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TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS

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Aims Regarding prognosis, patients with a non-ST elevation acute coronary syndrome (ACS) are a very heterogeneous population, with varying risks of early and long-term adverse events. Early risk stratification at admission seems to be essential for a tailored therapeutic strategy. We sought to compare the prognostic value of three ACS risk scores (RSs) and their ability to predict benefit from myocardial revascularization performed during initial hospitalization.

Methods and results We studied 460 consecutive patients admitted to our coronary care unit with an ACS [age: 63 $\pm$ 11 years, 21.5% female, 55% with myocardial infarction (MI)]. For each patient, the Thrombolysis In Myocardial Infarction (TIMI), Platelet glycoprotein IIb/IIIa in Unstable agina: Receptor Suppression Using Integrilin (PURSUIT), and Global Registry of Acute Coronary Events (GRACE) RSs were calculated using specific variables collected at admission. Their prognostic value was evaluated by the combined endpoint of death or MI at 1 year. The best cut-off value for each RS, calculated with receiver operating characteristic curves, was used to assess the impact of myocardial revascularization on the combined incidence of death or MI. Death or MI at 1 year was 15.4% (32 deaths/49 MIs). The best predictive accuracy for death or MI at 1 year was obtained by the GRACE RS (AUC) [area under the curve: 0.715; confidence interval (CI: 0.672–0.756)] but the performance of the PURSUIT RS (AUC: 0.630; CI: 0.584–0.674), and TIMI RS (AUC: 0.585; CI: 0.539–0.631) was also good. We found a statistically significant interaction between the risk stratified by the best cut-off value for the GRACE and PURSUIT RSs and myocardial revascularization, with a better prognosis for the high-risk patients. The high-risk patients represented 36.7, 28.7, and 57.8% of the population, for the GRACE, PURSUIT, and TIMI RSs, respectively.

Conclusion The RSs studied demonstrated a good predictive accuracy for death or MI at 1 year and enabled the identification of high-risk subsets of patients who will benefit most from myocardial revascularization performed during initial hospital stay.

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Introduction

Patients with non-ST elevation acute coronary syndromes (NSTE-ACS) are a heterogeneous population with varying risks of death and recurrent cardiac events, in long-term as well as short-term follow-up.[1,2] In these patients, early risk stratification plays a central role, as the benefit of newer and more aggressive and costly treatment strategies seems to be proportional to the risk of adverse clinical events.[3–5] Different scores are now available based on initial clinical history, ECG, and laboratory tests that enable early risk stratification on admission. The thrombolysis In Myocardial Infarction (TIMI)[6] and platelet glycoprotein IIb/IIIa in unstable agina: Receptor Suppression Using Integrilin (PURSUIT)[7] scores were developed with the databases from large clinical trials of NSTE-ACS. The more recent Global Registry of Acute Coronary Events (GRACE) score was developed from the registry,[8] with a population of patients across the entire spectrum of ACS. All these scores were developed for short-term prognosis: events in-hospital for the GRACE risk score (RS), at 14 days for the TIMI RS, and at 30 days for the PURSUIT RS. Nevertheless, a significant proportion of adverse events in NSTE-ACS patients occur after the first 30 days, and it is not known whether these RS can also predict their occurrence. On the other hand, it has been demonstrated that an early invasive strategy has a prognostic benefit in the long term.[9] Recently, the GRACE risk model has also been validated as a predictor of death or myocardial infarction (MI) 6 months following hospital presentation.[10]

The aim of this study was to compare the performance of these TIMI, PURSUIT, and GRACE scores in risk stratification of NSTE-ACS patients, both at 30 days and at 1 year, and to evaluate their ability to predict benefit from myocardial revascularization performed during initial hospitalization.

Methods

Study population

This was a retrospective study of consecutive patients admitted to a coronary care unit (CCU) with NSTE-ACS between March 1999 and July 2001. The inclusion criteria were a history of chest pain at rest or other symptoms suggestive of an ACS, with the most recent episode occurring within 24 h of admission. This could be associated with ST or T wave changes on the electrocardiogram suggestive of myocardial ischaemia or elevated levels of biomarkers of myocardial damage. The biomarkers used were cardiac troponin I (cTn I) and creatine kinase MB mass assay (CK-MB), with a threshold for positivity of 0.1 and 5 ng/mL, respectively (chemiluminescence assay—Access Immunoassay Analyser).

