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Journal of the Cardioprogress Foundation

Early markers of endothelial dysfunction in young professional athletes

Mineralocorticoid-receptor antagonists in the management chronic heart failure: the effectiveness and promising opportunities

The stenting of carotid-subclavian shunt for the primary prevention of acute cerebrovascular accident

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International Heart and Vascular Disease Journal

Journal of the «Cardioprogress» Foundation

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Contents

Editor's Welcome

Dear colleagues!

We present the next 34th issue of the International Heart and Vascular Disease Journal that includes the leading article, original and review articles, as well as clinical case report.

For the leading article section authors from Saint Petersburg presented their original work. The article is dedicated to primary prevention of atrial fibrillation in patients with metabolic syndrome and premature atrial contractions. The study included 426 patients who were prescribed with antiarrhythmic drug therapy with I–III antiarrhythmic agents (excluding amiodarone) and modulated kinesitherapy. Patients were followed up for one year. The results showed the reduction of the frequency of atrial fibrillation by 3 times compared with regular BP, blood glucose and lipids level correction.

The original article section presents two manuscripts. The first article is dedicated to the analysis of the prognostic criteria of mortality and chronic thromboembolic pulmonary hypertension in patients with pulmonary embolism. The study included 155 patients with pulmonary embolism. The following symptoms were associated with mortality: cardiac stroke volume reduction, the right ventricular to left ventricular diameter ratio over 0.9, blood pressure decrease less than 90/60 mm Hg, history of syncope, paradoxical interventricular septal motion, over 75 % of thrombotic occlusion of the pulmonary artery, elevated plasma concentrations of troponin level. The second article investigated early markers of endothelial dysfunction in professional athletes. The study included 78 athletes aged from 18 to 45 years old involved in various professional sports. The study found that professional athletes with the presence of risk factors showed increased pulse wave velocity that can indicate the presence of early-stage vascular remodeling, in case when the influence of genetic polymorphisms of the renin-angiotensin-aldosterone system was excluded.

The review article analyzed the results of randomized clinical trials on the use of mineralocorticoid-receptor antagonists in patients with myocardial infarction, chronic heart failure in combination with type 2 diabetes mellitus and chronic kidney disease. Another review focused on the main causes of iron deficiency, differential diagnosis between anemias, treatments features in patients with various comorbidities, such as cardiovascular diseases, as well as treatment options for iron deficiency anemia.

The issue also presents clinical case on the stenting of the proximal anastomosis of the carotid-subclavian shunt using the cerebral protection system with right femoral and left radial approaches. This clinical case demonstrates the possibilities of modern endovascular surgery in the management of patients with extremely high cardiovascular risk.

We invite everybody to collaborate with the journal. We are waiting for your original papers, review articles, discussions, and opinions about problems, treatment and prophylaxis recommendations.

Mekhman N. Mamedov
Editor-in-Chief
President of the "Cardioprogress" Foundation

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International medical reviews

The study "Metabolomic profiles of chronic distress predict future cardiovascular disease risk" is dedicated to the examination of the association between metabolite profile, distress and increased risk of cardiovascular disease in women. The distress assessment was based on case-control dataset (n=558 women) in the Nurses' Health Study (NHS).

Data were based on the biomarker levels in the blood samples that were taken from 2000 to 2002, depression-related data on questionnaires from 1992 through 2004, anxiety-related data on questionnaires in 1988 and in 2004.

Authors conclude that in the WHI-OS cohort the increase of the distress parameter by one standard deviation had the odds ratio (OR)=1.14 (95 % CI: 1.03–1.26) adjusting for known cardiovascular disease in patients with coronary artery disease.

In the PREDIMED cohort, each standard deviation increase of the distress was associated with OR=1.17 (95 % CI: 1.00–1.38), after adjusting for risk factors. Similar associations were observed in men and women.

medRxiv.org, 2022

According to the authors from the US, serious psychiatric disorders are associated with higher cardiovascular risk, even in young patients. These disorders include bipolar disorder and schizophrenia. They may significantly increase cardiovascular risk.

Researchers assumed that it is necessary to assess cardiovascular risk in patients with serious mental disorders and pay special attention to the prevention of diabetes mellitus, obesity and smoking cessation in this group of patients. This requires team work including physicians and family members.

For this analysis, the researchers assessed 579.924 patients without and 11.333 patients with serious mental illness as part of a cluster randomized trial of support and clinical decision making in primary medical care that aimed to reduce cardiovascular risk in patients with severe mental illness.

Average age of participants was 45 years. The percentage of women was 57.8 % in the serious mental illness group, and 54 % — in the group without psychiatric disorder.

https://www.heart.org/, 2022

The study was dedicated to the possibility of screening in elderly patients for atrial fibrillation during primary care visits similar to the assessment of arterial blood pressure, auscultation and the assessment of other vital parameters. Specialists from Mass General used single-lead devices that are connected to the tablet computer for the examination of over 35 000 men and women from 16 primary care sites associated with hospital research network.

Expert's opinion on the effectiveness of such screening differed. The European Society of Cardiology recommended the assessment of pulse rate and ECG at rest during primary care visits for patients aged over 65 years. The National Heart Foundation of Australia and the The Cardiac Society of Australia and New Zealand had similar guidelines.

Circulation, 2022

The prospective cohort study showed the association between infertility and higher risk of chronic heart failure development, especially heart failure with preserved ejection fraction (HFpEF).

Data showed that women with infertility had higher risk of chronic heart failure development, especially HFpEF compared with heart failure with reduced ejection fraction (HFrEF).

The research group prospectively assessed postmenopausal women for the development of HF. Among 38.528 postmenopausal women, who were included into the study, 14 % reported a history of infertility. Average age was 63 years old. Over a median follow-up of 15 years, 2.373 developed heart failure. Multivariable cause-specific Cox models were used to evaluate the association of infertility with incident overall HF and HF subtypes (HFpEF], HFrEF, general HF).

Journal of the American College of Cardiology, 2022

The study from Karolinska University Hospital found that the administration of acetylsalicylic acid before aortic valve surgery reduced the incidence of ascending aortic aneurysms at the time of the surgery. The study included 1468 patients who were scheduled for open-heart surgery for ascending aortic aneurysm and/or aortic valve disease. Tricuspid aortic valve was detected in 693 patients, bicuspid valve — in 775 patients. The reduced prevalence of ascending aortic aneurysm was seen only in patients with tricuspid aortic valves. Relative risk for the ascending aortic aneurysms after aspirin prescription in patients with a tricuspid valve was 0.68. According to the authors of the study, the effect of aspirin may be associated with the inhibition of the inflammatory process associated with cyclooxygenase-2. The expression of cyclooxygenase-2 in the portion of the ascending aorta was reduced in patients who received aspirin.

JAHA, 2022

The researchers evaluated the effect of lipoprotein (a) on the development of atrial fibrillation. The analysis showed: the increase of the level of these protein by every 50 nmol/l increased the risk of atrial fibrillation by 3 %. The decrease of its level by 80 % reduced the absolute risk of atrial fibrillation development by 0.4 %, and relative risk — by 8 %. The decrease of body mass index by 2 units or decrease of blood pressure by 5 mm Hg has similar effect.

Lipoprotein (a) is an independent risk factor for the development of coronary artery disease, ischemic stroke and aortic stenosis that increases the risk of atrial fibrillation. However, the analysis showed that atherosclerotic cardiovascular diseases can explain only 39 % of lipoprotein (a) effect. The effect lipoprotein (a) did not depend on the level of low-density lipoproteins and triglycerides.

JACC journal, 2022

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The use of antiarrhythmic drug treatment and modulated kinesitherapy for primary prevention of atrial fibrillation in patients with metabolic syndrome

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Abstract

Objective. *To assess the effectiveness antiarrhythmic drug treatment (ADT) and modulated kinesitherapy (MK) for primary prevention of atrial fibrillation (AF) in patients with metabolic syndrome (MS) and premature atrial contractions (PACs).*

Materials and methods. *The study included 426 patients with MS and PACs aged from 58 to 72 years (average age — 66.4±0.7 years) with high risk of primary AF development (during one-year follow-up after the inclusion into the study). ADT with I–III antiarrhythmic agents was used for the primary AF prevention (excluding amiodarone) in 149 (34.97%) patients, MK — in 121 (28.40%), and blood pressure (BP), blood glucose and lipids level correction — in the rest. The primary endpoint after one-year follow-up was: the maintenance of sinus rhythm or AF registration.*

Results. *The rate of paroxysmal and persistent AF in patients prescribed with ADT and MK for the primary prevention of AF with MS and premature atrial contractions within one year after the first examination was 26.45% and 31.54%, respectively. The use of ADT and MK in patients with MS reduced the frequency of AF by 3 times on average compared with the correction of potentially modifiable MS risk factors.*

Conclusion. *The implementation of ADT with I-III antiarrhythmic agents as well as MK for the AF primary prevention in patients with MK with PACs and the risk of AF development one year after the first examination allowed to reduce the frequency of this arrythmia by 3 times compared with regular BP, blood glucose and lipids level correction.*

Keywords: *metabolic syndrome, primary atrial fibrillation prevention, antiarrhythmic therapy, modulated kinesitherapy.*

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Introduction

Atrial fibrillation (AF) once developed in patients with metabolic syndrome (MS) usually recurs and transforms into permanent type [1]. Therefore, the primary prophylaxis of this arrhythmia in patients with MS is the basis for its prevention [1]. The primary prevention of AF includes the management of potentially modifiable MS risk factors, as well as the predictors for its development, such as premature atrial contractions (PACs) [1, 2]. Various types of physical activity are usually used for the management of MS [1, 2]. Modulated kinesitherapy (MK) is an aerobic exercise when patient walk in accordance with the heart rhythm [3]. Patients with MS with PACs and prognostic index for the development of AF ⩽ 1.5, have high risk of AF development during 1 year follow-up [4]. It can be assumed that the increase of the prognostic index for the development of AF compared with baseline, for example, after MK and antiarrhythmic drug therapy (ADT) or other treatment in patients with MS, can be used as the criterion for the primary AF prevention effectiveness before the onset of clinical result. However, we have not found literature the data on the use of ADT and MK for AF primary prevention in patients with MS and PACs with high risk of AF.

The aim of the study was to assess the effectiveness of ADT and MK for primary prevention of AF in patients with MS and PACs.

Materials and methods

The study included 426 patients with MS aged from 58 to 72 years (average age — 66.4±0.7 years). All the participants had the risk of AF development during 1-year follow up. The number of men and women was 186 (43.66%) and 240 (56.34%), respectively (p>0.05). MS was diagnosed according to generally accepted criteria [1].

After the clinical and instrumental examination that included echocardiography, daily electrocardiogram (ECG) monitoring, signal-averaged ECG registration, etc., the study inclusion criteria were determined among patients with MS. Instrumental methods for the determination of the left ventricular (LV) contractility and dysfunction, cardiac chambers volume, as well as the prognostic index for the development of AF, functional class of heart failure (assessed with 6-minute walk test), mean arterial blood pressure (BP) were described in details in previously published articles [4]. The prognostic index for AF development was calculated by the following formula: (A÷B)×(C÷N), where A and B are filtered "P" wave duration and dispersion determined by the data

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of signal-averaged atrial ECG and daily ECG monitoring, respectively (m/s), C — linear deviation of the corrected coupling interval of PACs, N — the number of PACs used for the study, expressed as number/hour [4]. At least 20 PACs were analyzed by the the corrected pre-ectopic interval in order to eliminate false positive results when determining the prognostic index of AF development [4]. The prognostic index for the development of AF ⩽ 1.5 in patients with MS with PACs predicted the occurrence of AF arrhythmia within one year after the examination [4]. It should be noted that the detection of PACs showed potential risk of primary AF development in patients with MS, however, the number of PACs per day or hour of observation did not affect the risk of AF [1, 2].

The CHARGE-AF risk score was used to determine the risk of AF development in dynamics by the following formula:

$$R_{CHARGE\text{-}AF} = 1 - 0.9718412736^{\exp[(\Sigma(\kappa_1,\kappa_2,\kappa_3,\kappa_4,\kappa_5,\kappa_6,\kappa_7,\kappa_8,\kappa_9,\kappa_{10},\kappa_{11}) - 12.5815600]},$$

where

$R_{CHARGE\text{-}AF}$ — the risk of AF development by the CHARGE-AF risk score (in units),

K1 — (age in years ÷5)×0.5083;

K2 — ethnicity (caucasian/white: 1×0.46491);

K3 — (height in cm÷10)×0.2478;

K4 — (body mass in kg ÷15)×0.1155;

K5 — (systolic BP in mmHg.÷20)×0.1972,

K6 — (diastolic BP in mmHg ÷10)×0.1013,

K7 — current smoking (1×0.35931),

K8 — antihypertensive therapy (1×0.34889),

K9 — diabetes mellitus (1×0.23666),

K10 — chronic heart failure (functional classes from I to IV×0.70127);

K11 — history of myocardial infarction (1×0.49659). High risk of AF development was determined with RCHARGE-AF values over 0.76 [5].

The inclusion criteria were: the presence of sinus rhythm, subjective sensation of PACs, class I-II, of chronic heart failure according to NYHA, the absence of AF registration during at least 4–5 procedures of 1–3-day ECG monitoring at least once in 1–2 weeks for 2–3 months, left ventricular ejection fraction (LV EF) ⩾ 54% [4], prognostic index for the development of AF ⩽ 1.5, written informed consent for the participation in the study from the patient [4].

Patients with cardiomyopathies, heart valve disease and other pathologies presented in previously published articles [4] were excluded from the study.

AH was registered in 358 (84.04%) patients, diabetes mellitus — in 297 (69.72%), chronic obstructive pulmonary disease — in 96 (22.54%).

All study participants underwent BP correction with antihypertensive therapy, such as: indapamide, telmisartan, valsartan, etc. In order to improve the levels glucose and blood lipids, in addition to healthy diet, hypoglycemic and lipid-lowering medications were prescribed. The correction of potentially modifiable MS risk factors was considered as basic treatment.

At first, all patients, along with the basic treatment, underwent ADT. In case when patient refused to use pharmacological treatment, had side effects or contraindications, MK was prescribed. In case when patient had negative reaction to the use of ADT or MK, only basic treatment was performed. These patients were included into the control group.

All the participants initially received class II antiarrhythmic drugs, and class I or III drugs when the first-line treatment had no effect, such as: metoprolol, propranolol, carvediol, allapinin, ethacizine, propafenone, sotalol in average therapeutic doses, excluding amiodarone that is used for myocardial contractile dysfunction [2]. At baseline and after ADT that was carried out from 3–4 to 7 days, the prognostic index for the development of AF was determined: the increase of the prognostic index for the development of AF compared with baseline was considered as positive effect [4].

MK included walking in accordance with the heart rate [3, 6]. At first, MK was performed 2 times a day or more for 30–60 minutes for 5–7 days [5]. When positive effect was reached that was determined by the increase of prognostic index for the development of AF compared with baseline [6] MK was performed for at least 150 min/day [3, 6].

The development of AF during one-year follow-up was the endpoint of the study. In case when AF developed, anticoagulants such as dabigatran and rivaroxaban were prescribed [1, 2]. All the investigations were performed during sinus rhythm at least once every 1–2 months. When AF (paroxysmal or persistent) was determined, the investigations were performed after the management of AF, and pharmacological cardioversion was applied after 5-7 half-lives

of antiarrhythmic drugs that were used to eliminate this arrhythmia.

The results of statistical analysis are presented as mean values and standard error (M±m), standard deviation (σ), 95% confidence interval of the mean values, Student's t-test, chi-square test. The statistical significance was set as p<0.05. The Kolmogorov–Smirnov test and the ±3σ rule (gaussian distribution) was used to assess the normality of distribution. The comparison of two binary variables was performed using multiple logistic regression with the assessment of the odds ratio (OR) and standard error (SE) using the "Statistica" software, version 11.0.

Study results

149 (34.97%) patients received ADT (ADT group), 121 (28.40%) — MK (MK group), the rest of the participants made up the control group. Groups did not differ significantly by gender, age, comorbid diseases, the results of clinical, laboratory and instrumental investigations.

Propranolol was the most effective medication in 33 (22.15%) patients from the ADT group, metoprolol — in 47 (31.54%), carvediol — in 26 (17.45%), ethacizine — in 15 (10.07%), allapinin — in 10 (6.71%), propafenone — in 8 (5.37%), sotalol — in the rest.

The studied parameters did not differ significantly between ADT and MK groups (Table 1).

During 1-year follow-up, paroxysmal and persistent types of AF were recorded in 32 (26.45%), 47 (31.54%) and 149 (95.51%) patients from ADT, MK and control group, respectively (p< 0.05), and the differences between the control and ADT and MK groups were statistically significant (Figure 1). The incidence of AF increased in patients over 65 years of age (OR = 8.93, SE = 0.94), with body mass index (BMI) > 35 kg/m^2 (OR = 5.5, SE = 0.92), left atrial end-diastolic volume index (LAEDVI) ⩾ 37 ml/m^2 (OR = 5.8, SE = 0.92), the ratio of the maximum early (E) to late (A) ventricular filling velocities (E /A) < 0.8 (OR = 2.5, SE = 1.3), prognostic index for the AF development < 0.5 units (OR = 12.8, SE = 1.6).

One year after the baseline, patients from the control group showed statistically significant decrease of the LV EF, E/A ratio, prognostic index for the development of AF parameters and 6-minute walk test, and the increase of LAEDVI, the number of PACs/hour, mean BP, BMI, RCHARGE-AF compared with baseline (table). The prognostic index for the development of AF statistically significantly increased and the number of PACs decreased in the ADT group, in the MK group — LV EF, the E/A ratio, the prognostic index for the development of AF, the results of the

Table 1. **Clinical and instrumental parameters, prognostic index for AF development, RCHARGE-AF in patients from ADT and MK groups at baseline (A) and one year after treatment (B)[1]**

Study group	Control group n=156		ADT group n=149		MK group n=121	
Parameters	**A**	**B**	**A**	**B**	**A**	**B**
LV EF, %	61.84±0.57 (54–69)	54.01±0.66† (46–62)	61.54±0.52 (55–68)	60.38±0.65 (52–70)	61.47±0.61 (54–68)	68.35±0.81‡ (59–77)
E/A, units	0.95±0.02 (0.71–1.23)	0.78±0.01† (0.61–0.95)	0.94±0.01 (0.75–1.15)	0.96±0.01 (0.84–1.08)	0.94±0.01 (0.74–1.15)	1.07±0.01† (0.92–1.21)
LAEDVI, ml/m^2	36.78±0.25 (34–39)	41.93±0.57† (35–46)	37.54±0.24 (33–41)	37.53±0.23 (34–41)	36.54±0.24 (32–42)	32.53±0.43‡ (27–38)
PERs, units	0.75±0.05 (0.01–1.49)	0.07±0.01† (0.02–0.12)	0.76±0.06 (0.02–1.50)	4.17±0.34* (0.42–8.12)	0.76±0.06 (0.03–1.49)	5.07±0.46* (0.72–9.34)
PACs/hour	172±6 (103–241)	398±22† (126–687)	182±7 (109–256)	36±3* (8–64)	180±7 (98–263)	33±2* (9–58)
Mean BP, mmHg	117±1 (103–131)	121±1† (106–131)	119±6 (102–132)	116±1 (102–128)	118±1† (104–131)	105±1† (95–116)
6-minute-walk test	436.5±6.7 (365–510)	375.7±5.1† (315–436)	447.9±6.3 (372–516)	442.7±6.7 (368–518)	422.9±7.3 (358–489)	546.5±9.8† (445–648)
BMI, kg/m2	32.9±0.32 (30.3–35.4)	35.9±0.33† (32.1–39.7)	32.7±1.02 (30.1–35.1)	33.1±0.34 (31.4–35.6)	33.9±0.32 (31.5–36.2)	28.4±0.24† (25.1–31.6)
RCHARGE-AF, units.	0.82±0.02 (0.79–0.91)	0.86±0.01† (0.81–0.93)	0.84±0.02 (0.78–0.93)	0.82±0.02 (0.75–0.87)	0.84±0.02 (0.79–0.93)	0.71±0.02‡ (0.67–0.78)

Comment. PERs — positron-emitting radiopharmaceuticals; 1 — M±m (top of the table); 95 % confidence interval (bottom of the table).
*— statistically significant difference compared with the control group with p < 0,001,
† — compared with baseline with p < 0,05,
‡ — with p < 0,01.

