ORIGINAL RESEARCH

Contemporary Risk Stratification After Myocardial Infarction in the Community: Performance of Scores and Incremental Value of Soluble Suppression of Tumorigenicity-2

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***Background*—**Current American Heart Association/American College of Cardiology guidelines recommend the GRACE (Global Registry of Acute Coronary Events) and TIMI (Thrombolysis in Myocardial Infarction) scores to assess myocardial infarction (MI) prognosis. Changes in the epidemiological characteristics of MI and the availability of new biomarkers warrant an assessment of the performance of these scores in contemporary practice. We assessed the following: (1) the performance of GRACE and TIMI to predict 1-year mortality in a cohort of patients stratified by ST-segment elevation MI (STEMI) and non-STEMI (NSTEMI) and (2) the incremental discriminatory power of soluble suppression of tumorigenicity-2, a myocardial fibrosis biomarker.

***Methods and Results*—**Olmsted County, Minnesota, residents with incident MI (N=1401) were recruited prospectively from November 1, 2002 to December 31, 2012 (mean age, 67 years; 61% men; 79% with NSTEMI). Baseline data were used to calculate risk scores; soluble suppression of tumorigenicity-2 was measured in stored plasma samples obtained at index MI. *C*-statistics adapted to survival data were used to assess the discriminatory power of the risk scores and the improvement gained by adding other markers. During the first year of follow-up, 190 patients (14%) died. The discriminatory performance to predict death was reasonable for GRACE and poor for TIMI, and was generally worse in those with NSTEMI versus those with STEMI. In people with NSTEMI, sequential addition of comorbidities and soluble suppression of tumorigenicity-2 substantially improved the *c*-statistic over GRACE (from 0.78 to 0.80 to 0.84) and TIMI (from 0.61 to 0.73 to 0.81), respectively (all $P \leq 0.05$).

***Conclusions*—**Guideline-recommended scores for risk assessment after MI underperform in contemporary community patients, particularly those with NSTEMI, which now represents most infarcts. Incorporating comorbidities and soluble suppression of tumorigenicity-2 substantially improves risk prediction, thereby delineating opportunities to improve clinical care. **(*J Am Heart Assoc*. 2017;6:e005958. DOI: 10.1161/JAHA.117.005958.)**

Key Words: biomarkers • mortality • myocardial infarction • risk scores

Recent American Heart Association/American College of Cardiology guidelines recommend using risk scores to assess prognosis in people with non–ST-segment elevation myocardial infarction (NSTEMI)[1] and ST-segment elevation myocardial infarction (STEMI).[2] Specifically, the TIMI (Thrombolysis in Myocardial Infarction) for NSTEMI,[3] the TIMI for STEMI,[4] and the GRACE (Global Registry of Acute Coronary Events) for both myocardial infarction (MI) types[5,6] were recommended for early risk assessment.[1,2] Because these scores were developed 2 decades ago, their performance must be reevaluated to ensure their relevance to contemporary practices. This is particularly important because major changes in the epidemiological characteristics of MI have taken place recently, characterized by a shift in case mix, improved short-term management and secondary prevention, decreased short-term case fatality, transitions from incident to recurrent events and from prehospital deaths to hospitalized MI, and an increasing burden of morbidity and mortality from noncardiac causes.[7–11] In Olmsted County, Minnesota, for example, the proportion of patients with NSTEMI has increased from 60% in 1979 to 1989 to 75% in 2000 to 2006 and the average age among all those with incident MIs increased from 67 to

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Clinical Perspective

What Is New?

- Major changes in the epidemiological characteristics of myocardial infarction and the availability of new biomarkers for risk stratification during the past decade call for an assessment of the performance of the GRACE (Global Registry of Acute Coronary Events) and TIMI (Thrombolysis in Myocardial Infarction) risk scores, currently recommended by American Heart Association/American College of Cardiology guidelines.
- Using a community-based cohort of patients with myocardial infarction, we demonstrated that TIMI and GRACE underperform in predicting mortality, particularly for those with non–ST-segment elevation myocardial infarction.
- Incorporating comorbidities and soluble suppression of tumorigenicity-2, a myocardial fibrosis and remodeling biomarker, substantially improved risk prediction.

What Are the Clinical Implications?

- Because accurate risk stratification after myocardial infarction is essential for informed decision making and management, these findings define an opportunity to improve clinical care.

69 years, respectively.[12] Thus, we do not know if the risk scores recommended in the guidelines, which are derived from older data, are still adequate for contemporary risk prediction.

We previously demonstrated that, among community patients with incident MI, the Charlson index[13] (a general measure of comorbidity) conveys important prognostic information, incremental to those of several proposed risk stratification scores.[14] Another promising variable to consider in MI risk classification is soluble suppression of tumorigenicity-2 (sST2). sST2, a member of the interleukin-1 receptor family, is a biomarker of myocardial fibrosis and remodeling that predicts outcomes and mortality.[15] Indeed, many studies have shown a substantial prognostic impact for sST2 in patients with heart failure,[16–19] and in those with MI,[20–23] with a suggested heterogeneity in its prognostic impact between STEMI and NSTEMI.[24,25] Because these studies were mostly conducted among randomized controlled trial participants, their generalizability to community patients is uncertain,[26] and the incremental value of sST2 over established risk scores remains to be established.[27]

The present study was designed to address these gaps in knowledge and evaluate the performance of guideline-recommended risk scores in a contemporary community cohort of patients with MI. Specifically, we sought to do the following: (1) assess the performance of GRACE and TIMI, overall and by STEMI/NSTEMI status; and (2) examine the incremental risk stratification value, beyond that of recommended scores, of comorbidity and of the emerging sST2 biomarker.

