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Risks of unfavourable clinical outcomes in patients with first diagnosed stroke-associated atrial fibrillation

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Abstract

Background—Atrial fibrillation (AF) is the most common arrhythmia often associated with cardioembolic stroke.

Hypothesis—We investigated cases of AF first diagnosed (fdAF) in the acute phase of stroke.This type of AF might be common, and might suggest poor prognosis for patients.

Methods— Following screening (n=1291) 661 patients with AF and a history of stroke were enrolled in this open-label, prospective study; patient average age was 68.0 years.

Results—A high level of co-morbidity was observed: hypertension (in 100% of patients), ischemic heart disease (in 61.4% of patients), diabetes mellitus (in 52.3% of patients), and chronic kidney disease (in 32.1% of patients). In 154 (23.3%) patients AF was first diagnosed at the onset of cardioembolic stroke. The HAS-BLED score, age, hypertension and ischemic heart disease rates among these patients were comparable with the rest of the group; however, the percentage of patients with chronic kidney disease, diabetes mellitus or myocardial infarction was significantly higher. The highest one-year death rate was seen in patients with fdAF (death reported in 46 [29.9%] patients). The age of patients with fdAF who died was significantly higher, and their neurological disorders were more severe.

Conclusions—The results show a high rate of fdAF and its poor prognosis in patients with cardioembolic stroke. Thus, the term "first diagnosed stroke-associated atrial fibrillation" seems relevant. The described condition has a negative predictive value, and is also associated with high co-morbidity burden in patients with fdAF.

Keywords: Anticoagulant Treatment, Novel Oral Anticoagulants (NOACs), Arterial Stiffness, Endothelial Dysfunction, Atrial Fibrillation, Cardioembolic Stroke

1 INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in the population highly associated with the development of fatal thromboembolic complications, and especially of cardioembolic stroke [1-5]. Stroke currently remains, and will remain up to 2030, as estimated by the World Health Organization experts, one of the leading causes of death worldwide [6]. Since life expectancy is increasing, the incidence rate of AF will certainly be rising [7].

Cardioembolic stroke is not only characterized by marked neurological disorders, severe disease course and development of permanent disability, but is also constituting a substantial proportion of deaths globally [8-10]. Unfortunately, adherence to guidelines on the management of patients with AF, including anticoagulant treatment for those who have survived cardioembolic stroke, is extremely poor [11]. This results from a number of factors, such as patient age and the history of cognitive disorders that may limit the use of anticoagulants. It should be noted that the risks of stroke development do not correlate with the types of AF, but in some cases AF is diagnosed at admission to a hospital with the stroke, and this observation requires comprehensive research. The aim of this study was to investigate the prognosis in patients with AF that was diagnosed in the acute phase of cardioembolic stroke.

2 METHODS

Over the period from 01 October 2013 to 31 March 2015 we conducted an open-label prospective study. Altogether, 1291 patients with a history of cardioembolic stroke were screened after discharge, while 661 of them complied with the enrollment criteria. Patient average age was 68.0 [62.0;74.0] years, with 421 (63.7%) subjects being female. The study protocol was approved by the Ethics Committee at Samara State Medical University. The study was conducted in compliance with Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki.

Study inclusion criteria were: 1) history of carotid cardioembolic stroke that occurred within previous 60 days; 2) non-valvular AF; 3) absence of hemodynamically significant carotid artery stenosis (confirmed by ultrasonography). Exclusion criteria were: 1) thyroid gland disorders; 2) history of malignancies; 3) inability to complete the questionnaires (by patient him/herself and (or) with communicant's assistance) due to neurological disorders.

The following data were recorded in case report forms: clinical and demographic data, including stroke severity estimated by the NIHSS (National Institutes of Health Stroke Scale) score; Barthel index which was used to measure performance of everyday activities and functioning of the patient; and information on prescribed medications. The NIHSS scale is a point scale that allows estimating stroke severity at discharge; it is a highly reliable and prognostically relevant tool that is applied both in clinical practice and in scientific research [12, 13]. The risk associated with the prescription of anticoagulant treatment was assessed by the HAS-BLED scale [14]. The follow-up period was 12 months.

The statistical analysis of data was performed using the IBM SPSS Statistics 21 software (license no. 20130626-3). We used descriptive statistics with a parametric test (Student's t-test) to perform the analysis. The description of normally distributed quantitative values is represented by the mean value and mean square deviation (standard deviation) (M ± SD), and non-normal data are represented by the median, 25th quartile and 75th quartile values – Me [Q25; Q75]. Parameter dynamics ANOVA with repeated measures was used to compare. Relationships between values were assessed using Pearson's correlation. The influence of the variables on the risk of death was estimated using Cox proportional hazard model and logistic regression. In both cases multivariate analysis was performed with stepwise inclusion of the predictors. The quality of prognosis determined by means of the logistic regression equation was evaluated on the basis of ROC analysis including the construction of a characteristic curve.