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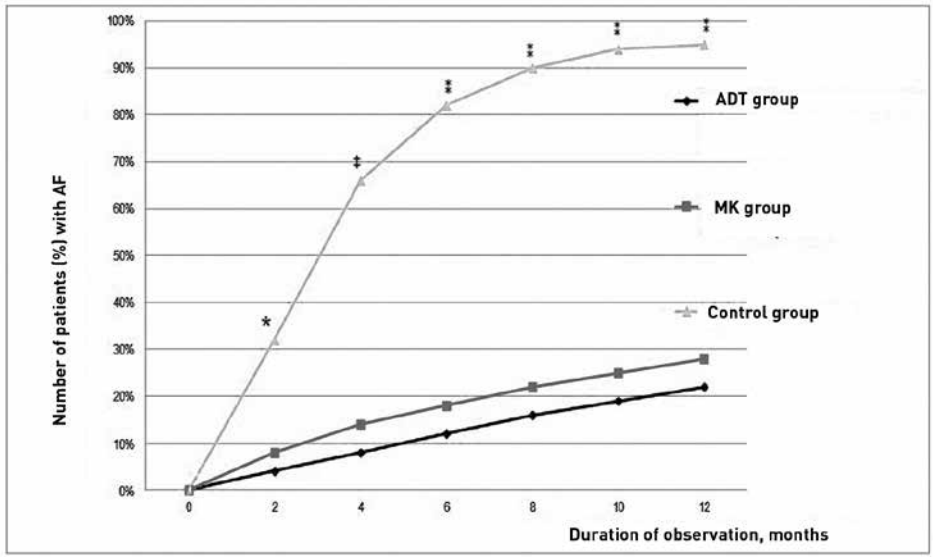

Figure 1. Cumulative proportion of patients (%) with the development of AF in ADT and MK groups.
Comment. * — statistically significant difference between ADT and the control group with p < 0,05, ‡ — with p < 0,01, ⁑ — with p < 0,001, † — compared with MK group with p < 0,05.

6-minute test statistically significantly increased, and the LAEDVI, the number of PACs, mean BP, BMI, RCHARGE-AF — decreased compared with baseline. The rest of the parameters did not differ significantly (see table). The positive effect of the ADT and MK as primary prevention for AF in patients with MK was associated with the increase of the prognostic index for the development of AF by over 1.5 units (OR = 12.1, SE = 0.94), the decrease of RCHARGE-AF values compared with baseline (OR = 7.1, SE = 0.92) and, to lesser extent, with the decrease of the number of PACs per day (OR = 0.89, SE = 1.1).

Discussion

The assessment of pulse rate according to the "pulse screening" principle that includes pulse palpation and its assessment with automatic or semi-automatic tonometers, followed by ECG recording by smartphone or by at the hospital is recommended for early diagnosis of AF in all patients, especially from older age group [7]. In recent years, patients with MS have been included into high-risk group for the development of AF. In case when their CHA2DS2VASc score of thromboembolic complications was ⩾ 1 and ⩾ 2 in men and women, respectively, — it is recommended to assess pulse rate daily and the increase of this score is associated with higher frequency of AF development [8, 9].

The study included 426 patients with MS aged from 58 to 72 years (average age — 66.4±0.7 years). The inclusion criteria were: sinus rhythm, the absence of AF registration, determined by at least 4–5 procedures of 1–3-day ECG monitoring at least once every 1–2 weeks for 2–3 months, the detection of PACs, the prognostic index for the development of AF ⩽ 1.5 that characterize the risk of AF development within one year after the inclusion into the study, and the presence of patient's written informed consent . The study endpoints were the maintenance of sinus rhythm or the development of AF.

Over the past years over 21 risk stratifications have been proposed, including the Framingham risk scales (1994–2019), in order to assesses the risk of AF development [10]. The meta-analysis of several risk stratifications (retrospective study) showed that the most informative model for 5-year prediction of AF onset of was the CHARGE-AF risk score [10] that include simple and available parameters, such as age, gender, anthropometric parameters, blood pressure, etc. [5]. The accuracy of RCHARGE-AF of 0.70–0.72 units by the CHARGE-AF risk score for primary AF prediction according to retrospective analysis of over 110.000 patients aged over 40 years old, is about 50%, and of 0.90 units — 90% [10, 11]. It should be noted that almost all patients with MS, especially those aged over 60 years old, who were assessed with CHARGE-AF score, had high or very high risk of AF development [5, 11].

Similar results were obtained in our study.

Currently, the mechanisms of AF development in patients with MS are not enough understood [1]. In

recent years, one the main hypothesis for AF development in this category of patients was the induction of AF by atrial cardiomyocytes overload with Ca++ ions during diastole caused by "oxidative stress" [1] that leads to atrial ectopic activity due to activation of trigger mechanisms and/or re-entry at the posterior wall of the left atrium that causes AF followed by its recurrence and/or preservation and transformation into permanent type [1]. It should be noted that the development of ectopic focus in the atria and/or pulmonary veins is quite rarely seen in patients with MS and AF [1, 2].

In most cases, PACs in patients with MS is interpreted as ectopia with potentially favorable prognosis that often does not require ADT, unless there is a subjective sensation of extrasystole that patient complain about [1, 2]. On the other hand, persistent and/or recurrent supraventricular ectopic activity can independently or indirectly disrupt cardiac conduction in the atria in this category of patients [1, 2]. However, the number of PACs per day is not associated with the risk of AF development in patients with MS [1, 2, 4].

In our study the risk of AF development was assessed by the prognostic index for the development of AF — the value of <1.5 units indicate the risk of AF registration within one year of observation [4].

To determine the prognostic index for the development of AF, we used signal-averaged atrial ECG data, P-wave dispersion, and the analysis of PACs preectopic interval [4]. The risk of AF development in patients with MS significantly increased with age, BMI, and its accuracy, in case of the decrease of this index in dynamics compared with baseline (<1.5 units), reached about 90% [4] .

The results of this study are consistent with previously obtained data.

The rate of AF registration was 26.45% and 31.54% in patients with MS who were administered with ADT and MK additionally to basic treatment for the primary prevention of AF, respectively (p>0.05). Positive effect of these methods for the primary prevention of AF in patients with MS highly correlated with the increase of the prognostic index for the development of this arrhythmia by > 1.5 units. Therefore, apparently, the increase of the prognostic index for the development of AF compared with baseline is a potential "preclinical" criterion that reflects the effectiveness of primary prevention of this arrhythmia in patients with MS, not only with ADT and MK, but also using other treatment. It should be noted that all patients with MS, both without and with the development of AF, showed significant decrease in the number of PACs compared with baseline (OR between positive result of AF primary prevention and the decrease of PACs frequency did not exceed 0.89), after ADT and MK treatment. Therefore, the decrease in the number PACs not only after ADT and MK, but also after other treatment in patients with MS, cannot be a reliable criterion to assess the effectiveness of ongoing primary AF prevention.

Positive effect of ADT in patients with MS seem to be mainly associated with the elimination of electrophysiological mechanisms for the development of PACs [2], since there was no significant change of hemodynamic parameters, class of chronic heart failure, BMI, RCHARGE-AF in ADT group after treatment.

The data on the use of antiarrhythmic drugs in patients with MS and atrial ectopic activity for the primary prevention of AF are scarce that can be associated with increased risk of adverse events compared with positive result [1, 2]. ADT for the primary prevention of AF in patients with MS with PACs, is mostly used in patients with high and very high risk of AF development, from several months to a year, in particular [2]. On the other hand, the absence of dynamics in the risk of AF development in patients with MS, according to the data obtained, which was determined by the CHARGE-AF risk score, despite the use of ADT, highlights the importance of the correction of potentially modifiable risk factors, such as obesity, smoking , etc., along with ADT [1, 2].

All patients with MS, along with a positive result of MK that was used as for the primary prevention of AF, showed the decrease of cardiac chamber size, LV dysfunction, BMI and RCHARGE-AF values.

The positive effect of MK in patients with MS can be explained by the decrease of cardiac afterload, LV dysfunction and left atrial volume, as consequence of the reduction of circulating blood volume due to the decrease of BMI, epicardial adipose tissue, and vasodilation [1, 2 , 3, 12], as well as due to the accumulation of stress-protective proteins, the increase of prostaglandin activity, which limit the activation of sympathetic-adrenergic system, increase the resistance of cardiomyocytes to the damaging effect of "oxidative stress" and eliminate the "arrhythmogenic substrate" for the development of AF [1, 2, 12].

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The use of the combination of ADT and MK for the primary prevention of AF in patients with MS will be the subject for further investigation.

Conclusion

The use of ADT and MK for the primary prevention of AF in patients with MS and the risk of AF development within one year after examination, allowed to reduce the frequency of its development by 3 times compared with the correction of potentially modifiable risk factors such as BP, blood glucose and lipid level. MK can be recommended for all the patients with MS, since it improves structural and functional cardiac characteristics, reduce BMI, class of chronic heart failure and the risk of AF development. This methods has no adverse effects and its effectiveness in the prophylaxis of AF is comparable to ADT. The increase of the prognostic index for the development of AF in dynamics compared with baseline and its value over 1.5 units can become a potential «preclinical» criterion that reflects the effectiveness of primary prevention of this arrhythmia not only with ADT and MK, but also using other treatment strategies.

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The prediction of adverse outcomes in patients with pulmonary embolism

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Abstract

Objective. *To establish the prognostic criteria of mortality and chronic thromboembolic pulmonary hypertension (CTEPH) in patients with pulmonary embolism (PE).*

Materials and methods. *The study included 155 patients with PE. During the study follow up, 42 patients deceased, 50 patients developed CTEPH 6 months after PE, 63 — complete recanalization of the pulmonary arteries. The course of the disease in these patients was analyzed in order to establish the most significant criteria for adverse outcomes.*

Results. *The symptoms of pulmonary embolism associated with mortality included: cardiac stroke volume reduction according to echocardiography (Echo-CG), the right ventricular to left ventricular diameter ratio over 0.9, blood pressure decrease less than 90/60 mm Hg, a history of syncope, paradoxical interventricular septal motion according to Echo-KG, jugular venous ectasia, SIQIII pattern in the electrocardiogram, over 75 % of thrombotic occlusion of the pulmonary artery according to computed angiopulmonography, concomitant anemia, elevated plasma concentrations of troponin level.*

The probability of CTEPH increased in patients with PE accompanied by: recurrent course of the disease, T-wave inversions in V1 to V3 leads in the electrocardiogram, late therapy initiation, over 60 % pulmonary arterial occlusion, the right ventricular to left ventricular diameter ratio over 0.9, over 30 mm Hg pressure elevation in pulmonary artery.

Conclusion. *Active methods of treatment can be recommended in patients who meet the criteria associated with mortality, including systemic thrombolysis and open or endovascular thrombectomy. Patients with high probability of CTEPH development may require dynamic monitoring followed by the treatment alteration when necessary: anticoagulant therapy correction or the performance of balloon pulmonary angioplasty.*

Keywords: *pulmonary embolism, adverse disease outcome, chronic thromboembolic pulmonary hypertension, mortality.*

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Introduction
Pulmonary embolism (PE) is an acute occlusion of pulmonary arteries by thrombi that are developed in the systemic circulation veins [1, 2]. The larger is the diameter and the number of occluded arteries, the greater is the risk of mortality or chronic thromboembolic pulmonary hypertension (CTEPH) development [3–5].

PE mortality ranges from 5 to 24 per 100.000 patients per year worldwide [6, 7]. In most cases, those patients who survived PE, present the reduction of the thrombi with complete hemodynamic parameters recovery. However, in 3–15 % of patients who experienced PE, thrombus organization cause the development of CTEPH, which leads to death in 10–15 % of patients in the following 3–5 years [8, 9].

Modern medicine relies on the establishment of certain risk factors in order to reduce the frequency of complications [10, 11]. Generally accepted, prognostically significant risk factors of early PE-related mortality (30 days after acute episode) include: the presence or absence of hemodynamic stability, elevated plasma troponin level, right ventricular volume overload according to echocardiography (Echo-CG) [12, 13]. The following risk factors are associated with high risk of CTEPH development: severe damage of the pulmonary vascular bed, recurrent PE, the ineffectiveness of ongoing anticoagulant therapy, the presence of right ventricular dysfunction at acute stage according to EchoCG, the initiation of treatment more than 2 weeks after PE [14, 15].

Despite the fact that many studies have been preformed recently, the determination of the most significant prognostic factors and the development of optimal management algorithms for the patients with PE is still highly relevant issue of modern medicine [11].

Materials and methods
In current study we retrospectively analyzed the disease course of 155 patients with PE, who were admitted to the hospital from 2010 to 2021, with high and moderate risk of early PE-related mortality according to the criteria of the European Society of Cardiology. Patients were divided into three groups depending on their disease outcome.

Group 1 included 42 deceased patients (fatal PE) — 18 men (42.9 %), 24 women (57.1 %). The age of patients ranged from 34 to 92 years, mean age was 66.5±12.0 years.

Group 2 included 50 patients with CTEPH that was diagnosed 6 months or more after PE — 26 men and 24 women. The age ranged from 23 to 95 years, mean age — 63.3±14.2 years.

Group 3 was the control group that included 63 patients aged from 26 to 88 years with mean age of 57.7±15.3 years — 32 men and 31 women.

Exclusion criteria were:

1. Limited laboratory and instrumental data;

2. Death or discharge of the patient before all required manipulations were performed.

All the patients on day 1 of admission and in dynamics underwent general and biochemical blood profile assessment that included the determination of the following parameters: D-dimer, homocysteine, antithrombin III, protein S, protein C, erythrocytes, hemoglobin, hematocrit, leukocytes, platelets, creatinine, urea, transaminases, bilirubin, fibrinogen, plasma troponin brain natriuretic peptide. Instrumental studies included the assessment of electrocardiogram phenomena (such as SIQIII, negative T waves, right bundle branch block), doppler ultrasonography of the lower extremity vessels with the establishment lesion and the degree of occlusion visualization, as well as the presence of floating thrombus assessment; Echo-CG with the assessment of qualitative and quantitative characteristics of the right ventricular and right atrial dilation, pulmonary hypertension, tricuspid regurgitation, left ventricular ejection fraction; the visualization of the localization and extent of the lesion of the pulmonary vascular bed using CT angiopulmonography.

The management of patients was performed according to the risk stratification by early PE-related mortality criteria of the European Society of Cardiology.

The study is retrospective and therefore does not conflict with the interests of patients.

The prevalence of clinical, laboratory and instrumental disease signs and its comparative analysis was performed using descriptive statistic methods. The odds ratio (OR) was calculated in order to the assess of the probability of PE adverse outcomes. Statistical analysis was carried out using the "Statistica 6.0" software.

Study results

PE developed as inpatient complication in 57.6% of deceased patients. Among them 75% were patients after surgical treatment. Death occurred within 1–7 hours from the onset of an acute PE episode.

All patients from the fatal PE group had thrombotic occlusion of over 50% of the pulmonary arteries, and 22% of patients from group 2 and 27% from group 3 had the occlusion of less than 50%. The frequency of over 75% pulmonary artery occlusion was statistically significantly higher ($p < 0.01$) in patients from fatal PE group: 54.8% versus 26% in CTEPH group and 17.5% in the control group.

Thrombotic occlusion of the pulmonary arteries of over 60% was seen in 56% of patients from group 2, however, it did not differ significantly from the control group ($p = 0.64$). Treatment outcomes of these patients mostly depended on the rate of disease regression and not on the amount of occlusion. Thus, 24% of patients from the PE with CTEPH group had over 50% decrease of occlusion in first 10 days of inpatient treatment, and in the control group this number reached 84.1% ($p<0.01$).

Potentially fatal PE showed more pronounced clinical signs and, therefore, patients seek medical attention at early stages of the disease. 71.4% of patients with fatal PE were admitted on the first day of PE manifestation. In contrast, only 22% and 23.8% of patients from groups 2 and 3 were admitted at the same period of time, respectively ($p<0.01$). 40% of PE patients with CTEPH were admitted more than 2 weeks after the manifestation of the first PE signs, that was comparable with the control group — 36.5% ($p = 0.7$).

It has been established that patients from with CTEPH were more likely to have recurrent PE course compared with patients from the fatal PE group and the controls — 46% versus 23.8% and 1.6%, respectively ($p<0.01$ and $p<0.01$).

The comparative analysis of clinical data has established that patients from the fatal PE group showed significantly higher frequency of pre- and syncopal states and jugular vein distention compared with the control group. Group with CTEPH did not differ significantly from the controls by the prevalence of these parameters (Table 1).

The analysis of laboratory data between study groups, has found that patients from the fatal PE group had significantly higher prevalence of elevated troponin level and anemia compared with other groups, and patients from the PE with CTEPH group had higher prevalence of N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) elevation (Fig. 1).

