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The level of growth differentiation factor 15 as a predictor of left atrial thrombosis in patients with nonvalvular atrial fibrillation

Aim — To study the role of blood concentration of growth differentiation factor 15 (GDF-15) as a predictor of left atrial/left atrial appendage (LA/LAA) thrombosis in patients with nonvalvular atrial fibrillation (AF).

Material and methods — 538 patients with nonvalvular AF were admitted to the Tyumen Cardiology Research Center in 2019–2020 for radiofrequency ablation and elective cardioversion. According to findings of transesophageal echocardiography (EcoCG), 42 (7.8%) of these patients had LA/LAA thrombosis and 79 (14.7%) of them had the effect of spontaneous echo contrast (SEC). This comparative, cross-sectional, cohort study included at the initial stage 158 successively hospitalized patients with nonvalvular AF: group 1 (with LA/LAA thrombosis, n=42) and group 2 (without LA/LAA thrombosis and without SEC, n=116). To eliminate significant differences in age between the groups, an additional inclusion criterium was introduced, age from 45 to 75 years. Finally, 144 patients were included into the study: group 1 (with LA/LAA thrombosis, n=42, mean age 60.9±7.2 years) and group 2 (without LA/LAA thrombosis and without SEC, n=116, mean age 59.5±6.0 years). 93 (91%) patients in group 1 and 40 (95%) patients in group 2 had arterial hypertension (p=0.4168); 53 (52%) and 29 (^ (%), respectively, had ischemic heart disease (p=0.0611). The groups did not differ in sex, profile of major cardiovascular diseases, or frequency and range of oral anticoagulant treatment. General clinical evaluation, EchoCG, and laboratory tests, including measurements of blood concentrations of GDF-15 and NT-proBNP, were performed.

Results — In the group with LA/LAA thrombosis, 1) persistent AF prevailed whereas paroxysmal AF was more frequently observed in patients without thrombosis; 2) a tendency toward more pronounced chronic heart failure was observed; 3) tendencies toward a high median CHA_2DS_2-VASc score and toward a greater proportion of patients with scores ≥3 were observed. According to EchoCG findings, group 1 had higher values of sizes and volumes of both atria and the right ventricle, left ventricular (LV) end-systolic volume and size, pulmonary artery systolic blood pressure, and LV myocardial mass index. LV ejection fraction (EF) was in the normal range in both groups but it was significantly lower for patients with LA/LAA thrombosis, 59.1±5.1 and 64.0±7.3, respectively (p=0.00006). Concentrations of GDF-15 (p=0.00025) and NT-proBNP were significantly higher in group 1 than in group 2 (p=0.000001). After determining the threshold values for both biomarkers using the ROC analysis, two independent predictors of LA/LAA thrombosis were obtained by the stepwise multiple regression analysis: GDF-15 >935.0 pg/ml (OR=4.132, 95% CI 1.305–13.084) and LV EF (OR=0.859, 95% CI 0.776–0.951). The ROC analysis assessed the model quality as good: AUC=0.776 (p<0.001), sensitivity 78.3%, specificity 78.3%.

Conclusion — For patients with nonvalvular AF, both increased GDF-15 (>935.0 pg/ml) and LV EF are independent predictors for LA/LAA thrombosis.

Keywords — Atrial fibrillation; biomarkers; growth differentiation factor GDF-15; left atrial/left atrial appendage thrombosis

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Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia associated with a two-fold increase in risk of death and a five-fold increase in risk of stroke [1]. Since the spread of AF in recent decades has reached epidemic proportions [2], there is an urgent need to find predictors of stroke in patients with AF.

The presence of a left atrial (LA)/left atrial appendage (LAA) clot is a surrogate marker of a potential stroke in patients with AF, since it is the main source of embologenous thrombosis in nonvalvular AF [3]. Transesophageal echocardiography (TEE) is used as the gold standard diagnostic technique [4].

The CHA_2DS_2 VASc score is currently used to stratify the risk of stroke in nonvalvular AF [3, 5]. However, there is evidence that it is not enough only to consider clinical factors [6]. Although CHA_2DS_2 VASc correlates well with the presence of LA/LAA thrombosis [7], there are patients with LA/LAA thrombosis at low risk of stroke in real-world clinical practice with a CHA_2DS_2 VASc equal to 0 [6, 8].

When stratifying the risk of adverse cardiovascular events in patients with AF, considerable attention has been paid recently to various biomarkers circulating in the blood [9]. Subanalysis using the RE-LY trial biomarkers has shown that high levels of NT-proBNP (>1402 ng/L) and high-sensitivity troponin I (≥0.040 μg/L) are associated with a higher incidence of cardiovascular death and thromboembolic events. Using the CHA_2DS_2 VASc score helps to increase its predictive value [10].

