The use of risk scores for stratification of non-ST elevation acute coronary syndrome patients

Ramjane Khalill MD, Lei Han MD, Chang Jing PhD, He Quan PhD

R Khalill, L Han, C Jing, He Quan. The use of risk scores for stratification of non-ST elevation acute coronary syndrome patients. Exp Clin Cardiol 2009;14(2):e25-e30.

OBJECTIVE: To review the methods available for the risk stratification of non-ST elevation (NSTE) acute coronary syndrome (ACS) patients and to evaluate the use of risk scores for their initial risk assessment.
DATA SOURCES: The data of the present review were identified by searching PUBMED and other databases (1996 to 2008) using the key terms "risk stratification", "risk scores", "NSTEMI", "UA" and "acute coronary syndrome".
STUDY SELECTION: Mainly original articles, guidelines and critical reviews written by major pioneer researchers in this field were selected.
RESULT: After evaluation of several risk predictors and risk scores, it was found that estimating risk based on clinical characteristics is challenging and imprecise. Risk predictors, whether used alone or in simple binary combination, lacked sufficient precision because they have high specificity but low sensitivity. Risk scores are more accurate at stratifying NSTE ACS patients into low-, intermediate- or high-risk groups. The Global Registry of Acute Cardiac Events risk score was found to have superior predictive accuracy compared with other risk scores in ACS population. Treatments based according to specific clinical and risk grouping show that certain benefits may be predominantly or exclusively restricted to higher risk patients.
CONCLUSION: Based on the trials in the literature, the Global Registry of Acute Cardiac Events risk score is more advantageous and easier to use than other risk scores. It can categorize a patient's risk of death and/or ischemic events, which can help tailor therapy to match the intensity of the patient's NSTE ACS.

Key Words: *Acute coronary syndrome; NSTEMI; Risk scores; Risk stratification; Unstable angina*

Despite therapeutic advances, cardiovascular disease remains the leading cause of death worldwide (1,2). The World Health Organization expects heart disease to be the number one cause of death in developing countries by 2010 (1,2). Knowing the poor survival rate in the high-risk patients, giving the right treatment becomes imperative. Estimated risk, based on clinical characteristics, is challenging and imprecise, yet risk assessment is needed to guide triage and key management decisions. Therefore, early risk stratification plays an important role in the optimal management of non-ST elevation (NSTE) acute coronary syndrom (ACS) (3).

Current guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) (3,4) and the European Society of Cardiology (ESC) (5) recommend that certain pharmacological and interventional strategies are most appropriate for higher-risk patients in the NSTE ACS group. Despite these recommendations, some contemporary registry data suggest that more aggressive therapy is not necessarily targeted in higher risk patients. A new study (6) has found that cardiac catheterization is not being used optimally in NSTE ACS patients, mainly because doctors are not risk-stratifying these patients correctly. Patients who underwent catheterization had lower in-hospital and one-year mortality rates compared with those who did not (Table 1). The other reason postulated by many medical practitioners behind the nonconcordance with the guideline is that they did not believe that the patients were at high enough risk. However, when these patients were further investigated, many turned out to be at intermediate to high risk according to their baseline risk score, thus representing the group of patients who benefited the most from an early invasive treatment strategy. The physicians may be focusing on only one or two risk factors (such as ST-segment depression or troponin status) when risk stratifying patients, while potentially underestimating and/or de-emphasizing other important factors (such as increasing age, heart failure and poor renal function). To overcome this problem of risk stratification, numerous risk scores (7-11) have been developed in the past but only few of them have been put in practice. The most popular are the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) (9) and Thrombolysis in Myocardial Infarction (TIMI) (10) risk scores, both derived from clinical trial populations, and the Global Registry of Acute Cardiac Events (GRACE) risk score (11), which was developed from an international registry.

TABLE 1
Mortality rates according to whether the patient had been referred for catheterization

Mortality	Referred	Not referred	P
In-hospital, %	0.8	3.7	<0.001
One year, %	4.0	10.9	<0.001

The present review will focus on the different risk stratification methods and risk scores used in NSTE ACS patients for initial risk assessment.

