

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.

JAMA. 2000;284:835-842

www.jama.com

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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)			

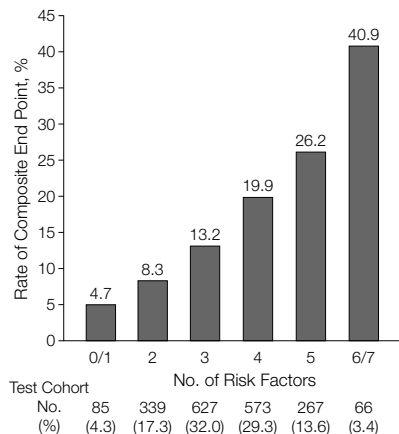
*UA/NSTEMI indicates unstable angina/non-ST elevation myocardial infarction; OR, odds ratio; CI, confidence interval; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty; IV, intravenous; and CHF, congestive 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 ($P=.15$).

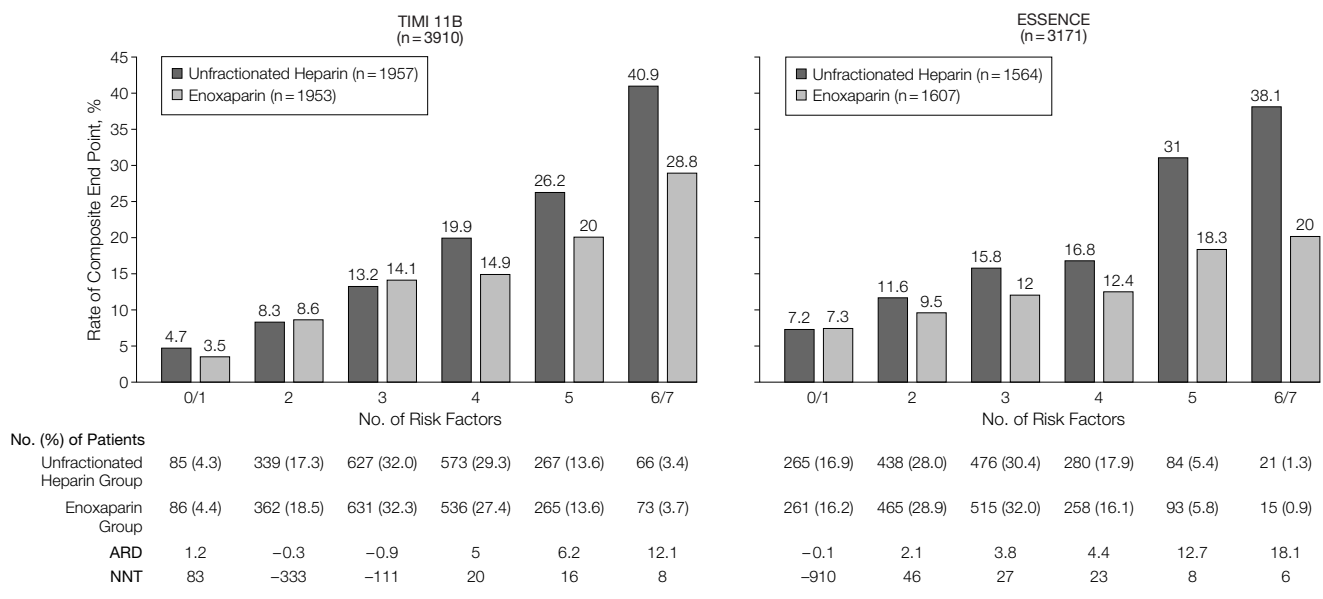
COMMENT

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.

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