ORACLE Risk Score in Evaluation of Bleeding Risk in Patients with Acute Coronary Syndrome and Atrial Fibrillation

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Aim. To study the prognostic value of the ORACLE risk score for assessing the risk of bleeding in patients with acute coronary syndrome (ACS) undergoing anticoagulants for atrial fibrillation using the combined database of the ORACLE II and RECORD 3 registers.

Material and methods. This analysis included patients with ACS from 2 observational studies: ORACLE II (ObseRvation after Acute Coronary syndrome for deveLopment of trEatment options; n=1803) and the RECORD-3 register (n=2370). In total, the database included 4173 patients, of which 246 (6.08%) received oral anticoagulants for atrial fibrillation. The mean age of patients was 64.7±11.9 years, 2493 (59.7%) were men. Hemorrhagic risk was assessed using the ORACLE, CRUSADE, ORBIT, and HAS-BLED risk score.

Results. Patients receiving anticoagulant therapy were older (69.9±11.3 years and 64.0±12.2 years, p<0.001). Among these patients there was a larger proportion of women, and a smaller proportion of patients with ACS with ST elevation, they were more likely to have chronic heart failure, chronic kidney disease, history of stroke. Among patients receiving anticoagulants and included in the ORACLE study, the frequency of percutaneous coronary intervention was higher than in patients included in the RECORD study. In the joint database, 71 significant bleeding was recorded during the hospitalization period – 64 (1.7%) in patients without anticoagulants and 7 (2.8%) among patients taking anticoagulants (p=0.06). Over 6 months, among patients who did not receive anticoagulants, there were 97 cases of bleeding (in 2.6% of patients), in the group of patients receiving anticoagulants – 12 cases of bleeding (4.9%) – the differences in frequency were significant (p=0.029). The ORACLE risk score had the greatest prognostic value (area under the ROC curve 0.874±0.0416, sensitivity 82.7%, specificity 79.1%). The predictive value of the HAS-BLED risk score was slightly lower (area under the ROC curve 0.710±0.0360, sensitivity 63.2%, specificity 56.8%). The value of the CRUSADE risk score (area under the ROC curve 0.612±0.0269, sensitivity 53.7%, specificity 59.5%) and ORBIT risk score (area under the ROC curve 0.606±0.0457, sensitivity 62.5%, specificity 58.3%) were lower (p<0.001 for all scales).

Conclusion. The use of the ORACLE bleeding risk score can be recommended for patients with ACS requiring anticoagulant therapy.

Key words: acute coronary syndrome, atrial fibrillation, anticoagulants, bleeding, risk score.

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Introduction

The wide implementation of interventional methods of the treatment of acute coronary syndrome (ACS) has led to the significant decrease in mortality rates among patients with the disease. This is resulted from both the elaboration of the procedure of percutaneous coronary intervention (PCI) and the implementation of contemporary antiplatelet agents. However up to 10% of the patients were found to be needed in anticoagulant treatment. Concomitant use of antiplatelet drugs from different groups significantly increases the risk of bleeding. Contemporary clinical guidelines suggest variation in a number of such drugs and the treatment duration according to the hemorrhagic risk. The standard CRUSADE score (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) which is used for calculation of hemorrhagic risk in ACS, is not applicable in this case as it does not take into account concomitant use of antiplatelet medications. Such bleeding risk scores as the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly), ORBIT and others are designed for stable patients with atrial fibrillation (AF). We have developed the first national score of the hemorrhagic risk assessment in ACS on the base of the ORACLE II observational study (ObseRvation after Acute Coronary syndrome for deveLopment of trEatment options; NCT04068909) [1] and validated it on the materials of the RECORD 3 observational study.

The aim of our study was to evaluate the prognostic value of the ORACLE score for estimation of the bleeding risk in the ACS patients receiving combined antiplatelet treatment on the integrated database of the ORACLE II and RECORD 3 registers.

