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An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes

Application of the TIMI Risk Score for UA/NSTEMI in PRISM-PLUS

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Aims We evaluated the TIMI Risk Score for Unstable Angina and Non-ST Elevation Myocardial Infarction for predicting clinical outcomes and the efficacy of tirofiban in non-ST elevation acute coronary syndromes.

Methods and Results Developed in TIMI 11B, the risk score is calculated as the sum of seven presenting characteristics (age $\geq$65 years, $\geq$3 cardiac risk factors, documented coronary disease, recent severe angina, ST deviation $\geq$0·5 mm, elevated cardiac markers, prior aspirin use). The risk score was validated in the PRISM-PLUS database (n=1915) and tested for interaction with the efficacy of tirofiban+heparin vs heparin alone. The risk score revealed an increasing gradient of risk for death, myocardial infarction or recurrent ischaemia at 14 days ranging from 7·7–30·5% (P<0·001). Dichotomized at the median, patients with a score $\geq$4 derived a greater relative risk reduction with tirofiban ($P_{(\text{Interaction})}$=0·025). Among patients with normal creatine kinase myocardial bands, the risk score showed a 3·5-fold gradient of risk (P<0·001) and identified a population that derived significant benefit from tirofiban (RR 0·73, P=0·027).

Conclusion The TIMI Risk Score is a simple clinical tool for risk assessment that may aid in the early identification of patients who should be considered for treatment with potent antiplatelet therapy.
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Introduction

An array of therapeutic strategies are available for management of the heterogeneous population of patients with non-ST elevation acute coronary syndromes[1,2]. The details of the clinical presentation weigh heavily in selecting among therapeutic alternatives, as patients at differing degrees of risk may vary substantially in the magnitude of benefit to be achieved from specific interventions. Furthermore, increasing economic pressures, as well as safety considerations, have prevented the uniform use of effective but sometimes costly therapies for this diverse group of patients. Effective risk assessment early after presentation is thus central to guiding the selection of higher risk patients for whom invasive or aggressive medical interventions may be most beneficial[1–3].

Analyses from clinical databases have identified important clinical indicators associated with higher risk of adverse outcomes among patients with unstable ischaemic heart disease[4–6]. Considered alone, individual clinical characteristics, electrocardiographic information and biochemical marker data, may each provide useful prognostic information[5,7,8]. However, patients with acute

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coronary syndromes typically present with complex risk profiles requiring the integration of information from multiple risk indicators. A clinical tool that aids the practitioner in producing a reliable assessment of risk using multiple independently prognostic factors is thus likely to prove useful, both for effective risk stratification as well as therapeutic decision-making[4,9].

The TIMI Risk Score for Unstable Angina (UA) and Non-ST Elevation Myocardial Infarction (NSTEMI) is a simple clinical score that may be used by the clinician at the bedside for risk assessment at presentation[4]. This risk stratification scheme incorporates multiple clinical predictors that add to prognostic information available from cardiac biomarkers and should be useful in recognizing higher risk patients for whom marker data are negative or not yet available. The TIMI Risk Score was developed previously using multivariable methods among patients treated with unfractionated heparin in TIMI 11B, a phase III trial of enoxaparin vs unfractionated heparin for non-ST elevation acute coronary syndromes[10]. The risk score was then validated among patients treated with enoxaparin vs placebo in the Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-wave Myocardial Infarction (ESSENCE) trial, confirming a significant graded pattern of increasing rates of death and recurrent ischaemic events with rising risk score[4]. Further, application of the TIMI Risk Score in the TIMI 11B and ESSENCE trials identified patients who derived particular benefit from treatment with the low molecular weight heparin, enoxaparin[4]. We now extend our evaluation of the TIMI Risk Score for UA/NSTEMI both for the prediction of death and recurrent ischaemic events among patients enrolled in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Trial, and for the identification of patients for whom treatment with the platelet glycoprotein-IIb/IIIa inhibitor tirofiban may be most beneficial.

Methods

Study population and treatments

PRISM-PLUS was a multicentre, randomized, parallel group trial of tirofiban with and without intravenous unfractionated heparin vs unfractionated heparin alone for the treatment of patients with unstable angina and non-Q wave myocardial infarction. The design and results of the PRISM-PLUS trial have been reported previously[11]. Study participants were required to have prolonged pain or repetitive episodes of angina at rest or during minimal exercise within 12 h prior to enrolment, with associated ST or T wave changes on the electrocardiogram or elevation in plasma levels of creatine kinase myocardial bands. Major exclusion criteria included persistent ST elevation, correctable causes of angina, and contraindications to anticoagulation with heparin and/or platelet inhibition.