Subanalysis using the ARISTOTLE trial biomarkers in patients with AF has demonstrated the potential use of growth differentiation factor 15 (GDF-15) to stratify the risk of major bleeding, as well as cardiovascular and all-cause death [11].

The association of GDF-15 with LA/LAA thrombosis has not been sufficiently studied in patients with nonvalvular AF [12], something which makes this study relevant.

Aim

The objective of this study was to investigate the role of GDF-15 as a predictor of LA/LAA thrombosis in patients with nonvalvular AF.

Material and methods

A total of 538 patients with nonvalvular AF were hospitalized in the Tyumen Cardiology Research Center in 2019–2020 for radiofrequency ablation and elective cardioversion. TEE detected LA/LAA thrombosis in 42 (7.8%) patients and spontaneous echo contrast (SEC) in 79 (14.7%) patients. A comparative cross-sectional cohort study included 158 consecutively hospitalized patients with nonvalvular AF at the baseline:Group 1 (with LA/LAA thrombosis, n=42); and Group 2 (without LA/LAA thrombosis and SEC, n=116). Considering the statistically significant age differences (mean age was 60.7±9.4 and 56.7±8.9 years, respectively, p=0.0104), an additional inclusion criterion by age (from 45 to 75 years) was introduced to eliminate the differences. A total of 144 patients were included in the final cohort: Group 1 (with LA/LAA thrombosis, n=42, mean age 60.9±7.2 years); and Group 2 (without LA/LAA thrombosis and SEC, n=102, mean age 59.5±6.0 years). Blood levels of GDF-15 were evaluated in all patients included in the study.

In addition to the main groups, a comparison group was formed after the assessment of GDF-15. This included 25 patients without AF who were similar to patients in Group 1 and Group 2 in sex, age, and main cardiovascular diseases (CVDs).

The exclusion criteria were: age less than 45 and more than 75 years; myocardial infarction within 12 months before the inclusion; acute or decompensated chronic comorbidities; chronic obstructive pulmonary disease; pregnancy; and refusal to participate in the study. Clinical characteristics of patients of Group1 and Group 2 are provided in Table 1.

When the signs of chronic heart failure (CHF) were identified, a 6-minute walk test (6MWT) was performed to clarify the functional class (FC).

Drug therapy included oral anticoagulants (OACs), antiarrhythmic drugs, and a background therapy of the underlying disease (Table 2). Treatment compliance, doses, and duration of OACs were not evaluated in this study.

All patients underwent transthoracic echocardiography using a Vivid E9 ultrasound scanner (General Electric Medical Systems, USA). The records were stored on a hard disk, and the mean scores of 3 consecutive cardiac cycles were calculated. This included assessing the sizes and volumes of the cardiac chambers, structural and functional state of the heart, including left ventricular (LV) systolic and diastolic functions following the current guideline of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [13, 14].

TEE was performed in all patients on a Vivid E9 scanner (General Electric Medical Systems, USA) using a 5.0–7.5 MHz transesophageal probe to assess the LA cavity, including LLA (SEC, thrombosis, blood flow velocity in LAA) [15].

Routine laboratory tests were performed. These included: a complete blood count; fasting glucose; creatinine; glomerular filtration rate (GFR) calculated using the CKD-EPI formula; NT-proBNP; cystatin C; and GDF-15.

In order to determine GDF-15, venous blood was collected in the fasting state, centrifuged for 15 minutes at 2 500 rpm, and blood serum was aliquoted for further freezing (–70°C). Serum GDF-15 was determined by a quantitative method using a direct enzyme immunoassay. We used a Stat Fax 4200 microplate photometer (USA), a Human GDF-15/MIC-1 ELISA analytical kit (BioVender, Czech Republic) intended for research use within the range of 35–2240 pg/mL. Following the instructions, the medians for different age groups of male and female patients (378–648 pg/mL and 444–653 pg/mL, respectively) are proposed as benchmark reference ranges.

