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The Risk of Developing Ischemic Stroke in Patients After Exacerbation of Ischemic Heart Disease

Aim	To develop a model for evaluating the risk of stroke in patients after exacerbation of ischemic heart disease who were admitted to the hospitals included into a vascular program.
Material and methods	This study included 1803 patients with acute coronary syndrome (ACS) from four institutions of Moscow, Kazan, Astrakhan, and Krasnodar where the vascular program was established. Mean age of patients was 64.9±12.78 years, 62,1% of them were men. The patients were followed up for one year after the discharge from the hospital. External validation of the developed prognostic model was performed on a cohort of patients with ACS included into the RECORD-3 study.
Results	During the follow-up period, 42 cases of ischemic stroke were observed. The risk of ischemic stroke was associated with the presence of atrial fibrillation (odd ratio (OR) 2.640; p=0.037), diabetes mellitus (OR 2.718; p=0.041), and chronic heart failure (OR 7.049; p=0.011). Protective factors were high-density lipoprotein cholesterol >1 mmol/l (OR 0.629; p=0.041), percutaneous coronary intervention during an index hospitalization (OR 0.412; p=0.042), anticoagulant treatment (OR 0.670; p=0.049), and achieving the blood pressure goal (OR 0.604; p=0.023). The prognostic model developed on the basis of regression analysis showed a good predictive value (area under the ROC curve, 0.780), sensitivity of 80%, and specificity of 64.6%. The diagnostic value of other scales for risk assessment was somewhat lower. The area under the ROC curve was 0.692±0.0245 for the GRACE scale and 0.708±0.0334 for CHA_2DS_2 VASc. In the external validation of the scale based on data of the RECORD-3 study, the diagnostic value was lower although satisfactory as well (area under the ROC curve, 0.651); sensitivity was 78.9%, and specificity was 52.3%.
Conclusion	The study resulted in development of a simple clinical scale, which will probably allow identifying groups at risk of stroke more precisely than with standard scales.

Keywords	Acute coronary syndrome; stroke; revascularization; risk scale
For citation	Brazhnik V. A., Minushkina L. O., Khasanov N. R., Kosmacheva E. D., Chichkova M. A., Erlikh A. D. et al. The Risk of Developing Ischemic Stroke in Patients After Exacerbation of Ischemic Heart Disease. Kardiologiia. 2020;60(8):46–53. [Russian: Бражник В. А., Минушкина Л. О., Хасанов Н. Р., Космачева Е. Д., Чичкова М. А., Эрлих А. Д. и др. Риск развития ишемического инсульта у больных, перенесших обострение ишемической болезни сердца. Кардиология. 2020;60(8):46–53]

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Ischemic stroke is an isolated problem associated with severe disability and high mortality among thrombotic complications in patients with a history of acute coronary artery disease (CAD). The rate of ischemic stroke in the GRACE register was approximately 0.34% within two weeks after the index event [1], and this rate can reach 3% within a two-year follow-up period [2]. Age, sex, ethnicity, systolic and diastolic blood pressure (BP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL–C) and low-density lipoprotein cholesterol (LDL–C), diabetes mellitus (DM), smoking, and antihypertensive, hypolipidemic, and antiplatelet treatment were predictive risk factors (RF) of stroke [3], as well as were factors included in the CHA_2DS_2 VASc score for assessing the risk of stroke and systemic thromboembolism in patients with atrial fibrillation [4].

However, there are no validated data concerning the risk of stroke in Russian patients with a history of acute CAD. Thus, the objective of this study was to create a model for assessing the stroke risk in patients with a history of acute CAD who were admitted to Russian hospitals with PCI center.

Material and Methods

This study is based on the results of an initiative, open-label, observational, multicenter study organized by the

ISSN 0022-9040. Kardiologiia. 2020;60(8). DOI: 10.18087/cardio.2020.8.n1197

Department of Therapy, Cardiology, and Functional Diagnostics with a course of Nephrology of the Central State Medical Academy of the Administration of the President of the Russian Federation.