All patients received aspirin (325 mg) at randomization and daily thereafter. The study medications were administered for a minimum of 48 h and coronary interventions postponed until after this period unless necessitated by clinical instability. Allocation to the tirofiban-only treatment group was discontinued early, on the recommendation of the Data and Safety Monitoring Board after enrolment of 345 patients in that arm[11]. Patients in this treatment group were included in the validation set for the TIMI Risk Score, but not in testing for treatment interactions. The primary end-point for PRISM-PLUS was a composite of death from any cause, new myocardial infarction, or refractory ischaemia at 7 days after randomization. This report focuses on the outcome of death, myocardial infarction or refractory ischaemia at 14 days for consistency with the original analysis of the TIMI Risk Score[4]. Data at 30 days and through 6 months of follow-up are also included.

TIMI Risk Score for UA/NSTEMI

The TIMI Risk Score for UA/NSTEMI is a risk assessment tool composed of seven independent clinical risk indicators evaluated at presentation [age $\geq$65 years, three or more risk factors for coronary artery disease, known significant coronary stenosis, ST deviation $\geq$0·5 mm, elevated cardiac marker, severe anginal symptoms ($\geq$2 episodes in prior 24 h), use of aspirin in prior 7 days][4]. For each patient, the score is calculated as the simple arithmetic sum of the number of risk indicators that are present (range 0–7). Applied as such, the TIMI Risk Score identifies a gradient of increasing risk for death and recurrent ischaemic events with rising risk score[4].

In the present analysis the TIMI risk score was applied to patients from the PRISM-PLUS trial using baseline clinical data collected prior to randomization. By virtue of the inclusion criteria for PRISM-PLUS, all patients were given 1 point for severe anginal symptoms. Patients with documented coronary artery disease (prior myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention) were assigned 1 point for significant coronary stenoses. Data regarding the extent of prior angiographic coronary disease were not collected at entry to PRISM-PLUS. All other variables included in the TIMI risk score were available in the PRISM-PLUS database with no missing data. Elevated baseline cardiac markers were defined by creatine kinase myocardial bands greater than the upper limit of normal or creatine kinase >2 $\times$ the upper limit of normal when creatine kinase myocardial bands was unavailable. ST-segment deviation of 1 mm or greater was recorded in the PRISM-PLUS database.

Statistical analysis

The primary end-point for this analysis was the composite of death from any cause, new myocardial

infarction or refractory ischaemia. Differences in the event rates for patients with increasing TIMI risk score values were assessed using logistic regression with the risk score treated as an ordinal independent variable. The discriminatory capacity of the TIMI risk score was expressed as the c-statistic, representing the area under the receiver operating characteristic curve for predicting death or recurrent ischaemic events by 14 days[12]. The goodness-of-fit of the model predictions to the observed event rates was evaluated with the Hosmer–Lemeshow statistic[13]. Low chi-square values and high corresponding P values for the Hosmer–Lemeshow statistic indicate good calibration between the event rates predicted by the model and the observed outcomes.

The TIMI Risk Score was next evaluated in an analysis stratified by treatment group. Patients in the tirofiban-only group were not included in the analysis of treatment interaction due to early discontinuation of this treatment arm. Testing for interaction between the TIMI risk score and the effect of tirofiban was performed using logistic regression (14 days) and Cox proportional hazards modelling (30 days and 6 months) with an interaction term. Testing of the proportional hazards assumption supported the use of Cox modelling. The predictive capacity of the model and the interaction with treatment allocation were evaluated for the entire population as well as those without elevated baseline creatine kinase myocardial bands. All statistical testing was performed using SAS version 6.12 (SAS Institute, Cary, NC, U.S.A.). P values <0·05 (two-sided) were considered to indicate statistical significance.

Results

The full cohort for validation of the TIMI Risk Score consisted of the 1915 patients with unstable angina and non-Q wave myocardial infarction enrolled in PRISM-PLUS. The baseline characteristics of this population have been reported previously and are notable for a high prevalence of prior coronary artery disease and ischaemic abnormalities on the presenting electrocardiogram[11]. As in the TIMI 11B derivation set[4], the risk score values generally followed a normal distribution. Because of the small number of patients in the highest and lowest groups (<2%), patients with a score of 1 or 2 and 6 or 7 were combined.

