"Do GRACE (Global Registry of Acute Coronary events) risk scores still maintain their performance for predicting mortality in the era of contemporary management of acute coronary syndromes?"

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Background Although the GRACE risk scores (RS) are the preferred scoring system for risk stratification in acute coronary syndromes (ACS), little is known whether these RS still maintain their performance in the current era. We aimed to investigate this issue in a contemporary population with ACS.

Methods The study population composed of patients enrolled in the MASCARA national registry. The GRACE RS were calculated for each patient. Discrimination and calibration were evaluated with the *C* statistic and the Hosmer-Lemeshow test, in the whole population and according to the type of ACS, risk strata, and whether the patient had a history of diabetes and/or chronic renal failure. We determined if left ventricular ejection fraction (LVEF) provides incremental prognostic information above that established by the RS and whether percutaneous coronary intervention (PCI) during admission affects the performance of the score for predicting 6-month mortality.

Results The 5,985 patients constituted the validation cohort for the in-hospital mortality RS and 5,635 the validation cohort for the 6-month mortality RS. Overall, both GRACE RS demonstrated excellent discrimination ($C > 0.80$) and calibration (all *P* values in Hosmer-Lemeshow >.1). Although similar results were seen in all subgroups, the 6-month mortality RS performed significantly less well in patients undergoing PCI compared to those patients who did not ($C = 0.73$ vs 0.76, $P < .004$). Adding LVEF to the RS did not convey significant prognostic information.

Conclusions The GRACE RS for predicting in-hospital and 6-month mortality still maintain their excellent performance in a contemporary cohort of patients with ACS. Further studies are needed to investigate the performance of the 6-month mortality GRACE score in patients undergoing in-hospital PCI. Left ventricular ejection fraction did not convey significant information over that provided by the RS. (Am Heart J 2010;160:826-834.e3.)

Acute coronary syndromes (ACS) are a heterogeneous population with varying risks of short-term and long-term death.[1-4] Early risk stratification plays a pivotal role, as the benefit of more aggressive treatment strategies seem to be proportional to the risk of adverse outcomes.[1-4] The Global Registry of Acute Coronary Events (GRACE) risk scores (RS)[5,6] are the preferred scoring system that current European acute coronary syndrome guidelines recommend to apply on admission and at discharge in daily clinical practice.

Although the validity of GRACE RS is well established,[7-13] there are still some points open to question. First, GRACE RS were developed in the late 1990s and early 2000s. The current predictive value of the GRACE RS in later cohorts of ACS could be different as now evidence-based therapies are used more often.[14] Second, although GRACE RS may perform less well in patients

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See online Appendix C for a complete listing of MASCARA study researches.

Submitted March 29, 2010; accepted June 16, 2010.

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0002-8703/$ - see front matter

doi:10.1016/j.ahj.2010.06.053

with higher risk, such as those with diabetes and/or chronic renal failure (CRF),[7] no formal validation of the GRACE models has been conducted in these specific subgroups. In addition, the impact of reduced left ventricular ejection fraction (LVEF) (not considered in the development of the GRACE scores) on the model performance is unknown. Third, the impact of revascularization on the validity of the GRACE models to predict adverse events is poorly known.

Accordingly, using data from the MASCARA Spanish registry, we aimed to (i) evaluate the performance of the GRACE RS for predicting in-hospital and 6-month postdischarge mortality across a spectrum of unselected contemporary patients with ACS; (ii) assess their performance among risk subgroups, specifically diabetes mellitus and/or CRF, and by subgroups according to their LVEF (<30%, 30%-49%, and ≥50%); (iii) determine if adding LVEF provides incremental prognostic information; and (iv) to evaluate the GRACE RS performance for predicting 6-month postdischarge mortality depending on whether the patients underwent in-hospital percutaneous coronary intervention (PCI).

Methods

Data sources

The MASCARA study design has been previously reported.[15,16] MASCARA was designed to assess the impact that guidelines had had on practice and clinical outcomes throughout a wide range of Spanish hospitals. Thirty-two randomly selected hospitals fulfilled the quality requirements to participate in MASCARA. From October 2004 to June 2005, all consecutive patients ≥18 years old within 24 hours of the onset of angina at rest and who were hospitalized in any study center were eligible. Patients were included if ACS were finally confirmed during the index hospitalization. Diagnosis of ACS was made if the patient had any of the following criteria: (1) cardiac biomarkers above the higher normal limit of each laboratory, (2) ST-segment deviation on electrocardiogram, (3) in-hospital stress testing showing ischemia, or (4) known history of coronary vessel disease. The only exclusion criteria were (1) noncardiac illness with expected survival et al 1 year, (2) ischemia due to noncardiac causes, or (3) impossibility of follow-up. At each site, the designated physician or study coordinator identified those patients with inclusion criteria and no exclusion criteria, requested the informed consent, and classified the patients into ST-elevation acute coronary syndrome (STEACS), non-STEACS (NSTEACS), and unclassified ACS (known left bundle branch block, ventricular pacemaker rhythm, or Wolff-Parkinson-White syndrome) according to the qualifying electrocardiogram. Thereafter, specifically trained external researchers recorded demographic and clinical data, in-hospital treatment, and outcomes on standardized case report forms. Patients were followed up by telephone call at 1 and 6 months after discharge to assess vital status. All calls were centralized and made by trained interviewers.

MASCARA registry has been funded with grants from the Fondo de Investigación Sanitaria (PI04/1408) and Red de Investigación Cardiovascular del Instituto Carlos III (RECAVA) and from an unrestricted grant of Bristol Myers Squibb. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Sample

MASCARA enrolled 7,251 patients. The initial cohort for this study was composed of 6,745 patients (93%) with valid vital status data at 6-month follow-up. Of 6,745 patients, 760 and 771 (11.3% and 11.4%, respectively) were excluded from the analyses of the GRACE score performance for in-hospital mortality and for 6-month mortality respectively because of missing data in some variable. In these patients, secondary analyses were performed to assess the impact of missing data on the results (see below). The validation cohort for the 6-month mortality GRACE score did not include patients who died in hospital (341, 5.1%). Thus, MASCARA validation cohorts for predicting in-hospital mortality and 6-month mortality were 5,985 and 5,635 patients, respectively (Figure 1).

