

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2000, 102:2031-2037

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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TIMI Risk Score for ST-Elevation Myocardial Infarction: A Convenient, Bedside, Clinical Score for Risk Assessment at Presentation

An Intravenous nPA for Treatment of Infarcting Myocardium Early II Trial Substudy

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Background—Considerable variability in mortality risk exists among patients with ST-elevation myocardial infarction (STEMI). Complex multivariable models identify independent predictors and quantify their relative contribution to mortality risk but are too cumbersome to be readily applied in clinical practice.

Methods and Results—We developed and evaluated a convenient bedside clinical risk score for predicting 30-day mortality at presentation of fibrinolytic-eligible patients with STEMI. The Thrombolysis in Myocardial Infarction (TIMI) risk score for STEMI was created as the simple arithmetic sum of independent predictors of mortality weighted according to the adjusted odds ratios from logistic regression analysis in the Intravenous nPA for Treatment of Infarcting Myocardium Early II trial (n=14 114). Mean 30-day mortality was 6.7%. Ten baseline variables, accounting for 97% of the predictive capacity of the multivariate model, constituted the TIMI risk score. The risk score showed a >40-fold graded increase in mortality, with scores ranging from 0 to >8 ($P<0.0001$); mortality was <1% among patients with a score of 0. The prognostic discriminatory capacity of the TIMI risk score was comparable to the full multivariable model (c statistic 0.779 versus 0.784). The prognostic performance of the risk score was stable over multiple time points (1 to 365 days). External validation in the TIMI 9 trial showed similar prognostic capacity (c statistic 0.746).

Conclusions—The TIMI risk score for STEMI captures the majority of prognostic information offered by a full logistic regression model but is more readily used at the bedside. This risk assessment tool is likely to be clinically useful in the triage and management of fibrinolytic-eligible patients with STEMI. (*Circulation*. 2000;102:2031-2037.)

Key Words: coronary disease ■ prognosis ■ myocardial infarction ■ mortality ■ risk factors

Considerable variability in short-term mortality risk exists among patients with ST-elevation myocardial infarction (STEMI) who receive fibrinolytic therapy.^{1,2} Careful risk assessment for each patient informs decisions regarding therapeutic interventions, triage among alternative levels of hospital care, and allocation of clinical resources. Algorithms that aid clinicians in assessing prognosis may therefore be useful in guiding management and in providing valuable information for patients and their families. To be practical clinically, a risk stratification tool should be simple and easily applied at the bedside and should make use of clinical data that are routinely available at hospital presentation. However, to perform accurately, the tool should use data that offer independent prognostic information and must take into account the complex profile of patients with multiple risk

factors. A risk model satisfying these objectives could also be useful in adjusting for baseline risk in epidemiological studies, such as those examining variation in practice patterns, provider types, or specific therapies.³⁻⁵

Sophisticated multivariable models developed for the prediction of mortality among patients with STEMI identify independent clinical predictors and quantify their relative contribution to mortality risk.⁶ Although such models offer important insight into the relationships between clinical data and prognosis, they are not readily applied in routine clinical practice. Therefore, we developed a clinical risk score that can be calculated easily at the bedside but is derived from a comprehensive multivariable analysis in a well-characterized population of nearly 15 000 patients with STEMI from the Intravenous nPA for Treatment of Infarcting Myocardium

Received April 27, 2000; revision received June 6, 2000; accepted June 7, 2000.

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Early II (InTIME II) trial. The prognostic performance of the Thrombolysis in Myocardial Infarction (TIMI) risk score for STEMI was then compared with that of other risk models and validated in an external data set composed of nearly 3700 patients with STEMI.

Methods

Study Population

The InTIME II trial enrolled patients with STEMI within 6 hours of symptom onset at >800 hospitals worldwide and assigned them to therapy with aspirin, heparin, and either the bolus fibrinolytic lanoteplase or alteplase. Eligible participants were aged ≥ 18 years and exhibited chest pain and ST elevation or left bundle branch block on the qualifying ECG. Exclusion criteria included any history of cerebrovascular disease, a systolic blood pressure of >180 mm Hg, a diastolic blood pressure of >110 , cardiogenic shock, or increased risk of severe bleeding. The InTIME II protocol was approved by the institutional committee on human research at each of the participating centers.

Clinical End Points

Vital status was assessed through 30 days and every 6 months until trial completion. The primary end point of the trial was death from any cause within 30 days of randomization. Mortality data after discharge were obtained through telephone follow-up or outpatient visitation.

