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The association of growth differentiation factor 15 (GDF-15) level with extent of left atrial fibrosis in patients with nonvalvular atrial fibrillation

Aim — To study the relationship between the serum level of growth differentiation factor 15 (GDF-15) and clinical and functional characteristics and severity of left atrial (LA) fibrosis in patients with nonvalvular atrial fibrillation (AF).

Material and methods — The study included 87 patients with nonvalvular AF (62 patients with paroxysmal AF and 25 patients with persistent AF) aged 27 to 72 years (mean age, 56.9±9.2 years, 32 women). 85% of these patients had arterial hypertension (AH), 33% had AH and ischemic heart disease, and 12.6% had isolated AF and were hospitalized for primary catheter ablation. General clinical evaluation, echocardiography, laboratory tests including measurement of GDF-15 and NT-proBNP concentrations in blood were performed. As a surrogate substrate of LA fibrosis during the electroanatomical voltage mapping, the area of low-voltage (<0.5 mV) zones in LA was calculated, including the total LA fibrosis area (Sf, cm^2) and a percentage of fibrosis of the total LA area (Sf%).

Results — Median concentration of GDF-15 was 767.5 [590.0; 951.0] pg/ml. The GDF-15 level positively correlated with age, presence and severity of AH and chronic heart failure, body mass index, and degree of obesity, CHA2DS2 VASc score, level of NT-proBNP, and LA fibrosis area (Sf and Sf%) and negatively correlated with the indexes of left ventricular diastolic function, e′ septal and e′ lateral. The area of fibrosis increased with increasing GDF-15 concentrations divided into quartiles; Sf% exceeded 20% at GDF-15 levels higher than median. After a comparative analysis of patients with Sf% ≤20% and >20%, statistically significantly different variables were included into a stepwise logistic regression analysis. Two independent predictors of LA fibrosis >20% were identified: a concentration of GDF-15 higher than median (odd ratio (OR), 3.318, 95% confidence interval (CI): 1.184–9.298) and LA volume index (OR, 1.079, 95% CI: 1.014–1.147). According to results of the ROC analysis, the area under the curve (AUC) was 0.762 (p=0.000), the model specificity was 72.3%, sensitivity was 72.4%, and the prediction accuracy was 72.4%.

Conclusion — Blood levels of GDF-15 were associated with the presence and severity of major risk factors for AF and the area of LA fibrosis. In this study, a level of GDF-15 above the median and the LA volume index were independent predictors of LA fibrosis>20% of the LA area.

Keywords — Atrial fibrillation; left atrial fibrosis; growth differentiation factor GDF-15; catheter ablation; electroanatomical mapping; low-voltage zones

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia, associated with a five-fold increase in the stroke risk and a two-fold increase in the death risk [1]. Left atrial (LA) fibrosis is an arrhythmogenic substrate of AF [2], and its severity correlates with the persistence of AF [3] and the likelihood of recurrent AF after catheter ablation (CA) [4]. Thus, finding a way to predict the severity of LA fibrosis in patients with AF referred for CA is a relevant task.

The concept of molecular biomarkers in risk stratification for patients with AF has been developed extensively in the past decade [5]. Growth differential factor 15 (GDF-15) is involved in myocardial remodeling and fibrosis processes. Its production in cardiomyocytes is stimulated by metabolic stress [6] or ischemic damage [7].

Determining the levels of cardiovascular stress and dysfunction biomarkers, including N-terminal pro-brain natriuretic peptide (NT-proBNP) and GDF-15, can

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significantly help to clarify the pathophysiology, improve risk stratification, and optimize management of each patient with AF [5].

GDF-15 is a predictor of thromboembolism, cardiovascular death, and major bleeding [8]. However, there are no data on the correlation between GDF-15 levels and LA fibrosis in patients with non-valvular AF.

Aim

The objective is to study the association between the levels of serum GDF-15, clinical and functional characteristics, and severity of LA fibrosis in patients with non-valvular AF.