Statistical analysis

Statistical analysis was carried out using the Statistica 12.0 and IBM SPSS Statistics 21.0 software

Table 1. Clinical characteristics of Group 1 and Group 2

Parameters	Group 1 (n=42)	Group 2 (n=102)	p (between groups)
Age, years	60.9±8.8	59.5±6.0	0.2455
Male, n (%)	22 (52)	62 (61)	0.2709
Form of AF, n (%)			
– Paroxysmal	15 (35.7)	78 (76.5)	0.0001
– Persistent	27 (64.3)	24 (23.5)	0.0001
Duration of AF, n (%)			
– less than 1 year	11 (26.2)	14 (13.7)	0.0718
– 1 to 3 years	9 (21.4)	28 (27.5)	0.4465
– more than 3 years	22 (52.4)	60 (58.8)	0.4808
Hypertension, n (%)	40 (95)	93 (91)	0.4168
CAD, n (%)	29 (69)	53 (52)	0.0611
History of MI, n (%)	2 (5)	4 (4)	0.7878
CAD combined with AH, n (%)	27 (64.3)	52 (51)	0.1449
CHF, n (%)	40 (95)	93 (91)	0.3923
FC II	27 (64.3)	48 (47)	0.0589
FC III	5 (11.9)	5 (5)	0.1405
6MWT distance, m	395.5±85.4	425.5±84.2	0.0552
CKD, n (%)	8 (19.0)	16 (15.7)	0.6291
GFR (CKD EPI), mL/min/1.73 m^2	73.4±16.7	79.7±15.6	0.0289
CHA_2DS_2-VASc: • median score • 0 • ≥3, n (%)	 2.5 [2.0; 3.0] 0 (0) 21 (50)	 2.0 [1.0; 3.0] 2 (2) 35 (34.2)	 0.0621 0.3394 0.0770
Carbohydrate disorders, n (%)	11 (26.2)	23 (22.5)	0.6345
Impaired fasting glycemia, n (%)	4 (9.5)	6 (5.9)	0.4440
Impaired glucose tolerance, n (%)	2 (4.8)	4 (3.9)	0.8059
Diabetes mellitus, n (%)	5 (11.9)	13 (12.7)	0.8949
BMI, kg/m2	31.6±4.8	31.0±4.8	0.4939
Obesity, n (%)	28 (66.7)	60 (58.8)	0.3768
Grade 1, n (%)	16 (38.1)	37 (36.3)	0.8387
Grade 2, n (%)	10 (23.8)	21 (20.5)	0.6611
Grade 3, n (%)	2 (4.8)	2 (2.0)	0.3560

AF, atrial fibrillation; AH, arterial hypertension; CAD, coronary artery disease; MI, myocardial infarction; CHF, chronic heart failure; FC, functional class; 6MWT, six-minute walking test; CKD, chronic kidney disease; GFR, glomerular filtration rate; BMI, body mass index.

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suites. The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. The data was presented as the mean and standard deviation (M±SD) in the normal distribution. The data was presented as the median and interquartile range (Me [25%; 75%]) in the non-normal distribution.

Depending on the nature of distribution, the Student's t-test or Mann-Whitney U-test was used to compare indicators in two independent groups. The categorical indicators were compared using the χ^2 test and two-sided Fisher's exact test. The correction for multiple testing was applied when three groups were compared.

The binary logistic regression method was used to search for predictors of LA/LAA thrombosis and construct the prediction model. ROC analysis was used to search for cut-off values of quantitative variables as predictors and a cut-off threshold for the possible use of the prediction model in practice, and to assess the quality and effectiveness of the model. Independent predictors of LA/LAA thrombosis were searched for by using a multivariate logistic regression analysis with incremental variable inclusion. The results were assessed as statistically significant at $p<0.05$, and at $p<0.1$ was considered as the presence of a statistical trend.

The study was performed following the Declaration of Helsinki. The protocol was approved by the ethics committee (report No. 136 dated 06.04.2018). All subjects signed informed consent.

Results

The following differences in clinical characteristics were observed between Group 1 and Group 2 (Table 1):

1) persistent AF was more common in patients with LA/LAA thrombosis, and paroxysmal AF was more frequent in patients without thrombosis;

2) in Group 1, there was a tendency towards a greater percentage of patients with CHF FC II and smaller 6MWD distance.

There were no differences between Group 1 and Group 2 in terms of the number of patients who did not take OACs at the time of hospitalization. No differences were found in the range of OACs administered (Table 2). In Group 1, patients were more likely to take diuretics and beta-blockers which was associated with more severe CHF and a greater percentage of patients with persistent AF.

The results of a comparative analysis of echocardiographic data are presented in Table 3. It mainly contains indicators with significant differences or a tendency towards significant differences.

