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Research article

Prognostic value of N-terminal Brain Natriuretic Peptide (NT-proBNP) in Risk Assessment of Adverse Cardiovascular Events in Patients with Atrial Fibrillation and Heart Failure with Reduced Left Ventricular Systolic Function

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According to Russian epidemiological studies, the incidence of chronic heart failure (HF) in the general population is approximately 7%, increasing from 0.3% in the group aged 20–29 years to 70% in patients aged > 90 years [1]. In the general population, the incidence of atrial fibrillation (AF) ranges from 1% to 2%, which increases with age, that is, from 0.5% at the age of 40–50 years to 5%–15% at the age of 80 years [2]. HF and AF aggravate significantly each other's course and mutually increase the risk of adverse outcomes [3, 4]. Moreover, the incidence of AF in patients with HF increases with increasing New York Heart Association (NYHA) grade; that is, among patients with HF of NYHA grade I, the incidence of AF is < 5%, whereas among patients with HF NYHA grade IV, the AF incidence in > 50% [5].

Chronic HF is a syndrome with complex pathophysiology, which is characterized by the activation of neurohumoral systems, namely, the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system (SNS), and insufficient activity of the natriuretic peptide (NUP) system. In the early stage of HF, i.e. asymptomatic dysfunction of the left ventricle, the activation of the SNS and RAAS plays a compensatory role aimed at maintaining cardiac output and circulatory homeostasis [6]. Moreover, the NUP system has a counter-regulatory function in relation to the RAAS and SNS, and with prolonged and excessive activation of the SNS and RAAS or with insufficient NUP system activity, imbalance occurs and HF progresses [7].

The brain natriuretic peptide (BNP) and biologically inactive N-terminal fragment of BNP (NT-proBNP) are the most studied and significant in clinical practice representatives of the NUP system. BNP and NT-proBNP are secreted by cardiomyocytes of the left ventricular (LV) myocardium in response to an increase in the mechanical load and stress of the LV myocardium. NT-proBNP is widely used as a test to rule out HF in patients with dyspnea. The NUP level also correlates with the severity and prognosis in patients with an established diagnosis of HF, and studies have reported that the NUP level acts as a criterion for treatment efficiency in patients with HF [8]. NT-proBNP is a biomarker not only for HF but also for several other conditions, such as acute coronary syndrome and myocardial infarction (MI), because it is associated with an increased risk of death from all causes, regardless of age, stable effort angina grade, myocardial infarction history, and LV ejection fraction (LVEF) [9].

NT-proBNP levels can be influenced by several additional factors such as age, obesity, or glomerular filtration rate. The prognostic value of NT-proBNP is relevant in comorbid patients with AF associated HF because AF can increase NT-proBNP levels independently [10]. Given that NUP secretion depends on intracardiac hemodynamics, the NT-proBNP levels may also depend on the approach to managing AF. Tachycardia is associated with high NT-proBNP levels [11].

The rhythm control approach has advantages over the heart rate control approach in patients with HF and LVEF < 50% to reduce mortality and the number of unplanned hospitalizations due to HF progression [12].

To date, the prognostic significance of NT-proBNP levels in relation to the risk of adverse events in patients with HF and reduced LV systolic function associated with AF, depending on the approach of AF management, remains unresolved.

This study aimed to assess the predictive value of NT-proBNP in relation to the development of adverse cardiovascular events in patients with permanent or persistent AF associated with HF and LVEF < 50%.

Keywords: atrial fibrillation; heart failure; NT-proBNP; prognostic value.

