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Atrial fibrillation progression in middle aged patients with comorbidities

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Abstract

Objective. *To study the features of atrial fibrillation (AF) in patients with arterial hypertension (AH) and extracardiac comorbidities depending on prescribed therapy, and to access their treatment adherence.*

Materials and methods. *This observational cohort study followed up for one year 536 patients aged 45–65 years with AF (paroxysmal and persistent forms) and AH. Patients were divided into 6 groups depending on the presence of extracardiac comorbidities: 1 — AH and AF without comorbidities (n= 56) — control group; 2 — AH/AF/chronic obstructive pulmonary disease (COPD) (n= 91); 3 — AH/AF/diabetes mellitus (DM) (n= 81); 4 — AH/AF/hypothyreosis (n= 87); group 5 — AH/AF/hyperthyreosis (n=65); group 6 — AH/FP/abdominal obesity (AO) (n= 104). All the patients underwent clinical examination, anthropometry, instrumental diagnostics: electrocardiography (ECG); 24-hour Holter ECG monitoring, echocardiography (EchoCG). DNA extraction and gene polymorphisms testing were performed with polymerase chain reaction. We studied the rs1378942 and rs2200733 polymorphisms of the CSK gene of the chromosome 4q25 and rs1800795 polymorphism of the IL-6 gene of 174G/C.*

Results. *During 1-year follow-up over 50 % of patients with extracardiac diseases had an increase in the frequency of AF paroxysms by more than 20 % (DM — 76 %; COPD — 63 %; hypothyreosis — 57 %; hyperthyreosis — 64 %; AO — 58 %). The transformation into the chronic form of AF was significantly more frequent in patients with DM (p= 0.041), AO (p=0.004) and hyperthyreosis (p<0.0001). The study established statistically significant predictors of AF progres-*

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sion that interact multiplicatively: galectin-3 — the increase of which by 1 ng/l increased the risk of AF progression by 1.003 (91.0006; 1.005) (p= 0.016), and matrix metalloproteinase-9 (MMP-9) — the increase of which by 1 n/ml increased the risk of AF progression by 0.16. Other predictors included: the size of left atrium (LA) (p<0.001): the increase of which by 1 cm was associated with 2.67 (91.58; 4.65) higher likelihood of AF progression, and left ventricular mass index (LVMI) — the increase of which by 1 g/m^2 increased the risk of AF progression by 0.9 times. When comparing the frequency of admission in patients with AF, emergency admission was significantly more frequent.

Conclusion. *Early verification of the AF progression risk factors and the development of personalized algorithms as a risk meter can be used to assess the prognosis of AF and the development of its complications in patients with AH in combination with DM, COPD, hypothyreosis, hyperthyreosis, and AO.*

Keywords: *atrial fibrillation, arterial hypertension, comorbid diseases.*

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Introduction

In recent years the prevalence of AF has increased, that cannot only be explained by higher life expectancy, heart valve disease and myocardial infarction frequencies [1]. Over 6 million people suffer from AF in Europe, and the number of patients is expected to double in the next 50 years due to increasing life expectancy of the population. AF increases the risk of stroke by 5 times and causes the occurrence of every fifth stroke [2]. Mortality, reoccurrence of stroke and disability rates are higher in patients with AF after the ischemic stroke compared with patients without AF. Accordingly, the risk of death in patients with stroke and AF is 2 times higher, and the cost of rehabilitation is 1.5 times higher [3].

The updated clinical guidelines indicate that patients with AF have increased risk of complications, especially when they are also diagnosed with AH. Up to 30–40 % of these patients are admitted to the hospital annually, 20–30 % of all strokes are associated with AF, and left ventricular dysfunction is by 20–30 % higher in among them [4]. AF develops in patients with many comorbid conditions, which can both pathogenetically contribute to the progression of AF, and independently aggravate the quality of life of patients and increase the probability of complications and sudden cardiac death. Any structural heart diseases, such as AH, chronic heart failure (CHF) can promote slow progression of structural remodeling of ventricles and atria. This process is associated with the proliferation and replacement of fibroblasts with myofibroblasts, as well as enhanced growths of connective tissue and fibrosis [5]. With the accumulation of the new data on the pathogenesis of AF, including data on the role of concomitant diseases, the division of AF to primary and idiopathic becomes questionable [6]. Thus, recent large-scale study, which included 3978 patients with AF (Euro Heart Survey), showed that only 3 % of the study participants had idiopathic or primary type of AF [7].

