Comparing the predictive validity of three contemporary bleeding risk scores in acute coronary syndrome

European Heart Journal: Acute Cardiovascular Care
1(3) 222–231

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DOI: 10.1177/2048872612453924

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Abstract

Aims: Haemorrhagic complications are strongly linked with adverse outcomes in acute coronary syndrome (ACS) patients. Various risk scores (RS) are available to predict bleeding risk in these patients. We compared the performance of three contemporary bleeding RS in ACS.

Methods: We studied 4500 consecutive patients with ACS. We calculated the ACTION, CRUSADE, and Mehran et al. (2010) bleeding RS, and evaluated their performance for predicting their own major bleeding events and TIMI serious (major or minor) bleeding episodes, in patients with either non-ST-elevation ACS (NSTEMACS) or ST-elevation myocardial infarction (STEMI). Calibration (Hosmer–Lemeshow test, HL) and discrimination (*c*-statistic) for the three RS were computed and compared.

Results: For RS-specific major bleeding, ACTION and CRUSADE showed the best prognostic discrimination in STEMI (*c*=0.734 and 0.791, respectively; *p*=0.04), and in NSTEMACS (*c*=0.791 and 0.810; *p*=0.4); being CRUSADE significantly superior to Mehran et al. in both ACS types (*p*<0.05). All RS performed well in patients undergoing coronary arteriography using either a radial or femoral approach (all *c*≥0.718); however, their discriminative capacity was modest in patients not undergoing coronary arteriography and in those previously on oral anticoagulant (all *c*<0.70). For TIMI serious bleeding, ACTION and CRUSADE displayed the highest *c*-index values in both STEMI (0.724 and 0.703, respectively; *p*=0.3) and NSTEMACS (*c*=0.733 and 0.744, respectively; *p*=0.6); however, calibration of ACTION was poor in both ACS types (HL *p*<0.05).

Conclusions: Of contemporary bleeding RS, the CRUSADE score was found to be the most accurate quantitative tool for NSTEMACS and STEMI patients undergoing coronary arteriography.

Keywords

Acute coronary syndrome, haemorrhage, risk score

Received: 3 June 2012; accepted: 15 June 2012

Introduction

In patients with acute coronary syndromes [ACS; ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTEMACS)], bleeding complications have been associated with an increased risk of subsequent serious adverse outcomes.^{1–8} Similarly to ischaemic risk, risk of bleeding is not homogeneous, and

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various predictive models have been developed to stratify bleeding risk in ACS patients.^{4–8} Contemporary bleeding risk scores (RS) in the setting of ACS comprise: CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines),⁶ ACTION (Acute Coronary Treatment and Intervention Outcomes Network),⁷ and that derived by Mehran et al. from the combined dataset of ACUITY/HORIZONS-AMI trials.⁸ While many clinical variables overlap among all these RS, the CRUSADE model was developed to help clinicians estimate a patient's baseline risk of in-hospital major bleeding during NSTEMI,⁶ whereas the ACTION and Mehran et al. models were derived from NSTEMI and STEMI patients,^{7,8} and thus offer quantitative tools for assessing bleeding risk in a broader spectrum of patients.

In the ACS scenario, there is a current consensus about the need for bleeding risk stratification,^{9,10} but it is not clear which of the available bleeding RS provides the best option as a complementary clinical tool in bleeding risk assessment.

We therefore investigated the performance of the CRUSADE, ACTION, and Mehran et al. scores, aiming to obtain evidence of which provides the most accurate and reliable quantitative clinical tool for predicting haemorrhagic complications in ACS patients.

Methods

Patient population

This was a retrospective study in which the study subjects were all patients admitted consecutively between January 2004 and December 2010 to the cardiology department of our institution and having a final diagnosis of ACS. The demographic, clinical, and angiographic data, as well as those relating to management and in-hospital complications, were collected prospectively and recorded on a computer database for ACS patients admitted to our institution. Data were gathered by the department's cardiologists in the hospitalization ward and coronary care unit. Diagnosis of ACS was therefore validated if the patient had new onset symptoms consistent with cardiac ischaemia and at least one of the following: cardiac biomarkers above the higher normal laboratory limit, electrocardiogram changes consistent with ACS, in-hospital stress testing showing ischaemia, or documented history of coronary vessel disease. Patients were classified as having STEMI or NSTEMI (unstable angina and NSTEMI). The diagnosis of unstable angina required the presence of suggestive symptoms together with objective evidence of myocardial ischaemia on stress testing or detection of a culprit lesion of $\geq 50\%$ on coronary angiography, in addition to cardiac biomarkers below the higher normal laboratory limit.