The optimal cut-off value was the probability of the outcome with the highest sum of sensitivity and specificity. The differences between values were considered statistically significant in case of $p < 0.05$.

3 RESULTS

We have performed the analysis of clinical and demographic data collected in all patients who experienced stroke (n = 661), and compared them with those who had AF first diagnosed at the onset of stroke. These baseline data are summarized in Table 1.

Table 1. Initial clinical and demographic indicators of all pts (n=661) and fdAF group (n=154).

Indicator	All pts n = 661	fdAF pts n = 154	p
Mean age, years (Me ± SD)	68,34 (6,17)	67,56 (6,84)	>0,05
Women, n, abs ./%	421/63,7	88/57,1	0,028
HAS-BLED scale, scores (Me ± SD)	2,15 (0,95)	2,23(0,92)	>0,05
NIHSS scale, scores (Me ± SD)	9,02 (2,88)	7,01(1,61)*	0,013
Barthel index, scores (Me ± SD)	35,12 (14,22)	32,79 (13,73)	0,009
Strok stagnation, days (Me ± SD)	60,15 (19,48)	55,66 (17,67)	>0,05
Anamnesis			
AF form, n, abs ./%: first diagnosed	154/23,3	154/100	
paroxysmal	153/23,1	-	
persistent	181/27,4	-	
constant	173/26,2	-	
Arterial hypertension, n, abs ./%	661/100,0	154/100,0	1,000
Diabetes mellitus, insulin-independent, n, abs ./%	305/46,1	83/53,9	0,011
Diabetes mellitus, insulin-dependent, n, abs ./%	41/6,2	7/4,5	0,037
CKD, n, abs ./%	212/32,1	75/48,7	0,008
IHD, n, abs. /%	406/61,4	97/63,0	0,059
Myocardial infarction, n, abs ./%	48/7,3	9/5,8	0,046
Warfarin or NOACs	70 (10,5%)	20 (13%)	0,028
ASA	532 (80,5%)	122 (79,2%)	0,076
Without ATT	59 (9,0%)	12 (7,8%)	0,033

Note. Abbreviations hereafter in Table 2-4: Me - mean value, SD - standard deviation, AF - atrial fibrillation, fdAF – first diagnosed atrial fibrillation, ASA - acetylsalicylic acid, ATT - antithrombotic therapy, IHD - ischemic heart disease, NOACs - new oral anticoagulants, CKD - chronic kidney disease.

Table 2. Characteristics of patients with fdAF, depending on the regimens of antiplatelet therapy.

Indicator	Without ATT,n=12	NOACs/ warfarinn=20	ASAn=122	p ANOVA
Mean age, years	64,83±2,95	63,10±4,17	68,57±7,11* p_1=0,005 p_2<0,001	0,001
Stagnation of the stroke, days	53,50±14,59	63,35±17,46	54,61±17,79	0,111
NIHSS scale, scores	6,33±1,37	6,60±1,35	7,14±1,65* p_1<0,001 p_2=0,018	0,121
HAS-BLED scale, scores	2,33±0,98	2,35±0,99	2,20±0,91	0,751
Barthel index, scores	35,00±11,68	40,00±11,36	31,39±13,95* p_1=0,021 p_2=0,015	0,028

Note. The data are presented as Me ± SD.

The criteria of first diagnosed AF (fdAF) included cardioembolic stroke that occurred in patients with no previous history of arrhythmia confirmed by the data from outpatient medical charts and the automated information system "Polyklinika", and abnormal rhythm values recorded on ECG during the initial examination by the emergency team in the pre-hospitalization period.

It should be noted that patients with AF with a history of stroke have multiple somatic co-morbidities associated with a number of diseases that produce a negative effect on the whole cardiovascular system via shared mechanisms. For example, in the whole group of patients with AF hypertension was verified in 100% of patients, ischemic heart disease in 61.4% of patients, diabetes mellitus in 52.3% of patients, and chronic kidney disease in 32.1% of patients. All patients had limitations in everyday activities resulting from significant neurological disorders, as well as motor, sensation, aphasic disorders and their combinations.

