The TIMI Risk Score for Unstable Angina/Non–ST Elevation MI: A Method for Prognostication and Therapeutic Decision Making

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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 χ² 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 pro-
file of patients with an acute coronary 
syndrome, multivariate analyses that 
adjust for several prognostic variables 
simultaneously provide a more accu-
rate tool for risk stratification.2,5,14

Reports of the results of random-
ized clinical trials of new therapeutic 
strategies for UA/NSTEMI typically pro-
vide a statement of the overall effec-
tiveness of a treatment in a population 
that is a mixture of patients at varying 
risk of the primary end point. Al-
though univariate subgroup analyses 
are frequently presented in clinical trial 
reports, these provide only a partial pic-
ture 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 allow-
ing clinicians to triage patients to the 
minimum 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 wide-
spread use of a prognostic scoring sys-
tem for patients with UA/NSTEMI, it 
must be readily applicable using stan-
dard patient features that are part of 
the routine 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 
we developed a new, more comprehensive 
risk score for UA/NSTEMI using the da-

tabase of the Thrombolysis in Myocar-
dial Infarction (TIMI) 11B trial, a phase 
3 trial comparing low-molecular-
weight heparin (enoxaparin) with un-
fractionated heparin.22 Our purpose in 
designing a simple risk score was to pro-
vide a tool that potentially could be ap-
plied in clinical settings in which pa-
tients with UA/NSTEMI present for 
evaluation.

METHODS

The design and results of the TIMI 11B 
and Efficacy and Safety of Subcutane-
ous Enoxaparin in Unstable Angina and 
Non-Q-Wave MI (ESSENCE) trials have 
been reported previously.22,23 All pa-
tients (n=3910 in TIMI 11B and n=3171 
in ESSENCE) presented within 24 hours 
of an episode of UA/NSTEMI at rest. Ad-
ditional enrollment criteria included at 
least 1 of the following: ST-segment de-

vation on the qualifying ECG (either 
transient ST elevation or persistent ST de-
pression 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 dis-

dease was acceptable initially but was 
dropped later as the sole supportive cri-
terion for UA/NSTEMI.) Major exclu-
sion criteria were planned revascular-
ization 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 writ-
ten informed consent, were randomly 
assigned to 1 of 2 antithrombotic strat-
egies. Both trials used a double dummy 
technique so that all patients received 
both an intravenous infusion (unfrac-
tionated heparin or matched placebo) 
and subcutaneous injections (enoxa-
parin or matched placebo). For the pur-
poses of developing the TIMI risk score 
for UA/NSTEMI, the prespecified pri-
mary 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 se-
vere recurrent ischemia prompting ur-
gent revascularization. The analyses 
shown herein are based on rates for the 
primary end point through 14 days af-
after randomization.

Initially, a multivariate model for 
prognostication of risk for experienc-
ing at least 1 element of the primary end 
point was developed. The model incor-
porated baseline characteristics that 
could be readily identified at presenta-
tion and was restricted to the cohort of 
patients assigned to unfractionated he-
parin in TIMI 11B (test cohort). The ra-
tionale for this approach was to focus on 
information that could be ascertained in 
a relatively short period after encoun-
tering a patient and establishing a model 
that could be used for efficient triage for 
patient care without waiting for addi-
tional tests or results of an initial pe-
riod of medical observation over sev-
deral days. Baseline characteristics that 
were evaluated include those previ-
ously reported to be important vari-
ables predicting outcomes in patients 
with UA/NSTEMI and are shown in 
TABLE 1.2,5,14,23,26

A total of 12 baseline characteristics 
arranged in a dichotomous fashion were 
screened as candidate predictor vari-
ables of risk of developing an end-
point event (Table 1). A multivariate lo-
gistic regression model was then used 
to assess the statistical significance of 
each candidate prognostic variable. Af-
ter each factor was tested independ-
ently in a univariate logistic regres-
sion model, those that achieved a 
significance level of P<.20 were se-
lected for testing in a multivariate step-
wise (backward elimination) logistic re-
gression model. Variables associated 
with P<.05 were retained in the final 
model. Maximum likelihood estimates 
of the parameter coefficients were ob-
tained 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 χ² 
values and high corresponding P 
values for the Hosmer-Lemeshow statistic 
indicate that the data can be ad-
equitably 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 χ² 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 unfractionated 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 1937 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 3.56df8, (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