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Научная статья

Прогностическая значимость N-терминального фрагмента мозгового натрийуретического пептида (NT-proBNP) в оценке риска развития неблагоприятных событий у пациентов с фибрилляцией предсердий в сочетании с сердечной недостаточностью со сниженной систолической функцией левого желудочка

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Актуальность. Наиболее значимым в клинической практике биомаркером сердечной недостаточности (СН) является N-терминальный фрагмент мозгового натрийуретического пептида (NT-proBNP). NT-proBNP также является прогностическим маркером развития тяжелых клинических исходов у пациентов с фибрилляцией предсердий (ФП) без диагностированной СН. Прогностическая значимость NT-proBNP в отношении риска развития неблагоприятных событий у пациентов с ФП и СН с фракцией выброса левого желудочка (ФВ ЛЖ) < 50 %, в зависимости от тактики ведения ФП, не достаточно изучена.

Цель. Оценить прогностическую ценность NT-proBNP в отношении развития неблагоприятных сердечно-сосудистых событий у пациентов с постоянной или персистирующей формой ФП в сочетании с СН с ФВ ЛЖ < 50 %.

Материалы и методы. Обследовано 152 пациента с ФП в сочетании с СН с ФВ ЛЖ < 50 %. Всем пациентам были выполнены: ЭХО КГ, 24-часовое мониторирование ЭКГ, определение уровня NT-proBNP. Конечная точка для оценки прогноза течения СН — декомпенсация СН и связанная с этим госпитализация, конечная точка для оценки прогноза течения ФП — рецидив ФП после успешной электрической кардиоверсии (ЭКВ). Определение предикторов неблагоприятного исхода проведено методом многофакторного регрессионного анализа.

Результаты. Период наблюдения составил в среднем 12,4 [от 11 до 14,5] месяца. Пациенты с персистирующей формой ФП и СН с ФВ ЛЖ < 50 %, имеющие уровень NT-proBNP ⩾ 1096 пг/мл перед ЭКВ, имели более высокий риск рецидива ФП, ОШ = 2,12 [95 % ДИ от 1,48 до 4,1]. Уровень NT-proBNP ⩾ 1184 пг/мл ассоциирован с повышенным риском декомпенсации СН и связанной с этим госпитализации у пациентов с постоянной формой ФП и диагностированной СН с ФВ ЛЖ < 50 %, ОШ = 2,61 [95 % ДИ от 1,15 до 5,85].

Выводы. Повышенный уровень NT-proBNP сохраняет свою прогностическую значимость в отношении риска развития неблагоприятных событий у пациентов с ФП и СН с ФВ ЛЖ < 50 %. Эти результаты демонстрируют универсальность и высокую информативность определения уровня NT-proBNP и позволяют адекватно оценивать как тяжесть и прогноз течения СН у пациентов на фоне ФП, так и риск рецидива ФП у пациентов с СН с ФВ ЛЖ < 50 %.

Ключевые слова: фибрилляция предсердий; сердечная недостаточность; NT-proBNP; прогностическая значимость.

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ЭКО•ВЕКТОР

MATERIALS AND METHODS

The study included 152 patients with AF associated with ischemic heart disease (IHD) that was associated with HF and LVEF < 50% (LVEF 42.0% [39; 45.5]). The inclusion criteria were as follows: persistent or permanent AF, age 35–70 years, and documented manifestation of HF with LVEF < 50% for at least 3 months before inclusion in the study. The exclusion criteria were as follows: paroxysmal AF, AF associated with organic valvular heart disease, acute myocardial infarction (MI) or MI < 6 months old, progressive exertional angina, acute myocarditis, operated valvular disease of any localization, hemodynamically significant stenosis of the coronary arteries, complete block of one of His bundle branches, severe renal failure (glomerular filtration rate [GFR] < 30 mL/min/m^2), changes in the levels of thyroid hormones, and electrolyte disorders. At the time of study inclusion, all patients underwent standard general clinical laboratory tests, transthoracic echocardiography (LVEF was assessed using the Simpson method in the B-mode), and 24-h ECG monitoring.

The NYHA grade was determined using a 6-min walk test. The HF phenotype was determined based on the LVEF according to the classification [13], where LVEF < 40% indicates heart failure with reduced left ventricular ejection fraction (HFrEF) and LVEF of 41%–49% indicates heart failure with a moderately reduced left ventricular ejection fraction (HFmrEF).