Clinical risk assessment using the TIMI Risk Score

The primary end-point for this analysis (all-cause mortality, new myocardial infarction, refractory ischaemia) occurred in 18·8% of patients by 14 days. Stratification of patients by the TIMI risk score, revealed an increasing gradient of risk for death or cardiac ischaemic events ranging from 7·7 to 30·5% with rising risk score (P<0·001, Fig. 1). The discriminatory capacity of the TIMI risk score in this external data set was comparable with that observed in its derivation set in TIMI 11B (c-statistic 0·64 vs 0·65). The model predictions demonstrated a good fit to the observed data (Hosmer–Lemeshow goodness-of-fit statistic of 3·85 with 3 degrees of freedom, P=0·28). This pattern persisted at 30 days, with a similar three- to four-fold gradient of increasing risk for the composite end-point (9·2–32·5%, c-statistic 0·63) and two-fold gradient of risk for death or myocardial infarction (6·6–14%, c-statistic 0·61).

Predicting the benefit of tirofiban

The TIMI risk score showed a graded association with the rate of death or recurrent ischaemic events in both the tirofiban+heparin and the heparin-alone groups (P<0·001, Fig. 2). However, a strong trend toward attenuation of this risk gradient was evident among patients treated with tirofiban plus heparin compared with heparin alone ($P_{(\text{Interaction})}$=0·05, Fig. 2). Dichotomized at the median risk score, patients with a risk score ≥4 derived a greater relative reduction in the risk of death or ischaemic events with tirofiban (20 vs 26·8%, RR=0·75, P=0·01) compared with patients with a risk score <4 (11·9 vs 9·1%, RR=1·3, P=0·2); (Logistic regression testing for heterogeneity of the odds ratios, $P_{(\text{Interaction})}$=0·025). Moreover, this pattern of increasing benefit of tirofiban among patients with higher risk scores persisted at 30 days ($P_{(\text{Interaction})}$=0·02) and 6 months of observation ($P_{(\text{Interaction})}$=0·09, Fig. 3). Data regarding the outcome of death or myocardial infarction at 30 days were directionally consistent with the primary composite end-point, as higher risk patients (risk score ≥4) exhibited a benefit with tirofiban plus heparin vs heparin alone (10·3 vs 15·5%, RR 0·64, P=0·016) compared with those with a risk score <4 (6·3 vs 6·2%, RR 1·0, P=0·97); ($P_{(\text{Interaction})}$=0·2).

Application among patients with normal creatine kinase myocardial bands

Of patients enrolled in PRISM-PLUS, 1288 (67%) had no elevation of creatine kinase myocardial bands at presentation. Application of the TIMI Risk Score using the six remaining clinical variables revealed a similar 3·5-fold gradient of increasing risk for the composite end-point (P<0·001). Further, categorization by the risk score identified a clinically higher risk population (risk score ≥4) without elevation of creatine kinase myocardial bands that derived significant benefit from therapy with tirofiban (20·9% vs 28·8%; RR 0·73, P=0·027). However, there was no detectable difference between treatment groups (14·2 vs 9·5%, RR 1·4, P=0·1) among patients with negative creatine kinase myocardial bands and lower risk scores (<4).