Risk scores

The three RSs—TIMI, PURSUIT, and GRACE—were calculated from the initial clinical history, electrocardiogram, and laboratory values collected on admission (*Table 1*). Although this was a retrospective study, these data were collected prospectively and

Table 1 Risk scores

PURSUIT (0–18)	Age, separate points for enrolment diagnosis Decade [UA (MI)]	
	50	8 (11)
	60	9 (12)
	70	11 (13)
	80	12 (14)
	Sex	
	Male	1
	Female	0
	Worst CCS-class in previous 6 weeks	
	No angina or CCS I/II	0
	CCS III/IV	2
	Signs of heart failure	2
	ST-depression on presenting ECG	1
TIMI (0–7)	Age ≥65 years	1
	≥3 risk factors for CAD	1
	Use of ASA (last 7 days)	1
	Known CAD (stenosis ≥50%)	1
	>1 episode rest angina in <24 h	1
	ST-segment deviation	1
	Elevated cardiac markers	1
GRACE (0–258)	Age (years)	
	<40	0
	40–49	18
	50–59	36
	60–69	55
	70–79	73
	≥80	91
	Heart rate (bpm)	
	<70	0
	70–89	7
	90–109	13
	110–149	23
	150–199	36
	>200	46
	Systolic BP (mmHg)	
	<80	63
	80–99	58
	100–119	47
	120–139	37
	140–159	26
	160–199	11
	>200	0
	Creatinine (mg/dL)	
	0–0.39	2
	0.4–0.79	5
	0.8–1.19	8
	1.2–1.59	11
	1.6–1.99	14
	2–3.99	23
	>4	31
	Killip class	
	Class I	0
	Class II	21
	Class III	43
	Class IV	64
	Cardiac arrest at admission	43
	Elevated cardiac markers	15
	ST-segment deviation	30

recorded on a computer database of ACS patients admitted to our institution's CCU. Thus, no patient was excluded from the analyses performed in this study due to missing data. When calculating the TIMI RS in patients without a prior coronary angiogram, for the variable 'known coronary artery disease (stenosis $\geq$50%)' we attributed 1 point to a history of MI or coronary revascularization. This methodology is closer to real-world practice, and it has been validated by the authors of the TIMI RS.[5]

Regarding the TIMI and PURSUIT RSs the values are easily obtained. For the TIMI RS, as all seven variables have the same magnitude, the result for each patient is the simple arithmetic sum of the number of variables present.[6] For the PURSUIT RS, the simple score for death and MI was used, instead of the more complex original score, and is obtained as the sum of the points given to each of the five predictive factors.[7]

For the more recently developed GRACE RS, although it was not published by the time this study was conducted, a program for PDAs (personal digital assistants) was available for download at the site of the GRACE project, and was used to calculate each patient score (GRACE ACS Risk Model 0.25, StatCoder.com) (available at http://www.umassmed.edu/outcomes/gracel).

Endpoint

All patients included were followed up for at least 1 year or until the occurrence of a major event. The study endpoint was the combination of all-cause mortality or non-fatal MI, according to the new ESC/ACC consensus definition.[11] This endpoint was analysed both at 30 days and at 1 year.

Statistical analysis

Continuous variables with a normal distribution were expressed as mean value and standard deviation. Normality was tested with the Shapiro–Wilks test. Discrete variables were expressed as frequencies and per cent values.

Statistical comparison of baseline characteristics and outcomes was performed using the χ^2 test with Yates correction or the Fisher exact test, when appropriate, for categorical variables, and the two-tailed Student's *t*-test for continuous variables.