Methods

Study Setting

This prospective community study was conducted in Olmsted County, Minnesota, under the auspices of the Rochester Epidemiology Project.[28] The latter is a medical records linkage system that links the records from Olmsted County providers (Mayo Clinic, Olmsted Medical Center, and a few private providers) that provide nearly all health care to local residents. All medical diagnoses are maintained through an electronic index, and patients can be identified through their inpatient and outpatient contacts across the local providers.[29] This study was approved by the appropriate institutional review boards.

MI Cohort and Mortality Follow-Up

This cohort study, previously described in detail,[8,30] included patients with incident (first-ever) MI from November 1, 2002 through December 31, 2012. Olmsted County residents admitted to Mayo Clinic hospitals in Rochester, MN, with a cardiac troponin T level of 0.03 ng/mL or higher were identified within 12 hours of the blood draw. Written consent was obtained from all patients, or if consent could not be granted by the patient, it was obtained from next of kin.

The validation of MI relied on standard algorithms integrating cardiac pain, electrocardiographic data, and biomarker data. According to current guidelines, each case was classified by troponin T[31]; as part of clinical practice, successive troponin T measurements were performed after infarction onset. A change (increase or decrease) between any 2 troponin T measurements was defined by a difference of at least 0.05 ng/mL, which is greater than the level of imprecision of the assay at all concentrations.[31] Cardiac troponin T was measured with a sandwich electrochemiluminescence immunoassay on the Elecsys 2010 in the laboratories of the Department of Medicine and Pathology at Mayo Clinic.

Participants were followed up through their complete medical records in the community from the index MI date to death or the most recent clinical contact through December 2014. All-cause death was ascertained using multiple sources, including autopsy reports, death certificates filed in Olmsted County, obituary notices, and electronic death certificates obtained from the Section of Vital Statistics, Minnesota Department of Health, as previously described.[8,28]

Table 1. Variables Included in Guideline-Recommended Scores for Post-MI Risk Stratification

GRACE (Range, 1–263)	TIMI-STEMI (Range, 0–14)	TIMI-NSTEMI (Range, 0–7)
Age (7 categories)	Age (2 categories)	Age ≥65 y
HF history	Diabetes mellitus, hypertension, or angina	3≥CAD risk factors*
Prior MI	Systolic blood pressure <100 mm Hg	Prior coronary stenosis >50%
Resting heart rate (7 categories)	Heart rate >100 bpm	ST-segment deviation
Systolic blood pressure (7 categories)	Killip class >1	Pre-MI angina
ST-segment deviation	Weight <67 kg	Aspirin use in past 7 d
Initial serum creatinine (7 categories)	LBBB or anterior ST elevation	Elevated cardiac biomarkers†
Elevated cardiac enzymes	Time to treatment >4 h	
No in-hospital PCI		

bpm indicates beats/min; CAD, coronary artery disease; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; LBBB, left bundle branch block; MI, myocardial infarction; NSTEMI, non–ST-segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI; and TIMI, Thrombolysis in Myocardial Infarction.
*Risk factors included family history of CAD, hypertension, hypercholesterolemia, or diabetes mellitus, or being a current smoker.
†Creatine kinase MB fraction and/or cardiac-specific troponin level.

Clinical Characteristics

The medical record was reviewed to determine cardiovascular risk factors, comorbid conditions, MI characteristics, and short-term interventions at the time of incident MI. The presence of ST-segment elevation was ascertained using the Minnesota code of the ECG.[32] Comorbidity was measured by the Charlson comorbidity index,[13] which consists of 17 comorbid conditions weighted according to the degree to which they predict death. Cigarette smoking was classified as current, former, or never smoker. Clinical definitions were used to assess whether patients had hypertension, diabetes mellitus, hypercholesterolemia, or a history of heart failure. Heart rate at admission and body weight were obtained. Killip class was determined within 24 hours of the index MI. Coronary artery disease was defined angiographically. Short-term interventions included reperfusion (thrombolytic therapy or percutaneous coronary intervention) and coronary artery bypass grafting during the initial hospitalization. All variables used for the calculation of GRACE,[6] TIMI for STEMI,[4] and TIMI for NSTEMI[3] risk scores are listed in Table 1.

sST2 Measurement

sST2 was measured from stored plasma samples obtained using a high-sensitivity sandwich monoclonal immunoassay (Presage ST2 assay). The antibodies used in the Presage assay were generated from a recombinant protein based on the human cDNA clone for the complete soluble sequence.[33] This platform offers improved accuracy in quantifying sST2 levels, particularly at lower concentrations. This specific assay has high sensitivity; the reliability of running the Presage ST2 assay on EDTA plasma samples stored at −70°C (as per biomarker core laboratory) has been established previously.[34] Calibration and standardization of this assay were performed according to the manufacturer's protocol. Previous reports document the intra-assay and interassay coefficients of variation as <2.5% and <4.0%, respectively.[33]

Statistical Analysis

Baseline characteristics were compared across subgroups of sST2 ("normal" versus "high") stratified by STEMI/NSTEMI status; they are presented as mean and SD for normally distributed continuous variables, median and 25th to 75th percentile for nonnormally distributed continuous variables, and frequencies for categorical variables. High and normal sST2 levels were defined according to published criteria,[35] which are age and sex dependent. Cut points were defined as follows (values in ng/mL): women, ≤44 years, 29.5; 45 to 54 years, 34.0; 55 to 64 years, 39.3; and ≥65 years, 45.3; men, ≤44 years, 46.7; 45 to 54 years, 48.7; 55 to 64 years, 50.8; and ≥65 years, 53.0. Cox proportional hazards regression models were constructed to estimate the hazard ratios and 95% confidence intervals for all-cause mortality associated with sST2. The latter was modeled as both a dichotomous variable (high versus normal) and a continuous variable. Because the sST2 distribution was skewed to the right, to limit the influence of extreme observations, the variable was log transformed when appropriate. Because the GRACE and TIMI scores were created for early risk assessment, follow-up was truncated at 1 year. Several models were examined to assess the independent association of sST2 with post-MI death: an age- and sex-adjusted model; the GRACE model[6]; and the TIMI (for STEMI[4] and NSTEMI,[3] as appropriate) model. The Charlson comorbidity index (log transformed and modeled as a continuous variable) was then added to the models. Associations were examined overall and specifically by STEMI/NSTEMI status.