We have also found that quantitative characteristics of laboratory parameters significantly deviated from the reference values in patients with fatal PE. Mean value of NT-ProBNP in this group was 4665.9±4272.1 pg/ml that is statistically significantly higher than in the control group, 2785.8±3337.4 pg/ml ($p<0.01$), and the mean hemoglobin level in these

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Table 1. **The characteristics of clinical signs in PE patients with various outcomes**

Clinical sign	Study group		p	Study group		p
	Fatal PE n=42	Controls n=63		PE with n=50	Controls n=63	
Systolic BP	114.1±27.3 MMHG	120.7±22.4 MMHG	0.18	128.5±21.5 MMHG	120.7±22.4 MMHG	0.08
Syncope/pre-syncope	57.1%	20.6%	<0.01	20%	20.6%	0.94
Chest pain	23.8%	33.3%	0.3	38%	33.3%	0.6
Cough	4.7%	20.6%	0.02	24%	20.6%	0.67
Dyspnea	85.7%	79.4%	0.41	84%	79.4%	0.53
Hemoptysis	0%	1.6%	0.41	4%	1.6%	0.43
Cyanosis	9.5%	17.5%	0.25	18%	17.5%	0.95
Jugular vein distention	23.8%	3.2%	<0.01	4%	3.2%	0.82
Respiratory rate > 20 per minute	42.9%	30.2%	0.19	42%	30.2%	0.19
Saturation < 90%	23.8%	29.5%	0.52	20%	29.5%	0.25
Heart rate >100 beats per minute	19%	33.3%	0.11	2%	33.3%	<0.01
Accentuated pulmonary component of second heart sound	14.3%	4.8%	0.09	10%	4.8%	0.29
Liver enlargement	14.3%	4.8%	0.09	8%	4.8%	0.52

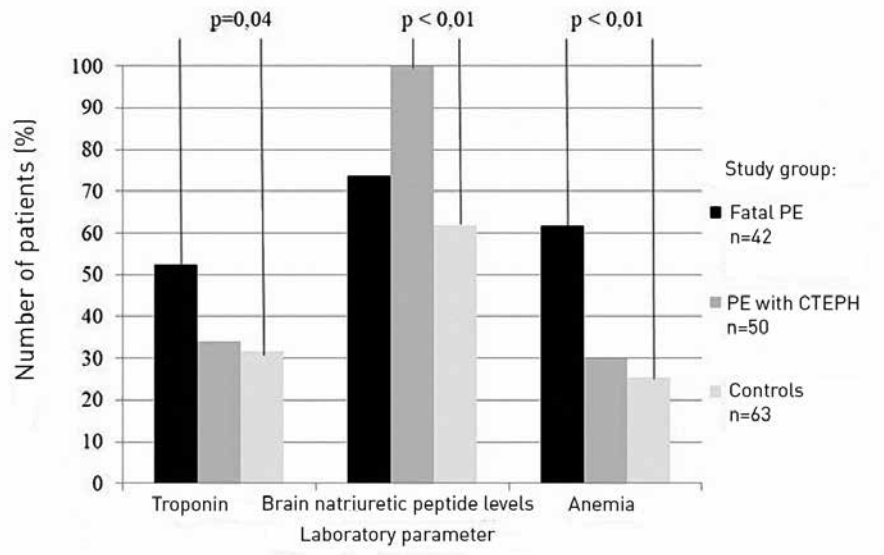

Figure 1. The prevalence of elevated plasma troponin level, brain natriuretic peptide level and anemia in PE patients with various outcomes

groups was 110.1+27.3 g/l and 132.7+20.7 g/l, respectively (p<0.01).

Patients with CTEPH did not differ significantly from the control group by the level of NT-proBNP — 3738±4754.7 vs. 2785.8±3337.4, respectively (p=0.21).

The analysis of the ECG results has established that deep S waves in lead I and Q wave in lead III were significantly more frequent in patients from the fatal PE group, and negative T waves in leads V1-V3 — in patients with CTEPH compared with the control group. (p<0.01) (Fig. 2).

The following Echo-CG parameters were statistically more prevalent in fatal PE group compared with the control group that indicate right heart chambers overload: right ventricle to left ventricle diameter ratio> 0.9, paradoxical movement of interventricular septum and reduced stroke volume, and in patients with CTEPH — right ventricle to left ventricle diameter ratio > 0.9, increased pulmonary artery pressure. It had also been established that death and CTEPH were statistically significantly more often recorded in patients with pulmonary ar-

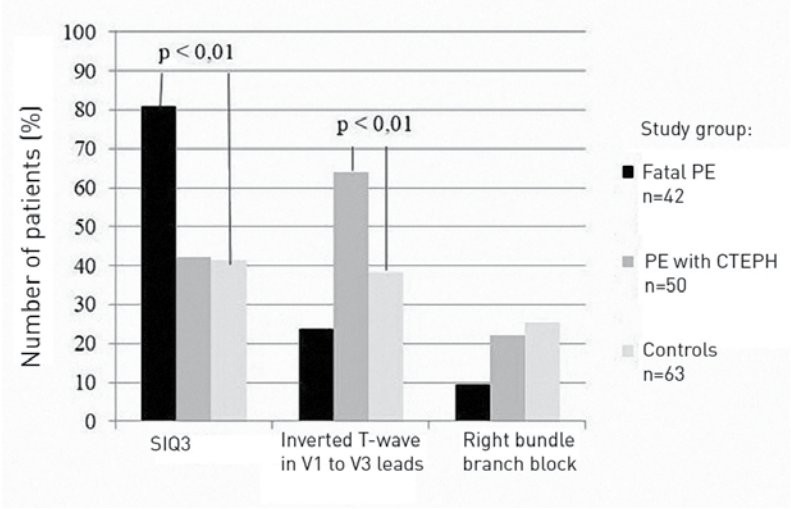

Figure 2. The analysis of ECG phenomena in PE patients with various outcomes

Table 2. **The features of ECG phenomena in PE patients with various outcomes**

Parameter	Study group		p	Study group		p
	Fatal PE n=42	Controls n=63		PE with CTEPH n=50	Controls n=63	
Right ventricle size (four chamber view)	4.4±1.1 cm	4.4±0.6 cm	0.99	4.35±0.64 cm	4.4±0.6 cm	0.67
Right ventricle–to–left ventricle diameter ratio> 0.9	61.8%	26.9%	< 0.01	38%	20.6%	0.04
Systolic pressure in pulmonary artery, mmHg	54.3±19.5	54.8±15.9	0.89	61.9±20.7	54.8±15.9	0.04
Pulmonary artery pressure > 70 mmHg	35.7%	9.5%	0.01	28%	9.5%	0.01
Tricuspid regurgitation ≥ 2 degree	45.2%	39.7%	0.58	54%	39.7%	0.13
Stroke volume	28.1±7 ml	56.7±14.6 ml	< 0.01	58.6±11.3 ml	56.7±14.6 ml	0.45
Inferior vena cava extension > 20 мм	40.5%	23.8%	0.07	28%	23.8%	0.48
Right atrium dilation> 65 ml	40.5%	46%	0.58	62%	46%	0.09
Right ventricular hypokinesis	4.8%	6.3%	0.75	2%	6.3%	0.27
Paradoxical movement of interventricular septum	31%	7.9%	< 0.01	12%	7.9%	0.47

tery systolic pressure over 70 mmHg at acute stage of PE (Table 2).

Thus, fatal outcome of PE is characterized by an acute thrombotic occlusion of over 75% of the pulmonary arteries with the predominance of arterial hypotension over 90/60 mmHg, pre-syncopal and syncopal state, jugular vein distention. The most common laboratory signs in these patients were elevated plasma troponin level and anemia. SIQIII phenomenon has often been registered by ECG in patients with fatal PE, and right ventricle to left ventricle diameter ratio> 0.9, paradoxical movement of interventricular septum, reduced stroke volume — by EchoCG,

The development of CTEPH is facilitated by the recurrent PE with occlusion of over 60% of the pulmonary vascular bed with the following signs of right ventricular overload according to Echo-CG: right ventricle to left ventricle diameter ratio> 0.9, increased pulmonary artery pressure (over 30 mmHg), as well as inverted T waves in V1-V3 leads according to ECG, and the NT-proBNP elevation.

The likelihood of death and CTEPH development, depending on the presence of estimated signs, was assessed using the OR calculation. The following signs increased the risk of death in descending order: reduced cardiac stroke volume according to EchoCG, right ventricle to left ventricle diameter ratio> 0.9, hypotension < 90/60 mmHg, the presence of pre- and syncopal state, paradoxical movement of interventricular septum, jugular vein distention, the presence of the SIQIII phenomenon according to ECG, occlusion of over 75% of the pulmonary vascular bed according to CT angiopulmonography, anemia, increased plasma troponin level (Table 3).

The following criteria increased the likelihood of CTEPH: recurrent PE course, inverted T waves in V1-V3 leads according to ECG, prolonged time to treatment initiation, occlusion of over 60% of the pulmonary vascular bed, right ventricle to left ventricle di-

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Table 3. **The significance of clinical signs, laboratory and instrumental parameters in deceased patients after PE**

Symptom	Parameters		
	p	OR	95% CI
Stroke volume reduction	< 0.01	29.5	7.8–81.1
Right ventricle–to–left ventricle diameter ratio> 0.9	< 0.01	16.4	1.9–46.2
Hypotension < 90/60 mmHg	< 0.01	14	5–44
Syncope/pre-syncope	< 0.01	11.79	4.1–34.5
Paradoxical movement of interventricular septum	< 0.01	11.4	2.9–44.9
Jugular vein distention	< 0.01	11.1	2.3–98.9
SIQIII phenomena	< 0.01	7.1	2.5–19.9
Pulmonary arteries occlusion over > 75%	< 0.01	6.9	2.3–20.9
Anemia	< 0.01	5.7	2.1–16.2
Elevated troponin level	< 0.01	4.5	1.6–12.8

Table 4. **The significance of clinical, anatomical, laboratory and instrumental features of PE in patients with CTEPH**

Symptom	Parameters		
	p	OR	95% CI
Recurrent PE	< 0.01	15.1	1.6–19.9
Inverted T-wave in V1 to V3 leads	< 0.01	6.5	2.7–15.8
Late treatment initiation	< 0.01	3.2	1.2–8.5
Lesion > 60% pulmonary vessels (blood flow absence in 13–15 segmental pulmonary arteries)	0.03	2.8	1.1–9.2
Right ventricle–to–left ventricle diameter ratio > 0.9	< 0.01	2.6	1.1–6.3
Pulmonary artery pressure > 30 mmHg	0.04	2.5	1.2–9.7
NT-proBNP elevation	0.24	0.37	0.1–2.0

ameter ratio > 0.9, increased pulmonary artery pressure over 30 mmHg. Increased plasma concentration of NT-proBNP did not statistically significantly affect the development of CTEPH (Table 4), and the reduction of pulmonary vascular bed lesion of over 50% in the first 10 days of treatment significantly reduced the likelihood of this complication (OR = 8.5; 95% CI 1.2–21.4, p<0.01).

Discussion

Nowadays, the risk stratification proposed by the European Society of Cardiology is widely used to determine the risk of PE-related death. The most significant factors that increase the risk of PE-related death are: systolic blood pressure systolic blood pressure < 90 mmHg or systolic blood pressure drop ⩾ 40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis, acute overload of the right heart with dysfunction of the right ventricular myocardium according to Echo-CG and its acute damage confirmed by elevated troponin level [12, 13]. We have confirmed the significance of blood pressure decrease < 90/60 mmHg and troponin level elevation. We also presented detailed EchoCG parameters that are the most significant for fatal outcome prediction in PE patients. The prognostic significance of reduced cardiac stroke volume according to EchoCG has been highlighted by our research and is rarely used today in clinical practice and scarcely mentioned in the literature. It should be emphasized that, according to our data, the presence of hemodynamic instability and EchoCG criteria of right ventricular overload is more prognostically significant for the PE adverse outcomes prediction than increased NT-proBNP level that is still debatable and requires further investigation [2, 13].

Other signs associated with the increase of PE-related death established in our study correspond to previous studies [2, 5, 6, 7, 12].

Unlike the immediate outcomes of acute PE, the long-term consequences of PE receive less attention from researchers. This can be explained by the fact that such unfavorable complication as CTEPH is quite rarely registered. According to our data, CTEPH was present in 32.3% of patients with a high and moderate early PE-related death that is comparable to the literature data [8, 9].

The most significant factors associated with high risk of CTEPH included the recurrent PE, occlusion of over 60% of pulmonary vascular bed, prolongation of treatment initiation for over 12–14 days after the first PE signs, the ineffectiveness of anticoagulant therapy [14, 15]. We have estimated detailed EchoCG criteria for right ventricular overload in acute PE that were associated CTEPH: right ventricle to left ventricle diameter ratio> 0.9, pulmonary artery pressure over 30 mmHg. To our knowledge no similar results were previously reported. The presence of T waves inversion in leads V1–V3 according to ECG was not associated with CTEPH development, and recanalization of over 50% of pulmonary arteries at first 10 days of treatment significantly reduced the risk of this complication.

Conclusion

The established prognostic criteria for PE-related mortality and the development of CTEPH will improve our knowledge and ability to predict the de-

velopment of these complications at an acute stage of PE. The assessment of such parameters at early stage of the disease will help healthcare professionals to chose adequate treatment strategy: systemic thrombolysis or thrombectomy in patients with high mortality risk; proper dynamic monitoring in patients with high risk of CTEPH with the correction of the amount and duration of anticoagulant treatment or pulmonary artery balloon angioplasty initiation if necessary.

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Early markers of endothelial dysfunction in young professional athletes

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Abstract

Objective. *To identify early markers of endothelial dysfunction (ED) in professional athletes depending on risk factors (RF) and genetic polymorphisms.*

Materials and methods. *The study included 78 athletes aged from 18 to 45 years old involved in various professional sports: athletics, soccer, volleyball, boxing, Greco-Roman wrestling, mixed martial arts. The analysis of physical activity was based on the Mitchell's sports classification (2005). The anonymous survey was performed to assess the presence of the main cardiovascular (CV) RF. All study participants, along with a physical examination, underwent blood pressure (BP) assessment and volumetric sphygmography. The association between gene polymorphisms (ACE, ADD1, AGT, AGTR1, AGTR2, CYP11B2, GNB3, NOS3), arterial wall parameters and CV RF was studied.*

Results. *Elevated BP was registered in 25 athletes (32.1%) with average systolic blood pressure (SBP) — 146.3±4.3 mmHg, diastolic blood pressure (DBP) — 83.8±7.43 mmHg. At the same time, differences in BP between various types of sports were not statistically significant (χ^2=1.67, df=1, p=0.196). The level of SBP was associated with pulse wave velocity (PWV) (r=0.463, p<0.05), the risk of ED development correlated with SBP level, expressed through PWV (χ^2=19.940, p<0.001; OR=44.6, 95% CI: 5.0–392.8).*

Conclusion. *Professional athletes with the presence of RF (grade 1 and stage I arterial hypertension) showed increased PWV values that reflected ED, which can indicate the presence of early-stage vascular remodeling, in case when the influence of genetic polymorphisms of the renin-angiotensin-aldosterone system was excluded.*

Keywords: *endothelial dysfunction, risk factors, physical activity.*

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Introduction
Nowadays, much attention is paid to the field of preventive medicine, and to one of the most significant risk factors (RF) for the development of cardiovascular diseases (CVD) is the level of adherence to physical activity (PA). The adverse effect of low PA on an organism has already been proven, especially in young people [1].

At the same time, intense PA in professional sports can also be considered as a risk factor that contributes to early development of CVD. Intense PA that exceeds body capabilities and does not consider morphological adaptation process, increases the risk of endothelial dysfunction (ED) and atherosclerosis [2].

Modern achievements of scientific technology have revealed new cellular and molecular elements of atherosclerosis, such as ED and vascular wall stiffness, which play the key role in its pathogenesis. At the same time, the influence of allelic variations in gene expression and its association with subclinical changes of vascular wall have not been studied enough yet. At the moment, it has been established that some genetic polymorphisms of the renin-angiotensin-aldosterone system (RAAS) can aggravate the prognosis of patients, for instance, they can play a pivotal role in the development of several CVDs, such as arterial hypertension (AH) that often causes structural changes in the arterial wall, and, eventually leads to ED.

Decreased nitric oxide synthase (NOS) activity lowers the bioavailability of NO that causes ED and triggers further vascular wall remodeling.

Endothelial function impairment can be used as early preclinical marker of vascular lesion assessed with new innovational low invasive methods that are used in clinical practice. For example, vascular stiffness parameters can be assessed with volumetric sphygmography [3].

Timely detection of vascular wall changes, especially in professional athletes, is an important issue of modern scientific research.

The objective of this study was to identify early markers of ED in professional athletes, depending on the presence of RF and genetic polymorphisms.

Materials and methods
The study included patients who have constant intense PA and are involved in professional sports.

This cross-sectional study was based on the Republican Medical and Sports Dispensary of Saransk and included 78 athletes involved in various professional sports (athletics, soccer, volleyball, boxing, Greco-Roman wrestling, mixed martial arts) aged from 18 to 35 years old who underwent a periodic medical examination. PA was assessed according the Mitchell's sports classification (2005). The sports experience of the participants ranged from 5 to 27 years.

The main exclusion criteria for the study were: acute stages of were chronic diseases, postoperative period and secondary symptomatic hypertension.

The study was conducted in accordance with the standards of good clinical practice and the principles of the Declaration of Helsinki. The study protocol was

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approved by the Ethics Committee of Moscow State University named after N.P. Ogaryova on January 29, 2019, protocol No. 71.

All study participants were enlightened with the study design and signed voluntary informed consent prior to the participation. RF assessment was carried out by face-to-face interviews and questionnaires in order to identify specific signs of cardiovascular pathology such as CVD in first-degree relatives and episodes of increased blood pressure (BP).

The questionnaire was developed at the Department of Internal Medicine of the Moscow State University named after N.P. Ogaryova. Physical examination was performed with the assessment of height, body weight and BP measurement.

Height (cm) was measured using mechanical stadiometer RP (Russia) in a standing position. Body weight (kg) was assessed with mechanical floor scale (Momert 5200, Hungary). Body mass index (BMI) was calculated using the following formula: BMI = body weight (kg)/height (m^2).

The measurement of "office" BP was performed by auscultatory method using a professional mechanical tonometer (Little Doctor LD-71, Singapore) while patient was sitting three times with 1–2 minutes interval. Volumetric sphygmography using the "VaSera VS-1500" device (Fukuda Denshi, Japan) recorded the level of BP in upper and lower extremities, and a visual assessment of the BP balance in four vascular beds was carried out.

The stage of arterial hypertension was assessed according to the clinical guidelines for arterial hypertension in adults (Russian Society of Cardiology, 2020) [4].

All athletes with elevated BP (over 140/90 mmHg) underwent additional examination: electrocardiogram (ECG) (Med-Mos ECG300G, China), echocardiography (Echo-CG) and carotid artery duplex scan (Toshiba Xario SSA-660A, Japan), urinalysis with albumin / creatinine ratio assessment (iChem Velocity, Beckman Coulter, USA), blood test with lipid profile assessment, serum creatinine level (Architect c8000, Abbott, USA) and calculation of glomerular filtration rate (GFR) in ml/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology formula.

To identify the signs of ED, a complex examination was performed and included the assessment of parameters that reflect the vascular wall stiffness. These parameters were assessed by volumetric sphygmography using the VaSera VS-1500 device (Fukuda Denshi, Japan) and included: ankle-brachial index (ABI), pulse wave velocity (PWV) and cardio-ankle vascular index (CAVI). The evaluation of indicators was performed in accordance with the guidelines for the use of the apparatus.

Genetic testing included the analysis of the presence of RAAS gene polymorphisms that are involved in the development of CVD, and may also contribute to vascular wall remodeling.

Molecular genetics analysis was carried out in the central research laboratory of the Penza Institute for Postgraduate Medical Education. Genetic polymorphisms were studied using a real-time polymerase chain reaction and a set of reagents "CardioGenetics Hypertension" by "DNA-Technology" (Russia) (Table 1).

The distribution of genotype frequencies of the studied genes corresponded to the Hardy-Weinberg equilibrium. Calculations were performed using the online calculator available by the following link: https://wpcalc.com/en/equilibrium-hardy-weinberg/.