WHAT THE GUIDELINES SAY

The ACC/AHA and the ESC consensus guidelines recognize the importance of early risk stratification in the management of NSTE ACS and recommend an integrated approach to risk assessment (3,5). The ability to assign relative risk to patients presenting with NSTE ACS assists the clinician in determining the appropriate strategy for an individual patient. The

Cardiology Department, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China.
Correspondence: Professor Lei Han, The First Affiliated hospital of Chongqing Medical University, Chongqing 400016, China.
Telephone 86-13-22-498-1900, e-mail khalill123@hotmail.com
Received for publication April 20, 2009. Accepted April 30, 2009

information required for this assessment is derived from the patient's history and physical examination, electrocardiogram (ECG) results and levels of serum biomarkers (troponins). Accordingly, both ACC/AHA and ESC guidelines contain a list of high-risk clinical features to facilitate categorization of patients into low-, intermediate- and high-risk groups for the development of subsequent cardiovascular events (recurrent ischemia, myocardioal infarction [MI] and death) (3-5). The ACC/AHA Guidelines for unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI) state that patients who are at intermediate or high risk for adverse outcomes should be admitted to a critical care environment with ready access to invasive cardiovascular diagnosis and therapy if needed (3,4). Class I recommendations for an early invasive strategy include patients with the following: recurrent angina at rest or low-level activity despite therapy, elevated troponins, new ST-segment changes, recurrent angina with symptoms of congestive heart failure, high-risk findings on noninvasive stress testing, hemodynamic instability, sustained ventricular tachycardia, percutaneous coronary intervention (PCI) within the previous six months, or previous coronary artery bypass surgery. The GRACE risk score or the PURSUIT risk model can be useful to assist in decision-making with regard to treatment options in patients with suspected ACS (level of evidence: B) (3,5).

Sex differences and role of risk scores

When men and women are directly compared, women are more likely to have a worse outcome following PCI. Very few women younger than 50 years of age need to undergo PCI because of the low rates of heart disease and heart attack in women of this age. However, when younger women have these procedures, they are more than twice as likely to die in the hospital than younger men (12-14). It may be that younger women who lose their natural protection against heart disease are at especially high risk compared with older women who develop heart disease after menopause. Women have smaller blood vessels than men even when compared with men of a similar size (15). PCI is trickier to perform in smaller blood vessels, and there is an increased risk of tearing the artery. In addition, smaller patients are more prone to bleeding problems during PCI. The other reasons for higher mortality in the different trials were because women were older, had more comorbidities and presented with ST-elevation myocardial infarction (STEMI) less often than men. When these factors are considered, some studies find that women are no more likely to die in the hospital than men, whereas others continue to find a small sex difference (16-19).

PCI offers greater angina relief and improvement in exercise tolerance than medicine alone, but has a greater risk of procedure-related complications in women. The guidelines (3,5) recommend the use of risk scores to properly risk stratify this group of patients and the use of an initial conservative (noninvasive) strategy as a possible treatment option in stabilized UA/NSTEMI patients and low-risk patients.

Risk assessment

ECG: The 12-lead ECG is central to the diagnostic and triage pathway for ACS and provides important prognostic information (20). Transient ST-segment changes (0.05 mV or greater [ie, 0.5 mm]) that develop during a symptomatic episode at rest strongly suggest acute ischemia due to severe coronary artery disease (CAD). Patients who present with ST-segment depression can have either UA or NSTEMI, the distinction being based on the later detection of biomarkers of myocardial necrosis. Inverted T waves, especially if marked (2 mm or greater [0.2 mV]), also can indicate UA/NSTEMI (21). Q waves suggesting prior MI indicate a high likelihood of CAD. However, a normal ECG does not completely exclude ACS: 1% to 6% of such patients prove to have had an NSTEMI, and at least 4% will be found to have UA (22). ST elevation has high specificity but low sensitivity for infarction, and three-quarters of those with acute coronary symptoms do not have ST elevation on presentation (23). Risk stratification cannot therefore rely simply on the presence of ST-segment deviation, and more accurate risk prediction tools are required.

