain has never been truly examined in the long-term with the longest follow-up of 1 year in a small sample of patients (8).

Although very similar to the current ACC/AHA guideline recommendations, the AHCPR classification does not include cardiac biomarker measurement since it antedated the troponin era. It is therefore considered a true clinical risk stratification tool, based on history, physical and ECG findings and can be applied rapidly upon arrival to the ED. In practice, both the ACC/AHA risk stratification tool (including biomarker assays) and the AHCPR guideline (purely clinical) are underutilized, and the current management of unselected acute chest pain patients is confusing and inconsistent because of the multiplicity of risk scores and protocols across institutions. Clinical risk stratification scores such as the TIMI (5) and GRACE (17), developed more recently, have been utilized more frequently. The TIMI score was developed by compiling patients participating in the TIMI 11B and ESSENCE trials, consisting of patients with UA/NSTEMI. The TIMI score was developed by selection of independent variables using multivariable logistic regression and seven individual components were eventually selected based upon their ability to predict risk individually and incrementally. The primary end-point was a composite of all-cause mortality, MI, or urgent revascularization. The seven risk factors were age 65 and older, at least 3 risk factors for coronary artery disease (CAD), prior coronary stenosis of 50% or more, ST-segment deviation on presentation ECG, at least two angina events in last 24 hours, aspirin use in the last 7 days, and elevated cardiac markers. The AHCPR classification (Table 1) is similar in that it includes age, ECG changes, angina severity but does not include prior knowledge of coronary anatomy, medication use, coronary risk factors, and cardiac marker estimation. The GRACE score, developed in an internationally diverse population including both ST elevation myocardial infarction (STEMI) and UA/NSTEMI, may be more representative of patients encountered in daily practice and also because it was validated both internally and externally, yielding consistent results. The GRACE score was developed to help predict short-term mortality and identified eight variables. These included Killip Class (equivalent of congestive heart failure (CHF)), systolic blood pressure (SBP), heart rate (HR), age, creatinine level, cardiac arrest at admission, ST-segment deviation, and elevated cardiac enzymes. The GRACE model is similar to the AHCPR model in that it incorporates easily identifiable clinical criteria but differs from TIMI in that it included patients with STEMI and those not eligible for clinical trials-sicker than those in TIMI. The GRACE cohort was derived from patients in 14 countries and 94 hospitals and perhaps represented a population more similar to our cohort than TIMI. We sought to validate the AHCPR guideline, rapidly

applicable upon patient presentation, and accordingly determine short and long-term patient outcomes to provide a compelling rationale for its routine use, especially in the era of resource-intensive strategies.

PATIENTS AND METHODS

Design Overview

Using written screening logs, we retrospectively identified all residents of Olmsted County, Minnesota, presenting to one of the County's three EDs with acute chest pain during the period January 1, 1985 through December 31, 1992. The complete medical records of the screened population were reviewed by an experienced nurse abstractor, who identified the study cohort comprising all county residents presenting with an episode of acute chest pain during the study period, consistent with an unstable coronary syndrome. This was defined according to the Diamond classification as follows: new onset or worsening pattern of ischemic chest pain, occurring at rest or with minimal exertion, and alleviated by sublingual nitroglycerine and/or rest (12).

Patients were excluded if they had ST segment elevation suggestive of acute MI on their baseline qualifying ECG (elevation greater than or equal to 1mm in two or more leads), or a definitive alternate etiology for the chest pain, including pleuritic pain, pneumonia, musculoskeletal pain, pericarditis and dissecting aortic aneurysm. These exclusions were made since the AHCPR criteria would not have much additive value in reaching these diagnoses.

