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CLINICAL COURSE AND RISK PREDICTION OF PERMANENT ATRIAL FIBRILLATION DEVELOPMENT IN PATIENTS WITH CHRONIC HEART FAILURE AND MID-RANGE EJECTION FRACTION OF THE LEFT VENTRICLE

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Ключові слова: *постійна форма фібриляції передсердь, хронічна серцева недостатність з помірно зниженою фракцією викиду лівого шлуночка, клінічний перебіг, прогноз*
Ключевые слова: *постоянная форма фибрилляции предсердий, хроническая сердечная недостаточность с умеренно сниженной фракцией выброса левого желудочка, клиническое течение, прогноз*

Abstract. Clinical course and risk prediction of permanent atrial fibrillation development in patients with chronic heart failure and mid-range ejection fraction of the left ventricle. Khaniukov O.O., Yalovenko M.I., Kalashnykova O.S., Kravchenko O.I. *The purpose of the study was to establish clinical features of permanent atrial fibrillation (AF) in patients with heart failure mid-range ejection fraction (HFmrEF) and to develop a mathematical model for predicting arrhythmia development. The study included 42 patients with ischemic heart disease (IHD), arterial hypertension (AH), permanent AF and HFmrEF (1 group), mean age – 68.0±1.2 years (21 men and 21 women) and 36 patients with IHD/AH and HFmrEF without AF, mean age- 67.5±0.7 years (22 men and 14 women). The results of the study show, that patients with permanent AF and HFmrEF are characterized by a higher diastolic arterial pressure, higher values of the LDLP, index of end-systolic volume of LV (iESV LV), interseptal thickness and lower EF of the LV in comparison with patients without AF. Patients with permanent AF and HFmrEF also have increased plasma levels of hsCRP, IL-1β, IL-6 and IL-10 in comparison with patients without AF. A mathematical model with scoring system of hsCRP, IL-1β, LV mass index, HDLP, LDLP was developed to assess the risk of AF development in patients with HFmrEF with accuracy of 85.9%, sensitivity of 85.7% and specificity of 86.1%.*

Реферат. Клиническое течение и прогнозирование риска развития постоянной формы фибрилляции предсердий у пациентов с хронической сердечной недостаточностью и умеренно сниженной фракцией выброса левого желудочка. Ханюков А.А., Яловенко М.И., Калашникова О.С., Кравченко А.И. *Целью исследования было установить особенности клинического течения постоянной формы фибрилляции предсердий (ФП) у пациентов с хронической сердечной недостаточностью с умеренно сниженной фракцией выброса левого желудочка (ХСНусФВ) и разработать математическую модель прогнозирования риска развития этой аритмии. В исследование было включено 42 пациента с ишемической болезнью сердца (ИБС), артериальной гипертензией (АГ), постоянной формой ФП и ХСНусФВ (21 мужчина и 21 женщина, средний возраст – 68,0±1,2 года) и 36 больных с ИБС, АГ и ХСНусФВ без ФП (22 мужчины и 14 женщин, средний возраст – 67,5±0,7 года). В результате проведенного исследования установлено, что у пациентов с постоянной формой ФП и ХСНусФВ выявлены более высокие цифры диастолического артериального давления (АД), значения холестерина липопротеидов низкой плотности (ХС ЛПНП), индекса конечно-систолического объема (иКСО) левого желудочка (ЛЖ) и толщины межжелудочковой перегородки (ТМЖП) в сравнении с больными без ФП. У пациентов с постоянной формой ФП и ХСНусФВ определено достоверное (в сравнении с больными*

без ФП) возрастание уровней высокочувствительного С-реактивного белка (вч-СРБ), интерлейкина-1β (ИЛ-1β), интерлейкина-6 (ИЛ-6) и интерлейкина-10 (ИЛ-10) в плазме крови, что свидетельствует о наличии более выраженного хронического системного воспаления. Разработана математическая модель, которая включает в себя уровни вч-СРБ, ИЛ-1β, значения индекса массы миокарда левого желудочка (ИММЛЖ), ХС ЛПНП, холестерина липопротеидов высокой плотности (ХС ЛПВП) у пациентов с ХСНусФВ, и позволяет по суммарной балльной оценке этих показателей прогнозировать риск развития постоянной формы ФП с точностью 85,9%, чувствительностью – 85,7%, специфичностью – 86,1%.