Table 2. Drug therapy in Group 1 and Group 2

Treatment	Group 1 (n=42)	Group 2 (n=102)	p (between groups)
No OAC, n (%)	5 (11.9)	11 (10.8)	0.8487
Warfarin, n (%)	6 (14.3)	17 (16.7)	0.7210
Apixaban, n (%)	9 (21.4)	24 (23.5)	0.7851
Rivaroxaban, n (%)	12 (28.6)	25 (24.5)	0.6088
Dabigatran, n (%)	10 (23.8)	25 (24.5)	0.9291
ACE inhibitors, n (%)	17 (40.5)	34 (33.3)	0.4115
Sartans, n (%)	16 (38.1)	42 (41.2)	0.7303
Statins, n (%)	31 (73.8)	72 (70.6)	0.6989
Diuretics, n (%)	23 (54.8)	31 (30.4)	0.0060
Antiarrhythmic drugs class 1, n (%)	8 (19.0)	24 (23.5)	0.5547
Beta-blockers, n (%)	22 (53.4)	26 (25.5)	0.0013
Amiodarone, n (%)	5 (11.9)	17 (16.7)	0.4671
Sotalol, n (%)	6 (14.3)	28 (27.4)	0.4671
Calcium antagonists, n (%)	7 (16.7)	18 (17.6)	0.8968

OAC, oral anticoagulants;
ACE, angiotensin-converting enzyme.

Table 3. Parameters of transthoracic echocardiography in Group 1 and Group 2

Parameters	Group 1 (n=42)	Group 2 (n=102)	p (between groups)
Aorta diameter, mm	33.7±3.7	30.6±5.1	0.00039
RA volume index, mL/m^2	30.5±11.1	24.4±7.5	0.0002
PV diameter, mm	28.4±5.9	26.8±3.2	0.04
LV diameter, mm	44.1±4.5	41.7±4.6	0.0036
LA index, mm/m^2	22.7±7.7	20.4±2.2	0.0076
LA volume index, mL/m^2	41.2±11.4	31.3±8.4	0.00004
LAEDV, mL	82.6±22.8	63.7±19.5	0.00051
LVESD, mm	33.6±4.1	31.2±4.4	0.0071
LVESV, mL	45.9±18.3	39.3±12.3	0.014
IVS, mm	11.8±1.7	11.3±2.0	0.127
LVPW, mm	10.3±0.7	9.9±1.4	0.074
LV mass index, g/m^2	100.9±15.6	93.0±21.9	0.0308
LVEF, %	59.1±5.1	64.0±7.3	0.00006
PASP, mm Hg	29.2±8.8	24.9±5.8	0.0011

RA, right atrium; RV, right ventricle; LA, left atrium;
LAEDV, left atrial end-diastolic volume; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume;
IVS, interventricular septum; LVPW, left ventricular posterior;
LVEF, left ventricular ejection fraction;
PASP, pulmonary artery systolic pressure.

Patients with LA/LAA thrombosis had larger sizes and volumes of both atria and the right ventricle, LV end-systolic volume and size, pulmonary artery systolic pressure (PASP), and LV mass index. Left ventricular ejection fraction (LVEF) was within normal range in both groups, but lower in patients with LA/LAA thrombosis than patients without thrombosis.

According to TEE, LAA blood flow velocity was lower in Group 1 than in Group 2: 35.3±10.7 cm/s vs 50.2±11.3 cm/s, respectively (p<0.001).

The levels of biomarkers for Group 1 and Group 2, and the comparison group without AF are presented in Table 4.

Patients with LA/LAA thrombosis had higher levels of GDF-15 and NT-proBNP, than patients without AF. There was also a trend towards higher levels of cystatin C. Patients in Group 2 had GDF-15 and NT-proBNP levels comparable with those of patients without AF, and there was also a trend towards higher levels of cystatin C.

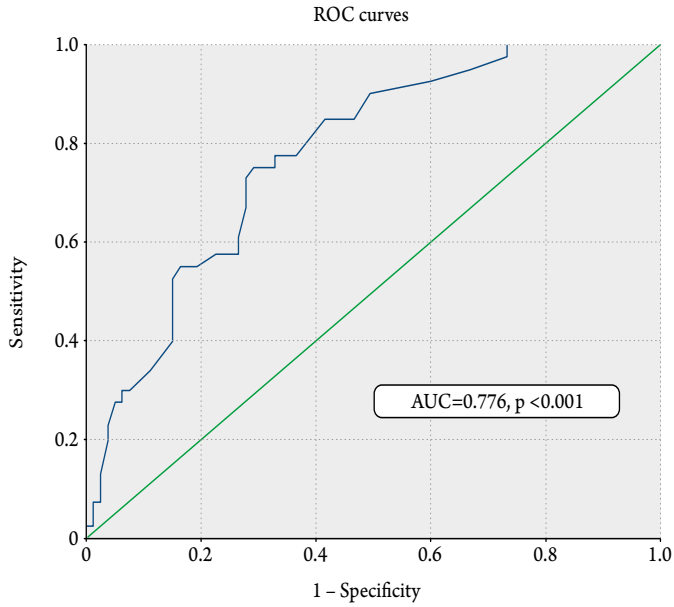
The comparison of biomarkers between Group 1 and Group 2 demonstrated that patients with LA/LAA thrombosis had higher levels of GDF-15 and NT-proBNP. Levels of cystatin C were comparable.