Statistical Analysis

Performance of the multivariate analysis and derivation of the risk score were based on patients with complete baseline data (93.7%), with subsequent reevaluation in the full population. Univariate relationships between baseline characteristics and 30-day mortality were assessed by logistic regression analysis. Thresholds for categorization of continuous variables were determined graphically and were based on prevalence in the population. Independent predictors of 30-day mortality were identified by stepwise logistic regression. All baseline variables entered the initial model and were maintained if $P < 0.05$.

Selection of independent predictors for inclusion in the TIMI risk score for STEMI was based on their relative prognostic contribution in the full logistic regression model. Variables were ranked by z score, and those with the least contribution were sequentially removed from the model until reaching 10 variables that captured 97% of the overall prognostic information from the full multivariate model (evaluated as a ratio of the global χ^2 statistic from the reduced compared with full model). For each patient, the TIMI risk score for STEMI was calculated as the simple arithmetic sum of point values assigned to each risk factor based on the multivariate-adjusted risk relationship: 1 point for odds ratio (OR) 1.0 to <2 , 2 points for OR 2.0 to 2.5, and 3 points for OR >2.5 . Age was weighted in 2 strata, with 2 points for an age range of 65 to 74 years and 3 points for ages ≥ 75 years. The 3 historical variables that remained in the model (diabetes, history of angina, and history of hypertension) had risk relationships of similar magnitude and were combined to form a single composite variable.

The discriminatory capacity of the risk score was assessed by using the area under the receiver operating characteristic curve (c statistic) as an index of model performance.⁷ The c statistic reflects the concordance of predictions with actual outcomes in rank order, with a c statistic of 1.0 indicating perfect discrimination.⁷ The prognostic performance of the TIMI risk score was compared with the full multivariable model as well as 2 previously described risk models.^{6,8} The reliability of risk score prediction was also evaluated by comparing the observed mortality rates with those predicted by the risk score across deciles of risk established by dividing patients according to predicted mortality from the multivariate model and then determining the actual mortality for each group.⁶ Risk score categories were collapsed (eg, >8) when the prevalence of a given

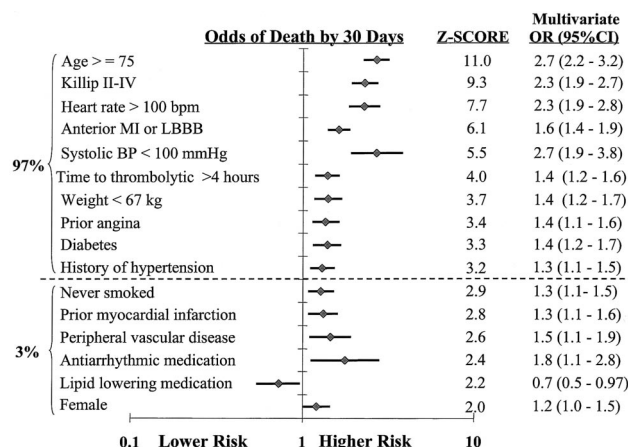


Figure 1. Independent predictors of 30-day mortality. Variables were ranked by z score, with those above dashed line selected for TIMI risk score for STEMI. Proportion of prognostic information captured by variables enclosed by braces is shown to the left. MI indicates myocardial infarction.

score was $<1\%$. For evaluation of the risk score in the full population, missing variables contributed a point value of 0 to the total score. A value of $P < 0.05$ was considered significant. Analyses were performed by use of S-PLUS (version 3.4, MathSoft) and SAS (version 6.12, SAS Institute).

Validation Set

The TIMI Risk Score for STEMI was assessed in an external data set from the TIMI 9 trial. TIMI 9A and 9B were multicenter randomized trials evaluating the safety and efficacy of hirudin as an adjunct to fibrinolytic therapy (tissue plasminogen activator or streptokinase at the physician's discretion).^{9,10} The combined database included 3687 patients with vital status established at 30 days.

Results

The InTIME II database included 15 078 patients enrolled between July 1997 and November 1998. Vital status through 30 days was available for 15 060 (99.9%) of patients, with full baseline clinical data available for 14 114. The baseline characteristics are summarized in Table 1. At 30 days after study entry, 6.7% of patients had died, 5.2% had suffered a recurrent acute myocardial infarction, and 26.2% had undergone revascularization. Of the total deaths by 30 days, 36% occurred in the first 24 hours, 56% by 72 hours, and 91% by hospital discharge (mean length of stay 10.5 days).