The NT-proBNP level was determined by enzyme immunoassay in the venous blood serum. The technique was performed according to the manufacturer's instructions, and the expected normal levels for NT-proBNP range from 0 to 125 pg/mL.

The primary endpoints of the study were AF recurrence (in patients with persistent AF) after successful electrical cardioversion (ECV) and hospitalization due to AF progression in patients with persistent AF. The criteria for recurrent AF include a documented episode of AF lasting ⩾30 s. The criteria for HF progression are an increase in clinical signs/symptoms of HF, a decline in the NYHA grade, and an increase in NT-proBNP levels.

Statistical data processing was performed using the STATISTICA 10 software package (StatSoft Inc.) and StatTech v. 2.6.6 (Stattech, Russia). Quantitative indicators were assessed for compliance with the normal distribution using the Shapiro–Wilk test (< 50 subjects). Levels of indicators between the two groups were compared using the non-parametric Mann–Whitney U-test. Descriptive statistics of numerical indicators were presented as Me [Lq; Uq], where Me is the median, Lq is the 25th percentile, and Uq is the 75th percentile. Qualitative indicators in the groups were described using absolute and relative frequencies of occurrence (percentage). Percentages in the analysis of four-field contingency tables were compared using Pearson's χ^2-squared test. To assess the diagnostic significance of the combinations of quantitative and qualitative attributes in predicting a certain outcome, direct enumeration and filtering of binary logistic regression models were employed. The threshold value of the level of statistical significance was taken as equal to 0.05.

All participants were informed about their inclusion in the study and signed an informed consent to participate. The study complies with the Declaration of Helsinki and was approved by the local ethics committee (Protocol No. 1 dated January 26, 2020).

RESULTS

Depending on the AF form, all patients were initially distributed into two groups. Group 1 included 60 patients with persistent AF and HF with LVEF < 50% (mean age, 57 [54; 61] years, 85% men), and group 2 included 92 patients with persistent AF and HF with LVEF <50% (mean age 56 [52; 65.5] years, 85.7% men).

The average follow-up duration was 12.4 [11–14.5] months. By the end of the follow-up period, 26 (43.3%) patients in group 1 maintained sinus rhythm (subgroup 1a), and 34 (56.7%) patients had an AF recurrence (subgroup 1b). The median sinus rhythm maintenance in the group with recurrent AF was 2.4 [1.3; 5.3] months. The compared subgroups did not differ in the regimens and doses of antiarrhythmic therapy at the time of inclusion in the study. Patients in both subgroups were comparable in terms of sex, age, major risk factors, and structure of cardiovascular diseases (CVDs). Individuals having their first episode of arrhythmia and those having a lower NYHA grade were more common in the group without AF recurrence. The characteristics of the studied subgroups are presented in Table 1.

Both subgroups initially did not differ in general laboratory parameters. However, at the time of study enrollment, patients with recurrent AF had significantly higher NT-proBNP levels. The NT-proBNP levels measured before the ECV were 676 [354; 958] pg/mL in subgroup 1a and 1481 [652; 2339] pg/mL in subgroup 1b (p = 0.0001).

The evaluation of EchoCG parameters measured before ECV revealed no statistically significant differences between the studied subgroups in terms of the left atrial volume (LAV; 130.2 [109.7; 143.4] mL versus 138.9 [108.8; 148] mL), LAV index (LAVI; 48.2 [39.7; 62.4] mL/m^2 versus 53.2 [40.4; 65.8] mL/m^2), left ventricular end-systolic dimension (LV ESD; 44 [41; 51.5] mm versus 47 [43.5; 51] mm), left ventricular end-diastolic dimension (LV EDD; 59 [56; 62.5] mm versus 61 [56.5; 64] mm), end-diastolic volume index of the left ventricle (LV EDVI; 98.7 [87.2; 111.8] mL/m^2 versus 106.4 [84.4; 118.5] mL/m^2), end-systolic volume index of the left ventricle (LV ESVI; 54.2 [43.2; 66.4] mL/m^2 versus 60.7 [44.1; 70.3] mL/m^2), LVEF (45% [39%; 47.5%] versus 42% [38%; 46%]), dimension of the right ventricle (25 [22; 26] mm versus 25 [24; 26] mm), LV myocardial mass (315 [278; 352] g versus 320 [289; 374.5] g), and LV

Table 1. General characteristics of the patients.