For each of the three RSs, receiver operating characteristic (ROC) curves were used to relate the calculated scores to the rate of adverse clinical events, both at 30 days and at 1 year. This procedure was also applied to the endpoints and time of follow-up used in the original study of each RS. The area under the curve (AUC), or C-statistic, was used as a measure of the predictive accuracy of the RS. The relative performance of each test was evaluated with the 95% confidence interval (CI) for the difference between two AUCs. The goodness of fit of the RSs was evaluated by calculating the Hosmer–Lemeshow statistic.

The cut-off points identified with the ROC curves for each score were used to separate the studied population in low- and high-risk patients. The 1-year endpoint rate for the low- and high-risk patients in each score was calculated, comparing in each subgroup patients who underwent or did not undergo a revascularization procedure during initial hospital admission.

For each score, logistic analyses were performed to test for an interaction between the score and the effect of myocardial revascularization on the 1-year outcome.

Two-tailed tests of significance are reported. For all comparisons, a *P*-value of <0.05 was considered statistically significant. When appropriate, CIs were calculated, with a 95% confidence level.

Statistical analysis was performed with SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) and MedCalc version 6.0 (MedCalc Software, Mariakerke, Belgium).

Results

Baseline characteristics

A total of 460 patients were included in this study. The final diagnosis of the ACS was unstable angina in 209 patients (45.4%) and NSTEAMI in the other 251 (54.6%). The baseline characteristics and in-hospital management are presented in *Table 2*.

Table 2 Baseline characteristics and in-hospital management

Age (years)	63.4 $\pm$ 10.8
Sex (%)	
Male	78.5
Female	21.5
Risk factors (%)	
Diabetes mellitus	23.5
Hypercholesterolemia	60.9
Systemic hypertension	61.7
Smoking	21.3
Previous history (%)	
Myocardial infarction	45.7
Myocardial revascularization	47.8
PCI	31.5
CABG	22.2
Peripheral arterial disease	11.0
TIA/stroke	8
Previous medication (%)	
Platelet inhibitors	71.5
ASA	60.2
Beta-blockers	48.3
Calcium channel antagonists	43.8
ACE inhibitors/ARBs	39.2
Statins	29.9
On admission	
Heart rate (bpm)	75.7 $\pm$ 17.5
Systolic BP (mmHg)	142.7 $\pm$ 26.1
Diastolic BP (mmHg)	80.6 $\pm$ 14.3
Signs of heart failure (%)	13.9
ST-segment depression $\geq$1 mm (%)	55.9
Tn I $>$ 0.1 ng/mL (%)	31.5
CK-MB mass $>$5 ng/mL (%)	29.1
LVEF $<$40%	12.3
Three vessels/left main CAD (%)	43.6
Pharmacological therapy (%)	
ASA	95.7
UFH/LMWH	78.9/41.7
GP IIb/IIIa inhibitors	38.7
Nitrates	91.1
Beta-blockers	86.3
Calcium channel blockers	15.2
ACE inhibitors	71.5
Statins	48.9
Revascularization (%)	
PCI	47.8
CABG	18.3

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; ASA, aspirin; ACE, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BP, blood pressure; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; GP, glycoprotein.

By 30-day follow-up, 13 patients had died (2.8%) and 24 had had a non-fatal MI (5.2%). The 30-day endpoint rate was 7.2%.

At 1 year, there were 32 deaths (7%) and 49 patients had had an MI (10.7%), with a total 1-year endpoint rate of 15.4%.

The univariate predictors of the 30-day endpoint were age, signs of heart failure on admission, and baseline serum creatinine. Regarding the 1-year endpoint, the predictors were age, both as a continuous variable and with a cut-off of 65 years, previous history of hypertension, chronic angina CCS III or IV in the last 6 weeks, heart rate on admission, signs of heart failure on admission, ST-segment depression, and baseline serum creatinine (*Table 3*).

RSs: endpoint rates in the different risk groups

The mean value in this population was 13 (range: 1–19) for the PURSUIT RS, 4 (range: 1–7) for the TIMI RS, and 122 (range: 50–237) for the GRACE RS.

As shown in *Figures 1–3*, the distribution of the 30-day and 1-year endpoint rates in the different risk groups, for the three RS, demonstrated a consistent gradient of risk.