It has been known previously that any arrhythmia tends to progress, but due to the increasing number of patients with AF in the population and the assumption that comorbid pathology is associated with such tendency, researchers have turned their attention to this problem [8]. In recent years many studies have shown the association between AF and pulmonary pathology, COPD in particular [9]. It has been proven that DM and / or AH are also associated with the development of AF [10]. Obesity is the most frequent concomitant and leading risk factor for the development of AH that contributes to the structural and functional remodeling of the myocardium, the so-called lipotoxicity phenomenon [11].

Several large studies have investigated the effect of the rs1378942 polymorphism of the CSK gene on the course of various pathological processes [12]. Studies from Japan, East Asia, and Europe have revealed the association of the rs1378942 polymorphism of the CSK gene with the development of AH and AF [13]. The role of this polymorphism of the CSK gene in the development of AH has also been confirmed in Russian Federation [14]. In addition, the role of polymorphisms rs1378942 and rs2200733 of the CSK gene of the chromosome 4q25 in the occurrence of vascular dysfunction in patients with AO was revealed [15]. However, no studies investigated common pathogenetic causes of AF, AH and AO.

Early diagnosis of the factors associated with AF progression, prescription of additional therapy for

Scheme 1

Step 1. Prospective cohort study of 308 patients with AF and AH in combination with extracardiac comorbidities. Age – 53,2 [49,5; 58] years, n=308					
AH/AF n = 56	AH/AF/DM n = 40	AH/AF/COPD n = 47	AH/AF/ hypothyreosis n = 59	AH/AF/ hyperthyreosis n = 42	AH / FP/ AO n = 64

Clinical examination (n = 308)	ECG (n=308) 24-hour Holter ECG monitoring (n=69) Treadmill cardiac stress test (n = 39)	Structural and function assessment of cardiac function– EchoCG (n = 308)	The assessment of cardiac fibrosis and remodeling markers: MMO-9, Galectin-3, NT-proBNP, inflammation markers: IL -1, IL-6, IL-8, IL-10 (n = 308)	Blood chemistry test: lipid profile, K+, glucose GFR, CRP, fibrinogen, creatinine, urea, uric acid (n = 308)	Genetic testing: polymorphism rs1378942 of the CSK gene, rs2200733 of the 4q25 chromosome and 174G/C (rs1800795) of the IL-6 gene and complex studying of the genotype frequencies andrs2200733 and rs 1378942 polymorphisms of the CSK gene of 4q25 choromosome and 174G/C (rs1800795) of the IL-6 gene (n = 167)

Comparative analysis, n = 308

secondary prevention of the arrhythmia and correct strategy for its management can slow down the progression of AF and the development of CHF that will improve not only clinical status of patients, but also their prognosis. Despite the fact that AF occurs mostly in elderly people with various manifestations of coronary heart disease, its prevalence in young and middle-aged patients with AH is constantly increasing [16]. The discussed above positions determine the objectives of this study.

Objective

To study the features of AF progression in middle-aged patients with various comorbidities.

Materials and methods

This observational cohort study followed up for one year 536 patients aged 45–65 years with AF (paroxysmal and persistent forms) and AH in combination with extracardiac comorbidities.

The first step was prospective cohort study of 308 patients with AF and AH in combination with extracardiac comorbidities from Novosibirsk Regional Clinical Cardiology Dispensary. Patients were divided into 6 groups depending on the presence of extracardiac comorbidities: 1 — AH and AF without comorbidities (n= 56); 2 — AH/AF/ COPD (n= 47); 3 — AH/AF/ DM (n= 40); 4 — AH/AF/hypothyreosis (n= 59); group 5 — AH/AF/ hyperthyreosis (n= 42); group 6 — AH/AF/AO (n= 64) (Scheme 1).