End point definitions

Primary end points were all-cause in-hospital and 6-month mortality, originally designated to be predicted by the GRACE models.[5,6]

Patients were classified as having acute myocardial infarction (AMI) with ST-segment elevation or ACS without ST-segment elevation (NSTEACS) (unstable angina and non-ST elevation AMI). "Unclassified" ACS (known left bundle branch block, ventricular pacemaker rhythm, or Wolff-Parkinson-White syndrome), were included, for present study purposes, in the NSTEACS group, because in GRACE models, ACS were finally categorized only on the presence or absence of ST-segment elevation at admission.

Statistical analysis

Kolmogorov-Smirnov test rejected normality assumption for all quantitative variables; thus, continuous variables are presented by median and interquartile range. Discrete variables are expressed as frequencies and percentages. χ^2 Test was used to compare discrete variables, and the Mann-Whitney test was used to compare quantitative variables. Wilcoxon signed rank test was used to compare the median values.

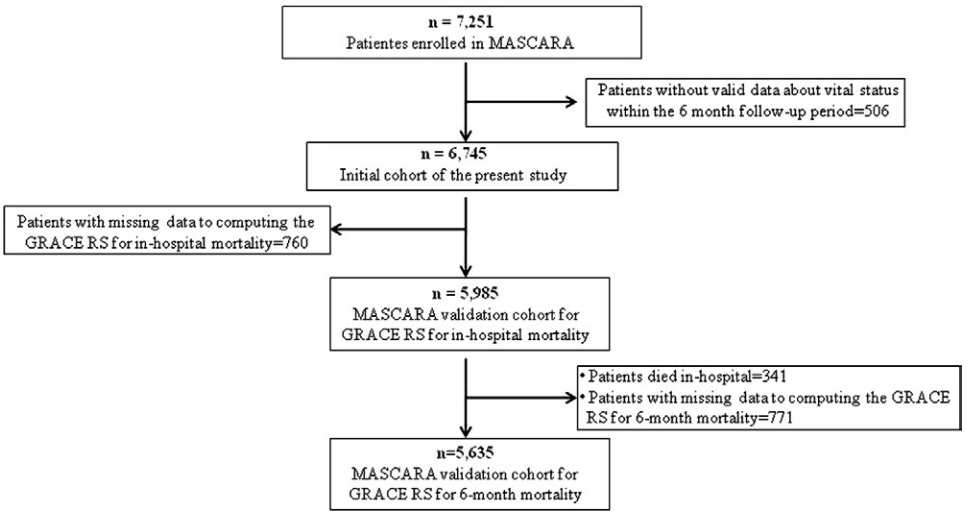
GRACE scores computation. GRACE RS were calculated in each patient from the corresponding prognostic variables scores (online Appendix A). Three risk subgroups (low, intermediate, and high) were defined in each validation cohort according with the respective GRACE scores.[17]

Calibration and discrimination. Indices of discrimination and calibration were used to assess the performance of the GRACE RS in this study. We used the Hosmer-Lemeshow (HL) goodness-of-fit test to assess calibration,[18] where the higher the *P* value, the better the calibration.

The GRACE risk model variables and the total RS were entered into separate logistic regression models to test their association with the in-hospital and 6-month mortality. The HL statistic from the regression modeling was used as an indicator of goodness-of-fit of the total score as a global predictor variable.

Model discrimination was assessed by the *C* statistic that is equivalent to the area under the receiver operating characteristics curve.[19] A model with a *C* statistic >0.75 is considered to have meaningful discriminatory ability.

Figure 1



Flowchart MASCARA validation study for GRACE models for predicting in-hospital and 6-month postdischarge mortality.

Models' performance was assessed in each cohort and in each subgroup of ACS and risk strata. We also checked their performance according to whether the patients had diabetes and/or CRF and in subgroups of AMI patients (ie, those with elevated cardiac biomarkers) according to their LVEF (<30%, 30%-49%, and ≥50%).

The calibration and discrimination of the GRACE RS for predicting 6-month death were also evaluated to examine the interaction between RS and performance of in-hospital PCI. Further analyses were made to assess if adding LVEF (as a continuous variable) to the RS improves their discrimination in AMI patients and to test for collinearity between the RS and LVEF in patients with AMI.

Missing data management

GRACE RS for in-hospital and 6-month mortality could not be calculated in 760 (11.3%) and 771 (11.4%) patients, respectively. The main reason was the lack of records of heart rate at admission (6.6%). These patients were excluded from the main analyses. To assess the impact of excluding these patients, we did a missing value analysis imputing the missing data. Little's test was used to determine whether values were missing completely at random (online Appendix B).

Significance was set at $P < .05$. Statistical analyses were performed using SPSS version 17.0 (SPSS Inc, Chicago, IL), MedCalc v.9.2.0 (Mariakerke, Belgium), and using the BSDA library in the R Free software v.2.9.1 (Vienna, Austria).[20]

Results

Patient characteristics

Compared to GRACE, patients in MASCARA study showed, overall, worse baseline cardiovascular risk profile (Table I). MASCARA patients were older and had higher prevalence of hypertension, diabetes, hyperlipidemia, and peripheral arteriopathy. In addition, they were more likely to be in Killip II to IV class, to present ST-segment deviation, and to be in cardiac arrest at admission than the patients enrolled in GRACE. A smaller proportion of the MASCARA patients had smoking history, previous AMI or congestive heart failure, or had undergone coronary artery bypass graft or PCI in prior admissions. There were no significant differences between MASCARA and GRACE patients concerning heart rate, systolic blood pressure, and serum creatinine level at admission.

Nearly half of MASCARA patients were scored into the high-risk strata (Table I). In-hospital PCI was performed in 2,409 (42.8%) of 5,635 patients surviving the index event and had valid data about the 6-month GRACE score. Among these patients, the median GRACE RS were significantly lower in those who underwent PCI compared to those patients who did not (123 [110-147] vs 144 [120-170], respectively; $P < .001$).