For this analysis, we used data from the ORACLE II (ObseRvation after Acute Coronary syndrome for deve-Lopment of trEatment options; reg. number: clinicaltrials.gov NCT04068909), which included patients with acute coronary syndrome (ACS), who had indications for percutaneous coronary intervention (PCI) due to an index episode. The impossibility of keeping contact with a patient after discharge was the exclusion criteria. All patients signed an informed consent form for inclusion in the study. During 2014–2017, 1,803 patients were included in the study at four hospitals situated in Moscow, Kazan, Astrakhan, and Krasnodar, in which specialized vascular departments were established under the Fight Against Cardiovascular Diseases federal project. The inclusion criteria were described earlier [5]. The Ethics Committee of the Educational and Scientific Medical Center (Central State Medical Academy since 2015) of the Administration of the President of the Russian Federation approved the study (Protocol No. 14/14 of October 20, 2014).

The data on adverse outcomes were collected at follow-up examinations or phone calls made on days 25, 90, 180, and 360 after inclusion in the study. The primary endpoint was all-cause death as verified by autopsy, if any, discharge summaries, outpatient records, and other medical documents. All cases of strokes were analyzed in this part of the study. The type of stroke was verified by medical records and imaging data, if available.

External validation of the resulting prognostic model was performed in a patient cohort of the RECORD-3 trial [6]. The clinical characteristics of the patients are presented in Table 1. The two patient cohorts were comparable in age, sex, and body mass index. Among the patients included in our study, a higher percentage of patients had ST-segment elevation ACS (STE-ACS), a significantly higher percentage of patients had undergone PCI for an index event, and there were more patients with atrial fibrillation (AF) who had received anticoagulants.

Statistical processing of the findings was performed using statistical software suites SPSS 23.0, MedCalc 19.0.3, and STATA 14.0. Nonparametric methods were used for analysis after evaluating the distribution of variables. Means and standard errors (M±SE) were calculated. Discrete values were compared using Pearson's chi-square test. Sensitivity analysis was performed to identify differences between centers in a multicenter trial by using the regression method in the STATA 14.0 statistical software suite. Logistic regression was used to evaluate the independence of the clinical variables. Variables that showed statistical significance in the univariate analysis were included in the multivariate analysis. Results of these analyses are expressed as odds ratio (OR) and 95% confidence interval (CI). The clinical significance and diagnostic accuracy of the scores tested were analyzed by constructing receiver operator characteristic (ROC) curves for each diagnostic criterion and by calculating the area under curves (AUC). Sensitivity and specificity were calculated for each diagnostic criterion tested. The results were considered significant at $p<0.05$ for all types of analyses.

Table 1. Clinical characteristics of patients

Variable	ORACUL II	RECORD 3	p
Total number of patients	1803	2370	–
Male	1120 (62.1%)	1440 (60.8%)	0.393
Age at inclusion, years	64.9±12.8	64.2±12.0	0.069
BMI, kg/m^2	28.5±4.9	29.0±5.1	0.330
STE-ACS	682 (37.8%)	821 (34.6%)	0.032
History of MI	529 (29.3%)	781 (33%)	0.01
History of hypertension	1584 (87.9%)	2035 (86%)	0.072
History of stroke	213 (11.8%)	165 (7%)	0.0001
CHF before current hospitalization	907 (50.3%)	1129 (48%)	0.141
Diabetes mellitus	410 (22.7%)	446 (19%)	0.003
Smoking	498 (27.6%)	647 (27.0%)	0.666
Atrial fibrillation	311 (17.2%)	313 (13%)	0.0002
Anticoagulant therapy	137 (7.6%)	122 (5%)	0.0005
PCI during index hospitalization	1013 (56.2%)	680 (31.3%)	<0.0001

Data are number and percentage or M ± SE. BMI, body mass index; STE-ACS, acute coronary syndrome with ST-elevation; MI, myocardial infarction; CHF, chronic heart failure; PCI, percutaneous coronary intervention.

Results

The follow-up period lasted for 12 mos (median follow-up was 366 days). During the follow-up period, 228 deaths were registered, including 144 coronary deaths, 14 stroke deaths, 25 decompensated heart failure deaths, and 6 pulmonary embolism deaths. There were 158 repeated episodes of non-fatal ACS. A total of 45 strokes were reported during the follow – up period in the ORACUL II trial, of which 42 cases were ischemic, and 3 cases were hemorrhagic. Twenty strokes occurred during the initial hospitalization period, ten strokes in the first 9 days after the onset of ACS (including one case of hemorrhagic nature), and the remaining ten episodes from day 10 after discharge from the hospital. Hemorrhagic strokes were reported on days 4, 14, and 50 from the time of ACS. Two patients had AF and received oral anticoagulation

