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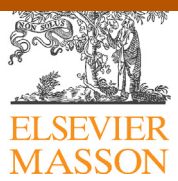

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CLINICAL RESEARCH

Improving risk stratification in non-ST-segment elevation myocardial infarction with combined assessment of GRACE and CRUSADE risk scores

L'utilisation combinée des scores GRACE et CRUSADE pour la stratification du risque d'infarctus du myocarde

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KEYWORDS
Myocardial infarction;
Risk;
GRACE;
CRUSADE

Summary
Background. — Risk assessment is fundamental in the management of acute coronary syndromes (ACS), enabling estimation of prognosis.
Aims. — To evaluate whether the combined use of GRACE and CRUSADE risk stratification schemes in patients with myocardial infarction outperforms each of the scores individually in terms of mortality and haemorrhagic risk prediction.
Methods. — Observational retrospective single-centre cohort study including 566 consecutive patients admitted for non-ST-segment elevation myocardial infarction. The CRUSADE model increased GRACE discriminatory performance in predicting all-cause mortality, ascertained

Abbreviations: ACS, acute coronary syndrome; AUC, area under the curve; CI, confidence interval; CRUSADE, can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the American College of Cardiology/American Heart Association guidelines; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio; IDI, integrated discrimination improvement; NRI, Net Reclassification Index; NSTEMI, non-ST-elevation myocardial infarction; ROC, receiver operating characteristic.

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by Cox regression, demonstrating CRUSADE independent and additive predictive value, which was sustained throughout follow-up. The cohort was divided into four different subgroups: G1 (GRACE < 141; CRUSADE < 41); G2 (GRACE < 141; CRUSADE ≥ 41); G3 (GRACE ≥ 141; CRUSADE < 41); G4 (GRACE ≥ 141; CRUSADE ≥ 41).
Results. — Outcomes and variables estimating clinical severity, such as admission Killip-Kimbal class and left ventricular systolic dysfunction, deteriorated progressively throughout the subgroups (G1 to G4). Survival analysis differentiated three risk strata (G1, lowest risk; G2 and G3, intermediate risk; G4, highest risk). The GRACE + CRUSADE model revealed higher prognostic performance (area under the curve [AUC] 0.76) than GRACE alone (AUC 0.70) for mortality prediction, further confirmed by the integrated discrimination improvement index. Moreover, GRACE + CRUSADE combined risk assessment seemed to be valuable in delineating bleeding risk in this setting, identifying G4 as a very high-risk subgroup (hazard ratio 3.5; $P < 0.001$).
Conclusions. — Combined risk stratification with GRACE and CRUSADE scores can improve the individual discriminatory power of GRACE and CRUSADE models in the prediction of all-cause mortality and bleeding. This combined assessment is a practical approach that is potentially advantageous in treatment decision-making.

MOTS CLÉS
Syndrome coronaire aigu ;
Risque ;
GRACE ;
CRUSADE

Résumé
Contexte. — L'évaluation des risques est fondamentale dans la gestion des syndromes coronariens aigus, permettant l'estimation du pronostic.
Objectifs. — Le but de notre étude était d'évaluer l'utilisation combinée des scores GRACE et CRUSADE pour la stratification de la mortalité et du risque hémorragique des patients pris en charge pour un infarctus aigu du myocarde en comparaison à l'utilisation isolée de chacun de ces scores.
Méthodes. — Cohorte rétrospective observationnelle monocentrique ayant inclus 566 patients consécutifs hospitalisés pour un syndrome coronarien aigu sans sus-décalage du segment ST. Le score CRUSADE a augmenté le pouvoir discriminant du score GRACE pour la prédiction de la mortalité globale, en utilisant la régression de Cox, ce qui démontre la valeur prédictive indépendante et additive du score CRUSADE, laquelle était maintenue tout au long du suivi. La cohorte a été divisée en 4 sous-groupes : G1 (GRACE < 141 ; CRUSADE < 41) ; G2 (GRACE < 141 ; CRUSADE ≥ 41) ; G3 (GRACE ≥ 141 ; CRUSADE < 41) ; G4 (GRACE ≥ 141 ; CRUSADE ≥ 41).
Résultats. — Les événements et variables qui évaluaient la sévérité clinique, comme la classe Killip-Kimbal à l'admission et la dysfonction systolique du ventricule gauche étaient plus fréquents de manière linéaire en fonction des sous-groupes (G1—G4). L'analyse de la survie a montré 3 groupes de risque (G1, risque bas ; G2 et G3, risque intermédiaire ; G4, risque plus élevé). Le modèle GRACE + CRUSADE a montré une performance pronostique supérieure (AUC 0,76) au score GRACE utilisé de manière isolé (AUC 0,70) pour la prédiction de la mortalité, ce qui a été confirmé par l'amélioration de l'index de la discrimination intégrée. De plus, l'évaluation combinée des scores GRACE + CRUSADE semble avoir une valeur additionnelle pour la prédiction de risque de saignement et permet d'identifier le groupe G4 comme étant à risque très élevé (HR 3,5 ; $p = 0,001$).
Conclusion. — L'utilisation combinée des scores GRACE et CRUSADE pourrait améliorer leur pouvoir discriminant en comparaison à leur utilisation isolée pour la prédiction de la mortalité globale ainsi que du risque hémorragique. Cette nouvelle approche semble apporter des avantages dans la pratique quotidienne et orienter la prise en charge thérapeutique.