Characteristics of patients	Subgroup 1a No AF recurrence (*n* = 26)	Subgroup 1b AF recurrence (*n* = 34)	*P*
Age, years	58 [53; 62]	59 [56; 64]	is
Male, *n* (%)	22 (84,6)	29 (85,3)	is
BMI, kg/m^2	31 [27,5; 34]	32 [29; 36]	is
GFR, mL/min/1.73 m^2	64 [51; 74]	59 [51; 69]	is
Dyslipidemia, *n* (%)	18 (69,2)	24 (70,6)	is
Duration of AF episode before ECV, months	3 [2; 5]	5 [2; 6]	is
New episode of AF, *n* (%)	19 (73.1)	14 (41.2)	0,01
Type 2 DM, *n* (%)	5 (19.2)	6 (17.6)	is
Comparative characteristics of patients according to the cardiovascular disease structure			
IHD, *n* (%)	26 (100)	34 (100)	is
SEA, *n* (%) total	21 (80.8)	27 (79.4)	is
Grade 1	6 (28.5)	5 (18.5)	is
Grade 2	11 (53.4)	13 (48.1)	is
Grade 3	4 (19.1)	9 (33.4)	is
History of MI, *n* (%)	5 (19.2)	7 (20.6)	is
CH (NYHA), *n* (%)			
Grade I	4 (15.4)	1 (2.9)	0,02
Grade II	20 (76.9)	19 (55.9)	is
Grade III	2 (7.7)	14 (41.2)	0,01
HFmrEF/HFrEF, *n* (%)	20 (76.9) 6 (23.1)	24 (70.6) 10 (29.4)	is
AH, *n* (%) total	23 (88.4)	29 (85.3)	is
Degree 1	3 (13.1)	2 (6.9)	is
Degree 2	19 (82.6)	23 (79.3)	is
Degree 3	1 (4.3)	4 (13.8)	is

Note: AH — arterial hypertension; BMI — body mass index; CVD — cardiovascular disease; GFR — glomerular filtration rate (CKD-EPI); HFmrEF — heart failure with moderately reduced left ventricular ejection fraction; HFrEF — heart failure with reduced left ventricular ejection fraction; IHD — ischemic heart disease; is — insignificant differences; MI — myocardial infarction; NYHA — New York Heart Association grade; SEA — stable effort angina.

myocardial mass index (152 [135; 177] g/m^2 versus 154 [134; 183] g/m^2). Patients with arrhythmia recurrence had a higher level of pressure in the pulmonary artery (41 [35; 47] mm Hg versus 35 [33.5; 44.5] mm Hg in subgroups 1b and 1a, respectively, $p < 0.01$).

To identify predictors of AF recurrence in patients with HF and LVEF < 50%, clinical, anamnestic, laboratory, and instrumental parameters were included in the univariate regression analysis (Table 2).

In the multivariate regression analysis, only the NT-proBNP level retained its predictive value for AF recurrence (OR = 1.35 [95% CI 1.14–3.04]). According to the ROC analysis results, the level of NT-proBNP of ⩾ 1096 pg/mL with a sensitivity of 86.0% and a specificity of 84.3% is associated with recurrent AF (area under the ROC curve, 0.89; 95% CI 0.81–0.95). Patients with persistent AF and HF with an LVEF < 50%, who have an NT-proBNP level of ⩾ 1096 pg/mL before ECV have an increased risk of recurrent AF (OR = 2.12 [95% CI 1.48–4.1]).