Material and methods

The analysis includes the data of 2 observational studies. A total of 1803 patients with ACS and indications for PCI, whether it was conducted or not, were enrolled in the multicenter ORACLE study in 2014-2018 years [1]. Patients of 4 vascular centers of Moscow, Kazan, Astrakhan and Krasnodar were included, mean age was 64.9±12.8 years. 38% of the patients had ACS with ST-segment elevation. PCI was conducted in 75.5% of the ACS patients with ST-segment elevation and in 48.9% – with non-ST-segment elevation. 307 patients (17.2%) had AF. 137 patients (7.8%) received anticoagulants. The register RECORD-3 included all patients, hospitalized for ACS in 47 centers of 37 Russian cities during 1 month (March-April 2015) [2]. Coronary angiography and PCI were available in 26 (55%) centers. A total of 2370 ACS patients participated in the RECORD-3 study, mean age was 64.2±12 years. The ACS with ST-segment elevation was diagnosed in 821 patients, others had non-ST-segment elevation ACS. 313 patients (13.2%) had AF. 1842 patients (84.7%) received dual antiplatelet therapy, 109 (4.5%) were anticoagulated.

To evaluate the diagnostic value of the ORACLE score (Table 1) in anticoagulated patients we had combined databases of the RECORD-3 and ORACLE II studies. The combined database included 4173 patients, 246 (6.08%) of them received oral anticoagulants due to AF. The hemorrhagic risk was then estimated on this database using the ORACLE [1], CRUSADE [3], ORBIT [4] and HAS-BLED [5] scores.

Statistical analyses were performed using the SPSS 23 and MedCalc 18.5 programs. We analyzed accordance of continuous variables distribution to the criteria of normality and calculated mean values and values of standard deviation (M±SD). When a distribution was considered to be normal Student's t-test was used to evaluate significance of distinctions, in other cases nonparametric methods of calculation were used. Discrete values were compared using Pearson's χ^2-test. The distinctions were considered statistically significant at $p<0.05$.

Diagnostic values of the scores were compared by the ROC-analysis. Characteristic curves were plotted to analyze the diagnostic value of a tested score. Sensitivity and specificity were calculated for each tested diagnostic criterion. To compare diagnostic values in different clinical groups areas under the ROC-curves were compared by the DeLong test.

Results

The analysis of clinical characteristics of the patients enrolled in the combined database (n=4173) revealed that the anticoagulated patients as com-

Table 1. The ORACLE scale

Parameter	Scores
Age, years	
<55	0
56-65	8
66-75	16
>75	24
Hemoglobin level at admission, g/l	
>125	0
100-125	48
<100	96
HF Killip class at admission	
1	0
2-4	17
Creatinine clearance, ml/min	
>90	0
60-89	6
<60	12
History of stomach or duodenum ulcer	20
Combined use of anticoagulants and antiplatelet agents after ACS (dual or triple antiplatelet therapy)	36
PCI during the index hospitalisation	38

The score is available at: https://oracul.msk.ru/calculators/index

HF – heart failure, ACS – acute coronary syndrome, PCI – percutaneous coronary intervention

pared to non-anticoagulated ones were older, the share of women was higher while the share of the ACS patients with ST-segment elevation was lower, they were more likely to have chronic heart failure, chronic kidney disease and the history of stroke (Table 2). Anticoagulated patients in the ORACLE study were older, more often suffered from chronic heart failure and chronic kidney disease and had higher rates of PCI as compared to the similar patients of the RECORD study (Table 3). A total of 71 significant bleeding events were registered during the hospitalization period in accordance with the combined database: 64 (1.7%) of the cases in the group of anticoagulated patients and 7 (2,8%) – in patients with no anticoagulant therapy (p=0.06). During the 6-month follow-up there were 12 (4.9%) and 97 (2.6%) significant bleedings, respectively (p=0.029). Incidence rate of bleeding complications under anticoagulant treatment during the index hospitalization was higher in the ORACLE patients, which could be resulted from higher rates of PCI performance and older age of the patients. There were no relevant distinctions in significant and major bleedings incidence rates during the 6-month follow-up.

