ORIGINAL ARTICLE

Evaluation of the Orbit Bleeding Risk Score as Predictor of Major Bleeding in Patients with Acute Coronary Syndrome

Evaluación del Orbit Bleeding Risk Score como predictor de sangrado mayor en pacientes con síndrome coronario agudo

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ABSTRACT

Background: Major bleeding is the most important complication of antithrombotic treatment in acute coronary syndrome (ACS) and is associated with higher mortality. Assessing the risk of bleeding is a challenge. The usefulness of the Orbit Bleeding Score (ORBIT) to assess the risk of bleeding in ACS has been scarcely studied.
Objective: The aim of this study was to evaluate the ORBIT score as a predictor of major bleeding in patients hospitalized for ACS in whom anticoagulation is decided as part of the antithrombotic strategy.
Methods: Patients admitted to two coronary care units with diagnosis of ACS who received anticoagulation as part of the antithrombotic therapy were retrospectively included in the study. The CRUSADE, ACTION-GWTG and ORBIT scores were calculated using the admission clinical data. The primary endpoint was major bleeding, defined as BARC 3 or 5 classification.
Results: The study included 762 patients. Major bleeding occurred in 3.4% of cases. In the univariate analysis, the three scores were predictors of major bleeding, while in the multivariate analysis only the ORBIT score was an independent predictor of major bleeding (OR: 2.46, 95% CI 1.61-3.97, p <0.001). The area under the ROC curve was 0.70, 0.68 and 0.80 for the ACTION-GWTG, CRUSADE and ORBIT scores, respectively. The ORBIT score presented a higher area under the curve than the CRUSADE score (p=0.03) but without significant difference with the ACTION-GWTG score (p=0.06)
Conclusions: The ORBIT score was the only independent predictor of major bleeding, presenting a better discrimination capacity than the CRUSADE score and a tendency to better capacity than the ACTION-GWTG score.

Key words: Acute Coronary Syndrome - Risk Assessment - Hemorrhage

RESUMEN

Introducción: El sangrado mayor es la complicación más importante del tratamiento antitrombótico en el síndrome coronario agudo (SCA), y se asocia a mayor mortalidad. Evaluar el riesgo de sangrado es un desafío. La utilidad del *Orbit Bleeding score* (ORBIT) para evaluar el riesgo de sangrado en SCA ha sido poco estudiada.
Objetivo: Evaluar al ORBIT como predictor de sangrado mayor en pacientes internados por SCA en los que se decide la anticoagulación como parte de la estrategia antitrombótica.
Materiales y métodos: Se incluyeron en forma retrospectiva pacientes internados en dos unidades coronarias con diagnóstico de SCA que recibieron anticoagulación como parte de la terapia antitrombótica. A todos se les calcularon los *scores* CRUSADE, ACTION-GWTG y ORBIT con los datos clínicos del ingreso. Se analizo el punto primario de sangrado mayor, definido como una clasificación de BARC 3 o 5.
Resultados: Se incluyeron 762 pacientes. El sangrado mayor se presentó en el 3.4%. En el análisis univariado los tres *scores* fueron predictores de sangrado mayor, mientras que en el multivariado sólo el ORBIT fue predictor independiente de sangrado mayor, con OR 2,46, IC95% 1,61-3,97, p<0,001. El área bajo la curva ROC fue de 0,70, 0,68 y 0,80 para los *scores* ACTION-GWTG, CRUSADE y ORBIT, respectivamente. El ORBIT presento una mayor área bajo la curva que el CRUSADE (p=0,03) sin diferencia significativa con el ACTION-GWTG (p=0,06)
Conclusiones: El ORBIT fue el único predictor independiente de sangrado mayor, con una mejor capacidad de discriminación que el CRUSADE, y tendencia a mejor capacidad que el ACTION-GWTG.