The initial cohort of the present study comprised 4729 patients. Patients whose ACS was precipitated in the context

of surgery, sepsis, trauma, or cocaine consumption ($n=61$) were excluded. Furthermore, 105 patients were excluded due to missing data for some variable in the RS (including 19 patients with missing data regarding bleeding events). Finally, we excluded patients who died within 24 hours of hospital admission ($n=63$), due to their not having sufficient time to develop bleeding. Thus, 4500 patients constituted the final study cohort. The study was approved by the Clinical Research Ethics Committee of our institution.

End points and definitions

Our primary end point focused on the predictive accuracy of the three contemporary RS available for classifying the risk of bleeding in ACS patients. Only haemorrhagic events that occurred during hospitalization but before cardiac surgery were taken into account. For bleeding patients, source documentation was available and it was re-evaluated. We had information on localization, imaging tests, admission and nadir haemoglobin/haematocrit levels, and blood transfusion. The lowest haemoglobin and haematocrit values, and the white blood cell count at admission, were collected retrospectively from the central laboratory database of our centre. In 19 patients, bleeding events could not be adjudicated (mainly due to missing values on admission and/or nadir haemoglobin/haematocrit levels). These patients were excluded jointly with the 86 patients with missing data to calculate the RS. In the 105 excluded patients, secondary analyses were performed to assess the impact of missing data on the results.

Bleeding episodes were assessed in line with bleeding criteria used in ACTION,⁷ CRUSADE,⁸ and Mehran et al. scores⁹ (Supplementary Table 1). Because each of these definitions is a composite of several events of different clinical relevance, we also used the TIMI (Thrombolysis In Myocardial Infarction) bleeding definition¹¹ as a 'gold standard' to compare the predictive ability of all scores. TIMI major bleeding was defined as intracranial haemorrhage, fatal bleeding (bleeding that directly results in death within 7 days), or clinically overt bleeding (including on imaging) associated with a drop in haemoglobin of ≥ 5 g/dl. The diagnosis of intracranial bleeding required confirmation by computed tomography or magnetic resonance imaging of the head. TIMI minor bleeding was defined as any clinically overt bleeding (including on imaging), resulting in haemoglobin drop of 3–5 g/dl. In this study, TIMI serious bleeding was defined as TIMI major or TIMI minor bleeding.

Statistical analysis

Continuous variables are presented as the median (25th and 75th percentiles) and categorical variables are presented as counts (%) and were compared by the χ^2 test of Fisher Exact test, as appropriate.

Table 1. Clinical characteristics and in-hospital management of study population

	Population (n=4500)
Age (years)	69 (58–77)
Female	1275 (28.3)
Weight (kg)	76 (68–85)
Past medical history	
Diabetes	1232 (27.4)
Peripheral arteriopathy	435 (9.7)
Stroke	306 (6.8)
Prior myocardial infarction	1017 (22.6)
Prior congestive heart failure	216 (4.8)
Prior percutaneous coronary intervention	513 (11.4)
Prior coronary artery bypass grafting	234 (5.2)
On dialysis	41 (0.9)
Home medication	
Aspirin	1224 (27.2)
Thienopyridine	616 (13.7)
Oral anticoagulant	285 (6.3)
On-admission data	
ST-elevation myocardial infarction	1476 (32.8)
Non-ST-elevation acute coronary syndrome	3024 (67.2)
Killip class	
I	3632 (80.7)
II	554 (12.3)
III	173 (3.8)
IV	141 (3.1)
Heart rate (beat/min)	75 (64–89)
Systolic blood pressure (mmHg)	135 (120–152)
Troponin I raised at presentation (≥ 0.1 ng/dl)	2854 (63.4)
Haemoglobin (g/dl)	14.1 (12.9–15.1)
Haematocrit	40.8 (37.7–43.7)
Anaemia	843 (18.8)
Serum creatinine (mg/dl)	1 (0.80–1.20)
Creatinine clearance (ml/min)	77.5 (56.5–100.8)
Leucocyte (giga/l)	9.2 (7.3–11.8)
In-hospital management	
Aspirin	4294 (95.4)
Thienopyridine	3676 (81.7)
Heparin	4292 (95.4)
Fondaparinux	70 (1.6)
Bivalirudin	120 (2.7)
Glycoprotein IIb/IIIa inhibitors	1810 (40.2)
Coronary arteriography	3985 (88.6)
Vascular access site	
Radial	3313 (83.1)
Femoral	672 (16.9)
Percutaneous coronary intervention	2862 (63.6)
Thrombolysis	97 (2.2)
Coronary artery bypass grafting	221 (4.9)

Values are n (%) or median (interquartile range).