Accuracy of GRACE scores for mortality prediction

Table II shows observed and predicted in-hospital and 6-month mortality rates in the global cohort, and types of ACS and risk strata. The 6-month rates are also compared for patients who had or not undergone in-hospital PCI.

Three hundred forty-one patients (5.7%) died in hospital. At 6 months, 451 (8%) of 5,635 patients surviving the index episode had died. As shown in Figure 2, the distribution of in-hospital and 6-month death rates in the different risk groups demonstrate a gradient of risk: the more the baseline risk, the higher the mortality rate, although these differences were more pronounced among high-risk patients than in those of low and intermediate risk.

Table I. Difference in baseline characteristics between the MASCARA validation cohort and the GRACE risk score derivation cohort for predicting in-hospital and 6-month postdischarge mortality

	GRACE RS for in-hospital death			GRACE RS for 6-m postdischarge death		
	MASCARA validation cohort (n = 5985)	**GRACE derivation cohort (n = 11 389)**	***P***	**MASCARA validation cohort (n = 5635)**	**GRACE derivation cohort (n = 15 007)**	***P***
Demographic data and medical history						
Age (y)*	69.8 (58-74)	66.3 (56-75)	.001	69.3 (58-77)	66 (55.5-74.6)	.001
Men (%)	4316 (72.1)	66.5	<.001	4088 (72.5)	66.8	<.001
Smoking (%)	2268 (37.9)	56.7	<.001	1807 (38.1)	57.8	<.001
Hypertension (%)	3637 (60.8)	57.8	<.001	3396 (60.3)	58.2	.007
Hyperlipidemia (%)	2845 (47.5)	43.6	<.001	2686 (47.7)	45.6	.007
Diabetes (%)	1861 (31.1)	23.3	<.001	1707 (30.3)	23.5	<.001
Myocardial infarction (%)	1369 (22.9)	32	<.001	1285 (22.8)	32	<.001
Peripheral arteriopathy (%)	711 (11.9)	10.3	.001	639 (11.3)	–	–
Stroke (%)	469 (7.8)	–	<.001	411 (7.3)	–	–
CRF (%)	383 (6.4)	7.2	.052	330 (5.9)	–	–
Congestive heart failure (%)	328 (5.5)	11	<.001	276 (4.9)	10.1	<.001
PCI (%)	744 (12.4)	14	.004	717 (12.7)	15.3	<.001
CABG (%)	328 (5.5)	12.6	<.001	323 (5.7)	13.4	<.001
On admission data						
Type of ACS (%)						–
STEMI	2344 (39.2)	35.3	<.001	2165 (38.4)	–	
NSTEACS	3641 (60.8)	64.7	<.001	3470 (61.6)	–	
Killip class (%)			<.001			<.001
I	4586 (76.6)	88.7		4422 (78.5)	84.2	
II	919 (15.4)	13.2		813 (14.4)	12.7	
III	351 (5.9)	3.1		280 (5)	2.7	
IV	129 (2.2)	1		57 (1.1)	0.4	
Heart rate (beat per min)*	77 (65-90)	76 (75-90)	.7	76 (65-90)	76 (65-89)	.8
Systolic blood pressure (mm Hg)*	140 (120-160)	140 (120-169)	.8	140 (123-160)	140 (122-160)	.87
Serum creatinine level (mg/dL)*	1 (0.85-1.24)	1 (0.9-1.20)	.9	1 (0.83-1.20)	1 (0.9-1.20)	.9
ST-segment shift (%)						
Deviation	3892 (65)	54.1	<.001	3884 (65)	52.5	<.001
Depression	1739 (29.1)	33.7	<.001	1462 (25.9)	32.1	<.001
Elevated of cardiac biomarkers (%)†	4987 (83.3)	31.6	<.001	4648 (82.5)	33.6	<.001
In-hospital PCI (%)	2510 (41.9)	–		2409 (42.8)	26.6	<.001
Cardiac arrest at admission (%)	152 (2.5)	1.5	<.001	127 (2.3)	1.2	<.001
GRACE score*	142 (116-169)	–		123 (99-146)	–	
GRACE risk category (%)		–			–	
Low	1377 (23)			1102 (19.6)		
Intermediate	1911 (31.9)			1648 (29.2)		
High	2687 (44.9)			2885 (51.2)		

CABG, Coronary artery bypass graft; *STEMI*, ST elevation myocardial infarction; *NSTEACS*, non-ST elevation ACS.
*Median (percentiles 25th, 75th).
†Peak level of cardiac biomarkers in MASCARA and initial level in GRACE.

Calibration of observed against expected in-hospital and 6-month mortality was acceptable for the total population and for all subsets of ACS, as shown by the HL *P* values, which were >.1 (χ^2 < 20) in all cases (Table III). Similarly, the models showed adequate discriminatory ability for in-hospital and 6-month mortality in the whole population and in both ST-segment elevation and NSTEACS subgroups (*C* values between 0.79 and 0.86), although the highest values corresponded to in-hospital mortality prediction.

The model for predicting 6-month mortality performed significantly less well in those patients who underwent in-hospital PCI compared to those who did not undergo PCI (*C* = 0.73 vs *C* = 0.77, *P* = .007). However, it performed equally well among those patients who did and did not undergo in-hospital coronary artery bypass graft (*C* = 0.82 vs *C* = 0.81, *P* = .77). Although both RS performed excellently in patients with and without CRF, discriminative power was better in patients without CRF in both validation cohorts (*C* = 0.86 vs 0.82, *P* = .004 for in-

Table II. Observed and predicted rates (95% CI) for in-hospital and 6-month postdischarge mortality in the entire cohorts and stratified by type of ACS, performing or not in-hospital PCI, and across risk subgroups