Palabras clave: Síndrome coronario agudo - Hemorragia - Medición de Riesgo

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INTRODUCTION

Antithrombotic treatment is imperative in acute coronary syndromes (ACS), regardless of invasive management. Antiplatelet and anticoagulation therapies are a fundamental part of ACS management and their implementation has been shown to reduce morbidity and mortality in coronary heart disease. (1,2) Bleeding is the most important complication of this treatment, both due to its frequency and its clinical implications. Major bleeding is associated with an increased risk of mortality and other adverse events. (3,4) For this reason, different risk scores have been developed to predict major bleeding in patients with ACS. One of the most used scores is the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) (5), developed to predict bleeding in patients with non-ST-segment elevation ACS (NSTEACS). The Acute Coronary Treatment and Intervention Outcomes Network Registry-Get with the Guidelines (ACTION-GWTG) is another risk model developed from a cohort of patients with ACS with and without ST-segment elevation. (6) These scores have moderate predictive capacity and relative calculation complexity.

On the other hand, risk models initially developed to predict bleeding in patients with atrial fibrillation (AF) have also been evaluated in the context of ACS. HAS-BLED is the most widely used bleeding score in AF and has also been evaluated in ACS, where it has a similar predictive capacity as the CRUSADE score, with the advantage of being easier to calculate. (7, 8) The Outcomes Registry for Better Informed Treatment Bleeding risk score (ORBIT) is also a simple risk model developed to predict bleeding in patients with AF. (9) Recently, the National Institute of Health and Care Excellence (NICE) guidelines recommend this model to assess the risk of bleeding in AF due to its greater predictive capacity. (10) The usefulness of this risk model in ACS has been scarcely studied.

The objective of the present study was to evaluate the ORBIT score as a predictor of major bleeding in patients hospitalized for ACS in whom anticoagulation is decided as part of the antithrombotic strategy.

METHODS

An observational, retrospective study was carried out in two coronary care units in Buenos Aires, Argentina, including patients with a diagnosis of ACS hospitalized between January 2015 and January 2021. The inclusion criteria were as follows: patients with a diagnosis of NSTEACS, with use of anticoagulation as an antithrombotic strategy on admission (with low molecular weight heparin, sodium heparin or fondaparinux) and antiplatelet therapy with aspirin and/or P2Y12 receptor inhibitors. Patients who did not receive anticoagulation as antithrombotic treatment and those with insufficient data to calculate risk scores were excluded from the study

Medical histories were reviewed and background information, clinical admission data of interest to calculate scores and in-hospital evolution were collected.

Risk score calculation

The CRUSADE, (5) ACTION-GWTG (6) and ORBIT (9) risk scores were calculated based on the variables considered in the original publications. Due to the procedural protocol in both services where the study was carried out, the CRUSADE score is routinely calculated in all patients admitted with a diagnosis of ACS since 2014. Therefore, the value calculated on admission was considered for the analysis. The data was not found in 95 patients, so it was calculated retrospectively with the admission clinical data. The ACTION-GWTG and ORBIT scores were totally calculated retrospectively. The points for each variable were assigned, and the total score of each individual patient was calculated by adding the variable points corresponding to each score model.

The CRUSADE score (5) includes hematocrit (Hct), creatinine clearance (ClCr) measured by the Cockcroft-Gault formula, heart rate (HR), systolic blood pressure (SBP), female gender, presence of signs of heart failure on admission, history of previous vascular disease (peripheral arterial disease and/or stroke) and previous diagnosis of diabetes variables.

The ACTION-GWTG (6) includes age, HR, SBP, creatinine, hemoglobin (Hb), female gender, body weight, history of diabetes, peripheral artery disease, presence of ST-segment elevation or depression, signs of heart failure or shock on admission and prior treatment with warfarin variables. On this last point, we consider treatment with oral anticoagulation with either warfarin, acenocoumarol or non-vitamin K antagonist anticoagulants.

The ORBIT score (9) considers age >74 years, presence of Hb <12 g/dL in women or <13 g/dL in men, or Hct <40% in men or <36% in women, or history of anemia, previous history of bleeding (gastrointestinal, intracranial or hemorrhagic stroke), estimated glomerular filtration rate (eGFR) by the CKD-EPI formula <60 mL/min/1.73m^2 and prior use of antiplatelet agents.