Background

Risk assessment is fundamental in acute coronary syndrome (ACS) management, enabling estimation of patient prognosis — a key issue for communicating with patients and relatives, and for therapeutic decision-making. Current recommendations propose an aggressive treatment approach for high-risk non-ST-elevation myocardial infarction (NSTEMI), including more potent antithrombotic therapies and a rapid invasive strategy [1,2]. Conversely, lower-risk cases may do well with less aggressive medical treatment and a more selective invasive strategy. Thus, it is essential to assess ischaemic risk on an individual basis, preferably using quantitative risk scoring systems such as the Global Registry of Acute Coronary Events (GRACE) model [3], use of which is favoured over other risk scores in the latest guidelines update [1,2]. However, with the greater use of more potent antithrombotic drugs and early

revascularization, bleeding occurs more frequently and has become a relevant clinical problem in the ACS setting, making haemorrhagic risk assessment a necessary tool to guide treatment strategies. The can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the American College of Cardiology/American Heart Association guidelines (CRUSADE) risk score [4] is one of the most popular bleeding risk algorithms, consisting of several recognized predictors of haemorrhage [5,6]. As bleeding results not only in an immediate threat but also in increased risk of adverse outcomes during follow-up [7], it remains to be determined if ACS risk assessment with combined ischaemic and bleeding risk assessment will prove advantageous. Our aim was to establish the appropriateness of the combined use of GRACE and CRUSADE risk stratification in NSTEMI patients and to evaluate potential gains in outcome prediction, compared with the separate use of the traditional risk-scoring systems.

Methods

Patient selection

This was an observational retrospective single-centre cohort study including all patients consecutively admitted to our University Hospital's Acute Cardiac Care Unit with a final diagnosis of myocardial infarction between 1 December 2006 and 31 May 2008. Myocardial infarction was defined according to the recently updated definition [8], excluding patients with unstable angina and those with myocardial injury (elevated cardiac biomarkers) without evidence of ischaemia (i.e. symptoms, electrocardiogram, imaging modalities). Furthermore, only NSTEMI cases were considered, with the final study cohort including a total of 566 patients.

Data collection and patient follow-up

Demographic and clinical features were collected at admission and during hospitalization. The electrocardiogram and analytical assessment (including complete blood count and biochemical and clotting tests) were performed according to the Acute Cardiac Care Unit standards: at admission and then at least daily, according to patient's clinical evaluation. Troponin I measurements were taken at admission, between 12 and 24 hours after admission and daily thereafter. The measurement of troponin I was performed with the chemiluminescent technique (Ortho Clinical Diagnostics VITROS® Troponin I ES Assay; Johnson & Johnson Ltd., Maidenhead, UK). The lower detection limit for this assay is 0.012 ng/mL. The 99th percentile upper reference limit is 0.034 ng/mL, with a reported imprecision of 10% coefficient of variation. Results > 0.034 ng/mL were considered positive. Creatinine clearance was estimated using the modification of diet in renal disease equation [9]. The reference for coronary angiography and potential percutaneous myocardial revascularization was an individually tailored decision, involving the Acute Cardiac Care Unit and the interventional cardiologist's clinical judgment, in accordance with the European Society of Cardiology guidelines for myocardial infarction management [1]. Finally, left ventricular ejection fraction was obtained from the predischarge transthoracic echocardiogram, in accordance with European Association of Cardiovascular Imaging standards [10].

Patients were followed for 21.1 ± 7.5 months after discharge by means of patient's clinical records, routine visits, consultation of the National Health System User Card database and telephone calls until the end of a 2-year period after discharge, and whenever clinical files were considered insufficient.

Risk assessment

We tested and compared the prognostic performance of GRACE [3] and CRUSADE [4] risk stratification models in this cohort, through evaluation of their overall discriminative performance and calibration in the prediction of all-cause mortality during the index event, follow-up and in-hospital bleeding, respectively. The traditional risk categories of GRACE and CRUSADE scores are depicted in Supplementary Table 1. The GRACE score for in-hospital mortality ($GRACE_{IH}$) is more commonly used in clinical practice than the 6-month postdischarge GRACE score, because the former may guide revascularization timing in NSTEMI (i.e. patients at high ischaemic risk [GRACE $\geq$ 141] should be considered for an early invasive strategy) [1,11]. Subsequently, the

Table 1 Cohort distribution according to GRACE and CRUSADE risk classes.