Material and methods

The cross-sectional cohort study included 87 patients with non-valvular AF, aged 27–72 (mean age 56.9±9.2 years old, 32 female and 55 male patients) admitted to the Tyumen Cardiac Research Center for primary CA of AF. This study is part of the prospective study designed to find CA predictors in patients with non-valvular AF and preserved left ventricular (LV) systolic function. The exclusion criteria were a clot in the left atrial appendage according to transesophageal echocardiography, acute or decompensated chronic co-morbidities, chronic obstructive pulmonary disease, pregnancy, and refusal of a patient to participate in the study.

Clinical characteristics of patients in the study group are provided in Table 1.

Most patients (71.3%) had paroxysmal AF, 85% had hypertension, and 35.6% had coronary artery disease (CAD). Isolated AF was observed in 11 patients (12.6%). Sixty-eight patients (78.2%) with preserved LV systolic function presented with signs of chronic heart failure (CHF) predominantly of functional class (FC) I and II.

Drug therapy included oral anticoagulants (OACs), antiarrhythmic drugs, and background therapy of the underlying disease. OACs were administered in all patients before their admission to the hospital and continued throughout the hospital stay. The following OACs were used: dabigatran (n=23 patients), rivaroxaban (n=26), apixaban (n=21), warfarin (n=17; target international normalized ratio [INR] to be maintained a t 2:3). The antiarrhythmic drug therapy included amiodarone (n=14), propanorm (n=18), sotalol (n=20), allapinin (n=6), beta-blockers (n=21); 8 patients did not receive antiarrhythmic drugs. As the background therapy, angiotensin-converting enzyme (ACE) inhibitors (n=20 patients), sartans (n=34), diuretics (n=24), statins (n=59), and calcium antagonists (n=11) were used.

All patients underwent the following examinations before surgery: standard 12-lead electrocardiography (ECG), transthoracic echocardiography with detailed structural and functional assessment of the heart. In addition to routine laboratory tests, levels of serum GDF-15 and NT-proBNP were determined. Bipolar endocardial voltage mapping (EVM) of LA was performed as an initial stage of catheter isolation of the pulmonary vein orifices.

Detailed transthoracic echocardiography included the assessment of sizes and volumes of the cardiac chambers [9] and systolic and diastolic LV functions, according to current guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [10].

LA EVM was performed as the first stage of the primary radiofrequency isolation of the pulmonary vein orifices. A 3D-navigation system, Carto 3 (Biosense Webster); a mapping ablation electrode Thermocool Smart Touch;

Table 1. Clinical characteristics of patients

Characteristics	Parameters
Age, years	56.9±9.2
Female, n (%)	32 (37)
Hypertension, n (%)	74 (85)
• Stage 1, n	10
• Stage 2, n	32
• Stage 3, n	32
CAD, n (%)	31 (35.6)
• Including CAD combined with hypertension, n	29
• History of MI, n	4
CHF, n (%)	68 (78.2)
• FC I, n	30
• FC II, n	34
• FC III, n	4
AF pattern:	
• Paroxysmal, n (%)	62 (71.3)
• Persistent, n (%)	25 (28.7)
Isolated AF, n (%)	11 (12.6)
Duration of AF history:	
• Less than 1 year, n	10
• 1–3 years, n	29
• More than 3 years, n	48
Method of AF termination (before CA):	
• Spontaneously, n	25
• Drug cardioversion, n	48
• Electric cardioversion, n	14
CHA_2DS_2 VASc, mean score:	1.9
• 0 point, n	5
• 1 point, n	28
• 2 point, n	29
• 3 point, n	18
• 4 point, n	5
• 5 point, n	1
• ≥2 point, n	53
HAS-BLED:	
• 0 point, n	65
• 1 point, n	18
• 2 point, n	4

AF, atrial fibrillation; CA, catheter ablation;
CAD, coronary artery disease; MI, myocardial infarction;
FC, functional class according to the New York Heart Association.

and/or a multi-pole circular mapping electrode Lasso NAV (Biosense Webster) were used. Bipolar mapping was mainly automatic, using a Confidence Mapping Module or manual with the point-by-point method. The LA voltage map was analyzed after surgery by an experienced electrophysiologist. Regions of low voltage were identified at the bipolar signal amplitude<0.5 mV [4].

The dimensions of fibrosis were calculated using an Area Measurement Module, followed by automatic calculation of LA fibrosis area. Areas of the mitral valve and the pulmonary orifices were excluded from the calculation. The following parameters were calculated: total area of LA fibrosis (severe fibrosis [Sf], cm^2, by summing up the individual zones), Sf (%), which is the percentage of fibrosis of the total area of LA.