Patients with permanent AF and HF with LVEF < 50%, who were hospitalized during the follow-up period due to HF progression, were included in subgroup 2a, and 67 (72.8%) patients with permanent AF and HF with LVEF < 50%, who were not hospitalized during the follow-up period, were included in subgroup 2b. During the follow-up, both subgroups were taking the main groups of drugs

Table 2. Data included in univariate regression analysis

Characteristics of patients	*p*-value	RR	CI –95%	CI +95%
Age	0.54	0.98	0.92	1.05
Sex	0.07	2.62	0.92	7.48
Cardiovascular disease heredity	0.69	0.83	0.33	2.09
AF heredity	0.83	1.13	0.37	3.44
Smoking	0.05	1.02	0.92	1.48
New AF episode	**0.03**	**1.03**	**1.002**	**1.14**
Age of AF, months	0.77	0.99	0.85	1.13
Body mass index, g/m^2	0.55	1.03	0.93	1.14
Type II diabetes mellitus	0.89	0.95	0.72	1.24
GFR, mL/min	0.4	0.99	0.97	1.01
NT-proBNP, pg/mL	**0.0003**	**1.53**	**1.19**	**4.64**
Average daily HR (before ECV), beats/min	**0.02**	**1.02**	**1.003**	**1.24**
LA volume, mL	0.87	1.12	0.91	1.49
LAVI, mL/m^2	0.23	1.08	0.96	1.18
LV EDD, mm	0.93	1.004	0.92	1.1
LV ESD, mm	0.33	1.04	0.96	1.12
LV EDVI, mL/m^2	0.71	1.012	0.91	1.1
LV ESVI, mL/m^2	0.44	1.03	0.89	1.05
LV SV, mL	0.26	0.98	0.96	1.01
LVEF, %	0.17	0.97	0.93	1.01
LV MM, g	0.87	0.98	0.75	1.27
LVMI, g/m^2	0.75	0.99	0.98	1.02
Systolic PAP, mm Hg	**0.001**	**1.15**	**1.09**	**1.65**

Note: AF — atrial fibrillation; EDD — end-diastolic dimension; EDVI — end-diastolic volume index; ESD — end-systolic dimension; ESVI — end-systolic volume index; GFR — glomerular filtration rate (CKD–EPI); LA — left atrium; LAVI — left atrial volume index; LV — left ventricle; LVMI — left ventricular mass index; HR — heart rate; MM — mass of the left ventricular myocardium; NT-proBNP — N-terminal fragment of brain natriuretic peptide; PAP — pulmonary artery pressure; SV — stroke volume.

indicated for HF, such as angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers/angiotensin receptor and neprilysin inhibitors, beta-adrenergic blocking agents, mineralocorticoid antagonist receptors, and diuretics. Groups 2a and 2b received comparable therapy in groups and doses of drugs taken.

In a retrospective analysis, both subgroups were comparable in terms of sex, age, major risk factors, and CVD structure. However, subgroup 2a included a significantly smaller number of patients with HFmrEF than subgroup 2b (10 patients [40%] versus 47 patients [70%]; p = 0.02), and subgroup 2a also had significantly more patients who had one or more episodes of hospitalization associated with HF progression (14 patients [56%] versus 19 [28%]; p = 0.03) (Table 3).

In a retrospective analysis, both subgroups did not differ in general laboratory parameters. However, in a retrospective analysis, subgroup 2a had significantly higher NT-proBNP levels at the time of study enrollment. The NT-proBNP level in the subgroup with repeated hospitalizations was 2293 [1300; 4675] pg/mL, and in the subgroup without hospitalizations, it was 989 [758; 1600] pg/mL (p < 0.0005).

At the time of study inclusion, groups 2a and 2b were comparable in terms of the level of systolic pressure in the pulmonary artery; however, compared with group 2b, group 2a was characterized by significantly higher values

Table 3. General characteristics of the patients.