Table 2. Baseline Characteristics According to sST2 Level, Overall and by STEMI/NSTEMI Presentation

Characteristic	Overall		STEMI		NSTEMI	
	Normal sST2 (n=682)	High sST2 (n=719)	Normal sST2 (n=148)	High sST2 (n=143)	Normal sST2 (n=534)	High sST2 (n=576)
sST2, median (25th–75th percentile), ng/mL	32.2 (25.2–39.1)	99.5 (62.0–200.0)*	32.1 (24.8–41.2)	88.2 (60.9–200.0)*	32.3 (25.2–38.6)	102.4 (62.5–199.8)*
Age, mean (SD), y	64.6 (13.8)	69.9 (15.5)*	59.8 (14.0)	63.8 (17.3)†	65.9 (13.5)	71.4 (14.7)*
Male sex, n (%)	491 (72)	362 (50)*	120 (81)	89 (62)*	371 (70)	273 (47)*
Smoking, n (%)						
Never	265 (39)	294 (41)	60 (41)	64 (45)	205 (38)	230 (40)
Former	270 (40)	292 (41)	47 (32)	44 (31)	223 (42)	248 (43)
Current	147 (22)	133 (19)	41 (28)	35 (24)	106 (20)	98 (17)
BMI, n (%)						
<18.5 kg/m^2 (underweight)	6 (1)	30 (4)*	2 (1)	4 (3)	4 (1)	26 (5)*
18.5–24.9 kg/m^2 (normal weight)	130 (19)	210 (29)	30 (20)	35 (24)	101 (19)	175 (30)
25.0–29.9 kg/m^2 (overweight)	281 (41)	232 (32)	66 (45)	53 (37)	215 (40)	179 (31)
≥30.0 kg/m^2 (obese)	264 (39)	246 (34)	50 (34)	51 (36)	214 (40)	195 (34)
Family history of CAD, n (%)	175 (26)	114 (16)*	43 (29)	26 (18)†	132 (25)	88 (15)*
Hypertension, n (%)	461 (68)	532 (74)*	85 (57)	83 (58)	376 (70)	449 (78)*
Hyperlipidemia, n (%)	460 (67)	465 (65)	92 (62)	84 (59)	368 (69)	381 (66)
Diabetes mellitus, n (%)	135 (20)	199 (28)*	20 (14)	38 (27)*	115 (22)	161 (28)†
History of HF, n (%)	42 (6)	137 (19)*	4 (3)	14 (10)*	38 (7)	123 (21)*
History of CAD, n (%)	87 (13)	145 (20)*	14 (10)	10 (7)	73 (14)	135 (23)*
Maximum troponin T, median (25th–75th percentile), ng/mL	0.60 (0.21–1.65)	0.67 (0.18–2.61)	1.76 (0.69–3.80)	3.11 (0.95–6.63)*	0.41 (0.17–1.19)	0.42 (0.14–1.52)
Killip class >1, n (%)	81 (12)	234 (33)*	26 (18)	44 (31)†	55 (10)	190 (34)*
STEMI, n (%)	148 (22)	143 (20)	…	…	…	…
Anterior MI, n (%)	185 (27)	317 (44)*	81 (55)	94 (66)	104 (20)	223 (39)*
Reperfusion/revascularization during hospitalization, n (%)	484 (71)	317 (44)*	120 (81)	104 (73)	364 (68)	213 (37)*
Charlson index, n (%)						
0	320 (47)	182 (25)*	78 (53)	53 (37)*	242 (45)	129 (22)*
1–2	203 (30)	245 (34)	52 (35)	48 (34)	151 (28)	197 (34)
≥3	159 (23)	292 (41)	18 (12)	42 (29)	141 (26)	250 (43)
eGFR, median (25th–75th percentile), mL/min per 1.73 m^2	63.9 (53.9–76.5)	57.2 (43.9–71.2)*	69.0 (59.9–82.2)	61.8 (47.7–70.9)*	62.6 (52.7–75.6)	56.2 (42.4–71.2)*
GRACE score, median (25th–75th percentile)	112 (92–133)	136 (104–160)*	99 (81–121)	109 (81–145)*	117 (96–135)	140 (114–162)*
TIMI score, median (25th–75th percentile)	3 (2–4)	3 (2–5)*	3 (2–5)	4 (2–7)*	3 (2–4)	3 (2–4)

Continued

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Table 2. Continued

Characteristic	Overall		STEMI		NSTEMI	
	Normal sST2 (n=682)	High sST2 (n=719)	Normal sST2 (n=148)	High sST2 (n=143)	Normal sST2 (n=534)	High sST2 (n=576)
Medication at discharge, n (%)						
Aspirin	627 (92.1)	521 (78.9)*	142 (95.9)	123 (94.6)	485 (91.0)	398 (75.1)*
Statins	596 (87.5)	457 (69.2)*	137 (92.6)	114 (87.7)	459 (86.1)	343 (64.7)*
β Blockers	608 (89.3)	533 (80.8)*	141 (95.3)	112 (86.2)*	467 (87.6)	421 (79.4)*
ACE/ARB	414 (60.8)	394 (59.7)	101 (68.2)	101 (77.7)	313 (58.7)	293 (55.3)

ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; MI, myocardial infarction; NSTEMI, non–ST-elevation MI; sST2, soluble suppression of tumorigenicity-2; STEMI, ST-elevation MI; and TIMI, Thrombolysis in Myocardial Infarction.