The second step was prospective cohort paired comparative study of 238 patients with AH and extracardiac comorbidities from Novosibirsk Regional Clinical Cardiology Dispensary. Patients were divided into 6 groups: 1 — AH without extracardiac comorbidities (n= 56); 2 — AH / COPD (n= 44); 3 — AH/DM (n= 41); 4 — AH/hypothyreosis (n= 28); group 5 — AH/hyperthyreosis (n= 50); group 6 — AH/AO (n=50) (Table 1). These groups were compared by all the parameters with the groups identified at the first step (Scheme 2).

Written informed consent was waived from all the participants before the study. The study was approved by the local Ethics Committee of Novosibirsk State medical University of the Ministry of health of Russia (Protocol № 147 from "18" may 2017). During the study, we followed-up patients for 1 year in order to assess the effect of comorbidities on the AF progression, the term "AF progression" was interpreted as the process of steady development of chronic form of AF from the paroxysmal

Scheme 2

Step 2. Prospective cohort paired comparative study of 238 patients with AH and extracardiac comorbidities, age – 45–60 years, n = 546					
AH n = 52	AH/DM n = 41	AH/COPD n = 44	AH/hypothyreosis n = 28	AH/hyperthyreosis n = 23	AH/AO n = 50

AH n = 52	AH/DM n = 41	AH/ COPD n = 44	AH/ hypo-thyreosis n =28	AH/ hyper-thyreosis n = 23	AH/AO n = 50		AH/AF n = 56	AH/AF/DM n = 40	AH/AF/COPD n = 47	AH/AF/hypo-thyreosis n = 59	AH/AF/ hyper-thyreosis n = 42	AH/AF/AO n =64
age 51 [45.5; 56] years, n=238							age 53.2 [49.5; 58] years, n = 308					

Comparative analysis, n = 546

AF [9]. Patients with severe stage of concomitant extracardiac pathology, heart valve pathology, systemic, oncological, acute and chronic inflammatory diseases, coronary heart disease, chronic kidney disease (CKD) above stage 3, liver pathology with impaired function, and history of strokes were excluded from the study.

All the patients underwent clinical examination, anthropometry, instrumental diagnostics: electrocardiography (ECG); 24-hour blood pressure and Holter ECG monitoring (SCHILLER, Switzerland), echocardiography (EchoCG) in accordance with the recommendations of the American Society of Echocardiography (ASE) in M and 2D modes on the Vivid 7 apparatus (General Electric, USA). All included patients underwent: standard general clinical examination; biochemical blood test, as well as determination of NT-proBNP concentration using the NTproBNP — ELISA — Best reagent kit and galectin-3 by ELISA — Bender MedSystems GmbH, (Austria), as markers of fibrosis and myocardial remodeling. DNA extraction and gene polymorphisms testing were performed with polymerase chain reaction followed by analysis of restriction fragment length polymorphism (Sibenzyme, Russia). We studied the rs1378942 and rs2200733 polymorphisms of the CSK gene of the chromosome 4q25 and rs1800795 polymorphism of the IL-6 gene of 174G/C.

Numerical data were compared using Mann-Whitney U-test, the bias of the distributions was calculated with 95 % confidence interval. Multiple group comparisons were performed using the Kruskal Wallis test. Pairwise comparison of all studied groups with the comparison group was carried out according to Dunnett's scheme, pairwise comparison of all groups was carried out using Tukey's method, to eliminate the effect of multiple pairwise comparisons, the Benjamini-Hochberg procedure was performed. To assess the dynamics of readmission, the Kaplan-Meier curves and the logrank test were used. The level of statistical significance was set up as $p<0.05$. The lower bound of the statistical significance was set as 80 %. All statistical calculations were performed in the Rstudio program (version 0.99.879 — © 2009–2016 RStudio, Inc., USA, 250 Northern Ave, Boston, MA 02210 844–448–121, info@rstudio.com) in the R language (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results and discussion