NT-proBNP levels (reference value up to 125 pg/mL) were determined by a competitive method (solid-phase chemiluminescent immunoassay) using an IMMULITE 2000 device (Siemens Diagnostics, USA).

GDF-15 levels were determined quantitatively (direct immunoenzymatic determination) using a Human GDF-15/MIC-1 ELISA analytical set (BioVender, Czech Republic) and a Stat Fax 4200 microplate reader (USA). The above analytical set is intended for research purposes. The definition range is from 35 to 2,240 pg/mL. According to the analytical kit manual, median values can be used as reference values for different gender groups: 378–648 pg/mL for males, 444–653 pg/mL for females.

Statistical Analysis

Statistical analysis was carried out using the Statistica 12.0 and IBM SPSS Statistics 21.0 software suites. The distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. Normally distributed data were expressed as the mean (M) and standard deviation (SD); if variables were not normally distributed, they were expressed as the median (Me) and interquartile range [25%; 75%]. Depending on the type of distribution, the values in two independent groups were compared using the Student's t-test or Mann-Whitney U-test. When three or more independent groups were compared, ANOVA or the Kruskal-Wallis test and the multiple-comparison approach were used. The categorical indicators were compared using the χ^2 test and Fisher's exact test. The correlations between the pairs of quantitative signs were evaluated using the nonparametric Spearman's rank correlation coefficient or Pearson's correlation analysis. Logistic regression was used to search for independent predictors and create a prediction model for the severity of fibrosis. ROC analysis was used to evaluate the quality and effectiveness of the model further. The results were estimated as significant at $p<0.05$.

The study is in line with the Declaration of Helsinki. The local ethics committee approved the study protocol. All subjects provided signed informed consent.

Results

GDF-15 ranged from 204 to 1,752 pg/mL; the median was 767.5 [590.0; 951.0] pg/mL. When the association of GDF-15 with demographic characteristics was studied, a moderate positive correlation of GDF-15 with age was found: r=0.52621 (p=0.0000). The comparative analysis did not show significant differences in GDF-15 levels between male and female patients: 750.0 [546.0; 924.5] pg/mL and 788.0 [665.0; 988.0] pg/mL, respectively (p=0.2471).

No association of GDF-15 levels with clinical characteristics, such as the duration of AF history, paroxysmal and persistent AF, or method of terminating AF, was found.

Patients with cardiovascular diseases had higher GDF-15 levels than patients with isolated AF: 810.7 [630.0; 965.0] pg/mL and 590.0 [381.0; 759.0] pg/mL, respectively (p=0.0231). More patients with CAD had higher levels of GDF-15 than those without CAD: 838.3 [692.0; 951.0] pg/mL and 720.0 [504.0; 961.5] pg/mL, respectively (p=0.0729).

The findings of correlation analysis of GDF-15 levels and quantitative variables of clinical characteristics, echocardiographic findings, and EVM are presented in Table 2. As seen in the table, GDF-15 was correlated with the presence and severity of risk factors for AF, such as age, body mass index (BMI), obesity and its degree, hypertension, CHF, glomerular filtration rate (GFR), rates of structural remodeling of both atria and LV diastolic function, NT-proBNP levels, and the degree of LA fibrosis.

We divided patients into groups according to the median and quartiles of GDF-15 to study the correlation of GDF-15 with the severity of LA fibrosis (Table 3).

As seen in Table 3, the area of fibrosis and its percentage of the LA area were statistically significantly higher and more than 20%, which was shown by comparison of LA fibrosis area, in groups with GDF-15 levels corresponding to the 2nd, 3rd, and 4th quartiles versus the 1st quartile, when the median is exceeded (i.e., the 3rd and the 4th quartiles).

A comparative analysis in patients with LA fibrosis ≤ 20% and >20% of the LA area was performed to evaluate GDF-15 as a predictor of fibrosis.