Logistic regression analysis was used to search for independent predictors and construct an LA/LAA thrombosis prediction model. The ROC analysis was preliminarily used to calculate threshold values of NT-proBNP and GDF-15, above which the detection rate of LA/LAA thrombosis increased significantly.

The cut-off value for NT-proBNP was: >143 pg/mL (area under the ROC-curve (AUC) =0.759, 95% confidence interval (CI): 0.670–0.849, p<0.001); sensitivity =69%; and specificity =64%. The cut-off value for GDF-15 was:>935.0 pg/mL (AUC=0.705, 95% CI: 0.609–0.800, p<0.001); sensitivity =70%; and specificity =63%.

Subsequently, the threshold values of NT-proBNP and GDF-15, clinical and echocardiographic parameters with significant (p<0.05) or close to significant (p<0.1) inter-group differences were included in the multivariate logistic regression analysis to search for independent predictors of LA/LAA thrombosis. As a result, a model containing two independent predictors of LA/LAA thrombosis was obtained: GDF-15 >935.0 pg/mL and LVEF (Table 5).

Figure 1. ROC analysis evaluating the LA/LAA thrombosis prediction model



The probability (P) of LA/LAA thrombosis was calculated using the logit function of the linear regression equation:

$$P=1/(1+e^{(-F)}),$$

wherein P is the probability of LA/LAA thrombosis; e is the mathematical constant equal to 2.718; F is the value of the linear regression equation.

The linear regression equation includes the coefficients resulting from logistic regression and is as follows:

$$F=7.747 + 1.419 \times \text{GDF-15}> 935.0\ (\text{pg/mL}) - 0.152 \times \text{LVEF}\ (\%)$$

Table 4. Biomarker levels in Group 1 and Group 2 versus patients without AF

Biomarkers	Patients without AF, n=25 (1)	Group 1, n=42 (2)	Group 2, n=102 (3)	p
GDF-15, pg/mL	990.5 [639.0; 1107.0]	1093.3 [877.3; 1431.5]	844.0 [694.0; 1026.0]	p_{1-2}=0.033 p_{1-3}=0.60 p_{2-3}=0.00025
NT-proBNP, pg/mL	63.4 [37.5; 126.5]	349.5 [128.0; 950.0]	96.0 [40.9; 194.0]	p_{1-2}=0.000014 p_{1-3}=0.1724 p_{2-3}=0.000001
Cystatin C, mg/L	0.75 [0.7; 0.9]	0.9 [0.7; 1.3]	0.8 [0.7; 1.1]	p_{1-2}=0.06 p_{1-3}=0.055 p_{2-3}=0.6263

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Table 5. Results of the logistic regression analysis

Predictors	B	Wald test	p	OR	95% CI for OR	
					Lower	Upper
GDF-15, > 935.0 pg/mL	1.419	5.820	0.016	4.132	1.305	13.084
LVEF, %	-0.152	8.619	0.003	0.859	0.776	0.951
Constant	7.747	5.694	0.017	2314.917	–	–

OR, odds ratio; LVEF, left ventricular ejection fraction.

The cut-off value equal to is 0.257 is used for the probability of thrombosis. According to the ROC analysis, the model is of good quality: AUC=0.776 (p<0.001); specificity =78.3%; and sensitivity =78.3% (Figure 1). Thus, our findings showed that the blood levels of GDF-15 are an independent predictor of LA/LAA thrombosis, as well as LVEF.The level >935.0 pg/mL is associated with a fourfold increase in the risk of LA/LAA thrombosis regardless of other clinical factors.

Discussion

This study included patients hospitalized for catheter ablation or elective cardioversion, subjected to obligatory TEE before the intervention, regardless of OAC administration, in order to exclude LA/LAA thrombosis. The percentage of patients not taking OACs at the time of hospitalization did not differ between the two groups. This confirms the established fact that adequate anticoagulant therapy does not guarantee the absence of an LA/LAA clot [16].

Clinical factors have been studied as predictors of LA/LAA thrombosis for a long time and are well established. These include: diabetes mellitus; arterial hypertension; coronary artery disease; chronic kidney disease; obesity and metabolic syndrome; CHF; persistent and permanent forms of AF [16–18]. The main clinical factors listed are included in the CHA_2DS_2 VASc score. Jia et al. showed that having CHA_2DS_2 VASc ≥2 is an independent predictor of LAA thrombosis [7]. Despite the fact that the CHA_2DS_2 VASc is more sensitive to the isolation of low-risk patients [3, 6, 19], they often have LA/LAA thrombosis. Wasmer et al. found that 5 (7.7%) of the 65 patients with confirmed LA thrombosis had CHA_2DS_2 VASc 0 [6].