Statistical analysis was performed using the Statistica v.10.0 program (StatSoft, USA). The normality of the distribution was assessed using the Kolmogorov–Smirnov test, and also considered the indicators of kurtosis and symmetry. For normally distributed parameters, the arithmetic mean and standard deviation (M±SD) were calculated. Categorical

Table 1. **Genetic polymorphisms characteristics**

Gene	Protein	Genetic marker	RS	Genotype variants
ACE	angiotensin converting enzyme	ALU INS/DEL	4646994	I/I; I/D; D/D
ADD1	α–adductin	G1378T	4961	G/G; G/T; T/T
AGT	angiotensinogen	T704C	699	T/T; T/C; C/C
		C521T	4762	C/C; C/T; T/T
AGTR1	angiotensin II receptor type 1	A1166 C	5186	A/A; A/C; C/C
AGTR2	angiotensin II receptor type 2	G1675A	1403543	G/G; G/A; A/A
CYP11B2	cytochrome 11b2 — aldosterone synthase	C344T	1799998	C/C; C/T; T/T
GNB3	G Protein Subunit Beta 3 — guanine — binding protein	C825T	5443	C/C; C/T; T/T
NOS3	nitric oxide synthase	T786C	2070744	T/T; T/C; C/C
		G894T	1799983	G/G; G/T; T/T

data are presented in absolute values and percentages (%). Comparative analysis of quantitative variables was performed using the Mann–Whitney test (U-test), for qualitative variables — chi-square test (χ^2). In addition, the odds ratio (OR) with 95% confidence interval (CI) were calculated. To determine the association between quantitative parameters, linear regression and correlation analysis Pearson correlation coefficient or Spearman's Rank correlation coefficient (r) were used. The level of statistical significance was set as $p<0.05$.

Study results

The study included 78 athletes with average age of 24.6±5.3 years old, and average sports experience of 11.6±6.5 years. The majority of the participants were male (91%) and 9% — female. Average age did not differ significantly between men and women (24.7±5.4 years for males and 23.7±4.7 years for females), (p = 0.731). Sports experience was also comparable between men and women (11.6±6.6 years and 11.6±6.0 years, respectively), (p = 0.889).

The analysis of family history and questionnaire results revealed that 22 (28.2%) athletes were predisposed to CVDs. Most often, athletes had relatives with elevated BP. Family history of AH was detected in 16 (20.5%) athletes, MI in 3 (3.8%) athletes, and pulmonary embolism in 1 (1.3%) athlete. The presence of CVD was on the mother's side in 15 (68.2%) athletes, on the father's side — in 3 (13.6%) athletes, and on both sides — in 4 (18.2%) athletes. Family history of CVD was more common in male athletes (86.4%).

The anthropometric data revealed that men were taller (180.9±7.9 cm) than women (164.0±5.7 cm) and had higher average body mass (in men 78.4±12.4 kg, in women 54, 4±5.2 kg) ($p<0.001$). The average BMI was 23.7±3.8 kg/m^2 in men that was significantly higher value (24.0±3.8 kg/m^2) compared with women (20.2±1.5 kg/m^2) ($p < 0.001$).

According to the office BP assessment, the average level of systolic BP (SBP) was 133.2±11.2 mm Hg, diastolic BP (DBP) — 78.7±6.9 mm Hg. Mean SBP in women was 124.3±8.8 mmHg, DBP — 75.0±5.8 mm Hg, mean SBP in men — 134.1±11.1 mm Hg, DBP — 79.1±7.0 mmHg. SBP was significantly lower in women (p=0.032), and DBP did not differ significantly (p=0.115).

According to three-time simultaneous and dynamic (within 1 week) BP assessment by volumetric sphygmography and within the classification of AH [4], 32 (41%) athletes, showed BP within reference values. In 9 athletes both SBP and DBP levels corresponded to optimal BP, and in 23 — to normal BP. High normal blood pressure was detected in 21 (26.9%) athletes with the mean SBP of 134.5±2.9 mmHg, DBP — 78.4±5.2 mm Hg. Elevated BP ⩾140/90 mm Hg was revealed in 25 (32.1%) athletes that corresponded to stage 1 AH with mean SBP — 146.3±4.3 mm Hg, DBP — 83.8±7.43 mm Hg. There was no statistically significant difference of BP values depending on the type of sport (χ^2=1.67, df=1, p=0.196).

The combination of family history of CVD and elevated BP was seen in 10.2% athletes.

Thus, we identified athletes with RF (family history of CVD and/or elevated BP) and without RF. Subsequently, all the athletes were divided into 2 groups.

Group 1 consisted of athletes without RF (n=31), group 2 included athletes (n=47) with RF (with AH and/or family history of CVD).

The characteristics of study groups are presented in Table 2. The groups were comparable by gender, sports experience, age and anthropometric data.

The main difference between groups was the level of BP. All athletes with BP values exceeding normal values according to AH classification [4] underwent additional examination in order to detect hypertensive target organ damage (TOM). According to ECG and ECHO-CG, there were no signs of left ventricular hypertrophy. Carotid artery duplex scan did not reveal any atherosclerotic plaques. Blood creatinine level and estimated GFR were within reference values. The albumin-creatinine ratio in a single urine portion was normal. The lipid profile of all study participants remained normal.

Considering the formation of study groups depending on the presence of RF, the assessment of vascular wall stiffness parameters was carried out using volumetric sphygmography in order to identify the subclinical signs of ED.

The parameters of vascular wall stiffness were comparable between groups regardless of the presence of RF (table 3). Despite the fact that PWV parameters were significantly higher in athletes with RF compared with the group without RF (table 3), revealed parameters of arterial stiffness were within reference values.

The analysis of PWV indicators between the groups showed ambiguous results and, therefore, they were divided into subgroups depending on the obtained PWV values (normal/above normal) (table 4).

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Table 2. **Clinical characteristics of study participants depending of the presence of RF**

Parameter		Data presentation	Group 1 (without risk factors) n=31	Group 2 (with risk factors) n=47	p
Gender	Male	ABS. (%)	28 (90.3)	43 (91.5)	0.810
	Female		3 (9.7)	4 (8.5)	
Sports experience, years		M ± SD	10.6±7.0	12.3±6.1	0.192
		95% CI	8.1–13.2	10.5–14.1	
Age, years		M ± SD	24.5±5.6	24.7±5.1	0.914
		95% CI	22.5–25.6	23.1–26.2	
Height, cm		M ± SD	178.3±8.0	180.0±9.7	0.339
		95% CI	175.4–181.2	177.2–182.9	
Body mass, kg		M ± SD	73.4±10.3	78.2±15.4	0.244
		95% CI	69.6–77.1	73.7–82.7	
BMI, kg/m²		M ± SD	23.0±2.5	24.1±4.5	0.500
		95% CI	22.1–23.9	22.8–25.4	
SBP, mmHg		M ± SD	124.9±8.2	138.7±9.4	0.001
		95% CI	122.0–128.0	135.9–141.4	
DBP, mmHg		M ± SD	75.1±5.3	81.1±6.9	0.001
		95% CI	73.1–77.0	79.1–83.1	
Pulse BP, mmHg		M ± SD	49.9±7.1	57.6±8.7	0.001
		95% CI	47.3–52.3	55.0–60.1	
Mean BP, mmHg		M ± SD	92.1±6.2	100.8±7.2	0.001
		95% CI	89.8–94.4	98.7–102.9	
Heart rate, beats/min		M ± SD	60.5±14.0	59.9±10.6	0.744
		95% CI	55.4–65.6	56.8–63.0	

Table 3. **Vascular wall stiffness parameters that reflect endothelial dysfunction in athletes**

Parameter	Group 1 (without risk factors) n=31	Group 2 (with risk factors) n=47	p
R-CAVI	5.6±0.7	5.8±0.7	0.211
L–CAVI	5.8±0.7	6.0±0.6	0.345
R-ABI	1.1±0.1	1.1±0.1	0.159
L-ABI	1.1±0.1	1.1±0.1	0.140
PWV	4.7±0.8	6.5±2.9	0.002

Table 4. **Vascular wall stiffness parameters that reflect endothelial dysfunction in athletes**

Parameter	Group 2 (with risk factors) n=47		p
	Normal PWV (n=29)	Above normal PWV (n=18)	
R-CAVI	5.9±0.7	5.8±0.8	0.792
L–CAVI	6.0±0.6	5.9±0.7	0.704
R-ABI	1.1±0.1	1.1±0.1	0.616
L-ABI	1.1±0.1	1.0±0.1	0.275
PWV	4.8±1.1	9.6±2.7	0.001

The results of PWV indicators analysis in the subgroups attracts attention to the ratio of athletes with family history of CVD as well as with elevated BP. Thus, in the subgroup with normal PWV values, 5 athletes had a combination of RF (family history of CVD and elevated BP), 21 had family history of CVD, and 3 — elevated BP.

In the subgroup with high PWV, 3 athletes had combination of RF (family history of CVD and elevated BP), 1 athlete had family history of CVD and 14 athletes had elevated BP.

The correlation analysis between SBP and PWV indicators was performed in order to find the cause of PWV elevation in the group with RF (figure 1). The parameters showed statistically significant positive correlation ($r=0.463$, at $p<0.05$).

The odds ratio (OR) was also calculated in order to identify the risk of ED development by the PWV and BP values elevation (table 5). Elevated BP increased the risk of ED development by 44.6 times that was estimated by PWV. At the same time, multiple regression analysis did not reveal statistically significant association between PWV and gender, age, anthropometric parameters (height, body mass, BMI), sports experience, DBP, pulse and mean BP, heart rate, and family history of CVD ($p>0.05$).

Considering the role of genetics in the development of CVD, especially those genes that are associated with the RAAS system, we also performed the screening for 10 genes of the RAAS system in all athletes, depending on the presence of RF (Table 6).

The comparison analysis did not reveal any significant differences between groups depending on the

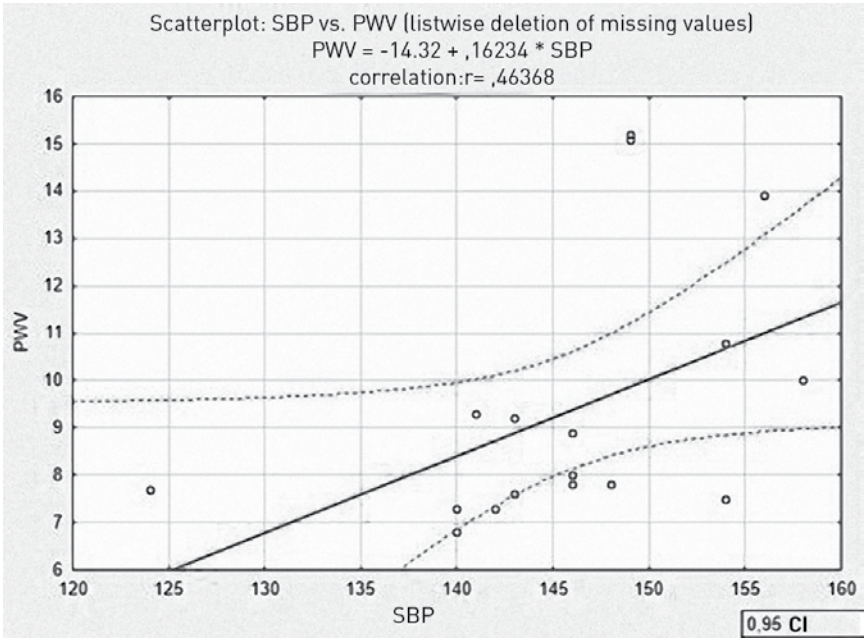

Figure 1. The association between PWV and SBP

Table 5. **Relative risk of PWV increase in athletes with elevated SBP**

BP	Above normal PWV (n=18)	Normal PWV (n=29)	Pearson's chi-squared test	OR (95% CI)
	%	%		
SBP ⩾ 140 mmHg (n=25)	94.4	27.6	19.940 P<0.001	44.625 (5.0–392.8)
SBP < 140 mmHg (n=22)	5.6	72.4		

presence of RF. The analysis of genetic polymorphisms of the RAAS system, including endothelial nitric oxide synthase (eNOS), did not reveal any statistically significant difference (p>0.05) depending the PWV value.

Discussion

In the last years excessive PA in professional sports has been discussed as the factor that can lead to the development of AH, atherosclerosis and sudden cardiac death.

The results of the studies dedicated to the investigation of AH prevalence showed ambiguous results on the frequency of elevated BP depending on the PA type.

According to the data of foreign literature review, the prevalence of AH in athletes involved in weightlifting and American football ranged from 8.8 to 25.6%, which is higher than in athletes involved in other sports [5].

The data on the AH prevalence in domestic studies are also noteworthy. Thus, elevated BP was diagnosed in 37% of athletes in heavyweight categories that include athletes involved in such sports as bodybuilding, powerlifting, weightlifting [6].

The results of our study showed that athletes with elevated BP were commonly involved in dynamic and static exercising (χ^2=1.67, df=1, p=0.196). Similar data were obtained in the Yakut population, where there was also no relationship between AH, type of sport and sportsmanship (χ^2=3.48, df=1, p=0.062) [7].

At the same time, it has been established that high-intensity exercising accelerated the development of ED and atherosclerosis.

Thus, Smirnov I. E. et al. [8] performed quantitive analysis of blood levels of angiogenin, vascular endothelial growth factor, homocysteine, endothelin and nitric oxide in young athletes that showed the change of ED parameters during myocardial overload due to physical activity.

Nowadays, ED can be interpreted as universal mechanism that implements the action of all CVD RF. Clinical trial [9] and, in particular, the Rotterdam study [10], showed that early signs of an atherosclerosis can be detected with PWV that is a local indicator of elastic properties of the arteries and can be used as early a marker of ED, and elevated BP is the factor of microvascular lesion.

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Table 6. **Genetic polymorphisms frequency in groups depending on the RF**

Genetic polymorphism	Genotype	Group 1 (without risk factors) n=31	Group 2 (with risk factors) n=47	p
ACE: Alu Ins/Del	I/I	63.2	57.9	0.159
	I/D	36.8	42.1	0.306
	D/D	0	0	0
ADD1: G1378T	G/G	56.5	72.2	0.215
	G/T	34.8	27.8	0.569
	T/T	8.7	0	0.072
AGT: T704C	T/T	34.8	16.7	0.111
	T/C	52.2	52.8	0.964
	C/C	13.0	30.6	0.124
AGT: C521T	C/C	73.9	73.5	0.975
	C/T	26.1	23.5	0.826
	T/T	0	3.0	0.383
AGTR1: A1166C	A/A	45.5	65.7	0.132
	A/C	50.0	31.4	0.161
	C/C	4.5	2.9	0.736
AGTR2: G1675A	G/G	47.8	50.0	0.873
	G/A	8.7	2.9	0.340
	A/A	43.5	47.1	0.791
CYP11B2: C344T	C/C	30.5	22.9	0.520
	C/T	47.8	51.4	0.789
	T/T	21.7	25.7	0.730
GNB3: C825T	C/C	46.7	39.4	0.636
	C/T	33.3	54.5	0.116
	T/T	20	6.1	0.143
NOS3: T786C	T/T	43.5	38.9	0.727
	T/C	39.1	44.4	0.688
	C/C	17.4	16.7	0.943
NOS3: G894T	G/G	69.9	51.4	0.171
	G/T	21.7	42.9	0.098
	T/T	8.7	5.7	0.662

There is a fairy significant evidence base on the effect of AH on the parameters of vascular wall stiffness both in general population and in professional athletes. It also has been shown that the values of vascular wall stiffness correlated with high SBP at the 5th stage of the test with dosed PA in young athletes [11].

The analysis of BP parameters in our study revealed grade 1 AH in the examined athletes without target organ damage with the increase of PWV parameters. Elevated BP and PWV positively correlated with each other ($r=0.46$ at $p<0.05$). It has also been shown that grade 1, stage 1 AH increased the risk of PWV elevation by 44.6 times (CI — 5.0–392.8). The analysis of the association between elevated PWV and the following RF: age, types of PA sports experience, BMI, did not reveal any significant correlations. Thus, the revealed grade 1 stage 1 AH can be considered as the RF, and PWV — as an early marker of ED.

It should also be noted that ED can be genetically determined. However, the role of genetic screening in atherosclerosis prediction is controversial. In this regard, several studies on the potential association between the allelic variations of genes and subclinical changes of the arteries are currently underway.

Akopyan A. A. et al.[12] was the first one who have found that the presence of the D allele of the ACE gene increased the risk of arterial stiffness by 1.89 times (95 % CI: 1.16–3.12), and the presence of the DD genotype — by 3.42 times (95 % CI: 1.39–9.36). The association between ED and the c.894G>T polymorphism of the NOS3 gene have also been established. The presence of the GG genotype increased the risk of ED by 2.65 times (95 % CI: 1.26–5.72), according to the literature, the TT genotype of the NOS3 gene polymorphism was also associated with atherosclerosis. Lack of consistent results in numerous studies, including investigations in different populations, makes uncertain the role of genetic polymorphisms in the pathogenesis of atherosclerosis.

We have selected allelic variants of the RAAS genes (ACE, ADD1, AGT, AGTR1, AGTR2, CYP11B2, GNB3, NOS3), that could be possibly associated with

the parameters of arterial wall and identified CVD RF. The results of comparative analysis between groups of athletes depending on the presence of RF and PWV and carriage of genetic polymorphisms have not found any significant differences.

This may be explained by little effect of the individual genetic variants on the risk of vascular remodeling, atherosclerotic changes in particular. Its effects are enhanced in synergy with other genetic and behavioral factors.

In addition, the absence of genetic predisposition to CVD in athletes can be explained by the selection of practically healthy young people for professional sports.

Conclusion

Thus, in young professional athletes aged from 18 to 35 years old with elevated BP (grade 1, stage 1 AH) that was considered as the risk factor, PWV was increased. PWV is included in the criteria that determine the stages of vascular wall stiffness and can be used as early marker of ED.

No association between PWV and RAAS gene polymorphisms in this study can be explained by the features of study sample — young professional athletes.

Considering the fact that traditional scales for the assessment of cardiovascular risk may underestimate the occurrence of cardiovascular complications, the determination of vascular wall stiffness by volumetric sphygmography and PWV indicators in particular, has high prognostic value. This method of examination is especially relevant for people with intense PA that may "mask" subjective sensations.

Genetic screening can be recommended for individuals with family history of AH.

Conflict of interests: none declared.

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Mineralocorticoid-receptor antagonists in the management chronic heart failure: the effectiveness and promising opportunities

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Abstract

This article presents the results of randomized clinical trials on the use of mineralocorticoid-receptor antagonists in patients with myocardial infarction, chronic heart failure in combination with type 2 diabetes mellitus, with and without chronic kidney disease. The review highlights pathogenetic aspects of the implementation of these medications in patients with cardiorenal pathology and its effect on the prognosis. Issues of tolerability and limitations when prescribing various mineralocorticoid receptor antagonists representatives are discussed.

Keywords: *chronic heart failure, myocardial infarction, diabetes mellitus, chronical kidney disease, mineralocorticoid-receptor antagonists, spironolactone, eplerenone, finerenone.*

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Introduction

The prevalence of chronic heart failure (CHF) with clinical manifestations is about 4.5% of general population. Additionally, the amount of patients who require permanent diuretic therapy has increased by 2.5 times since 1998 [1]. The prognosis of patients with CHF can be serious especially in patients with III–IV functional class of CHF where median survival is estimated as 3.8 years [2]. Arterial hypertension (AH) and coronary artery disease (CAD) are the leading causes of CHF [2]. The role of diabetes mellitus (DM) has significantly increased in the development of CHF [2]. The development of micro- and marcrovacular complications of DM can aggravate the course of CHF and deteriorate the prognosis. Various classes of pharmacological agents have proved its efficacy in the decrease of mortality and admissions in patients with CHF with reduced ejection fraction (HFrEF) of the left ventricle, including patients with DM. These agents include: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) or angiotensin/neprilysin receptor inhibitors (ARNIs), beta-blockers (BBs), and mineralocorticoid receptor antagonists (MRAs). All of them affect the imbalance of neurohumoral systems that cause CHF.