The severity of LA fibrosis more than 20% was conditionally chosen as a dependent variable to evaluate the significance of the GDF-15 level as a predictor of LA fibrosis. This severity corresponded to LA fibrosis grade 3 following the UTAH classification used to estimate LA fibrosis dimensions in delayed contrast – enhancement magnetic resonance imaging [11, 12]. Variables including clinical data,

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Table 2. Statistically significant correlations of GDF-15 with clinical, laboratory, echocardiographic, and EVM findings

Clinical characteristics and echocardiographic data	GDF-15 correlation coefficient	Significance level (p)
Age	0.52621	0.000
BMI	0.216981	< 0.05
Obesity (WHO classification)	0.280059	< 0.05
CHF FC	0.451856	< 0.05
6MWD	-0.3503	0.002
Hypertension stage	0.341173	<0.05
Hypertension grade	0.367099	<0.05
CHA2DS2 VASc score	0.404846	<0.05
GFR	-0.250568	<0.05
RA volume	0.22738	0.041
LA diameter index	0.22276	0.047
LA volume index	0.24426	0.0289
e′ septal	-0.3553	0.005
e′ lateral	-0.3670	0.004
NT-proBNP	0.240715	<0.05
Sf (cm^2)	0.2959	<0.05
Sf (%)	0.3050	<0.05

BMI, body mass index; CHF FC, functional class of chronic heart failure; 6MWD, six-minute walk distance; GFR, glomerular filtration rate; RA, right atrium; LA, left atrium; e′ septal, septal-mitral annular velocity in diastole; e′ lateral, lateral mitral annular velocity in diastole; Sf, a total area of the left atrial fibrosis; Sf (%), Sf % of the left atrial area; exact p values are given for Pearson's correlation analysis; < 0.05, results of the correlation analysis using Spearman's rank coefficient.

echocardiographic parameters, levels of NT-proBNP, and GDF-15 were used as the potential predictors of LA fibrosis >20% (Table 4), which showed statistically significant or near-significant differences in comparative analysis. The predictor characterizing GDF-15 was presented as a value higher than the median (767.5 pg/mL) to make the model more convenient. Results of step-by-step logistic regression analysis are provided in Table 5.

Table 5 shows that only GDF-15 was included in the final model to predict LA fibrosis >20%, and NT-proBNP was excluded from the model. According to the data obtained, GDF-15 above the median (i.e., >767.5 pg/mL), increases 3,318-fold the likelihood of fibrosis >20%. LA volume index (mL/m^2) is another independent predictor: when it increases by one, the possibility of fibrosis >20% increases by 7.9%.

ROC analysis was used to evaluate the quality of the model (Figure 1): area under the curve (AUC)=0.762 (p<0.000), specificity 72.3%, sensitivity 72.4%, prediction accuracy 72.4%.

Discussion

Growth differentiation factor (GDF-15; MIC-1) is a member of the cytokine superfamily of the transforming growth factor β (TGF-β) [5, 13]. GDF-15 was initially cloned as a macrophage-inhibiting cytokine (MIC-1) [14]. It is expressed by a wide range of cells, such as adipocytes and myocytes, in response to inflammation and stress: e.g., cell ischemia, mechanical and oxidative stress [6, 7, 15].

Although the current understanding of GDF-15 receptors and involved signal pathways is incomplete, the

Table 3. GDF-15 (quartile) levels and LA fibrosis parameters

Parameters of LA fibrosis	GDF-15 (1st quartile) <590.0 pg/mL (n=21)	GDF-15 (2nd quartile) 590.0–767.5 pg/mL (n=22)	GDF-15 (3rd quartile) 767.5–951.0 pg/mL (n=23)	GDF-15 (4th quartile) >951.0 pg/mL (n=21)	p*
Sf (cm^2)	4.7 (2.4; 8.6)	8.1 (3.2; 12.7)	15.2 (8.4; 30.5)	15.3 (4.0; 25.0)	0.0114
	–	P_{I-II}=0.3138	P_{I-III}=0.0045	P_{I-IV}=0.0586	
Sf (%)	6.1 (4.6; 13.3)	12.0 (4.6; 21.5)	22.4 (10.3; 54.6)	24.4 (5.7; 36.1)	0.0159
	–	P_{I-II}=0.2624	P_{I-III}=0.00694	P_{I-IV}=0.03812	

GDF-15, growth differential factor-15; LA, left atrium; Sf, LA fibrosis area; *, Kruskal–Wallis analysis.