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, which is considered a new non-infectious epidemic of the millennium [7, 9]. Many patients have a progressive course of AF [5]: from short and rare paroxysms to longer and more frequent episodes. Over time, in most patients arrhythmia becomes persistent and progresses to a permanent form [10]. During the first year of AF in 15-20% of patients arrhythmia transfors from paroxysmal to persistent form, then every decade of the patient's age the risk of transformation of AF to a permanent form doubles [7]. Only in a small part (2-3% of patients) AF persists at the level of paroxysmal form for several decades [9].

The highest probability of risk of AF progression from paroxysmal to persistent and permanent forms is associated with old age and the presence of chronic heart failure (CHF) [4, 12], valvular heart disease [9], increased size of the left atrium (LA) [6], the presence of hyperthyroidism [3, 5], asymptomatic arrhythmia and lack of timely treatment [13].

Recently, much attention has been paid to the study of the impact of chronic inflammation on the development and progression of cardiac arrhythmias. Such indicator markers include: highly sensitive C-reactive protein (hs-CRP), interleukin - 6 (IL-6), interleukin – 1 beta (IL-1β), tumor necrosis factor – alpha (TNF-alpha), endothelin – 1 and others [1].

CHF is one of the risk factors for the occurrence and rapid progression of AF [8, 14]. AF and CHF have common risk factors, they often coexist and the prognosis of patients with AF and CHF is worse than that of patients with only one of these pathologies. However, the prognostic consequences of AF in patients with CHF remain controversial. Most current data suggest that AF is associated with increased mortality in patients with CHF with low ejection fraction (HFlEF) compared with patients with CHF and preserved ejection fraction (HFpEF). At the same time, according to the long-term register of the European Society of Cardiology, AF is not associated with a poor prognosis in patients with CHF [8]. Compared with HFpEF and HFlEF, the clinical characteristics and prognosis of patients with CHF and mid-range ejection fraction (HFmrEF) remain understudied, mortality and hospitalization rates differ significantly in studies published [2, 6], management strategies for such patients are not well defined. In a study by Startipy U. et al. the incidence of AF in patients with HFpEF was 23.1%, with HFmrEF – 21.5% and with HFlEF – 55.4%. Patient groups did not differ in the factors associated with AF, but the incidence of mortality, hospitalization and stroke was higher in patients with HFpEF [5].

Thus, the aim of the study is to establish the features of the clinical course of the permanent form of AF in patients with HFmrEF and to develop a mathematical model for predicting the development of this arrhythmia.

MATERIALS AND METHODS OF RESEARCH

The study included 42 patients with ischemic heart disease/hypertension, persistent AF and HFmrEF (group 1), mean age – 68.0±1.2 years and 36 patients with ischemic heart disease/hypertension and HFmrEF without AF (group 2), mean age – 67.5±0.7 years (22 men and 14 women). IHD: stable angina II FC diagnosed in 42 (53.8%), III FC – 36 (46.2%). The study groups of patients were statistically comparable ($p>0.05$) by sex and age. The average duration of AF from the first episode according to the words of patients and ambulatory card data was about 8.5±0.3 years (Table 1).

In patients included in the study, complaints were analyzed in detail, anthropometric, clinical, laboratory and instrumental indicators were evaluated. Verification of the diagnosis of CHF was established in accordance with the recommendations of the European Society of Cardiology (ESC) in 2012 for the diagnosis and treatment of chronic heart failure [7]. After the publication in 2016 of updated ESC recommendations for the diagnosis and treatment of chronic heart failure, the examined patients were related to the group of HFmrEF [8]. Verification of the diagnosis of AF was performed in accordance with the recommendations of the ESC in 2016 for cardiac arrhythmias [9].

Echocardiography was performed according to the standard method on the device "Mylab 40 Esaote" or "Q40 SG HealthCare", taking into account the recommendations of the American Society of Echocardiography [11].