Characteristics of patients	Subgroup 2a AF + HF Hospitalized due to HF progression (*n* = 25)	Subgroup 2b AF + HF Not hospitalized due to HF progression (*n* = 67)	*p*
Age, years	56 [50; 65]	61 [53; 66]	is
Male, *n* (%)	21 (84)	58 (86)	is
BMI, kg/m^2	31 [26,4; 35]	30 [27; 34,7]	is
GFR, mL/min/1.73 m^2	59 [49; 73]	68 [53; 74]	is
Dyslipidemia, *n* (%)	15 (60)	39 (58)	is
AF duration, months	17 [12; 62]	23 [12; 44]	is
1 or more episodes of hospitalization due to HF progression in history, *n* (%)	14 (56)	19 (28)	0,03
Comparative characteristics of patients according to the structure of cardiovascular disease			
IHD, *n* (%)	24 (96)	67 (100)	is
SEA, *n* (%) total	11 (44)	19 (28)	is
Grade 1	2 (8)	3 (4)	is
Grade 2	5 (20)	6 (9)	is
Grade 3	4 (16)	10 (15)	is
History of MI, *n* (%)	4 (16)	20 (30)	is
HF (NYHA), *n* (%)			
Grade I	1 (4)	3 (5)	is
Grade II	15 (60)	43 (64)	is
Grade III	9 (36)	21 (31)	is
HFmrEF/HFrEF, *n* (%)	10 (40)/15 (60)	47 (70)/20 (30)	0,02
AH, *n* (%) total	23 (92)	61 (91)	is
Degree 1	3 (12)	4 (6)	is
Degree 2	19 (76)	49 (73)	is
Degree 3	1 (4)	5 (7)	is
Type II DM, *n* (%)	5 (20)	16 (24)	is

Note: AH — arterial hypertension; BMI — body mass index; CVD — cardiovascular disease; DM — diabetes mellitus; GFR — glomerular filtration rate (CKD–EPI); HFmrEF — heart failure with moderately reduced left ventricular ejection fraction; HFrEF — heart failure with reduced left ventricular ejection fraction; IHD — ischemic heart disease; is — insignificant differences; MI — myocardial infarction; NYHA grade — New York Heart Association grade; SEA — stable effort angina.

of the LAV (138.8 [119.7; 151.4] mL versus 119.3 [99.5; 135.1] mL/m^2, p = 0.02), LAVI (74.2 [51.9; 87.5] mL/m^2 versus 59.9 [43; 75.5] mL/m^2, p = 0.015), higher LV EDD (64 [60; 65] mm versus 59.5 [55; 63] mm, p = 0.002), LV ESD (49 [47; 53] mm versus 44 [41; 52] mm, p = 0.01), LV EDVI (106.9 [100; 122.7] mL/m^2 versus 94.4 [79.6; 104.4] mL/m^2, p = 0.01), and LV ESVI (68 [51.7; 75.8] mL/m^2 versus 51.9 [43.2; 66.2] mL/m^2, p = 0.01). In group 2a, a tendency toward a lower LVEF was found; however, the level of statistical significance was not reached (39 [34; 45]% versus 42 [38; 46]%, p = 0.09).

To identify predictors of readmissions due to HF progression among patients with AF and HF with reduced LV systolic function, a univariate regression analysis was

Table 4. Data included in the univariate regression analysis.