The assessment of the AF progression was performed by the analysis of the frequency of AF episodes over the last year. It was established that over 50 % of patients with extracardiac diseases had increased frequency of paroxysms by over 20 % (DM — 76 %; COPD — 63 %; hypothyreosis — 57 %; hyperthyreosis — 64 %; AO — 58 %), and patients without concomitant diseases had less than 20 % frequency of AF paroxysms (AF/AH — 17 %). Comparative analysis revealed that the transformation of paroxysmal AF to chronic AF, which is the indicator of arrythmia progression, in patients with AO occurred after at 5.5 (3; 7) months on average ($p= 0.004$). In patients with DM — at 4 (3; 7) months, it was also significantly faster compared with the control group ($p= 0.041$), and patients with COPD, significantly more often ($p= 0.001$) had the transformation of paroxysmal AF into persistent form. The progression of the paroxysmal AF into the chronic form in patients with hyperthyroid was noted at 5.8 months (4.5; 11) ($p<0.001$), which is also significantly faster compared with the control group.

The regression analysis was performed in order to establish factors associated with the AF progression. Univariate and multivariable regression models were used to assess AF progression risk factors. We assessed the following parameters: the stage and functional class of CHF according to NYHA, EchoCG, biochemical markers of cardiac remodeling such as: galectin-3 and NT-proBNP, biochemical parameters: C-reactive protein (CRP), cytokines, MMP-9, uric acid, GFR, fibrinogen.

Only models with $p<0.2$ significance level were selected from the one-factor model for all the predictors. The association between variables was also assessed with Spearman's correlation coefficient in order to eliminate the effect of predictors collinearity. In absolute value numbers over 0.35 indicate the presence of a relationship between predictors. We selected the predictor with the lowest achieved level of significance from the groups of related predictors in the multivariate linear regression model in the univariate logistic regression model for one predictor. Optimal linear regression models were constructed using forward and backward selection algorithms and model minimizing criterion — the Akaike information criterion (AIC). Therefore, statistically significant predictors of AF progression were revealed: with the elevation of CHF by 1 functional class ($p= 0.035$) — the risk of AF progression increased by 1.36 (91.03; 1.82) times.

Table 1. **Calculation and comparison of binary indicators between groups with electrical and medical cardioversion**

Parameter	Electrical cardioversion group n = 332 n, % [95 % CI]	Medical cardioversion group n = 214 n, % [95 % CI]	Relative risk [95 % CI]	*Fisher's exact test*
AF progression (yes/no)	64 % [58 %; 71 %]	61 % [48 %; 72 %]	1,061 [0,85; 1,33]	0,65
Admission during the year	51 % [44 %; 58 %]	28 % [16 %; 37 %]	0,651 [0,54; 0,79]	< 0,001*

CI — confidence interval, * — statistically significant parameters

When constructing a multivariate logistic regression model, the full model included covariates with correlation coefficients with absolute value less than 0.5. We established the presence of related, statistically significant predictors of AF progression that function multiplicatively. These were indicators of cardiac remodeling: galectin-3, the elevation of which by 1 ng/L increased the risk of AF progression by 1.003 (91.0006; 1.005) times (p= 0.016) and MMP-9 — the elevation of which by 1 n / ml increased the risk of AF progression by 0.16 times. Other statistically significant predictors of AF progression included LA size (p<0.001): its increase by 1 cm was associated with elevation of the AF progression by 2.67 (91.58; 4.65) times and LVMI, the increase of which by 1 g/m^2 increased the risk of AF progression by 0.9 times; as well as inflammation markers — IL-6 elevation by 1 pg/1 was associated with increase of AF risk by 0.6 times.

During the assessment of emergency hospital admissions, it was established that 51 % (44 %; 58 %) of patients were urgently admitted after electrical cardioversion and 26 % (916 %; 37 %) — after medical cardioversion, p<0.001. The relative risk was 0.651 (90.54; 0.79) (Table 1).

The second step was prospective cohort paired comparative study. This stage consisted of two substages: first — 308 patients with AH and without AF with concomitant extracardiac diseases (DM, COPD, hypothyreosis, hyperthyreosis, AO) with average age of 52 (46.5; 57) years, and second — comparative analysis of the data of 238 patients with AF, AH and extracardiac diseases with the data of 308 patients with AH with extracardiac diseases without AF).