Clinical symptoms: Recognition of symptoms of UA/NSTEMI must occur before evaluation and treatment can be pursued. Many people are unaware that symptoms besides chest discomfort, such as shortness of breath (24), diaphoresis (25) or extreme fatigue, can represent anginal equivalents (26,27). The average UA/NSTEMI patient does not seek medical care for approximately 2 h after symptom onset (27). A clinical diagnosis of 'suspected ACS' has low diagnostic accuracy when based only on the clinical symptoms (28,29). Conversely, pains of atypical distribution may herald acute infarction, and up to one-third of those who evolve MI do not have typical chest pains (30). Fewer than one-half of the patients who are admitted with chest pain have a final diagnosis of ACS (31,32). Up to 6% of those discharged from the emergency department have a 'missed' MI (33).

Troponin assay: The introduction of troponin assays has helped significantly in identifying patients with MI (34,35). Favourable features of biomarkers of necrosis are high concentrations in the myocardium and absence in nonmyocardial tissue, release into the blood within a convenient diagnostic time window and in proportion to the extent of myocardial injury, and quantification with reproducible, inexpensive, rapid and easily applied assays (36). The cardiac troponins, which possess many of these features, have gained wide acceptance as the biomarkers of choice. However, the negative predictive value of troponins on arrival is poor, because of the time required for efflux of this marker from cardiomyocytes (37). Serum troponin has consistently emerged as a potent stratifier of risk, with elevations of this biomarker associated with adverse outcomes (32). However, not all troponin-positive patients are at the same level of risk, and a significant gradient of increased risk of mortality with increasing troponin level has been observed (33).

Although patients with ACS share key pathophysiological mechanisms, they present with diverse clinical, electrocardiographic and enzyme characteristics and experience a wide range of serious cardiovascular outcomes (3,38). Estimated risk based on clinical characteristics is challenging and imprecise, yet risk assessment is needed to guide triage and key management decisions. Regulatory authorities such as the National Institute for Health and Clinical Excellence and guideline groups (ACC/AHA and ESC) recommend treatments according to specific clinical and risk grouping, and trials show that certain benefits may be predominantly or exclusively restricted to higher risk patients (3,5,39). Binary methods of stratifying risk (for example, normal or raised troponin concentration or abnormal or normal findings on ECG) lack sufficient precision (6,7,9).

Risk scores

TIMI: The TIMI risk score (10) was derived in a test cohort of patients with NSTE ACS by selection of independent prognostic variables using multivariate logistic regression, assignment of value of 1 when a factor was present and 0 when it was absent, and summing the number of factors present to categorize patients into risk strata. Outcomes were TIMI risk score for developing at least one component of the primary end point (all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization) through 14 days after randomization. The seven TIMI risk score predictor variables were age 65 years or older, at least three risk factors for CAD, prior coronary stenosis of 50% or more, ST-segment deviation on ECG at presentation, at least two anginal events in the previous 24 h, use of acetylsalicylic acid in the previous seven days and elevated serum cardiac markers (Table 2). Event rates increased significantly as the TIMI risk score increased in the test cohort in TIMI 11B: 4.7% for a score of 0/1; 8.3% for 2; 13.2% for 3; 19.9% for 4; 26.2% for 5; and 40.9% for 6/7 ($P<0.001$ by 2 for trend). The TIMI risk score has also been externally validated (40-42).

PURSUIT: The PURSUIT risk score (9) predicts 30-day risk and incorporates information from early vital signs. The score ranges from 0 to 25, and is comprised of age, sex, worst Canadian Cardiovascular Society angina class in the previous six weeks, heart rate, systolic blood pressure, signs of heart failure and ST depression. The combination of death and (re) infarction yielded similar predictors, with the exception that male sex was a more important predictor of the composite end point, but older age remained the most important predictor. The investigators proposed a scoring system to estimate 30-day risk of death, or death or infarction, with the point assignment higher in patients with NSTEMI than in those with UA for age and heart rate. This risk stratification method was independently validated in a cohort of consecutive patients with UA who presented to a community hospital (43).

