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Application of the Thrombolysis In Myocardial Infarction Risk Index in Non–ST-Segment Elevation Myocardial Infarction

Evaluation of Patients in the National Registry of Myocardial Infarction

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OBJECTIVES The purpose of this research was to evaluate the Thrombolysis In Myocardial Infarction risk index (TRI) to characterize the risk of death among patients with non–ST-segment elevation myocardial infarction (NSTEMI).

BACKGROUND The TRI, calculated from baseline age, systolic pressure, and heart rate, was established in patients with ST-segment elevation myocardial infarction (STEMI) and is predictive of mortality. Patients presenting with NSTEMI are increasing compared to STEMI and constitute a group with varied risk.

METHODS The TRI was calculated in 337,192 patients from the National Registry of Myocardial Infarction with NSTEMI. Values and outcomes were compared with 153,486 patients with STEMI classified by reperfusion status. Comparisons of baseline characteristics and clinical outcomes stratified by TRI were made.

RESULTS There was a graded relationship between the TRI and mortality in patients with NSTEMI with a >30-fold difference in mortality rates between lowest and highest deciles ($p < 0.0001$). The index showed good discrimination ($c = 0.73$). Overall mortality in the group with NSTEMI was higher (10.9%) than patients with STEMI treated with (6.6%) but lower than for STEMI patients not receiving reperfusion therapy (18.7%). The higher risk in comparison to patients with STEMI treated with reperfusion therapy was explained largely by the higher-risk profile of the population with NSTEMI.

CONCLUSIONS There is a graded relationship between TRI and mortality in patients with NSTEMI. This simple risk index provides important information about mortality in patients across the spectrum of myocardial infarction, STEMI and NSTEMI. Early identification of NSTEMI patients who are at high risk of in-hospital mortality may provide clinicians with important information for initial triage and treatment. (J Am Coll Cardiol 2006;47:1553–8) © 2006 by the American College of Cardiology Foundation

The Thrombolysis In Myocardial Infarction risk index (TRI) is a simple metric using baseline age, systolic blood pressure, and heart rate to predict early mortality in patients with myocardial infarction (MI) (1). It was derived from and validated in clinical trials of patients with ST-segment elevation myocardial infarction (STEMI) (1). In this population the TRI maintained much of the predictive value of more complex risk scores (2–8) that typically include data obtained during the course of the in-hospital evaluation including laboratory testing. The TRI was subsequently shown to be associated with mortality in an unselected population of patients with STEMI from the National Registry of Myocardial Infarction (NRMI) (9). The value of the TRI in predicting early mortality among patients with non–ST-segment elevation myocardial infarction (NSTEMI) is not known (10).

The proportion of patients with acute MI who present without ST-segment elevation continues to rise progressively (11). The overall population of patients with STEMI are generally considered as being at higher risk of early mortality compared to patients with NSTEMI (12–14). This early hazard with STEMI has been attributed to fatal arrhythmias, pump failure, and mechanical complications, which are considered to be less frequent in NSTEMI. In usual clinical practice, perhaps owing to the perceived lower short-term risk, patients with NSTEMI are less likely to be cared for by cardiologists or in a coronary care unit (15), and are also less likely to be treated with proven therapies such as aspirin, beta-blockers, and lipid-lowering therapy (11,16,17).

In part as a result of these disparities in management between STEMI and NSTEMI, we sought to evaluate the performance of the TRI for identifying patients with NSTEMI who are at significant risk for in-hospital mortality. An additional goal was to employ the index to characterize differences between patients presenting with these two forms of MI (18).