Table 1

Clinical characteristics of patients under study

Indicator	IHD/AH, HFmrEF and AF (n=42)	IHD/AH, HFmrEF without AF (n=36)	Difference between groups (p)
Men/women, (%)	21/ 21 (50.0% / 50.0%)	22/ 14 (61.1% / 38.9 %)	$\chi2$=0.97; p=0.74
Age, years, M±m	68.0 ± 1.2	67.5±0.7	t=1.98; p=0.57
BMI	27.8±0.61	26.5±0.45	t=1.73; p=0.46
Smokers, (%)	11 (26.2 %)	10 (27.8 %)	$\chi2$=0.14; p=0.68
IHD: stable angina II	19 (45.3 %)	17 (47.3 %)	$\chi2$=1.04; p=0.75
IHD: stable angina III	23 (54.7 %)	19 (52.7 %)	
NYHA II	16 (38.1 %)	20 (55.5 %)	$\chi2$=3.63; p=0.47
NYHA III	26 (61.9 %)	16 (44.5 %)	
SBP, mm Hg.	158.0±1.58	155.2±0.93	t=1.45; p=0.06
DBP, mm Hg.	95.3±0.58	90.0±0.68	t=5.93; p=0.001

Notes. * – by Student's t-criterion, in other cases - by Pearson's $\chi2$ criterion.

The content of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL cholesterol) was determined using a colorimetric test of sets of "Spinelab" (Ukraine), triglycerides (TG) – using the "Dialipon DS set (Russia); the level of low-density lipoprotein cholesterol (LDL cholesterol) was calculated by Friedwald's formula.

The degree of activity of systemic inflammation in patients of these groups was determined by the levels of hs-CRP and IL-1β, -6 and -10 by enzyme-linked immunosorbent assay, conducted on the basis of the Diagnostic Center of LLC "Pharmacies of the Medical Academy" (Dnipro) using sets of reagents produced by "Vector-Best" (Russia).

Statistical processing of research materials was performed using biostatistics methods implemented in the packages of licensed programs Statistica 6.1 and MedCalc Statical Software 11.5.0. For mathematical analysis logistic regression with the calculation of odds ratio (OR) and ROC-analysis with the calculation of curves and area under them (AUC), sensitivity (CT) and specificity (SP) with confidence intervals (CI), equal to 95% was used. Logistic regression and sequential Wald's analysis were used to build mathematical models and prediction. The analysis included indicators under conditions of statistical significance (p) at the level of <0.05 (5%).

RESULTS AND DISCUSSION

During hospitalization in the cardiology department, 35 (83.3%) patients complained of headache in the first group, and 29 (80.6%) in the second group ($\chi2$=0.10; p=0.75). 40 (95.2%) patients of the first group and 34 (94.4%) patients of the second group ($\chi2$=0.03; p=0.87) experienced palpitations without significant difference between the groups. Heart failure was noted by half of the patients of the first group 22 (52.4%) with permanent AF and half as many patients of the second group without AF – 8 of 36 (22.2%) patients ($\chi2$=7.45; p=0.006). Shortness of breath was noted by 37 (88.1%) patients of the first group and 28 (77.8%) patients of the second group without significant difference between the groups ($\chi2$=1.49; p=0.22). Edema 2+ / 3+ was revealed in all patients of the first – 42 (100.0%) and the second group – 36 (100.0%). Such a complaint as sleep disorders associated with manifestations of heart failure was noted by 40 (95.2%) patients of the first group and 32 (88.9%) of the second group, respectively ($\chi2$=1.1; p=0.29).

The degree of hypertension in patients of both groups met the criteria of 1 and 2 degrees, according to the recommendations of the European Hypertension Association (2018). Among patients with AF, half of the patients in each group met the criteria of 1 and 2 degree of hypertension. In the group without AF, 1 degree of hypertension was determined in 21 (58.3%) patients, 2 degree – in 15 (41.6%) ($\chi2$=0.54; p=0.46) patients. The average level of SBP and DBP of the first group was 158.0±1.58 and 95.3±0.58 mm Hg of the second group – 155.2±0.93 and 90.0±0.68 mm Hg. without significant differences between them.

One of the significant factors in cardiovascular risk is overweight. BMI in the examined patients of the first group ranged from 20.2 to 35.4 kg/m^2 and averaged 27.8±0.61 kg/m^2, in the second group – from 22.3 to 32.9 kg/m^2 (average – 26.5±0.45 kg/m^2), which indicates overweight in patients of all study groups without significant differences between groups (t=1.73; p=0.46).