During the assessment of AH duration, it was found that patients with AF had significantly longer AH duration compared with patients without AF, except for the group of patients with COPD. The development of AF correlated with the duration of AH (r= –0.332, p= 0.044) (Table 2).

The level of MMP-9 increased in all groups of patients with AF compared with patients without AF, the level of MMP-9 also correlated with the development and progression of AF (Figure 1).

The level of serum galectin-3 in all patients with AF was significantly higher compared with patients without AF (Figure 2).

A comparative analysis of 174G/C (rs1800795) polymorphism of the IL-6 gene in patients with AH with various concomitant diseases with and without AF revealed that patients with AF more frequently had CC genotype (Table 3).

Table 2. **Clinical indicators in patients with or without AF**

Parameters	AF and AH n= 308 Median [IQR]	AH without AH n= 238 Median [IQR]	Difference [95 % CI]	Mann–Whitney U test
Age, years	56 [53; 60]	50 [45; 56]	6 [2; 11]	0,005*
Total cholesterol, mmol/l	5,02 [4,16; 6,04]	5,85 [5; 6,95]	0,76 [0,04; 1,45]	0,034*
LDL-cholesterol, mmol/l	2,42 [2,13; 3,02]	3,45 [2,65; 4,5]	0,98 [0,33; 1,58]	0,005*
Potassium, mmol/l	4,0 [3,8; 4,2]	4,4 [4,23; 4,47]	0,3 [0,15; 0,5]	< 0,001*
GFR, ml/min	57,9 [50,32; 70,7]	78,0 [64; 90]	9 [3; 25,99]	0,014*
IL-6, pg/ml	8,4[1,48;9,35]	4,3 [0,96; 10,93]	0,3 [0,33; 1,67]	0,004*
MMP-9, ng/ml	437,0[313,25; 659,3]	362,0 [205,3; 493,1]	73 [0,33; 1,49]	0,005*
NT-proBNP, pg/ml	101,36 [94,92; 116,7]	87,99 [33,5; 134,2]	33,71 [1,48; 59,58]	0,047*
Galectin, ng/ml	52,80 [13,99; 100,33]	14,05 [7,06; 14,76]	38,04 [5,77; 57,24]	< 0,001*
Systolic blood pressure, mmHg	154 [145; 165]	168 [158,25; 178,25]	13 [4; 22]	< 0,001*
End-diastolic volume, cm	5,8 [5,3; 6,2]	5,6 [5,27; 5,73]	0,3 [0,1; 0,5]	0,062*
Left ventricular diastolic dysfunction, (E/A, ms)	1,44 [1,2;1,6]	0,6 [0,4;0,8]	0,84 [0,75;0,9]	0,003*
AH duration, years	5 [4; 7]	3 [2; 5,25]	2 [1; 3]	< 0,001*

CI — confidence interval, IQR — interquartile range, * — statistically significant parameters

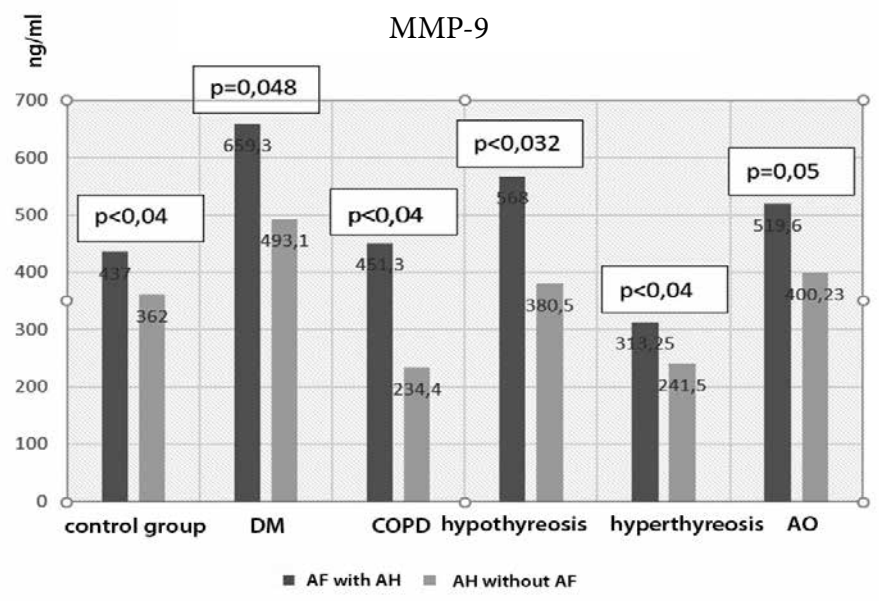

Figure 1. The level of matrix metalloproteinase-9: p — the level of significance compared with groups without AF