					HL		
		n	Observed (%)	Predicted (%)	χ^2	*P*	C statistic (95% CI)
In-hospital mortality	Total	5985	5.7 (5.13-6.32)	5.4 (4.84-6.01)	7.1	.53	0.85 (0.833-0.873)
	STEMI	2344	7.6 (6.61-8.81)	7.08 (6.09-8.21)	12	.15	0.86 (0.834-0.890)
	NSTEACS	3641	4.4 (3.81-5.18)	4.21 (3.58-4.92)	2.7	.95	0.84 (0.810-0.869)
	CRF						
	Yes	383	14.1 (10.85-18.08)	13.3 (10.16-17.23)	5.8	.67	0.82 (0.795-0.842)*
	No	5602	5.1 (4.57-5.74)	4.4 (3.88-4.97)	8.2	.41	0.86 (0.844-0.881)*
	Diabetes						
	Yes	1861	8.1 (6.88-9.41)	7.7 (6.58-9.07)	6.3	.61	0.86 (0.841-0.879)
	No	2124	4.6 (3.78-5.62)	4.2 (3.48-5.26)	11.5	.17	0.86 (0.839-0.879)
	LVEF (%)						
	<30	455	18 (14.66-21.93)	17.1 (13.86-21)	11	.19	0.84 (0.821-0.864)
	30-49	1217	5.3 (4.1-6.71)	4.9 (3.81-6.34)	3.5	.90	0.83 (0.811-0.857)
	≥50	2492	1.7 (1.23-2.29)	1.5 (1.1-2.11)	9.2	.33	0.85 (0.834-0.874)
	Not assessed	823	16.3 (13.86-19.02)	15.4 (13.07-18.12)	3.3	.91	0.85 (0.834-0.875)
6-m mortality	Total	5635	8 (7.31-8.75)	7.36 (6.69-8.07)	3.3	.91	0.81 (0.789-0.830)
	STEMI	2165	5.8 (4.85-6.86)	5.5 (4.59-6.56)	17.4	.14	0.79 (0.745-0.826)
	NSTEACS	3470	9.4 (8.45-10.43)	8.5 (7.61-9.49)	8.1	.42	0.81 (0.790-0.838)
	CRF						
	Yes	330	27.6 (22.89-32.79)	25.8 (21.20-30.89)	3.9	.87	0.78 (0.756-0.801)†
	No	5305	6.8 (6.13-7.50)	4.8 (4.29-5.47)	11.1	.20	0.81 (0.790-0.830)†
	Diabetes						
	Yes	1707	12.7 (11.13-14.35)	11.9 (10.41-13.54)	6.34	.61	0.81 (0.785-0.826)
	No	3928	6 (5.27-6.78)	5.2 (4.55-5.97)	9.3	.32	0.81 (0.788-0.828)
	PCI						
	Yes	2409	3.5 (2.77-4.27)	3.3 (2.62-4.09)	12	.15	0.73 (0.677-0.773)*
	No	3226	11.4 (10.34-12.57)	10.1 (9.07-11.18)	6.6	.58	0.77 (0.746-0.795)*
	CABG						
	Yes	303	8.6 (5.44-11.05)	7.92 (4.86-10.94)	12.6	.13	0.82 (0.740-0.894)
	No	5332	8 (7.27-8.73)	7.37 (6.6-8.0)	10.3	.23	0.81 (0.790-0.832)
	LVEF (%)						
	<30	369	18.2 (14.44-22.56)	16.8 (13.21-21.10)	8.8	.36	0.80 (0.774-0.818)
	30-49	1147	9 (7.42-10.82)	8.3 (6.78-10.07)	4.2	.84	0.81 (0.785-0.829)
	≥50	2444	4.8 (4.03-5.77)	4.2 (3.47-5.11)	8.8	.36	0.81 (0.784-0.828)
	Not assessed	688	15.3 (12.70-18.22)	14.1 (11.63-16.98)	5.3	.73	0.80 (0.781-0.824)

HL, Hosmer-Lemeshow; *STEMI*, ST elevation myocardial infarction; *NSTEACS*, non-ST elevation acute coronary syndrome; *CABG*, coronary artery bypass graft.
*$P < .01$, differences between the *C* values.
†$P = .03$, differences between the *C* values.

hospital mortality RS and 0.81 vs 0.78, $P = .03$ for the 6-month mortality RS) (Table II). In patients with and in those patients without history of diabetes, the models' performance was also adequate. No significant differences were observed regarding the models' discriminative power in these subgroups.

Left ventricular ejection fraction could be assessed in 4,164 of 4,987 patients with AMI in the validation cohort for in-hospital mortality and in 3,960 of 4,648 patients in the validation cohort for 6-month mortality. Models' performance was excellent in each subgroup of LVEF, even in patients whose LVEF was not assessed. Adding LVEF to the total scores of both models did not significantly improve their discriminative power ($C = 0.86$ vs 0.85, $P = .54$, and $C = 0.82$ vs 0.81, $P = .50$). Collinearity test showed that LVEF was closely related to GRACE score (condition index 24.9 and 26 for in-hospital and 6-month mortality scores, respectively).

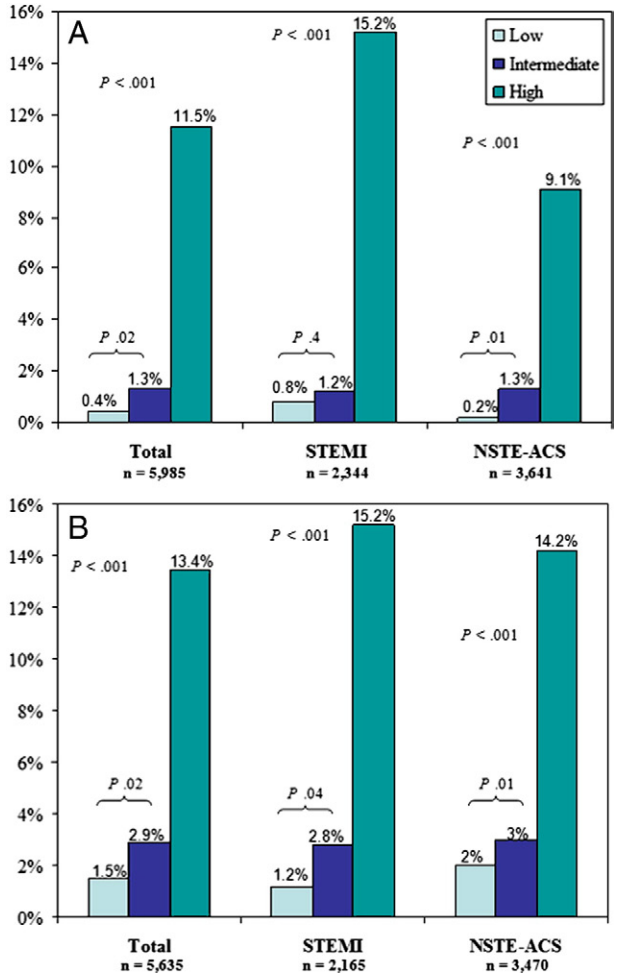
Table IV shows the differences between the odds ratios for outcomes reported in GRACE and the respective odds ratios in MASCARA, using a multivariable model with the GRACE component variables. Each of the component variables of the GRACE RS, except elevated cardiac markers in the validation cohort of the GRACE RS for 6-month death, was independently associated with the outcome of interest.