Table 2. Clinical characteristics of patients depending on outcome: with or without ischemic stroke

Variable	Patients without stroke (n=1761)	Patients with ischemic stroke (n=42)	p
Male/female	1096 (62.2%)/665 (37.8%)	24 (57.1%)/18 (42.9%)	0.754
Age at inclusion, years	64.7±12.8	71.0±11.9	0.002
75 years old and older	480 (27.3%)	15 (35.7%)	0.228
BMI, kg/m^2	28.52±4.941	26.64±4.463	0.024
STE-ACS	587 (33.4%)	16 (38.1%)	0.204
History of CAD	1265 (72.0%)	34 (81.0%)	0.199
History of MI	516 (29.3%)	13 (31.0%)	0.879
Hypertension	1539 (87.6%)	42 (100%)	0.015
BP target levels achieved at discharge	1100 (71.5%)	15 (35.7%)	0.001
Atrial fibrillation	295 (16.8%)	16 (38.1%)	0.001
History of stroke	208 (11.8%)	5 (11.9%)	0.897
Diabetes mellitus	402 (23.0%)	8 (19.0%)	0.551
Diabetes mellitus and impaired glucose tolerance	525 (29.8%)	15 (35.7%)	0.024
Aortic stenosis	101 (5.7%)	3 (7.1%)	0.622
CHF before index hospitalization	870 (49.6%)	35 (83.3%)	0.0001
Peripheral atherosclerosis	445 (25.5%)	20 (47.6%)	0.001
BCA atherosclerosis	343 (19.5)	19 (45.2)	0.0052
Atherosclerosis of leg vessels	140 (7.95)*	4 (9.52)*	0.8016
Smoking	488 (28.1%)	10 (23.8%)	0.304
Alcohol use	797 (46.1%)	19 (45.2%)	0.915
AHF, Killip II-IV	382 (21.7%)	16 (38.1%)	0.001
Recurrent ACS during hospitalization	20 (1.7%)	3 (8.1%)	0.021
Episodes of severe ischemia during hospitalization	125 (7.4%)	3 (7.5%)	0.008
CKD	641 (36.8%)	27 (64.3%)	0.001
Creatinine clearance, ml/min during index hospitalization	81.94±34.17	67.60±30.91	0.014
Total cholesterol, mmol/l, during index hospitalization	5.51±1.44	5.21±1.02	0.132
LDL-C, mmol/l, during index hospitalization	3.24±1.52	3.22±0.66	0.926
HDL-C, mmol/l, during index hospitalization	1.18±0.505	0.99±0.271	0.031
HDL-C > 1 mmol/l, during index hospitalization	1002 (56.9%)	13 (31.0%)	0.001
Glucose during index hospitalization	8.06±3.81	7.86±3.85	0.737
Increased markers of myocardial damage during index event	1504 (87.0%)	29 (69.0%)	0.047
PCI during index hospitalization	997 (56.7%)	15 (35.7%)	0.022
Prescription of antiplatelet therapy at discharge	1654 (94.1%)	38 (90.5%)	0.087
Prescription of oral anticoagulants at discharge	133 (7.6%)	2 (4.7%)	0.02
Prescription of statins at discharge	1555 (88.5%)	35 (83.3%)	0.358

Data are number and percentage or M±SE. BMI, body mass index; STE-ACS, acute coronary syndrome with ST-elevation; CAD, coronary artery disease; MI, myocardial infarction; BP, blood pressure; CHF, chronic heart failure; BCA, brachiocephalic arteries; AHF, acute heart failure; ACS, acute coronary syndrome; CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PCI, percutaneous coronary intervention. *, some patients had multiple damages of carotid and leg arteries.

ISSN 0022-9040. Kardiologiia. 2020;60(8). DOI: 10.18087/cardio.2020.8.n1197

therapy. One patient had severe, resistant hypertension. We then analyzed the clinical features of the 42 patients who developed ischemic stroke. Patients who developed hemorrhagic stroke were considered in this analysis to have had a favorable outcome until a poor outcome occurred, and later these patients were designated as «lost for follow-up». Clinical characteristics of the patients with and without ischemic stroke are presented in Table 2.