METHODS

The National Registry of Myocardial Infarction, described elsewhere (19,20), is an observational study of demograph-

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Abbreviations and Acronyms

CHF	= congestive heart failure
IQR	= interquartile range
LBBB	= left bundle branch block
LV	= left ventricle/ventricular
MI	= myocardial infarction
NRMI	= National Registry of Myocardial Infarction
NSTEMI	= non–ST-segment elevation myocardial infarction
STEMI	= ST-segment elevation myocardial infarction
TIMI	= Thrombolysis In Myocardial Infarction
TRI	= Thrombolysis In Myocardial Infarction risk index

ics, practice patterns, and health outcome among patients with MI in the U.S. Patient data from NRMI 3 (1,553 hospitals, April 1998 to June 2000) and NRMI 4 (1,272 hospitals, July 2000 to October 2002) were included. Overall mortality was 10.9% and 10.8% in NRMI 3 and 4, respectively, and all analyses were conducted on the combined dataset. All management decisions were at the discretion of the treating physician. Patients with ST-segment elevation or presumed new left bundle branch block (LBBB) were identified as presenting with STEMI and classified into those managed with and without early reperfusion therapy. Patents with MI but without ST-segment elevation or new LBBB were considered to have NSTEMI. Patients with complete data and a heart rate between 50 and 150 beats/min were included as in the derivation of the index (1).

The TRI was calculated using the equation: [heart rate $\times$ (age/10)^2/systolic pressure] (1). This index was initially derived from 12,353 patients enrolled in the Intravenous nPA for Treatment of Infarcting Myocardium Early (InTIME II-TIMI 17) trial (21), a randomized trial of lanoteplase versus alteplase as reperfusion therapy for STEMI. A significant graded relationship of the TRI with mortality at 24 h and at 30 days was observed and independently validated in patients with STEMI from the Thrombolysis In Myocardial Infarction (TIMI) 9A and 9B trials (1). Because of the broader spectrum of age and blood pressure observed in a community-based population compared to selected patients enrolled in clinical trials, application of the TRI was then updated to use 10-point intervals for simple clinical reference across a greater range (9). The same 10-point intervals were used in the present analysis, which compared patients with NSTEMI and those with STEMI enrolled in NRMI. Comparisons were made between NSTEMI and patients with STEMI. The patients with STEMI are divided into two separate groups, those who received early reperfusion and those who did not, as in previous work from this dataset (9). Main comparisons are made between patients with NSTEMI and these two groups of patients with STEMI. Formal comparison of the two STEMI groups has been previously published (9).

The prognostic discriminatory capacity of the TRI was expressed as the c-statistic, representing the area under the receiver operator curve for prediction of in-hospital death (22). Differences in event rates across risk index ranges were assessed using the chi-square test for trend. For the measure of general association, a chi-square test was used. Two-tailed p values <0.05 were considered significant. Statistical analyses were performed using SAS 8.02 (SAS Institute, Cary, North Carolina).

RESULTS

Performance of the TRI in NSTEMI. The analysis included a total of 490,678 patients; 337,192 with NSTEMI and 153,486 with STEMI (81,679 treated with reperfusion therapy). A strong graded relationship with in-hospital mortality (1.0% to 34.4%, $p < 0.001$) was evident among patients with NSTEMI when stratified by the TRI (Fig. 1). Although somewhat lower than in the STEMI patients in which it was derived, the majority of the discriminative capacity of the risk index in STEMI was retained in patients with NSTEMI (c-statistic = 0.73).

Baseline characteristics. When compared to patients with STEMI receiving reperfusion therapy, patients with NSTEMI were older (mean 71.9 vs. 62.5, $p < 0.001$), more often women (45.0 vs. 31.5), had higher rates of diabetes mellitus, were less likely to smoke, more likely to have had a history of hypertension, renal failure, and a history of congestive heart failure (CHF), MI, or coronary artery bypass grafting (Table 1). On the other hand, the baseline characteristics of patients with NSTEMI were more similar to those with STEMI who did not receive reperfusion therapy (Table 1). For example, 24% of the subjects with NSTEMI or with STEMI not receiving reperfusion had a prior history of CHF, compared to 4% of subjects with STEMI who did receive reperfusion therapy. A small proportion of patients with NSTEMI received immediate reperfusion therapy in this analysis (6.3%). These patients also exhibited a strong graded relationship of TRI with mortality.

