New Risk Score for Patients With Acute Chest Pain, Non-ST-Segment Deviation, and Normal Troponin Concentrations: A Comparison With the TIMI Risk Score

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New Risk Score for Patients With Acute Chest Pain, Non–ST-Segment Deviation, and Normal Troponin Concentrations

A Comparison With the TIMI Risk Score

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OBJECTIVES The purpose of this research was to develop a risk score for patients with chest pain, non–ST-segment deviation electrocardiogram (ECG), and normal troponin levels.

BACKGROUND Prognosis assessment in this population remains a challenge.

METHODS A total of 646 consecutive patients were evaluated by clinical history (risk factors and chest pain score according to pain characteristics), ECG, and early exercise testing. ST-segment deviation and troponin elevation were exclusion criteria. The primary end point was mortality or myocardial infarction at one year. The secondary end point was mortality, myocardial infarction, or urgent revascularization at 14 days (similar to the Thrombolysis In Myocardial Infarction [TIMI] risk score).

RESULTS Primary and secondary end point rates were 6.7% and 5.4%. A risk score was constructed using the variables related to the primary end point: chest pain score ≥10 points (hazard ratio [HR] = 2.5; 1 point), ≥2 pain episodes in last 24 h (HR = 2.2; 1 point), age ≥67 years (HR = 2.3; 1 point), insulin-dependent diabetes mellitus (HR = 4.2; 2 points), and prior percutaneous transluminal coronary angioplasty (HR = 2.2; 1 point). Patients were classified into five categories of risk ($p = 0.0001$): 0 points, 0% event rate; 1 point, 3.1%; 2 points, 5.4%; 3 points, 17.6%; ≥4 points, 29.6%. The accuracy of the score was greater than that of the TIMI risk score for the primary (C index of 0.78 vs. 0.66, $p = 0.0002$) and secondary (C index of 0.70 vs. 0.66, $p = 0.1$) end points.

CONCLUSIONS Patients presenting with chest pain despite no ST-segment deviation or troponin elevation show a non-negligible rate of events at one year. A risk score derived from this specific population allows more accurate stratification than when using the TIMI risk score. (J Am Coll Cardiol 2005;46:443–9) © 2005 by the American College of Cardiology Foundation

The availability of troponin assay in emergency departments has afforded substantial improvement in the diagnosis and management of patients with non–ST-segment elevation acute coronary syndrome (ACS). Troponin is a very sensitive and specific marker of myocardial necrosis (1) and is helpful as a guide to best management, including early revascularization (2,3). The ST-segment depression in the initial electrocardiogram (ECG) is also helpful for identifying patients with ACS at medium to high risk of events, and for guiding their management (4,5). In contrast to these high-risk markers, diagnosis and prognosis assessment in patients with chest pain without ST-segment deviation or troponin elevation remains a challenge. Though some data suggested that a normal troponin result implies excellent prognosis (6), other studies report a non-negligible 3% rate of myocardial infarction or death at 30 days (7), which increased to 4.8% at six months of follow-up (8). Therefore, careful risk stratification seems mandatory.

Several risk scores have been described for non–ST-segment elevation ACS (9–13). The Thrombolysis In Myocardial Infarction (TIMI) risk score is the most widely used. Such scores derive from populations that include high-risk subsets (including ST-segment deviation and/or positive cardiac markers). Consequently, the applicability of these scores to lower-risk patients may not be adequate. Furthermore, troponin was not routinely used as marker of necrosis in most of these studies, and patients were not managed by a chest pain unit protocol, which seems to be the most appropriate management for these lower-risk patients (14).

The present study examined a series of patients with acute chest pain without ST-segment deviation and presenting normal troponin concentrations. They were managed by a chest pain unit protocol and were followed-up for one year. A risk score was elaborated using the predictors of poor outcome, and its performance was compared to the TIMI risk score.