Interestingly, patients who had ischemic strokes during the follow-up period were older, more often were hypertensive, and so less often had effectively controlled BP. These patients were more likely to have carbohydrate metabolism disorders, more severe renal dysfunction, peripheral atherosclerosis, AF, and chronic heart failure (CHF). Patients with a history of strokes were less likely to undergo PCI during the index hospitalization and to receive anticoagulant therapy.

Univariate and multivariate logistic regression analyses were performed to assess the impact of various clinical factors on stroke risk. A sensitivity analysis was performed due to possible differences in patient management between the centers. The differences from the reference center (Moscow) were significant for several parameters (Appendix 1). Correction factors were applied during the regression analysis (Appendix 2). The analysis results are presented in Table 3.

A clinical model for calculating stroke risk was created using regression analysis. The regression factors were reduced to whole numbers. The calculated scores are presented in Table 4. The resulting model had high diagnostic significance. The classification was adequate and met the Hosmer – Lemeshow test (χ^2=2.465; p=0.789). The area under the ROC curve was 0.780 (Figure 1). The sensitivity of the score was 80%, and specificity was 64.6%.

Table 3. Factors associated with stroke risk in patients with acute episodes of CAD

Factor	Univariate analysis		Multivariate analysis		Multivariate analysis (model adjusted for intercenter differences)	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age, 10-year increase	1.512 (1.178 – 1.940)	0.015	1.145 (0.732 – 1.790)	0.553	1.272 (0.536 - 3.547)	0.798
BMI, kg/m^2	0.921 (0.860 - 0.986)	0.018	0.968 (0.569 – 1.645)	0.996	0.978 (0.526 – 1.848)	0.886
Hypertension	4.47 (0.02 – 44.69)	0.877	–	–	–	–
BP target levels achieved at discharge	0.33 (0.17 – 0.63)	0.001	0.604 (0.214 – 0.906)	0.023	0.687 (0.294 – 0.928)	0.028
Atrial fibrillation	3.04 (1.61 – 5.75)	0.001	2.640 (1.532 – 5.057)	0.037	2.202 (1.367 – 4.986)	0.039
Diabetes mellitus and impaired glucose tolerance	2.68 (1.16 – 6.17)	0.02	2.718 (1.473 – 6.237)	0.041	2.689 (1.246 – 8.334)	0.047
CHF before current hospitalization	5.08 (2.24 – 11.49)	0.001	7.049 (1.557 – 31.913)	0.011	5.967 (1.023 – 28.443)	0.022
AHF, Killip II-IV, at admission	3.04 (1.52 – 6.07)	0.002	2.447 (0.911 – 6.569)	0.076	1.998 (0.869 – 4.998)	0.098
Peripheral atherosclerosis	2.65 (1.43 – 4.91)	0.002	1.465 (0.510 – 4.211)	0.476	1.888 (0.635 – 3.297)	0.121
Recurrent ACS during index hospitalization	1.017 (0.31 – 3.34)	0.978	–	–	–	–
CKD	3.09 (1.63 – 5.85)	0.001	2.013 (0.685 – 5.914)	0.221	2.013 (0.685 – 5.914)	0.221
Creatinine clearance during index hospitalization	0.985 (0.973 – 1.027)	0.103	–	–	–	–
HDL-C during index hospitalization	0.287 (0.092 – 0.890)	0.031	0.645 (0.275 – 1.513)	0.314	0.784 (0.128 – 2.689)	0.462
HDL-C >1 mmol/L during index hospitalization	0.324 (0.147 – 0.712)	0.005	0.629 (0.311 – 0.996)	0.041	0.629 (0.311 – 0.996)	0.041
Increased markers of myocardial damage during index event	1.051 (0.244 – 4.525)	0.947	–	–	–	–
PCI during index hospitalization	0.418 (0.216 – 0.809)	0.01	0.412 (0.169 – 0.987)	0.042	0.458 (0.124 – 0.898)	0.041
Anticoagulant therapy at discharge	0.746 (0.553 – 0.986)	0.047	0.670 (0.580 – 0.907)	0.049	0.667 (0.546 – 0.928)	0.049