Table 4. Results of comparative analysis of variables according to LA fibrosis area (≤ 20% and >20%)

Parameter	LA fibrosis area ≤ 20% (n=48)	LA fibrosis area >20% (n=39)	p
Age, years	55.1±9.9	59.6±7.8	0.0428
NT-proBNP, pg/mL	57.3 [24.2; 140.0]	146 [67.8; 276.0]	0.0011
GDF-15, pg/mL	693.0 [514.5; 881.5]	874.5 [732.0; 1081.0]	0.0038
RA volume index, mL/m^2	22.1±7.5	27.3±7.1	0.0027
LVMI, g/m^2	86.0 [76.5; 100.5]	93.75 [80.8; 112.3]	0.0909
LA diameter index, mm/m^2	19.7±2.2	21.2±2.2	0.0002
LA volume index, mL/m^2	28.9±8.8	35.2±8.1	0.0014

RA, right atrium; LA, left atrium; GDF-15, growth differential factor-15; LVMI, left ventricular mass index.

Table 5. Independent predictors of LA fibrosis >20% (logistic regression results)

Predictors	B	Wald test	p	OR	95% CI for OR	
					Lower	Upper
LA volume index, mL/m2	0.076	5.796	0.016	1.079	1.014	1.147
GDF-15 (pg/mL) is above the median (>767.5 pg/mL)	1.199	5.203	0.023	3.318	1.184	9.298
Constant	-4.735	13.050	0.000	0.009	–	–

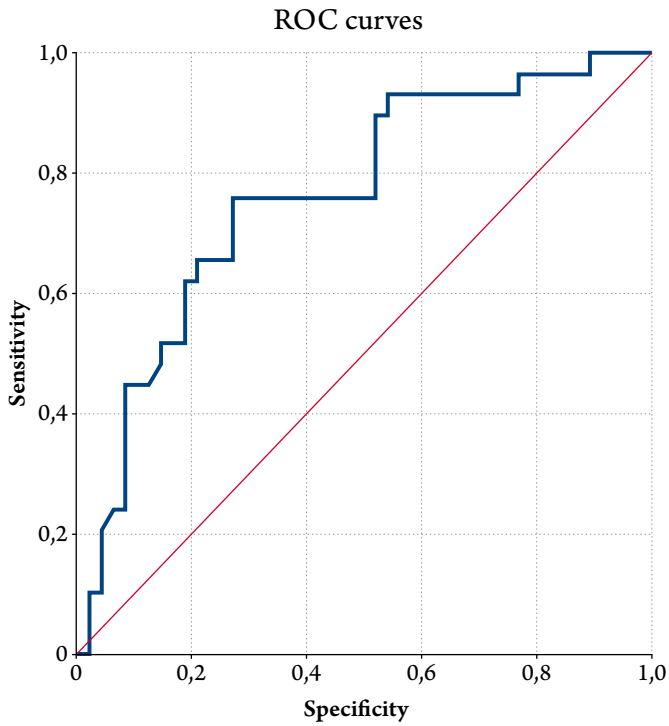
LA, left atrium; OR, odds ratio, CI, confidence interval.

expression and blood concentration of GDF-15 is believed to be a manifestation of the integral signal of cellular stress, organ dysfunction, and biological aging of the cardiovascular and renal systems [5]. The identified correlations between GDF-15 and such indicators as age, BMI, obesity, the presence and severity of hypertension, CHF, CAD, GFR, and NT-proBNP fully confirm this. Patients included in our study had preserved LV systolic function. However, they also had risk factors of AF, each of which contributed to AF's pathogenesis and might contribute to the development of LA fibrosis through the formation of latent LV diastolic dysfunction [16]. According to our data, GDF-15 turned out to be such an integral biomarker, combining all pathogenetic links implemented through the LV diastolic dysfunction, since GDF-15 was significantly inversely correlated with such indicators of the LV diastolic function as septal and lateral mitral annular velocities in diastole (e' septal and e' lateral) and directly correlated with the LA diameter and volume.