Risk score calculation and categorization. RS were calculated in each patient from the corresponding prognostic variables scores (Supplementary Table 2). Both CRUSADE and ACTION RS were constructed to assign patient into five risk strata (very low, low, moderate, high, and very high risk), whereas the Mehran's score categorize patients into four risk groups (low, moderate, high, and very high). For our study, patients were categorized into three bleeding risk strata for all scores by considering the very high and high risk categories as a unique category (high risk) and the very low and low risk categories as a low-risk category.

Prognostic accuracy of the risk scores. Discrimination and calibration were evaluated for each of the three scores for the prediction of its own major bleeding events and, in a separate analysis, for the prediction of TIMI serious bleeding. Discrimination, a measure of how well the model can separate cases from controls,¹² was evaluated by receiver operating characteristics curves and expressed by the *c*-statistic. The discriminatory abilities of the three RS for TIMI serious bleeding were computed and compared according to the non-parametric method described by DeLong.¹³ Calibration, a measure of the agreement between observed and predicted outcomes, was assessed using the Hosmer–Lemeshow goodness-of-fit test.¹⁴ A significant *p*-value indicates a lack of fit.

Missing data management. Risk scores could not be calculated in 105 (2.3%) patients. The main reason was the lack of records of heart rate at admission. 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 (Supplementary Table 5).

Sensitivity analysis. Finally, a sensitivity analysis was conducted after including patients who had died within 24 hours of admission, in order to evaluate overall performance of each RS in predicting TIMI bleeding events. For all analyses, a 2-sided *p* < 0.05 was considered statistically significant. All data were processed using the SPSS 17.0 (Chicago, Illinois, USA) and MedCalc software (Mariakerke, Belgium).

Results

Baseline patient characteristics are summarized in Table 1. Almost 60% presented with NSTEMI (16.3% [n=734]) had unstable angina. The majority of patients underwent coronary arteriography (88.6%), and the vascular access site was usually radial (83.1%).

Table 2. Calibration and discrimination for the three risk scores for the prediction of their own major bleeding events in different risk groups