The missing values of the GRACE score were imputed using the expectation-maximization algorithm to predict the missing value. A comparison of the patients with and without missing data indicated that the missing values were completely at random (online Appendix B).

Discussion

In this unselected and contemporary sample of ACS, GRACE RS have shown an excellent discriminative power

Figure 2



In-hospital (**A**) and 6-month postdischarge mortality (**B**) rates in the MASCARA validation cohorts as a whole and by type of ACS.

and calibration for predicting both in-hospital and 6-month postdischarge mortality. This is true for the whole population, regardless of the baseline risk, and for subgroups of patients with and without history of diabetes and/or CRF. However, model performance was significantly lower in patients who had undergone in-hospital PCI. In addition, our study shows that LVEF is not useful to improve the performance of the model to predict 6-month postdischarge mortality.

Although the validity of the GRACE scores has been tested in a number of studies,[7-13] several points could limit their current applicability. Actually, most of these validations were performed in patient populations recruited between 1999 and 2002,[9-13] when several breakthroughs for management of ACS had not yet been widely used. In addition, studies of more contemporary populations had validated the GRACE RS only for in-hospital mortality[8] or did not report calibration data.[7] Furthermore, part of the patients in a study was also in the validation cohort of the GRACE RS, thus not representing a purely "external" validation.[8] Thus, our study provides a full evaluation of the GRACE models in an independent data set representing the contemporary management of ACS even if dating from 2004 to 2005.

The calibration of the GRACE models across risk strata has not been evaluated since its development. In our study, mortality rates predicted by GRACE RS closely approximate the observed values across the 3 risk categories in the whole population and in all subsets of ACS. Moreover, performance was adequate even in patients with diabetes and/or CRF, where it was previously suggested that GRACE models underestimated risk.[7] These findings indicate the excellent ability of GRACE RS to capture global baseline risk in contemporary patients with ACS, where such stratification is mandatory to select those potentially benefiting more from aggressive management.

The discriminative power of GRACE models was similar regardless LVEF, and adding this information to the total scores did not significantly improve their global performance. It is not surprising, given that reduced LVEF is a surrogate of short- or medium-term adverse outcomes,[21] and thus, it is likely to be correlated with several variables in a simple summary prognostic index as GRACE RS. The high collinearity between GRACE RS and LVEF found in our analyses support this view. In addition, this indirectly indicates the benefit of GRACE RS over other prognostic scoring systems. For instance, Singh et al[22] found that the LVEF added incremental prognostic information to TIMI and PREDICT RS in AMI patients, suggesting that these scores captured less prognostic information than GRACE RS. On the other hand, the unavailability of LVEF at the time of initial patient assessment does not limit the prognostic value of these models because LVEF does not significantly contribute to their performance. Furthermore, the models had the same operating characteristics among patients with preserved and impaired left ventricular systolic function, and therefore, the RS are applicable to a broad spectrum of patients with ACS.

In spite of the global performance of the model of GRACE RS, its discriminative capacity for 6-month mortality was reduced in those patients who had undergone in-hospital PCI. To put this finding in perspective, it should be taken into account that PCI patients constitute a specific population that represented only the 26.6% of the development cohort of GRACE RS. Therefore, other variables not included in GRACE RS could play a more important role in the assessment of the short- to medium-term risk of this specific population, as it has been recently shown.[23] In addition, other factors related to differences between MASCARA and GRACE cohorts as well as other specific characteristic related to the process of care in MASCARA could also account for

Table III. Observed and predicted rates (95% CI) of in-hospital and 6-month postdischarge death in each risk category in the whole population and by type of ACS

In-hospital mortality			6-m postdischarge mortality		
Total (n = 5985)	**Observed (%)**	**Predicted (%)**	**Total (n = 5635)**	**Observed (%)**	**Predicted (%)**
Low risk (n = 1377, 23%)	0.4 (0.18-1.0)	0.37 (0.13-0.90)	Low risk (n = 1102, 19.6%)	1.5 (0.93-2.51)	1.36 (0.79-2.29)
	HL 9, *P* = .34			HL 7.5, *P* = .49	
Intermediate risk (n = 1911, 31.9%)	1.3 (0.82-1.89)	1.2 (0.78-1.83)	Intermediate risk (n = 1648, 29.2%)	2.9 (2.18-3.87)	2.61 (1.92-3.53)
	HL 6, *P* = .65			HL 7.6, *P* = .48	
High risk (n = 2687, 44.9%)	11.5 (10.36-12.81)	11.4 (10.22-12.66)	High risk (n = 2885, 51.2%	13.4 (12.17-14.69)	13.1 (11.87-14.36)
	HL 4.8, *P* = .78			HL 7.6, *P* = .48	
STEMI (n = 2344)			STEMI (n = 2165)		
Low risk (n = 520, 22.2%)	0.77 (0.25-2.10)	0.72 (0.25-2.10)	Low risk (n = 599, 27.7%)	1.2 (0.51-2.5)	1.11 (0.51-2.50)
	HL 12, *P* = .15			HL 7, *P* = .54	
Intermediate risk (n = 729, 31.1%)	1.2 (0.60-2.42)	1.0 (0.42-2.06)	Intermediate risk (n = 707, 32.7%)	2.8 (1.78-4.41)	2.32 (1.35-3.73)
	HL 10.2, *P* = .25			HL 7.9, *P* = .48	
High risk (n = 1095, 46.7%)	15.2 (13.11-17.45)	15.05 (13.03-17.36)	High risk (n = 859, 39.7%)	11.4 (9.40-13.77)	11.16 (9.19-13.52)
	HL 11.2, *P* = .19			HL 5, *P* = .76	
NSTEACS (n = 3641)			NSTEACS (n = 3470)		
Low risk (n = 857, 23.5%)	0.2 (0.04-0.94)	0.19 (0.04-0.94)	Low risk (n = 503, 14.5%)	2 (1.01-3.75)	1.79 (0.88-3.49)
	HL 3.6, *P* = .89			HL 11, *P* = .2	
Intermediate risk (n = 1182, 32.5%)	1.3 (0.74-2.14)	1.22 (0.68-2.03)	Intermediate risk (n = 941, 27.1%)	3 (2.02-4.33)	2.53 (1.68-3.83)
	HL 10.4, *P* = .24			HL 7, *P* = .53	
High risk (n = 1602, 44%)	9.1 (7.17-10.59)	9.03 (7.71-10.59)	High risk (n = 2026, 58.4%)	14.2 (12.74-15.83)	13.83 (12.36-15.42)
	HL 7.2, *P* = .51			HL 8.6, *P* = .38	