There are especially broad prospects for using GDF-15 as an independent prognostic biomarker of cardiovascular events associated with CAD or heart failure, including in the population of apparently healthy elderly people [17]. As for patients with non-valvular AF, biomarker subanalyses ARISTOTLE [8] and RE-LY [18] have been published, which demonstrate that GDF-15 is an independent predictor not only of thromboembolism, cardiovascular and all-cause mortality, but also of major bleeding [8]. GDF-15, as a predictor of adverse cardiovascular events, does not depend on the presence of LV hypertrophy [18].

We have not found studies on the association of GDF-15 with fibrosis in patients with non-valvular AF. In this study, the area of LA low-voltage zones was used as a surrogate marker of LA fibrosis, which, as shown above, is well correlated in patients with AF with the fibrous substrate dimensions assessed with delayed contrast – enhancement magnetic resonance imaging [12]. When we compared the area of LA fibrosis at various levels of GDF-15, we noted that an increase in GDF-15 was accompanied by an increase in the area of LA fibrosis: when GDF-15 is higher than the median, the area of fibrosis is significantly higher than when GDF-15 is within the lower quartile range. Our results are consistent with the findings of Yong-Ming Zhou et al. [19]

Figure 1. ROC curves used to predict LA fibrosis >20%, AUC=0.762 (p=0.000)



published in 2015, in that instance concerning patients with AF and rheumatic heart disease. Specifically, the authors identified positive correlations between the levels of plasma GDF-15 and the levels of GDF-15 μRNA in atrial tissue samples collected from the atrial appendages resected during heart-valve surgeries. The authors concluded that GDF-15 may be involved in the development and maintenance of atrial fibrosis in patients with AF and rheumatic heart disease and suggested it could later be used as a new biomarker to evaluate myocardial fibrosis [19].

We attempted to evaluate the approximate dimensions of fibrosis that can be predicted using the GDF-15 level. Fibrosis of more than 20% of the LA area was randomly selected as the target for the prediction. The comparable value was obtained in comparative analysis of the LA fibrosis area in patients with GDF-15 levels above the median. The step-by-step logistic regression analysis included variables as potential predictors of fibrosis >20%, for which statistically significant or near-significant differences were obtained

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*В сравнении с другими сартанами (валсартан, лозартан, телмисартан). **Удержание АД на кандесартане в течение 36 часов после пропуска дозы, предположительно, связано с блокированием АТ1 рецепторов. 1. Lacourciere Y., Asmar R.A. Comparison of the efficacy and duration of action of candesartan cilexetil and losartan as assessed by clinic and ambulatory blood pressure after a missed dose, in truly hypertensive patients: a placebo-controlled, forced titration study. Candesartan/Losartan study investigators. Am J Hypertens. 1999; 12 (12 Pt 1–2): 1181–7. 2. Weisser B., Gerwe M., Braun M., Funken C. Investigations of the antihypertensive long-term action of candesartan cilexetil in different dosages under the influence of therapy-free intervals. Arzneimittelforschung 2005; 55 (9): 505–13. 3. Инструкция по медицинскому применению Ордисс®, Ордисс Н®. 4. Minatoguchi S., Aoyama T., Kawai N. et al. Comparative effect of candesartan and amlodipine, and effect of switching from valsartan, losartan, telmisartan and olmesartan to candesartan, on early morning hypertension and heart rate. Blood Pressure, 2013; 22 (Suppl 1): 29–37. 5. Kjeldsen S.E., et al. Effects of losartan vs candesartan in reducing cardiovascular events in the primary treatment of hypertension. Journal of Human Hypertension. 2010; 24: 263-273. 6. Lin J.W., Chang C.H., Caffrey J.L. et al. Examining the association of olmesartan and other angiotensin receptor blockers with overall and cause-specific mortality // Hypertension 2014, 63(5): 968-76.