Predictors of Mortality

Each of the baseline clinical characteristics was evaluated as a univariate predictor of mortality (Table 1). When all of the candidate variables were assessed simultaneously in multivariate analysis, 16 remained significant predictors of mortality (Figure 1). Assessed by the area under the receiver operating characteristic curve (concordance of the predictions with actual outcomes), the full 16-variable regression model demonstrated a strong discriminatory capacity (c statistic 0.784). Ten characteristics accounted for 97% of the predictive capacity of the multivariate model and were selected for inclusion in the TIMI risk score for STEMI (Figure 1), with the 3 historical characteristics (diabetes, history of hypertension, and prior angina) subsequently grouped as a composite variable (adjusted OR 1.6, 95% CI 1.4 to 1.9).

TABLE 1. Univariate Risk of 30-Day Mortality Stratified by Presenting Characteristics

	Overall Population (n=15 060)	OR (95% CI)	P
Demographics			
Age, y	62 (52, 70)		
>75 y	2 068 (13.7)	4.4 (3.9–5.1)	<0.0001
>65 y	6 307 (41.9)	4.9 (4.2–5.7)	<0.0001
Female	3 717 (24.7)	2.2 (1.9–2.5)	<0.0001
Weight, kg	77 (69, 86)		
<67 kg	2 887 (19.2)	2.0 (1.7–2.3)	<0.0001
White	14 234 (94.5)	0.8 (0.6–1.0)	0.09
Risk factors			
Smoking status			
Current	6 738 (44.7)	0.4 (0.4–0.5)	<0.0001
Past	3 972 (26.4)	1.2 (1.1–1.4)	0.006
Never	4 274 (28.4)	1.9 (1.7–2.2)	<0.0001
Diabetes	2 095 (13.9)	1.7 (1.5–2.0)	<0.0001
History of hypertension	4 583 (30.4)	1.7 (1.5–1.9)	<0.0001
Cardiovascular history			
Prior myocardial infarction	2 410 (16.0)	1.8 (1.5–2.1)	<0.0001
Peripheral vascular disease	782 (5.2)	1.9 (1.5–2.3)	<0.0001
Cerebrovascular disease	145 (1.0)	2.1 (1.3–3.5)	0.005
Prior angina	3 198 (21.2)	2.0 (1.8–2.3)	<0.0001
Prior PCI	672 (4.5)	0.8 (0.6–1.1)	0.2
Prior CABG	405 (2.7)	1.5 (1.1–2.1)	0.02
Diabetes/HTN/prior angina	7 161 (47.6)	2.1 (1.8–2.4)	<0.0001
Medications at presentation			
β-Blockers	2 345 (15.6)	1.4 (1.2–1.6)	0.0003
Calcium channel blockers	2 364 (15.7)	1.8 (1.5–2.0)	<0.0001
Lipid-lowering	1 407 (9.3)	0.8 (0.7–1.1)	0.1
Antiarrhythmic	198 (1.3)	3.2 (2.2–4.6)	<0.0001
Presenting characteristics			
Infarct location			
Anterior or LBBB	6 428 (42.7)	1.9 (1.7–2.2)	<0.0001
Inferior	8 567 (56.9)	0.5 (0.5–0.6)	<0.0001
Other	65 (0.4)	2.0 (0.9–4.1)	0.1
Killip class II–IV	1 890 (12.6)	3.6 (3.1–4.2)	<0.0001
Heart rate, bpm	74 (63, 86)		
Heart rate >100 bpm	1 165 (7.7)	3.1 (2.6–3.6)	<0.0001
Systolic BP, mm Hg	140 (122, 155)		
Systolic BP <100 mm Hg	396 (2.6)	2.9 (2.2–3.8)	<0.0001
Treatment			
Time to treatment >4 h	3 657 (24.3)	1.6 (1.4–1.8)	<0.0001

Data are shown as n (%) for dichotomous variables and median (25, 75th percentile) for continuous variables. PCI indicates percutaneous interventions; HTN, hypertension; diabetes/HTN/prior angina, history of any one of these 3 characteristics; LBBB, left bundle branch block; and BP, blood pressure.