HL, Hosmer-Lemeshow; *STEMI*, ST elevation myocardial infarction; *NSTEACS*, non-ST elevation ACS.

Table IV. Comparison of values of odds ratio (95% CI) for in-hospital and 6-month postdischarge mortality predictors reported by GRACE and the corresponding values obtained in MASCARA

	In-hospital mortality		6-m mortality	
Predictors	**GRACE**	**MASCARA**	**GRACE**	**MASCARA**
Age per 10-y increase	1.7 (1.55-1.85)	1.9 (1.643-2.103)	1.8 (1.64-1.91)	1.9 (1.712-2.127)
Pulse per 30/min increase	1.3 (1.16-1.48)	1.3 (1.096-1.477)	1.3 (1.16-1.43)	1.3 (1.120-1.472)
Systolic blood pressure per 20-mm Hg decrease	1.4 (1.27-1.45)	1.3 (1.221-1.432)	1.1 (1.08-1.20)	1.1 (1.046-1.202)
Initial serum creatinine level per 1-mg/dL increase	1.2 (1.15-1.35)	1.3 (1.185-1.427)	1.2 (1.11-1.24)	1.5 (1.335-1.585)
Cardiac markers elevation*	1.6 (1.32-2.0)	1.9 (1.148-3.165)	1.6 (1.39-1.89)	1.03 (0.672-1.581)
Heart failure*	2 (1.81-2.29)	2.6 (2.250-2.899)	2.2 (1.97-2.59)	1.8 (1.427-2.206)
History of myocardial infarction	–	–	1.5 (1.26-1.75)	1.7 (1.120-2.475)
ST-segment shift†	2.4 (1.90-3.0)	1.9 (1.433-2.581)	1.4 (1.22-1.69)	1.4 (1.082-1.684)
Cardiac arrest at hospital arrival	4.3 (2.80-6.72)	3.2 (1.922-5.443)	–	–
No in-hospital PCI	–	–	1.6 (1.24-1.96)	2.2 (1.665-2.827)

* Killip class (per increase in class) at admission and to history of heart failure (prior heart failure and/or index event-related) in the GRACE RS for in-hospital and 6-month mortality RS, respectively.
† ST-segment deviation and ST-segment depression in the GRACE RS for in-hospital and 6-m mortality, respectively.

this discrepancy in the 6-month mortality performance of GRACE RS. First, the rate of PCI performed in MASCARA study was substantially higher than in GRACE (41.9% vs 26.6%); second, the independent effect of PCI on 6-month mortality was remarkably different in GRACE and MASCARA (Table IV); and finally, median GRACE score value of those patients who underwent in-hospital PCI in MASCARA was significantly lower than in those who did not undergo this procedure, a phenomenon previously described as *treatment-risk paradox* (ie, most interventions are performed in lower risk patients). In any case, it is important to keep in mind that the main use of GRACE RS is to stratify on admission those patients who will derive significant benefit from invasive procedures. The in-hospital mortality GRACE RS, which is aimed at this purpose, performed equally well in all subgroups of patients in MASCARA. By contrast, the generalizability of a risk score used for specific subpopulations when a variable more dependent on the process of care such as "in-hospital PCI" is included, as with the 6-month mortality GRACE RS, could be more arguable.

The performance of the models was good in most of analyses despite substantial differences between the original derivation cohorts of GRACE and the MASCARA

population. This is not surprising considering that the GRACE RS were developed from a multinational cohort of "real-life" patients reflecting different health care and practice patterns, with considerably high generalizability and, in consequence, support the validity of the RS in many different contexts. Pieper et al,[24] who recently updated the GRACE RS for predicting in-hospital mortality and evaluated the interaction between years of enrollment and geographic region, observed that neither contribution was large enough to warrant the inclusion of these variables in the updated model. The variables in the updated model closely mirror those in the original GRACE score, illustrating that the factors associated with risk have remained stable over time. In addition, variables involved in the GRACE models are powerful independent prognostic factors in many different scenarios,[1-4] which is also the case in MASCARA. For instance, all variables of GRACE RS excepting elevated cardiac biomarkers were significantly associated with 6-month mortality in the MASCARA cohort. However, in MASCARA, peak instead of initial cardiac biomarkers were collected. Consequently, almost all patients (83.3%) had raised cardiac biomarkers, so that variable did not contribute to the model, although it was retained in the calculation of RS to assess the models' performance.

Another way of risk stratifying patients with ACS that has lately been widely acknowledged is the addition of new serum biomarkers to the current models to predict risk of cardiovascular events.[25,26] New biomarkers may give greater accuracy to the clinical scores for risk prediction of ACS and add new important information regarding major adverse events. This information would be complementary to troponin or clinical scales. However, the possibility of classifying patients in new risk groups is still more interesting. This finding may be certainly important given that new high-risk groups could be managed more aggressively in drugs and interventions.