The group of patients with fdAF was comprised of 154 subjects, which made up 23.3% of all patients with AF and a history of stroke. According to our data, the age, HAS-BLED score, and hypertension and ischemic heart disease incidence rates of patients with fdAF were comparable with the rest of the group. However, among patients with fdAF statistical significance was seen in the lower number of female subjects and lower severity of neurological disorders, while the number of patients with chronic kidney disease, diabetes mellitus, and myocardial infarction was significantly higher. During the follow-up period, in the group of patients with AF and cardioembolic stroke, death was reported in 106 (16.0%) patients (59 women, mean age 71.8 ± 2.45 years), with 69 patients dying in hospital and 37 of them at home. According to death certificates, 69 (65.1%) patients died from recurrent acute cerebrovascular event, in 17 (16.0%) patients death occurred due to myocardial infarction, in 4 (3.8%) patients — due to malignant tumor, in one (0.9%) patient— due to acute kidney injury, and in 15 (14.2%) patients death was considered sudden.

According to Kaplan-Meier analysis (Figure 1) the highest death rate during one year was observed in the group of patients with fdAF.

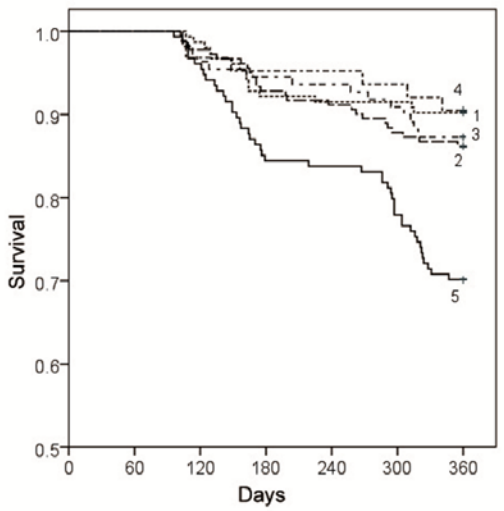

Fig. 1. **Annual survival rate (Kaplan-Meier curves) of patients depending on the AF form (1 – paroxysmal up to 1 year, 2 – paroxysmal, 3 – persistent, 4 – constant, 5 – fdAF)**

In this group, the number of deaths was almost two-fold higher (46 [29.9%] patients, of which 24 were women) than in the whole group of patients with AF and a history of cardioembolic stroke, or in the population of patients with other types of AF ($p < 0.001$).

The age of patients with fdAF at time of death was significantly ($p < 0.001$) higher than that of those who survived (71.72 ± 6.65 years vs. 65.80 ± 6.14 years). Moreover, patients with fdAF demonstrated more severe neurological disorders as assessed by the NIHSS score.

Findings from the multivariate Cox regression analysis (Table 3) demonstrate that throughout the group of patients with AF and a history of cardioembolic stroke mortality hazards were as follows: NIHSS score for stroke severity >5 (95% CI: 1.34 (1.09 – 1.64); p = 0.006); fdAF (95% CI: 3.99 (1.29 – 12.35); p = 0.016); treatment with acetylsalicylic acid (95% CI: 3.84 (1.18 – 12.48); p = 0.025); history of chronic kidney disease (95% CI: 3.41 (2.14 – 5.44); p < 0.001) and age greater than 70 years (95% CI: 0.92 (0.88 – 0.96); p<0.001).

Table 3. Death risk factors for patients with AF who suffered a stroke (multivariate model - Cox regression), (n = 661).

Indicator	Gradations	RR (95% CI)	p
Age	increase by 1	0,92 (0,88–0,96)	<0,001
NIHSS scale	increase by 1	1,34 (1,09–1,64)	0,006
Barthel index	increase by 1	0,95 (0,93–0,98)	<0,001
CHF	without CHF - reference	1	–
	CHF 2 stage	5,84 (2,69–12,68)	<0,001
	CHF 3 stage	9,71 (3,93–23,94)	<0,001
CKD	present	3,41 (2,14–5,44)	<0,001
Accepted drugs	Warfarin or NOACs — reference	1	–
	ASA	3,84 (1,18–12,48)	0,025
AF nature	paroxysmal - reference	1	–
	constant	8,49 (2,77–26,02)	<0,001
AF form	paroxysmal - reference	1	–
	fdAF	3,99 (1,29–12,35)	0,016

Note. Abbreviations: RR - risk ratio, CI - confidence interval, CHF - chronic heart failure, fdAF - first diagnosed AF.

According to the results of the multivariate Cox regression analysis (Table 4), in the group of patients with fdAF mortality hazards are associated with stroke severity and the history of ischemic heart disease, chronic heart failure or chronic kidney disease. In general, the quality of the model was $X_2 = 149$, $p < 0.001$.

Table 4. Death risk factors for patients with fdAF (multivariate model - Cox regression), (n = 154).