Risk score	Risk group	n	Observed	Predicted	HL		c-statistic (95% CI)
					χ^2	p	
ACTION	Overall	4500	8.7 (7.9–9.6)	7.9 (7.1–8.7)	11	0.2	0.783 (0.758–0.808)
	STEMI	1476	11.7 (10.1–13.3)	10.2 (8.7–11.9)	8.7	0.3	0.734 (0.692–0.776)
	NSTEACS*	3024	7.2 (6.3–8.2)	6.6 (5.8–7.6)	8.7	0.4	0.791 (0.763–0.820)
	Cardiac catheterization						
	Yes	3985	8.4 (7.6–9.3)	8.3 (7.5–9.2)	10	0.3	0.788 (0.763–0.812)
	No	515	11.1 (8.6–14.2)	9.9 (7.5–12.9)	4	0.9	0.666 (0.593–0.738)
	Vascular access site						
	Radial	3313	6.2 (5.4–7.1)	5.8 (5.1–6.7)	7	0.5	0.789 (0.755–0.822)
	Femoral	672	16.2 (13.6–19.3)	13.1 (10.7–15.9)	13	0.1	0.764 (0.710–0.818)
	Home oral anticoagulant						
	Yes	285	10.2 (7.0–14.4)	9.1 (6.1–13.2)	12	0.2	0.676 (0.592–0.760)
	No	4215	8.7 (7.8–9.5)	7.8 (7.0–8.7)	11	0.2	0.781 (0.757–0.805)
	Thrombolysis						
	Yes	97	10.3 (5.3–18.6)	9.3 (4.6–17.3)	6	0.4	0.768 (0.741–0.799)
	No	4403	8.7 (7.8–9.5)	7.9 (7.1–8.7)	9	0.6	0.779 (0.755–0.802)
CRUSADE	Overall	4500	8.1 (7.4–9.0)	7.5 (6.7–8.3)	7	0.5	0.800 (0.778–0.822)
	STEMI	1476	11.0 (9.5–12.7)	9.8 (8.3–11.4)	9	0.11	0.791 (0.757–0.825)
	NSTEACS*	3024	6.7 (5.9–7.7)	6.3 (5.5–7.2)	13	0.4	0.810 (0.782–0.838)
	Cardiac catheterization						
	Yes	3985	7.9 (7.1–8.8)	7.3 (6.5–8.1)	5	0.8	0.823 (0.800–0.846)
	No	515	9.9 (7.5–12.9)	8.9 (6.7–11.8)	6	0.7	0.628 (0.547–0.708)
	Vascular access site						
	Yes	3313	6.3 (5.5–7.2)	5.9 (5.1–6.8)	7	0.6	0.830 (0.802–0.858)
	No	672	15.9 (13.3–19.0)	13.2 (10.8–16.1)	8	0.5	0.774 (0.731–0.818)
	Home oral anticoagulant						
	Yes	285	9.1 (6.2–13.2)	8.4 (5.6–12.4)		0.4	0.615 (0.517–0.714)
	No	4215	8.1 (7.3–8.9)	7.4 (6.6–8.2)	8	0.5	0.810 (0.788–0.833)
	Thrombolysis						
	Yes	97	9.3 (4.6–17.3)	8.2 (3.9–16.1)	7	0.5	0.840 (0.725–0.954)
	No	4403	8.1 (7.3–9.0)	7.4 (6.7–8.3)	6	0.6	0.800 (0.778–0.822)
Mehran et al.	Overall	4500	10.3 (9.4–11.2)	9.2 (8.4–10.1)	10	0.3	0.748 (0.725–0.772)
	STEMI	1476	13.7 (12.0–15.6)	11.8 (10.2–13.6)	4	0.8	0.731 (0.693–0.769)
	NSTEACS*	3024	8.7 (7.7–9.7)	7.9 (7.0–8.9)	7	0.5	0.750 (0.719–0.780)
	Cardiac catheterization						
	Yes	3985	10.1 (9.1–11.0)	9.1 (8.2–10.0)	8	0.4	0.757 (0.732–0.782)
	No	515	12.2 (9.6–15.4)	10.7 (8.2–13.7)	14	0.07	0.675 (0.607–0.742)
	Vascular access site						
	Yes	3313	8.1 (7.2–9.1)	7.5 (6.7–8.5)	5	0.7	0.765 (0.734–0.795)
	No	672	19.9 (17.0–23.2)	16.2 (13.6–19.3)	8	0.5	0.718 (0.671–0.766)
	Home oral anticoagulant						
	Yes	285	13.3 (9.7–18.0)	11.6 (8.2–16.0)	7	0.5	0.644 (0.547–0.741)
	No	4215	10.1 (9.2–11.1)	9.1 (8.2–10.0)	10	0.2	0.753 (0.729–0.777)
	Thrombolysis						
	Yes	97	11.3 (6.1–19.8)	10.3 (5.3–18.6)	8	0.4	0.752 (0.607–0.897)
	No	4403	10.3 (9.4–11.2)	9.2 (8.4–10.1)	10	0.3	0.749 (0.725–0.772)

HL, Hosmer–Lemeshow test; NSTEACS, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation acute myocardial infarction. *The discriminatory power of the three risk scores according to the type of NSTEACS (unstable angina or non-STEMI patients) are shown in Supplementary Table 4.

Figure 1. Distribution of ACTION, CRUSADE, and Mehran et al. major bleeding rates with regard to risk categories overall and by type of acute coronary syndrome

**p*-values for comparisons across the different risk categories of each score. NSTEMI, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction.

Major bleeding rates

Major bleeding rates, according to ACTION and CRUSADE definitions, were 8.7% and 8.1%, respectively. In contrast, 10.3% experienced major bleeding as defined by the Mehran et al. score. Few patients received thrombolysis (2.2%) and coronary artery bypass grafting (4.9%). The rates of individual criteria of the bleeding definitions used in each RS are represented in Supplementary Table 3 – only a third of bleeding events were classed as having been at a vascular access site; most originated from gastrointestinal, genitourinary, or other sites.