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Abbreviations and Acronyms

ACS = acute coronary syndrome
CABG = coronary artery bypass graft
CI = confidence interval
HR = hazard ratio
IDDM = insulin-dependent diabetes mellitus
PTCA = percutaneous transluminal coronary angioplasty
ROC = receiver-operating characteristic
TIMI = Thrombolysis In Myocardial Infarction

METHODS

The study group consisted of 646 consecutive patients (from January 15, 2001 to November 30, 2003) coming to the emergency room with acute chest pain of possible coronary origin. ST-segment deviation (≥1-mm elevation or depression) in the initial ECG or troponin I elevation were exclusion criteria. Troponin I was determined in our institution on arrival and at 6 h (in patients arriving within the first 2 h from pain onset), 8, and 12 h after pain onset (8,15,16). All patients had normal troponin concentrations at all determinations.

Troponin I was determined immunologically using an Immulite assay (Diagnostic Products Corp., Los Angeles, California). According to the instructions of the manufacturer, the Immulite troponin kit was used to test 255 serum samples from healthy laboratory volunteers and from hospitalized patients who had been shown to be negative for troponin I by another immunometric method. The median values for these samples was non-detectable; 98% of the values were below 1.0 ng/ml. Troponin I increase was defined as ≥1 ng/ml (upper limit of normality). The troponin I assay was tested in our laboratory, the coefficient of variation being <10%. Coefficients of variation were obtained at two levels: one within the normal range and the other above the normal range.

Patients were evaluated by a chest pain unit protocol that included evaluation of the clinical history and ECG, and early exercise testing in patients without contraindication to exercise (physical incapacity or abnormalities in the baseline ECG) (8,12,13).

Clinical evaluation. The clinical characteristics of chest pain presentation were assessed. On the basis of these characteristics, the semiquantitative score previously reported by Geleijnse et al. (17) was calculated (Appendix). In addition, the following variables were recorded, including those variables collected in the TIMI risk score study (9): gender, age, smoking, arterial hypertension, diabetes mellitus, insulin-dependent diabetes mellitus (IDDM), hypercholesterolemia, family history of ischemic heart disease, at least three risk factors for coronary artery disease, ≥2 chest pain episodes in last 24 h, Killip class >1 at presentation, evidence of prior coronary stenosis ≥50%, use of aspirin in the last seven days, prior myocardial infarction, prior percutaneous transluminal coronary angioplasty (PTCA), prior coronary artery bypass graft (CABG), and a history of heart failure. The TIMI risk score was calculated in all patients.

An ECG was recorded in the emergency room and evaluated for T-wave inversion (≥1 mm) or confounding ECG (left bundle branch block of paced rhythm).

Early exercise testing. A total of 322 patients (50%) were eligible for early exercise testing (within the first 24 h after arrival). A symptom-limited Bruce protocol was used. The result was considered positive in the case of ischemia induction (indicated by a 1-mm horizontal or downsloping depression of the ST-segment at 80 ms from the J point, or a 1-mm ST-segment elevation). A negative test was considered when at least a submaximal test was performed without ST-segment changes. An inconclusive test was considered if the patient was unable to reach submaximal heart rate (85% of the theoretical-age-predicted heart rate) without ischemia. All 190 patients with a negative result were discharged after the exercise test, while all 52 with a positive test were hospitalized. In the case of an inconclusive test, the final decision was left to the criterion of the supervising physician.

In-hospital management. Overall, 216 patients were early discharged and 430 hospitalized. All hospitalized patients were treated with aspirin, low-molecular-weight heparin, and beta-blockers (unless contraindicated). Patients underwent invasive management in case of recurrent chest pain or evidence of ischemia in noninvasive tests. Cardiac catheterization was performed in 227 patients (35% of the global population and 53% of the hospitalized patients). During hospitalization 68 patients underwent PTCA and 31 CABG. Creatine kinase-MB mass (5 ng/ml upper limit of normal) was routinely determined 12 and 24 h after a revascularization procedure. Fifty-seven patients had normal coronary arteries.

End points. Patients were followed-up for one year. Complete follow-up was obtained in 98% of the patients (a total of 11 cases were missed). The end points considered in the TIMI risk score study were used in the present study (9). Therefore all-cause mortality, acute myocardial infarction, and urgent revascularization were recorded. An acute myocardial infarction was defined as a new episode of chest pain with increased troponin I. Acute myocardial infarction was also considered if creatine kinase-MB mass increased to ≥3 times the upper limit of normal after PTCA or to ≥5 times the upper limit of normal after coronary bypass surgery. Severe recurrent ischemia requiring urgent revascularization was defined as an episode of recurrent angina prompting the performance of coronary revascularization on the index hospitalization or an episode of recurrent angina after discharge that resulted in re-hospitalization during which coronary revascularization was performed.

The primary end point was a composite of all-cause mortality or non-fatal myocardial infarction at one year. The secondary end point was a composite of all-cause mortality, non-fatal myocardial infarction, or urgent revas-

cularization at 14 days (similar to the primary end point of the TIMI risk score study).

Statistical analysis. To analyze the predictors for the end points, data from the clinical history were taken as independent variables. Continuous variables were expressed as the mean ± SD and compared by the unpaired *t* test or the analysis of variance test for more than two groups. Categorical variables were expressed as percentages and compared by the chi-square test. Continuous variables, such as age and chest pain score, were dichotomized, taking the best cutoff point of the receiver-operating characteristic (ROC) curves for primary end point prediction. Multivariate analysis by Cox regression models tested variables that were significant at $p < 0.1$ in the univariate analysis. The hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. A risk score was developed using the five variables associated with the primary end point in the multivariable analysis. For the construction of the risk score, each variable was considered as 1 point except IDDM, which was considered as 2 points because its HR was twice the value of the HR of the remaining variables. The ROC curves were used to test the accuracy of the new risk score and of the TIMI risk score for predicting the primary and secondary end points. The ROC curves corresponding to both risk scores were compared.

Calculations were performed using the SPSS software version 9.0 (SPSS Inc., Chicago, Illinois). Comparison between ROC curves was performed using the STATA software version 8.2 (Stata Corp., College Station, Texas). Statistical significance was considered for $p < 0.05$.

Validation cohort. The new risk score was validated in a second cohort comprising 171 consecutive patients coming to the emergency room of our hospital with acute chest pain without ST-segment deviation and with normal troponin levels, in the period immediately after the inclusion of the first cohort (from December 1, 2003 to February 1, 2005). The primary end point (death or myocardial infarction) was recorded for a median follow-up of 28 weeks.

RESULTS

Patient population characteristics. Table 1 shows the clinical and ECG characteristics of the global patient population.

During one year of follow-up, 21 patients died (3.3%) and 29 suffered acute myocardial infarction (4.5%). Two deaths and six infarctions were related to revascularization procedures. The primary end point (death or myocardial infarction) occurred in 43 patients (6.7%). At 14 days of follow-up, 5 patients died (0.8%), 17 suffered acute myocardial infarction (2.6%), 26 underwent urgent revascularization (4%), and 35 (5.4%) reached the secondary end point (death, myocardial infarction, or urgent revascularization).

Predictors of the primary end point. Table 2 lists the predictors of the primary end point by univariate and multivariate analysis. Chest pain score (11.6 ± 2.4 points vs. 10.3 ± 2.8 points, $p = 0.002$) and age (70 ± 11 years vs. 64 ± 12 years, $p = 0.001$) were associated with the primary end point. According to their ROC curves, these variables were dichotomized as ≥10 points and ≥67 years, respectively, for predictive analysis.

Table 1. Characteristics of the Patient Population (n = 646)

Clinical history	
Chest pain score (points)	10.4 ± 2.8
≥2 chest pain episodes in last 24 h	229 (35%)
Killip class >1	20 (3%)
Age (yrs)	64 ± 12
Men	425 (68%)
Current smokers	131 (20%)
Hypertension	380 (59%)
Hypercholesterolemia	341 (53%)
Diabetes mellitus	166 (26%)
IDDM	45 (7%)
Family history of ischemic heart disease	78 (12%)
At least three risk factors*	81 (13%)
Prior coronary stenosis ≥50%	156 (24%)
Use of aspirin in last 7 days	278 (43%)
Prior myocardial infarction	163 (25%)
Prior PTCA	59 (9%)
Prior CABG	50 (8%)
History of heart failure	13 (2%)
ECG	
T-wave inversion	66 (10%)
Confounding ECG	56 (9%)

*Risk factors included family history of ischemic heart disease, hypertension, hypercholesterolemia, diabetes, or being a current smoker.

CABG = coronary artery bypass grafting; ECG = electrocardiogram; IDDM = insulin-dependent diabetes mellitus; PTCA = percutaneous transluminal coronary angioplasty.

In order to evaluate the influence of early exercise testing, the patient population was divided into four groups according to the performance and results of the exercise test as follows: negative result, inconclusive result, positive result, and not performed. The rates of the primary end point were 1.6%, 3.9%, 9.6%, and 10%, respectively ($p = 0.002$ for the trend), significance being reached for the differences between the subgroup with a negative result and the subgroup with inability to perform the test ($p = 0.004$). Thus, a negative result in the early exercise test and inability to perform the test were incorporated to the predictive analysis as independent variables (Table 2).

By multivariable Cox regression analysis, the independent factors that increased the risk of the primary end point were a chest pain score ≥10 points (HR = 2.5, 95% CI 1.2 to 5.6, $p = 0.02$), ≥2 chest pain episodes in last 24 h (HR = 2.2, 95% CI 1.2 to 4.2, $p = 0.01$), age ≥67 years (HR = 2.3, 95% CI 1.2 to 4.4, $p = 0.01$), IDDM (HR = 4.2, 95% CI 2.1 to 8.4, $p = 0.0001$), and prior PTCA (HR = 2.2, 95% CI 1.1 to 4.8, $p = 0.04$).

Risk score. A risk score was constructed taking the five variables independently related to the primary end point. To this effect, 1 point value was assigned to those variables having a similar HR, as chest pain score ≥10 points, ≥2 chest pain episodes in the last 24 h, age ≥67 years, and prior PTCA. On the other hand, a 2-point value was used for IDDM because its HR was two-fold greater. The variables

Table 2. Predictors of the Primary End Point (Death or Myocardial Infarction)

	Univariate	Multivariate		
	p Value	p Value	HR	95% CI
Clinical history				
Pain score ≥10 points	0.001	0.02	2.5	1.2–5.6
≥2 chest pain episodes in last 24 h	0.001	0.01	2.2	1.2–4.2
Killip >1	0.1	0.7		
Age ≥67	0.004	0.01	2.3	1.2–4.4
Men	0.4			
Current smokers	0.2			
Hypertension	0.4			
Hypercholesterolemia	0.6			
Diabetes mellitus	0.001	0.2		
IDDM	0.0001	0.0001	4.2	2.1–8.4
Family history of ischemic heart disease	0.6			
At least three risk factors	0.8			
Prior coronary stenosis ≥50%	0.1	0.7		
Use of aspirin in last 7 days	0.02	0.6		
Prior myocardial infarction	0.1	0.9		
Prior PTCA	0.05	0.04	2.2	1.1–4.8
Prior CABG	0.1	0.8		
History of heart failure	0.6			
ECG				
T-wave inversion	0.4			
Confounding ECG	0.09	0.3		
Early exercise test				
Negative result	0.0001	0.07		
Inability to exercise	0.001	0.2		

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

of the stress test were not included in the final score because they were not significant in the Cox regression analysis. Distribution of the patient population according to the risk score was as follows: 0 points, n = 111 (17.2%); 1 point, n = 198 (30.7%); 2 points, n = 206 (31.9%); 3 points, n = 103 (15.9%); 4 points, n = 16 (2.5%); 5 points, n = 11 (1.7%); and 6 points, n = 1 (0.2%). Because of the small number of patients in the extreme upper score range, patients with 4 to 6 points were combined (n = 28, 4.3%). Five categories were therefore distinguished (Fig. 1): very low-risk (0 points, primary end point = 0%), low-risk (1 point, primary end point = 3.1%), intermediate-risk (2 points, primary end point = 5.4%), high-risk (3 points, primary end point = 17.6%), and very high-risk (≥4 points, primary end point = 29.6%). The statistical significance for the trend was p = 0.00001, the differences between the very low-, low- and intermediate-risk categories being significant compared with the very high- (p = 0.0001, p = 0.0001, and p = 0.0001, respectively) and high-risk (p = 0.002, p = 0.0001, p = 0.0001, respectively) categories.

Comparison with the TIMI risk score. The accuracy of the new risk score for the primary end point was tested by a ROC curve, showing a C index of 0.78 (p = 0.0001). The TIMI risk score was also associated with the primary end point (C index of 0.66, p = 0.0001). However, the C index of the new risk score was significantly greater (p = 0.0002, Fig. 2). The accuracy of both risk scores was also tested for the secondary end point consisting of death, myocardial infarction, or urgent revascularization at 14 days, for which

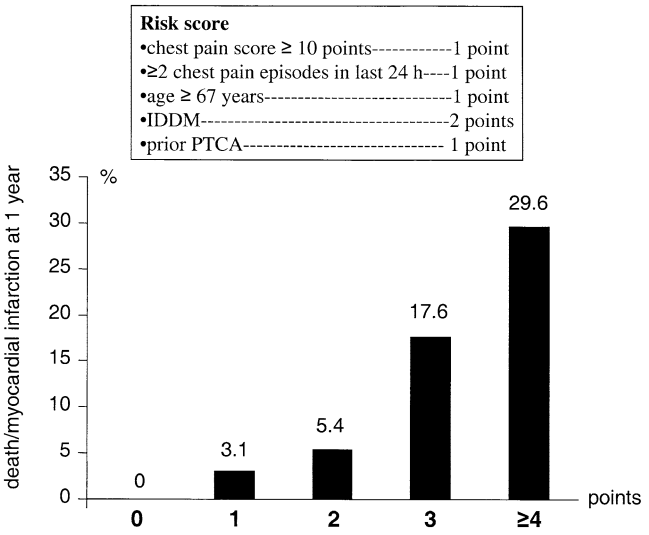

Figure 1. Risk categories according to risk score: very low-risk (0 points, primary end point = 0%), low-risk (1 point, primary end point = 3.1%), intermediate-risk (2 points, primary end point = 5.4%), high-risk (3 points, primary end point = 17.6%), and very high-risk (≥4 points, primary end point = 29.6%). The statistical significance for the trend was p = 0.00001; the differences between the very low-, low-, and intermediate-risk categories being significant compared to the very high- (p = 0.0001, p = 0.0001, and p = 0.0001, respectively) and high-risk (p = 0.002, p = 0.0001, p = 0.0001, respectively) categories. IDDM = insulin-dependent diabetes mellitus; PTCA = percutaneous transluminal coronary angioplasty.

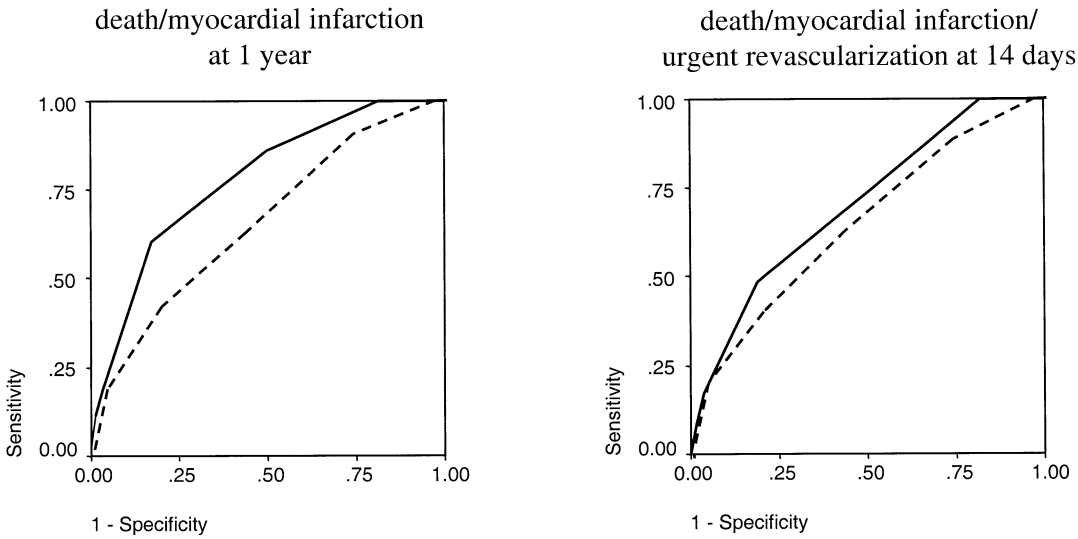

Figure 2. Receiver-operating characteristic curves of the new risk score and of the Thrombolysis In Myocardial Infarction (TIMI) risk score for the primary end point (death or myocardial infarction at 1 year) **(left)** and the secondary end point (death or myocardial infarction or urgent revascularization at 14 days) **(right)**. The accuracy of the new risk score was greater for both the primary (C index of 0.78 vs. 0.66, p = 0.0002) and secondary (C index of 0.70 vs. 0.66, p = 0.1) end points. **Solid line** = new risk score; **dashed line** = TIMI risk score.

the TIMI risk score was originally designed (9). The new risk score (C index of 0.70, p = 0.0001) and the TIMI risk score (C index of 0.66, p = 0.002) were both correlated to the secondary end point, but without significant differences between them (p = 0.1).

Validation cohort. In the validation cohort the primary end point occurred in eight patients (4.7%). The new risk score was associated with the primary end point (C index of 0.78, p = 0.007) and was more accurate (p = 0.05) than the TIMI risk score (C index of 0.70, p = 0.06).

DISCUSSION

Main findings. The present study included a series of patients presenting to the emergency department with acute chest pain, non–ST-segment deviation in the initial ECG, and normal troponin concentrations. After one year of follow-up, a 6.7% rate of mortality or nonfatal myocardial infarction was found. Clinical data at presentation allowed risk stratification. Using clinical predictors, a risk score proved to be useful for prognostic categorization. This new risk score evidenced superior accuracy than the TIMI risk score for this specific population.

Prognosis of patients with chest pain and normal troponin levels. The introduction of troponin as a diagnostic tool facilitates the triage of patients with acute chest pain. However, though a negative troponin result identifies a lower risk, this does not necessarily imply a low-risk group (18). Although initial studies reported an excellent short-term prognosis for troponin-negative patients (6), later data found a non-negligible 3% rate of major events at 30 days (7) and 4.8% at 6 months (8). In the present study, in which ST-segment deviation in the initial ECG was an exclusion criterion, the rate of death or myocardial infarction was 6.7% at one year. For a longer period of follow-up, a 10% event rate has been observed at 31 months (19). These data, therefore, point to the need for careful prognostic assessment in this population despite its apparent low risk.

Risk score. Evaluation of the clinical history in the emergency room is of utmost importance in patients with chest pain, mainly in the absence of other objective signs as is the case of a non–ST-segment deviation ECG and negative markers of necrosis. In the present study, a risk score was constructed with five clinical variables of the clinical history that were shown to have important prognostic value: typical presentation of chest pain (evaluated by a chest pain score); two or more chest pain episodes in the last 24 h; a patient age of 67 years or older; IDDM; and prior PTCA. This score was useful for patient classification into five progressive risk categories (0%, 3.1%, 5.4%, 17.6%, and 29.6% event rate).

One of the major problems with chest pain symptoms is that they are variable and perceived very differently by patients (20). In order to define the characteristics of chest pain, we used a chest pain score previously published by Geleijnse et al. (17) that has been shown to possess prognostic value in a previous series of patients with chest pain and negative troponin levels with or without ST-segment depression in the initial ECG (8). The chest pain score was associated with poorer outcome, reflecting that a typical presentation increases the probability of a cardiac origin of the pain. Recurrence of chest pain within 24 h before admission increased the risk as a marker of instability. Older age was another predictor of risk, as seen in all risk scores for non–ST-segment ACS (9–12). Diabetes mellitus was an independent factor in the univariate analysis, though, in the multivariate model, IDDM was the variable included, its HR being twice the value of the remaining factors. The longer evolution of their metabolic

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disturbance as well as the more diffuse coronary disease and smaller arterial size observed in diabetics treated with insulin could explain this finding (21). Finally, a previous PTCA as hallmark of a documented history of coronary artery disease requiring revascularization also exerted prognostic influence.

Comparison to the TIMI risk score. Among the risk scores described for non–ST-segment elevation ACS, the TIMI risk score is the most widely used (9). Although it was not designed for the whole spectrum of patients with acute chest pain, its use tended to be generalized in all patients with non–ST-segment elevation chest pain. The present study demonstrates that the new risk score is more accurate than the TIMI risk score in patients with non–ST-segment deviation ECG and normal troponin values, especially for predicting major events at one year. Its predictive accuracy for short-term cardiac events for which the TIMI risk score was originally calculated was similar. The main explanation for this could be that the TIMI risk score was not designed for such a low-risk population. The TIMI risk score was designed to facilitate risk stratification in patients with non–ST-segment elevation ACS. It was not designed to aid in the diagnosis of this syndrome, which continues to be based on clinical parameters that may be supported by appropriate ECG changes or elevations of biomarkers of necrosis. In addition, the characteristics of chest pain presentation were not evaluated in the TIMI risk score, probably because of their lesser role in high-risk patients. Finally, diabetes and IDDM were not tested as individual risk factors.

Study limitations. The risk score was verified on a separate validation cohort. However, this validation cohort examined the primary end point after a median follow-up of 28 weeks, as opposed to the primary end point in the original cohort that examined outcome after 52 weeks.

Conclusions. In patients presenting with acute chest pain, the presence or absence of ST-segment deviation or troponin elevation differentiates a high- from a low-risk group of patients. The latter patients, however, show a non-negligible 6.7% rate of major events at one year. Clinical variables at presentation, such as typical characteristics of the chest pain, two or more chest pain episodes in the last 24 h, patient age 67 years or older, IDDM, and prior PTCA, allow the construction of a risk score that has been shown to be useful for early prognostic stratification. The predictive accuracy of this score for one-year major cardiac events is greater than that of the TIMI risk score.

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APPENDIX

Chest Pain Score (Geleijnse et al. [17])

Location	
Substernal	+3
Precordial	+2
Neck, jaw, epigastrium	+1
Apical	−1
Radiation	
Either arm	+2
Shoulder, back, neck, jaw	+1
Characteristics	
Crushing, pressing, squeezing	+3
Heaviness, tightness	+2
Sticking, stabbing, pinprick, catching	−1
Severity	
Severe	+2
Moderate	+1
Influenced by	
Nitroglycerin	+1
Stature	−1
Breathing	−1
Associated symptoms	
Dyspnea	+2
Nausea or vomiting	+2
Diaphoresis	+2
History of exertional angina	+3

New Risk Score for Patients With Acute Chest Pain, Non-ST-Segment Deviation, and Normal Troponin Concentrations: A Comparison With the TIMI Risk Score

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