GRACE: GRACE is a large multinational registry encompassing the full spectrum of acute coronary disease (44,45). Launched in 1999, the GRACE study collected information from patients admitted with an ACS to 94 hospitals in 14 countries in North and South America, Europe, the United Kingdom, and Australia and New Zealand. The data were collected between 1999 and 2002 and the population comprised 68,937 patients with a diagnosis of ACS. A prognostic model that predicts the risk of death and MI has been established (c index 0.84 for death) (44,46). The GRACE model for calculating the risk for all-cause mortality or new MI across the spectrum of ACS was developed and validated in cohorts from the GRACE registry. The GRACE ACS risk model has also been published as an online risk calculator and in downloadable versions for handheld devices (http://www.outcomes-umassmed.org/Grace/acs_risk.cfm). The components of the GRACE risk score (range 2 to 372) are age, heart rate, systolic blood pressure, Killip class, cardiac arrest, serum creatinine, ST-segment deviation and cardiac biomarker status.

The prognostic importance of an elevated initial serum creatinine on admission with an ACS is noteworthy. In the GRACE registry (47) and randomized studies (48-50), renal impairment was more common in older, female patients, and more likely to occur with other comorbidities including hypertension, diabetes mellitus and cardiac failure. More importantly, renal impairment has been shown to independently predict higher in-hospital (47) and short-term (90 days [48] and 180 days [49]) mortality after an ACS, regardless of the ACS subset. Of note, in patients with documented left ventricular impairment post-MI, even mild renal dysfunction (creatinine clearance less than 75 mL/min/1.73 m^2) can be a strong, independent predictor of mortality and cardiovascular complications. This risk increases proportionally with the decline in renal function (50). The GRACE algorithm does not only include renal impairment, but also takes it as a continuous variable like age, heart rate or blood pressure, allowing more refined prognostic prediction (Table 3).

TABLE 2
Predictors of the Thrombolysis in Myocardial Infarction (TIMI) risk score for unstable angina and non-ST elevation myocardial infarction

1. Age ≥65 years
2. Three or more coronary artery disease risk factors (eg, high cholesterol, family history, hypertension, diabetes mellitus, smoking)
3. Prior coronary artery disease
4. Acetylsalicylic acid in the past seven days
5. At least two angina-related events in the previous 24 h
6. ST-segment deviation
7. Elevated cardiac biomarkers (creatine kinase-MB or troponin)

Each variable is assigned a value of 1 or 0 depending on whether they are present or absent, respectively. Range 0 to 7

DISCUSSION

Despite the proven utility of risk scores in prognostication and guidance of treatment strategies (6-11,40,42,51-55), it is not known how often they are actually used in routine practice. Physicians may be reluctant to use risk scores at the bedside because they find it inconvenient and time-consuming. Others believe that they can readily discern and integrate high-risk features into overall risk estimation without the aid of risk scores. Although there are numerous established prognostic markers, they usually coexist and their importance hinges on the inter-relationship of many factors. Because patients often present with complex risk profiles, assimilation of all the relevant information from history, physical examination and laboratory investigations is a highly complicated process and a daunting task for a busy clinician (3,56). The risk of future events in this population depends in part on the factors that contribute to acute ischemic risk, and in part on the underlying risk of the patient (including the impact of age, heart failure and renal dysfunction) (5,46). Thus, the most useful risk score will not only provide information on the future risks of death, but also the risks of MI (related to ischemic risk). The latter may be potentially amenable to antithrombotic and revascularization strategies during the index hospitalization, whereas the former may be ameliorated by secondary prevention measures.