Based on the original publications, the patients were classified into risk categories. In the case of the CRUSADE and ACTION-GWTG models, they were classified into five risk categories (very low, low, moderate, high and very high risk), while for the ORBIT three risk categories were considered (low, moderate and high risk).

Primary endpoint of major bleeding

To define the primary endpoint of in-hospital major bleeding, the Bleeding Academic Research Consortium Definition of Bleeding (BARC) classification was used. (11) BARC classification type 3 or 5 was considered major bleeding. Type 3 is divided into A (drop in Hb between 3 and 5 g/dL or need for transfusion), B (drop in Hb >5 g/dL or cardiac tamponade, or surgical requirement) and C (intracranial or retinal hemorrhage). Type 5 is fatal bleeding (probable, 5-A, or definite, 5-B). Bleeding in the context of cardiac surgery (type 4 of the BARC classification) was not considered.

Statistical analysis

Continuous variables with normal distribution are expressed as mean ± standard deviation (SD), or as median and interquartile range (IQR) in the case of non-normal distribution. Categorical variables are expressed as percentage.

Univariate analysis was performed by logistic regression using major bleeding as the dependent variable and each score as the independent variable. In a later stage, a multivariate analysis was performed exploring the three scores simultaneously in a logistic regression model. As previously mentioned, the scores were analyzed as continuous and cate-

gorical variables divided into the risk categories corresponding to each score.

In order to determine the discrimination power of the scores, ROC (receiver operating characteristic) curves were built to establish the area under the curve (AUC) with its corresponding 95% confidence interval (95% CI). The scores' AUC were compared using the chi-square test for homogeneity of areas. A p value <0.05 was considered significant. Statistix 7 and Epidat 3.1 softwares were used for the analysis.

Statistical analysis

Continuous variables are described as mean ± standard deviation or median and interquartile range according to their distribution, and categorical variables are expressed as numbers and percentages. For the biva.

RESULTS

A total of 890 patients were recruited, 53 of which were excluded for not having received anticoagulation and 75 for lack of data to calculate the scores; so 762 patients were finally included in the study. The admission diagnosis was NSTEACS in 580 patients (450 diagnosed with non-ST-segment elevation myocardial infarction and 130 with unstable angina) and ST-segment elevation ACS (STEACS) in 182 patients.

Mean age was 68±11 years, and 35% were women; the remaining population characteristics are shown in Table 1.

One hundred percent of patients received aspirin as antithrombotic treatment, and 96.3% (n=734) P2Y12 receptor inhibitors (clopidogrel in 85% of cases, ticagrelor in 13%, and prasugrel in 2%). All patients had anticoagulation with enoxaparin and 9.5% fibrinolytics (n=72); among the latter, 65 patients received rTPA and 7 streptokinase. Coronary angiography was performed during hospitalization in 89% of the patients, (n=685) and 69.9% underwent revascularization (n=533).

The major bleeding endpoint occurred in 3.4% of the patients (n=26), 20 of which were classified as BARC 3 A, 4 as BARC 3 B and 2 as BARC 3 C. No patient presented fatal bleeding.

The median CRUSADE score was 25 (IQR 15-36), for the ACTION-GWTW score it was 25 (IQR 20-29), and for the ORBIT score 1 (IQR 1-2). Table 2 shows the risk categories of each score and the rate of major bleeding according to each category. As shown in Table 3, in the univariate analysis, the three scores were predictors of major bleeding when analyzed as continuous variables: ACTION-GWTW (OR 1.12, CI 95% 1.02-1.19, p=0.001); CRUSADE (OR 1.06, CI 95% 1.03-1.08, p=0.01), and ORBIT (OR 2.56, CI 95% 1.81-3.36, p<0.01), while in the multivariate analysis, only the ORBIT score was an independent predictor of major bleeding (OR: 2.46, 95% CI 1.61-3.97, p<0.001). Table 4 presents the univariate and multivariate analysis considering the different risk categories.