	Low-risk class	Intermediate-risk class	High-risk class
$GRACE_{IH}$	77 (13.6)	135 (23.9)	354 (62.5)
$GRACE_{6M}$	155 (27.3)	219 (38.7)	192 (34.0)
CRUSADE	222 (39.2)	126 (22.3)	218 (38.5)

Cross-tabulation of CRUSADE and GRACE risk categories

	GRACE		
	Low-risk class	Intermediate-risk class	High-risk class
CRUSADE			
Low-risk class	58 (26.1)	83 (37.4)	81 (36.5)
Intermediate-risk class	12 (9.5)	28 (22.2)	86 (68.3)
High-risk class	6 (2.8)	28 (12.8)	184 (84.4)

Data are number (%). CRUSADE: in-hospital major bleeding; $GRACE_{6M}$: 6-month postdischarge mortality; $GRACE_{IH}$: in-hospital mortality.

cohort was divided into four different groups according to the presence of at least one high-risk category (using in-hospital GRACE and CRUSADE cut-offs used in clinical practice) [1,2]: group 1 (G1: GRACE < 141 non-high-risk class; CRUSADE < 41 non-high-risk class), group 2 (G2: GRACE < 141, non-high-risk class; CRUSADE ≥ 41, high-risk class); group 3 (G3: GRACE ≥ 141, high-risk class; CRUSADE < 41, non-high-risk class); group 4 (G4: GRACE ≥ 141, high-risk class; CRUSADE ≥ 41, high-risk class). Each group was evaluated in terms of baseline characteristics and study endpoints.

In this study, major bleeding was defined in accordance with the CRUSADE investigators [4]: intracranial haemorrhage, documented retroperitoneal bleed, haematocrit drop ≥ 12% (from baseline), any red blood cell transfusion when baseline haematocrit was ≥ 28% or any red blood cell transfusion when baseline haematocrit was < 28% with witnessed bleed.

Study endpoints

The primary outcome measures were in-hospital all-cause mortality, all-cause mortality during follow-up and in-hospital major bleeding.

Statistical analysis

Statistical analyses were done using SPSS® software, version 17.0 (StataCorp LP, College Station, Texas, USA). When needed, baseline characteristics were described with means ± standard deviations for continuous and counts and proportions for categorical data. The Kolmogorov–Smirnov test was used to test the normal distribution of continuous variables. The Chi^2 test and Student's *t* test were used for quantitative and nominal comparisons between two groups, and non-parametric equivalent tests were used when appropriate. Regression estimation techniques were applied to replace missing values whenever the number of missing values was negligible, otherwise cases with missing values were omitted. *P* values < 0.05 (two-sided) were considered statistically significant.

Univariate analysis was performed to evaluate the potential association between each previously defined myocardial infarction group and the study endpoints. Cox regression was used to evaluate the predictive value of the CRUSADE score compared with the GRACE algorithm for follow-up mortality. The analysis of variance (or equivalent non-parametric test, when necessary) was used to determine differences among the predefined myocardial infarction subgroup means. Discrimination, measured in terms of the area under the receiver operating characteristic (ROC) curve (AUC), was performed to assess the predictive power of the GRACE score in-hospital ($GRACE_{IH}$) and 6 months postdischarge ($GRACE_{6M}$) for in-hospital and follow-up mortality, respectively, and of the CRUSADE model for in-hospital major bleeding. Finally, the combined GRACE and CRUSADE model (GRACE + CRUSADE) was tested for in-hospital and follow-up mortalities and major bleeding. Other measures of incremental value have been proposed, which examine the extent to which a model reclassifies subjects, such as the net reclassification index (NRI) and the integrated discrimination improvement (IDI) [12]. The NRI method, described by Pencina et al. [13], states that a positive and significant NRI translates a net overall successful reclassification of subjects into a more appropriate risk category. The IDI, which may be seen as a continuous form of the NRI, assesses improvement in risk discrimination by estimating the change in the difference of the average of predicted probabilities of an event between those with and without the event under consideration [14]; it is a more appropriate measure of risk reclassification when comparing scores with different risk categorization (e.g. GRACE stratifies patients into three risk strata and GRACE + CRUSADE stratifies patients into four risk categories). Calibration of each score was also assessed using the Hosmer–Lemeshow test. Finally, Kaplan–Meier curves were constructed to evaluate survival during follow-up according to each predefined myocardial infarction group.

Results

Cohort characteristics

The cohort included 566 patients with a mean age of 70.4 ± 12.3 years (range 31–92 years), 61.3% of whom were men. Patients' baseline clinical, analytical and imaging characteristics are shown in Supplementary Table 1. The cohort distribution according to GRACE and CRUSADE risk values/categories are given in Table 1. In 270 (47.7%) cases there was overall concordance between $GRACE_{IH}$ and CRUSADE risk categories; 184 (32.5%) patients were classified as high-risk by both GRACE and CRUSADE risk models (Table 1).