Predictive accuracy of the RSs

Both the PURSUIT and the GRACE scores showed a good discriminatory accuracy to predict death and recurrent MI as a combined endpoint at 30 days and at 1 year, as demonstrated by the C-statistic.

The discriminatory accuracy of the TIMI score was not as high, but this score had a good fit with both the 30-day and the 1-year endpoint, as demonstrated by a probability value of the Hosmer–Lemeshow χ^2 of 0.803 and 0.760, respectively.

For both the PURSUIT and the GRACE scores, regarding the 30-day endpoint, the probability value of the Hosmer–Lemeshow was adequate but not optimal. Nevertheless, for the 1-year endpoint, both scores had a good fit (*Table 4*).

The discriminatory accuracy of the three scores was also analysed to predict the standard endpoints in the original follow-up for which they were developed. The TIMI score had a C-statistic of 0.60 (95% CI: 0.56–0.65) for predicting death, MI or recurrent ischaemia with the need for urgent revascularization at 14 days. For the GRACE score, the C-statistic for predicting intra-hospital death was 0.76 (95% CI: 0.72–0.80). Regarding the PURSUIT score, the endpoints and the follow-up were the same in this study.

Table 3 Univariate predictors

	30 days			1 year		
	With events ($n = 33$)	Without events ($n = 427$)	*P*-value	With events ($n = 71$)	Without events ($n = 389$)	*P*-value
Age (years)	67.7 ± 12.1	63.0 ± 10.6	**0.017**	67.7 ± 10.9	62.6 ± 10.6	<0.001
≥ 65	22 (67)	204 (48)	0.056	49 (69)	177 (46)	<0.001
Male [*n* (%)]	28 (85)	333 (72)	0.481	60 (85)	301 (77)	0.235
Risk factors [*n* (%)]						
Diabetes mellitus	8 (24)	100 (23)	1.00	21 (30)	87 (22)	0.244
Hypercholesterolemia	22 (67)	258 (60)	0.60	42 (59)	238 (61)	0.850
Systemic hypertension	21 (64)	263 (62)	0.963	53 (75)	231 (59)	0.021
Smoking	7 (21)	91(21)	1.00	13 (18)	85 (22)	0.608
≥3 risk factors	5 (15)	67 (16)	1.00	13 (18)	59 (15)	0.622
Previous history [*n* (%)]						
≥2 episodes rest angina <24 h	32 (97)	411 (96)	1.000	68 (96)	375 (94)	1.000
≥3 CCS angina last 6 weeks	23 (97)	325 (96)	0.537	46 (65)	302 (78)	0.030
Myocardial infarction	15 (45)	195 (46)	1.000	32 (45)	178 (46)	1.000
Revascularization	16 (48)	204 (48)	1.000	38 (54)	182 (47)	0.360
PCI	5 (15)	140 (33)	0.057	23 (32)	122 (31)	0.974
CABG	12 (36)	90 (21)	0.069	21 (30)	81 (21)	0.139
Known CAD	20 (61)	277 (65)	0.761	45 (63)	252 (65)	0.927
ASA in the last 7 days	17 (52)	260 (61)	0.381	38 (54)	239 (61)	0.262
On admission						
Systolic BP (mmHg)	140.5 ± 28.0	142.9 ± 25.9	0.601	143.7 ± 27.4	142.6 ± 25.8	0.739
Heart rate (bpm)	79.1 ± 20.6	75.5 ± 17.3	0.248	83.5 ± 21.9	74.3 ± 16.3	<0.001
Signs of heart failure [*n* (%)]	10 (30)	54 (13)	**0.010**	20 (28)	44 (11)	<0.001
ST depression ≥1 mm [*n* (%)]	22 (67)	235 (55)	0.265	48 (68)	209 (54)	0.265
Tn I > 0.1 ng/mL [*n* (%)]	12 (36)	133 (31)	0.669	26 (37)	119 (31)	0.669
Creatinine (mg/dL)	2.8 ± 1.9	1.2 ± 0.5	**<0.001**	2.2 ± 1.7	1.2 ± 0.5	<0.005

CCS, Canadian Cardiovascular Society; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CAD, coronary artery disease; ASA, acetylsalicylic acid; BP, blood pressure.