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

<table>
<thead>
<tr>
<th>Characteristics†</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, ≥65 y</td>
<td>β Coefficient</td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td>0.4681</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Prior MI</td>
<td>0.2386</td>
<td>.06</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>0.3004</td>
<td>.07</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>0.4828</td>
<td>.004</td>
</tr>
<tr>
<td>ST deviation</td>
<td>0.3356</td>
<td>.02</td>
</tr>
<tr>
<td>Severe anginal symptoms</td>
<td>0.4521</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Use of aspirin in last 7 days</td>
<td>0.6179</td>
<td>.002</td>
</tr>
<tr>
<td>Use of IV unfractionated heparin within 24 hours of enrollment</td>
<td>0.1665</td>
<td>.19</td>
</tr>
<tr>
<td>Elevated serum cardiac markers§</td>
<td>0.3486</td>
<td>.004</td>
</tr>
</tbody>
</table>

*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.

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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, M1, 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-

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 χ² 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 results 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=1.38 (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.
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 outcome, 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 illness, and indicators of the extent of myocardial ischemia and necrosis. 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. The approach taken in developing the TIMI risk score is similar to that taken by Centor et al, 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, who developed a simple clinical prediction rule for nonbacterial thrombotic endocarditis based on clinical findings ascertained in the emergency department.

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

<table>
<thead>
<tr>
<th>No. (%) of Patients</th>
<th>TIMI 11B (n = 3910)</th>
<th>ESSENCE (n = 3171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated Heparin Group</td>
<td>85 (4.3)</td>
<td>265 (16.9)</td>
</tr>
<tr>
<td>Enoxaparin Group</td>
<td>86 (4.4)</td>
<td>261 (16.2)</td>
</tr>
<tr>
<td>ARD</td>
<td>1.2</td>
<td>0.1</td>
</tr>
<tr>
<td>NNT</td>
<td>83</td>
<td>910</td>
</tr>
</tbody>
</table>

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 $x^2$ for trend). C statistics were 0.63 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.

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identifying nerve function impairment in patients with leprosy.

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

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

<table>
<thead>
<tr>
<th>TIMI Risk Score, Rate of Events, %</th>
<th>P Value by χ² for Trend</th>
<th>C Statistic</th>
<th>Slope</th>
<th>P Value for Comparison of Slopes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0/1 2 3 4 5 6/7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>0 0.9 1.8 2.6 7.1 10.6</td>
<td>&lt;.001</td>
<td>0.78</td>
<td>1.88</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>2.3 1.1 1.7 2.4 4.2 2.7</td>
<td>.05</td>
<td>0.72</td>
<td>0.61</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>3.5 1.8 4.0 5.9 9.7 16.7</td>
<td>&lt;.001</td>
<td>0.68</td>
<td>2.47</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1.2 2.5 3.3 4.1 7.2 15.1</td>
<td>&lt;.001</td>
<td>0.65</td>
<td>1.85</td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>1.2 6.2 9.1 14.0 15.0 27.3</td>
<td>&lt;.001</td>
<td>0.64</td>
<td>3.93</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1.2 5.8 10.0 10.3 13.6 15.1</td>
<td>&lt;.001</td>
<td>0.62</td>
<td>2.43</td>
</tr>
<tr>
<td>All-cause mortality or nonfatal myocardial infarction</td>
<td>3.5 2.4 4.8 7.5 13.5 22.7</td>
<td>&lt;.001</td>
<td>0.70</td>
<td>3.53</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>2.3 3.3 4.6 5.8 9.4 16.4</td>
<td>&lt;.001</td>
<td>0.65</td>
<td>2.15</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 available. 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 attractive 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 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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11. Wallentin L, Bertagnoli M, Bhatt DL, et al. TIMI Ancillary Study of GUSTO III: the relationship between release of cardiac biomarkers and prognosis, it is possible that the treatment benefit from enoxaparin decreases as the risk score increases (Figure 2). As shown in Figure 3, the risk score also appears useful for stratification of patients at risk for the individual components of the risk score as such measurements become more widely available. 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 attractive 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 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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