Aldosterone effects

Aldosterone is one of the main components of the renin-angiotensin-aldosterone system (RAAS) that activates in both cardiovascular and renal pathologies. It is synthesized in the cells of the zona glomerulosa of the adrenal cortex from deoxycorticosterone and is considered as one of the most active mineralocorticoids. Aldosterone is locally synthesized in endothelial and smooth muscle cells of blood vessels and myocardium. Aldosterone affects mineralocorticoid receptors (MR) in epithelium as well as in myocardium, blood vessels, kidneys, and the central nervous system. By activating MR, which are nuclear receptors, aldosterone causes transcription of the $\alpha 1$, $\beta 1$ and γ genes that are the subunits of Na+/K+-ATPase in renal cells and, therefore, increases sodium transport across the basolateral cell membrane [4, 5].

Hyperaldosteronemia causes the decrease of potassium and magnesium microelements, followed by the prolongation of the QT interval that serves as a substrate for the development of life-threatening arrhythmias. It has been estabilished that aldosterone activates the Na+/H+ exchanger that leads to hydrogen secretion and sodium reabsorption. The expression of Na+/H+ exchanger isoform 3 (NHE3) in the epithelium of the nephron proximal tubule increases in patients with CHF [6]. The non-genomic effects of aldosterone are exposed through the activation of non-epithelial MR, that leads to the development of endothelial dysfunction in the long-term [7]. Aldosterone not only increases the expression of angiotensin-converting enzyme (ACE) mRNA in cardiomyocytes with local activation of angiotensin II, as well as increases the number of angiotensin II type 1 and endothelin receptors, but also activates the sympathetic nervous system. In addition to its hemodynamic effects and impact on electrolyte balance, aldosterone stimulates the synthesis of types I and III collagen, fibroblast proliferation, and free radical oxidation that leads to cell apoptosis [8, 9].

The effectiveness of spironolactone in patients with CHF

The effectiveness of MRAs that was revealed in randomized clinical trials lead to the inclusion of these pharmacological agents into the clinical guidelines for the management of patients with heart failure with reduced ejection fraction (HFrEF) as the third neurohumoral blocker. The first large-scale RALES trial showed the reduction in the risk of death from any cause by 30% (relative risk (RR) — 0.70; 95% confidence interval (95% CI) — 0.60–0.82; p<0.001), sud-

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den death from cardiac causes — by 31 % (RR 0.69; 95 % CI — 0.58–0.82; p<0.001), death from progressive heart failure — by 36 % (RR 0.64; 95 % CI — 0.51–0.80; p<0.001) in patients with HFrEF who were prescribed with spironolactone at a dose of 12.5–50 mg/day (average dose — 26 mg/day) in addition to ACE inhibitors for 24 months [10]. Most of the participants had NYHA class III of CHF with an average left ventricular ejection fraction (LV EF) of 25 %. The study excluded patients with primary operable valvular heart disease, acute coronary syndrome (ACS), patients who had undergone heart transplantation or were awaiting the procedure as well as with a plasma creatinine level of more than 221 μmol/l and a potassium level of more than 5.0 mmol/l. The RALES trial also showed the effectiveness and safety of combination use of ACE inhibitors and MCAs in patients with HFrEF with aldosterone escape phenomena after long-term therapy with ACE inhibitors or ARNIs. In the main group, the exacerbation of symptoms and the reduction admission risk due to CHF decreased by 35 % (RR 0.65; 95 % CI — 0.54–0.77; p<0.001). Not all the participants from RALES study received optimal therapy for HFrEF. Patients from the observational group received loop diuretics, about 95 % — ACE inhibitors, over 70 % — cardiac glycosides, and only 10 % of patients received BBs. The median creatinine concentration in the spironolactone group increased from 4 to 9 μmol per liter and the median potassium concentration increased by 0.30 mmol per liter compared with the placebo group (p<0.001). Unfortunately, about 10 % of patients did not tolerate the medication due to the development of gynecomastia or pain in the mammary gland. Adverse endocrine effects were more common in the spironolactone group compared with in the placebo group (10 vs. 1, p=0.006).

Evidence base of eplerenone effectiveness in patients with cardiovascular disease and CHF

The long-term use of MRAs in patients with CHF has high risk of side effects development that can lead to discontinuation of the medication, therefore, initiated the invention of selective MRAs. Eplerenone, another MRAs, was included into the guidelines for the patients with CHF. This agent has lower affinity to MR compared with spironolactone, but shows similar antialdosterone effect due to lower plasma protein binding. The high selectivity of eplerenone and low affinity to androgen and progesterone receptors provides better tolerability compared with spironolactone. The results of randomized placebo-controlled EPHESUS trial were published in 2003. The study evaluated the effectiveness of eplerenone in 6.632 patients 3 to 14 days after acute myocardial infarction (AMI), clinical manifestations of NYHA class I–IV CHF and reduced LV EF ⩽ 40 % (mean EF — 33 %) [11]. 32 % of patients had DM, about 15 % of patients had a history of CHF, and about 7 % of them had already been admitted to the hospital due to CHF. Exclusion criteria were the use of potassium-sparing diuretics, a serum creatinine concentration of more than 220 μmol per liter, and a serum potassium concentration of more than 5.0 mmol per liter. The average creatinine clearance (CC) according to the Cockcroft-Goult formula was 79 ml/min. Most of the participants received optimal pharmacotherapy for MI and CHF, including ACE inhibitors or ARNIs (86 %), BBs (75 %), diuretics (60 %), aspirin (88 %), statins (47 %). Coronary reperfusion therapy was performed in 45 % of patients. The mean dose-equivalent of the eplerenone was 42.6 mg. The mean follow-up period was 16 months. The two primary endpoints were time to death from any cause and time to death from cardiovascular causes or first hospitalization for a cardiovascular event, including CHF, recurrent AMI, stroke, or ventricular arrhythmia. Eplerenone significantly reduced both all-cause mortality by 15 % (RR 0.85; 95 % CI 0.75–0.96; p=0.008) and the hospitalization for cardiovascular events by 13 % (RR 0.87; 95 % CI 0.79–0.95; p=0.02). The risk of cardiovascular events was reduced by 17 % (RR 0.83; 95 % CI 0.72–0.94; p=0.005); risk of sudden cardiac death — by 21 % (RR 0.79; 95 % CI 0.64–0.97; p=0.03); the risk of hospitalization due to CHF — by 15 % (RR 0.85; 95 % CI 0.74–0.99; p=0.03), in the eplerenone group compared with the placebo group. Patients with LV EF < 30 % and symptoms of CHF showed more pronounced effect of therapy. Hyperkalemia (113 cases vs. 66 cases in the placebo group, p<0.001) and creatinine increase were more frequently registered in the eplerenone group. The rate of serious hyperkalemia (over 6 mmol/l) was more frequent in eplerenone group (180 cases vs. 126 in the placebo group, p=0.002), however, this condition did not increase mortality. The risk of severe hyperkalemia was higher in patients with reduced CC. On the other hand, it is very important to reduce the risk of hypokalemia that is often seen in patients with

CHF who regularly receive diuretics and can increase mortality [12].

In the EPHESUS trial, the risk of hypokalemia was more than twice as high as the risk of severe hyperkalemia, and eplerenone significantly reduced it. Thus, in the eplerenone group, cases of severe hypokalemia were significantly less frequent (potassium level less than 3.5 mmol/l) — 273 cases vs. 424 in the placebo group, p<0.001. Eplerenone did not aggravate the course of endocrine diseases, unlike spironolactone. The incidence of gynecomastia and erectile dysfunction among men in eplerenone group was comparable to the placebo that can be attributed to the fact that eplerenone has greater selectivity for the MR. The study showed the effectiveness of low dose (25 mg / day) of eplerenone in patients during first two weeks after AMI.

The placebo-controlled EMPHASIS-HF trial investigated the effects of eplerenone in patients with HFrEF. The study included 2737 patients with NYHA class II CHF and systolic dysfunction (LV EF of no more than 30% or, if >30 to 35%, a QRS duration of >130 msec on electrocardiography, 26.2% on average) within 6 months after hospitalization for a cardiovascular reason or the plasma level of B-type natriuretic peptide (BNP) of at least 250 pg per milliliter or the plasma level of N-terminal pro-BNP of at least 500 pg per milliliter in men and 750 pg per milliliter in women [13]. Average duration of CHF was 4.7 years. Approximately 1/3 of patients had DM. Participants received medical therapy for CHF: ACE inhibitors and/or ARNIs — 94% of patients; BBs — about 87%; diuretics — 84–85%; antithrombotic agents — 88%. The mean estimated glomerular filtration rate (eGFR) was about 70 ml/min/1.73 m^2. More than 30% of patients had eGFR less than 60 ml/min/1.73 m^2. Eplerenone was started at a dose of 25 mg once daily and was increased after 4 weeks to 50 mg once daily provided the serum potassium level was no more than 5.0 mmol per liter. In case when the estimated GFR was 30 to 49 ml per minute per 1.73 m^2 the medication was started at 25 mg on alternate days, and increased to 25 mg daily. Then dose adjustment was carried out every 4 months, depending on the results of patients examination. If the serum potassium level was 5.5 to 5.9 mmol per lite, the dose of the medication was decreased, if the serum potassium level was 6.0 mmol per liter or more, it was withheld. Potassium level was remeasured within 72 hours after the dose reduction or study-drug withdrawal, and the study drug was to be restarted when level was below 5.0 mmol per liter. Average eplerenone dose was 39.1±13.8 mg/day. The median follow-up period was 21 months. Thus, the frequency of primary endpoint (cardiovascular event or hospitalization for CHF) decreased by 37% (RR 0.63; 95% CI 0.54–0.74; p <0.001) in the eplerenone group compared with placebo. In the eplerenone group, the risk of death from any cause or hospitalization for CHF was by 35% (RR 0.65; 95% CI 0.55–0.76; p<0.001) lower than in the control group. The drug also reduced the primary outcome in selected subgroups of high-risk patients: among patients aged over 75 years the risk decreased by 34% (RR 0.66; 95% CI 0.49–0.88; p=0.0044); in patients with LV EF less than 35% — by 35% (RR 0.65; 95% CI 0.53–0.78; p=0.0001); in patients with type 2 DM — by 46% (RR 0.54; 95% CI 0.42–0.70; p=0.0001); in patients with eGFR less than 60 ml/min/1.73 m^2 — by 38% (RR 0.62; 95% CI 0.49–0.79; p=0.0001); in patients with blood pressure less than 123 mmHg — by 38% (RR 0.62; 95% CI 0.51–0.79; p=0.0001). Eplerenone reduced both the risk of death from any cause by 24% (RR 0.76; 95% CI 0.62–0.93; p = 0.008) and the risk dearth from cardiovascular event by 24% (RR 0.76; 95% CI 0.61 to 0.94; p=0.01) compared with placebo. The medication significantly reduced the risk of hospitalization for any reason by 23% (RR 0.77; 95% CI — 0.67–0.88; p<0.001), the risk of hospitalization for CHF — by 42% (RR 0.58; 95% CI — 0.47–0.70; p<0.001). The total number of hospitalizations (including second and subsequent hospitalizations) was also lower in the eplerenone group (750, vs. 961 in the placebo group, for a 24% reduction; P<0.001), as were the total numbers of hospitalizations for cardiovascular reasons (509 vs. 699, for a 29% reduction; P<0.001) and hospitalizations for CHF (273 vs. 429, for a 38% reduction; P<0.001). It is also worth noting that the risk of hospitalizations due to renal function impairment and the development of hyperkalemia was comparable between groups.

At 1 month, the mean change in serum creatinine level from baseline was 13.3±30.9 μmol per liter in the eplerenone group, as compared with 6.2±25.6 μmol per liter in the placebo group. At the trial cutoff date, the serum creatinine level had increased from baseline by 8.0±32.7 μmol per liter in the main group and 3.5±35.4 μmol per liter — in the placebo group. At 1 month and at the trial cutoff date, the mean change

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in potassium level from baseline was 0.16±0.51 mmol per liter and 0.16±0.56 mmol per liter in the finerenone group, as compared with 0.04±1.16 mmol per liter and 0.05±0.53 mmol per liter, in the placebo group (P=0.001, p<0.001), respectively. A serum potassium level above 5.5 mmol per liter was reported more frequently (11.8 %) in the eplerenone group than in placebo group (7.2 %) (P<0.001). The frequency of serum potassium level above 6.0 mmol per liter was comparable between groups (p=0.29). A serum potassium level below 4.0 mmol per liter as well as below 3.5 mmol per liter was significantly less frequently reported in eplerenone group (38.8 % and 7.5 % of patients, respectively) compared with the placebo (48.4 % and 11.0 %, respectively) (p<0.001; P<0.001).

The analysis of the eplerenone effectiveness in subgroups showed that its positive effect was more pronounced in women, patients younger than 65 years of age, patients with eGFR less than 60 ml / min / 1.73 m^2, patients with DM. The incidence of gynecomastia did not differ significantly between groups. Algorithm for the prescription and titrating of MRAs doses in patients with CHF was developed based on the results of mentioned above trials and considered the level of eGFR and potassium. Eplerenone not only improved the prognosis and reduced the number of hospitalizations in patients with CHF, but also reduced the risk of CHF development after AMI.

The study of the eplerenone effectiveness in patients with AMI continued in multicentral, randomized placebo-controlled REMINDER trial that included 1012 patients with previously diagnosed CHF. The medication was administered in the first 24-hours after MI with ST-segment elevation [14]. About half of patients had the history of arterial hypertension, average eGFR was 86.5 ml/min/1.73m^2, the number of patients with DM and with eGFR less than 60 ml/min/1.73m^2 was lower in eplerenone group compared with placebo group 12.8 % and 15.4 %; 6.8 % and 10.0 %, respectively.

The study showed that the addition of eplerenone to standard treatment of AMI lead to the significant decrease of primary composite endpoint (cardiovascular mortality, rehospitalization, extended initial hospital stay due to diagnosis of CHF, sustained ventricular tachycardia or ventricular fibrillation, LV EF ⩽ 40 % at 1 month or later after randomization, BNP over reference data) by 42 % (RR 0.58; 95 % CI — 0.45–0.76; p<0.0001) compared with placebo. The effect was due to a 40 % lower risk of the increase of BNP, the main marker of CHF, in eplerenone group (RR 0.60; 95 % CI 0.45–0.79; p=0.0003) compared with placebo. BNP above 200 pg/mL or NT-proBNP above 450 pg/mL (in patients aged below 50); above 900 pg/mL (age 50–75 years), or above 1800 pg/mL (patients older than 75) after 1 month was considered as elevated. The results of the study showed the role of eplerenone in the prevention of CHF development in patients after AMI. The medication was well tolerated. As in other studies involving eplerenone, episodes of hyperkalemia were more frequently recorded in the drug group (p = 0.09). The incidence of severe hyperkalemia (over 6.0 mmol/l) was rare and did not differ from placebo group (p=0.11). Episodes of hypokalemia in patients administered with eplerenone developed significantly less frequently (1.4 %) than in placebo group (5.6 %; p = 0.0002) that is of special importance in patients with AMI since low serum potassium levels are associated with increased risk of arrhythmias and mortality.

Nephroprotective potential of MRAs in patients with CHF and chronic kidney disease (CKD)

According to various data, from 25 to 60 % of patients with CHF have impaired renal function. GFR below 60 ml/min/1.73 m^2 increases the risk of death by more than 2 times in patients with CHF, and by 3.8 times — in patients with HFrEF and renal failure [15]. The kidney dysfunction in patients with CHF is not only associated with poor prognosis, but also with higher risk of repeated hospitalizations (RR 1.95, p<0.001 and RR 1.30, p=0.022, respectively) [16]. The addition of MRAs to standard therapy with ACE inhibitors and ARNIs may provide additional nephroprotective effect. Several meta-analyses have been published in 2009, 2014, 2020 evaluating the effects of selective (eplerenone) and nonselective (spironolactone or canrenone) or nonsteroidal (finerenone) MRAs on major cardiovascular events and death, kidney function, progression to end-stage renal disease and safety of its use in patients with CKD [17]. The authors mention the antiproteinuric and hypotensive effects of MRAs. However, the effect of the addition of MRA to ACE inhibitors or ARNIs on the mortality risk, major cardiovascular events, and renal failure in patients with CKD and

proteinuria remains uncertain. The administration os pharmacological agents from this group can lead to the development of hyperkalemia, acute kidney injury, gynecomastia. The management of patients with CHF and CKD is a difficult task that requires additional monitoring of biochemical parameters and electrolyte balance, dose adjustment of many medications prescribed for pathogenetic therapy of HFrEF.

The effectiveness of finerenone in patients with CHF, type 2 DM and CKD

Finerenone proved to be a promising agent from the MRAs group in patients with concomitant CKD. Similar to eplerenone, the medication is selective mineralcorticoid receptor antagonist and does not affect glucocorticoid, androgen, progesterone and estrogen receptors. Therefore, the risk of side effects that are usually seen in non-selective MCRAs is lower. Unlike eplerenone, finerenone is a derivative of dihydropyridine and does not belong to steroids. The drug has high affinity to MR, and effectively inhibits collagen formation and prevents the development of interstitial fibrosis [18]. Finerenone is not registered in the Russian Federation.