Limitations

As any other observational study, our results should be interpreted with caution. The 6-month follow-up could not be achieved in 560 patients. Of the 6,745 patients in the initial cohort of this study, GRACE scores could not be calculated in 760 and in 771 for predicting in-hospital mortality and 6-month postdischarge death, respectively. Although these facts could theoretically result in selection bias, missing data analysis showed that values were missing completely at random. Similarly, LVEF was not available in the entire cohort. Information bias is also possible. However, external researchers were specifically trained to collect data from clinical records according to standardized definitions, thus minimizing the possibility of such bias. Although in this study the LVEF plus GRACE makes a small and nonsignificant extra contribution to risk assessment, this contribution was tested by the *C* statistic. It should be reminded that *C* statistic was really designed to compare 2 single predictors in a head-to-head fashion and is not ideal to compare a combination of predictors versus a single predictor. New methods for evaluating improvement in risk stratification such as the use of event-specific reclassification tables and integrated discrimination improvement may change the predictive accuracy of some patients even when little change is observed in the *C* index values.[27]

Clinical implications and conclusions

GRACE risk score is a valid and powerful predictor of in-hospital and 6-month postdischarge mortality across the wide range of current patients with ACS. Although the RS for predicting mortality at 6 months performed significantly less well in patients undergoing in-hospital PCI, its performance overall is excellent and to be maintained in all patients subgroups despite the time elapsed since its development. In AMI patients, LVEF did not convey significant prognostic information over that provided by the GRACE RS. The substantial differences in the mortality rates and clinical features between the studies' original derivation cohorts and MASCARA population did not affect the robustness of these models. This applies even to those patients with clinical conditions not included in GRACE RS (ie, diabetes, CRF, and/or reduced LVEF). Physicians, patients, and health care providers can be reassured about the reliability and applicability of these models for risk stratification in patients with ACS.

References

1. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. Eur Heart J 2008;29:2909-45.
2. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non–ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598-660.
3. Kushner FG, Hand M, Smith Jr SC, et al. Focused updated: ACC/AHA guidelines for the management of patients with ST elevation myocardial infarction. Circulation 2009;120:2271-306.
4. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST elevation myocardial infarction. Circulation 2007;116:e148-304.
5. Granger CB, Goldberg RJ, Dabbous OH, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003;163:2345-53.
6. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004; 291:2727-33.
7. Gale CP, Manda SO, Weston CF, et al. Evaluation of risk scores for risk stratification of acute coronary syndromes in the Myocardial Infarction National Audit Project (MINAP) database. Heart 2009;95: 221-7.
8. Elbarouni B, Goodman SG, Yan RT, et al. Validation of the global registry of acute coronary event (GRACE) risk score for in-hospital

mortality in patients with acute coronary syndrome in Canada. Am Heart J 2009;158:392-9.
9. Yan AT, Yan RT, Tan M, et al. Risk scores for risk stratification in acute coronary syndromes: useful but simpler is not necessarily better. Eur Heart J 2007;28:1072-8.
10. Bradshaw PJ, Ko DT, Newman AM, et al. Validity of the GRACE (Global Registry of Acute Coronary Events) acute coronary syndrome prediction model for 6-month postdischarge death in an independent data set. Heart 2006;92:905-9.
11. Alter DA, Venkatesh V, Chong A. Evaluating the performance of the Global Registry of Acute Coronary Events risk-adjustment index across socioeconomic strata among patients discharged from the hospital after acute myocardial infarction. Am Heart J 2006;151: 323-31.
12. de Araujo Gonçalves P, Ferreira J, Aguiar C, et al. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTEACS. Eur Heart J 2005;26:865-72.
13. Yan AT, Jong P, Yan RT, et al. Clinical trial-derived risk model may not generalize to real-world patients with acute coronary syndrome. Am Heart J 2004;148:1020-7.
14. Fox KA, Steg PG, Eagle KA, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. JAMA 2007;297: 1892-900.
15. Permanyer-Miralda G, Ferreira-Gonzalez I, Marrugat J, et al. Rationale and conceptual design of MASCARA study: a challenge in the evaluation of the effectiveness. Med Clin (Barc) 2005;125:580-4.
16. Ferreira-Gonzalez I, Permanyer-Miralda G, Marrugat J, et al. MASCARA (Manejo del Síndrome Coronario Agudo. Registro Actualizado) study. General findings. Rev Esp Cardiol 2008;61: 803-16.
17. GRACE ACS Risk Score. Available at: http://www.outcomes-umassmed.org/grace/grace_risk_table.cfm.
18. Lemeshow S, Hosmer D. A review of goodness of fit statistic for use in the development of logistic regression models. Am J Epidemiol 1982: 92-106.
19. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143: 29-36.
20. R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2009, Available at: http://www.R-project.org.
21. Moller JE, Hillis GS, Oh JK, et al. Wall motion score index and ejection fraction for risk stratification after acute myocardial infarction. Am Heart J 2006;151:419-25.
22. Singh M, Reeder GS, Jacobson SJ, et al. Scores for postmyocardial infarction risk stratification in the community. Circulation 2002;106: 2309-14.
23. Peterson ED, Dai D, DeLong ER, et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. J Am Coll Cardiol 2010;55:1933-5.
24. Pieper K, Gore J, FitzGerald G, et al. Validity of a risk-prediction tool for hospital mortality: the global registry of acute coronary events. Am Heart J 2009;157:1097-105.
25. Acharjee S, Qin J, Murphy S, et al. Distribution of traditional and novel risk factors and their relation to subsequent cardiovascular events in patients with acute coronary syndromes (from the PROVE IT-TIMI 22 Trial). Am J Cardiol 2010;105:619-23.
26. Ang D, Wei L, Kao M, et al. A comparison between B-type natriuretic peptide, Global Registry of Acute Coronary Events (GRACE) score and their combination in ACS risk stratification. Heart 2009;95:1836-42.
27. Pencina MJ, D'Agostino Sr RB, D'Agostino Jr RB, et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157-72.