TRI profile. The distribution of TRI values by 10-point intervals is shown in Figure 2. The distributions of TRI scores (i.e., the TRI profile) (Fig. 2) was similar in patients with NSTEMI (median TRI 32, interquartile range [IQR] 21.1 to 45.6) and patients with STEMI not receiving reperfusion therapy (median 36.1, IQR 24.5 to 50.0). In contrast, patients with STEMI who received early reperfusion therapy had a lower risk profile (median 21.1, IQR 14.7 to 30.3, $p < 0.001$). The percentage of subjects with NSTEMI (10.3%) that were at high risk with TRI >60 was similar to the 14.1% of STEMI subjects without reperfusion therapy, in contrast to the very small percentage of STEMI patients receiving reperfusion therapy that were at high risk (2.1%, $p < 0.001$). Among NSTEMI patients, those with higher risk index values by definition were older, had higher heart rates, and lower blood pressures. In addition to these features, they are more often women, lighter, Killip class >I, less frequently smokers, and have more frequent comor-

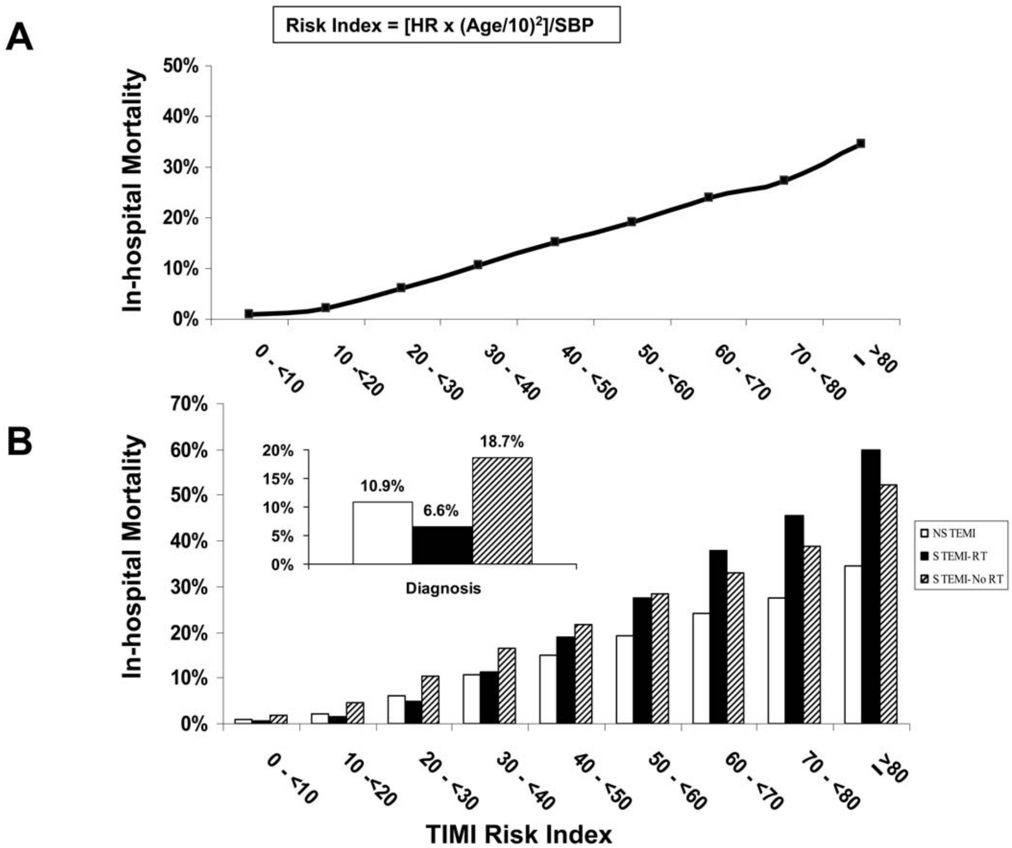

Figure 1. **(A)** Relationship between Thrombolysis In Myocardial Infarction (TIMI) risk index and mortality in non–ST-segment myocardial infarction (NSTEMI) (**line** smoothed to fit data). **(B)** Relationship between TIMI risk index and mortality in ST-segment myocardial infarction (STEMI), NSTEMI. **Inset graph** shows mortality in full group by diagnosis. HR = heart rate; RT = reperfusion therapy; SBP = systolic blood pressure.

bidities including CHF, chronic obstructive pulmonary disease, and renal failure (Table 2).