On the basis of evidence from randomised trials of interventional versus conservative strategies in NSTE ACS (6,39,55,57,58), ACC/AHA and ESC guidelines advocate revascularization for moderate- or higher-risk patients, but not for low-risk patients, particularly in the female patients (3-5). Similarly, in studies of STEMI, subgroup analysis shows that the absolute benefits of revascularisation are highest among

TABLE 3
Predictors of the Global Registry of Acute Cardiac Events (GRACE) risk score

Predictor	Score
Age, years	
<40	0
40–49	18
50–59	36
60–69	55
70–79	73
80	91
Heart rate (beats/min)	
<70	0
70–89	7
90–109	13
110–149	23
150–199	36
>200	46
Systolic blood pressure (mmHg)	
<80	63
80–99	58
100–119	47
120–139	37
140–159	26
160–199	11
>200	0
Creatinine (μmol/L)	
0–34	2
35–70	5
71–105	8
106–140	11
141–176	14
177–353	23
≥354	31
Killip class	
I	0
II	21
III	43
IV	64
Cardiac arrest at admission	43
Elevated cardiac markers	15
ST-segment deviation	30

The GRACE risk score ranges from 2 to 372

patients with more extensive infarction (59). Clinical practice would therefore be expected to reflect this evidence. In contrast, the opposite is seen in most studies. An inverse relationship between the rate of PCI (or the rate of angiography) and the risk status of the patient, irrespective of whether the patient had UA, NSTEMI or STEMI, is observed. In the study by Van de Werf et al (38) of patients enrolled in the GRACE database, patients admitted to hospitals with catheterization facilities were more likely to undergo intervention than were patients admitted to sites without such facilities, but they had a higher risk of death within six months of discharge. This later risk may reflect hazards of intervention among low-risk patients. The randomized trial evidence and the guidelines support the use of revascularization in moderate- or high-risk patients, irrespective of the presence of on-site catheterization facilities.

Several multivariable prognostic models have been developed, most of which were derived from clinical trial databases or specific subgroups of patients with ACS. Patients with complications and comorbidity tend to be excluded from such trials, thus limiting their applicability. In contrast, the GRACE registry spans the spectrum of ACS and is based on an unselected contemporary population. Independent studies suggest that the unselected GRACE mortality model is superior to either the TIMI or the PURSUIT models (40,41,60). A number of reasons may account for the differences in discriminatory capacities of TIMI, PURSUIT and GRACE risk scores. Although advanced age, ST-segment deviation and biomarker status are common components of all three risk scores, PURSUIT and GRACE incorporate hemodynamic variables also, whereas renal dysfunction is included in GRACE only. These clinical characteristics, which have been shown to be powerful independent prognosticators (61-65), were not evaluated as candidate variables when the TIMI risk score was initially developed (10). Exclusion of patients with these high-risk features from clinical trials may also have diminished the prognostic significance of these variables, which were therefore eliminated during model development. (Because of the low incidence of signs of heart failure on admission in the population of the TIMI 11B trial used for the development of the TIMI score, this variable was not included in the model, unlike in the other two scores. This is an important limitation, especially because the occurrence of heart failure is much more frequent in the real world than in the selected patients from clinical trials, and its prognostic value is well established [10].) Furthermore, the TIMI risk score is composed of dichotomous variables only, and with a limited range of 0 to 7, likely incurred a trade-off between its ease of use and predictive accuracy. GRACE and PURSUIT risk scores were better than the TIMI risk score (40) in predicting death or MI. However, due to the complexity of the PURSUIT risk score, it is less favoured among physicians and has not gained much popularity.

CONCLUSION

Risk scores are simple prognostication scheme that categorize a patient's risk of death and ischemic events. Their use can help tailor our therapies to match the intensity of the patient's NSTE ACS. Knowing how time plays an important role in the management of ACS patients, the faster we can identify the high-risk patients the more the benefit can be achieved by administering the optimal treatment early. For instance, high-risk patients will benefit more from very early invasive strategy while low-risk patients can be spared potentially harmful treatment. ACC/AHA guidelines state that "estimation of the level of risk is a multivariable problem that cannot be accurately quantified with a simple table" (3) and the use of a risk score could only benefit, especially in women. The ideal score for risk stratification on admission for NSTE ACS patients should have a good balance between complexity and utility. When the scores include continuous variables such as age, heart rate and serum creatinine they are more powerful, but also more complex to calculate. However, personal digital assistant applications may significantly simplify these complex calculations such that, at the present time, the complexity of a score is essentially determined by factors related to data collection, rather than the