Risk score performance

The discrimination performances of $GRACE_{IH}$ (for in-hospital mortality), $GRACE_{6M}$ (for follow-up mortality) and CRUSADE (for major bleeding) were tested in our cohort, and their discrimination performances are displayed in Table 2. All scores showed good calibration, as demonstrated by Hosmer–Lemeshow test *P* values > 0.05.

Table 2 Cohort risk model performances, using as continuous variables and as risk score categories (low-, intermediate- and high-risk classes).

	AUC (95% CI)	*P*
Continuous variable		
$GRACE_{IH}$	0.81 (0.75–0.88)	< 0.001
$GRACE_{6M}$	0.78 (0.73–0.83)	< 0.001
CRUSADE	0.70 (0.62–0.77)	< 0.001
Categorical variable		
$GRACE_{IH}$	0.70 (0.64–0.76)	< 0.001
$GRACE_{6M}$	0.74 (0.69–0.83)	< 0.001
CRUSADE	0.69 (0.62–0.76)	< 0.001
GRACE + $CRUSADE_{IH}$	0.76 (0.70–0.82)	< 0.001
GRACE + $CRUSADE_{6M}$	0.78 (0.73–0.83)	< 0.001
GRACE + $CRUSADE_{bleed}$	0.66 (0.59–0.74)	< 0.001

AUC: area under the curve; CI: confidence interval; CRUSADE: in-hospital major bleeding; $GRACE_{6M}$: 6-month postdischarge mortality; $GRACE_{IH}$: in-hospital mortality; GRACE + $CRUSADE_{6M}$: follow-up mortality; GRACE + $CRUSADE_{bleed}$: in-hospital major bleeding; GRACE + $CRUSADE_{IH}$: in-hospital mortality.

Table 3 Cohort subgroup analysis.

	Subgroups				*P*
	G1 (GRACE < 141; CRUSADE < 41) (*n* = 173; 30.6%)	G2 (GRACE < 141; CRUSADE ≥ 41) (*n* = 53; 9.4%)	G3 (GRACE ≥ 141; CRUSADE < 41) (*n* = 168; 29.6%)	G4 (GRACE ≥ 141; CRUSADE ≥ 41) (*n* = 172; 30.4%)	
Age (years)	59.7 ± 11.1	69.2 ± 9.7	74.3 ± 8.6	78.3 ± 8.3	< 0.001
Men	139 (80.3)	15 (28.3)	119 (70.8)	74 (43.0)	< 0.001
Killip-Kimball class (admission)	1.0 ± 0.4	1.1 ± 0.7	1.2 ± 0.7	1.8 ± 0.9	< 0.001
Systolic arterial pressure (mm Hg)	140.9 ± 23.8	148.4 ± 34.1	127.9 ± 20.0	128.0 ± 27.0	< 0.001
Heart rate (bpm)	72.8 ± 15.4	76.5 ± 17.0	75.9 ± 16.7	84.6 ± 22.7	< 0.001
Haemoglobin (g/dL)	14.6 ± 1.6	12.2 ± 1.5	13.5 ± 1.7	11.9 ± 1.9	< 0.001
Haematocrit (%)	43.8 ± 4.7	36.6 ± 4.7	40.4 ± 5.0	35.7 ± 5.9	< 0.001
Glycaemia (mmol/L)	7.4 ± 3.6	8.6 ± 5.1	8.1 ± 3.8	10.5 ± 5.5	< 0.001
Haemoglobin A1c (%)	6.2 ± 1.3	6.3 ± 1.6	6.4 ± 1.3	7.1 ± 1.8	< 0.001
Serum creatinine (μmol/L)	83.6 ± 20.0	168.8 ± 167.4	89.9 ± 28.9	204.1 ± 174.8	< 0.001
Creatinine clearance[a] *(mL/min)*	78.5 ± 26.2	43.6 ± 22.9	68.0 ± 25.9	45.4 ± 26.7	< 0.001
Maximum troponin I (ng/mL)	12.9 ± 20.5	16.7 ± 34.5	20.9 ± 25.6	25.2 ± 46.1	0.006
NT-proBNP (pg/mL)	857.3 ± 1131.9	3173.9 ± 3497.9	3382.3 ± 3745.2	19785.8 ± 26710.7	< 0.001
GRACE score					< 0.001
Inhospital	111.6 ± 21.1	127.4 ± 17.0	166.9 ± 21.0	195.7 ± 31.6	< 0.001
6-month	92.7 ± 19.2	110.9 ± 15.6	138.0 ± 17.1	161.91 ± 23.2	
CRUSADE score	27.9 ± 12.9	49.0 ± 9.5	32.73 ± 9.8	50.9 ± 14.5	< 0.001
LVEF < 40%[b] [3,4]	10 (5.8)	8 (15.1)	35 (20.8)	61 (35.5)	< 0.001
Myocardial revascularization	96 (55.5)	25 (47.2)	75 (44.6)	46 (26.7)	< 0.001
Percutaneous coronary revascularization	83 (48.0)	21 (39.6)	69 (41.1)	39 (22.7)	< 0.001
Surgical coronary revascularization	13 (7.5)	4 (7.5)	6 (3.6)	7 (4.1)	0.062
Three-vessel coronary disease	14 (8.1)	4 (7.5)	13 (7.7)	24 (13.9)	0.061
Inhospital mortality	0 (0)	2 (3.8)	11 (6.5)	24 (14.0)	< 0.001
Follow-up mortality	5 (3.4)	7 (13.2)	25 (14.9)	64 (37.2)	< 0.001
Major bleeding	5 (2.9)	8 (15.1)	8 (4.8)	31 (18.0)	< 0.001
Reinfarction	12 (6.9)	6 (11.3)	23 (13.7)	35 (20.3)	< 0.001
Heart failure hospitalization	18 (10.4)	8 (15.1)	29 (17.3)	57 (33.1)	< 0.001