Mortality results and index performance. Overall mortality in the patients with NSTEMI (10.9%) was significantly higher than among patients with STEMI treated with contemporary reperfusion therapy (6.6%), but lower than the patients with STEMI not receiving reperfusion (18.7%) (Fig. 1B, inset). In low-risk patients (TRI <30), representing 46% of the NSTEMI patients and 57% of the STEMI patients, the mortalities were similar. However, in patients at intermediate or high risk (TRI ≥30), the NSTEMI mortality was lower than STEMI with or without reperfusion therapy.

Ventricular function and risk index. Left ventricular (LV) function was determined in 230,267 (68%) of patients in the dataset with NSTEMI and reported in a binary fashion (≥40% or <40%). Patients who had higher risk index values were less likely to have an LV function measure reported. Among those with TRI ≥80, only 51% reported a measure of LV function, compared to 76% of patients with TRI 0 to <10. Among those who did have LV function measured and reported, when stratified by TRI values there was an increasing likelihood of having LV function <40% with increasing TIMI risk index (Fig. 3, $p_{trend} < 0.001$) with a range of 10% (TRI 0 to <10) to 48% (TRI 70 to <80) of subjects.

DISCUSSION

This analysis demonstrates that a simple risk index calculated from age, systolic blood pressure, and heart rate derived from and validated in STEMI (1,9) is also strongly associated with in-hospital mortality in a nationally representative sample of 337,192 patients with NSTEMI. It might have been anticipated that an early risk index developed for STEMI would not perform well in predicting early mortality in NSTEMI, which is not considered to cause the same levels of myocardial dysfunction, hemodynamic compromise, or serious arrhythmias as STEMI. However, the predictive capacity of the TRI for short-term mortality in patients with NSTEMI was similar to that for patients with STEMI. Despite the differences in pathophysiology and treatment of patients with STEMI and NSTEMI, the three components of the risk index have a bearing on ultimate outcome in both conditions. These findings are consistent with a previous single-center study showing the utility of the TRI across the spectrum of ACS (23). Moreover, the TRI provides a tool to identify patients with NSTEMI at high

JACC Vol. 47, No. 8, 2006
April 18, 2006:1553–8

Table 1. Baseline Characteristics

Characteristics	NSTEMI (n = 337,192)	STEMI RT (n = 81,679)	STEMI No RT (n = 71,807)
Age, yrs	71.9 ± 13.9	62.5 ± 13.4	73.6 ± 13.9
≥65 (%)	71.0	43.4	75.2
>75 (%)	48.4	21.2	53.7
Female gender (%)	45.0	31.5	48.8
Weight, kg	77.8 ± 21.0	83.5 ± 19.5	75.1 ± 20.3
Smoker	19.8	38.2	19.1
DM	33.5	20.1	33.1
HTN	62.4	49.3	60.4
Renal failure	13.4	2.6	12.0
History of CHF	24.0	4.4	24.4
History of COPD	18.0	8.6	16.2
History of CVA	12.9	4.5	14.4
MI	28.3	17.0	26.6
Angina	14.2	8.3	12.2
PCI	11.3	11.8	8.2
CABG	16.8	6.8	13.2
Killip class >1	30.8	10.7	35.8
Heart rate, beats/min	90.2 ± 21.6	80 ± 18.6	92.5 ± 22.0
SBP, mm Hg	146.3 ± 32.6	141.3 ± 30.1	141.2 ± 33
TIMI risk score (STEMI) median (25th, 75th percentile)	NA	2.0 (1, 4)	5 (3, 6)
TRI median (25th, 75th percentile)	32.0 (21.1, 45.6)	21.1 (14.7, 30.3)	36.1 (24.5, 50.0)

CABG = coronary artery bypass grafting; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; DM = diabetes mellitus; HTN = hypertension; MI = myocardial infarction; NSTEMI = non–ST-segment elevation MI; PCI = percutaneous coronary intervention; RT = reperfusion therapy; SBP = systolic blood pressure; STEMI = ST-segment elevation MI; TIMI = Thrombolysis In Myocardial Infarction; TRI = Thrombolysis In Myocardial Infarction risk index.

risk who may warrant intensive monitoring and care similar to that given to patients with STEMI.