TIMI Risk Score for STEMI

The TIMI risk score for STEMI (Figure 2) showed a strong association with mortality at 30 days, with a >40-fold graded

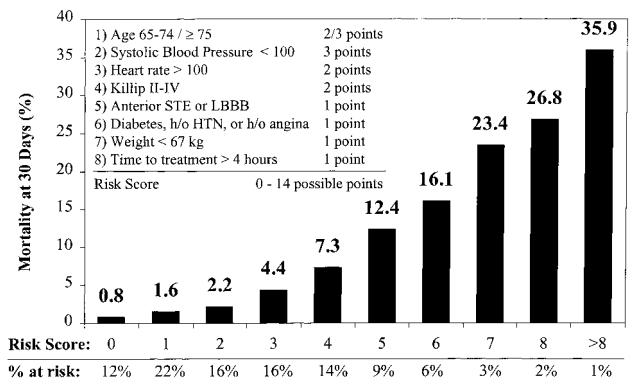


Figure 2. TIMI risk score for STEMI for predicting 30-day mortality. STE indicates ST elevation; h/o, history of.

increase in mortality between those with a risk score of 0 and those with a score >8 ($P_{\text{trend}} < 0.0001$). At the high end, a score >5 identified 12% of patients with a mortality risk >2-fold higher than the mean for the population. In contrast, the 12% of patients with a risk score of 0 had a mortality rate <1%. Discriminating among the lower risk groups, nearly two thirds of the population had risk scores of 0 to 3, with a 5.3-fold gradient in mortality over this range ($P < 0.0001$, Figure 2).

The TIMI risk score demonstrated a strong predictive capacity, comparable to the full multivariable model (c statistic 0.779 versus 0.784). The reliability of the TIMI risk score predictions were assessed by comparison with the observed mortality rates across the population divided into deciles of risk. Excellent concordance of the risk score predictions with observed mortality rates was evident (correlation coefficient 0.994).

Comparison With Other Models

To evaluate the TIMI risk score in the context of previously developed models, we tested the performance of the logistic regression equation developed in the Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO)-I trial⁶ as well as an unweighted risk score derived in the TIMI 2 trial⁸ in the InTIME II data set. The TIMI risk score offered prognostic capacity comparable to both the multivariable model from GUSTO-I (c statistic 0.803) and the risk score from TIMI 2 (c statistic 0.753).

Predictive Consistency and Validation

The prognostic capacity of the TIMI risk score was stable over multiple time points, ranging from 24 hours to 365 days after presentation (Table 2). Furthermore, the discriminatory capacity of the model remained good for prediction of 1-year mortality among 30-day survivors (c statistic 0.725, Figure 3). Notably, the proportion of deaths occurring by 30 days increased with ascending TIMI risk score, ranging from 44% among those with a score of 0 to 77% for those with risk scores >8 ($P_{\text{trend}} < 0.0001$).

The risk score was predictive of 30-day mortality among important subgroups, such as men and women and smokers

TABLE 2. Stability of TIMI Risk Score for STEMI Over Time

Time Point	Risk Score										c Statistic
	0	1	2	3	4	5	6	7	8	>8	
24 h	0.1	0.3	0.8	1.0	2.7	4.3	6.6	8.2	12.9	15.2	0.813
In hospital	0.7	1.3	1.9	3.9	6.5	11.6	14.7	21.5	24.4	31.7	0.784
6 mo	1.5	2.0	3.3	6.4	9.8	16.0	20.5	29.4	35.9	43.5	0.773
1 y	1.9	2.6	4.0	7.2	11.3	18.3	22.6	32.7	38.8	46.9	0.765

Data are reported as mortality (%).

$P_{(\text{trend})} < 0.0001$ for each time point, indicating significant increase in mortality with rising risk score.

and nonsmokers (Table 3), with a similar graded relationship between the risk score and mortality across each of these subgroups. The model was also evaluated in the full 15 060 patient population (including patients with missing risk score variables) without substantial change from the derivation set (c statistic 0.776, Table 3).

The risk score was also strongly associated with 30-day mortality in an external population of patients treated with fibrinolytics for STEMI (Figure 4). Application of the TIMI risk score for STEMI in the TIMI 9A/B population revealed a similar nearly 40-fold gradient in mortality risk. Mortality was again <1% among patients with a risk score of 0. In addition, a high discriminatory capacity of the TIMI risk score was evident in this external validation set (c statistic 0.746).