Data are number (%) or mean ± standard deviation. bpm: beats per minute; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide.
[a] Clearance of creatinine as per the modified diet in renal disease equation.
[b] Predischarge transthoracic echocardiogram.

Study endpoint analysis

The in-hospital mortality rate was 6.7% (*n* = 38) and 19.5% of patients (*n* = 103) died during follow-up. Patients who reached the primary endpoints were older and had several worse clinical and analytical findings, and higher GRACE and CRUSADE scores (Supplementary Table 2). Predictors of death in the univariate analysis are shown in Supplementary Table 3, showing myocardial revascularization (either percutaneous or surgical), which was associated with a lower risk of in-hospital mortality (hazard ratio [HR] 0.20, 95% confidence interval [CI] 0.11—0.34; *P* < 0.001) and follow-up mortality (HR 0.24, 95% CI 0.14—0.41; *P* < 0.001). Moreover, major bleeding was also related to follow-up mortality (HR 2.27, 95% CI 1.16—4.44; *P* = 0.015). In-hospital major bleeding occurred in 52 (9.2%) patients.

Subgroup analysis

The cohort was divided into four different subgroups, according to GRACE and/or CRUSADE high-risk categorization. Each group's baseline characteristics and outcomes are shown in Table 3.

The subgroups G1, G3 and G4 each included a similar number of cases. Patients' average age, admission Killip-Kimbal class and left ventricular systolic dysfunction increased across the four groups, with G3 (high-risk GRACE/low-risk CRUSADE) and G4 (high-risk GRACE/high-risk CRUSADE) showing the highest values. Admission systolic blood pressure was reduced and peak troponin I and N-terminal pro-brain natriuretic peptide values were higher in the groups with GRACE ≥ 141 (G3 and G4).

In those groups with higher CRUSADE scores, such as G2 (low-risk GRACE/high-risk CRUSADE) and G4, patients had lower haemoglobin and haematocrit and higher creatinine and admission glycaemia values.

The lowest-risk patients (G1) (low-risk GRACE/low-risk CRUSADE) were significantly more often revascularized than patients in higher-risk groups, especially compared with G4 (highest-risk group). In terms of revascularization strategy, the proportion of patients referred for percutaneous coronary intervention or surgery was balanced between groups (Table 3). Complex coronary disease (three-vessel disease) was more frequent in G4 and, simultaneously, fewer revascularization options (percutaneous or surgical) were considered suitable for the highest-risk group (G4). Follow-up reinfarction and heart failure hospitalization increasingly occurred throughout the risk subgroups (G1 to G4), with G4 showing the highest rates.

Overall, the subgroup analysis allowed the identification of a low-risk class (G1) and a high-risk class (G4) plus two intermediate-risk classes (G2 and G3). Although G1 and G2 included patients with GRACE < 141, G2 (CRUSADE ≥ 41) patients had a poorer outcome than those in G1 (CRUSADE < 41). Moreover, while both G3 and G4 comprised patients with GRACE ≥ 141, G4 (CRUSADE ≥ 41) had the worst prognosis.

Subgroup mortality analysis

Deaths in-hospital and during follow-up occurred more frequently in groups with high-risk GRACE values (≥ 141; G3 and G4). However, death was more commonly observed in G2 (GRACE < 141, CRUSADE ≥ 41) than in the lowest-risk category (G1).