Analysis of the lipid profile did not reveal statistically significant differences in the level of total cholesterol (TC) and triglycerides (TG) in patients of the first and second groups. The level of HDL cholesterol significantly differed in both groups of the study and was higher in the second group, which indicates more pronounced antiatherogenic properties and less progressive endothelial dysfunction in the future. The level of LDL cholesterol in the first group was significantly higher than in the second group, which indicates a higher rate of adhesion of cholesterol in the vessels of patients with AF. The index of atherogenicity (IA) in the first group was significantly higher than the second group, because the determining indicator in the calculation of this index is HDL cholesterol, which was lower in patients of the first group, despite the fact that the initial level of TC in both groups was not significantly different. The increase in IA directly indicates higher proatherogenic activity in patients with permanent AF compared with patients without this arrhythmia (Table 2).

Table 2

Average level of lipid profile indicators in patients of both groups at the onset of study (M±m)

Indicator	IHD/AH, HFmrEF and AF (n=42)	IHD/AH, HFmrEF without AF (n=36)	Difference between groups (p)
TC, mmol/l	5.57±0.08	5.38±0.05	t=1.79; p=0.08
HDLP, mmol/l	1.08±0.01	1.15±0.03	t=-2.62; p=0.02
LDLP, mmol/l	4.06±0.06	3.67±0.06	t=4.08; p=0.001
TG, mmol/l	2.69±0.02	2.62±0.03	t=1.69; p=0.09
IA	4.48±0.09	4.23±0.06	t=2.13; p=0.01

Notes: * – by Student's t-criterion; p – difference between first and second group.

Renal excretory function was assessed by calculating the glomerular filtration rate (GFR). In patients with a permanent AF and CHF, a significant decrease in GFR (68.4±0.5 ml/min / 1.73 m^2) was observed compared with patients with CHF without AF. 0.4 ml/min / 1.73 m^2, p=0.03).

In patients with a permanent AF, the parameters of the volume of LV cavity were significantly higher (iESV) – 48.85±0.99 ml/m^2 against 44.35±0.90 ml/m^2, p=0.001), and the indicators that characterize contractile function of the myocardium, significantly lower (LV EF – 44.2±0.39% vs. 47.1±0.6%, p=0.001) of the corresponding indicators of the group without AF. Also in the first group TIVS was significantly higher (1.31±0.007 cm) compared with the second group (1.29±0.005 cm, p=0.01) (Table 3).

In patients with IHD/AH, HFmrEF and AF, indicators of cytokines and hs-CRP were significantly higher compared with patients with IHD/AH, HFmrEF without AF: IL-6 (7.09 pg/ml [5,87; 13, 77] vs. 5.89 pg/ml [4.61; 12.90], p=0.04), IL-1β (11.21 pg/ml [4.64; 17.24] vs. 4.57 pg/ml [3.52; 12.44], p=0.03), IL-10 (33.04 pg/ml [15.91; 35.54] vs. 14.50 pg/ml [6.49; 21.74], p<0.001) and hs-CRP (4.12 mg/l [3.51; 6.77] vs. 3.15 mg/l [2.67; 5.24], p=0.005) , indicating the presence of greater activity of systemic inflammation in patients without arrhythmia.

ROC-analysis determined the optimal cut-off points for the studied indicators that influenced the development of AF. The most significant operational characteristics for predicting permanent AF in patients with IHD/AH, HFmrEF were the level of LVMMI>195.2 g/m^2 – area under the ROC curve AUC=0.786 (95% CI 0.678-0.871) with sensitivity indicators (ST) – 54.8%, specificity (SP) – 97.2%, p=0.001; HDLP level ≤1 mmol/l – AUC =0.657 (95% CI 0.541-0.761), ST – 47.6%, SP – 83.3%, p=0.03; LDLP level >3.5 mmol/l – AUC =0.743 (95% CI 0.632-836), ST – 90.5%, SP – 52.8%, p=0.001, plasma IL-1β level ≥8.64 pg/ml (AUC =0.640; 95% CI 0.523-0.745; ST=61.9%; SP=72.2%) and the level of hs-CRP in plasma up to 3.18 mg/l and higher (area under ROC- curve AUC =0.687; 95% CI 0.572-0.787; ST =92.9%; SP =52.8%).