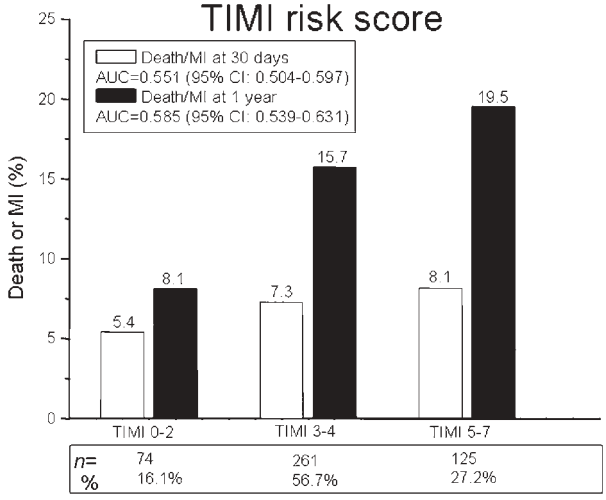

Figure 1 Distribution of the 30-day and 1-year endpoint rates in the different risk groups for the TIMI score.

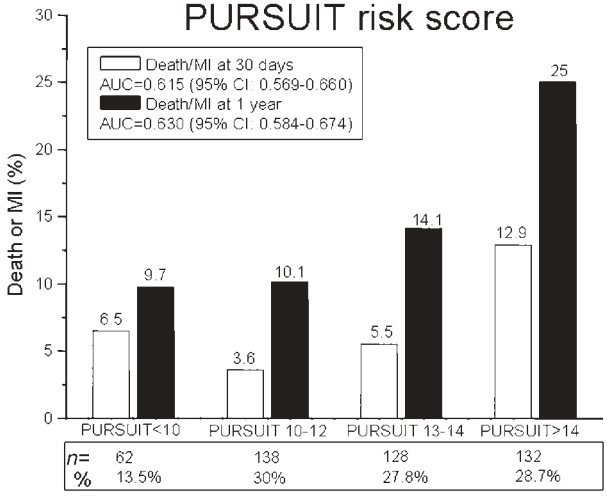

Figure 2 Distribution of the 30-day and 1-year endpoint rates in the different risk groups for the PURSUIT score.

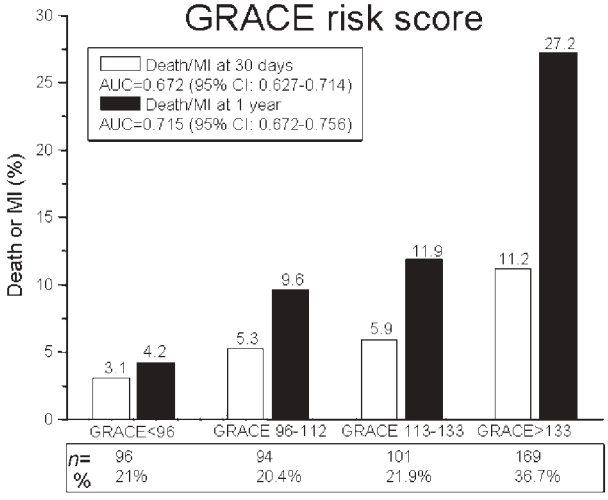

Figure 3 Distribution of the 30-day and 1-year endpoint rates in the different risk groups for the GRACE score.

There were no significant differences in the discriminatory accuracy of the three scores for the 30-day endpoint. However, for the 1-year endpoint, the discriminatory accuracy of the GRACE score was superior to that of the other two scores, this difference being statistically significant (*Table 5*).

Interaction between RSs and myocardial revascularization

There were no significant differences, in the study population, in the endpoint rate between patients who underwent and patients who did not undergo a revascularization procedure (either PCI or CABG). However, using the cut-off points for the three RSs identified with the ROC curves of the 1-year endpoint, there was an interaction between the admission score and the prognostic impact of myocardial revascularization performed during initial hospital stay (*Figure 4*). For the PURSUIT and GRACE scores, this interaction reached statistical significance.