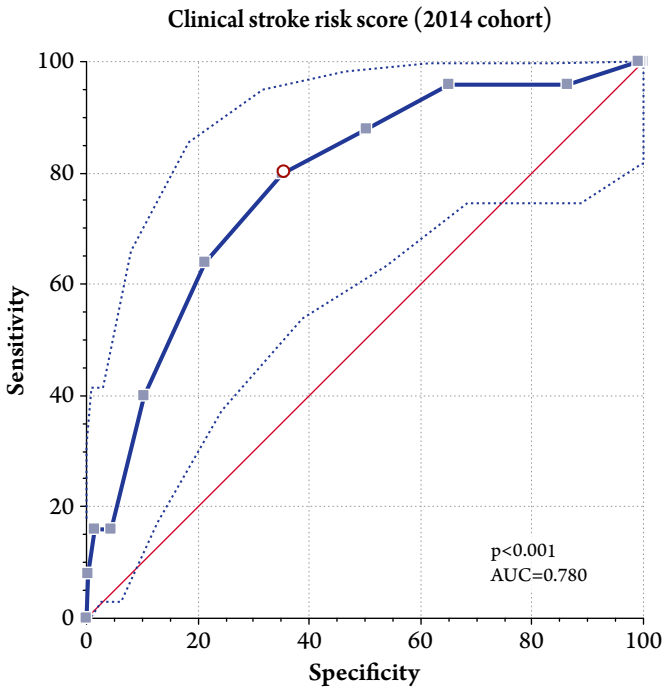
OR, odds ratio; CI, confidence interval; BMI, body mass index; MI, myocardial infarction; BP, blood pressure; CHF, chronic heart failure; AHF, acute heart failure; ACS, acute coronary syndrome; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; PCI, percutaneous coronary intervention.

Table 4. Post-ACS ischemic stroke risk score

Factor	Score
BP target levels achieved at discharge	-1
Atrial fibrillation	+3
Chronic heart failure	+2
Diabetes mellitus or impaired glucose tolerance	+2
Chronic kidney disease	+1
HDL-C >1 mmol/L	-1
PCI for index event	-1
Use of anticoagulants at discharge	-3

ACS, acute coronary syndrome; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; PCI, percutaneous coronary intervention.

Figure 1. ROC analysis of the resulting prediction score (%)



The stroke risk assessment score was tested in the patient cohort of the RECORD-3 registry (Figure 2). During the 12-mo follow-up period, 33 strokes were reported. The database did not include information about a type of stroke (hemorrhagic or ischemic). Besides, there was no data on the levels of HDL–C. The score's prognostic significance with these limitations was lower with area under the ROC curve of 0.651, the model's sensitivity was 78.9%, and specificity was 52.3%.

CHA_2DS_2 VASc and GRACE scores was also used to assess stroke risk. The diagnostic significance of different scores was compared using the area under the ROC curves (Figure 3). Table 5 shows the parameters of the area under the ROC curve, sensitivity, and specificity of all tested scores.

Discussion

We have analyzed the clinical predictors of stroke after an ACS episode. Based on multivariate regression analysis, our prognostic model included the presence of AF, chronic kidney disease (CKD), DM and CHF, which were RFs, as well as the achievement of target BP levels,

Figure 2. Validation of the stroke risk score on the RECORD-3 database (%)