Randomized, placebo-controlled phase 2 study that ended in 2012 showed comparable efficacy of finerenone at dose of 5–10 mg / day and spironolactone at dose of 25–50 mg / day in the reduction of BNP, proBNP and albuminuria in patients with HFrEF in combination with CKD. However, finerenone was associated with significantly lower mean increase of serum potassium level than spironolactone (0.04–0.30 and 0.45 mmol/L, respectively, p<0.0001–0.0107), and lower incidence of hyperkalemia (5.3 % and 12.7 %, respectively, p=0.048) and kidney function impairment [19]. The phase 2b ARTS-HF trial for the first time compared the effectiveness of various finerenone and eplerenone doses in patients with HFrEF decompensation (LV EF 40 % and lower over the last year) that required intravenous diuretics as well as with DM and/or CKD (eGFR of.30 mL/min/1.73 m^2 in patients with DM and 30–60 mL/min/1.73 m^2 in patients without DM) [20]. Over 60 % of patients had CAD, over 70 % had arterial hypertension, and about half of patients had a high/very high level of albuminuria. Most patients from observation group had class III CHF according to NYHA. The average LV EF was about 29 %. All patients received optimal pharmacological therapy for CHF. Participants who received spironolactone, eplerenone, renin inhibitors discontinued its intake 24 hours before randomization (48 hours for spironolactone). All of the 1066 patients included into the program were divided into 6 observation groups. Group 1 received 25 mg per day of eplerenone. The medication was increased to 25 mg once daily on day 30, and to 50 mg once daily on day 60. Patients of the remaining 5 groups received finerenone once-daily at a dose of 2.5, 5, 7.5, 10, or 15 mg, uptitrated to 5, 10, 15, 20, or 20 mg, respectively, on day 30 if the serum potassium level did not exceed 5.0 mmol/L. The medication was discontinued with hyperkalemia over 5.6 mmol/l. The duration of this therapy was 90 days. After that, patients were followed up for another month. The primary endpoint was the percentage of individuals with a decrease of 30 % in plasma NT-proBNP from baseline to day 90 that occurred in 37.2 % of patients in the eplerenone group and 30.9, 32.5, 37.3, 38.8, and 34.2 % in the finerenone groups, respectively (P=0.42–0.88). Except for the 2.5–5 mg finerenone group, the composite clinical endpoint of death from any cause, cardiovascular hospitalization, or emergency presentation for worsening chronic HF occurred numerically less frequently in finerenone-treated patients compared with eplerenone. It is noteworthy that of the parameter decreaseed in 10–20 mg group compared with eplerenone group (HR 0.56, 95 % CI -0.35; 0.90; P=0.02). This can be explained by positive dynamics of individual components of the secondary endpoint in the 10–20 mg finerenone group compared with the eplerenone group: death from any cause (RR 0.13; 95 % CI — 0.02–1.07), cardiovascular hospitalization (RR 0.56; 95 % CI: 0.34–0.93) and emergency presentation for worsening of CHF (RR: 0.58; 95 % CI: 0.33–1.02). The changes in concentrations of galectin 3 and N-terminal pro- collagen III peptide from baseline to Day 90 were not significant. Mean scores of the KCCQ and the EuroQoL Questionnaire improved in all treatment groups. The incidence of adverse events was comparable between groups. Hyperkalaemia (serum potassium concentration ⩾5.6 mmol/L) was observed in 44 patients (4.3 %) with a balanced distribution among the finerenone dose groups and the eplerenone group. Hyperkalemia ⩾5.6 mmol/l was registered in 44 patients (4.3 %) with a uniform distribution between the finerenone groups and the eplerenone group. Hyperkalemia >6.0 mmol/l was

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detected in five patients (1/212 (0.5 %) in the eplerenone group and in 1/164 (0.6 %) and 3/160 (1.9 %) in the finerenone groups at a dose of 7.5–15 mg and 15–20 mg, respectively). However, mean change from baseline to day 90 in serum potassium concentration was greater in the eplerenone group (+0.262 mmol/ L) than in each of the finerenone dose groups (+0.119–0.202 mmol/L). Mean systolic blood pressure decreased approximately by 3 mmHg in all treatment groups. Mean eGFR increased slightly in the two lowest finerenone groups and decreased in the other groups. There were isolated cases of decrease in eGFR by ⩾ 25, ⩾ 30, ⩾ 40 and ⩾ 57 % in all groups. There were five renal events leading to hospitalization: two in the eplerenone group and one each in the finerenone 2.5–5, 7.5–15, and 15–20 mg dose groups. The use of MRAs in patients with HFrEF is pathogenetically justified, but the prescription of medication at a therapeutic dose is often limited by the risk hyperkalemia, kidney function impairment, and the development of endocrine disorders (in nonselective drugs). Therefore, finerenone can become an alternative MR blocker, especially in groups of patients with high risk of hyperkalemia. The results of the ARTS-HF trial contributed to further investigation of new MRAs agents in patients with CHF at a dose of 10–20 mg/day.

The 2018 systematic review and meta-analysis of three studies that included 1520 patients with CHF showed the comparable effect of finerenone to steroidal MRA (spironolactone, eplerenone) in the reduction of the NT-proBNP level. The effectiveness of the medication depended its dose. Finerenone at the dose of 10 mg/day was superior to steroidal MRA (p>0.05). However, the frequency of side effects was significantly lower compared with steroidal MRA at the dose of 25–50 mg/day (RR=0.81; 95 % CI, 0.66–0.99; p=0.04). The serum potassium level in the 10 mg/day finerenone group was lower than in the 25–50 mg/day steroidal MRAs group, and eGFR was higher in patients who received finerenone compared with patients administered with steroidal MRAs (p = 0.05). Based on the meta-analysis, the researchers concluded that finerenone has dose-dependent effect in patients with CHF. The dose of 10 mg/day was comparable to steroidal MRAs at the dose of 25–50 mg/day. At the same time finerenone has less effect on potassium level and eGFR [21].

The investigation of finerenone effectiveness continued in several phase III trials involving over 18.600 patients with DM, CKD, CHF such as FIDELIO-DKD, FIGARO-DKD, FINEARTS-HF. The results of the FIDELIO-DKD study were published in autumn 2020 [22]. The multicentral, randomized, placebo-controlled trial included 5734 patients with CKD and type 2 DM. The study included patients with less than 4.8 mmol/l serum potassium level. The median follow-up period was 2.6 years. Finerenone was administered at 10 and 20 mg/day additionally to hypoglycemic therapy and high doses of RAAS inhibitors (ACE inhibitors and ARNIs). The primary outcome, (composite of kidney failure, a sustained decrease of at least 40 % in the eGFR from baseline over a period of at least 4 weeks, or death from renal causes) decreased in finerenone group by 18 % (RR 0.82; 95 % CI — 0.73–0.93, p=0.0014) compared with placebo. Finerenone reduced the risk of kidney failure by 13 % (RR 0.87; 95 % CI 0.72–1.05), the risk of a sustained decrease in the eGFR ⩾ 40 % from baseline by 19 % (RR 0.81; 95 % CI — 0.72–0.92). During the study follow-up, 4 deaths from kidney disease were registered (2 in each group). The frequency of secondary composite outcome (cardiovascular event, non-fatal MI, non-fatal stroke, or hospitalization for CHF) was lower by 14 % compared with placebo (RR 0.86; 95 % CI 0.75–0.99; p=0.0339) as well as its individual components: cardiovascular event risk by 14 % (RR 0.86; 95 % CI — 0.68–1.08); nonfatal MI by 20 % (RR 0.80; 95 % CI 0.58–1.09) and the risk of hospitalization for CHF by 14 % (RR 0.86; 95 % CI 0.68–1.08). In February 2021, the randomized, placebo-controlled, phase III FIGARO-DKD trial that started in 2015 has ended [23, 24]. The median follow-up was 3.4 years. This trial included a population of patients with type 2 DM and CKD (7437 patients) similar to FIDELIO-DKD, but the primary outcome assessed the effectiveness and safety of finerenone in the reduction of cardiovascular events, non-fatal MI, non-fatal stroke, or hospitalization for CHF frequency. Secondary outcome included: time to kidney failure (sustained decrease from baseline of ⩾40 % in GFR, or death from renal cause); time to death from any cause; time to hospitalization for any reason; change of albumin / creatinine ratio 4 months after medication prescription compared with baseline; time to first occurrence of a combined endpoint (onset of kidney failure, a sustained decrease from baseline ⩾ 57 % eGFR for

at least 4 weeks, or death from renal cause). The study included patients with moderate albuminuria (albumin/creatinine ratio over 30 mg/g and less than 300 mg/g in the urine) and eGFR from 25 to 90 ml/min/1.73 m^2 (CKD stages 1–4) and patients with severe albuminuria (albumin/creatinine ratio from 300 mg/g to 500 mg/g) and eGFR of at least 60 ml/min/1.73 m^2 (CKD stages 1–2). Potassium level over 4.8 mmol/L was an exclusion criterion. The mean age of participants was 64.1±9.8 years. About 45% of patients had a history of cardiovascular disease. In the majority (over 60%) of patients, eGFR was over 60 ml/min/1.73 m^2, and the mean value of albumin/creatinine ratio was 308 mg/g. About 98% of patients permanently received hypoglycemic therapy, and only 8.4% received sodium-glucose co-transporter-2 (SGLT2) inhibitors and 7.5% — glucagon-like peptide-1 (GLT-1) agonists. The initial dose of medication depended on the eGFR. Patients with an eGFR of 25–60 ml/min/1.73 m^2 at the screening visit received an initial dose of 10 mg once daily, and those with an eGFR of ≥60 at the screening visit received an initial dose of 20 mg once daily. An increase in the dose to 20 mg was encouraged, in case when the serum potassium level was ≤4.8 mmol/L and the eGFR was stable. With hyperkalemia was over 5.5 mmol/l, the drug was discontinued. Finerenone showed its effectivenes in the significant reduction of the primary outcome by 13% compared with placebo (RR 0.87; 95% CI 0.76–0.98; p=0.03). The result was largely due to the decrease of the frequency of hospitalizations for CHF (RR 0.71; 95% CI 0.56–0.90). Events of the secondary combined outcome were less frequently recorded in the finerenone group (in 350 patients — 9.5%) than in the control group (in 395 patients — 10.8%) (RR 0.87; 95% CI — 0.76–1.01). The medication also demonstrates good tolerability that was comparable to placebo. However, in the main group, hyperkalemia was registered more often (in 1.2% of patients), which required discontinuation of the medication, compared with the placebo group (in 0.4% of patients). Episodes of hypokalemia were almost 2 times less common in the finerenone group. The analysis of the adverse events associated with COVID-19 development displayed lower number of complications in finerenone group, including severe cases, compared with placebo (38 — 1.0% vs. 63 — 1.7%). The results of performed studies showed that among patients with HFrEF, type 2 DM, CKD, finerenone can be an effective treatment choice. The FIGARO-DKD study revealed a positive effect of finerenone on the prognosis in patients with the initial stages of CKD (stages 1–2).

In 2020 the study of the the effectiveness and safety of finerenone in patients with symptomatic CHF with moderately reduced and preserved LV EF was initiated. Unfortunately, to this date, there is not enough evidence of a positive effect on the prognosis of any medication in this group of patients, therefore, the FINEARTS-HF study (NCT04435626) is highly relevant. According to the information published in the U.S. National Library of Medicine Clinical Trials Database, this is a multicenter, randomized, placebo-controlled study of 5.500 patients aged over 40 years with NYHA II–IV classes of CHF, LV EF ⩾ 40%, who regularly received diuretic treatment for at least 30 days prior to randomization, and have one of the following structural heart changes: left atrial diameter (LAD) ⩾3.8cm, left atrial area (LAA) ⩾20cm^2, left atrial volume index (LAVI) >30 mL/m^2, left ventricular mass index (LVMI) ⩾115 g/m^2 (in men)/ 95 g/m^2 (in women), septal thickness or posterior wall thickness ⩾1.1 cm. Patients with eGFR < 25 ml/min /1.73m^2, plasma potassium level > 5.0 mmol/l, acute myocarditis, MI, coronary artery bypass grafting, stroke or transient ischemic attack within 90 days prior to randomization, percutaneous coronary intervention within 30 days prior to randomization, with an alternative cause of CHF symptoms were excluded from the study. The planned follow-up period for patients is 42 months. The dose of finerenone depended on the eGFR. For participants with an eGFR ⩽60 mL/min/1.73m^2: starting dose is 10 mg per day and maximum dose — 20 mg per day. For participants with an eGFR >60 mL/min/1.73m^2 starting dose is 20 mg per day and maximum dose — 40 mg per day. The effectiveness of the medication will be assessed by its impact on the risk of cardiovascular event and the course of CHF. The study also intends to study the dynamics of patients' life quality by using the Kansas City Cardiomyopathy Questionnaire (KCCQ) after 6, 9, 12 months of treatment, renal outcomes (sustained decrease in estimated glomerular filtration rate (eGFR) ⩾40% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m^2 or initiation of dialysis or renal transplantation), risk of death from any cause.

Conclusion

The review of clinical trials presented in this article clearly demonstrates the effectiveness of MRAs in patients with MI, CHF in combination with type 2 DM and CKD. The use of MRAs in patients with HFrEF is necessary, but in some cases it is limited by high risk of hyperkalemia and impaired renal function development, especially in groups of patients with concomitant DM and CKD. The evidence obtained for the effectiveness and safety of the non-steroidal MRA finerenone shows that it can be widely used in patients with severe course of the disease and poor prognosis. Further studies on the use of the combination therapy of finerenone and of hypoglycemic agents (such as SGLT2 inhibitors and GLT-1 agonists) with proven nephroprotective effect is required. This combination may contribute to the long-term reduction of cardiorenal risk. The results of ongoing trials, as well as the initiation of new ones involving patients with Herat failure with preserved ejection fraction, will allow to develop more specific patient-oriented guidelines for the management of patients with high risk and several comorbid pathologies.

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Diagnosis and management of anemia in clinical practice and its association with cardiovascular pathology

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Abstract

Anemia is a syndrome that can be presented in many medical conditions that primary healthcare professionals face during their practice. Anemia has become widespread (up to 25 % of the world's population), which makes this health issue highly relevant. The causes of anemia may include: acute and chronic blood loss, impaired absorption of iron and vitamins, hemolysis, inhibition of bone marrow hematopoiesis, impaired erythropoietin synthesis. Since the manifestations of anemia are nonspecific (weakness, shortness of breath during exercise, dizziness, tachycardia), they can be interpreted as chronic heart, lung or kidney disease that can lead to late diagnosis and treatment of this pathology. General practitioners have to be aware of the etiology, pathogenesis, and clinical signs of anemia as well as actively apply laboratory and instrumental diagnostic tools, and have a good understanding of the mechanisms of action of anemia medications and consider its indications and contraindications when prescribing.

The review focuses on the main causes of iron deficiency, differential diagnosis between anemias, treatment options for iron deficiency anemia.

Keywords: *iron deficiency anemia, anemia of chronic disease, hemoglobin, transferrin, hepcidin, iron preparations, erythropoietin.*

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Anemia is a clinical and laboratory syndrome characterized by the decrease of red blood cell count or hemoglobin per unit of blood volume due to various pathological (physiological) processes [1].

The most common causes of anemia in clinical practice include:

— iron deficiency — 29 %;
— chronic diseases — 27 %;
— acute bleeding — 17.5 %;
— hemolysis –17.5 %.

There is no generally accepted classification of anemia, but its severity can be classified by mean cell volume (MCV) of red blood cells:

- microcytic hypochromic anemia (MCV < 80 fL);
- normocytic normochromic anemia (MCV = 80–95 fL);
- macrocytic hyperchromic anemia (MCV > 95 fL).

Pathophysiologically, anemia can be:

- associated with decreased development of red blood cells and/or Hb;
- associated with increased breakdown of red blood cells.

Based on the hemoglobin level, anemia can be classified as:

- severe (Hb<70 g/l);
- moderate (Hb 70–100 g/l);
- mild (Hb > 100 g/l).

In clinical practice, it is convenient to divide anemia into the following groups in order to select the optimal treatment strategy:

Group 1 — "deficiency" anemia that is associated with iron (including post-hemorrhagic) or vitamin B12 (folic acid) deficiency;

Group 2 — anemia associated with chronic diseases such as chronic infectious, inflammatory, autoimmune and oncological diseases;

Group 3 — "hematological" anemia associated with bone marrow failure (hemoblastosis, aplastic anemia), or with increased breakdown of red blood cells (hemolytic anemia) [2].

Iron deficiency anemia

Iron deficiency anemia (IDA) is widely spread worldwide. It is the most common type of anemia (90 % among children, 80 % among adults).

IDA is polyetiological pathology that is mainly associated with iron deficiency due to impaired iron intake, absorption or increased loss of this element, characterized by microcytic hypochromic anemia.

It is widely known that anemias, including IDA, may be associated with socioeconomic status, nutrition, bleeding, parasitic diseases, etc. Experts from the World Health Organization found that anemia is commonly seen in developing countries, especially in infants and pregnant women (Table 1) [3].

Table 1. **The prevalence of anemia worldwide depending on age, gender, socioeconomic status**

Demographic group	Anemia prevalence, %		
	Developed countries	Developing countries	Worldwide
Children 0–4 years old	12	51	43
Children 5–12 years old	7	46	37
Men	2	26	18
Pregnant women	14	59	51
Women	11	47	35

Iron metabolism

Adult's organism contains approximately 3–5 g of bound iron, 70 % of which is stored in hemoglobin. Most of the iron that is absorbed in the intestine is then stored in the bone marrow, where it is used for proerythroblasts synthesis. The lifespan of erythrocytes ranges from 100 to 120 days, after which they clearance by macrophages in liver, spleen and bone marrow. The iron released in this process is then used for the synthesis of hemoglobin. Sufficient meat intake generally provides human organism with necessary amount of iron. When there is an iron deficiency (due to bleeding or impaired absorption), the depot activates. Ferritin is a protein of mass 474 kDa that stores and deposits iron.

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Physiologically, the amount of ferritin is comparable to the amount of iron (when there is more ferritin, there is also more iron). Chief storage depots of iron are liver, spleen, and bone marrow.

About 10–20 % of iron from food is absorbed into the bloodstream in the small intestine. It is possible to assimilate only the bivalent iron (Fe2+), since trivalent iron (Fe3+) is practically not absorbed [4].

Transferrin and transferrin's receptors play pivotal role in iron transport. Transferrin have a molecular mass of 80 kDa and mediate the transport of iron through blood plasma to tissues (bone marrow, liver, spleen). It is produced in the liver in accordance with the amount of iron (iron deficiency activates transferrin synthesis). Transferrin transports both iron absorbed from food and iron released from depots (by macrophages). However, it cannot be transported from the transferrin–iron complex directly to the cell. This process requires another protein — the transferrin receptor. The transferrin-transferrin receptor complex is immersed into the cell, where iron releases.

Hepcidin in another key protein that is produced by the liver. Hepcidin is a regulator of iron release from monocyte–macrophage cells. It inhibits iron absorption from blood by intestine and its release from hepatic and splenic macrophages. Chronic inflammation is the main cause of hepcidin overproduction. It is often seen in patients with inflammatory bowel diseases that is accompanied by iron deficiency and anemia.

Only 10–15 % (about 2.5 mg) of iron that comes from food is absorbed, while about 1 mg of iron per day is excreted in stools, urine, hair, nails, and exfoliated epidermal cells. In young menstruating women this number is even higher. Therefore, in order to restore the daily loss of this element, the amount of absorbed iron should be 5–10 times higher.

The following stages of iron deficiency are identified:

I. Prelatent iron deficiency (iron stores are low or absent);

II. Latent iron deficiency (iron transport is low);

III. Iron-deficiency anemia.

Increased iron consumption leads to iron stores depletion followed by the reduction of ferritin, while transferrin saturation and serum iron as well as the level of red blood cells and hemoglobin remain within reference values, and the patient does not present clinical signs of anemia. This stage is called prelatent iron deficiency.

The continuation of iron consumption when iron stores are low leads to transferrin saturation and serum iron reduction, while hemoglobin and red blood cell count remain normal. This stage is called latent iron deficiency.

Finally, the stage of iron deficiency anemia is characterized by the drop of hemoglobin along with depletion of iron stores and the reduction of serum iron and transferrin saturation. At this stage patient usually have clinical signs of IDA.

Main IDA causes

According to the main mechanisms of iron deficiency, IDA can be caused by blood loss, increased iron need, insufficient dietary intake or malabsorption [6].

1. Blood loss:

a) uterine bleeding (uterine fibroids, cervical cancer, endometriosis, ovarian insufficiency, etc.);

b) gastrointestinal bleeding (peptic ulcer, hemorrhoids, cancer, ulcerative colitis, Crohn's disease, diverticular disease, NSAID-induced enteropathy, Meckel's diverticulum);

c) pulmonary hemorrhage (cancer, bronchiectasis, isolated pulmonary hemosiderosis);

d) kidney hemorrhage (urolithiasis, hematuric nephritis, tumors);

e) nosebleeds.

2. Increased iron need:

a) pregnancy, lactation;

b) growth and puberty;

c) chronic infections, tumors;

d) helminthiases.

3. Iron malabsorption:

a) stomach resection;

b) enteritis, sprue syndrome;

c) coeliac disease.

4. Impaired iron transport due to transferrin deficiency in patients with primary liver pathology.

5. Inadequate dietary intake:

a) children who are formula-fed without iron supplement;

b) vegetarian diet, malnutrition.

6. Iatrogenic causes:

a) blood and organ donation;

b) hemodialysis;

c) frequent blood sampling.

It should be also noted that IDA can have combined ethnology.

IDA progresses over the following stages:

Stage 1. Iron storage depletion due to excessive iron consumption and low intake. At this stage iron absorption usually increases.