*$P\leq0.01$.

†$P\leq0.05$.

Discrimination (the model's ability to separate those who did and did not die during the first year of follow-up) was assessed through *c*-statistics adapted to survival data, and the difference between competing prediction models was formally tested.[36] The latter step was taken to evaluate the added predictive value of a new marker by comparing predictions made using a baseline set of risk markers with predictions that also included information about the examined risk marker. The GRACE and TIMI risk scores served as baseline prediction models, on top of which the Charlson comorbidity index and sST2 (both log transformed and treated as continuous variables) were sequentially added. Calibration was assessed by the Hosmer-Lemeshow goodness-of-fit test, which determines how close the predicted and observed incidence of events, as derived from logistic regression models, is over a range of scores. The tests showed acceptable calibration ($P>0.05$) in all the adjusted models. Analyses were performed using R statistical software, version 3.3.1 (R Development Core Team[37]), IBM SPSS Statistics, version 23, and SAS statistical software, version 9.4.

Results

A total of 2104 patients had incident MI validated between November 1, 2002 and December 31, 2012, of whom 1401 (66.6%) had a stored plasma sample available for sST2 analysis and were included in the study. The average (SD) age of this cohort was 67.3 (15.0) years, 61% were male, and 79% were seen with NSTEMI. The median sST2 level was 49 (25th–75th percentile, 33–103) ng/mL; 719 patients (51%) were considered to have a high sST2. The median scores (25th–75th percentile) for GRACE, TIMI-STEMI, and TIMI-NSTEMI were 123 (96–148), 4 (2–6), and 3 (2–4), respectively. The 703 patients who did not have sST2 measured were, on average, older (70.2 versus 67.3 years), included more women (47% versus 39%), and had more comorbidities (diabetes mellitus, 29% versus 24%; history of heart failure, 21% versus 13%) than patients with available sST2.

Compared with patients with normal sST2 levels, patients with elevated sST2 were older, were more likely to be women, and had a higher burden of comorbidity, a worse cardiovascular risk profile, and more severe MI, regardless of STEMI/NSTEMI status. In addition, patients with a high sST2 were less likely to be prescribed aspirin, statins, and β blockers at hospital discharge (Table 2). Log sST2 was moderately correlated with GRACE (Pearson $r=0.37$) and weakly with TIMI (Pearson $r=0.16$). After a 1-year follow-up, 190 patients (13.6%) died (164 [14.8%] with NSTEMI and 26 [8.9%] with STEMI). Adjusted for age and sex, sST2 was a strong inverse predictor of 1-year survival after MI, whereas STEMI/NSTEMI status was far less predictive of survival (Figure 1). Fitting different adjustment models with GRACE and TIMI risk scores

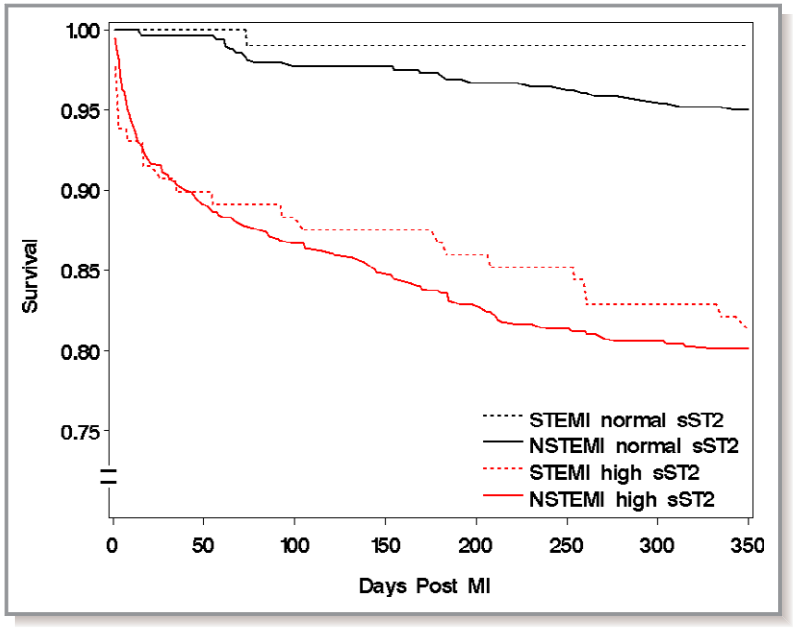

Figure 1. Age- and sex-adjusted survival after myocardial infarction (MI) in mutually exclusive groups defined by ST-segment elevation MI (STEMI) vs non-STEMI (NSTEMI) presentation and normal vs high soluble suppression of tumorigenicity-2 (sST2) measurement.

and Charlson comorbidity index as covariates, the hazard ratio for death increased ≈3-fold per 1 log-unit increase in sST2. The associations between sST2 and death were stronger among patients with STEMI than among those with NSTEMI (Figure 2). A similar pattern (with more extreme hazard ratio estimates) was observed when treating sST2 as a dichotomous variable (data not shown). In addition, the association of sST2 with death was stronger at 30 days than at 1 year of follow-up. For example, the age- and sex-adjusted hazard ratios (95% confidence intervals) per 1 log-unit increase in sST2 were 4.95 (3.56–6.82) at 30 days and 3.16 (2.61–3.84) at 1 year.