Application as an Epidemiological Tool

To illustrate the utility of the TIMI risk score for STEMI in adjusting for baseline risk profile, we performed an analysis of regional revascularization practice patterns among patients treated with fibrinolytics in the InTIME II study. For the purpose of this example, we used the risk score as a framework to stratify revascularization rates (coronary artery bypass grafting or percutaneous intervention) in the US and non-US sites participating in the InTIME II study. A consistent pattern of increased utilization of revascularization procedures in the United States was evident across all groups as stratified by risk score (Figure 5). Furthermore, a pattern of decreasing frequency

of revascularization among the highest risk patients was apparent among US and non-US centers.

Discussion

We used the prognostic information from a multivariable analysis in a large and diverse cohort of patients treated with fibrinolytics for STEMI to develop a convenient bedside clinical score that may be applied at the time of patient presentation to assess short-term mortality risk. The TIMI risk score for STEMI identified a significant gradient of mortality risk by using variables that captured the majority of prognostic information available in the multivariable model. The predictive capacity of this risk score was stable over multiple time points, in men and women, and in smokers and nonsmokers. Furthermore, the TIMI risk score performed well in a large external data set of patients with STEMI.

Effective risk stratification is integral to the management of patients with acute coronary syndromes.¹¹ Even among patients with STEMI, for whom initial therapeutic options are well-defined, patient risk characteristics have an impact on early therapeutic decision making.^{1,12,13} In addition, increasing economic pressures have intensified the need for appropriate triage and clinical resource utilization, including decisions regarding transfer to tertiary centers.¹⁴ In particular, the capacity to reliably identify patients at very low risk for fatal recurrent events may offer the opportunity to select low-risk patients for early hospital discharge.^{15,16} Tools that enhance the clinician's ability to rapidly and accurately assess risk are thus of substantial interest.

Risk Modeling in STEMI

Carefully performed multivariable analysis for mortality prediction in the GUSTO-I trial provided significant information regarding demographic, clinical, and historical factors that offer independent prognostic information among fibrinolytic-eligible patients with STEMI.⁶ The complex (>20-term) model produced in the GUSTO-I analysis allowed for the interplay of risk markers, including nonlinear relationships and interaction between variables. The risk estimates offered by the GUSTO-I and other multivariable models for mortality in STEMI were highly accurate in their derivation data sets but required a computer for calculation.^{6,17}

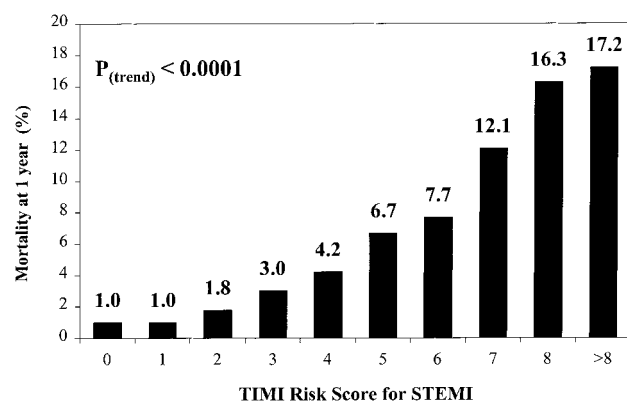


Figure 3. TIMI risk score for STEMI for predicting 1-year mortality (30-day survivors).

TABLE 3. TIMI Risk Score for STEMI in Important Subgroups

Population	Risk Score										c Statistic
	0	1	2	3	4	5	6	7	8	>8	
Men	0.8	1.5	2.3	3.8	6.5	12.0	16.7	22.6	22.5	35.7	0.774
Women	0.7	1.8	1.9	6.2	9.0	13.0	15.4	24.5	30.0	36.0	0.745
Smokers	1.0	1.6	2.2	4.2	7.1	9.6	15.7	20.5	26.7	31.5	0.763
Never smokers	0	1.4	2.1	4.7	7.2	15.8	16.1	26.7	25.7	37.8	0.769
Full population	0.9	1.8	2.6	5.0	8.5	13.7	17.7	24.4	30.4	35.9	0.776

Data are reported as mortality (%). Full population indicates 15 060 patients, including those with missing baseline data.

$P_{\text{interaction}}$ = NS for men vs women and smokers vs never smokers, consistent with a similar graded increase in mortality risk in each subgroup. $P_{\text{(trend)}} < 0.0001$ for each subgroup, indicating significant increase in mortality with rising risk score.