Table 3

Echocardiographic characteristics of state of myocardium in patients with permanent AF and without AF (M±m)

Indicators	IHD/AH, HFmrEF and AF (n=42)	IHD/AH, HFmrEF without AF (n=36)	Difference between groups (p)
Area index of LA, cm^2/m^2	11.7±0.2	11.5±0.15	t=0.72; p=0.08
Area index of RA, cm^2/m^2	9.4±0.1	9.2±0.13	t=1.15; p=1.02
iESV, ml/m^2	48.85±0.99	44.35±0.90	t=3.32; p=0.001
iEDV, ml/m^2	87.7±1.9	83.8±1.3	t=1.64; p=1.05
TIVS, cm	1.31±0.007	1.29±0.005	t=2.64; p=0.01
EF, %	44.2±0.39	47.1±0.6	t=-4.13; p=0.001
iMMLV, g/m^2	152.8±2.9	146.5±2.3	t=1.64; p=1.07

Notes: * – by Student's t-criterion; p – difference between the first and second group.

Taking into account the obtained critical values, by means of Wald sequential analysis, the scores for each indicator were determined. In particular, the value of hs-CRP was estimated at +4 or -7 scores, if its level was ≥3.18 mg/l or <3.18 mg/l, respectively; the value of IL-1β was estimated at +3 scores at the level of ≥8.64 mg/l or -3 scores in the opposite case (Table 4).

Table 4

Scale of diagnostic/prognostic scores for defining risk of prediction of permanent AF development in patients with HFmrEF

Indicators	ROC-analysis				Wald's analysis
	range of values	sensitivity, %	specificity, %	prognostic significance (p)	scores
hs-CRP, mg/l	<3.18 ≥3.18	92.9	52.8	0,002	- 7 +2
IL-1β, pg/ml	<8.64 ≥8.64	61.9	72.2	0,025	-3 + 3
LVMMI, g/m^2	≤195.2 >195.2	54.8	94.4	<0,001	-3 +10
HDLP, mmol/l	≤1 >1	47.6	83.3	0,012	+5 -2
LDLP, mmol/l	≤3.5 >3.5	90.5	52.8	<0,001	-7 +3
	Probability of AF development (P_{AF})				Total scores (∑S)
Very low	≤ 0.05				≤ -14
Low	0.06 - 0.24				from -13 to -5
Moderate	0.25 - 0.49				from -4 to 0
High	0.50 - 0.89				from 0 to +10
Very high	≥0.90				≥ +11

Further, the total risk score for the development of permanent AF (∑S) for each patient was calculated and used as an argument for the logistic regression equation:

$$R_{AF} = 1: (1+\exp(z)), z = A + A1 * \sum S,$$

where: P_{AF} - the probability of developing permanent AF in patients with IHD/AH and HFmrEF, c.u;

exp - exponential function (indicative function e^z, where the constant e ~ 2,718 is used as the basis of the degree);

A = -0.0379, A1 = 0.21039 - calculated coefficients of the regression equation;

∑S – total of estimated scores.

The adequacy of the created model of logistic regression was assessed by the initial data according to Pearson's criterion $\chi 2$ ($\chi 2$=49.5, p<0.001) and the level of significance of regression coefficients according to Wald's criterion (p<0.001). Estimation of the discriminative ability of the regression equation according to the shape of the ROC-curve also showed the high quality of the model: the area under the ROC-curve AUC=0.912 (95% CI 0.826-0.964); p<0.001; cut-off threshold – R_{AF}≥0.50; ST=85.7%; SP=86.1%; prognostic accuracy PA=85.9%.

Classification of the degree of risk by the value of the total score allowed to identify 5 gradations of risk: if ∑S≤ -14, the risk is very low (probability R_{AF}=0.05); if -13≤∑S≤ -5 – the risk is low (R_{AF} 0.06-0.24); if -4≤∑S≤0 – the risk is moderate (R_{AF} 0.25-0.49); at 0<∑S≤+10 – high risk (R_{AF} 0.50-0.89); if ∑S≥+11 – the risk is very high (R_{AF} ≥0.90) (Table 4).

There are no analogues of the created prognostic model of the risk of developing permanent AF in patients with IHD/AH and HFmrEF which would take into account the activity of markers of systemic inflammation and individual clinical and laboratory-instrumental indicators.