The overall discriminatory ability in predicting death was reasonable for the GRACE score (*c*-statistic=0.80) and poor for the TIMI score (*c*-statistic=0.63), which was outperformed by a model with only age and sex (*c*-statistic=0.74). Inclusion of the Charlson comorbidity index and sST2 contributed incrementally to the models' discriminatory power (Figure 3; Table 3). In general, the discriminatory power was better in those with STEMI than in those with NSTEMI for both scores, GRACE and TIMI. In patients with NSTEMI, sequential addition of the Charlson comorbidity index and sST2 markedly improved the *c*-statistic over GRACE (from 0.78 to 0.80 to 0.84) and TIMI (from 0.61 to 0.73 to 0.81), respectively. In patients with STEMI, only sST2 significantly improved discrimination over both risk scores. Notably, in patients with both STEMI and NSTEMI, the model, including age, sex, Charlson index, and sST2, had a higher *c*-statistic than either GRACE or TIMI, alone or when augmented by the Charlson index (Table 3). Stratified by sex, a better discriminatory ability was found in men (Table 4) than in women (Table 5), overall and for both STEMI and NSTEMI, which was consistent throughout all models. Last, in a sensitivity analysis, the category-less net reclassification index was assessed, showing a substantial improvement with the addition of sST2 over both TIMI (net reclassification index=0.449, *P*=0.005) and GRACE (net reclassification index=0.397, *P*=0.03), thus supporting the results of the main analysis.

Discussion

In this contemporary community cohort of patients with first MI, the American Heart Association/American College of Cardiology guideline-recommended GRACE and TIMI risk scores underperformed in predicting 1-year survival, particularly for NSTEMI and in women. This is of substantial importance because NSTEMI accounts for up to 80% of patients with MI, and women represent a large proportion of patients treated for NSTEMI. Adding the Charlson comorbidity index to the risk scores improved their discriminatory performance, particularly for TIMI, which showed poor discrimination otherwise. Adding sST2 had a substantial incremental impact on the discriminatory power, regardless of the risk score or MI type. In general, a model with age, sex, comorbidity, and sST2 had superior discriminatory ability compared with either GRACE or TIMI, overall and for both patients with STEMI and patients with NSTEMI. This

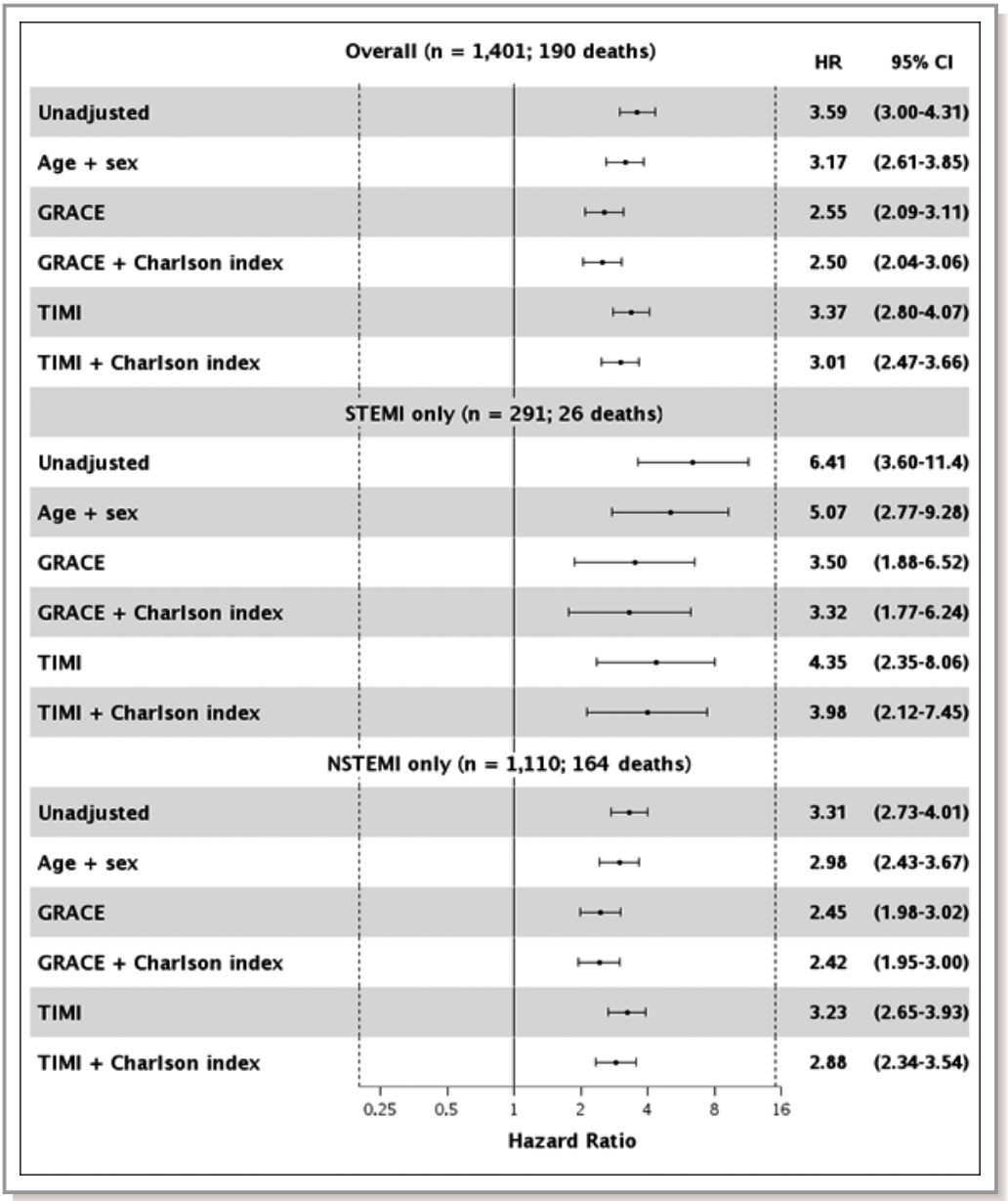

Figure 2. Association between soluble suppression of tumorigenicity-2 (sST2) and 1-year mortality after myocardial infarction (MI), overall and by ST-segment elevation MI (STEMI)/non-STEMI (NSTEMI) subtype, applying different adjustment approaches. Hazard ratios (HRs; 95% confidence intervals [CIs]) are reported per 1 log-unit increase in sST2. Charlson comorbidity index is log transformed and modeled as a continuous variable. GRACE indicates Global Registry of Acute Coronary Events; and TIMI, Thrombolysis in Myocardial Infarction.

superiority persisted even after the Charlson comorbidity index was added to the GRACE and TIMI scores, demonstrating the large predictive power of sST2 in acute MI. Thus, regardless of hypothetical therapeutic targets,[38,39] sST2 appears as a promising prognostic indicator.