Stage 2. Significant storage depletion (transferrin saturation <17.8 %, serum iron level <10.7 μmol/l).

Stage 3. Mild (compensated) anemia — hemoglobin level — 100–120 g/l.

Stage 4 — Moderate (subcompensated) anemia — hemoglobin level < 100 g/l.

Stage 5 — Severe anemia — hemoglobin level 60–80 g/l with the development of tissue hypoxia and vascular lesions.

IDA diagnosis is based in the clinical picture and laboratory parameters of absolute iron deficiency.

The main IDA clinical signs are sideropenia and hypoxia [7]. Sideropenia symptoms are typical for IDA. Particular changes are seen in tissues that constantly regenerate: skin has pale color, becomes dry and covered with fissures. There is usually a slight jaundice of nasolabial triangle and fingers, associated with carotene metabolism impairment in patients with iron deficiency. Angular cheilitis with red, swollen patches in the corners of the mouth may develop.

Nails may become concave in shape or spoon-shaped with peeling (the condition is called "koilonychia").

Tongue may develop glossitis (redness and soreness, as well as atrophy of the papillae).

Hair turns gray, falls out, becomes brittle and dry.

Muscle weakness develops even during low physical activity. Dysuria or involuntary urination may develop due to sphincter weakness.

Picachlorotica — taste and smell perversions — the patient has desire to consume inedible substances, such as: chalk, earth, sand, raw cereals; inhale substances with pungent odor: gasoline, acetone, etc.

Hypoxia can lead to the impairment of cardiovascular system (CVS), central nervous system, gastrointestinal tract (GIT).

Cardiovascular symptoms may include:

- tachycardia;
- hypotension;
- dyspnea;
- cardialgia;
- lower extremity edema;
- exacerbation of angina pectoris and cardiac decompensation, especially in elderly patients.

Chronic IDA can lead to myocardial dystrophy that can manifest as systolic heart murmur at the apex and pulmonic areas [8, 9].

Nervous system impairment can present with headache, dizziness, poor concentration, fatigue during exercising, and decreased intelligence in children.

Changes in the **gastrointestinal tract** are associated with tissue hypoxia due to iron deficiency and can manifest as gastritis, dysphagia, poor appetite, achlorhydria, bloating, diarrhea, or constipation. At the same time, the decrease in hydrochloric acid secretion and in chronic gastritis is considered as the consequence, and not as the cause of iron deficiency, and can be explained by dysregenerative processes in the gastric mucosa. It is assumed that iron deficiency can cause increased absorption of iron antagonist metals in the intestinal wall followed by its accumulation, such as cadmium [10].

Despite the bright clinical picture of IDA, laboratory parameters are superior in the IDA diagnosis [11].

Laboratory parameters of IDA

1. Complete blood count (CBC). CBC determine hemoglobin, the red blood cell count and calculate the average amount of hemoglobin in RBCs (MCH), hematocrit (Hct) and the level of immature red blood cells (reticulocytes). In patients with IDA all the above indicators decrease, and morphological examination show microcytic hypochromic anemia.

2. Biochemical makers of iron metabolism determine the iron serum level, transferrin, the transferrin saturation (TS), the total iron-binding capacity (TIBC), and ferritin. IDA is characterized by low ferritin level that indicates iron storage depletion, increased levels of TIBC and transferrin. The iron serum level and the TS are usually reduced.

3. It is necessary to exclude celiac disease in patients with impaired iron absorption in the small intestine and the development of anemia that resistant to treatment with oral preparations. Therefore, it is essential to assess antibodies to tissue transglutaminase (anti-tTG) and endomysium (Anti-EMA). In case when leukopenia and thrombocytopenia are present in CBC, a bone marrow aspiration is indicated [12].

4. In order to verify the diagnosis, patients with IDA should undergo the following instrumental investigations:

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— endoscopy (esophagogastroduodenoscopy and colonoscopy, to exclude a possible causes of blood loss and impaired iron absorption);

— abdominal, pelvic and thyroid ultrasound;

— electrocardiography (ECG);

— echocardiography (Echo-CG);

— X-ray or computed tomography of the chest.

The conducted instrumental investigations allow to determine the cause of blood loss in the gastrointestinal tract, however, it should be kept in mind that IDA can develop in patients with nosebleeds, hematuria (with urolithiasis, nephritis and nephropathy), and iatrogenic causes (frequent blood sampling for research and bloodletting). Iron deficiency can also develop due to injuries, tumors and endometriosis.

Differential diagnosis of IDA

Differential diagnosis of IDA should be carried out in patients with anemia and chronic inflammatory and neoplastic diseases ("anemia of chronic diseases" and hypochromic anemia with iron overload: α- and β-thalassemia, porphyria).

Differential diagnosis between iron deficiency anemia and anemia of chronic disease (ACD) is presented in Table 2.

Table 2. **Differential diagnosis between iron deficiency anemia and anemia of chronic disease**

Parameters	Reference values	IDA	ACD
Serum iron level	10.7–32.2 μmol/l	↓	↓ N
TIBC	46–90 μmol/l	↑	N or ↓
TS	17.8–43.3 %	↓	N↓↑
Serum ferritin	11.0–306.8 ng/ml	↓	N or ↑

Comment. N — parameter is within the reference values; ↓ — decreased level of the parameter; ↑ — increased level of the parameter.

IDA treatment

The main principles of IDA treatment have been formulated by L.I. Idelson in 1981 and remain valid today:

— it is impossible to treat IDA only with diet;

— first-line treatment is oral iron supplements that should be prescribed in sufficient dosages (100–200 mg/day) and for at least 3 months;

— the improvement of Hb level is not the reason to stop treatment, it is necessary to restock iron storages (determined by the level of serum ferritin);

— blood transfusion in case of IDA should be performed only for health reasons [13].

There are two groups of iron supplements: those containing divalent iron (ionic, saline) and trivalent iron (non-ionic) based on hydroxide polymaltose complex (HPC) and protein succinylate [14]. The daily dosage of iron should range between 100 and 200 mg. The degree of absorption of divalent iron salts is higher compared with trivalent form, therefore they have faster effect and improves Hb levels more quickly. Preparations with hydroxide polymaltose complex (trivalent iron) are better tolerated by the gastrointestinal tract, thus, they are preferable for the treatment of patients with gastroenterological pathology and in children [15].

Parenteral iron preparations are prescribed for patients with intolerance to oral forms, or with the need for rapid restock of iron storages (severe IDA, postoperative period), impaired absorption of iron (for example, with celiac disease, inflammatory bowel disease). It is recommended to administer parenteral forms of iron intravenously, since intramuscular administration is less effective and may cause post-injection infiltrates [16].

Anemia of chronic disease (ACD): focus on CHF

ACD is ranked second in the prevalence after IDA and develops in patients with acute and chronic diseases (especially common in elderly and senile patients). It is usually mild, normochromic microcytic anemia with Hb level between 90 and 120 g/L and hematocrit of 30–40 %. In chronic and long-term course, this anemia becomes hypochromic [17].

ACD develops in many diseases and conditions: infections (bacterial, viral, fungal), autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, systemic scleroderma, hemoblastosis and malignant neoplasms, inflammatory bowel disease, sarcoidosis, chronic kidney disease, diabetes mellitus). The main mechanism of the ACD development is the formation of the hepcidin protein, which is produced by hepatocytes during inflammation. Hepcidin inhibits the absorption of iron from the small intestine and its re-utilization from iron depots, leading to the decrease of the serum iron level. In addition, the synthesis of erythropoietin in kidneys decreases due to elevation of pro-inflammatory cytokines — interferon-α (IFN-α), tumor necrosis factor-α (TNF-α) and interleukins (IL-1.6) [18,19].

Cardiovascular diseases are often associated with anemia, the prevalence of anemia increases along with the progression of heart failure and reaches 80 % in patients with class IV New York Heart Association (NYHA) clinical classification of heart failure. Anemia is an additional risk factor for mortality and complications (due to impaired exercise tolerance and low cardiac ejection fraction). The progression of CHF contributes to renal dysfunction leading to the activation of the renin-angiotensin system, vasoconstriction, and decreased erythropoietin synthesis. Timely treatment of anemia can prevent heart failure complications and renal dysfunction (cardiorenal continuum) that decreases the frequency of admissions and allow to reduce the dosage of diuretics and subsequently improves patient's quality of life [20].

Diagnosis of ACD

ACD is usually diagnosed in patients chronic diseases of cardiovascular, autoimmune, infectious origin [21]. The diagnosis of ACD can be considered in patients with long lasting anemia that is refractory to treatment with oral iron preparations. ACD can be differentiated from IDA by the level of serum ferritin, that stores iron. Ferritin level is reduced in patients with IDA while in patients with ACD it is within the reference values or even increased, since ferritin increases during inflammation. The level of transferrin (iron binding protein) is significantly increased in patients with IDA, and, conversely, reduced in patients with ACD.

Since the clinical signs of anemia are nonspecific (weakness, shortness of breath while exercising, dizziness, tachycardia), the additional examination in order to exclude or confirm cardiovascular pathology is necessary. In addition to medical history assessment and objective examination, it is necessary to conduct laboratory and instrumental investigations (ECG, Holter-ECG monitoring, Echo-CG, 24-hour BP monitoring, etc.)

ACD treatment

The main principle of ACD management is the treatment of the disease that caused it [22]. It has been proven that ACD aggravate the course of many chronic diseases (autoimmune diseases, inflammatory bowel disease, cardiovascular diseases, diabetes mellitus, etc.) and serves as the predictor of high mortality. It has been established that patients with AHD have 2 times higher risk of death compared with patients with mild anemia. The management of anemia can significantly improve the course of the disease.

There are 3 main types of ACD treatment [23]:

- blood components transfusion;
- administration of iron supplements;
- administration of erythropoiesis stimulants.

Blood components transfusion is widely used therapeutic intervention with rapid effect. Blood transfusion is indicated for patients with life-threatening anemia (Hb<65 g/l). It can also be used in patients with severe (Hb<80 g/l) or complicated by bleeding ACD. However, it should be noted that blood components transfusion give short-term effect, and due to the destruction of red blood cells in the bloodstream can lead to immune complications up to anaphylactic shock. In addition, it is impossible to exclude the transmission of blood borne infections (HIV, viral hepatitis, etc.). Repeated blood transfusions can lead to endogenous erythropoietin synthesis suppression and erythropoiesis inhibition.

Iron supplements administration

The treatment of ACD with iron supplements has low effectiveness, since hepcidin produced by hepatocytes disrupts iron absorption from the intestine. Only in patients with ACD and concomitant iron deficiency oral supplements has positive effect [24].

Considering the pathogenesis of ACD, the use of intravenous iron therapy seem more effective, however, even in this case, it is not always possible to achieve treatment targets, since the production of erythropoietin decreases in patients with ACD. Therefore, the most effective treatment for ACD is the combination of erythropoietin and intravenous iron preparations. Modern parenteral iron therapy allow to achieve good results with 1–2 infusions and to maintain the level of hemoglobin for a long time.

Erythropoiesis stimulants administration

Recombinant human erythropoietin medications were implemented into clinical practice in the 1980s and are used to replace endogenous erythropoietin that is insufficiently produced in patients with ACD. Erythropoietin stimulates the growth and differentiation of erythroid precursor cells in the bone marrow, and counteracts antiproliferative effect of cytokines [25].

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Subcutaneous injections of erythropoietin at the dosage of 150 IU/kg 3 times a week are recommended, followed by dosage increase up to 300 IU/kg 3 times a week in patients who did not respond to previous treatment. The use of 10.000 IU 3 times a week is considered optimal and allow to control the development of possible side effects and discontinue treatment when needed (arterial hypertension and thrombosis development). Currently, the subcutaneous administration of erythropoietin at the dosage of 40.000 IU per week is recommended.

Conclusion

Thus, anemia of various origin has high prevalence and significantly impairs not only life quality and physical activity of patients, but also aggravates the course of concomitant diseases. It is of special importance to establish the cause of anemia in order to choose treatment strategy that can be done with correct interpretation of laboratory data. Primary measures should aim to exclude etiological factor of anemia with varying severity. The optimal approach for patients with mild to moderate IDA are the prescription of oral iron supplements and for patients with severe anemia — the combination of intravenous iron and erythropoietin medications. Adequate treatment of anemia result in cardiovascular pathology improvement (decompensation of heart failure decreases: shortness of breath, edema, tachycardia), exercise tolerance increase according to the 6-minute walk test, self-assessment of the general health state (life quality) improvement, the progression of CHF slow down, functional class according to NYHA decrease.

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The stenting of carotid-subclavian shunt for the primary prevention of acute cerebrovascular accident

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Abstract

Acute cerebrovascular accident prevention is one of the most important medical and social issues. Revascularization after open reconstructive surgery is of particular technical difficulty due to structural changes of vascular bed and adhesion-related complications. Repeated carotid artery bypass grafting is not enough investigated and technically complex method that is associated with high operational risk. We performed stenting of the proximal anastomosis of the carotid-subclavian shunt using the cerebral protection system with right femoral and left radial approaches. This clinical case demonstrates the possibilities of modern endovascular surgery in the management of patients with extremely high cardiovascular risk.

Keywords: *atherosclerosis, restenosis, stroke, prevention, stenting.*

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Introduction

Acute cerebrovascular accident (CVA) is one of the main causes of disability and mortality worldwide. According the Ministry of Health of the Russian Federation, the incidence of stroke is up to 3 cases per 1000 population, while its mortality reaches 30 % [1].

The most common cause of stroke is brachiocephalic atherosclerosis that can be prevented by surgical techniques (endovascular stent grafting, carotid endarterectomy) in addition to pharmacotherapy [2–4]. Moreover, in patients with certain pathologies (subclavian steal syndrome, brachiocephalic artery stenosis, aortic arch replacement), carotid artery bypass can be used to preserve antegrade blood flow [5]. However, despite the success in the management of aortic arch atherosclerosis with invasive procedures, the issue of restenosus after carotid interventions is still highly relevant. From 10 to 15 % of patients reported restenosis during the first year after carotid stenting, and over 50 % — in 10 years. [6]. There are several methods of graft revascularization, however, according to various studies, stenting is the most effective treatment strategy compared with other interventions [7–10]. The development of cerebral embolic protection devices significantly reduced the risks of intraoperative complications during carotid angioplasty and stenting. Data on carotid shunting, in turn, are scarce. In this article we present clinical case of the stenting of carotid-subclavian shunt proximal anastomosis and its impact on the life quality that was performed at the Department of Innovative Endovascular Therapy for the Prevention and Treatment of Cardiovascular Diseases of the National Medical Research Center for Therapy and Preventive Medicine of the Ministry of Healthcare of the Russian Federation.

Materials and methods

The analysis of endovascular treatment of patient with restenosis of the carotid-subclavian proximal anastomosis shunt including the examination of patient's medical history and the assessment of long-term consequences of treatment.

Clinical case

Patient M., 78-years woman, was admitted to the Department of X-ray Endovascular Diagnostic Methods and Treatment in October 2020. Patient had dizziness and unsteadiness, diffuse compressive headaches, memory loss, tinnitus, as well as syncopal episode and short-term right-sided hemiparesis 2 weeks prior to hospitalization.

According to medical history patient has been suffering from arterial hypertension for over 30 years (despite multicomponent pharmacological treatment, the mean blood pressure (BP), self-measured for 3 weeks before the procedure, was 150/70 mmHg)). In 1993, she underwent right side mastectomy followed by chemotherapy. In 2012 she had left subclavian artery occlusion that was treated with Amplatzer system, stenting of the aortic arch and descending aorta, followed by carotid-subclavian bypass grafting (left common carotid artery (CCA) prosthesis and bypass grafting of the left subclavian artery from the right CCA with a Vascutek 8 mm synthetic prosthesis). She also had stroke 2 years prior to hospitalization which manifested with loss of consciousness, right leg paresis, fine motor disability in both hands.

According to the duplex scanning of the brachiocephalic arteries, two months prior to hospitalization she had occlusion of the left CCA and left subclavian artery, the carotid-subclavian alloprothesis anastomosed "end-to-side" with the proximal segment of

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the right CCA (critical 90 % stenosis of the prosthesis), 45 % stenosis of the bifurcation of the left CCA.

According to multi-slice computed tomography (MSCT) data of the thoracic aorta and brachiocephalic arteries: condition after arthroplasty of the aortic arch, shunting of the left brachiocephalic arteries from the right CCA, hemodynamically significant (90 %) stenosis of the proximal anastomosis. Since the summer of 2019, the patient began to notice episodes of a rare pulse with presyncope phenomena, a sick sinus syndrome was diagnosed, for which a pacemaker was implanted. It is known that 2 weeks prior to the current hospitalization she had a syncope with short-term right-sided leg weakness. She received conservative treatment at the Department of Neurology of the City Clinical Hospital after which she was transferred to the National Medical Research Center for Therapy and Preventive Medicine of the Ministry of Healthcare of the Russian Federation for endovascular treatment.

Selective angiography of the brachiocephalic arteries revealed: occlusion of the CCA orifice and left subclavian artery, 95 % stenosis of the proximal anastomosis of the carotid-subclavian bypass (Figure 1).

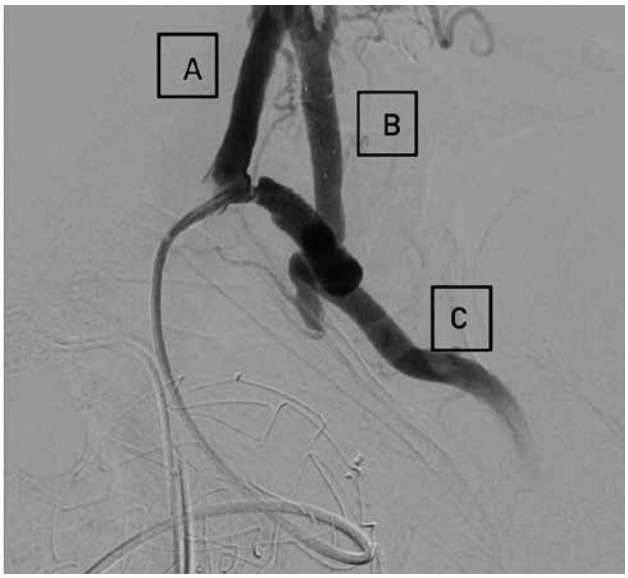

Figure 1. Stenosis of the proximal anastomosis of the carotid-subclavian bypass
A — right CCA;
B — left CCA (graft installed);
C — left subclavian artery (graft installed).

Considering neurological symptoms, as well as the anatomical characteristics of the carotid-subclavian bypass stenosis that can be improved by endovascular treatment (favorable angle of alloprosthesis), it was decided to perform angioplasty with stenting of the proximal anastomosis using cerebral embolic protection device.

The right femoral artery approach has been chosen for the intervention. An introducer and the Judkins Right 7Fr guiding catheter were installed. The guiding catheter was passed beyond the area of stenosis to the proximal part of the left internal carotid artery. The cerebral embolic protection device with 7 mm diameter was installed ("umbrella filter" that prevents microembolization of cerebral arteries by particles of atheromatous debris during the stent dilatation and implantation). The occluded section of the proximal anastomosis of the carotid-subclavian bypass was predilated with 5x20 mm balloon catheter that had 10 atm. inflation pressure (Figure 2).