The Kaplan–Meier analysis is shown in Fig. 1. The survival curve of G1 (low risk) separates early from the other subgroup curves. The G2 and G3 (intermediate risk) curves were similar during the average follow-up, displaying a much better survival course than those patients classified in G4 (high risk). Differences in survival between groups were sustained and cumulative throughout follow-up.

As previously mentioned, revascularization was associated with higher follow-up and in-hospital survival. In the subgroup analysis, revascularization impacted on survival only in the groups with GRACE > 140: G3 (in-hospital mortality, HR 0.23, 95% CI 0.03–2.07, $P = 0.15$; follow-up mortality, HR 0.20, 95% CI 0.07–0.59, $P = 0.002$); and G4 (in-hospital mortality, HR 0.42, 95% CI 0.11–0.63, $P = 0.003$; follow-up mortality, HR 0.35, 95% CI 0.16–0.75, $P = 0.006$).

The time-to-event model (Cox regression) revealed that the prognostic value of the CRUSADE score (HR 1.03, 95% CI 1.01–1.04; $P < 0.001$) was independent and additive to that

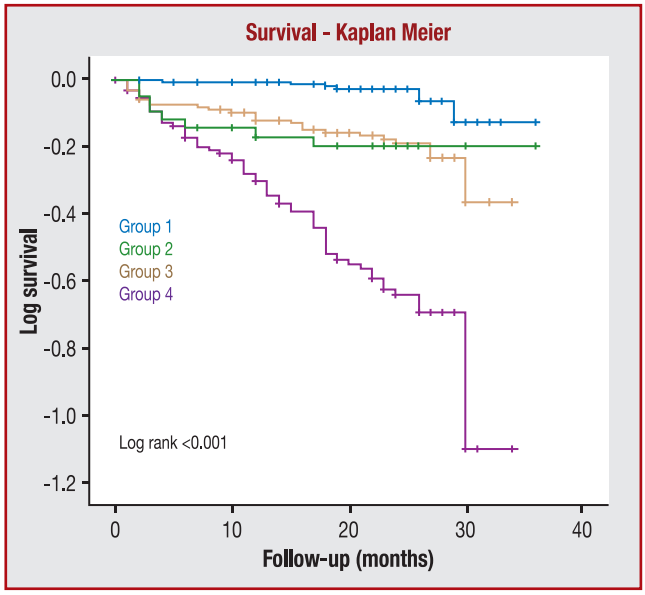

Figure 1. Survival analysis according to predefined subgroups.

of the $GRACE_{6M}$ score (HR 1.02, 95% CI 1.01–1.03; $P < 0.001$) for the prediction of mortality during follow-up.

The ROC curve comparison (Table 2) between GRACE (low-, intermediate- and high-risk categories), CRUSADE (low-, intermediate- and high-risk categories) and GRACE + CRUSADE combined (G1, G2, G3 and G4) showed that the combination had higher discriminatory performance for in-hospital and follow-up mortality prediction, although differences were not statistically significant ($P > 0.05$). However, IDI (Table 4) confirmed that GRACE + CRUSADE improved risk reclassification for both in-hospital and follow-up mortalities (GRACE + $CRUSADE_{IH}$, relative IDI 17.1%; GRACE + $CRUSADE_{6M}$, relative IDI 11.5%).

Subgroup bleeding analysis

Major bleeding rate was increased in the subgroups with a high-risk CRUSADE category (G2, G4). In the groups with a low-risk CRUSADE score (G1 and G3), bleeding was significantly more frequent in patients with GRACE ≥ 141 (G3) than in patients with GRACE < 141 (G1). Moreover, major bleeding risk was 4.5 times lower in G1 than in the other subgroups (HR [G2–G4] 4.5, 95% CI 1.8–11.7; $P = 0.001$), establishing G1 as a very low bleeding risk. Additionally, patients in G4 had a very high risk of major bleeding (HR 3.5, 95% CI 2.0–6.3; $P < 0.001$) compared with the remaining subgroups, including G2, which already comprised patients with CRUSADE > 41 (high bleeding risk).

Discussion

The combined risk assessment with GRACE and CRUSADE models improved the overall risk stratification provided by each score individually in the NSTEMI setting. This combined evaluation enabled the distinction of a very–low-risk group (GRACE < 141, CRUSADE < 41) and a very–high-risk group (GRACE ≥ 141, CRUSADE ≥ 41) from the other cases with an intermediate-risk pattern (presence of either GRACE or

Table 4 Integrated discrimination improvement comparing GRACE + CRUSADE model with GRACE and CRUSADE risk categories.