This analysis demonstrates the relatively high overall mortality risk of patients presenting with NSTEMI to hospitals in the U.S. This high risk relates largely to the high baseline risk profile of the population. Patients with NSTEMI in NRMI, as in previous data sets, are more likely to be women, and more likely to have significant medical comorbidities than are patients with STEMI (12,17,24). These findings primarily reflect differences between the NSTEMI patients and those STEMI patients treated with early reperfusion therapy. These attributes may in part explain the increased total mortality in these patients (10.9%) compared to the patients with STEMI receiving reperfusion therapy (6.6%). Nevertheless, the TRI retains a good ability to stratify risk in such patients with NSTEMI without direct measurement of these comorbid factors, in part because age correlates well with comorbidities and is an

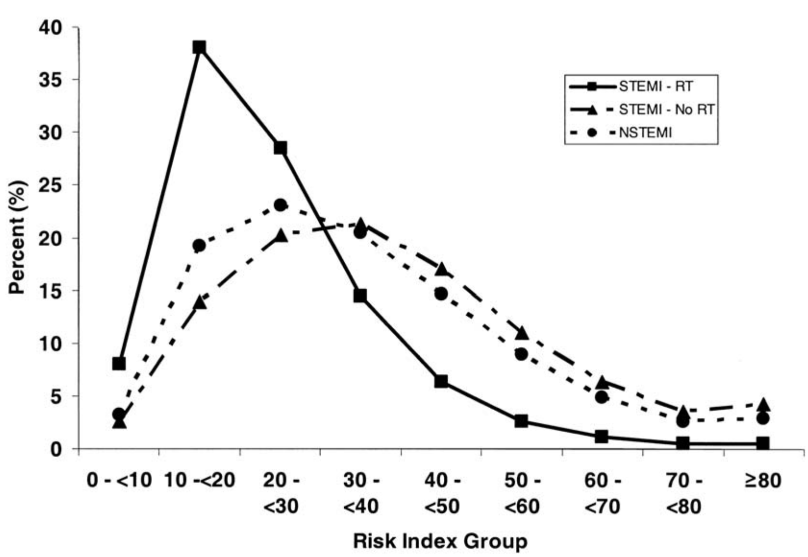

Figure 2. Distribution of Thrombolysis In Myocardial Infarction risk index in patients with ST-segment myocardial infarction (STEMI) versus non–ST-segment myocardial infarction (NSTEMI). RT = early reperfusion therapy.

Table 2. Baseline Demographic Risk By Risk Index Value

	NSTEMI Patients			
	TRI Category			
Characteristics	**<30 (n = 153,590)**	**30–60 (n = 148,723)**	**>60 (n = 34,879)**	**Total (n = 337,192)**
Age, yrs	61.7 ± 12.1	79.3 ± 8.3	85.7 ± 7.0	71.9 ± 13.9
≥65 (%)	41.4	94.9	99.4	71.0
>75 (%)	15.3	72.0	93.4	48.4
Female gender (%)	35.4	52.1	57.3	45.0
Weight, kg	85.5 ± 21.3	72.4 ± 18.4	65.8 ± 16.7	77.8 ± 21.0
Smoker	31.3	11.1	6.4	19.8
DM	32.4	36.1	27.2	33.5
HTN	61.4	64.6	57.4	62.4
Renal failure	9.6	16.3	17.4	13.4
History of CHF	12.5	32.2	40.2	24.0
History of COPD	12.3	22.8	23.1	18.0
History of CVA	8.4	16.5	17.8	12.9
MI	25.6	31.1	28.6	28.3
Angina	13.6	15.2	12.6	14.2
PCI	14.4	9.5	4.7	11.3
CABG	17.7	17.5	9.9	16.8
Killip class >1	16.6	41.1	49.8	30.8
Heart rate, beats/min	80.7 ± 18.0	95.0 ± 20.0	112.0 ± 19.7	90.2 ± 21.6
SBP, mm Hg	157.9 ± 30.3	142.7 ± 29.5	110.4 ± 24.7	146.3 ± 32.6
TRI median (25th, 75th percentile)	20.2 (14.9, 25.0)	40.9 (35.1, 48.3)	70.9 (64.5, 82.1)	32.0 (21.1, 45.6)

Abbreviations as in Table 1.

important component of the TRI. Our previous work suggests that the TRI contributes independent information when considered along with these comorbid factors (1).