Characteristics of patients	*p*-value	RR	CI – 95%	CI + 95%
Age	0.57	0.98	0.90	1.08
Sex	0.05	2.12	0.92	6.88
Heredity for cardiovascular diseases	0.75	0.88	0.42	1.09
Smoking	0.05	0.99	0.87	1.18
Age of AF, months	0.80	2.08	0.85	4.43
Body mass index, g/m^2	0.72	1.89	0.97	2.24
Type 2 diabetes mellitus	0.03	2.07	0.82	1.14
GFR, mL/min	0.4	0.93	0.99	1.88
NT-proBNP, pg/mL	**0.0001**	**2.83**	**1.29**	**3.24**
Average daily HR, beats/min	0.62	1.02	0.93	1.14
LA volume, mL	0.055	1.13	0.99	1.38
LAVI, mL/m^2	**0.04**	**1.21**	**1.02**	**1.27**
LV EDD, mm	**0.03**	**1.34**	**1.02**	**1.17**
LV ESD, mm	0.06	1.04	0.98	1.72
LV EDVI, mL/m^2	**0.04**	**1.21**	**1.04**	**3.92**
LV ESVI, mL/m^2	0.06	1.13	0.98	1.21
LVEF, %	0.81	1.36	0.85	1.47
LV MM, g	0.02	1.06	1.009	1.14
LVMI, g/m^2	0.75	0.99	0.98	1.02
Systolic pressure in PA, mm Hg	0.65	1.15	0.96	1.05

Note: GFR — glomerular filtration rate; LA — left atrium; LAVI — left atrial volume index; LV EDD — left ventricular end-diastolic dimension; LV EDVI — left ventricular end-diastolic volume index; LV ESD — left ventricular end-systolic dimension; LV ESVI — left ventricular end-systolic volume index; LV MM — mass of the left ventricular myocardium; LVEF — left ventricular ejection fraction; LVMI — left ventricular mass index; PA — pulmonary artery.

performed, including clinical anamnestic, laboratory, and instrumental parameters (Table 4).

In the multivariate regression analysis, NT-proBNP levels retained their predictive value for the progression of HF symptoms, with an OR of 1.28 [95% CI 1.12–4.16]. According to the results of the ROC analysis, the level of NT-proBNP of ⩾ 1184 pg/mL with a sensitivity of 79.7% and a specificity of 65.3% is associated with HF progression in patients with permanent AF and diagnosed HF with LVEF < 50% (area under the ROC curve, 0.714 [95% CI 0.573–0.854]). Patients with persistent AF and HF with an LVEF < 50%, who had NT-proBNP levels of ⩾1184 pg/ml, had a 2.61-fold increased risk of progression of HF symptoms [95% CI 1.15–5.85].

DISCUSSION

As the prevalence of AF increases, the prevention of its complications has important public health and economic benefits. Despite significant progress in the prevention of thromboembolic complications, particularly ischemic stroke, less attention has been paid to methods for preventing the adverse course of HF. The chronology of HF and AF development is of practical interest because it can affect the prognosis. It is assumed that AF development in the presence of HF is associated with an unfavorable outcome. Conversely, AF may contribute to HF development [14]. HF decompensation develops, and 20%–30% of all patients with AF need hospitalization [15]. Generally, AF development increases significantly the risk of lethal outcomes from CVD and common causes in patients with HF, both with reduced LVEF and in patients with preserved LVEF. The presence of AF presages a greater risk of mortality, especially among individuals with HFrEF (OR 2.72; 95% CI 2.12–3.48) compared with HF with preserved LVEF (OR 1.83; 95% CI 1.41–2.37) [16, 17].

When assessing the risk of HF progression and hospitalization in patients with AF and HF with an

LVEF < 50%, depending on the chosen approach for AF management, patients with HF and persistent AF had a lower risk of hospitalization because of HF progression, who could maintain sinus rhythm throughout the follow-up period compared with patients with persistent AF who had AF recurrence and compared with patients with permanent AF.

AF and atrial flutter are associated with higher blood levels of BNP/NT-proBNP, with NT-proBNP levels in patients with AF typically above diagnostic thresholds for HF. To assess the prognosis of the HF course, due to the uncertainty of the threshold value of the NT-proBNP level in the presence of AF, randomized controlled trials in patients with HF traditionally focus on higher threshold values of NT-proBNP [18]. Despite attempts at developing models for predicting the risk of HF in patients with AF, none of these models included the BNP/NT-proBNP levels [19].