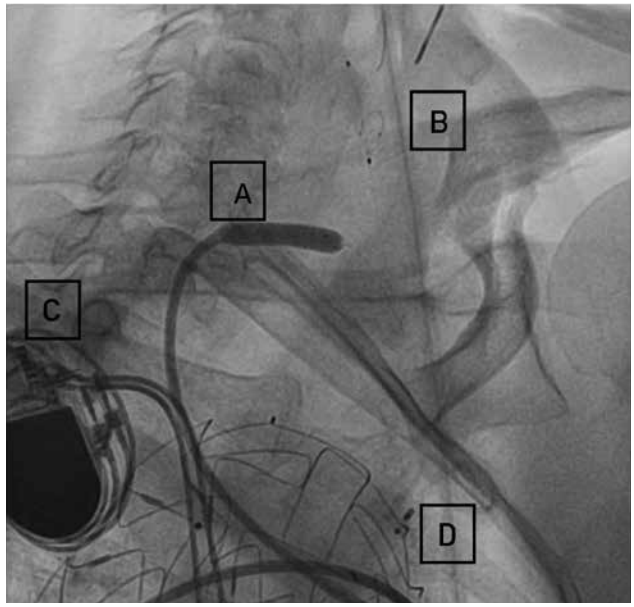

Figure 2. The predilation of the occlusion with 5×20 mm balloon catheter
A — balloon catheter;
B — distal part of the cerebral embolic protection device;
C — cardiac pacemaker;
D — contours of previously implanted stent-graft of the aortic arch.

For more precise stent placement at the carotid-subclavian shunt and the control of its implantation, the left radial access has been chosen. The stent was implanted using angioscopy control and maximum coverage of the proximal anastomosis area (Figure 3).

During the operation, the patient was conscious, verbally communicated with the stuff, did not present any active complaints or focal neurological signs and her hemodynamic parameters remained stable. The

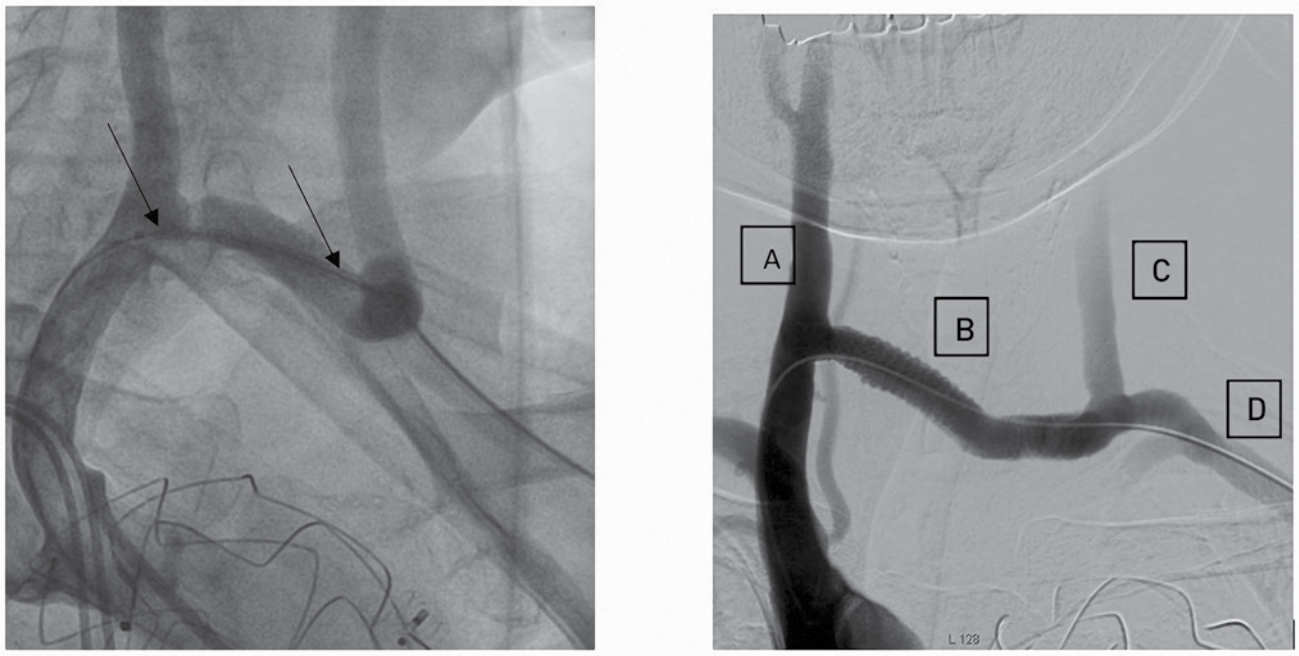

Figure 3. Left: stent placement (arrows indicate the contours of the stent); Right: control angiogram after stent placement.
A — right CCA; B –carotid-subclavian alloprosthesis; C –left CCA; D — left subclavian artery.

patient was discharged two days after the surgery. In the immediate and late postoperative period (control visits at months 3 and 12), she was stable and has no neurological pathology.

Study results

78-year old woman was admitted to the National Medical Research Center for Therapy and Preventive Medicine of the Ministry of Healthcare of the Russian Federation with complaints of dizziness and unsteadiness, diffuse compressive headaches, memory loss, tinnitus, as well as syncopal episode and short-term right-sided hemiparesis 2 weeks prior to hospitalization. Additional examination revealed a hemodynamically significant (90 %) stenosis of the proximal anastomosis of the carotid-subclavian shunt. Successful stenting was performed in the restenosis zone with a good angiographic and clinical results, no relapses of neurological symptoms were detected in 12 months after the surgery.

Discussion

Since there is no evidence base on the revascularization strategy of the carotid arteries with previously installed stunts, the decision on the revascularization method should be made by the the surgeon [11]. Patients with multifocal ischemic pathology, previous intervention on carotid arteries and aortic arch present a special category with extremely high risk of periprocedural complications [12]. In the case presented above, considering patient's severe neurological symptoms (history of transient ischemic attack, dizziness and unsteadiness, diffuse compressive headaches, memory loss, tinnitus), as well as favorable anatomical characteristics of carotid subclavian shunt lesion for endovascular treatment, it was decided to perform endovascular revascularization. This method, due to high risk of complications in the early postoperative period, has been chosen as the safest, especially with the use of cerebral embolic protection device that allowed to perform the surgery without circulatory arrest.

Conclusion

In this clinical case we demonstrated the possibilities of modern endovascular treatment in patients with extremely high cardiovascular risk. The minimal invasive procedure, as well as the availability of necessary surgical instruments and the presence of experienced operator, significantly reduced perioperative complications and provided good long-term prognosis.

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in the International heart and vascular disease journal

Edit from December, 2021

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The General criteria for the publication of articles in the International heart and vascular disease journal are the relevance, novelty of the material and its value in theoretical and/or applied aspects.

The languages of publications are Russian and English. Journal is peer-reviewed, with multistage editing. Editorial board is presented by the leading cardiologists from different countries and Russia.

International heart and vascular disease journal aims to ensure that its publications fulfill the requirements of international publishing standards, such as the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, by the International Committee of Medical Journal Editors, ICMJE (http://www.icmje.org), and the recommendations by the Committee on Publication Ethics, COPE (http://www.publicationethics.org.uk).

All clinical trials should be performed and described in full accordance with the CONSORT standards (http://www.consort-statement.org), observational research — STROBE (http://www.strobe-statement.org), systematic reviews and meta-analyses — PRISMA (http://www.prisma-statement.org), diagnostic accuracy — STAR (http://www.stard-statement.org).

I. The International heart and vascular disease journal accepts the following manuscripts:

1) *Original papers* present the results of clinical studies. The word limit is 3.000 (including references, tables, and figure legends). The maximal number of references is 15. The structured abstract should contain 5 sections (**Aim, Material and Methods, Results, Conclusion**, and **Key words**), and be no longer than 300 words.

2) *Lectures*, or clinically oriented reviews, are written by experts in broader areas of medicine. Lectures could be focused on epidemiology, pathophysiology, diagnostics, treatment, and prevention. The word limit is 5.000 (including references, tables, and figure legends). The maximal reference number is 80. The unstructured abstract is no longer than 150 words.

3) *Literature reviews* are focused on more specific topics, compared to lectures. The word limit is 4.500 (including references, tables, and figure legends). The maximal reference number is 50. The unstructured abstract is up to 150 words.

4) *Clinical case* is a brief report on a complex diagnostic problem and its solution, or a description of

a rare clinical observation. The word limit is 600 (including references, tables, and figure legends). The maximal number of references is 5. No abstract is required.

5) *Clinical opinion* informs the readers on the topics of cardiovascular medicine and related disciplines. The word limit is 2.500 (including references, tables, and figure legends). The maximal number of references is 15.

The journal accepts for publication original phase 2, 3 and 4 clinical studies. Literature reviews should be based on sources not older than 5 years.

II. Information about the article, which includes the following sections, is combined into a single file "letter (cover)":

1) the manuscript is not under consideration in another edition; 2) has not been previously published; 3) contains a full disclosure of the conflict of interest; 4) all authors meet the criteria of authorship, it was read and approved; 5) the author (s) are responsible for the power of attorney submitted in the manuscript materials. 6) all contact information of the author responsible for correspondence; 7) information about previous publications of the authors on the same topic or pre-publication.

If the manuscript is a part of the thesis, it is necessary **to specify** the estimated terms of thesis defense.

The "letter of direction (accompanying)" should be made out on one or two sheets. Using the form of the official institution-at the choice of the author's team. In the address: "to The chief editor of the Russian cardiology journal, academician of RAS, Professor Oganov R. G.". The signatures of **all authors** should be placed at the bottom.

"Directional (cover) letter" is scanned. File format. jpeg attached as an additional file of the manuscript.

The absence of a letter or incomplete text of the letter (not containing the above items) is the basis for refusal to accept the manuscript for consideration.

III. Registration on the Website and information about the authors.

1. **Any of the authors can submit an article to the journal.** Usually it is the one who then conducts correspondence with the editorial office and to whose mail notification letters come (when submitting a manuscript through the site, you can choose to send notifications to all authors).

The author registers on the site, entering his full name. In the form to be filled in when submitting an article, all authors and all additional information (places of work, positions, academic titles, institutions, ORCID — all authors) are indicated.

If the author has several places of work, it is written: 1. "The name of the institution..." 2. "Name of institution."... The name of the institution is written in abbreviated form, for example, Moscow state University, Moscow. Brackets are not put.

How to fill in the article metadata: all data that is entered in the "article metadata" must exactly match the data specified in the text of the article!

1. Authors ' names (you can not write in full, the format of the journal provides for the publication of names and initials. Therefore, in the "Windows", where the name and patronymic of the authors are written in capital letters with a dot (example: A.).

2. Names of institutions (write the official name. At the same time — there is a reduction of Federal, STATE, etc.; the quotation marks are placed; Ministry of health of Russia, a city without the letter G.

3. Positions and titles (using traditional abbreviations: PhD, senior researcher, leading researcher, PhD, C.b.N., MD), head reduces to the head., then write the full name of the laboratory/Department / Department; Director, head, Professor — is not reduced.

4. The order of the authors. Authors ' priority should be entered into the system in accordance with the order of the article. The movements are made by small arrows "top" / "bottom", which are located under the data of each of the authors. The data of the author responsible for the correspondence, put a dot in a circle denoting this information. Other authors point do not put.

5. Summary. Sections of the abstract should exactly match the sections prescribed In the rules for authors. If the sections are not correct, the Editors will ask to correct them. What the authors are currently publishing on the site will then be included in all systems after the final publication. Be careful!

6. Making literary references. Submitted article will not be reviewed until the correction of literary references in accordance with the rules for authors is made. The authors "forget" and somewhere to remove point (such inconsistencies can be corrected in the Revision), but if the design literature is radically different from what is required or present hyperlinks,

the Editors will not start with the article to eliminate errors.

7. Keyword. They are written with a small letter, separated by a semicolon. At the end put a point. In the text of the article the keywords are written separated by commas.

A file is prepared separately in Word, which is then sent as an additional file. The file must contain:

1. Title page of the manuscript. The title of the manuscript is written in capital letters, without hyphenation, in bold. Initials and surnames of authors-Ivanov I. I., Petrov P. p. the full name of organization (s) from which (s) there was a manuscript, the city, the country is Given. Footnotes are in Arabic numerals after the authors ' names and before the names of institutions.

Example of design:

THE PREVALENCE OF RISK FACTORS OF NONCOMMUNICABLE DISEASES IN THE RUSSIAN POPULATION IN 2012–2013. THE RESEARCH RESULTS OF THE ESSE-RF

Muromtseva G. A. [1], Kontsevaya A. V. [1], Konstantinov V. V. [1], Artamonova G. V. [2], Galaganova T. M. [3],...

[1] FGBU State research center of preventive medicine of the Ministry of health of Russia, Moscow;

[2] FGBU Research Institute of complex problems of cardiovascular diseases SB RAMS, Kemerovo;

[3] RD VPO North Ossetian state medical Academy, Vladikavkaz;..., Russia.

2. Information about the authors, where indicated: full name, place of work of all authors, their positions, ORCID; full contact information is required for one (or more) of the author and includes e-mail, available phone number.

All members of the group of authors should meet all four criteria of authorship set forth in the ICMJE recommendations: 1) concept and design development or data analysis and interpretation, and 2) manuscript justification or verification of critical intellectual content, and 3) final approval for publication of the manuscript, and 4) consent to be responsible for all aspects of the work, and assume that issues relating to the thoroughness and diligent execution of any part of the study submitted are duly investigated and resolved. This information should also be contained in the document.

If the submitted material has authors who do not meet the criteria of authorship, but have made some contribution to the work, they should be listed in this document and at the end of the article in the section of Acknowledgements.

3. Information on conflict of interest / funding.

The section contains the disclosure by all authors of possible relations with industrial and financial organizations that may lead to a conflict of interest in connection with the material presented in the manuscript. It is desirable to list the sources of funding for the work. If there is no conflict of interest, it is written: "Conflict of interest is not declared." Information on the existence of a conflict of interest should also be reflected in the Conflict of interest section at the end of the article.

4. Information about grants. Should be mentioned at the end of the article in the section Acknowledgements and at the end of the section Material and methods — with a full description of the role of the source of funding in the performance of work (design, information collection, analysis, data interpretation, etc.).

5. Information and ethics in the study.

Example of design:

The study was carried out in accordance with the standards of good clinical Practice (Good Clinical Practice) and the principles of the Helsinki Declaration. The study Protocol was approved by the Ethical committees of all participating clinical centers. Prior to being included in the study, written informed consent was obtained from all participants.

This information should also be reflected in the Material and methods section of the article.

All additional information (permits, questionnaires, etc.) can be requested from the authors in addition to the preparation of the work for printing.

6. Information on overlapping publications (if available).

7. Copyright. The use of any material (tables, figures) marked with a copyright icon in the article should be confirmed by a special permission from the author or publisher.

8. Information about the obtained consent in patients for the study.

Obtaining consent from patients for the study should also be reflected in the Material and methods.

9. For all clinical trials: information about the registration and placement of data on the study in any public register of clinical trials. The term "clinical study" refers to any research project that affects people (or groups of subjects) with/or without a com-

parative control group, studies the interaction between interventions to improve health or the results obtained. The world health organization offers the primary register: International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/network/primary/en/index.html). The clinical study is considered to be reliable in a group of more than 20 patients.

10. The number of words in the article (excluding summaries, sources of literature, figure captions and tables), the number of tables and figures.

The absence of an information file or incomplete text (not containing the above items) is the basis for refusal to accept the manuscript for consideration.

IV. Manusctipt submision check-list

Since the main file of the manuscript is automatically sent to the reviewer for» blind review», it should not contain the names of the authors and institutions. The file contains only the following sections:

1. Article title
2. Summary with key words
3. List of abbreviations
4. Text
5. Acknowledgements (if any)
6. List of references
7. Tables, figures (if they can be embedded in the text of Word format).

The article title is written in capital letters (PREVALENCE of RISK FACTORS...), the end point is not needed. The title should clearly reflect the purpose of the work.

Summary with key words-sections are drawn up each with a separate line, highlighted in bold. The abstract should contain only those sections that are described in the rules for authors. For example, there is no section "Relevance" in the summary. The authors prescribe the relevance of their work in the introductory section of the manuscript.

List of abbreviations — when compiling a list of abbreviations to the article, including text, tables and figures, only those used by the author 3 or more times are included. Usually shrink often used in manuscripts of the terms (e.g., hypertension, CHF FC) and title of clinical trials (SOLVD, TIMI, HOPE).

The first reference to an abbreviation is always accompanied by the full spelling of the abbreviated concept, and the abbreviation is indicated in brackets. For example, blood pressure (BP); heart rate (HR). Capital letters are more often used to denote abbreviations. If abbreviations are used only in tables and figures, and are not used in the text, they should not be included in the list of abbreviations, but should be given a transcript in the note to the table or figure. The summary of the article, as a separate document, is subject to the same rules as the article (abbreviations are made when they are used 3 or more times).

Abbreviations should be generally accepted and understandable to the reader, in accordance with the generally accepted norms in the scientific literature. Undesirable abbreviations that coincide in writing with others that have a different meaning.

Abbreviations in the list of abbreviations are written in alphabetical order, separated by commas, in solid text, using "dash". **Example of design:** BP-blood pressure, HR-heart rate.

Text — the text of the manuscript of the original works should be structured: Introduction, Material and methods, Results, Discussion and Conclusion. The text of reviews and lectures can be unstructured.

Text is printed on A4 sheet, font size — 12 pt, line spacing — 1.5, margins 2 cm on all sides. The system of SI units is used for processing the material, the% sign is put through a space from the number, the value of p is written with a semicolon: $p < 0.0001$; the value of n is written with a small letter (n=20); signs >, <, ±, =, +, — when numerical values are written without a space; the value of "year" or "year" is issued — 2014 or 2002–2014.

The article should be carefully verified by the author (s). The authors are responsible for the correctness of citation, doses and other factual materials.

Introduction — it is necessary to describe the context and prerequisites of the work (what is the essence of the problem and its significance). It sets certain goals or describes the object of the study, or a hypothesis that needs to be tested by comparison or observation. Only those sources that directly indicate the problem are cited.

Statistics — all published materials are reviewed by an expert in statistics and must meet "Uniform requirements for manuscripts submitted to biomedical journals" (Uniform Requirements for Manuscripts Submitted to Biomedical Journals, Ann Intern Med 1997, 126: 36–47). In the preparation of the statistical part of the work it is recommended to use special guidelines, for example, the European journal of cardiology: www.oxfordjournals.org/our_journals/eurheartj/for_authors/stat_guide.html

Statistical methods are described in detail in the Material and methods section.

Acknowledgements — all participants who do not meet the authorship criteria should be listed in the Acknowledgements section, which is located at the end of the article before the Literature section.

Making graphs, diagrams and drawings — tables and figures should provide the reader with visual information, be interesting and educational. They should be placed after the text of the article, as the reviewer and editor look at the manuscript as a whole. However, to print in the journal (at the stage of creating a layout) graphics, diagrams and drawings are required in electronic form in the formats "MS Excel", "Adobe Illustrator", "Corel Draw", "MS PowerPoint", photos with a resolution of at least 300 dpi.

The names of the graphs and figures, as well as notes to them should be placed under the figure/graph or placed at the end of the article.

These files are referred to as additional files. Figures should not repeat the materials of the tables.

Tables should contain the compressed, necessary data. Each table is placed at the end of the text (after the list of references) with the number, name and explanation (note, abbreviations).

The tables should clearly indicate the dimension of the indicators and the form of data (M±m; M±SD; