

The TIMI Risk Score for Unstable Angina/Non-ST Elevation MI

A Method for Prognostication and Therapeutic Decision Making

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PATIENTS PRESENTING WITH AN acute coronary syndrome without ST-segment elevation are diagnosed as having unstable angina/non-ST elevation myocardial infarction (MI) (UA/NSTEMI). Given the heterogeneous nature of UA/NSTEMI, such patients have a wide spectrum of risk for death and cardiac ischemic events.¹⁻⁵ Many attempts to estimate a gradient of risk among patients with UA/NSTEMI focus on a single variable, such as presence or absence of electrocardiographic (ECG) changes⁶⁻⁹ or elevated serum cardiac markers.¹⁰⁻¹³

Prognostication schemes have been developed that categorize patients qualitatively into high, intermediate, or low risk, but they do not provide a quantitative statement about finer gradations of risk that exist clinically.² Although univariate analyses are informative as an initial assessment of the importance of a potential prognos-

Context Patients with unstable angina/non-ST-segment elevation myocardial infarction (MI) (UA/NSTEMI) present with a wide spectrum of risk for death and cardiac ischemic events.

Objective To develop a simple risk score that has broad applicability, is easily calculated at patient presentation, does not require a computer, and identifies patients with different responses to treatments for UA/NSTEMI.

Design, Setting, and Patients Two phase 3, international, randomized, double-blind trials (the Thrombolysis in Myocardial Infarction [TIMI] 11B trial [August 1996–March 1998] and the Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave MI trial [ESSENCE; October 1994–May 1996]). A total of 1957 patients with UA/NSTEMI were assigned to receive unfractionated heparin (test cohort) and 1953 to receive enoxaparin in TIMI 11B; 1564 and 1607 were assigned respectively in ESSENCE. The 3 validation cohorts were the unfractionated heparin group from ESSENCE and both enoxaparin groups.

Main Outcome Measures The TIMI risk score was derived in the test cohort 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. Relative differences in response to therapeutic interventions were determined by comparing the slopes of the rates of events with increasing score in treatment groups and by testing for an interaction between risk score and treatment. Outcomes were TIMI risk score for developing at least 1 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.

Results The 7 TIMI risk score predictor variables were age 65 years or older, at least 3 risk factors for coronary artery disease, prior coronary stenosis of 50% or more, ST-segment deviation on electrocardiogram at presentation, at least 2 anginal events in prior 24 hours, use of aspirin in prior 7 days, and elevated serum cardiac markers. 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 ($P < .001$ by χ^2 for trend). The pattern of increasing event rates with increasing TIMI risk score was confirmed in all 3 validation groups ($P < .001$). The slope of the increase in event rates with increasing numbers of risk factors was significantly lower in the enoxaparin groups in both TIMI 11B ($P = .01$) and ESSENCE ($P = .03$) and there was a significant interaction between TIMI risk score and treatment ($P = .02$).

Conclusions In patients with UA/NSTEMI, the TIMI risk score is a simple prognostication scheme that categorizes a patient's risk of death and ischemic events and provides a basis for therapeutic decision making.

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See also p 876 and Patient Page.

tic variable, because of the complex profile of patients with an acute coronary syndrome, multivariate analyses that adjust for several prognostic variables simultaneously provide a more accurate tool for risk stratification.^{2,5,14}

Reports of the results of randomized clinical trials of new therapeutic strategies for UA/NSTEMI typically provide a statement of the overall effectiveness of a treatment in a population that is a mixture of patients at varying risks of the primary end point. Although univariate subgroup analyses are frequently presented in clinical trial reports, these provide only a partial picture of the effect of the new treatment in a given subgroup unless adjustment is made for covariates. Given the spectrum of clinical presentations, it is plausible that the magnitude of the treatment effect of a therapy may vary depending on the profile of risk in any specific patient.¹⁵

Prognostication of patient risk, therefore, is useful not only for allowing clinicians to triage patients to the optimum location for delivery of medical care (eg, intensive care unit vs hospital ward vs outpatient care)^{16,17} but also for identification of patients who may be best served by potent but expensive—and sometimes risky—new therapies.^{5,18-20} To facilitate widespread use of a prognostic scoring system for patients with UA/NSTEMI, it must be readily applicable using standard patient features that are part of the routine medical evaluation of such patients.

The primary goal of this article is to report the development, testing, and clinical utility of a risk stratification tool for evaluation of patients with UA/NSTEMI. Previously, we reported that a risk stratification scheme based on age 65 years or older, ST deviation on ECG, and positive serum cardiac markers segregated patients with UA/NSTEMI into low-, intermediate-, and high-risk groups, and the treatment effect of enoxaparin was greatest in the highest risk group.²¹ However, that risk stratification scheme used only a limited number of baseline characteristics. We

developed a new, more comprehensive risk score for UA/NSTEMI using the database of the Thrombolysis in Myocardial Infarction (TIMI) 11B trial, a phase 3 trial comparing low-molecular-weight heparin (enoxaparin) with unfractionated heparin.²² Our purpose in designing a simple risk score was to provide a tool that potentially could be applied in clinical settings in which patients with UA/NSTEMI present for evaluation.

METHODS

The design and results of the TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave MI (ESSENCE) trials have been reported previously.^{22,23} All patients (n=3910 in TIMI 11B and n=3171 in ESSENCE) presented within 24 hours of an episode of UA/NSTEMI at rest. Additional enrollment criteria included at least 1 of the following: ST-segment deviation on the qualifying ECG (either transient ST elevation or persistent ST depression of ≥ 0.05 mV in TIMI 11B and ≥ 0.01 mV in ESSENCE), documented history of coronary artery disease, and elevated serum cardiac markers. (In TIMI 11B, a history of coronary artery disease was acceptable initially but was dropped later as the sole supportive criterion for UA/NSTEMI.) Major exclusion criteria were planned revascularization in 24 hours or less, a correctable cause of angina, and contraindications to anticoagulation.

All patients received aspirin (100-325 mg/d) and, after providing written informed consent, were randomly assigned to 1 of 2 antithrombotic strategies. Both trials used a double dummy technique so that all patients received both an intravenous infusion (unfractionated heparin or matched placebo) and subcutaneous injections (enoxaparin or matched placebo). For the purposes of developing the TIMI risk score for UA/NSTEMI, the prespecified primary efficacy end point from TIMI 11B was applied to both trials in a fashion similar to that reported for the TIMI 11B-ESSENCE meta-analysis.²⁴ This end point was a composite of all-cause

mortality, new or recurrent MI, or severe recurrent ischemia prompting urgent revascularization. The analyses shown herein are based on rates for the primary end point through 14 days after randomization.

Initially, a multivariate model for prognostication of risk for experiencing at least 1 element of the primary end point was developed. The model incorporated baseline characteristics that could be readily identified at presentation and was restricted to the cohort of patients assigned to unfractionated heparin in TIMI 11B (test cohort). The rationale for this approach was to focus on information that could be ascertained in a relatively short period after encountering a patient and establishing a model that could be used for efficient triage for patient care without waiting for additional tests or results of an initial period of medical observation over several days. Baseline characteristics that were evaluated include those previously reported to be important variables predicting outcomes in patients with UA/NSTEMI and are shown in TABLE 1.^{4,5,14,25,26}

A total of 12 baseline characteristics arranged in a dichotomous fashion were screened as candidate predictor variables of risk of developing an end-point event (Table 1). A multivariate logistic regression model was then used to assess the statistical significance of each candidate prognostic variable. After each factor was tested independently in a univariate logistic regression model, those that achieved a significance level of $P < .20$ were selected for testing in a multivariate stepwise (backward elimination) logistic regression model. Variables associated with $P < .05$ were retained in the final model. Maximum likelihood estimates of the parameter coefficients were obtained using SAS PROC LOGISTIC (SAS Institute Inc, Cary, NC). The goodness of fit of the model to the observed event rates was evaluated by calculating the Hosmer-Lemeshow statistic.²⁷ Low χ^2 values and high corresponding P values for the Hosmer-Lemeshow statistic indicate that the data can be ad-

equately fit to a logistic function. The ability of the model to classify patients (ie, its predictive performance) was evaluated using the C statistic, a term equivalent to the area under a receiver operating characteristic curve for dichotomous outcomes.²⁸ Assessment of the impact of missing information for predictor variables was carried out by Monte-Carlo simulations that randomly set fixed proportions of the data to missing and then repeating the logistic regression analyses.

After development of the multivariate model, the TIMI risk score for UA/NSTEMI was developed for the test cohort using those variables that had been found to be statistically significant predictors of events in the multivariate analysis. The score was then constructed by a simple arithmetic sum of the number of variables present. Differences in the event rates for increasing TIMI risk score values were assessed using the χ^2 test for trend.

The risk score was then validated in 3 separate cohorts of patients: the enoxaparin group from TIMI 11B (n=1953), the unfractionated heparin group from ESSENCE (n=1564), and the enoxaparin group from ESSENCE (n=1607). We tested for homogeneity of the unfrac-

tionated heparin control groups in TIMI 11B and ESSENCE by comparing the slope of the increase in the rate of events with increasing TIMI risk score using least squares linear regression analysis. Differences between the unfractionated heparin and enoxaparin groups in both TIMI 11B and ESSENCE were also assessed by comparing the slope of the increase in rate of events with increasing TIMI risk score using least squares linear regression analysis. In addition, using a merged database of the TIMI 11B and ESSENCE studies, testing for a heterogeneous treatment effect stratified by risk score was carried out by examining the statistical significance of the interaction term in a multivariate logistic regression model of the following form: outcome=constant + risk score + treatment (eg, unfractionated heparin vs enoxaparin) + risk score * treatment.

The asterisk in the model designates an interaction between the adjoining terms. To explore whether the interaction of risk score * treatment was affected by the trial in which the patient was enrolled, we tested for statistical significance of terms for trial (TIMI 11B vs ESSENCE) and interaction of trial with risk score and treatment when added to the model.

As a secondary goal, we examined the ability of the TIMI risk score to predict development of each of the individual components of the composite primary end point as well as the composite end point of all-cause mortality or nonfatal MI.

RESULTS

The test cohort for development of the TIMI risk score consisted of the 1957 patients assigned to receive unfractionated heparin in TIMI 11B.²² The primary end point (all-cause mortality, MI, or urgent revascularization) occurred by 14 days in 16.7% of patients in the test cohort. Of the 12 original candidate variables, 7 remained statistically significant in the multivariate analysis and formed the final set of predictor variables (Table 1). The Hosmer-Lemeshow statistic was 3.56_{df8}, (P=.89). The C statistic for the model in the test cohort was 0.65.

Since the parameter estimates for each of the 7 predictor variables were of a similar magnitude (Table 1), the risk score was calculated by assigning a value of 1 when a variable was present and then categorizing patients in the test cohort by the number of risk factors present, as shown in FIGURE 1. The

Table 1. Baseline Characteristics Analyzed for Development of TIMI Risk Score for UA/NSTEMI*

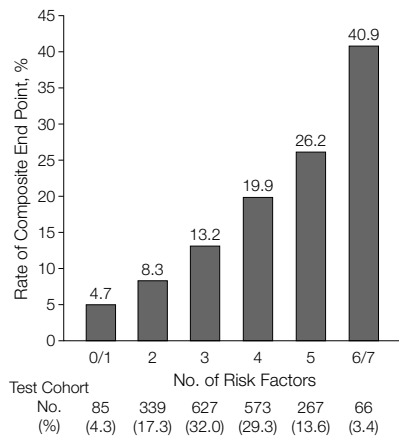
Characteristics†	Univariate Analysis			Multivariate Analysis		
	β Coefficient	P Value	OR (95% CI)	β Coefficient	P Value	OR (95% CI)
Age, ≥ 65 y	0.4681	<.001	1.60 (1.25-2.04)	0.5575	<.001	1.75 (1.35-2.25)
At least 3 risk factors for CAD‡	0.3717	.009	1.45 (1.10-1.91)	0.4336	.003	1.54 (1.16-2.06)
Significant coronary stenosis (eg, prior coronary stenosis $\geq 50\%$)	0.5473	<.001	1.73 (1.34-2.23)	0.5284	<.001	1.70 (1.30-2.21)
Prior MI	0.2386	.06	1.27 (0.99-1.63)			
Prior CABG	0.3004	.07	1.35 (0.97-1.88)			
Prior PTCA	0.4828	.004	1.62 (1.16-2.26)			
ST deviation	0.3356	.02	1.40 (1.06-1.85)	0.4125	.005	1.51 (1.13-2.02)
Severe anginal symptoms (eg, ≥ 2 anginal events in last 24 h)	0.4521	<.001	1.57 (1.24-2.00)	0.4279	.001	1.53 (1.20-1.96)
Use of aspirin in last 7 days	0.6179	.002	1.86 (1.26-2.73)	0.5534	.006	1.74 (1.17-2.59)
Use of IV unfractionated heparin within 24 hours of enrollment	0.1665	.19	1.18 (0.92-1.51)			
Elevated serum cardiac markers§	0.3486	.004	1.42 (1.12-1.80)	0.4420	<.001	1.56 (1.21-1.99)
Prior history of CHF	-0.1058	.70	0.90 (0.53-1.53)			

*UA/NSTEMI indicates unstable angina/non-ST elevation myocardial infarction; OR, odds ratio; CI, confidence interval; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty; IV, intravenous; and CHF, congestive heart failure.

†Bold indicates variables that remained statistically significant in the multivariate analysis and were used as the final set of predictor variables.

‡Risk factors included family history of CAD, hypertension, hypercholesterolemia, diabetes, or being a current smoker.

§Creatine kinase MB fraction and/or cardiac-specific troponin level.

Figure 1. TIMI Risk Score

Rates of all-cause mortality, myocardial infarction, and severe recurrent ischemia prompting urgent revascularization through 14 days after randomization were calculated for various patient subgroups based on the number of risk factors present in the test cohort (the unfractionated heparin group in the Thrombolysis in Myocardial Infarction [TIMI] 11B trial; $n=1957$) (see Table 1). Event rates increased significantly as the TIMI risk score increased ($P<.001$ by χ^2 for trend).

pattern of the number of risk factors was normally distributed. Because of the small number of patients with extreme risk scores, patients with 0 or 1 risk factor(s) and 6 or 7 risk factors were combined. There was a progressive, significant pattern of increasing event rates as the TIMI risk score increased in the test cohort ($P<.001$ by χ^2 for trend).

In the final model, an age cutoff of 65 years was used because this value was close to the median age for the unfractionated heparin group (66 years) and was the median age for the enoxaparin group. Use of different age cutoffs showed very little effect on performance of the model: the C statistic ranged between 0.63 and 0.66 for varying age cutoffs in 5-year increments from 50 to 80 years. Furthermore, treating age as a continuous variable (problematic for the development of a simple risk score) also had little effect on model performance: the C statistic was 0.66 in a model using age as a continuous variable.

One of the 7 predictor variables shown in Table 1, prior coronary stenosis of 50% or more, requires knowledge of the re-

sults of a prior cardiac catheterization. Construction of the TIMI risk score using the TIMI 11B database was accomplished from the case report form data for each patient and, therefore, complete information for the predictor of prior coronary stenosis of 50% or more was available for all patients; a value of 0 was assigned if no cardiac catheterization had been previously performed or if a prior cardiac catheterization revealed no coronary stenoses of 50% or more; a value of 1 was assigned if a prior cardiac catheterization revealed at least 1 coronary stenosis of 50% or more.

Since the results of a prior cardiac catheterization might not be immediately available to a clinician attempting to use the TIMI risk score when a patient with UA/NSTEMI presents for evaluation, we investigated the effect of missing values on the prior coronary stenosis of 50% or more variable. Using Monte-Carlo simulation, a fixed proportion of data on prior coronary stenosis of 50% or more was randomly set as missing. The model was reevaluated assuming 0 for missing patients and then reevaluated once again excluding the missing patients. When 10%, 30%, or 50% of the prior coronary stenosis data were randomly set as missing and a 0 was assumed for the missing patients, the variable for prior coronary stenosis of 50% or more remained a significant predictor of the composite outcome at 14 days: for 10% missing, odds ratio (OR)=1.44 (95% confidence interval [CI], 1.18-1.75; $P<.001$); for 30% missing, OR=1.35 (95% CI, 1.09-1.68; $P=.007$); and for 50% missing, OR=1.58 (95% CI, 1.25-2.01; $P<.001$). For the same assumptions of data randomly set as missing but excluding missing patients, the variable for prior coronary stenosis of 50% or more also remained a significant predictor, with ORs of 1.53 (95% CI, 1.25-1.88), 1.50 (95% CI, 1.19-1.90), and 1.63 (95% CI, 1.25-2.13), respectively ($P<.001$ for all). Therefore, under a variety of assumptions about missing values, prior coronary stenosis of 50% or more remained a significant predictor of outcome.

Validation of Risk Score

Validation of the TIMI risk score is shown in Figure 2. The unfractionated heparin control groups in TIMI 11B and ESSENCE showed a homogeneous pattern when patients were stratified by risk score since the slope of the increase in event rates with increasing number of risk factors was not statistically different ($P=.13$) in the 2 unfractionated heparin groups (Figure 2). For all 3 validation cohorts (the enoxaparin group from TIMI 11B, the unfractionated heparin group from ESSENCE, and the enoxaparin group from ESSENCE) there was a significant increase in the rate of events as the TIMI risk score increased ($P<.001$).

Application of TIMI Risk Score

As shown in Figure 2, the relative rate of increase in events among patients with higher TIMI risk scores was different for the unfractionated heparin and enoxaparin groups. For both TIMI 11B and ESSENCE, the slope of the increase in event rates with increasing numbers of risk factors was significantly lower in the enoxaparin groups (3.92 vs 6.41; $P=.01$ in TIMI 11B; 2.18 vs 4.36; $P=.03$ in ESSENCE). A generally consistent pattern of increasing absolute risk difference and corresponding decrease in the number of patients requiring treatment to prevent 1 end point event by 14 days after randomization favoring enoxaparin was seen in both trials as the TIMI risk score increased.

Using a merged database from the TIMI 11B and ESSENCE trials ($N=7081$), multivariate logistic regression analysis revealed that the TIMI risk score and treatment (unfractionated heparin vs enoxaparin) were significant predictors ($P<.001$ for both terms) of all-cause mortality, MI, or urgent revascularization by 14 days after randomization (C statistic=0.63). An interaction term for TIMI risk score * treatment was also a significant predictor of the composite outcome at day 14 ($P=.02$). However, the following terms were not significant pre-

dictors of the composite outcome at day 14: trial ($P=.18$), trial * treatment ($P=.51$), trial * TIMI risk score ($P=.13$), and trial * treatment * TIMI risk score ($P=.84$); inclusion of these in the logistic regression analysis had no effect on overall model performance (C statistic=0.63).

The ability of the TIMI risk score to predict outcomes other than all-cause mortality, MI, or urgent revascularization was assessed in TIMI 11B. In the entire trial population, there were progressive, significant ($P<.001$) increases in the rates of all-cause mortality, MI, urgent revascularization, and the composite of all-cause mortality or nonfatal MI as the TIMI risk score increased (FIGURE 3). The event rates stratified by risk score for the unfractionated heparin and enoxaparin groups in TIMI 11B are shown in TABLE 2. For both treatment groups, there was a consistent, significant increase in the rate of events for each outcome with increasing risk score. Also, for each out-

come, the slope of the increase in events with increasing risk score was lower in the enoxaparin group: 68% lower for all-cause mortality ($P=.02$), 25% lower for MI ($P=.41$), 38% lower for urgent revascularization ($P=.05$), and 39% lower for all-cause mortality or nonfatal MI ($P=.15$).

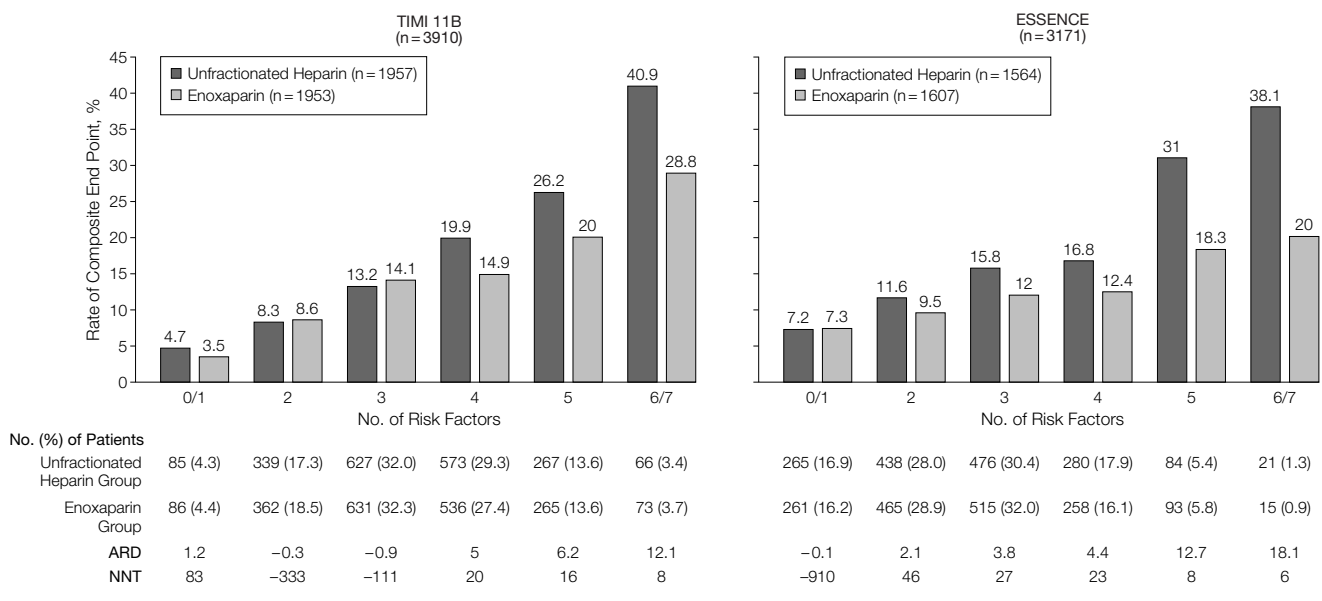
COMMENT

Our results indicate that standard clinical characteristics routinely obtained during the initial medical evaluation of patients with UA/NSTEMI can be used to construct a simple classification system that is predictive of risk for death and cardiac ischemic events. The TIMI risk score includes variables that can be easily ascertained when a patient with UA/NSTEMI presents to the medical care system. The variables used to construct the score were based on observations from prior studies of risk stratification and incorporate demographic and historical features of the patient, measures of the tempo and acuity of the presenting ill-

ness, and indicators of the extent of myocardial ischemia and necrosis.^{2,9,17,29-31} The predictor variables were derived from a logistic regression model that confirmed their independent predictive power after multivariate adjustment in the TIMI 11B and ESSENCE data sets.

The simple arithmetic sum of the number of variables present that constitutes the risk score can be calculated without the aid of a computer. This distinguishes the TIMI risk score from other scoring systems that are more complex computationally since they require weighting terms for the predictor variables and cannot be implemented easily without computer assistance.²⁵ The approach taken in developing the TIMI risk score is similar to that taken by Centor et al,³² who introduced a scoring system for assessment of the likelihood of streptococcal pharyngitis based on clinical findings ascertained in the emergency department, and Croft et al,³³ who developed a simple clinical prediction rule for

Figure 2. Validation of TIMI Risk Score and Assessment of Treatment Effect According to Score



Rates of all-cause mortality, myocardial infarction, and severe recurrent ischemia prompting urgent revascularization through 14 days after randomization were calculated for the enoxaparin and unfractionated heparin groups in the Thrombolysis in Myocardial Infarction (TIMI) 11B trial and the Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave MI trial (ESSENCE), based on the TIMI risk score. The pattern of increasing event rates with increasing TIMI risk score was confirmed in all 3 validation cohorts ($P<.001$ by χ^2 for trend). C statistics were 0.65 for the unfractionated heparin group and 0.61 for the enoxaparin group in TIMI 11B; and 0.65 for the unfractionated heparin group and 0.59 for the enoxaparin group in ESSENCE. The rate of increase in events as more risk factors were present was significantly lower in the enoxaparin group in both studies (for TIMI 11B, $P=.01$; for ESSENCE, $P=.03$). Positive values for absolute risk difference (ARD) and number needed to treat to prevent 1 event (NNT) indicate calculations favoring enoxaparin, while negative values indicate calculations favoring unfractionated heparin.

identifying nerve function impairment in patients with leprosy.

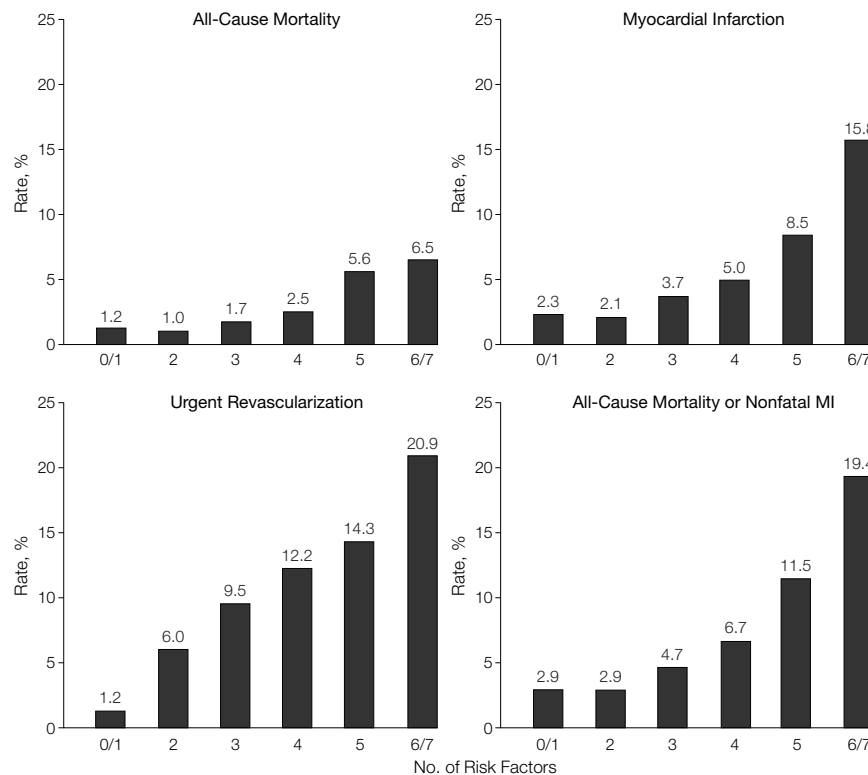
The TIMI risk score appears statistically robust in that it was validated in-

ternally within TIMI 11B as well as in 2 separate cohorts of patients from the ESSENCE trial. The model is easy to recall and apply clinically since a simple

age cutoff of 65 years provided similar predictive ability to a more complex model using age as a continuous variable. Also, variables such as knowledge of whether the patient had a previously documented coronary stenosis of 50% or more appeared relatively insensitive to missing information and remained a significant predictor of events.

The TIMI risk score offers several promising applications for clinical use. It categorizes patients with UA/NSTEMI into groups that span a wide range of risk for clinical events—about a 5- to 10-fold range of risk. A contribution of the TIMI risk score that has not been emphasized in other risk stratification studies is the actual testing of its use for identifying patients who would be expected to show particular benefit from new antithrombotic regimens such as enoxaparin.⁴ As evidenced by the lower slope of the increase in event rates with increasing risk score in Figure 2 and the statistical significance of the interaction term between risk score and treatment, the benefit of enoxaparin was greatest in those patients with higher TIMI risk scores. That the logistic regression modeling did not indicate that the trial in which the patient was enrolled was a predictor of outcome and that the interactions between trial and risk score were not significant are consistent with an independent effect of enoxaparin across the 2 trials and illustrates the use of the TIMI risk score for therapeutic decision making. The abso-

Figure 3. Outcomes for Individual Components of the Composite Primary End Point Stratified by TIMI Risk Score



Rates of all-cause mortality, myocardial infarction (MI), urgent revascularization, and all-cause mortality or nonfatal MI through 14 days after randomization were calculated for the entire population in the Thrombolysis in Myocardial Infarction (TIMI) 11B trial based on the TIMI risk score. There was a progressive, significant increase in the rate of events for each end point as the TIMI risk score increased ($P < .001$ by χ^2 for trend for all). C statistics for the 4 end points shown were 0.74 (all-cause mortality), 0.66 (MI), 0.68 (urgent revascularization), and 0.63 (all-cause mortality/MI), respectively.

Table 2. Event Rates in TIMI 11B Stratified by TIMI Risk Score*

	TIMI Risk Score, Rate of Events, %						P Value by χ^2 for Trend	C Statistic	Slope	P Value for Comparison of Slopes
	0/1	2	3	4	5	6/7				
All-cause mortality										
Unfractionated heparin	0	0.9	1.8	2.6	7.1	10.6	<.001	0.78	1.88	.02
Enoxaparin	2.3	1.1	1.7	2.4	4.2	2.7	.05	0.72	0.61	
Myocardial infarction										
Unfractionated heparin	3.5	1.8	4.0	5.9	9.7	16.7	<.001	0.68	2.47	.41
Enoxaparin	1.2	2.5	3.3	4.1	7.2	15.1	<.001	0.65	1.85	
Urgent revascularization										
Unfractionated heparin	1.2	6.2	9.1	14.0	15.0	27.3	<.001	0.64	3.93	.05
Enoxaparin	1.2	5.8	10.0	10.3	13.6	15.1	<.001	0.62	2.43	
All-cause mortality or nonfatal myocardial infarction										
Unfractionated heparin	3.5	2.4	4.8	7.5	13.5	22.7	<.001	0.70	3.53	.15
Enoxaparin	2.3	3.3	4.6	5.8	9.4	16.4	<.001	0.65	2.15	

*TIMI 11B indicates the Thrombolysis in Myocardial Infarction 11B trial.

lute difference in event rates increased and the corresponding number of patients needed to treat for prevention of 1 event with enoxaparin decreased as the risk score increased (Figure 2). As shown in Figure 3, the risk score also appears useful for stratification of patients at risk for the individual components of composite end points used in many contemporary trials of therapies for UA/NSTEMI. The strength of the evidence of a greater treatment effect of enoxaparin with increasing risk score is not as strong for the individual components as for the composite primary end point. This may reflect lower power to detect a treatment benefit from enoxaparin due to lower absolute event rates for the individual elements of the end point, although statistical significance favoring enoxaparin was observed for all-cause mortality and for urgent revascularization (Table 2).

Several limitations of our analyses should be acknowledged. The TIMI risk score was developed in cohorts of patients who qualified for enrollment in 2 recent phase 3 trials of treatment for UA/NSTEMI. Its performance in cohorts of patients who present to emergency departments and physicians' offices with chest pain must be assessed to determine its generalizability to a variety of clinical settings. The precise numerical relationship between the TIMI risk score and event rates described for TIMI 11B and ESSENCE may be altered as the risk score is applied to other populations. We did not have quantitative data on the results of serum cardiac markers; instead, we used that predictor as a dichotomous variable. Given the quantitative relationship between release of cardiac biomarkers and prognosis, it is possible that the performance of the model could be improved by incorporating a weighting term for small, moderate, and large releases of biomarkers detected at the time of presentation.^{11,12} Other novel markers such as C-reactive protein may provide additional prognostic information and may need to be incorporated in future refinements of the risk score as such measurements become more widely avail-

able. Although introduction of weighting factors for predictor variables or expansion of the list of predictor variables may lead to improvement in statistical measures of the predictive performance of the model (eg, C statistic), this is likely to occur at the cost of a loss of simplicity. Risk score development requires judgment to determine when a model predicts a sufficiently large gradient of risk to be clinically useful, and further refinement of the model produces unattractive levels of complexity.

Risk assessment of patients with UA/NSTEMI is a continuous process that initially involves integration of data at presentation of the patient and later incorporates hospital-phase data such as the results of noninvasive and invasive testing, monitoring for episodes of spontaneous recurrent ischemia, and response to initial therapeutic maneuvers.⁴ The TIMI risk score for UA/NSTEMI described herein was designed for prognostication at the time of initial presentation. Updating of the risk score, as hospital-phase data become available, is an area worthy of further investigation.

Since patients with an acute coronary syndrome are at increased risk of death and nonfatal cardiac events, clinicians must assess prognosis on an individual basis to formulate plans for evaluation and treatment. The TIMI risk score for UA/NSTEMI is a simple prognostication scheme that enables a clinician to categorize a patient's risk of risk of death and ischemic events at the critical initial evaluation. A promising clinical application of this score is identification of a patient for whom new antithrombotic therapies would be especially effective. Other considerations may bear on the decision to prescribe new therapies, even in lower risk groups, in whom the treatment benefit may be smaller. Finally, the TIMI risk score for UA/NSTEMI offers the opportunity for evaluation of cost-effectiveness of other drugs, such as glycoprotein IIb/IIIa inhibitors, as well as an early invasive vs early conservative strategy in patients with an acute coronary syndrome.