Comparative performance of scoring systems using RS-specific major bleeding definitions

The observed bleeding rates in all RS increased monotonically from low- to high-risk categories. Overall and in terms of ACS subgroups, the lowest bleeding rates observed in patients classified as low risk corresponded to CRUSADE (Figure 1).

Table 2 shows the performance of each RS in predicting its own major bleeding events, in the entire sample and by different risk groups. In the whole population, CRUSADE and ACTION had the highest *c*-index values (*c*=0.800 and 0.783, respectively; *p*=0.30), which were both significantly higher than that obtained with the Mehran et al. score (*c*=0.748; *p*=0.001 when compared with CRUSADE and ACTION).

In STEMI patients, CRUSADE (*c*=0.791) significantly outperformed the other RS (*p*=0.035 and 0.008, compared with ACTION and Mehran et al. RS, respectively). In NSTEMI/ACS patients, the highest *c*-index values corresponded to CRUSADE (*c*=0.810), followed by ACTION (*c*=0.791; *p*=0.4). A significant difference was only

observed when comparing CRUSADE with Mehran et al. RS (*c*=0.749; *p*=0.01); in contrast, comparing ACTION with Mehran et al. score showed no significant difference (*p*=0.09).

All RS performed well in patients undergoing coronary arteriography, but CRUSADE (*c*=0.823) and ACTION (*c*=0.788) performed better than the Mehran et al. model (*c*=0.757). However, the only significant difference was between CRUSADE and Mehran et al. scores (*p*=0.002). Similarly, all scores performed well in patients undergoing coronary arteriography using either a radial or femoral approach. However, discrimination of the three RS was modest in patients who did not undergo coronary arteriography and in those patients previously on oral anticoagulant (all *c*<0.70; *p*>0.30 for comparisons of *c*-index values).

Comparative performance of RS using TIMI serious bleeding as a comparator

TIMI serious bleeding rate was 4.4% overall (6% and 3.5% for STEMI and NSTEMI/ACS, respectively). As shown in Figure 2, the distribution of the TIMI serious bleeding rates in the different risk groups showed a consistent gradient of risk for each of the three RS. Overall and in both ACS, the lowest TIMI serious bleeding rates observed in patients classified as low risk corresponded to the CRUSADE system.

In Table 3, the *c*-index values of the three scores are represented and compared. Overall, the highest *c*-index values were found in CRUSADE and ACTION (*c*=0.734 and 0.728, respectively), and the lowest in the Mehran et al. model (*c*=0.689). In STEMI patients, there were no significant differences in the discriminatory power of each RS, but the highest *c*-index values were observed with

Figure 2. Distribution of TIMI serious bleeding rates with respect to risk categories for ACTION, CRUSADE, and Mehran et al. bleeding risk scores, in the overall population and by type of acute coronary syndrome

**p*-values for comparisons across the different risk categories of each score. NSTEMI, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction.

Table 3. Comparison of the discriminative power of the three risk scores for predicting TIMI serious bleeding

Risk score	c-statistic (95% CI)	Risk scores	p-value
Overall (n=4500)			
CRUSADE	0.734 (0.721–0.747)	CRUSADE vs. ACTION	0.67
ACTION	0.728 (0.721–0.747)	CRUSADE vs. Mehran et al.	0.02
Mehran et al.	0.689 (0.675–0.702)	ACTION vs. Mehran et al.	0.03
STEMI (n=1476)			
CRUSADE	0.724 (0.700–0.747)	CRUSADE vs. ACTION	0.31
ACTION	0.703 (0.679–0.727)	CRUSADE vs. Mehran et al.	0.18
Mehran et al.	0.688 (0.664–0.712)	ACTION vs. Mehran et al.	0.62
NSTEMI (n=3024)			
CRUSADE	0.744 (0.728–0.759)	CRUSADE vs. ACTION	0.6
ACTION	0.733 (0.717–0.749)	CRUSADE vs. Mehran et al.	0.002
Mehran et al.	0.671 (0.654–0.688)	ACTION vs. Mehran et al.	0.02

NSTEMI, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation acute myocardial infarction.

CRUSADE ($c=0.724$). In NSTEMI patients, however, CRUSADE and ACTION had c -index values of 0.744 and 0.733, respectively, each significantly higher than that of the Mehran et al. RS ($c=0.671$; $p<0.05$).