It is worth noting that the proportion of patients who derived clear benefit from myocardial revascularization during initial hospital admission, in this model of multivariable analysis, was only 28.7% for the PURSUIT and 36.7% for the GRACE score.

Discussion

This single-centre study, based on a consecutive NSTE-ACS cohort, demonstrated the superiority of the GRACE RS, compared with the PURSUIT and TIMI RSs, in the estimation of 1-year prognosis. This study validates the 1-year prognostic value of the GRACE and PURSUIT RSs, as for the TIMI score, this has already been evaluated.[12]

Short-term prognosis

All three RSs were able to discriminate patients with and without events at 30 days, which is not surprising, as they were all developed for short-term prognosis.

As expected, the performance of the TIMI and GRACE scores was superior when the original follow-up time and composite endpoints used for their development were tested.

The univariate analysis identified age, as a continuous variable, heart failure at admission and baseline serum creatinine as significant predictors of prognosis. The first two variables are generally identified as prognostic markers.[13,14] Serum creatinine has only recently been identified as a powerful risk variable,[15] as it was not generally included in ACS databases in the past.

In the present study, traditional risk markers like ST-segment depression on admission ECG or elevated cardiac biomarkers[14,16–18] did not reach statistical significance. This may be related to the more aggressive antithrombotic and early invasive management adopted for these high-risk patients in our institution. In contrast, studies that established the prognostic value of cardiac

Table 4 Predictive accuracy and goodness of fit of the risk scores

	30 days		1 year	
	C-statistic (95% CI)	*P*-value (Hosmer–Lemeshow χ^2)	C-statistic (95% CI)	*P*-value (Hosmer–Lemeshow χ^2)
PURSUIT	0.615 (0.569–0.660)	0.137	0.630 (0.584–0.674)	0.656
TIMI	0.551 (0.504–0.597)	0.803	0.585 (0.539–0.631)	0.760
GRACE	0.672 (0.627–0.714)	0.125	0.715 (0.672–0.756)	0.884

Table 5 Comparison of the predictive accuracy of the risk scores

	30 days		1 year	
	Δ (95% CI)	*P*-value	Δ (95% CI)	*P*-value
PURSUIT vs. TIMI	0.064 (−0.054 to 0.183)	0.288	0.044 (−0.043 to 0.131)	0.319
GRACE vs. PURSUIT	0.057 (−0.058 to 0.171)	0.332	0.086 (0.004 to 0.168)	0.04
GRACE vs. TIMI	0.121 (−0.002 to 0.243)	0.054	0.130 (0.040 to 0.220)	0.004

Δ, Difference between the two AUCs.

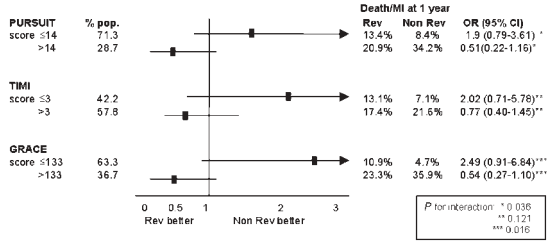

Figure 4 Interaction between the admission score and the prognostic impact of myocardial revascularization performed during initial hospital stay.

biomarkers used peak instead of baseline level, analysed for our admission RSs study.

The relative performance of the different RSs can be explained by their respective composition. Only the GRACE score, which presented the best discriminatory accuracy (AUC = 0.672 for 30 days), included all three identified prognostic variables.

The performance of the PURSUIT score, whose composition does not include serum creatinine, was somewhat inferior (AUC = 0.615). Nevertheless, its discriminatory accuracy might have been overestimated by the fact that the same follow-up time and composite endpoint—death and MI at 30 days—were used for its original development and in the present study. This apparent benefit was not observed for the other two scores.