Setting and Participants

For all eligible patients, the complete medical record was abstracted to determine the history of the qualifying episode, including past medical history and detailed physical examination findings. This was executed through the Rochester Epidemiology Project, which allows essentially complete capture of the health care experience, including outpatient care, for all residents of Olmsted County, Minnesota (20). The Olmsted County Health Care Utilization and Expenditures Database, which is linked to the Rochester Epidemiology Project, contains detailed line-item information on all health services utilized and expenditures incurred by every member of the population for as long as they remain a resident in the county. Therefore, unlike any other geographically defined community in the United States, a complete clinical and health services utilization history is available for all county residents regardless of their identity, the affiliation of their health care provider, the site where care was delivered (inpatient, outpatient, nursing home), or the health plan in which they participated. The qualifying ECG was interpreted by a staff cardiologist from the Mayo Clinic and verified by one of the study physicians.

Intervention

Using the AHCPR criteria (Table 1) (6), patients were classified based upon their initial ED presentation. Patients found to have a CK-MB or CK level greater than twice the upper limit of normal anytime within the first 24-hours of ED presentation were classified as the evolving myocardial infarction (MI) group.

Outcomes and Follow Up

Long-term data were collected in two phases. In the first phase, with a median duration of 7.3 years, major adverse cardiovascular and cerebrovascular events (MACCE) including death, MI, stroke and need for revascularization were measured. Study subjects who did not have ongoing medical care visits in Olmsted County were contacted to determine vital status. The contact was initiated with a letter to the last recorded address. For patients for

whom a response was not received, verification of status was confirmed through telephone contact with the patient directly or with family members, attending physicians, medical institutions or nursing homes. Ninety-three percent of patients were followed through at least 1995.

In the second phase, the last known alive dates or death dates as of January 2007 were added. Death dates were obtained through State of Minnesota Electronic Death Certificates, State of Minnesota Death Tapes, Olmsted County Electronic Death Certificates, and Mayo Clinic records. Thirty-seven patients were excluded at this time for refusal to allow use of their records for research purposes (as required by Minnesota State statute). Additionally, 11 patients who died at presentation to the ED were also excluded since they were ineligible for prospective risk assessment and classification. Therefore, 97.9% of the cohort was studied for long-term mortality.

Statistical Analysis

Patients were classified as high, intermediate or low-risk by the AHCPR criteria, and comparisons were made across risk groups for MACCE. Thirty-day events excluded presenting events, and were compared with Pearson's chi-squared test. Long-term survival rates were estimated by Kaplan-Meier methods and compared using the log-rank statistic. We compared the performance of the AHCPR criteria, a clinical risk stratification model with our derivation of the TIMI risk score (TRS), which is a biomarker based risk stratification model ranging from 0–7 points for predicting short term events, and has been validated for long term outcomes as well (5). Patients were classified into high (5–7), intermediate (3 or 4) or low (0–2) risk according to the TRS definition (19, 16); Prior PCI or CABG was used to identify patients meeting the criteria of prior stenosis ≥50%. Any of the following were considered to meet the criteria of severe anginal symptoms: angina with S3 or new/worsening rales; rest angina; and nocturnal angina. A mosaic plot is used to display the frequency of patients found in each AHCPR and TIMI risk level combination (Figure 2).

Logistic regression analyses were used to estimate unadjusted and adjusted odds ratios for primary MACCE within the first 30 days of arrival to the ED. Cox proportional hazards regression models were used to estimate hazard ratios for long-term survival and survival free of MACCE. Multiple regression models were developed as follows. Covariates with significant unadjusted associations with the endpoint were selected to create a multiple regression “covariate-only” model. To this model, three more models were created by adding the AHCPR and TRS separately and together. Likelihood ratio tests of these models were used to estimate the partial significance of these risk scores.

RESULTS

There were 6,801 residents of Olmsted County, Minnesota who presented to an ED with an episode of acute chest pain during the study period, January 1, 1985 through December 31, 1992. Of these 2,271 (33.4%) met eligibility criteria and were followed as study subjects. Ineligible patients were excluded for both cardiac and non-cardiac reasons.

Cardiac causes accounted for 4.4% of patients including MI with ST elevation in 3.6% patients, stable angina in 0.7% and aortic dissection in 0.1%. Non-cardiac causes accounted for the exclusion of 40% patients. Another 11.7% patients were excluded because they were non-residents, and 10.4% for other reasons.