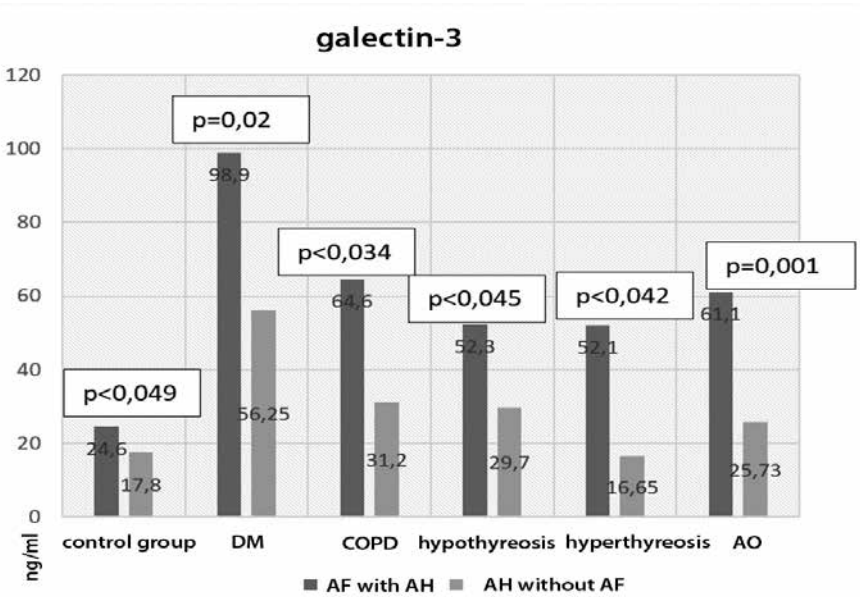

Figure 2. The level of galectin-3: p — the level of significance compared with groups without AF.

Table 3. **Genetic determinants in patients with AH and with or without AF**

Parameters	AH and AF n= 164	AH without AF n= 188	Fisher's exact test
rs2200733 polymorphism of the 4q25 chromosome CT CC	46 % [18 %; 67 %] 54 % [38 %; 87 %]	51 % [28 %; 71 %] 49 % [29 %; 60 %]	0,883
rs1378942 polymorphism of the CSK gene AA AC CC	51 [35 %; 62 %] 45 % [18 %; 47 %] 4 % [18 %; 47 %]	38 % [22 %; 47 %] 50 % [23 %; 71 %] 12 % [7 %; 26 %]	0,424
174G/C (rs1800795) polymorphism of the IL-6 gene CG CC GG	79 % [38 %; 97 %] 21 % [18 %; 35 %] 14 % [18 %; 47 %]	30 % [18 %; 57 %] 46 % [21 %; 62 %] 4 % [1 %; 7 %]	< 0,003*

* — statistically significant parameters

Table 4. **The development of complications in patients with AH and with or without AF**

Parameters	AH and AF n=308 n, % [95% CI]	AH without AF n= 238 n, % [95% CI]	RR [95% CI]	Fisher's exact test
Admission during 1-year follow-up	25, 47% [34%; 60%]	17, 94% [74%; 99%]	0.499 [0,37; 0,68]	< 0,001*
Cardioembolic strokes during 1-year follow-up	21% [12%; 33%]	6% [1%; 26%]	3,736 [0,52; 26,95]	0,073
CHF+/–	91% [80%; 96%]	89% [67%; 97%]	1,019 [0,85; 1,23]	> 0,999

CI — confidence interval, RR — relative risk, * — statistically significant parameters

A comparative analysis of cardioembolic strokes, CHF progression and all-cause emergency hospital admission during 1-year follow-up depending on the presence of AF was performed. Only emergency hospital admission differed significantly, and the incidence of cardioembolic strokes tended to increase in AF patients — 11.2% versus 1.6% in patients without AF (Table 4).