The ACTION-GWTG score presented an AUC of 0.70 (95% CI 0.58-0.82), the CRUSADE score an AUC of 0.68 (95% CI 0.57-0.80) and the ORBIT score an AUC of 0.80 (95% CI 0.72-0.90). The ORBIT score presented higher AUC than the CRUSADE score (p=0.03) without significant differences with the ACTION-GWTG score (p=0.06) (Figure 1).

Table 1. Baseline population characteristics (n=762)

Variables	
Age (years)	68±11
Women, n (%)	269 (35.3)
History	
Hypertension, n (%)	587 (77)
Diabetes, n. (%)	220 (28.8)
Current smoking, n (%)	190 (24.9)
Dyslipidemia, n (%)	388 (50.9)
Previous PCI, n (%)	92 (12)
Previous CABG, n (%)	65 (8.5)
PAD, n (%)	70 (9.1)
Previous stroke, n (%)	31 (4)
History of bleeding, n (%)	7 (0.9)
VKA treatment, n (%)	34 (4.4)
Admission Data	
SBP – mmHg (mean ± SD)	142±27
HR – bpm (mean ± SD)	76±16
Weight – Kg (mean ± SD)	79±11
Hct - % (mean ± SD)	39 ±16
Hb mg/dL (mean ± SD)	13.8±2.6
Creatinine - mg/mL (median and IQR)	0.98 (0.78–1.11)
CrCl < 60 ml/min/1,73m^2, n (%)	76 (9.9)
eGFR < 60 ml/min/1,73m^2, n (%)	61 (8)
Cardiogenic shock, n (%)	7 (0.9)
Signs of HF, n (%)	32 (4.1)
ST segment elevation, n (%)	182 (23.8)
ST segment depression, n (%)	202 (26.5)

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; PAD: peripheral arterial disease; VKA: Vitamin K antagonists; SBP: Systolic blood pressure; HR: Heart rate; Hct: Hematocrit; Hb: Hemoglobin; CrCl: Creatinine clearance measured using the Cockroft Gault formula; eGFR: Glomerular filtration rate estimated using the CKD-EPI formula; HF: Heart failure; SD: standard deviation.

DISCUSSION

In our work we analyzed the performance of three risk scores to predict bleeding in a population of patients with NSTEACS, in whom anticoagulation was used as part of the antithrombotic treatment. In our population, only the ORBIT score resulted an independent predictor of major bleeding, with a good predictive capacity (AUC 0.80). The CRUSADE and ACTION-GWTG scores were predictors in the univariate analysis, but they were not independent predictors in the multivariate analysis. The predictive capacity of the ACTION-GWTG score was moderate (AUC 0.70), while that of the CRUSADE score was fair (AUC 0.68). When comparing the curves, the ORBIT score showed greater predictive capacity than the CRUSADE score, and a tendency to better capacity than the ACTION-GWTG score.