The mean age of the cohort upon presentation was 63 years, with 57.5% males and 14.8% with diabetes mellitus (Table 2). Using AHCPR criteria, 436 patients (19.2%) were classified as high risk, 1,557 (68.6%) as intermediate risk and 278 (12.2%) as low risk.

High-risk patients were more likely to be elderly (<0.001). On applying the TRS to this population, 96 patients were classified as high risk (4.2%), 650 as intermediate risk (28.6%) and 1525 (67%) as low risk. The TRS reclassified over 60% of the patients into a lower risk category compared to their AHCPR classification (Figure 2).

30 Day Events

Over the first 30 days of follow-up after the qualifying ED visit, 153 (6.7%) patients suffered at least one primary MACCE (Table 3). According to the AHCPR criteria, the 30-day event rate was 11.5% in the high-risk group, 6.2% in the intermediate group and 2.5% in the low-risk group ($p<0.001$). Those in the AHCPR intermediate and high-risk groups with elevated biomarkers (evolving MI) at presentation suffered a higher rate of subsequent events than those without biomarker elevation. Biomarker elevation did not confer additional risk for subsequent events in the low risk AHCPR group since coronary revascularization accounted for all the 30-day events in the AHCPR low-risk group, except for one stroke.

In univariate logistic regression analysis, the following variables were significantly associated with 30-day MACCE: increasing age, prior MI, prior stable angina, an abnormal index ECG, diabetes mellitus, hypertension, and decreasing systolic blood pressure. All variables except prior MI and diabetes mellitus remained significant in a multiple logistic regression model. Sex, unstable angina, left bundle branch block (LBBB), diastolic blood pressure, hypercholesterolemia, smoking status, and family history were not associated with 30-day events in our study.

Long-term Follow-up

During the first phase of long-term follow up at a median of 7.3 years, we observed a MACCE in 1136 patients, 709 of which died. Unadjusted Kaplan Meier survival curves show a reduced cardiac event free survival rate for AHCPR high- and intermediate-risk compared to low-risk patients (Figure 1). In our cohort, the AHCPR risk score was significantly associated ($p<0.001$) with follow-up MACCE after adjusting for the following variables. Compared to patients classified as low risk by the AHCPR criteria, both intermediate risk (HR 1.91; 95% CI 1.33–2.75) and high-risk patients (HR 2.45; 95% 1.67–3.58) were significantly more likely to suffer MACCE on long-term follow-up. Age, prior MI, unstable angina, stable angina, diabetes, smoking status, hypertension, an abnormal ECG, LBBB, and systolic blood pressure were all significantly associated with follow-up MACCE. All of these variables except for systolic blood pressure had significant adjusted associations in the multivariable regression model. In the second phase, we observed 1208 deaths over a median follow-up of 16.6 years, translating into a mean annualized mortality rate of 4.7 % for the cohort. Unadjusted Kaplan Meier survival curves show a reduced survival rate for AHCPR highrisk and intermediate-risk compared to low-risk patients. Importantly, for each risk group, survival was similar regardless of whether the patient had an initial elevation of cardiac biomarkers (Figure 3). After adjusting for other risk factors, high-risk patients demonstrated a 1.68 fold (95% CI 1.13–2.50, $p = 0.011$) increase in mortality compared to low-risk patients while intermediate-risk patients had a 1.38 fold (95% CI 0.95–2.01, $p=0.09$) increase in mortality. When the TRS model was added to the multivariable regression model, it did not provide incremental prognostic value either alone ($p=0.60$) or in combination with the AHCPR classification ($p=0.69$).

DISCUSSION

The effectiveness of clinical prediction models has been demonstrated for cardiovascular risk assessment in stable populations (15). However, optimal triage and management of

unselected patients with acute ischemic chest pain remains challenging, and expensive despite a multitude of risk-stratification protocols (22). In a large, population-based cohort of consecutive patients, we validate that the history, physical examination and ECG-based AHCPR model predicts short and long-term cardiovascular events. The ease, rapidity of implementation, and effectiveness of the AHCPR-based risk-stratification model affords a major logistic and financial advantage over other resource-intensive protocols. The overall 30-day cardiovascular event rate in our cohort was 6.7%, which is comparable to that observed in randomized controlled trials (RCTs) (18,21,24). Additionally, the previously unreported 4.7% average annual mortality rate over 16.6 years for a population presenting with ischemic chest pain is informative for designing future studies in similar unselected populations.

Impact on Short and Long-Term Management of Acute Ischemic Chest Pain

In our study, cardiac biomarkers identified patients at higher 30-day risk (evolving MI group), and provided incremental prognostic information in the high and intermediate-risk AHCPR groups (Table 3). Therefore, the AHCPR model in conjunction with ultrasensitive modern biomarkers could prove to be a highly sensitive, specific, and efficient tool for reliable risk stratification of unselected chest pain patients in the ED. This approach needs validation in a prospective setting and the findings from our study provide a robust body of evidence to design such a study.

Notwithstanding the need for a short-term prospective study, the high long-term event rates in intermediate and high-risk patients by AHCPR criteria, regardless of initial biomarker status, should serve as an opportunity for aggressive management, both during hospital admission and outpatient risk factor modification (4). By contrast, those stratified as low-risk by AHCPR experienced a significantly lower 30-day event rate and the vast majority would have been suitable for early stress testing. Contemporary practice contraindicates stress testing in the 7% (18/278) subset of patients within the low risk group with marker elevation (evolving MI) but the low event rate including no recurrent MIs at 30-days suggests false positive enzyme elevation in several cases. The current literature also suggests a similar 7% false positive cardiac enzyme elevation in these patients, consistent with the rate observed in our study (13). The safety and efficacy of early stress testing in unselected chest pain populations has been examined and advocated by other groups (3). Risk stratification in the AHCPR guideline based intermediate risk group was clarified by the CHEER trial, which increased the proportion of chest pain patients suitable for discharge from the ED to nearly 50% (14). In this group, biomarkers play a major role in triage; marker negative patients are eligible for stress testing and those failing the chest pain unit observation period or a positive stress test are admitted. The preponderance of adverse cardiovascular events within the first month of hospital admission for NSTEMI also supports the use of an efficient clinical risk stratification model in the ED (6, 2, 10).

As previously alluded, alternative risk stratification protocols such as the TRS and the GRACE Registry Score have been used for triaging undifferentiated chest pain patients in the ED. The TRS can predict higher cardiovascular risk in ACS patients at intermediate to high risk according to national guidelines but was not designed as a prognostic tool for short- and long-term follow-up in unselected chest pain populations. In our consecutive cohort, clinical risk stratification with AHCPR performed more reliably than the derived TRS model in predicting short term MACCE. When used alone, 67% of patients were classified as low-risk by TRS compared with only 12% by AHCPR. The low risk TRS group had a higher event rate of 4.5% with a sizeable proportion suffering MIs (1.1%) compared to the 2.5% event rate in the low risk AHCPR group with no recurrent MIs at 30 days. At least part of this difference is likely related to the limitations of applying the TRS to an unselected population. In one large unselected chest pain population, a TRS of 1 was associated with a

30 day rate of death, MI and revascularization of nearly 8%, a large increase from a rate of 1.7% for a score of 0 (11). Long-term outcome data regarding patients presenting with UA/NSTEMI are limited despite numerous randomized controlled trials in ACS (1). Our study is unique in that it is the only population-based study of consecutive, unselected patients, documenting the natural history and long-term outcomes of patients presenting with acute ischemic chest pain. We demonstrate for the first time that a clinical classification successfully predicted long-term mortality. Importantly, the long-term event rates, regardless of index risk profile, were not influenced by biomarker abnormality on presentation, further supporting the importance of simple, clinical risk stratification as the foundation for short and long-term risk stratification. Additionally, the AHCPR model for risk stratification is likely to be clinically applicable to a variety of ethnic populations given the experiences noted in large international studies (15, 25).

The AHCPR model may be advantageous from the resource utilization perspective because it is rapidly implemented and provides a strong framework for the proper interpretation of abnormal biomarker values. In addition, it does not require definition of the coronary anatomy for risk assessment. It is possible that if this cohort had been assembled in the present era, the outcomes could have been different because of the advances in diagnostic (particularly imaging, for e.g. CT angiography) and therapeutic (anti-thrombotic treatments such as clopidogrel, platelet glycoprotein IIb-IIIa receptor antagonists, etc.) modalities. However, our cohort with near complete long-term follow up was followed over a period of extensive changes in diagnostic and therapeutic modalities, thereby providing insights into real-world outcomes. The extensive resources required to replicate such short- and long-term cohorts in developing countries makes our findings globally pertinent. The additional costs accruing from extensive diagnostic testing in countries with limited healthcare budgets make the AHCPR model an attractive means for risk assessment and triage (26). We believe that our patient population was more similar to the GRACE population than the TRS population because it included consecutive patients. The biggest dissimilarity between our patients and GRACE patients was our exclusion of STEMI patients. Similar to GRACE, we also observed in multivariable analysis that increasing age, an abnormal index ECG, and decreasing systolic blood pressure were independently associated with 30-day events. These similarities further validate our findings. Unlike TIMI and GRACE, cardiac marker elevation did not portend a poor short-term prognosis in our population. This could have resulted from fewer events and non-availability of troponin assays in our cohort. Our study has limitations. This analysis was conducted in Olmsted County, Minnesota. The fact that the majority of our cohort is white Caucasian may impact the generalizability of our findings. However, the AHCPR guideline has been validated in an urban multiethnic population in the US (9). In addition, the INTERHEART study showed that risk factors affecting risk for recurrent events remain the same in populations across 52 countries (25). We also do not have detailed information about the causes of death in the 11 patients who died at presentation also Olmsted County non-residents who accounted for a small percentage of patients. Including these patients in our cohort may have impacted the baseline and long-term event rates, but the impact is likely to be small. In addition, since all the events were either captured during hospital admission and were self-reported, the reported event rate may have been an underrepresentation of the actual event rate. However, the ascertainment and reporting of events in the Olmsted County is likely to be more reliable than others because it is geographically and financially confined. It would have been desirable to also compare the AHCPR to a GRACE risk score model akin to the TRS, but we did not have access to all the patients' renal function, precluding such modeling. Finally, troponin assays were not widely available at the time these patients were identified. For this reason, the results of the long-term mortality analysis demonstrating that patient risk was not affected by marker positivity at the index event may have been different.

CONCLUSION

In an unselected acute chest pain population, a simple clinical risk stratification strategy performed favorably for prediction of long-term cardiovascular events. This provides clinicians with an opportunity to identify patients at highest risk and most likely to benefit from optimization of their cardiovascular risk factor management. This is particularly important in populations where the ED serves as the first and sometimes only venue to assess risk and in healthcare systems where resources are limited.

Acknowledgments

Funding: This study was made possible by the Rochester Epidemiology Project (Grant #R01-AR30582 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases).

REFERENCES

1. Abrahamsson P, Rosengren A, Dellborg M. Improved long-term prognosis for patients with unstable coronary syndromes 1988-1995. *Eur Heart J.* 2000; 21:533-539. [PubMed: 10775008]
2. Allen LA, O'Donnell CJ, Camargo CA Jr, Giugliano RP, Lloyd-Jones DM. Comparison of long-term mortality across the spectrum of acute coronary syndromes. *Am Heart J.* 2006; 151:1065-1071. [PubMed: 16644337]
3. Amsterdam EA, Kirk JD, Diercks DB, Lewis WR, Turnipseed SD. Immediate exercise testing to evaluate low-risk patients presenting to the emergency department with chest pain. *J Am Coll Cardiol.* 2002; 40:251-256. [PubMed: 12106928]
4. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction. *J Am Coll Cardiol.* 2007 Aug 14; 50(7):e1-e157. Erratum in: *J Am Coll Cardiol.* 2008 Mar 4;51(9):974. [PubMed: 17692738]
5. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA.* 2000 Aug 16; 284(7):835-842. [PubMed: 10938172]
6. Braunwald E.; Brown, J.; Brown, L.; Cheitlin, MD.; Concannon, CA.; Cowan, M.; Edwards, C.; Fuster, V.; Goldman, L.; Green, LA.; Grines, CL.; Lytle, BW.; McCauley, KM.; Mushlin, AI.; Rose, GC.; Smith, E., III; Swain, JA.; Topol, EJ.; Willerson, JT. Clinical practice guideline: Unstable Angina diagnosis and management. AHCPR Publication No. 94-0603. 1994 Mar.
7. Braunwald E. Unstable Angina: a classification. *Circulation.* 1989; 80:410-414. [PubMed: 2752565]
8. Brotons C, Permanyer-Miralda G, Calvo F, Campreciós M, Santos MT, Cascant P, Moral I, Ribera A, Soler-Soler J. Validation of the Agency for Health Care Policy and Research (AHCPR) classification for managing unstable angina. 1999 Oct; 52(10):959-965.
9. Calvin JE, Klein LW, VandenBerg BJ, Meyer P, Condon JB, Snell RJ, Ramirez-Morgen LM, Parillo JE. Risk stratification in NSTEMI ACS. Prospective validation of the Braunwald classification. *JAMA.* 1995; 273(2):136-141. [PubMed: 7799494]
10. Capewell S, Murphy NF, Macintyre K, Frame S, Stewart S, Chalmers J, Boyd J, Finlayson A, Redpath A, McMurray JJ. Short-term and long-term outcomes in 133,429 emergency patients admitted with angina or myocardial infarction in Scotland 1990-2000: population-based cohort study. *Heart.* 2006; 92:1563-1570. [PubMed: 16775090]
11. Chase M, Robey JL, Zogby KE, Sease KL, Shofer FS, Hollander JE. Prospective validation of the Thrombolysis in Myocardial Infarction Risk Score in the emergency department chest pain population. *Ann Emerg Med.* 2006; 48:252-259. [PubMed: 16934646]

12. Diamond GA. A clinically relevant classification of chest discomfort (letter) . J Am Coll Cardiol. 1983; 1:574–575. [PubMed: 6826969]
13. Ellis AK. Serum protein measurements and the diagnosis of acute myocardial infarction. Circulation. 1991; 83:1107–1109. [PubMed: 1999018]
14. Farkouh ME, Smars PA, Reeder GS, Zinsmeister AR, Evan RW, Meloy TD, Kopecky SL, Allen M, Allison TG, Gibbons RJ, Gabriel SE. A clinical trial of a chest-pain observation unit for patients with NSTEMI ACS. Chest Pain Evaluation in the Emergency Room (CHEER) . N Engl J Med. 1998; 339(26):1882–1888. [PubMed: 9862943]
15. Gaziano TA, Young CR, Fitzmaurice G, Atwood S, Gaziano JM. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. Lancet. 2008 Mar 15; 371(9616):923–931. [PubMed: 18342687]
16. Gombert-Maitland M, Murphy SA, Moliterno DJ, Cannon CP. Are we appropriately triaging patients with unstable angina? Am Heart J. 2005 Apr; 149(4):613–618. [PubMed: 15990742]
17. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA. Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003 Oct 27; 163(19):2345–2353. [PubMed: 14581255]
18. Gold HK, Johns JA, Leinbach RC, Yasuda T, Grossbard E, Zusman R, Collen D. A randomized, blinded, placebo-controlled trial of recombinant human tissue-type plasminogen activator in patients with unstable angina pectoris. Circulation. 1987; 75:1192–1199. [PubMed: 3105913]
19. Ilkhanoff L, O'Donnell CJ, Camargo CA, O'Halloran TD, Giugliano RP, Lloyd-Jones DM. Usefulness of the TIMI Risk Index in Predicting Short- and Long-Term Mortality in Patients With Acute Coronary Syndromes. Am J Cardiol. 2005 Sep 15; 96(6):773–777. [PubMed: 16169358]
20. Kurland LT, Molgaard CA. The patient record in epidemiology. Scientific American. 1981; 245:54–63. [PubMed: 7027437]
21. Lewis HD, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE III, Schnaper HW, LeWinter MM, Linares E, Pouget JM, Sabharwal SC, Chester E, DeMots H. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. N Engl J Med. 1983; 309:396–403. [PubMed: 6135989]
22. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, Griffith JL, Selker HP. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med. 2000 Apr 20; 342(16):1163–1170. [PubMed: 10770981]
23. Theroux P, Lidon RM. NSTEMI ACS: pathogenesis, diagnosis and treatment. Current Problems in Cardiology. 1993; 13:159–231.
24. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, Pelletier E, Juneau M, Stasiak J, DeGruise P, Pelletier GB, Rinzler D, Waters DD. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med. 1988; 319:1105–1111. [PubMed: 3050522]
25. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364:937–952. [PubMed: 15364185]
26. World Bank. World Development Indicators 2007. Washington, DC: World Bank; 2007.

Figure 1.
Major Adverse Cardiovascular and Cerebrovascular Events at a Median Follow-up of 7.3 Years

No. at Risk						
Low	278	247	203	126	65	19
Intermediate	1557	1186	916	568	281	102
High	436	265	201	126	65	34

Figure 2.
Mosaic plot of TIMI and AHCPR

Figure 3.
Overall Mortality by AHCPR Risk Level

TABLE 1

AHCPR Classification *

High Risk	Intermediate Risk	Low Risk
At least 1 of the following features must be present:	No high-risk feature but must have any of the following:	No high- or intermediate-risk feature but may have any of the following features:
Prolonged ongoing (>20 min) rest pain	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD	Increased angina frequency, severity, or duration
Pulmonary edema, most likely related to ischemia	Rest angina (>20 min or relieved with rest or sublingual nitroglycerin)	Angina provoked at a lower threshold
Angina at rest with dynamic ST changes >1 mm	Nocturnal angina	New-onset angina with onset 2 wk to 2 mo before presentation
Angina with new or worsening MR murmur Angina with S3 or new/worsening rales	Angina with dynamic T-wave changes New-onset CCS III or IV angina in the past 2 weeks with moderate or high likelihood of CAD	Normal or unchanged ECG
Angina with hypotension [†]	Pathologic Q waves or resting ST depression <1 mm in multiple lead groups (anterior, inferior, lateral)	
	Age > 65 yr	

Abbreviations: CAD = coronary artery disease; CCS = Canadian Cardiovascular Society.

* Adapted from AHCPR Clinical Practice Guidelines No. 10, Unstable Angina: Diagnosis and Management, May 1994. Estimation of the short-term risks of death and nonfatal cardiac ischemic events in unstable angina (or NSTEMI) is a complex multivariable problem that cannot be fully specified in a table such as this; therefore, this table is meant to offer general guidance and illustration rather than rigid algorithms.

[†] Definition of hypotension: systolic blood pressure <90 mm Hg or >30% below starting mean arterial pressure levels if significant hypertension is present.