The comparative analysis of the frequency of all-cause hospital admission in patients with AH with extracardiac pathology, depending on the presence of AF during 1-year follow-up revealed that patients with AF combined with hyperthyreosis, AO and DM were admitted more frequent compared with patients without AF.

The development of personalized algorithms for the formation of risk groups for the development of complications and progression of AF in patients with AH and extracardiac diseases was performed with various statistical methods, where logistic regression model was superior to others. It was established that groups with hypothyreosis, DM and AO correlated with the progression of AF. According to Pearson correlation coefficient the functional class of CHF correlated with the progression of AF, which also correlates with total cholesterol, low density lipoproteins and rs1378942 polymorphism of the CSK gene.

In the multivariate logistic regression model, the following statistically significant predictors of AF progression were identified (corresponds to 1 unit (U) of the indicator measurement): the elevation functional class (NYHA) of CHF by 1 U increased the risk of AF progression by 25.49 (5.05; 377.32) times (p= 0.002), end-diastolic volume — by 0.13 (0.02; 0.65) times (p= 0.025), ejection fraction — by 0.87 (0.76; 0.97) times (p= 0.027), glucose — by 0.29 (0.09; 0.71) times (p= 0.017), CRP — by 0.41 (0.19; 0.74) times (p=0.009). The predictors of cardioembolic stroke included total cholesterol, the elevation of which by 1 U increased the risk of cardioembolic stroke by 0.72 [0.55; 0.92] times, and triglycerides — by 1.27 [1.02; 1.59] times. No statistically significant predictors of CHF progression were identified, although in the univariate model, statistically significant indicators included: the LA size, the enlargement of which by 1 cm increased the risk of CHF progression by 5.04 (1.80; 16.18) times, and NT-proBNP — by — 1.01 (1.00; 1.02) times.

The final result of the personalized algorithms for the formation of risk groups for the development of complications and progression of AF was tested with comparative analysis and mathematical calculation, and the key parameters of the optimal logistic regression model were: functional class (NYHA) of CHF, LVMI, LA size, end-diastolic volume and galectin-3 (Table 5).

Findings

1. The duration of AH (p= 0.001), and its combination with DM (p= 0.041) and AO (p= 0.004) were prognostically negative in patients with AH and AF.

2. The study showed the prognostic value of fibrosis and remodeling biomarker such as galectin-3 and MMP-9, as well as inflammation markers — IL-6, IL-8 and IL-10, in the AF development and progression in patients with AH and extracardiac diseases.

3. Rs1378942 polymorphism of the CSK gene and 174G / C (rs1800795) of the IL6 gene were associated with the risk of AF reoccurrence in patients with AH and DM, COPD, hyperthyreosis and AO. The increase of CC genotype was found in patients with AF during the comparative analysis of 174G / C (rs1800795) of

Table 5. **Optimal logistic regression model of the AF progression**

Predictor	RR [95% CI]	p
Optimal logistic regression model		
CHF (NYHA)	1.4 [0.93; 2.13]	0.013*
LVMI	0.99 [0.97; 1]	0.014*
Left atria size	3.07 [1.74; 5.63]	<0.001*
End-diastolic volume	7.85 [2.39; 35.88]	0.002*
Galectin-3	1.002[0.76; 1.004]	0.009*

CI — confidence interval, * — statistically significant parameters

IL-6 gene in patients with AH and various comorbidities with and without AF.

4. Personalized algorithm for the formation of risk groups for the development of complications and progression of AF in patients with AH and extracardiac diseases was developed and tested. This method is based on the determination of galectin-3, MMP-9, pro- and anti-inflammatory cytokines levels, the E / A index, LVMI, LA size assessment, and the determination of genotypes of polymorphism rs1378942 of the CSK gene and 174G / C (rs1800795) of the IL-6 gene.

Conflict of interest: none declared.

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