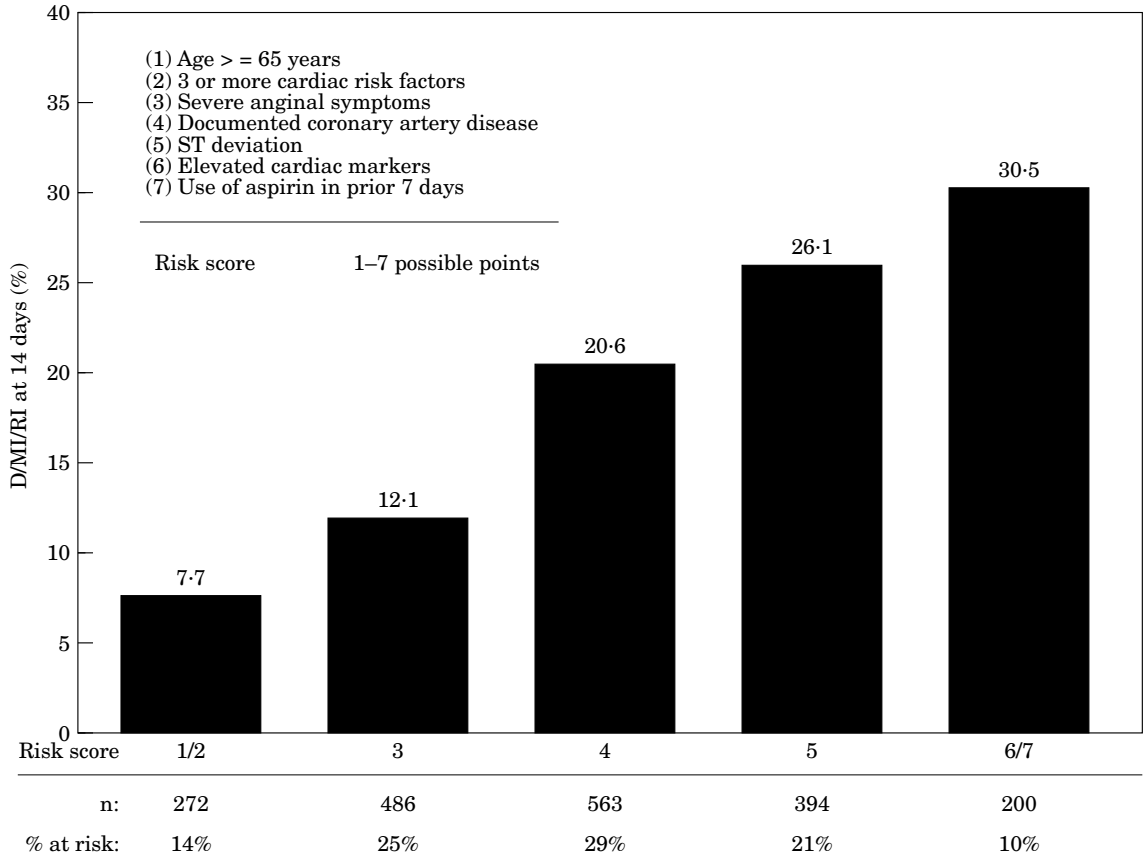

Figure 1 **Risk of death, new myocardial infarction or refractory ischaemia (D/MI/RI) through 14 days in PRISM-PLUS (n=1915) stratified by the TIMI Risk Score.**

Discussion

Our results demonstrate the potential use of the TIMI Risk Score for UA/NSTEMI for identifying patients who are most likely to benefit from treatment with the platelet glycoprotein IIb/IIIa inhibitor tirofiban in addition to heparin and aspirin. Notably, the TIMI Risk Score integrates information from multiple clinical characteristics that offer prognostic information independent of and complementary to data from biochemical markers[4]. As such, the risk score might be especially useful for the early assessment of patients waiting for cardiac marker results, as well as for selecting patients who remain at higher risk in spite of negative baseline cardiac markers. In both of these cases, the risk score may facilitate the early identification of patients who should be considered for treatment with intravenous glycoprotein IIb/IIIa inhibition.

Early institution of effective therapy may be necessary to optimize the management of patients with non-ST elevation acute coronary syndromes. As most events in this population occur early, delay of therapy may reduce the benefit[14]. In addition, data from several studies have indicated the potential for early institution of intravenous glycoprotein IIb/IIIa inhibitor to minimize the degree of myocardial injury in non-ST elevation ischaemic syndromes[15,16]. For example, among patients with normal baseline cardiac-specific troponin, treatment with tirofiban was associated with lesser degrees of myocardial injury ascertained by peak levels of cardiac troponin I and creatine kinase myocardial bands[15].

The TIMI Risk Score for UA/NSTEMI, which had been previously developed and validated among patients enrolled in two trials of enoxaparin, demonstrated a strong prognostic discriminatory capacity in this external validation set. The TIMI Risk Score integrates clinical data routinely available at the time of presentation and may be calculated easily at the bedside by any care provider. It is thus readily applied for the effective categorization of risk of death and recurrent ischaemic events in the very early stages of the clinical evaluation. The TIMI Risk Score shows promise not only for triage, but also for therapeutic decision-making with respect to novel antithrombotic therapies. The potential clinical applications of the TIMI Risk Score are now expanded in this analysis to include the identification of patients for whom intravenous platelet glycoprotein IIb/IIIa inhibition may be especially effective. Moreover, the TIMI Risk Score may additionally prove useful in the selection of appropriate patients for randomized clinical trials evaluating antiplatelet and antithrombin agents in non-ST elevation acute coronary syndromes.