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Регистрационный номер: ЛП-002127 от 05.07.2013. **Торговое название:** Ордисс®. **МНН:** кандесартан. **Активное вещество:** кандесартана цилексетил 8,0 мг/16,0 мг/ 32,0 мг. **Лекарственная форма:** таблетки. **Показания к применению:** артериальная гипертензия, хроническая сердечная недостаточность и нарушение систолической функции левого желудочка (снижение ФВЛЖ≤40%) в качестве дополнительной терапии к ингибиторам ангио-превращающего фермента (АПФ) или при непереносимости ингибиторов АПФ (см. раздел «Фармакодинамика»). **Противопоказания:** повышенная чувствительность к кандесартану и другим компонентам препарата; непереносимость лактозы; дефицит лактазы; синдром глюкозо-галактозной мальабсорбции; тяжелое нарушение функции печени и/или холестаз; беременность; период грудного вскармливания; детский возраст до 18 лет; одновременное применение с алискиреном или препаратами, содержащими алискирен, у пациентов с сахарным диабетом и/или умеренными или тяжелыми нарушениями функции почек (скорость клубочковой фильтрации (СКФ) менее 60 мл/мин/1,73 м² площади поверхности тела), одновременное применение с ингибиторами АПФ у пациентов с диабетической нефропатией. **Способ применения и дозы:** препарат Ордисс® следует принимать один раз в сутки вне зависимости от приема пищи. Артериальная гипертензия. Рекомендуемая начальная и поддерживающая доза препарата Ордисс® составляет 8 мг один раз в сутки. Пациентам, которым требуется дальнейшее снижение артериального давления, рекомендуется увеличить дозу до 16 мг один раз в сутки. Пациентам, которым не удалось достаточно снизить артериальное давление после 4 недель приема препарата Ордисс® в дозе 16 мг в сутки, рекомендуется увеличить дозу до 32 мг один раз в сутки. У пациентов с легким или умеренным нарушением функции почек (клиренс креатинина 30-80 мл/мин/1,73 м² площади поверхности тела), включая пациентов, находящихся на гемодиализе, начальная доза препарата составляет 4 мг/сут (1/2 таблетки по 8 мг). Хроническая сердечная недостаточность (ХСН). Рекомендуемая начальная доза препарата Ордисс® составляет 4 мг (1/2 таблетки по 8 мг) один раз в сутки. Повышение дозы до 32 мг один раз в сутки или до максимально переносимой дозы проводится путем ее удвоения с интервалами не менее 2 недель (см. раздел «Особые указания»). Полную информацию см. в инструкции по применению. **Побочное действие:** артериальная гипертензия. Наиболее часто – головокружение/вертиго, головная боль и респираторные инфекции, часто – нарушение функции почек, включая почечную недостаточность у предрасположенных пациентов. Хроническая сердечная недостаточность. Часто – гиперкалиемия, артериальная гипотензия, нарушение функции почек, включая почечную недостаточность у предрасположенных пациентов. **С осторожностью:** гемодинамически значимый стеноз аортального и митрального клапанов, цереброваскулярные заболевания, ишемическая болезнь сердца, гипертрофическая обструктивная кардиомиопатия, состояние после трансплантации почки, двусторонний стеноз почечных артерий или стеноз артерии единственной почки, первичный гиперальдостеронизм, почечная недостаточность тяжелой степени (клиренс креатинина менее 30 мл/мин), гемодиализ, гиперкалиемия; у пациентов со сниженным объемом циркулирующей крови, проведение общей анестезии и хирургических вмешательств (риск развития артериальной гипотензии, вследствие блокады РААС). Полную информацию см. в инструкции по применению. **Срок годности:** 2 года. **Условия отпуска:** отпускают по рецепту. Полная информация по препарату содержится в инструкции по медицинскому применению. CAN-RU-NP-00005