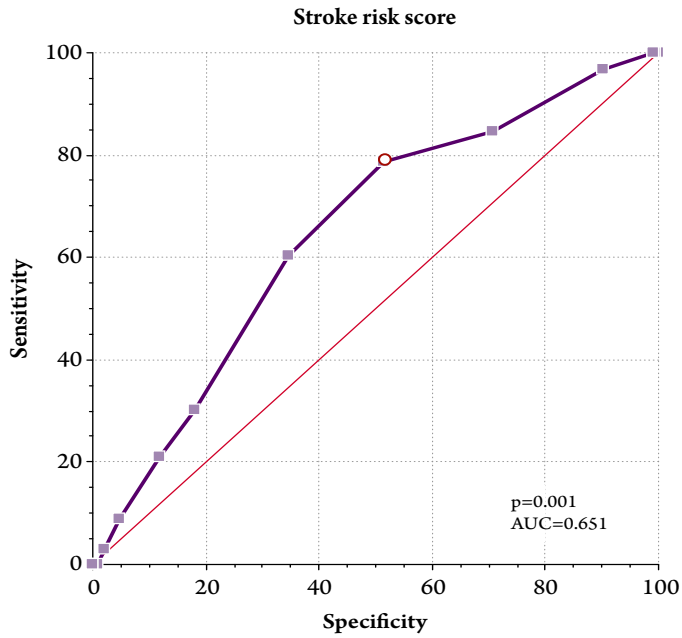
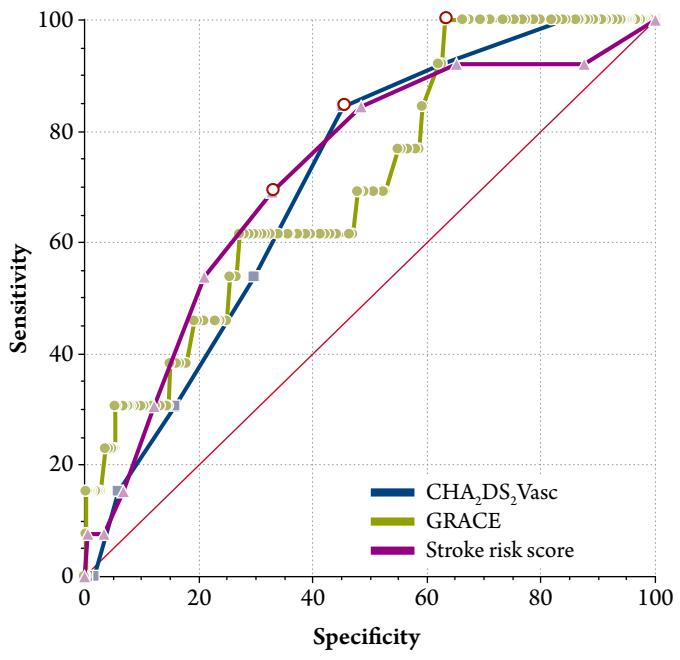


Figure 3. Diagnostic value of different stroke risk scores in patients with a history of acute episode of coronary artery disease (%)



ISSN 0022-9040. Kardiologiia. 2020;60(8). DOI: 10.18087/cardio.2020.8.n1197

Table 5. Diagnostic value of different stroke risk scores

Score	Area under the ROC curve	Sensitivity, %	Specificity, %	p (to ORACLE stroke risk score)
ORACLE Stroke risk score	0.780±0.045	80.0	64.6	–
GRACE	0.692±0.025	72.2	63.9	0.084
CHA_2DS_2 VASc	0.708±0.033	73.8	42.6	0.200

Data are M±SE or percentage.

high HDL–C levels, PCI during index hospitalization and anticoagulant therapy, which were protective factors. It should be noted that the majority of these factors have been also associated with stroke risk in the past, including in studies with ACS patients. Thus, according to the American registry, which included more than 73 thousand patients observed in 2008–2011, age, female sex, African-American or Hispanic ancestry, CKD, CHF, DM, and AF were independently associated with the risk of stroke. A history of hyperlipidemia before the episode of ACS was a protective factor [2]. In the international multicenter PROMETHEUS trial, which included 19,914 patients with ACS, 244 strokes were reported during 12 mos of follow-up, i.e., in 1.5% of patients. A history of stroke was a factor that increased mortality after ACS. A history of cerebrovascular disease, myocardial infarction with or without ST elevation, hypertension, smoking, female sex, and age were factors associated with stroke. Patients with unstable angina had a lower risk of stroke. Statins were prescribed protectively at the time of discharge [7]. Factors such as PCI and anticoagulant therapy did not significantly affect stroke risk in that multivariate analysis, unlike in our study's findings, according to which PCI during index hospitalization was a protective factor. The PROMETHEUS trial analysis showed that patients who had undergone PCI for an episode of ACS were more likely to receive the best possible drug therapy, i.e., antihypertensive and antithrombotic treatment. Mortality and the risk of recurrent cardiovascular complications were lower during the best possible therapy. The number of strokes was also slightly lower. However, the differences were not significant, possibly due to insufficient sample size [8]. Another study showed that patients who had undergone PCI were more compliant with hypolipidemic therapy and more often reached the LDL–C target levels, which may have also contributed to a lower risk of adverse outcomes [9]. Thus, a possible mechanism for PCI's effect on stroke risk is better compliance with drug therapy in patients who have undergone revascularization.