The TIMI score presented the lowest discriminatory accuracy. Of all the risk markers identified in our univariate analysis, this score only includes age, and as a categorical variable. This is a reductive approach to the continuous prognostic value observed in the entire spectrum of age. The same is not observed in the GRACE and PURSUIT scores. Because of the low incidence of signs of heart failure on admission in the population of the TIMI 11B trial used for the development of the TIMI score, this variable was not included in the model, unlike in the other two scores. This is an important limitation, especially because the occurrence of heart failure is much more frequent in the real world than in the selected patients from clinical trials, and its prognostic value is well established.[7,19,20]

Long-term prognosis

For the 1-year prognosis, the best performance was achieved by the GRACE score, but all three RSs presented higher discriminatory accuracies than observed for the short term. These results and the relative performance of each RS can be explained by their composition and the univariate analysis for 1-year follow-up, which identified seven variables with prognostic impact. Besides the three variables already described for the short term, a past history of hypertension, recent onset of severe angina, heart rate at admission, and ST-segment depression on admission ECG were also identified as significant prognostic markers. The long-term prognostic value of these characteristics has been described in previous studies,[14,19] except for recent onset of severe angina and baseline serum creatinine. Although these specific variables have not been evaluated, their long-term prognostic value is established for a past history of coronary artery disease as well as for previous renal failure.[7,21]

The number of those seven variables included in each RS is 5 for GRACE, 4 for PURSUIT and only 2 for the TIMI RS. The composition of the TIMI RS is clearly different from the other two scores. The main difference between the GRACE and PURSUIT scores is based on the inclusion of renal function in the former, which represents a significant advantage, as renal failure is an

important independent predictor of poor long-term prognosis.[21,22] Another advantage of the GRACE score is derived from the real-world population of this clinical registry, in contrast to the more selected population of PURSUIT.

Interaction with the benefit of myocardial revascularization

We found a statistically significant interaction between the risk of death or MI at 1 year, stratified by the best cut-off value for the GRACE and PURSUIT scores, and the benefit of myocardial revascularization. For the TIMI score this interaction was not statistically significant.

The proportion of patients stratified as high risk by the best cut-off value was higher in the TIMI score (two-third vs. one-third for the other two scores), demonstrating a poorer ability to discriminate between scores 5–7 and 3–4.

Our results also demonstrated that the long-term benefit of myocardial revascularization performed during initial hospital admission was only clearly observed in high-risk patients, who accounted for about one-third of the study population. These results are in agreement with those of the FRISC II and TACTICS-TIMI 18 studies, which established the benefit of an early invasive strategy, but only for high-risk patients.[3,16] In the former study, high risk was defined by the combined occurrence of elevated troponin T and ST-segment depression on admission ECG, and this accounted for 33.9% of the studied population. In TACTICS-TIMI 18, the benefit of an early invasive strategy on top of tirofiban was observed for patients with a TIMI RS of at least 3 or an elevated troponin level, corresponding to 75 and 59% of the study population, respectively.

Applicability

The ideal score for risk stratification on admission for a NSTE-ACS should have a good balance between complexity and utility. Scores that include continuous variables such as age, heart rate, and serum creatinine are more powerful, but also more complex to calculate. However, PDA applications may significantly simplify these complex calculations such that, at the present time, the complexity of a score is essentially determined by factors related to data collection, rather than the methodology involved in the calculations. In regard to this aspect, the GRACE score is more advantageous as all its variables are objective data.

Limitations

This is a small single-centre retrospective study and the analysis of the interaction between the RSs and the effect of myocardial revascularization on outcome was based on nonrandomized data.

Conclusions

The use of RSs developed from databases of clinical trials (PURSUIT and TIMI) or registries (GRACE) in the risk stratification of patients with NSTE-ACS revealed a fair to good discriminatory accuracy in predicting major adverse cardiac events at both 30 days and 1 year.

The GRACE RS was the best for predicting the risk of death or MI at 1 year after admission.

There was a significant interaction between the benefit of myocardial revascularization performed during initial hospitalization and the extent of risk evaluated by the GRACE and PURSUIT scores.

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