Сокращенная информация по применению лекарственного препарата Ордисс Н®
Регистрационный номер: ЛП-002097 от 10.06.2013. **Торговое название:** Ордисс Н®. **МНН:** гидрохлоротиазид + кандесартан. **Активные вещества:** кандесартана цилексетил 16,0 мг/32,0 мг/ 32,0 мг; гидрохлоротиазид 12,5 мг/12,5 мг/25,0 мг. **Лекарственная форма:** таблетки. **Показания к применению:** лечение артериальной гипертензии у пациентов, которым показана комбинированная терапия. **Способ применения и дозы:** препарат Ордисс Н® следует принимать один раз в сутки вне зависимости от приема пищи. Рекомендуемая доза – 1 таблетка 1 раз в сутки. Рекомендуется титрование дозы кандесартана перед переводом пациента с монотерапии гидрохлоротиазидом на терапию препаратом Ордисс Н®. При необходимости пациентов переводят с монотерапии препаратом Ордисс® на терапию препаратом Ордисс Н®. Основной гипотензивный эффект достигается, как правило, в первые 4 недели после начала лечения. Полную информацию см. в инструкции по применению. **Противопоказания:** повышенная чувствительность к кандесартану, гидрохлоротиазиду, другим компонентам препарата и к другим производным сульфонамида; беременность; период грудного вскармливания; непереносимость лактозы; дефицит лактазы; синдром глюкозо-галактозной мальабсорбции; первичный гиперальдостеронизм; подагра; тяжелое нарушение функции почек (скорость клубочковой фильтрации (СКФ) менее 30 мл/мин/1,73 м² площади поверхности тела); тяжелые нарушения функции печени; холестаз; рефрактерная гипокалиемия, гиперкальциемия; состояние после трансплантации почки, детский возраст до 18 лет; одновременное применение с алискиреном или алискиренсодержащими препаратами у пациентов с сахарным диабетом и/или умеренными или тяжелыми нарушением функции почек (скорость клубочковой фильтрации (СКФ) менее 60 мл/мин/1,73 м² площади поверхности тела), одновременное применение с ингибиторами АПФ у пациентов с диабетической нефропатией. **Побочное действие:** головокружение, гипергликемия, гиперурикемия, гипонатриемия, гипокалиемия, вертиго, глюкозурия, слабость, респираторные инфекции, повышение концентрации холестерина, триглицеридов в плазме крови. Полную информацию см. в инструкции по применению. **С осторожностью:** нарушение функции почек (КК более 30 мл/мин), недостаточность функции печени; тяжелая хроническая сердечная недостаточность; двусторонний стеноз почечных артерий; стеноз артерии единственной почки; гемодинамически значимый стеноз аортального и/или митрального клапана; ишемическая болезнь сердца; гипертрофическая обструктивная кардиомиопатия; снижение объема циркулирующей крови (ОЦК); сахарный диабет, цереброваскулярные заболевания; острая миопия; закрытоугольная глаукома; системная красная волчанка. **Срок годности:** 2 года. **Условия отпуска:** отпускают по рецепту. Полная информация по препарату содержится в инструкции по медицинскому применению. CANH-RU-NP-00003

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ОТКРЫВАЯ ВОЗМОЖНОСТИ
ДЛЯ ДОСТУПНОГО ЗДОРОВЬЯ

using the criterion of the presence or absence of this condition. Only two predictors were included in the final model: the level of GDF-15 above the median and the LA volume index. The published results of our previous study showed that NT-proBNP, structural cardiac remodeling in the form of eccentric LV hypertrophy, and LA volume index >34 mL/m^2 may be independent predictors of severe (>35%) LA fibrosis [20]. In this study, there were no differences in heart geometry types between patients with different GDF-15 levels. Thus, the types of structural LV remodeling were not included in the model. The NT-proBNP level also proved to be a less potent predictor than GDF-15 and was excluded from the model. It was obviously due to a «softer» measure of >20% taken as a criterion for the severity of LA fibrosis than that in the above study [20]. Therefore, patients with fibrosis >20% had a relatively low median NT-proBNP level (146 pg/mL) and did not exceed the reference level (125 pg/mL). The second independent predictor was LA volume index, which is well expected since it is generally accepted that LA fibrosis is proportional to the degree of LA dilatation [16], which in turn is a consequence of LV diastolic dysfunction, the indicators of which were shown to be statistically significantly correlated with the level of GDF-15.

Thus, GDF-15 may be not only a prognostic marker of adverse outcomes in patients with non-valvular AF but also an independent predictor of the severity of LA fibrosis.

Limitations

The study included a relatively small number of patients. GDF-15 was measured using an analytical set for research purposes, therefore requiring an expanded study and the definition of peculiar reference values, including for individual age categories. The point-by-point EVM did not establish the optimal parameters of mapping density. EVM was performed in some patients with AF, which could cause an error in calculating the LA areas of low voltage.

Conclusion

The level of growth differentiation factor-15 is associated with the presence and severity of the main risk factors of atrial fibrillation and the severity of left atrial fibrosis. Elevated growth differentiation factor-15 above the median and left atrial volume index are independent predictors of left atrial fibrosis more than 20% of the left atrial area in patients with preserved left ventricular systolic function.

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