Calibration of observed against predicted TIMI serious bleeding was acceptable for each of the three RS in the total cohort (all Hosmer–Lemeshow p -values >0.2 ; Supplementary Figure 1). However, in terms of ACS subgroups, only CRUSADE provided good calibration, with the predicted probability approximating more closely the observed probability of TIMI serious bleeding than did the ACTION and Mehran et al. scores, as shown in Figure 3.

After repeating the analyses to include patients who died within 24 hours of hospitalization, the discriminative power of all scores for TIMI serious bleeding, in the population as a whole, remained almost unchanged, with c -indices of

0.730, 0.723, and 0.685 for CRUSADE, ACTION, and Mehran et al. scores, respectively.

Seventeen patients (0.38%) experienced intracranial haemorrhage. The rate of intracranial haemorrhage, as a component of each of the bleeding definitions used in this study, is shown in Supplementary Table 3. The discrimination capacity of ACTION, CRUSADE, and Mehran et al. scores, for predicting intracranial haemorrhage, was 0.697 (95% CI 0.684–0.711), 0.717 (95% CI 0.704–0.731), and 0.662 (95% CI 0.648–0.676), respectively (p -values for each pairwise comparison were ≥ 0.4).

The missing values of the RS 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 (Supplementary Table 5).

Figure 3. Comparing observed vs. predicted TIMI serious bleeding with ACTION, CRUSADE, and Mehran et al. risk scores in STEMI patients (A–C), and among those patients with NSTEMI (D–F). NSTEMI, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction.

Discussion

In the unselected and contemporary sample of ACS studied, ACTION, CRUSADE, and Mehran et al. bleeding RS performed well in the prediction of major bleeding as defined by each RS, although the greatest accuracy was obtained with the CRUSADE method. This was true not only for the population as a whole but also when considering STEMI and NSTEMI patients. In contrast, when using the neutral definition of TIMI serious bleeding, only

the CRUSADE model, followed by the ACTION score, was able to discriminate patients with and without bleeding events well; however, the ACTION model was poorly calibrated. In addition, the observed CRUSADE and TIMI bleeding rates in patients classified as low risk using the CRUSADE system were the lowest in both the overall patient population and in both ACS types, suggesting that the CRUSADE system has the ability to classify as low risk only patients who are truly at low risk, with few events in such patients.

In this study, all RS performed equally well with regard to vascular access site used for coronary arteriography. This is an important finding since all RS were originally developed in patient cohorts in whom the femoral approach was principally used, and none has previously been validated for the radial approach which is now recommended in both coronary angiography and percutaneous coronary intervention.^{9,10} In our study, only a third of bleeding events were classed as having been at a vascular access site; most originated from gastrointestinal, genitourinary, or other sites. Because bleeds at these sites would not be expected to be altered by the method of angiography, it is not surprising that the three RS have performed well regardless of the method of angiography.

However, all RS showed a modest discrimination capacity (all $c < 0.70$) in patients who did not undergo coronary arteriography as well as in those patients previously on oral anticoagulant.

The present study is the first to compare predictive value in the three contemporary bleeding RS, using an independent dataset of ACS patients. Previously, the CRUSADE model was shown to perform well in a cohort of patients with NSTEMI.¹⁵ However, the external validity of the CRUSADE score for STEMI had not previously been evaluated. Moreover, the comparative validity of CRUSADE with respect to the more recently developed ACTION and Mehran et al. bleeding RS was conspicuous by its absence.

The CRUSADE model is the preferred method for bleeding risk stratification which current European NSTEMI guidelines recommend to apply before initiating a management strategy.⁹ However, both of the more recently developed ACTION and Mehran et al. RS offer the advantage of providing quantitative tools for assessing bleeding risk in a broader spectrum of ACS patients with acceptable discriminative abilities as was shown in their validation cohorts ($c = 0.71$ and 0.74 for ACTION and Mehran et al., respectively). Because the CRUSADE score was developed in NSTEMI patients, with no data available for its performance in STEMI patients, it would have been difficult to convince a busy physician to use CRUSADE for NSTEMI patients while still using a different RS for STEMI patients. In our analysis, we found that the predictive ability of CRUSADE is not exclusively confined to NSTEMI patients. Recently, good stratification of bleeding risk in STEMI patients using the CRUSADE system has been also found by Kodakia et al.,¹⁶ which is not surprising given that all the clinical variables used in the CRUSADE model are also potent prognosticators of bleeding development in the STEMI scenario.^{7,8}