We had compared diagnostic values of the 3 tested scores in patients under anticoagulant treatment. The ORACLE score demonstrated the best diagnostic value with sensitivity of 82.7% and specificity of 79% (Table 4). An area under the ROC-curve for this score was significantly higher than under the ROC-curves for the HAS-BLED, ORBIT and CRUSADE risk scores (Figure 1).

Table 2. Clinical characteristics of the ACS patients, depending on anticoagulants intake

Parameter	No anticoagulants (n=3927)	Anticoagulant therapy (n=246)	p
Age, years	64.0±12.2	69.9±11.3	<0.0001
ACS with ST-segment elevation, n(%)	1365 (34.7)	64 (24.2)	0.0002
Acute HF during the index hospitalization, (Killip 2-4), n (%)	914 (23.3)	72 (29.3)	0.0605
Male sex, n (%)	2372 (60.4)	121 (49.2)	0.0001
History of myocardial infarction, n (%)	1180 (30.0)	82 (33.3)	0.512
Diabetes mellitus, n (%)	770 (19.6)	50 (20.3)	0.967
History of stroke, n (%)	311 (7.9)	39 (15.9)	0.0001
Chronic heart failure, n (%)	1787 (45.6)	152 (61.8)	0.0001
PCI in the index hospitalization, n (%)	1669 (42.5)	98 (39.8)	0.209
Chronic kidney disease, n (%)	879 (22.4)	72 (29.3)	0.0262
Significant bleedings during the index hospitalization, n (%)	64 (1.6)	7 (2.7)	0.0603
Significant bleedings during the 6-month follow-up, n (%)	97 (2.6)	12 (4.9)	0.029
Major bleedings during the 6-month follow-up, n (%)	45 (1.1)	5 (2.0)	0.024

HF – heart failure, ACS – acute coronary syndrome, PCI – percutaneous coronary intervention

Table 3. Clinical characteristics of the patients receiving anticoagulants in the RECORD 3 and ORACLE studies

Parameter	RECORD 3 (n=109)	ORACLE (n=137)	p
Age, years	67.5±11.0	72.3±11.5	
ACS with ST-segment elevation, n(%)	28 (25.6)	36 (26.3)	0.9012
Acute HF during the index hospitalization, (Killip 2-4), n (%)	39 (35.7)	33 (24.1)	0.0474
Male sex, n (%)	47 (43.1)	74 (54.0)	0.0900
History of myocardial infarction, n (%)	32 (29.4)	50 (36.5)	0.2416
Diabetes mellitus, n (%)	25 (22.9)	25 (18.2)	0.3634
History of stroke, n (%)	10 (9.2)	29 (21.2)	0.0107
Chronic heart failure, n (%)	51 (46.7)	101 (73.7)	0.001
PCI in the index hospitalization, n (%)	31 (28.4)	67 (48.9)	0.0011
Chronic kidney disease, n (%)	24 (22.0)	48 (35.0)	0.0261
Significant bleedings during the index hospitalization, n (%)	2 (1.9)	5 (3.7)	0.0406
Significant bleedings during the 6-month follow-up, n (%)	4 (3.7)	8 (5.8)	0.4147
Major bleedings during the 6-month follow-up, n (%)	2 (1.8)	3 (2.2)	0.8468

HF – heart failure, ACS – acute coronary syndrome, PCI – percutaneous coronary intervention

Table 4. Sensitivity and specificity of the tested scores in comparison with the ORACLE score

Score	ORACLE	CRUSADE	HAS-BLED	ORBIT
Area under the ROC-curve	0.874	0.612	0.710	0.606
SE	0.0269	0.0416	0.0360	0.0457
Sensitivity, %	82.7	53.7	63.2	62.5
Specificity, %	79.1	59.5	56.8	58.3
Differences in area under the ROC-curve in comparison with the ORACLE score (95%CI)	-	0.262 (0.181-0.343)	0.164 (0.095-0.231)	0.268 (0.215-0.321)
z-criterion (in comparison with the ORACLE score)	-	6.316	4.729	5.054
p (in comparison with the ORACLE score)	-	<0.0001	<0.0001	<0.0001