Investigators have developed a number of simplified risk stratification schemes, which may be calculated at the bedside without the aid of a computer.^{4,8,18} Several of these models were developed before the widespread use of thrombolysis.^{18–20} Of those derived in the era of reperfusion, several were formed by using general measures of severity of illness, such as the Acute Physiology and Chronic Health Evaluation II scoring system,²¹ whereas others were based on expert opinion and prior investigation.⁸ Models that have integrated weighting information from multivariate regression in a fashion similar to the TIMI risk score are few and have not been derived for prediction of short-term outcomes in STEMI.⁴

TIMI Risk Score for STEMI

The clinical data included in the TIMI risk score for STEMI are all routinely collected at hospital presentation. Consistent with prior observations,^{2,6,22} all of the variables included in this model were independent predictors of 30-day mortality in the InTIME II population. Notably, the finding of an association between low body weight and increased mortality risk reported by others^{3,6} was again observed to be significant. When used in combination with a simple integer-weighting system, these basic risk factors constitute a robust risk scoring scheme that can be calculated at the bedside by any care provider with the aid of a simple score card (Figure 6). The TIMI risk score for STEMI reliably identifies patients at very high risk while

maintaining good discriminatory capacity in the low-risk range, where smaller absolute differences are more likely to impact clinical decisions.

Used as an epidemiologic tool, the TIMI risk score provides a convenient mechanism to identify baseline differences in risk profile and offers a framework for analyses stratified by risk group at presentation. In our illustrative example, stratification of revascularization rates by risk score effectively demonstrated differences in regional practice among similar risk patients. In addition, this approach highlighted the disproportionate number of lower-risk patients undergoing revascularization and the need to evaluate whether interventions that might improve outcomes are being performed less frequently for the highest-risk patients, who may derive the greatest benefit.^{13,23}

The TIMI risk score for STEMI may also be used in designing clinical trials. By eliminating patients with low risk scores, a population with higher event rates can be identified. This strategy permits testing for a relative treatment effect with a smaller sample size for the trial.

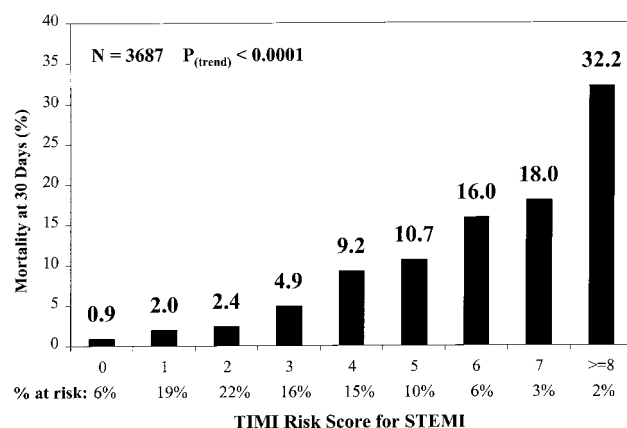


Figure 4. TIMI risk score for STEMI in TIMI 9A/B validation set.

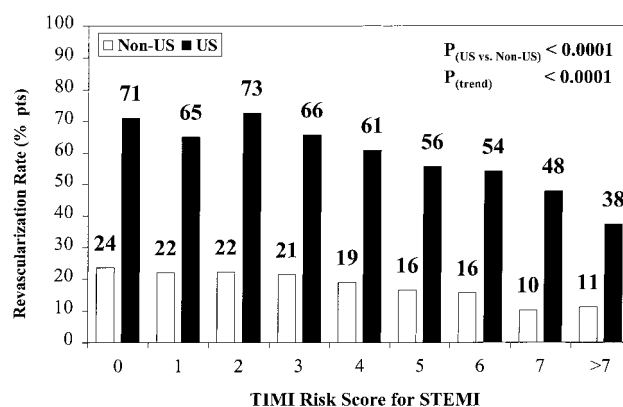


Figure 5. Illustrative example of TIMI risk score for STEMI as epidemiological tool adjusting for baseline risk. Revascularization rates are for US and non-US sites in InTIME II, expressed as percentage of patients (pts) in each risk group undergoing revascularization. $P_{\text{(US vs. Non-US)}} < 0.0001$ indicates significantly higher revascularization rates among US sites after adjusting for risk score. $P_{\text{(trend)}} < 0.0001$ indicates significant decline in revascularization rates with rising risk score among US and non-US sites.

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