Regardless of the chosen approach of AF management, in patients with AF associated with HF with LVEF < 50%, the NT-proBNP level retains prognostic significance. This can be due to the pathophysiological relationship between HF and AF, which consists of the development and progression of pathological myocardial remodeling. Despite the reversibility of LV dysfunction, after the restoration of sinus rhythm, factors for the development of arrhythmia and adverse outcomes of HF persist [20]. Neurohumoral activation, structural and functional remodeling of the atrial and ventricular myocardium, endothelial dysfunction, inflammation, and activation of the prothrombotic system do not ensure a reduction in the risk of acute cardiovascular events even after the restoration of sinus rhythm and reversible LV dysfunction [21, 22]. Based on our results, an elevated NT-proBNP level is associated with an increased risk of adverse outcomes in patients with HF-associated AF, both in patients with permanent AF and patients with successfully restored sinus rhythm. In both patients with recurrent AF and with developed HF decompensation, comparative analysis revealed a tendency to larger LA sizes, indicators of LV volumes and sizes, and tendency to a lower LVEF value. However, these widely used markers of the adverse clinical course of both AF and HF have not been revealed to be predictive in the multivariate analysis.

The results of our study are consistent with those of Brady et al. [23], who stated that in patients with HF and LVEF < 35%, higher NT-proBNP levels are associated with hospitalization due to HF or death from CVD, both in patients with AF and patients without a history of AF episodes.

In this study, we also assessed the predictive value of NT-proBNP levels in relation to the risk of AF recurrence after successful ECV, associated with HF with an LVEF < 50%, while a high NT-proBNP level, determined immediately on the day before ECV, was considered a predictor of AF recurrence. Clinical manifestations of AF, in particular heart rate, correlate significantly with NT-proBNP levels. This was confirmed by Kuroda et al. [24], who reported that the BNP levels decreased significantly immediately after the restoration of sinus rhythm in comparison with the level measured immediately before cardioversion. A decrease in the BNP level may be associated with both a decrease in AF severity and a slowdown in the processes of LV myocardial remodeling, which is associated with the sinus rhythm. However, the development of reverse myocardial remodeling is a long-term process, and a rapid decrease in BNP levels after cardioversion indicates a decrease in hemodynamic load and a positive effect on sinus rhythm. Patients with more hemodynamically significant AF showed a more pronounced decrease in BNP levels after cardioversion.

The most beneficial approach to managing patients with HF-associated AF is rhythm control. Routine determination of the NT-proBNP levels before the restoration of sinus rhythm will enable assessment of the level of LV myocardial stress and optimization of the methods of management and monitoring in the short and long-term follow-up period to increase the probability of maintaining sinus rhythm.

In their recent study, Hamatani et al. [25] established that BNP/NT-proBNP is a significant prognostic marker for severe clinical outcomes, including stroke, all-cause death, and hospitalization associated with HF progression in patients with AF without HF. In this study, in patients with HF-associated AF with LVEF < 50%, both of these diseases can distort the possibility of interpreting the NT-proBNP level. According to our results, an elevated NT-proBNP level retains its prognostic value in relation to the risk of adverse events in patients with HF-associated AF with LVEF < 50%. These results demonstrate the universality and high informative value of NT-proBNP levels, which enables adequate assessment of both HF severity and prognosis in patients with AF and the risk of AF recurrence in patients with HF and reduced LV systolic function.

CONCLUSIONS

1. NT-proBNP level of ⩾1184 pg/mL is associated with an increased risk of HF decompensation and associated hospitalization in patients with permanent AF and HF with LVEF < 50% by 2.5 [95% CI 1.15–5.85] times.

2. NT-proBNP level of ⩾1096 pg/ml is associated with an increased risk of arrhythmia recurrence in patients with HF-associated AF with LVEF <50% after successful ECV by 2.12 [95% CI 1.48–4.1] times.

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