SE – standard error, CI – confidence interval

Discussion

In accordance with the literature data up to 10-17% of the ACS patients suffer from AF. At that the share of the AF patients receiving anticoagulants after ACS turns out to be significantly lower. As the New Zealand register of ACS patients reported, only 11.6% of the patients with AF were prescribed anticoagulants at discharge from hospital [6]. According to the Swedish register of ACS patients only 6.6% of 2,243 patients were anticoagulated [7]. In our combined cohort about 6% of the ACS patients received anticoagulants – nearly a half of all AF patients. The risk of bleeding complications substantially limits possibilities of anticoagulants prescription, the more so because the patients with indications for anticoagulation are older and have more risk factors and concomitant diseases as our study had demonstrated.

According to the New Zealand register of the ACS patients, estimation of risks of stroke and bleeding events using the CHA2DS2-VASc and CRUSADE scores was inaccurate [6]. The Swedish study used the HAS-BLED score for the bleeding risk estimation, it had demonstrated satisfactory diagnostic value (area under the curve of 0.67; 95% confidence interval 0.54-0.79; p=0.048) [7]. The Brazil register of the ACS patients had reported similar prognostic value of the HAS-BLED score (C-statistics of 0.71) [8]. Its value in bleeding events prediction was higher than of other used at present scores. In accordance with the Japanese register of the patients undergone ACS the HAS-BLED, ORBIT and PRECISE-DAPT scores revealed the patients at the high risk of major bleeding by the TIMI classification but were less effective in the estimation of the risk for less significant bleeding [9].

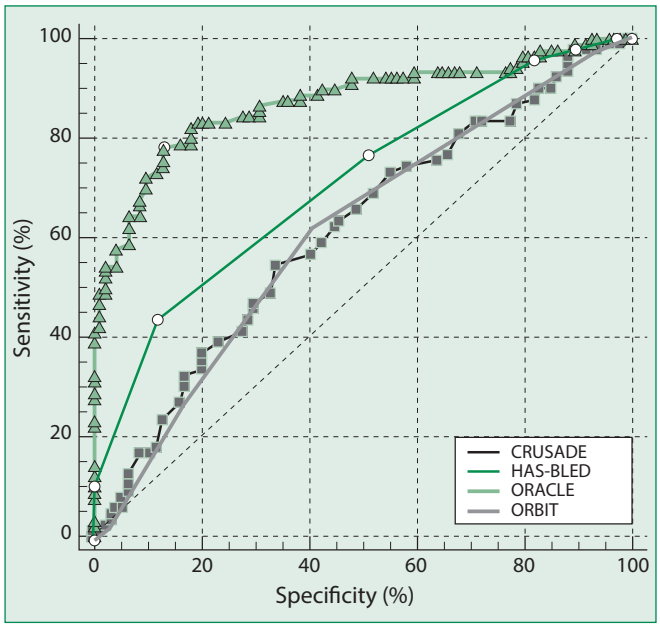

Figure 1. Predictive value of different bleeding risk scales

Another study reported very low diagnostic value of the HAS-BLED score. It was inferior to the CRUSADE score in prediction of the bleeding risk in anticoagulated patients in particular, which did not allow risk stratification in these patients and influenced on triple and dual antiplatelet treatment duration [10].

The RECORD register had earlier demonstrated moderate diagnostic value of the CRUSADE score for major in-hospital bleedings prediction (C-statistics of 0.681) [11]. Diagnostic value of the CRUSADE score in our study was lower (C-statistics of 0.612). The ORBIT score also revealed low diagnostic value (C-statistics of 0.606). The HAS-BLED score had moderate sensitivity and specificity. Maximal diagnostic possibilities were demonstrated for the ORACLE score, earlier developed by ourselves.

Conclusion

Use of the ORACLE score can be recommended for the anticoagulant-requiring ACS patients with AF.

Relationships and Activities: none.

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