methodology involved in the calculations. Using the GRACE risk score, one could calculate even more precisely the risk and the associated mortality rate compared with other risk scores. In regard to the above discussed aspects, the GRACE risk score is more advantageous and easier to use in comparison with other available risk scores. Hence, using GRACE risk score in the daily risk assessment of ACS patients can only help us. However, it should be emphasized that risk scores are clinical tools that can supplement but not replace sound clinical judgment.

REFERENCES

1. American Heart Association 2001 Heart and Stroke Statistical Update. <www.americanheart.org/statistics/pdf/HSSTATS2001_1.0.pdf> (Version current at May 25, 2009).
2. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997; 349:1269-76.
3. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non–ST-Elevation Myocardial Infarction): Developed in collaboration with the American College of Emergency Physicians, American College of Physicians, Society for Academic Emergency Medicine, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2007;50:e1-157.
4. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol 2004;44:e1-e211.
5. J-P Bassand, CW Hamm, D Ardissino, et al. Management of ACS in patients presenting without persistent ST-segment elevation. Eur Heart J 2007;28:1598-660.
6. Lee CH, Tan M, Yan AT, et al. Use of cardiac catheterization for non-ST-segment elevation acute coronary syndromes according to initial risk. Reasons why physicians choose not to refer their patients. Arch Intern Med 2008;168:291-6.
7. Calvin JE, Klein LW, VandenBerg BJ, et al. Risk stratification in unstable angina. Prospective validation of the Braunwald classification. JAMA 1995;273:136-41.
8. Jacobs DR Jr, Kroenke C, Crow R, et al. PREDICT: A simple risk score for clinical severity and longterm prognosis after hospitalization for acute myocardial infarction or unstable angina: The Minnesota heart survey. Circulation 1999;100:599-607.
9. Boersma E, Pieper KS, Steyerberg EW, et al, for the PURSUIT Investigators. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation: Results from an international trial of 9461 patients. Circulation 2000;101:2557-67.
10. 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.
11. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. Arch Intern Med 2003;163:2345-53.
12. Abramson JL, Veledar E, Weintraub WS, Vaccarino V. Association between gender and in-hospital mortality after percutaneous coronary intervention according to age. Am J Cardiol 2003;91:968-71.
13. Mehilli J, Kastrati A, Dirschinger J, Bollwein H, Neumann FJ, Schomig A. Differences in prognostic factors and outcomes between women and men undergoing coronary artery stenting. JAMA 2000;284:1799-805.
14. Lansky AJ, Mehran R, Dangas G, et al. Comparison of differences in outcome after percutaneous coronary intervention in men versus women <40 years of age. Am J Cardiol 2004;93:916-9.
15. Sheifer SE, Canos MR, Weinfurt KP, et al. Sex differences in coronary artery size assessed by intravascular ultrasound. Am Heart J 2000;139:649-53.
16. Watanabe CT, Maynard C, Ritchie JL. Comparison of short-term outcomes following coronary artery stenting in men versus women. Am J Cardiol. 2001;88:848-52.
17. Beinart SC, Vaccarino V, Abramson JL, Hewitt K, Weintraub WS. Effect of gender according to age on in-hospital mortality in patients with acute myocardial infarction in the ACC-National Cardiovascular Data Registry. J Am Coll Cardiol 2003;41(Suppl A):540A. (Abst)