TABLE 2
Baseline Characteristics of the Acute Chest Pain Cohort, by AHCPR Risk Criteria

Characteristic	Total No. (%)	High Risk No. (%)	Intermediate Risk No. (%)	Low Risk No. (%)	p Value
No.	2271	436 (19.2)	1557 (68.6)	278 (12.2)	
Mean age, yr (range)	63 (21–101)	68 (31–99)	64 (22–101)	48 (21–65)	<.001
Sex (Male)	1306 (57.5)	242 (55.5)	907 (58.3)	157 (56.5)	0.55
Previous MI	490 (21.6)	130 (29.8)	360 (23.1)	0 (0)	<.001
Previous NSTEMI ACS	201 (8.9)	62 (14.2)	139 (8.9)	0 (0)	<.001
Previous stable angina	679 (29.9)	164 (37.6)	515 (33.1)	0 (0)	<.001
Incidence cases	1352 (59.5)	211 (48.4)	863 (55.4)	278 (100)	<.001
Diabetes mellitus	336 (14.8)	84 (19.3)	247 (15.9)	5 (1.8)	<.001
Current smoking	490 (21.6)	91 (20.9)	316 (20.3)	83 (29.9)	0.002
Hypertension	1039 (45.8)	234 (53.7)	756 (48.6)	49 (17.6)	<.001
Hypercholesterolemia* (>220 mg/dL)	794 (35.0)	138 (31.7)	568 (36.5)	88 (31.7)	0.08
Aspirin use (pre)	395 (17.4)	90 (20.6)	298 (19.1)	7 (2.5)	<.001
Admitted	2174 (95.7)	430 (98.6)	1500 (96.3)	244 (87.8)	<.001
Any ECG abnormality	1257 (55.4)	319 (73.2)	877 (56.3)	61 (21.9)	<.001
LBBB	102 (4.5)	35 (8.0)	66 (4.2)	1 (0.4)	<.001
Family history [†] of CAD	588 (25.9)	114 (26.1)	395 (25.4)	79 (28.4)	0.56
Mean (range) systolic BP at index date, in mm Hg	153 (60–300)	152 (60–300)	154 (90–248)	148 (105–220)	0.009
Mean (range) diastolic BP at index date, in mmHg	87 (34–170)	88 (38–170)	87 (34–160)	89 (50–155)	0.08

Abbreviations: See previous table; BP = blood pressure, LBBB = left bundle branch block, MI = myocardial infarction, NSTEMI ACS = non-ST-segment elevation acute coronary syndrome,

* Could not be determined in 484 (21.3%) of patients.

[†] Family history of CAD: At least 1 parent with validated premature cardiovascular disease (before age 55 yr in a father or before age 65 yr in a mother).

TABLE 3

Thirty-Day Events* (Excludes ED Deaths) by AHCPR Category

	AHCPR Risk Group							
	High Risk		Intermediate Risk		Low Risk		Total	
	CK-MB Positive		CK-MB Positive		CK-MB Positive		CK-MB Positive	
	Yes (n=154) No. (%)	No (n=282) No. (%)	Yes (n=241) No. (%)	No (n=1316) No. (%)	Yes (n=18) No. (%)	No (n=260) No. (%)	Yes (n=413) No. (%)	No (n=1858) No. (%)
Total death	15 (9.7)	15 (5.3)	7 (2.9)	20 (1.5)	0 (0)	0 (0)	22 (5.3)	35 (1.9)
CV death	13 (8.4)	13 (4.6)	6 (2.5)	18 (1.4)	0 (0)	0 (0)	19 (4.6)	31 (1.7)
MI	6 (3.9)	3 (1.1)	12 (5.0)	26 (2.0)	0 (0)	0 (0)	18 (4.4)	29 (1.6)
Stroke	3 (1.9)	2 (0.7)	0 (0)	8 (0.6)	0 (0)	1 (0.4)	3 (0.7)	11 (0.6)
Revascularization	8 (5.2)	4 (1.4)	12 (5.0)	29 (2.2)	1 (5.6)	5 (1.9)	21 (5.1)	38 (2.0)
Any event[†]	29 (18.8)	21 (7.4)	26 (10.8)	70 (5.3)	1 (5.6)	6 (2.3)	56 (13.6)	97 (5.2)

Abbreviations: See previous tables. CV = cardiovascular.

* Subsequent to CK-MB positive.

[†]Any event: includes multiple events per patient.