Echocardiographic indices are also well known as predictors of LA/LAA thrombosis. These include: increased size and volume of the LA and LV: reduced LVEF with different threshold values: decreased LAA peak flow velocity: spontaneous echo contrast: and LAA morphological type [17, 18, 20–22].

Only LVEF of all echocardiographic parameters was an independent predictor of LA/LAA thrombosis in our study. Although only patients with preserved LVEF were included in the study, patients with LA/LAE thrombosis had significantly lower LVEF, and the risk of thrombosis decreased by 14% with a 1% increase in LVEF. It may be explained by a progressive decrease in LV systolic function, associated with more pronounced LA remodeling and impaired wall motion, and blood stasis in the LA [22].

Our findings demonstrated that the absence of clear criteria for the LV systolic and especially diastolic dysfunction severity leads to an underestimation of the significance of this factor in assessing the risk of stroke. This is despite the presence of heart failure as a risk factor in the CHA_2DS_2 VASc score. There is evidence that impaired LV diastolic function is correlated to the presence of LAA thrombosis [23]. Since our study includes only 15 patients with LA/LAA thrombosis and paroxysmal AF, we were able to assess LV diastolic function in sinus rhythm and we did not include indicators of LV diastolic function in the exploratory analysis used to search for predictors.

Given the above, exploring the role of circulating biomarkers as predictors of LA/LAA thrombosis, especially in patients with low risk of stroke, seems particularly promising.

The concept of molecular biomarkers in risk stratification for patients with AF has developed extensively in the past decade [24].

Growth differentiation factor 15 (GDF-15; MIC 1) is a member of the cytokine superfamily of the transforming growth factor-beta (TGF-β) [25, 26]. It is expressed by a range of cells, such as adipocytes and myocytes, in response to inflammation and stress, e.g., cell ischemia, mechanical and oxidative stress [24, 27, 28].

Using GDF-15 as a potential predictor of LA/LAA thrombosis was justified by the results of a subanalysis using biomarkers from the ARISTOTLE trial [11] and a large meta-analysis of 31 prospective studies [29].This confirmed that GDF-15 is a predictor of

thromboembolic events, cardiovascular and all-cause death, and major bleeding [11].

The association of GDF-15 levels with LA/LAA thrombosis is not very well studied. We found only one publication on this problem by Hu et al. in the available literature [12]. The trial included 894 patients with non-valvular AF who did not receive anticoagulant drugs. Compared to our study, the patients were older (mean age 60.62±6.70 years) with patients with LA/LAA thrombosis being older than patients without thrombosis (63.75±5.32 and 60.36±6.74 years, respectively, p <0.001). It should be noted that the use of the additional age-related criteria made it possible to eliminate the baseline differences in age. This is important because there is ample evidence that GDF-15 is a marker of aging, associated with the deterioration of biological functions [30]. The multivariate logistic regression analysis allowed Hu et al. to identify several clinical parameters (age, duration of AF history, CHA_2DS_2 VASc, LA diameter). And GDF-15 level expressed in quartiles as independent predictors of LA/LAA thrombosis [12]. The threshold value of GDF-15 calculated using the ROC analysis was 809.9 ng/L (AUC=0.709, 95% CI: 0.644–0.770, p<0.001), sensitivity =75.3%, and specificity =61.5%.

Thus, our results which confirm the level of GDF-15 as an independent predictor of LA/LAA thrombosis are consistent with the results of the trial by Hu et al.. Elevated levels of GDF-15 are associated with a low risk of stroke LA/LAA thrombosis. They can be potentially helpful in the algorithm for detecting LP/LAA clots in patients with non-valvular AF, especially those at low risk of stroke [12].

There is no precise explanation for the relationship between GDF-15 and prothrombotic status, since the GDF-15 receptor and the signaling pathways involved are not precisely known. The increase in GDF-15 levels is likely secondary. Previous trials have shown that GDF-15 levels are associated with cardiovascular risk factors and the presence and severity of some CVDs, that is, with the same clinical factors associated with LA/LAA thrombosis [31]. Thus, the GDF-15 levels can be interpreted as an integral signal of the disease severity in several different pathological conditions.

However, there is growing evidence for a potential role of inflammation in prothrombotic status in AF. According to Maehama et al., increased plasma levels of C-reactive protein were correlated with the presence of LA/LAA clots, including in patients classified by clinical criteria as having a low or moderate risk of stroke [32]. Cianfrocca et al. found that the increased C-reactive protein concentration was associated with the presence of an LAA clot. However, there was no association with the LAA flow velocity as assessed by echocardiography [33]. The authors suggested that inflammation is an independent risk factor for thrombogenesis in patients with AF.