Early assessment of risk after MI guides initial clinical evaluation and treatment and, thereby, influences the acuity, intensity, duration, and location of care. It can provide the patient and family with a more informed sense of potential outcome.[1–5] The American Heart Association/American College of Cardiology recommend using validated scores for risk stratification in acute coronary syndrome, taking into consideration that physicians who rely on subjective assessment of risk may fail to consider important prognostic factors. Higher risk scores generally imply that higher-intensity treatments may be appropriate within the context of the patient's health status. At present, either GRACE[5,6] or TIMI[3,4] risk scores are advocated by the guidelines.[1,2] Both risk scores were developed on the basis of patients recruited during the late 1990s and early 2000s. Since then,

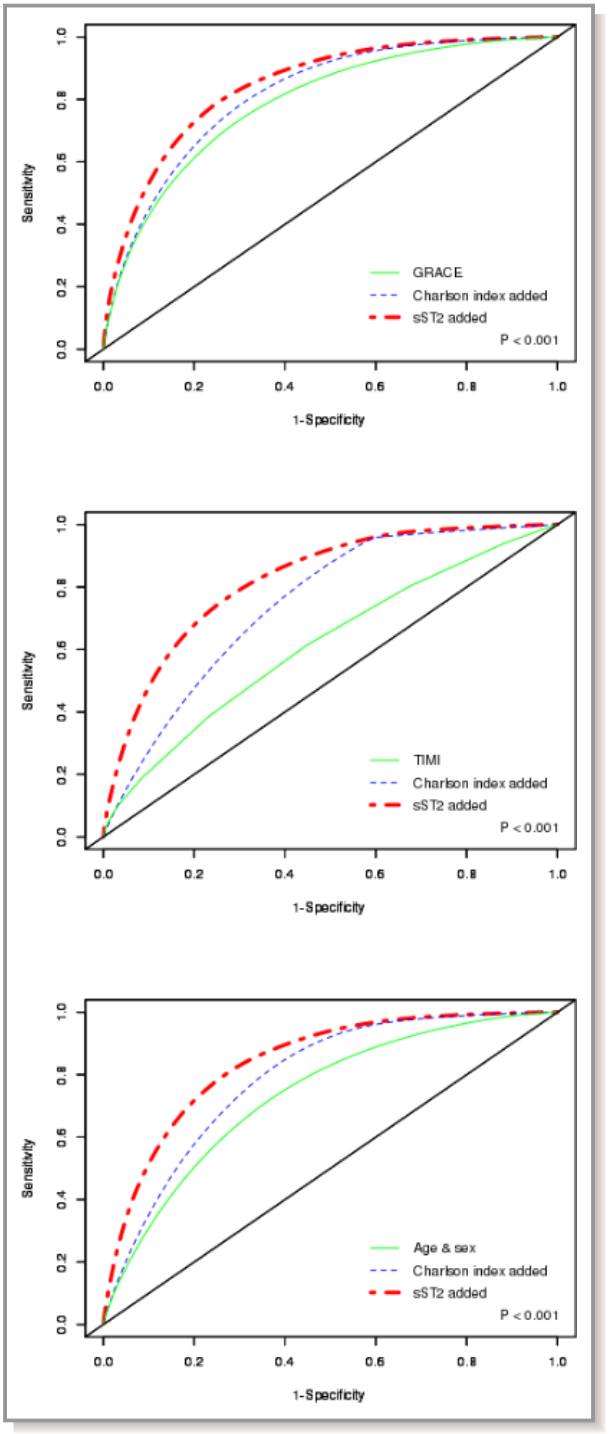

Figure 3. Receiver operating characteristic curves for the predicted probabilities of selected risk scores before (green line) and after the addition of Charlson comorbidity index (blue dashed line) and soluble suppression of tumorigenicity-2 (sST2; red dashed line). The models are GRACE (Global Registry of Acute Coronary Events; top panel), TIMI (Thrombolysis in Myocardial Infarction; middle panel), and age and sex (bottom panel).