The significance of AF as a risk factor of stroke has been repeatedly confirmed in the analysis of two national registers of ACS patients conducted in Italy. There the incidence of stroke was 1.7% in patients with AF and 0.4% in patients without AF (p=0.04) [11].

A large meta-analysis that included 14 studies and more than 290 thousand patients showed that newly diagnosed AF in ACS is an independent RF of stroke, especially in patients with STE-ACS. This association remained when groups were standardized by the main RFs included in the CHA_2DS_2 VASc score [12]. In our study, AF was an independent RF included in the prognostic model. It should be noted that anticoagulant therapy was a protective factor equal to the presence of AF. This may suggest that a significant number of strokes may be of cardioembolic nature in this group of patients.

One of the factors associated with stroke in our prognostic model was HDL–C levels, which were protective. There are no similar data concerning patients with ACS. However, similar trends were previously detected in patients with DM [13], hypertension [14], and in the general population (Multi-Ethnic Study of Atherosclerosis trial) [15].

The resulting clinical score for assessing stroke risk was of high predictive value and had relatively high sensitivity and specificity. It should be noted that the GRACE and CHA_2DS_2 VASc scores had a slightly lower predictive value in our study. The same scores were tested in a cohort of 4,227 patients with ACS who were followed up for five years after discharge in Spain. During the follow-up period, 183 cases of stroke were reported, and only 16% of them were associated with AF. The GRACE and CHA_2DS_2 VASc scores did not have a very high diagnostic value. The areas under the ROC curves were 0.62 and 0.60, respectively. The CHA_2DS_2 VASc score's sensitivity was higher, but it had lower specificity than the GRACE score [16].

Conclusion

We have developed a relatively simple clinical score that may identify stroke risk groups more accurately than standard scores.

No conflict of interest is reported.

The article was received on 15/05/2020

Appendix 1. Significance of differences of the Astrakhan, Kazan, and Krasnodar centers from the reference center (Moscow) as determined by sensitivity analysis

Фактор	p, Astrakhan (n=389)	p, Kazan (n=309)	p, Krasnodar (n=141)
Age	0.99019	0.77424	0.51144
BMI. kg/m^2	0.99955	0.73694	0.51507
Hypertension	0.33190	0.82335	0.50125
BP target levels achieved at discharge	**0.00966**	**0.00230**	0.29123
Atrial fibrillation	0.78647	0.79160	0.51649
Diabetes mellitus and impaired glucose tolerance	**0.01724**	**0.00037**	0.17970
CHF before current hospitalization	**0.00599**	**0.01596**	0.22986
AHF. Killip II-IV. at admission	0.93469	0.82854	0.46717
Peripheral atherosclerosis	0.05985	**0.01072**	0.11570
Recurrent ACS during index hospitalization	0.98635	0.79463	0.42548
CKD	**0.00985**	**0.00236**	0.22309
Creatinine clearance during index hospitalization	0.99997	0.69472	0.59276
HDL-C during index hospitalization	0.87604	0.75746	0.72486
HDL-C >1 mmol/L during index hospitalization	0.81175	0.78046	0.71012
Increased markers of myocardial damage during index event	0.14159	0.05932	0.09997
PCI during index hospitalization	0.87831	0.85006	0.40382
Anticoagulant therapy at discharge	0.06991	0.20884	0.24568

Appendix 2. Corrections of the factors included in the regression model used to build a final regression model

Factor	Moscow, reference center (n=967)	Astrakhan (n=389)	Kazan (n=309)	Krasnodar (n=141)
BP target levels achieved at discharge	1.0	0.86219 (0.20918 – 1.51520)	0.98572 (1.61959 – 0.35185)	**No correction**
Diabetes mellitus and impaired glucose tolerance	1.0	1.03263 (1,88246 – -0.18280)	1.17573 (1.82266 – 0.52879)	**No correction**
CHF before current hospitalization	1.0	-1.18560 (-2.03115 – 0.34004)	0.79705 (1.44533 – 0.14877)	**No correction**
Peripheral atherosclerosis	1.0	**No correction**	0.86897 (1.53640 – 0.20154)	**No correction**
CKD	1.0	-0.85530 (-1.50482 – -0.20579)	0.98734 (1.62368 – 0.35099)	**No correction**

Data are OR (95% Cl). BMI, body mass index; CHF, chronic heart failure; AHF, acute heart failure; CKD, chronic kidney failure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention.

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