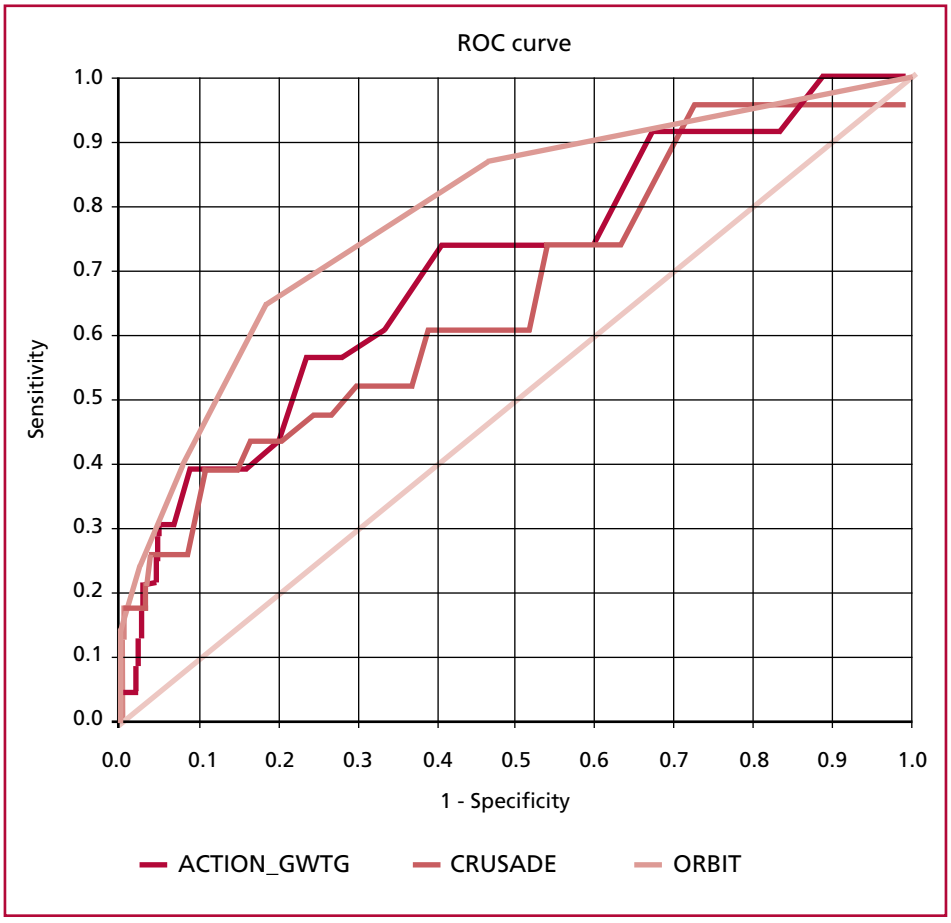

Fig. 1. Comparison of ROC curves

ORBIT categories	Total population n	Total population %	Major bleeding n	Major bleeding %
Low (0-2)	601	79	9	1.5
Moderate (3)	76	10	6	7.8
High (4 or more)	85	11	11	12.9
ACTION-GWTG categories				
Very low (<20)	198	26	2	1
Low (21-30)	403	52.9	12	2.9
Moderate (31-40)	137	18	9	6.5
High (41-50)	16	2.1	2	12.5
Very high (>50)	8	1	1	12.5
CRUSADE categories				
Very low (<20)	304	40	6	1.9
Low (21-30)	190	25	4	2.1
Moderate (31-40)	153	20	5	3.2
High (41-50)	69	9	5	7.2
Very high (>50)	46	6	6	13

Table 2. Distribution of bleeding according to the risk category.

The first thing to highlight is that, of the three scores evaluated, the one with the best performance, ORBIT, was developed to predict bleeding in anticoagulated patients for AF and not for ACS. However, this model uses variables strongly associated with an increased risk of bleeding, such as age, kidney function, anemia, and history of previous bleeding. Age is an important predictor of bleeding in ACS. (12) An analysis of more than 24 000 patients enrolled in the GRACE registry published several years ago showed that the adjusted risk of major bleeding increases by 30% for each decade of life. (13) In the ORBIT model,

Table 3. Univariate and Multivariate Analysis for Major Bleeding. Scores as continuous variable

	UNIVARIATE			MULTIVARIATE		
	OR	95% CI	p	OR	95% CI	p
ACTION-GWTG	1.12	1.02 - 1.19	0.001	0.99	0.90-1.08	0.782
CRUSADE	1.06	1.03 - 1.08	0.012	1.01	0.98-1.05	0.122
ORBIT	2.56	1.81 - 3.36	<0.001	2.56	2.62-3.97	<0.001

Table 4. Univariate and Multivariate Analysis for Major Bleeding. Scores according to risk categories