widespread major changes in the epidemiological characteristics and management of MI have taken place and been extensively reported. These changes included a major decline in the incidence of STEMI, an increasing proportion of NSTEMI, improved short-term treatment and secondary prevention measures, reduced short-term case fatality rates, and an increasing burden of morbidity and mortality from noncardiovascular causes.[7–12] In this context, we relied on a prospective contemporary cohort of community-dwelling patients with validated MI to assess risk scores' performance. Our results indicate that the GRACE score outperformed the TIMI score in predicting death at 1 year. The superiority of GRACE, previously reported,[40] may be attributable to several factors. First, the TIMI risk scores were designed for early risk assessment: 14 days for NSTEMI[3] and 30 days for STEMI.[4] The GRACE score was designed for both in-hospital[5] and 6-month[6] risk assessments, notwithstanding several studies showing good longer-term predictive performance for both TIMI and GRACE.[4,41–45] The TIMI score for NSTEMI in our cohort showed particularly poor discriminatory power (inferior to that of a model including only age and sex), possibly because, unlike the other scores, which used all-cause mortality as the primary end point, it also included recurrent MI and severe ischemia requiring urgent revascularization in its composite outcome. Second, the 2 TIMI scores are simpler to use than the GRACE score, because they were designed for easy bedside application without the aid of a computer as, "further refinement of the model produces unattractive levels of complexity (p. 841)."[3] The GRACE score, on the other hand, is more complex and requires more data, with the rationale that most clinicians have personal digital devices, making the use of more sophisticated and more accurate models practical.[5] Notably, it was previously suggested that risk prediction models with a *c*-statistic of 0.6 to 0.7 are of limited clinical value, whereas those with a *c*-statistic between 0.7 and 0.8 have modest value.[46] Third, the selection of patients in whom GRACE and TIMI were derived was different. Although the TIMI risk score was originally developed in nearly 15 000 patients with STEMI from the InTIME II (Intravenous nPA for Treatment of Infarcting Myocardium Early II) trial,[4] and the TIMI for unstable angina/NSTEMI was developed from 2 phase 3, international, randomized, controlled trials,[3] the GRACE model was developed from a multinational registry of population-based patients involving 94 hospitals in 14 countries. The GRACE model was thus designed to reflect an unbiased and generalizable sample that predicts mortality risk across the spectrum of patients being seen with acute coronary syndrome; hence, it is likely more generalizable to other community settings, such as ours.

Scores, such as GRACE and TIMI, enable a more systematic approach to risk stratification, theoretically superior to subjective risk assessment. However, the ability of the scoring systems to discriminate patients' risks is not optimal, partly because of the stochastic nature of cardiovascular events and the difficulty in predicting outcome based on risk assessment

Table 3. Discriminatory Power of Prediction Models for Men and Women Combined

Variables Added	*C*-Statistic (95% Confidence Interval)		
	GRACE	TIMI*	Age and Sex
Overall: 1401 subjects (190 deaths)			
None	0.80 (0.77–0.83)	0.63 (0.59–0.67)	0.74 (0.70–0.77)
Charlson index	0.82 (0.79–0.84)†	0.75 (0.72–0.78)‡	0.79 (0.76–0.82)‡
sST2	0.86 (0.84–0.88)‡	0.83 (0.81–0.85)‡	0.85 (0.82–0.87)‡
STEMI only: 291 subjects (26 deaths)			
None	0.89 (0.84–0.93)	0.80 (0.72–0.89)	0.78 (0.69–0.88)
Charlson index	0.90 (0.83–0.96)	0.85 (0.76–0.93)	0.84 (0.75–0.92)
sST2	0.94 (0.90–0.97)†	0.91 (0.87–0.96)†	0.92 (0.88–0.96)†
NSTEMI only: 1110 subjects (164 deaths)			
None	0.78 (0.74–0.81)	0.61 (0.57–0.65)	0.72 (0.68–0.76)
Charlson index	0.80 (0.76–0.83)†	0.73 (0.69–0.77)‡	0.77 (0.74–0.81)‡
sST2	0.84 (0.81–0.87)‡	0.81 (0.79–0.84)‡	0.83 (0.80–0.86)‡

sST2 and Charlson comorbidity index are log transformed and modeled as continuous variables, along with age. GRACE indicates Global Registry of Acute Coronary Events; NSTEMI, non–ST-elevation myocardial infarction; sST2, soluble suppression of tumorigenicity-2; STEMI, ST-elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.
*Specific TIMI scores were used for STEMI/NSTEMI, as appropriate.
†$P \leq 0.05$ for comparison with previous (ie, above) model.
‡$P \leq 0.01$ for comparison with previous (ie, above) model.

at a single point in time.[47] Nevertheless, we were able to demonstrate substantial improvement in risk stratification in those with STEMI and NSTEMI by adding comorbidity and sST2, a myocardial fibrosis and remodeling biomarker, to the models. As the burden of coronary disease shifts toward older age groups and short-term case fatality is improving constantly,[7–12] MI is increasingly becoming a disease of elderly people, such that the impact of comorbidity on outcome becomes increasingly important. In this context, women in our cohort, who were, on average, 7 years older than men (72

Table 4. Discriminatory Power of Prediction Models for Men

Variables Added	*C*-Statistic (95% Confidence Interval)		
	GRACE	TIMI*	Age
Overall: 853 subjects (99 deaths)			
None	0.84 (0.81–0.87)	0.68 (0.63–0.73)	0.77 (0.73–0.82)
Charlson index	0.85 (0.82–0.88)	0.80 (0.76–0.83)†	0.82 (0.78–0.86)†
sST2	0.88 (0.85–0.91)†	0.85 (0.82–0.88)†	0.87 (0.84–0.90)†
STEMI only: 209 subjects (14 deaths)			
None	0.91 (0.87–0.96)	0.82 (0.69–0.95)	0.79 (0.66–0.92)
Charlson index	0.92 (0.83–1.00)	0.87 (0.74–0.99)	0.86 (0.73–0.99)
sST2	0.96 (0.91–1.00)‡	0.94 (0.88–1.00)	0.95 (0.90–0.99)
NSTEMI only: 644 subjects (85 deaths)			
None	0.81 (0.78–0.85)	0.65 (0.60–0.71)	0.75 (0.71–0.80)
Charlson index	0.83 (0.79–0.87)	0.78 (0.73–0.83)†	0.81 (0.76–0.85)†
sST2	0.86 (0.82–0.89)‡	0.84 (0.80–0.87)†	0.85 (0.81–0.89)†

sST2 and Charlson comorbidity index are log transformed and modeled as continuous variables, along with age. GRACE indicates Global Registry of Acute Coronary Events; NSTEMI, non–ST-elevation myocardial infarction; sST2, soluble suppression of tumorigenicity-2; STEMI, ST-elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.
*Specific TIMI scores were used for STEMI/NSTEMI, as appropriate.
†$P \leq 0.01$ for comparison with previous (ie, above) model.
‡$P \leq 0.05$ for comparison with previous (ie, above) model.