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REFERENCES

- Farhi JJ, Cohen M, Fuster V. The broad spectrum of unstable angina pectoris and its implications for future controlled trials. *Am J Cardiol.* 1986;58:547-550.
- Braunwald E, Mark DB, Jones RH, et al. *Unstable Angina: Diagnosis and Management.* Rockville, Md: Dept of Health and Human Services; 1994. Clinical Practice Guideline 10.
- Calvin JE, Klein LW, VandenBerg BJ, et al. Risk stratification in unstable angina: prospective validation of the Braunwald classification. *JAMA.* 1995;273:136-141.
- Armstrong PW, Fu Y, Chang WC, et al. Acute coronary syndromes in the GUSTO-IIb Trial: prognostic insights and impact of recurrent ischemia. *Circulation.* 1998;98:1860-1868.
- Zaacks SM, Liebson PR, Calvin JE, Parrillo JE, Klein LW. Unstable angina and non-Q wave myocardial infarction: does the clinical diagnosis have therapeutic implications? *J Am Coll Cardiol.* 1999;33:107-118.
- Cohen M, Hawkins L, Greenberg S, Fuster V. Usefulness of ST-segment changes in greater than or equal to 2 leads on the emergency room electrocardiogram in either unstable angina pectoris or non-Q-wave myocardial infarction in predicting outcome. *Am J Cardiol.* 1991;67:1368-1373.
- Nyman I, Areskog M, Areskog NH, Swahn E, Wallentin L. Very early risk stratification by electrocardiogram at rest in men with suspected unstable coronary heart disease. *J Intern Med.* 1993;234:293-301.
- Willich SN, Stone PH, Muller JE, et al. High-risk subgroups of patients with non-Q wave myocardial infarction based on direction and severity of ST segment deviation. *Am Heart J.* 1987;114:1110-1119.
- Cannon CP, McCabe CH, Stone PH, et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. *J Am Coll Cardiol.* 1997;30:133-140.
- Lindahl B, Venge P, Wallentin L. Relation between troponin T and the risk of subsequent cardiac

events in unstable coronary artery disease. *Circulation*. 1996;93:1651-1657.

11. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med*. 1996;335:1342-1349.
12. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. *N Engl J Med*. 1996;335:1333-1341.
13. Luscher MS, Thygesen K, Ravkilde J, Heikendorff L, for the TRIM Study Group. Applicability of cardiac troponin T and I for early risk stratification in unstable coronary artery disease. *Circulation*. 1997;96:2578-2585.
14. Maseri A, Rebuszi AG, Cianflone D. Need for a composite risk stratification of patients with unstable coronary syndromes tailored to clinical practice. *Circulation*. 1997;96:4141-4142.
15. Schmid CH, Lau J, McIntosh MW, Cappelleri JC. An empirical study of the effect of the control rate as a predictor of treatment efficacy in meta-analysis of clinical trials. *Stat Med*. 1998;17:1923-1942.
16. Hutter AM, Amsterdam EA, Jaffe AS. Task force 2: acute coronary syndromes: section 2B: chest discomfort evaluation in the hospital. *J Am Coll Cardiol*. 2000;35:853-862.
17. Selker HP, Beshansky JR, Griffith JL, et al. Use of the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) to assist with triage of patients with chest pain or other symptoms suggestive of acute cardiac ischemia: a multicenter, controlled clinical trial. *Ann Intern Med*. 1998;129:845-855.
18. Reperfusion Therapy Consensus Group. Selection of reperfusion therapy for individual patients with evolving myocardial infarction. *Eur Heart J*. 1997;18:1371-1381.
19. Hamm CW, Goldmann BU, Heeschen C, Kreyman G, Berger J, Neinertz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med*. 1997;337:1648-1653.
20. Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. *N Engl J Med*. 1999;340:1623-1629.
21. Holper EM, Antman EM, McCabe CH, et al. A simple, readily available method for risk stratification of patients with unstable angina or non-Q myocardial infarction: a TIMI 11B substudy. *Circulation*. 1998;98:1-493.
22. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 11B trial. *Circulation*. 1999;100:1593-1601.
23. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med*. 1997;337:447-452.
24. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. *Circulation*. 1999;100:1602-1608.
25. Lee KL, Woodlief LH, Topol EJ, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an international trial of 41,021 patients. *Circulation*. 1995;91:1659-1668.
26. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatid in patients with acute coronary syndromes. *N Engl J Med*. 1998;339:436-443.
27. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley & Sons Inc; 1989.
28. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29-36.
29. Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. *N Engl J Med*. 1999;341:226-232.
30. Jayes RL Jr, Beshansky JR, D'Agostino RB, Selker HP. Do patients' coronary risk factor reports predict acute cardiac ischemia in the emergency department? a multicenter study. *J Clin Epidemiol*. 1992;45:621-626.
31. Lee TH, Cook EF, Weisberg M, Sargent RK, Wilson C, Goldman L. Acute chest pain in the emergency room: identification and examination of low-risk patients. *Arch Intern Med*. 1985;145:65-69.
32. Centor RM, Meier FA, Dalton HP. Throat cultures and rapid tests for diagnosis of group A streptococcal pharyngitis. *Ann Intern Med*. 1986;105:892-899.
33. Croft RP, Nicholls PG, Steyerberg EW, Richardus JH, Smith WCS. A clinical prediction rule for nerve-function impairment in leprosy patients. *Lancet*. 2000;355:1603-1606.

The investigator may be made to dwell in a garret, he may be forced to live on crusts and wear dilapidated clothes, he may be deprived of social recognition, but if he has time, he can steadfastly devote himself to research. Take away his free time and he is utterly destroyed as a contributor to knowledge.

—Walter B. Cannon (1871-1945)