	UNIVARIATE			MULTIVARIATE		
	OR	95% CI	p	OR	95% CI	p
ACTION-GWTG	2.27	1.31 -2.12	0.003	1.19	0.98–2.43	0.629
CRUSADE	1.56	1.15- 2.12	0.004	1.01	0.66–2.43	0.925
ORBIT	3.26	2.06-5.17	<0.001	3.06	1.69–5.52	<0.001

age has an important weight in the score, since it assigns 1 point to age >74 years, out of a maximum total of 7 points. On the other hand, the CRUSADE score does not consider this parameter and in the ACTION-GWTG model, age has less weight within the total score. Renal function and anemia are considered in all three scores. However, anemia is defined differently in the three models. The CRUSADE model includes only the Hct value and the ACTION-GWTG model that of Hb, while in the ORBIT model the definition is broader, considering both Hb and Hct (both differentiated according to female/male gender) and it includes the history of anemia. This may result in more patients adding points for this variable. In addition, anemia has a very important weight in this score, adding 2 points out of a total of 7. In the CRUSADE and ACTION-GWTG models, anemia has less weight in the final score. Several studies have shown that the presence of anemia in ACS is an important prognostic marker for both cardiovascular events and bleeding. (14,15)

Renal dysfunction is an important predictor of bleeding. In the previously mentioned analysis of the GRACE registry, it was documented that kidney failure increases the risk of bleeding by 50%. (13) Although it is considered in the three risk models, the variables that define renal function are different. The ACTION-GWTG score incorporates the isolated creatinine value, while the CRUSADE and the ORBIT scores include the calculation of glomerular filtration rate, which is more specific to assess renal function. (16)

Another aspect that can explain the performance of the ORBIT score is that it takes into account the history of bleeding, not included in the other two. In the analysis of the GRACE registry, a history of bleeding almost triplicates the risk of in-hospital bleeding in ACS. (13) Although this antecedent was very infrequent in our patients, among the 7 who presented it, 2 had major bleeding, representing a warning signal regarding the choice of antithrombotic strategy in these patients.

CRUSADE is the most used score in clinical practice and is recommended in different guidelines. (2,17) Although it was developed for NSTEACS, it has been extensively studied in the entire spectrum of ACS. (18,19) The ACTION-GWTG model was built including patients with and without STEACS. Several studies have compared both scores, finding a similar predictive capacity. (20,21) A recent meta-analysis, (19) of 17 studies with more than 18 thousand patients, reported a moderate predictive capacity of both scores (AUC 0.71 and 0.76, respectively), somewhat higher than that found in our work (0.68 and 0.70).

On the other hand, the CRUSADE and the ACTION-GWTG scores share several variables such as female gender, renal function, signs of heart failure, diabetes, SBP and HR, which could partly explain why in the multivariate analysis they tend to cancel each other as predictors. In addition, our population presented relatively few events for the multivariate analysis (26 bleedings for 3 scores), although the bleeding rate is similar to that reported in other studies. (3,5,6,12)

ORBIT is not the first score developed for AF that is studied in ACS. HASBLED has been studied as a predictor of bleeding in ACS, (7,8) with a similar predictive capacity than the CRUSADE score, although in the aforementioned meta-analysis, (19) the performance was somewhat lower. Considering that bleeding predictors are similar in patients with ACS and AF, and that the scores developed for the latter pathology are easy to calculate at the patient's bedside, it is reasonable to assess their usefulness in ACS.

Limitations

Our work has several limitations. It is a retrospective study carried out in only two centers, so the results cannot be extrapolated to other populations. Although the size of the study is moderate, relatively few events were recorded for the variables analyzed (26 events for 3 scores), which may influence the results.

CONCLUSIONS

In conclusion, the three scores evaluated were predictors in the univariate analysis, but the ORBIT score was the only independent predictor of major bleeding, presenting a better discrimination capacity than the CRUSADE score and a tendency to better capacity

than the ACTION-GWTG score. ORBIT is an easy score to calculate at the patient's bedside, and may be useful for predicting bleeding in patients with ACS.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material).

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