Table 5. Discriminatory Power of Prediction Models for Women

Variables Added	*C*-Statistic (95% Confidence Interval)		
	GRACE	TIMI*	Age
Overall: 548 subjects (91 deaths)			
None	0.75 (0.69–0.80)	0.57 (0.51–0.62)	0.69 (0.63–0.75)
Charlson index	0.77 (0.72–0.83)	0.68 (0.63–0.74)†	0.74 (0.68–0.79)†
sST2	0.83 (0.79–0.86)†	0.80 (0.76–0.84)†	0.81 (0.78–0.85)†
STEMI only: 82 subjects (12 deaths)			
None	0.82 (0.65–0.98)	0.71 (0.55–0.87)	0.70 (0.53–0.86)
Charlson index	0.85 (0.73–0.98)	0.78 (0.64–0.92)	0.79 (0.67–0.91)
sST2	0.88 (0.79–0.97)	0.87 (0.77–0.97)	0.87 (0.77–0.97)
NSTEMI only: 466 subjects (79 deaths)			
None	0.73 (0.67–0.80)	0.55 (0.48–0.63)	0.69 (0.62–0.75)
Charlson index	0.76 (0.70–0.82)	0.67 (0.61–0.73)†	0.73 (0.67–0.80)†
sST2	0.81 (0.77–0.86)†	0.78 (0.74–0.83)†	0.81 (0.76–0.86)†

sST2 and Charlson comorbidity index are log transformed and modeled as continuous variables, along with age. GRACE indicates Global Registry of Acute Coronary Events; NSTEMI, non–ST-elevation myocardial infarction; sST2, soluble suppression of tumorigenicity-2; STEMI, ST-elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.
*Specific TIMI scores were used for STEMI/NSTEMI, as appropriate.
†$P \leq 0.01$ for comparison with previous (ie, above) model.

versus 65 years), were less accurately risk stratified by both GRACE and TIMI. This may not be surprising, because standardized risk scores have typically been developed and validated in younger patients. As to sST2, the concept of augmenting risk scoring systems by adding biomarkers is particularly appealing.[3,48] Indeed, risk scores include focused clinical dimensions and biomarkers capture distinct aspects of MI pathophysiological characteristics that may provide additional information. A variety of biomarkers were examined for their value in risk assessment, including high-sensitivity C-reactive protein, B-type natriuretic peptide, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and growth differentiation factor 15 (GDF-15). The results of these investigations were somewhat disappointing.[43,49,50] This may be partly because of the relatively high correlations (Pearson $r>0.5$) of GRACE with B-type natriuretic peptide, NT-proBNP, and GDF-15.[47,49] Recently, however, Widera et al,[47] studying 1122 patients with NSTEMI or unstable angina, have shown that measurements of GDF-15 and NT-proBNP on admission enhance the predictive value of GRACE. Adjustment of the GRACE score by GDF-15 increased the *c*-statistic from 0.79 to 0.85, similar to the improvement observed on adjusting the GRACE by NT-proBNP. We report herein an improvement over GRACE of similar magnitude by the addition of sST2. sST2 is part of the interleukin-1 receptor family related to cardiac mechanical strain. Expressed by cardiomyocytes and cardiac fibroblasts, an excess of circulating sST2 leads to the binding and subsequent reduced bioavailability of the circulating cardioprotective ligand interleukin-33. This ligand reduces myocardial fibrosis, prevents myocyte hypertrophy, reduces apoptosis, and improves myocardial function.[51] A possible pathophysiological importance of sST2 in infarct remodeling was further suggested by Weir et al,[52] who reported an association of sST2 with infarct magnitude/evolution over 24 weeks of observation in patients with acute MI with resultant left ventricle systolic dysfunction. Clinically, the prognostic value of sST2 in MI was demonstrated in various settings.[20–25,53] More important sST2 only weakly correlated with other biomarkers of myocardial injury, inflammatory activation, and hemodynamic stress.[21] Furthermore, sST2 has a modest correlation with GRACE and a weak correlation with TIMI risk scores, as shown herein.

Thus, sST2 conveys prognostic information likely reflecting pathways distinct from those detected by established biomarkers.[21] Furthermore, interleukin-33/sST2 not only represents a promising cardiovascular biomarker, but also a novel mechanism of intramyocardial fibroblast-cardiomyocyte communication that may prove to be a therapeutic target for the prevention of heart failure and death after MI.[39]

Some limitations of our study should be acknowledged to aid in data interpretation. The racial and ethnic composition of the study population (predominantly white) may limit the generalizability to groups not adequately represented. In this context, one third of the patients during the study period did not have sST2 measured. These patients tended to be older and to have more comorbid conditions than patients who had sST2 measured. Because all the analyses were performed using the same sample, the results of the additional candidate

predictors (including sST2) over GRACE and TIMI may be overoptimistic.[47] We examined only sST2 to the exclusion of other biomarkers. Yet, the correlations between sST2 and several other biomarkers were shown to be weak to moderate, at most. As a consequence, their confounding potential is negligible. Whether other biomarkers, such as NT-proBNP and GDF-15, provide incremental predictive value over sST2 necessitates a multimarker approach. Finally, we have limited power when analyzing the data for patients with STEMI because of few deaths in this group.

Conclusion

In conclusion, in this community cohort of contemporary patients with MI followed up for mortality, the GRACE and TIMI scoring systems, recommended by current guidelines, had a reasonable-to-good discriminatory capacity in patients with STEMI but only poor-to-moderate value in patients with NSTEMI. Addition of comorbidity and, particularly, of sST2 markedly improved risk prediction. Because accurate risk stratification is essential for informed decision making and management, these findings define an opportunity to improve clinical care.

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