Since GDF-15 is a stress-sensitive cytokine mainly expressed by macrophages activated by inflammatory stimuli [34], the probable mechanisms linking inflammation and thrombosis include endothelial activation and/or dysfunction, production of tissue factor by monocytes, platelet hyperreactivity, increased clotting, and increased fibrinogen expression [35, 36].

In our study, GDF-15 exceeded NT-proBNP as an independent predictor of LA/LAA thrombosis. There are only a few papers which compare the relationship of these biomarkers with indicators of hemostasis. Matusik et al. studied the relationship between the levels of GDF-15, NT-proBNP, and high-sensitivity cardiac troponin with hemostasis parameters in patients with AF and high risk of stroke [37]. The patients were older than the patients in our study (71 [65; 76] years) and had a higher mean CHA_2DS_2 VASc score (4.6±1.7). The authors found that GDF-15 was superior to NT-proBNP as an independent predictor of prolonged clot lysis time, and that NT-proBNP was an independent predictor of increased endogenous thrombin potential.

It was concluded that the independent association of NT-proBNP with both increased endogenous thrombin potential and longer clot lysis time supports their earlier findings that NT-proBNP is more effective than GDF-15 as a predictor of thromboembolic risk in AF [38]. The difference in our data on the superiority of GDF-15 over NT-proBNP as an independent predictor of LA/LAA thrombosis is probably due to younger age and lower risk of stroke in our patients.

Thus, our results are consistent with previous papers confirming that elevated levels of GDF-15 level are a predictor of LA/LAA thrombosis, thromboembolic events, cardiovascular and all-cause death in patients with non-valvular AF [11, 12, 29]. More detailed clinical trials are required to introduce the determination of GDF-15 into clinical practice for risk stratification in AF patients, especially those with low risk of stroke, according to CHA_2DS_2 VASc.

Limitations

This was a single-center study including a limited number of patients. There is no information on treatment compliance, doses, and duration of the previous administration of OACs in patients included

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ДОБАВЬТЕ | Апбрави
селексипаг

ЛАГ прогрессирует незаметно[1]

ВРЕМЯ БЕСЦЕННО...
ДОБАВЬТЕ АПБРАВИ

На **42%** снижает риск прогрессирования заболевания/смерти у пациентов с ЛАГ при добавлении в качестве второго препарата к монотерапии иФДЭ-5[2,3]

На **64%** снижает риск прогрессирования заболевания/смерти у пациентов с ЛАГ при раннем добавлении* в тройной комбинированной терапии[4]

5-летняя выживаемость пациентов составляет **72,7%**[5]

CP-232489

КРАТКАЯ ИНФОРМАЦИЯ ПО МЕДИЦИНСКОМУ ПРИМЕНЕНИЮ АПБРАВИ[6]