18. Lansky AJ, Pietras C, Costa RA, et al. Gender differences in outcomes after primary angioplasty versus primary stenting with and without abciximab for acute myocardial infarction: Results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. Circulation 2005;111:1611-8.
19. H Jneid, GC Fonarow, CP Cannon, et al. Sex differences in medical care and early death after acute myocardial infarction. Circulation 2008;118:2803-10.
20. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. JAMA 1999;281:707-13.
21. de Zwaan C, Bar FW, Janssen JH, et al. Angiographic and clinical characteristics of patients with unstable angina showing an ECG pattern indicating critical narrowing of the proximal LAD coronary artery. Am Heart J 1989;117:657-65.
22. Slater DK, Hlatky MA, Mark DB, Harrell FE, Pryor DB, Califf RM. Outcome in suspected acute myocardial infarction with normal or minimally abnormal admission electrocardiographic findings. Am J Cardiol 1987;60:766-70.
23. Carruthers KF, Dabbous OH, Flather MD, et al, on behalf of the GRACE Investigators. Contemporary management of acute coronary syndromes: Does the practice match the evidence? The Global Registry of Acute Coronary Events (GRACE). Heart 2005;91:290-8.
24. Abidov A, Rozanski A, Hachamovitch R, et al. Prognostic significance of dyspnea in patients referred for cardiac stress testing. N Engl J Med 2005;353:1889-98.
25. Goff Jr DC, Sellers DE, McGovern PG, et al. Knowledge of heart attack symptoms in a population survey in the United States: The REACT Trial. Rapid Early Action for Coronary Treatment. Arch Intern Med 1998;158:2329-38.
26. Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: A summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002;136:161-72.
27. Goff Jr DC, Feldman HA, McGovern PG, et al. Rapid Early Action for Coronary Treatment (REACT) Study Group prehospital delay in patients hospitalized with heart attack symptoms in the United States: The REACT trial. Am Heart J 1999;138:1046-57.
28. Goodacre S, Locker T, Morris F, Campbell S. How useful are clinical features in the diagnosis of acute, undifferentiated chest pain? Acad Emerg Med 2002;9:203-8.
29. Bertrand ME, Simoons ML, Fox KA, et al. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2002;23:1809-40.
30. Goodacre SW, Angelini K, Arnold J, Revil S, Morris F. Clinical predictors of acute coronary syndromes in patients with undifferentiated chest pain. Q J Med 2003;96:893-8.
31. Blatchford O, Capewell S, Murray S, Blatchford M. Emergency medical admissions in Glasgow: General practices vary despite adjustment for age, sex and deprivation. Br J Gen Pract 1999;49:551-5.
32. Clancy M. Chest pain units. Br Med J 2002;325:116-7.
33. Collinson PO, Premachandram S, Hashimi K. Prospective audit of incidence of prognostically important myocardial damage in patients discharges from emergency department. Br Med J 2000;320:1702-5.
34. Fox KA. Management of acute coronary syndromes: An update. Heart 2004;90:698-706.
35. Scirica BM, Morrow DA. Troponins in acute coronary syndromes. Progress Cardiovasc Dis 2004;47;177-88.
36. Wu AH, Apple FS, Gibler WB, Jesse RL, Warshaw MM, Valdes RJ. National Academy of Clinical Biochemistry Standards of Laboratory Practice: Recommendations for the use of cardiac markers in coronary artery diseases. Clin Chem 1999;45:1104-21.