Appendix A. Component variables of the GRACE RS

	Predictor	Score
GRACE RS for in-hospital mortality (0-258)	Killip	
	I	0
	II	21
	III	43
	IV	64
	Systolic blood pressure (mm Hg)	
	<80	63
	81-99	58
	100-119	47
	120-139	37
	140-159	26
	160-199	11
	>200	0
	Heart rate (beats per min)	
	<70	0
	70-89	7
	90-109	13
	110-149	23
	150-199	36
	>200	46
	Age, y	
	<40	0
	40-49	18
	50-59	36
	60-69	55
	70-79	73
	≥80	91
	Serum creatinine level (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
	Cardiac arrest at admission	39
	Elevated cardiac markers	15
	ST-segment deviation	30
GRACE RS for 6 month postdischarge mortality (0-372)	Age (y)	
	<40	0
	40-49	18
	50-59	36
	60-69	55
	70-79	73
	80-89	91
	≥90	100
	History of Congestive heart failure	24
	History of myocardial infarction	12
	Heart rate (beats per min)	
	≤49.9	0
	50-69.9	3
	70-89.9	9
	90-109.9	14
	110-149.9	23
	150-199.9	35
	≥200	43
	Systolic blood pressure (mm Hg)	
	≤79.9	24
	80-99.9	22
	100-119.9	18
	120-139.9	14
	140-159.9	10
	160-199.9	4
	≥200	0
	ST-segment depression	11
	Serum creatinine level (mg/dL)	
	0-0.39	1
	0.4-0.79	3
	0.8-1.119	5
	1.2-1.59	7
	1.6-1.99	9
	2-3.99	15
	≥4	20
	Elevated cardiac markers	15
	No in-hospital PCI	14

Appendix A (*continued*)

Appendix B. Baseline and on admission data differences between the population with missing and without missing data

	MASCARA validation cohort of GRACE RS for in-hospital death			MASCARA validation cohort of GRACE RS for 6-m postdischarge death		
	Not missing (n = 5985)	Missing* (n = 760, 11.3%)	*P*	Not missing (n = 5985)	Missing† (n = 771, 11.4%)	*P*
Demographic data and medical history						
Age (y)*	69.8 (58-74)	69.5 (58-77)	.33	69.3 (58-77)	69 (59-77)	.93
Men (%)	4316 (72.1)	539 (71)	.51	4088 (72.5)	527 (72.4)	.91
Smoking (%)	2268 (37.9)	228 (40.4)		1807 (38.1)	216 (39.7)	.68
Hypertension (%)	3637 (60.8)	462 (60.9)	.9	3396 (60.3)	449 (61.8)	.44
Hyperlipidemia (%)	2845 (47.5)	372 (49.1)	.41	2686 (47.7)	377 (51.9)	.03
Diabetes (%)	1861 (31.1)	250 (33)	.29	1707 (30.3)	233 (32)	.33
Angina (%)	1839 (30.7)	223 (29.4)	.46	1736 (30.8)	214 (29.4)	.45
Myocardial infarction (%)	1369 (22.9)	186 (24.5)	.31	1285 (22.8)	177 (24.3)	.35
Peripheral arteriopathy (%)	711 (11.9)	77 (10.1)	.16	639 (11.3)	70 (9.6)	.16
Stroke (%)	469 (7.8)	58 (7.7)	.87	411 (7.3)	57 (7.9)	.59
Congestive heart failure (%)	328 (5.5)	35 (4.6)	.33	276 (4.9)	38 (5.2)	.69
CRF (%)	383 (6.4)	41 (5.4)	.28	330 (5.9)	–	–
PCI (%)	744 (12.4)	107 (14.1)	.18	717 (12.7)	38 (5.2)	.23
CABG (%)	328 (5.5)	46 (6.1)	.74	323 (5.7)	47 (6.5)	.42
On admission data						
Type of ACS (%)			.41			.25
STEMI	2344 (39.2)	286 (37.6)		2165 (38.4)	264 (36.2)	
NSTEACS	3641 (60.8)	474 (62.4)		3470 (61.6)	465 (63.8)	
Killip class (%)			.05			.40
I	4586 (76.6)	516 (78.9)		4422 (78.5)	563 (81)	
II	919 (15.4)	86 (13.1)		813 (14.4)	94 (13.5)	
III	351 (5.9)	30 (4.6)		280 (5)	28 (4)	
IV	129 (2.2)	22 (3.4)		57 (1.1)	10 (1.4)	
Heart rate (beat per min)‡	77 (65-90)	78 (62-92)	.44	76 (65-90)	79 (65-90)	.01
Systolic blood pressure (mm Hg)‡	140 (120-160)	140 (121-168)	.13	140 (123-160)	143 (125-170)	<.001
Serum creatinine level (mg/dL)‡	1 (0.85-1.24)	1 (0.81-1.21)	.53	1 (0.83-1.20)	1 (0.82-1.20)	.60
ST-segment shift (%)						
Deviation	3892 (65)	489 (64.3)	.71	3884 (65)	464 (63.6)	.80
Depression	1739 (29.1)	226 (29.7)	.70	1462 (25.9)	201 (27.6)	.35
Elevated cardiac biomarkers (%)	4987 (83.3)	496 (83.7)		4648 (82.5)	474 (83.3)	.62
In-hospital PCI (%)	2510 (41.9)	270 (35.5)	.001	2409 (42.8)	272 (37.3)	.005
Cardiac arrest at admission (%)	152 (2.5)	31 (4.1)	.01	127 (2.3)	21 (2.9)	.28
Mortality (%)	341 (5.7)	40 (5.3)	.63	452 (7.6)	48 (6.2)	.18

CABG, Coronary artery bypass graft; *STEMI*, ST elevation myocardial infarction; *NSTEACS*, non-ST elevation ACS.
* Little test: $\chi^2 = 21.8$, $P = .67$; peak level of cardiac biomarkers.
† Little test: $\chi^2 = 24.5$, $P = .14$.
‡ Median (percentiles 25th, 75th).

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