Регистрационный номер: ЛП-005577. **Торговое наименование:** Апбрави. **Международное непатентованное наименование:** селексипаг. **Лекарственная форма:** таблетки, покрытые плёночной оболочкой. **Показания:** Апбрави показан для длительного лечения лёгочной артериальной гипертензии у взрослых пациентов (ЛАГ, группа I по классификации ВОЗ) II-IV ФК по классификации ВОЗ, с целью замедления прогрессирования заболевания. Прогрессирование заболевания включало: смерть, госпитализацию по поводу ЛАГ, начало внутривенного или подкожного введения простаноидов, или другие случаи прогрессирования заболевания (снижение дистанции в тесте 6-минутной ходьбы, ассоциированное с ухудшением симптомов ЛАГ или необходимостью в дополнительной ЛАГ-специфической терапии). Апбрави эффективен в комбинации с АРЭ или иФДЭ-5, или в составе тройной терапии с АРЭ и иФДЭ-5, или в монотерапии. Эффективность Апбрави доказана в отношении идиопатической и наследственной ЛАГ, ЛАГ, ассоциированной с заболеваниями соединительной ткани, ЛАГ, ассоциированной с компенсированным простым врождённым пороком сердца. **Противопоказания:** повышенная чувствительность к действующему и вспомогательным веществам; тяжёлая ишемическая болезнь сердца или нестабильная стенокардия; инфаркт миокарда, перенесённый в течение предшествующих 6 месяцев; декомпенсированная сердечная недостаточность при отсутствии пристального наблюдения врача; тяжёлые нарушения сердечного ритма; цереброваскулярные заболевания (например, преходящее нарушение мозгового кровообращения, инсульт), перенесённые в течение предшествующих 3 месяцев; врождённые или приобретённые пороки сердца с клинически значимыми нарушениями функции миокарда, не связанными с ЛАГ; совместное применение с мощными ингибиторами CYP2C8 (например, гемфиброзилом); беременность и период грудного вскармливания; детский возраст до 18 лет (эффективность и безопасность не изучены). **С осторожностью:** у пациентов с артериальной гипотензией, у пациентов с веноокклюзионной болезнью лёгких, у пациентов старше 75 лет (ограниченный опыт применения), у пациентов с нарушением функции печени тяжёлой степени (класс С по классификации Чайлд-Пью), у пациентов с нарушением функции почек тяжёлой степени (рСКФ < 30 мл/мин/1,73 м2), у пациентов с гипертиреозом и у женщин детородного возраста. **Способ применения и дозы:** Апбрави применяют внутрь два раза в сутки (утром и вечером), запивая водой. *Титрование дозы.* Для каждого пациента с помощью титрования дозы должна быть подобрана индивидуальная максимальная переносимая доза, в диапазоне от 200 мкг два раза в день до 1600 мкг два раза в день (индивидуальная поддерживающая доза). Рекомендуемая начальная доза – 200 мкг два раза в день с интервалом примерно 12 ч между приёмами. Дозу увеличивают с шагом 200 мкг два раза в день, обычно с периодичностью 1 раз в неделю. В начале терапии и в начале каждого этапа повышения дозы рекомендуется принимать первую дозу вечером. **Побочное действие:** наиболее часто отмечавшимися нежелательными реакциями являются головная боль, диарея, тошнота, рвота, боль в челюсти, миалгия, боль в конечностях, артралгия, приливы крови к лицу и верхней половине тела. Данные реакции наиболее часто наблюдаются во время титрования дозы. Также отмечались: анемия, снижение гемоглобина, гипертиреоз, снижение концентрации ТТГ в крови, снижение аппетита, снижение веса, синусовая тахикардия, артериальная гипотензия, назофарингит, заложенность носа, боль в животе, кожная сыпь, крапивница, эритема, боль. **Особые указания:** Селексипаг обладает вазодилатирующими свойствами, которые могут приводить к снижению давления крови в сосудах. До назначения Апбрави следует оценить, могут ли определённые патологические состояния у пациента ухудшаться вследствие вазодилатирующих эффектов селексипага. В случае появления симптомов гипертиреоза рекомендованы исследования функции щитовидной железы. В случае появления признаков отёка лёгких при приёме Апбрави, пациент должен быть обследован на предмет веноокклюзионной болезни лёгких. У пациентов с нарушением функции печени средней степени Апбрави должен применяться один раз в день. Женщины детородного возраста должны применять надёжные методы контрацепции во время приёма селексипага.

ПОЖАЛУЙСТА, ОЗНАКОМЬТЕСЬ С ПОЛНОЙ ИНСТРУКЦИЕЙ ПО МЕДИЦИНСКОМУ ПРИМЕНЕНИЮ ПЕРЕД НАЗНАЧЕНИЕМ ПРЕПАРАТА.

Литература: 1. Lau EMT et al. Nat Rev Cardiol 2015; 12(3): 143-155. **2.** Lang IM et al. Paper presented at: European Society of Cardiology International Congress 2015; August 29-September 2, 2015; London, United Kingdom. Abstract P-2365. **3.** Sitbon O et al; GRIPHONInvestigators. N Engl J Med. 2015;373:2522-2533. **4.** Coghlan JG, Channick R, Chin K, et al. Targeting the prostacyclin pathway with selexipag in patients with pulmonary arterial hypertension receiving double combination therapy: insights from the randomized controlled GRIPHON study. Am J Cardiovasc Drugs. 2018;18 (1):37-47. **5.** Galiè N. Presentation "Long-term survival and safety with selexipag in patients with pulmonary arterial hypertension: Results from the GRIPHON study and its open-label extension", Department of Experimental, Diagnostic, and Specialty Medicine Alma Mater Studiorum, University of Bologna on behalf of the GRIPHON steering committee, 2018. **6.** Инструкция по медицинскому применению лекарственного препарата Апбрави от 19.03.2021. Регистрационный номер ЛП-005577. * при добавлении пациентам с ФК II.

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in the study. GDF-15 was measured using an analytical set for research purposes. This requires an expansion of the study and defining peculiar reference values, including for individual age categories. The resulting LA/LAA thrombosis prediction model is subject to validation.

Conclusion

Our findings demonstrated that elevated (> 935.0 pg/mL) levels of GDF-15, as well as LVEF, are an independent predictor of LA/LAA thrombosis in patients with non-valvular AF.

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