	$GRACE + CRUSADE_{IH}$	$GRACE_{IH}$	$GRACE + CRUSADE_{6M}$	$GRACE_{6M}$
Average of estimated probabilities of an event	0.119	0.103	0.350	0.327
Average of estimated probabilities of a non-event	0.064	0.065	0.173	0.181
Cross-tabulation for IDI and relative IDI calculation				
GRACE + CRUSADE	IDI, 0.017; relative IDI, 17.07%		IDI, 0.031; relative IDI, 11.45%	

$GRACE_{6M}$: 6-month postdischarge mortality; $GRACE_{IH}$: in-hospital mortality; $GRACE + CRUSADE_{6M}$: follow-up mortality; $GRACE + CRUSADE_{IH}$: in-hospital mortality; IDI: integrated discrimination improvement.

CRUSADE high-risk classes). CRUSADE significantly enhanced the prognostic performance of the GRACE score.

There is considerable variability in patient characteristics and outcomes across the ACS spectrum, and a systematic assessment of the probability of adverse events by quantitative risk models can help to guide treatment strategies. Although several ACS risk prediction tools have been proposed in recent years, the most robust ones for evaluating ischaemic and bleeding risk are the GRACE and CRUSADE scores, respectively [1,2]. These risk algorithms are recommended by contemporary guidelines and have been incorporated into clinical practice with potential improvements in decision-making. However, some concerns have also been raised concerning the 'treatment—risk' paradox in current international practice [14], in which higher-risk patients are less likely to receive more aggressive treatment than lower-risk cases. Notwithstanding, the early versus delayed timing of intervention in patients with acute coronary syndromes (TIMACS) trial [11,15] showed early coronary angiography to be advantageous in patients with GRACE > 140, similar to what was observed for ST-segment elevation myocardial infarction in each GRACE category [16]. However, there are no other studies evaluating the impact of ACS risk scores in other treatment modalities, such as antithrombotic or anticoagulation therapies.

Major bleeding is one of the most common serious adverse events in patients admitted with an ACS [4]. In this clinical setting, there is a strong relationship between bleeding and mortality, even when the haemorrhage is not considered to be severe. Major bleeding is associated with a 60% increase in hospital death [17] and a fivefold increase in 1-year mortality [7]. The bleeding-mortality interaction seems to be attributable to more than the specific bleeding episode. A significant haemorrhage may lead to complete cessation of antithrombotic therapy and potential ischaemic recurrences. Moreover, the advancing ACS therapies are increasingly offered to higher-risk patients (e.g. the elderly, those with co-morbidities) who also have an increased risk of bleeding complications. Therefore, ACS risk stratification needs to be reliable in outlining the patient's risk profile. We believe that ischaemic and bleeding risks should be evaluated simultaneously. Bleeding has an impact beyond the index event and ACS management is much more than total ischaemic burden. Besides, ischaemia and bleeding share overlapping risk factors (e.g. older age, diabetes, renal dysfunction), and it is not uncommon to find an ACS patient who is at high risk of death/ischaemic recurrences and is simultaneously at increased risk of dismal bleeding complications. In our cohort, we found concordance between GRACE and CRUSADE risk categories in approximately 50% of cases, with nearly one-third of patients presenting concurrent GRACE and CRUSADE high-risk categories. Patient management in these cases is challenging and we ought to understand more about ACS risk profiles and related outcomes.

We assessed the strength of the combined evaluation by GRACE and CRUSADE models using a cut-off (GRACE $\geq$ 141) related to the optimal revascularization timing in NSTEMI and the high-risk bleeding category (CRUSADE $\geq$ 41). Through these division criteria, which are easily obtainable, we sought to define four different NSTEMI risk profiles: low ischaemic and bleeding risk patients (GRACE < 141; CRUSADE < 41); high ischaemic and bleeding risk cases (GRACE $\geq$ 141; CRUSADE $\geq$ 41); and to identify significant differences between the intermediate-risk profiles (GRACE < 141; CRUSADE $\geq$ 41/GRACE $\geq$ 141; CRUSADE < 41) and the former subgroups. Our results suggest that these subgroups are very different from each other in terms of patient characteristics and outcomes. Several clinical variables, such as admission Killip-Kimbal class and left ventricle systolic dysfunction, and outcomes deteriorated significantly throughout the subgroups (G1 to G4). Patients with GRACE $\geq$ 141 were expected to have a poorer outcome. However, those with a GRACE score < 141 but with a high-risk CRUSADE score had a worse prognosis than patients in the G1 group (lowest-risk group). Similarly, patients in G3 (high-risk GRACE class) did not have a worse clinical picture than that observed in G4 (highest-risk group).

The CRUSADE model increased the discriminatory performance of GRACE in the prediction of all-cause mortality, ascertained by a time-to-event model (Cox regression), showing CRUSADE to have an independent and additive predictive value that is sustained throughout follow-up. This improved performance of the GRACE + CRUSADE model was demonstrated by survival curves (Fig. 1) that clearly differentiate three strata (G1, lowest-risk curve; G2 and G3, intermediate-risk curve; G4, highest-risk curve). The GRACE + CRUSADE prognostic performance was measured using ROC analysis, establishing a higher

combined risk model AUC (GRACE + CRUSADE$_{IH}$, AUC 0.76; GRACE + CRUSADE$_{6M}$, AUC 0.78) than GRACE categories (GRACE$_{IH}$, AUC 0.70; GRACE$_{6M}$, AUC 0.74) for both in-hospital and follow-up mortalities, although the difference was not statistically significant. As AUC cannot always measure a clinically meaningful improvement in reclassification, an extended statistical evaluation with IDI documented a successfully improvement in reclassification, strongly suggesting that the combined risk model would be clinically valuable.