37. Fox KA, Birkhead J, Wilcox R, Knight C, Barth JH. British Cardiac Society Working Group on the definition of myocardial infarction. Heart 2004;90:603-9.
38. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The task force on the management of acute myocardial infarction of the European Society of Cardiology. Eur Heart J 2003;24:28-66.
39. Fox KA, Poole-Wilson P, Clayton TC, Henderson RA, Shaw TR, Wheatley DJ. 5 year outcome of an interventional strategy in non ST elevation acute coronary syndrome: The British Heart Foundation RITA 3 randomised trial. Lancet 2005;366:14-20.
40. De Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: Sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J 2005;26:865-72.
41. Eagle KA, Lim MJ, Dabbous O, et al. A validated prediction model for all forms of acute coronary syndrome. JAMA 2004;291:2727-33.
42. Scirica BM, Cannon CP, Antman EM, et al. Validation of the Thrombolysis in Myocardial Infarction (TMI) risk score for unstable angina pectoris and non-ST-elevation myocardial infarction in the TIMI III Registry. Am J Cardiol 2002;90:303-5.
43. Brilakis ES, Kopecky SL, Williams BA, Vinar J, Clements IP. Use of the PURSUIT risk score can provide accurate early risk stratification in a nonselected, community-based population with non-ST-elevation acute myocardial infarction. J Am Coll Cardiol 2001;37(Suppl):344A. (Abst)
44. Global Registry for Acute Coronary Events (GRACE). <www.outcomes.org/grace> (Version current at May 25, 2009).
45. The GRACE investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) project: A multinational registry of patients hospitalised with acute coronary syndromes. Am Heart J 2001;141:190-9.
46. Fox KA, Dabbous OH, Goldberg RJ, et al, for the GRACE Investigators. Prediction of risk of death and myocardial infarction in the six months following presentation with ACS: A prospective, multinational, observational study (GRACE). BMJ 2006;333:1091-4.
47. Santopinto JJ, Fox KA, Goldberg RJ, et al. Creatinine clearance and adverse hospital outcomes in patients with acute coronary syndromes: Findings from the Global Registry of Acute Coronary Events (GRACE). Heart 2003;89:1003-8.
48. Reddan DN, Szczech L, Bhapkar MV, et al. Renal function, concomitant medication use and outcomes following acute coronary syndromes. Nephrol Dial Transplant 2005; 20: 2105-12.
49. Al Suwaidi J, Reddan DN, Williams K, et al. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. Circulation 2002;106:974-80.
50. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351:1285-95.
51. Morrow DA, Antman EM, Snapinn SM, 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.
52. Singh M, Reeder GS, Jacobsen SJ, Weston S, Killian J, Roger VL. Scores for post-myocardial infarction risk stratification in the community. Circulation 2002;106:2309-14.
53. Yan AT, Jong P, Yan RT, et al. Clinical trial-derived risk model may not generalize to real-world patients with acute coronary syndromes. Am Heart J 2004;148:1020-7.
54. Yan AT, Yan RT, Tan M, et al. In-hospital revascularization and one-year outcome of acute coronary syndrome patients stratified by the GRACE risk score. Am J Cardiol 2005;96:913-6.
55. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879-87.
56. Weintraub W. Prediction scores after myocardial infarction. Value, limitations, and future directions. Circulation 2002;106:2292-3.
57. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review of 23 randomised trials. Lancet 2003;361:13-20.
58. FRISC II Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999;354:708-15.
59. FTT Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet 1994;343:311-22.
60. Tu JV, Donovan LR, Lee DS, et al. Quality of Cardiac Care in Ontario. EFFECT (Enhanced Feedback For Effective Cardiac Treatment). Toronto: Institute for Clinical Evaluative Sciences, 2004.
61. Gibson CM, Dumaine RL, Gelfand EV, et al. Association of glomerular filtration rate on presentation with subsequent mortality in non-ST-segment elevation acute coronary syndrome; observations in 13,307 patients in five TIMI trials. Eur Heart J 2004;25:1998-2005.
62. Gibson CM, Pinto DS, Murphy SA, et al. Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality. J Am Coll Cardiol 2003;42:1535-43.
63. Freeman RV, Mehta RH, Al Badr W, Cooper JV, Kline-Rogers E, Eagle KA. Influence of concurrent renal dysfunction on outcomes of patients with acute coronary syndromes and implications of the use of glycoprotein IIb/IIIa inhibitors. J Am Coll Cardiol 2003;41:718-24.
64. Khot UN, Jia G, Moliterno DJ, et al. Prognostic importance of physical examination for heart failure in non-ST-elevation acute coronary syndromes. The enduring value of Killip classification. JAMA 2003;290:2174-81.
65. Steg PG, Dabbous OH, Feldman LJ, et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: Observations from the Global Registry of Acute Coronary Events (GRACE). Circulation 2004;109:494-9.