In the work of the Belarusian author D.A. Bubeshko and co-authors modern data on the activity of markers of systemic inflammation in patients with AH and persistent AF with HFmrEF were obtained. According to the results of this study, the median hs-CRP was 8.67 mg/l [6.85; 10.32] vs. 4.12 mg/l [3.51; 6.77] in our work, IL 1-β – 2.53 pg/ml [0.95; 2.87] vs. 11.21 pg/ml [4.64; 17.24], IL-6 – 3.16 pg/ml [1.82; 3.35] vs. 7.09 pg/ml [5.87; 13.77], IL-10 – 6.83 pg/ml [6.22; 8.59] vs. 33.04 pg/ml [15.91; 35.54]. Thus, we can conclude that the level of hs-CRP in our work was by 2.1 times lower, IL-1β – by 4.4 times higher, IL-6 – by 2.2 times higher and IL-10 exceeded by 5,5 times [1].

The difference in these works can be explained by the fact that in the study the author D.A. Bubeshko included patients with a permanent AF with a history of about 6 months. Our work included patients in whom a permanent AF was observed for 8.5±0.3 years. That is, it can be concluded that the activity of hs-CRP is relatively reduced, but the activity of "pro-inflammatory" and "anti-inflammatory" markers of systemic inflammation remains high.

This paper also presents the state of activity of systemic inflammation markers in patients with IHD/AH and HFmrEF without AF, which is comparable to the second group of our study. Thus, in the work of D.A. Bubeshko the concentration of hs-CRP was 7.68 mg/l [4.63; 9.88] vs. 3.15 mg/l [2.67; 5.24], IL-1β – 3.64 pg/ml [1.71; 4.42] vs. 4.57 pg/ml (3.52; 12.44], IL-6 – 1.82 pg/ml (1.29; 3.33] vs. 5.89 pg/ ml [4.61; 12.90], IL-10 – 4.32 pg/ml [3.67, 4.85] vs. 14.50 pg/ml [6.49; 21.74]. If we compare, in our work the activity of hs-CRP was higher by 2.4 times, the activity of IL-1β was almost comparable, IL-6 was higher by 3.2 times and the activity of "anti-inflammatory" IL-10 was higher by 3.3 times [1].

The results of the X-Vert study were unexpected, they did not confirm the association of AF duration with high levels of IL-6 and hs-CRP in determining their levels at the time of inclusion in the study and before the administration of oral anticoagulants. However, among patients with AF and CHF these indicators were higher compared with patients with AF without CHF (hs-CRP: 3.47 mg/l vs. 2.29 mg/l and 2.73 mg/l vs. 2.27 mg/l respectively). In our study, the concentration of hs-CRP and IL-6 among patients with AF and HFmrEF was 4.12 mg/l and 7.09 pg/ml. It should be noted that in the X-Vert study IHD was diagnosed in 8% of patients, GFR was more than 80 ml/min in 60% of patients, prolonged persistent AF – in 3.7% of patients.

The above indicates the relevance of further implementation of determining the activity of systemic inflammation in patients with cardiovascular disease in clinical practice. This leads to an expansion of the mechanisms of understanding the pathogenetic role of inflammation and adds to the justification of the need for development and further research of drugs, the action of which will be aimed at reducing the systemic inflammatory response. However, the definition of only hs-CRP, which is currently more accessible than interleukins, is insufficient because the balance of pro-inflammatory and anti-inflammatory processes must be assessed in a complex.

CONCLUSIONS

1. Patients with IHD/AH, HFmrEF and persistent AF are characterized by higher diastolic blood pressure, LDL cholesterol, iESV and TIVS,

decreased left ventricular systolic function compared with patients with IHD/AH and HFmrEF without AF.

2. In patients with IHD/AH, HFmrEF suffering from a permanent AF, a significant increase in the level of hs-CRP, IL-1β, IL-6 and IL-10 in plasma compared with patients without arrhythmia was revealed, indicating more active chronic systemic inflammation.

3. The use of a mathematical model that takes into account the indicators of hs-CRP, IL-1β, LVMMI, HDL cholesterol and LDL cholesterol in patients with IHD/AH, HFmrEF allows to predict the risk of permanent AF by the total score of these indicators with prognostic accuracy of 85,9%, sensitivity – 85.7%, specificity – 86.1%.

Conflict of interest. The authors declare no conflict of interest.

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