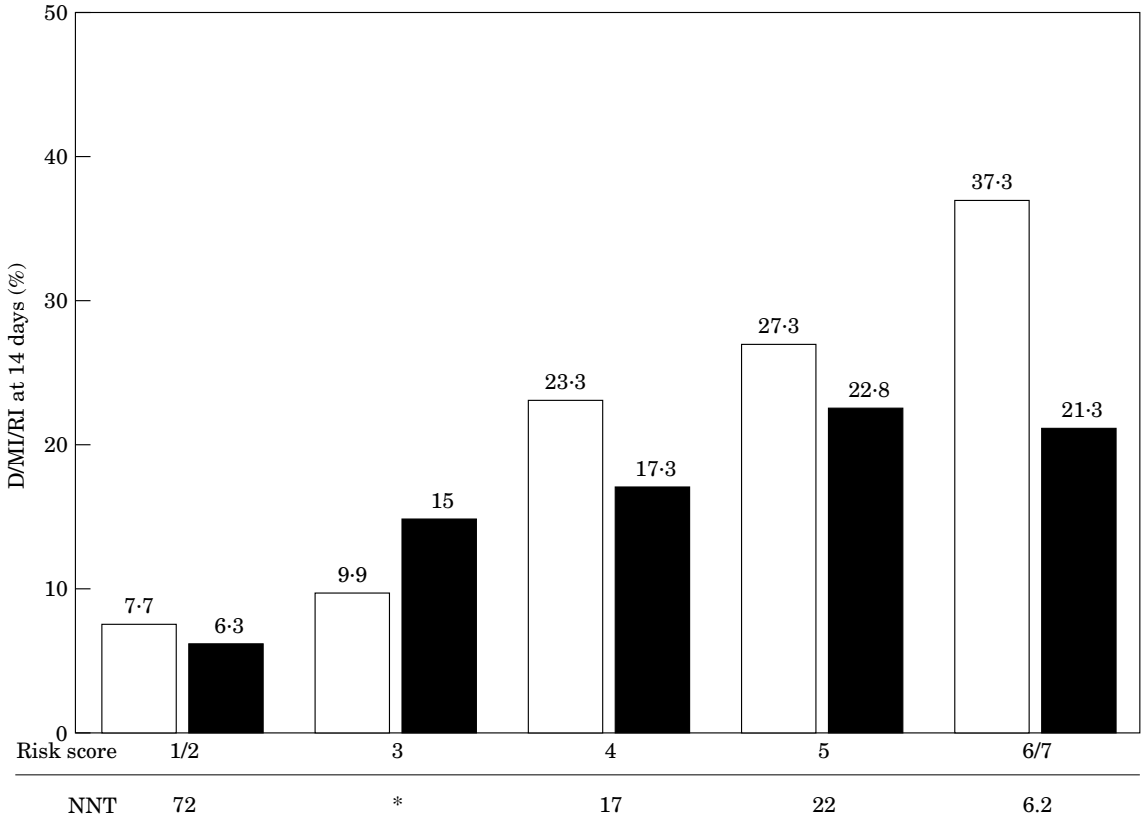

Figure 2 **Interaction of the benefit of treatment with tirofiban and the TIMI Risk Score. D/MI/RI: death, new myocardial infarction or refractory ischaemia; NNT=number needed to treat with tirofiban to avoid one death or severe ischaemic event over 14 days. White bars, heparin (n=797); black bars, tirofiban+heparin (n=773).**

Limitations

Several limitations to our analysis should be recognized. Two generalizations were made in evaluating the TIMI Risk Score in this data set. First, all patients were deemed to have severe anginal symptoms on the basis of the PRISM-PLUS inclusion criterion and thus given one point. This assignment represents an extension of the criteria for severe angina used in TIMI 11B, which did not include patients with exertional chest pain. The resulting upward skew in the risk scores may have curtailed the discriminatory range of the risk score in the low range but is unlikely to have altered the overall pattern of risk relationships observed in this study. Second, the variable, history of severe angiographic stenosis, was modified in this analysis to include any documented history of myocardial infarction or coronary revascularization. As discussed in our original report of the TIMI Risk Score, it was anticipated that the risk score might undergo some refinement during future application to facilitate wider clinical use[4]. The strong prognostic performance of the risk score as applied in PRISM-PLUS supports expansion of this variable to include such historical information that may be more widely available than angiographic data alone.