Indicator	Gradations	RR (95% CI)	p
Barthel index	increase by 1	0,93 (0,91–0,96)	<0,001
IHD	present	5,67 (0,97–33,26)	0,047
CHF	without CHF - reference	1	
	CHF 3 stage	5,45 (1,51–19,65)	0,010
CKD	present	2,87 (1,39–5,94)	0,005

Note. Abbreviations: RR - risk ratio, CI - confidence interval, CHF - chronic heart failure.

With a view to the conclusions regarding the prognostic significance of fdAF, multivariate logistic regression was performed for this group of patients. The reliable predictors of death in patients with fdAF appeared to be: stroke severity of less than 45 points (by Barthel index) – odds ratio 0.86 (95% CI: 0.81–0.91; $p < 0.001$), history of ischemic heart disease – odds ratio 43.65 (95% CI: 6.12–311.17; $p < 0.001$) and chronic kidney disease – odds ratio 10.89 (95% CI: 3.16–37.50; $p < 0.001$). The quality of prognosis is presented in Figure 2 as a ROC curve (area under the curve 0.954 ± 0.015, data cut-off value = 0.25, sensitivity = 87%, specificity = 88%).

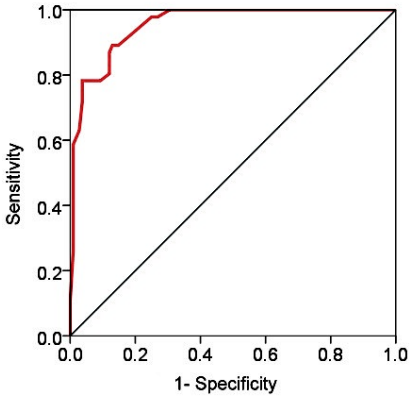

Fig. 2. **Prognostic model ROC-curve for death predicting in patients with fdAF.**

4 Discussion

Almost every fourth patient with stroke that resulted from a cardioembolic event was first diagnosed with AF at the time of hospitalization; moreover, in these patients one-year death rate comprised 30%. AF that first emerged in the acute phase of cardioembolic stroke had an extremely negative predictive value associated with high mortality and development of permanent disability [15]. Such a peculiarity in the development of cardioembolic stroke had not been observed before. This observation may be interpreted from multiple points of view.

Firstly, it seems quite reasonable to suggest that in some patients with fdAF episodes of AF did occur before hospitalization, although we have noted that, according to source medical documentation, no episodes of AF had been reported in any patient prior to the development of cardioembolic stroke. We might, however, suggest poor screening and high concern about AF, especially in elderly population. It is well known that ECG screening and use of various monitoring methods (24-hour monitoring, event recorders) lead to a significant increase in the incidence rate of AF. In one of the studies almost 80% of patients had a CHA2DS2-VASc score of 2 or more, i.e. the risk of stroke was relatively high for
these patients [16] Meta-analysis of data collected in population studies demonstrated that previously unknown episodes of AF (14 studies, 67,772 subjects) are revealed in 1.0% (CI: 0.89-1.04%) of patients, and in 1.4% (CI: 1.2-1.6%) among subjects who are 65 years and over (8 studies, 8,189 subjects), of which 67% are at high risk of stroke [17].

Secondly, our data showed great mortality risk for patients who experienced cardioembolic stroke and had first been diagnosed with AF. It should be noted that our study enrolled elderly and senior patients with multiple somatic co-morbidities.

It is known that age is a major factor responsible for the increase of AF morbidity rate in overall population [18]. Except for age, the collected data demonstrate that independent predictors of unfavourable outcome within one year after cardioembolic stroke included also stroke severity, and AF concurrent with ischemic heart disease, chronic kidney disease or chronic heart failure. The primary care screening programs aimed at early detection of AF should probably be focused on these categories of patients.

Thirdly, the high incidence rate of AF first diagnosed in the acute phase of stroke raises the need for further investigation of the mechanism responsible for thrombi formation. Considering the pathogenic mechanism of thrombi formation, it seems hardly possible that an episode of fdAF could cause thromboembolism leading to cerebral blood flow abnormalities and development of extensive brain damage

with such severe neurological disorders. Perhaps, further studies should be related to, but not limited to, investigation of peculiarities of left atrial appendage geometry and its anatomic and morphological features that promote thrombi formation over such a short period of time [19]. Certainly, these problems require specifically designed studies to be conducted in the population of patients with fdAF.

5 CONCLUSIONS

Our findings demonstrate a high rate of fdAF characterized by poor prognosis in patients with cardioembolic stroke. It is possible that in this case the term "first diagnosed stroke-associated atrial fibrillation" is applicable, which is logically relevant. The importance of focusing on this type of AF is explained by unfavourable prognosis associated with this condition, as well as by low adherence to anticoagulant therapy and high co-morbidity burden in this group of patients.

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