Also, it is likely that patients with NSTEMI who exhibit hemodynamic disturbance (i.e., decreased systolic pressure and/or increased heart rate) may have limited myocardial reserve, multivessel coronary artery disease, or additional comorbidities that result in an impaired ability to tolerate myocardial ischemia. This is supported by the correlation of higher risk index values with lower LV ejection fraction (at least on a population basis). Recognition that a patient with MI and a high TRI is at high risk for mortality regardless of whether the presenting electrocardiogram exhibits ST-segment elevation or not may help in the development of strategies and interventions.

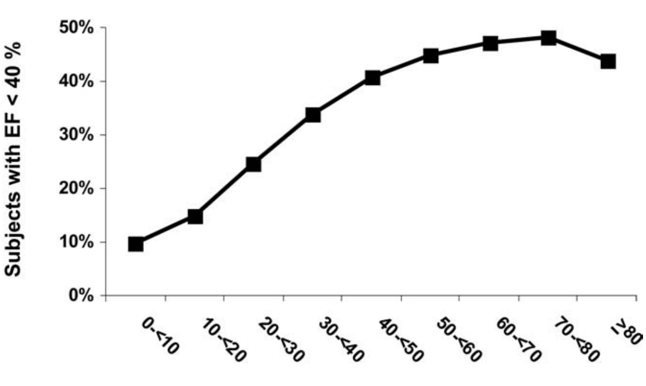

Figure 3. Relationship of left ventricular (LV) ejection fraction to risk index value. TIMI = Thrombolysis In Myocardial Infarction.

Overall, when examined by distribution of risk index, patients with NSTEMI are quite similar to patients with STEMI who do not receive reperfusion therapy, and both of these groups of patients have higher values of the TRI than those with STEMI who received early reperfusion therapy (Fig. 2). The combination of a higher-risk profile than STEMI patients who were reperfused and better short-term outcomes than STEMI patients not treated with early reperfusion therapy with similar TRI profiles results in an overall mortality rate for NSTEMI that is intermediate between the two groups of patients with STEMI.

Study limitations. This is an observational study, and baseline and treatment differences among patients with STEMI and NSTEMI may exist that were not quantified in this analysis. In addition, decisions regarding reperfusion therapy in patients with STEMI were made by treating physicians. This may have affected outcomes for patients and altered the relationships among the groups studied. This analysis also does not account for patients who would have been included but died before hospitalization. Similarly, this analysis (and the NRMI database) is limited to in-hospital outcomes, and it is possible that the relationship between TRI and outcomes in NSTEMI and STEMI differs for long-term outcomes.

Patients were categorized into these analyses by presence or absence of diagnosis of STEMI; therefore, it is possible that the NSTEMI group contains some patients with unstable angina rather than NSTEMI. It is also possible that patients with true posterior STEMI with only precordial ST-segment depressions could be classified as

JACC Vol. 47, No. 8, 2006
April 18, 2006:1553–8

NSTEMI. Because NRMI enrollment requires both suggestive presentation and clinical evidence of MI (electrocardiogram, enzymes, scintigraphy, or autopsy) and a discharge diagnosis of MI, we believe the contribution of these two groups is likely to be small. It is also worth noting that for NSTEMI, as with STEMI, the risk index provides an initial assessment of risk that should be updated as the patient's course progresses and more information becomes available.

Conclusions. The TRI, calculated from baseline age, systolic pressure, and heart rate of patients presenting with MI, was derived from and validated among patients with STEMI. This index provides prognostic information across the spectrum of patients with acute MI including patients with NSTEMI. Early identification of patients with NSTEMI who are at risk of in-hospital mortality may provide clinicians with important information for initial triage and treatment of this growing population of patients with acute coronary syndromes.

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