The relative performance of the different RS can be explained by their respective composition. Both CRUSADE and ACTION RS outperformed Mehran et al. in our study, which is not surprising given that, in addition to the clinical variables in the Mehran et al. model,⁸ CRUSADE and ACTION also include several other variables, such as heart

rate and systolic blood pressure at admission, history of vascular disease, diabetes mellitus, and heart failure at presentation.^{6,7} All these variables have been demonstrated to be independent predictors of in-hospital bleeding occurrence.^{1–10} Moreover, the CRUSADE and ACTION models are derived from ‘real-world’ population, in contrast to the more selected derivation population of the Mehran et al. model which might limit its generalizability. However, the differences in performance found in our study between the CRUSADE and ACTION scores might be attributable to how specific variables are coded, combined, and weighted in each RS.

Each of the three scores performed modestly in patients who did not undergo cardiac catheterization. This finding may be attributable to the underrepresentation, in the derivation populations of the three scores, of the subgroup of patients managed medically (without cardiac catheterization). Similarly, none of the three RS performed well in the subgroup of patients on home oral anticoagulant. The CRUSADE and Mehran et al. models excluded patients previously on oral anticoagulant, and it is therefore not surprising that the two scores have not performed well in these patients. However, the modest discrimination of the ACTION score – which includes the variable ‘home oral anticoagulant use’ – could be explained, at least partly, due to the fact that bleeding complications in patients on home oral anticoagulant depend also largely on management patterns (antithrombotic agents and invasive procedures) used according to the patient’s INR (international normalized ratio) levels at admission, not only on receiving or not home oral anticoagulant therapy.

Clinical implications

In the current era of risk-tailored and personalized cardiovascular care, studies on prediction models have been proliferated leading to multiple, overlapping, and competing RS. Authorities on clinical prediction rules advocate independent testing before their general clinical application.^{17,18} This is important since models with insufficient accuracy increase the likelihood that patients’ bleeding risks may be misclassified being particularly problematic, in prognostic terms, if high-risk patients are presumed to be low risk and vice versa. The superiority that we found of CRUSADE over the other RS suggests that CRUSADE could be better at stratifying global baseline bleeding risk in contemporary patients with ACS. Notably, such stratification becomes especially important in patients at high bleeding risk who are often at highest risk of thrombotic complications and who hence need a more careful treatment approach to maximize the efficacy of therapy to reduce thrombotic risk while reducing bleeding risk. In this regard, CRUSADE could help clinicians to identify those patients at increased risk of haemorrhagic complications who would potentially benefit from the use of effective treatments with lower risk

of bleeding, e.g. low-dose acetylsalicylic acid, fondaparinux,¹⁹ and bivalirudin,²⁰ and from those strategies which have been shown to reduce the risk of bleeding, such as the use of the radial approach, and minimize the duration of the antithrombotic treatment exposure.²¹ Because bleeding is associated with substantial risk of mortality and morbidity,^{1–6} longer hospital stay,²² and increased economic costs,²³ all efforts should be made to reduce bleeding whenever possible. Although any score cannot replace the clinical evaluation, data from our study suggests that CRUSADE score represents an objective clinical tool which could lead to improvements in ACS care, including those with STEMI, by helping clinicians to make judicious treatment selections, prescribe appropriate doses of antithrombotic medications, and choose strategies that are most likely to reduce bleeding risk,^{19–21} thus optimizing patient-centred care and increasing the net clinical benefit.

Limitations

One limitation of this study is that which is inherent to retrospective studies. A further limitation of the study is its single-institution nature, as the management of patients is relatively homogenous which reduces the generalizability of our findings to populations with different therapeutic management patterns. Additionally, in this study the performance of the Mehran et al. score was assessed regarding in-hospital bleeding events while it was originally designed to predict 30-day bleeding. Finally, RS could not be calculated in 105 patients from our initial cohort, because of the absence of data for heart rate on admission. Although this fact could theoretically result in selection bias, missing data analysis showed that values were missing completely at random.

In conclusion, among patients hospitalized either for NSTEMI or STEMI who undergo coronary angiography, the CRUSADE bleeding risk index constitutes an accurate, robust, and well-calibrated risk-stratification tool for predicting haemorrhagic complications. However, the performance of the three existing bleeding RS in ACS is modest in patients managed medically as well as in those patients previously on oral anticoagulants.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

None declared.

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