Myocardial revascularization was associated with follow-up and in-hospital survival advantage. In the subgroup analysis, revascularization benefits were only evident in those with GRACE > 140, mostly G4 (highest-risk patients). Yet, the higher rate of revascularization was seen in the lowest risk group (G1) ('treatment—risk' paradox). Our results seemed to indicate that cases of lower ischaemic risk and high bleeding hazard (G3) might be better managed with a more conservative revascularization approach.

Another key section of this study was to assess the strength of GRACE + CRUSADE in major bleeding prediction and to determine whether the combined risk assessment is of greater value than CRUSADE evaluation only. As expected, G2 and G4 (CRUSADE $\geq$ 41) had a higher rate of bleeding. Notwithstanding, the addition of the GRACE algorithm made it possible to differentiate bleeding risk profiles: G3 had higher bleeding rates than G1 (although both had CRUSADE < 41) and the G4 subgroup had an increased bleeding hazard compared with G2 (Table 3). Remarkably, patients in G4 had bleeding risk that was 3.5 times higher than all remaining groups.

Currently, ACS guidelines do not advise on tailoring medical treatment in NSTEMI, assuming that all ischaemic cases will derive similar and potential benefit from several treatment modalities (i.e. anticoagulation and newer antiplatelet regimens), unless contraindicated. Nevertheless, this four-group approach may potentially alter a patient's usual management regarding preload doses or other treatment options, to ensure that they gain most advantage from them. In the future, it might be suitable to use a more conservative management strategy for patients with low ischaemic burden (e.g. no preloading dose or weaker antiplatelet regimens [clopidogrel versus ticagrelor/prasugrel]). Nevertheless, as previously discussed, G2 did not behave like a low-risk group, showing a worse ischaemic prognosis compared with G1 (although both had GRACE < 141), and could possibly benefit more from antithrombotic therapies and preloading. Moreover, concerning the groups at highest ischaemic risk (G3 and G4), one should focus on the bleeding risk. G4 had the higher incidence of bleeding events as well as the worst long-term prognosis. Because bleeding is strongly associated with mortality and as bleeding events occur early in the course of myocardial infarction, it would be appropriate to refrain from giving preloading doses or combined antiplatelet therapies or stronger anticoagulation regimens to these patients. Presently, we do not fully understand the heterogeneous group of NSTEMI or its best management, and upcoming ACS recommendations need to address the possibility of patient-tailored therapy, regarding the specificities of each risk group and the aetiological nature of the myocardial infarction.

In our view, this study increased comprehension of the ACS risk profiles, their characteristics and, more importantly, their outcomes. They study supports the concept that ACS patients should be seen as a whole and that bleeding should be prevented intensely due to its huge prognostic impact. Importantly, combined assessment with GRACE + CRUSADE significantly improved the discriminatory power of both GRACE and CRUSADE when used separately. Without new risk assessment tools, this combined and practical approach might be a step forward in the future management of NSTEMI.

Study limitations

This was a single-centre case-control study, which was retrospective in nature, with a small-to-moderate sample size. Because patient inclusion began in 2006, this study sample may not represent the state of the art in ACS management, as it has changed importantly in the past decade regarding medical treatment and revascularization procedures. Moreover, the relatively small number of patients included in some groups (e.g. G2, $n = 53$) may have limited interpretation of results. Nonetheless, it is our impression that larger groups, such as in the case of G2, would rather enhance those differences found, such as those concerning haemorrhagic events. Another limitation of this study was the use of risk models that shared overlapping risk variables (e.g. heart rate, systolic blood pressure, Killip-Kimbal class, creatinine clearance [Supplementary Table 4]), which could have led to a redundant clinical assessment.

Although this study attempts to improve myocardial infarction risk stratification with a highly practical component, it cannot be extrapolated to other populations. Our results warrant further validation in larger and independent cohorts before drawing any definite clinical applicability from these data.

Conclusions

A combined risk stratification strategy with both the GRACE and CRUSADE models enables a more accurate prediction of all-cause mortality and bleeding risk in patients with NSTEMI. The two scores complement each other in the prognostication of these patients, potentially allowing more accurate identification of patients who will benefit from more aggressive therapies and those who are suited to a more conservative approach.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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and interpretation. The authors revised the article drafts and approved the final version.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.acvd.2014.06.008.

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