Data regarding the cardiac specific troponins were collected in only a very small proportion of patients enrolled in PRISM-PLUS. Thus, observations regarding patients with negative cardiac markers in this analysis are limited to patients with normal creatine kinase myocardial bands. Given the prognostic and therapeutic importance of low-level troponin elevations,[17,18] it is possible that the performance of this model might be further enhanced with the availability of troponin data. Nevertheless, the incorporation of both clinical and biomarker data remains central to the effective evaluation of patients with non-ST elevation acute coronary syndromes[2]. The incremental information derived from the electrocardiogram and clinical variables in the TIMI risk score bears further assessment with the inclusion of cardiac troponins.

Lastly, the TIMI Risk Score has been developed and validated among patients enrolled in phase III clinical trials. It is recognized that patients excluded from clinical trials may be at higher risk for adverse outcomes. Thus, the absolute event rates observed in PRISM PLUS may not apply to other populations. Nevertheless, the strong consistency between the major risk indicators incorporated in the risk score, and those identified in registries outside of clinical trials suggest

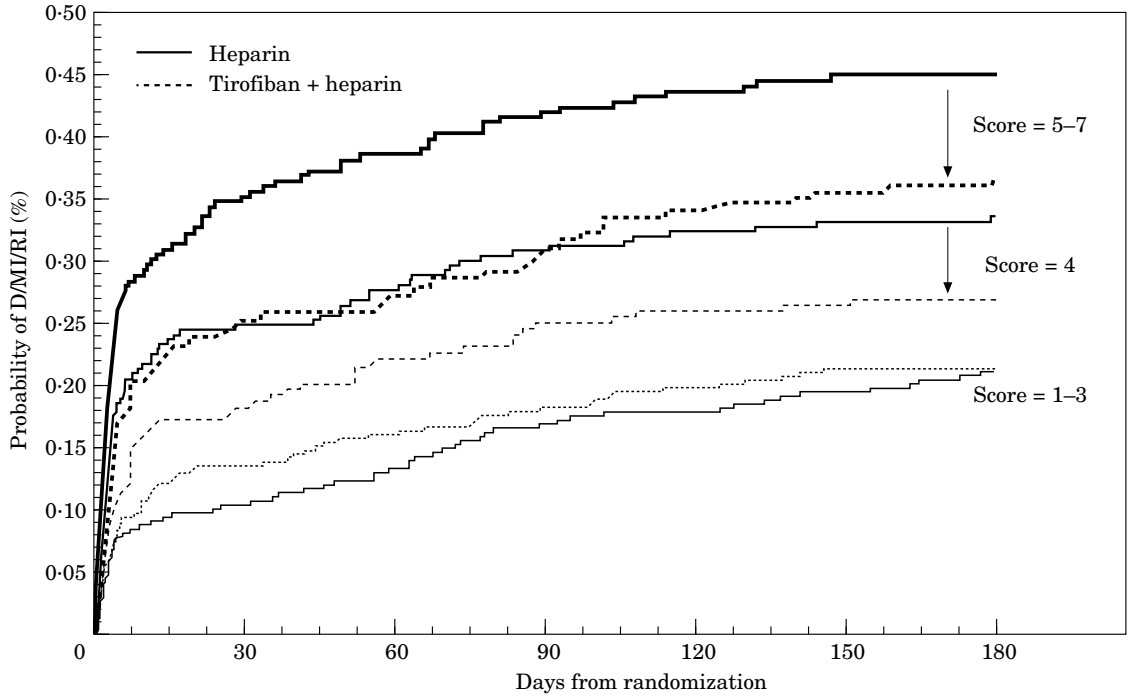

Figure 3 **Kaplan–Meier Curves showing the probability of death, new myocardial infarction or refractory ischaemia (D/MI/RI) through 6 months of follow-up. Score refers to the TIMI Risk Score for UA/NSTEMI.**

that the risk relationships are likely to be similar. Evaluation of the TIMI Risk Score in cohorts of patients presenting to the emergency department or physician's offices with chest symptoms will aid in determining its generalizability to a variety of clinical settings.

Conclusions

Effective risk assessment is fundamental to clinical decision-making regarding triage and initiation of appropriate treatment for non-ST elevation acute coronary syndromes. The TIMI Risk Score for UA/NSTEMI is a simple clinical tool for risk stratification that may aid in the early identification of patients who should be considered for therapy with intravenous glycoprotein IIb/IIIa inhibitor.

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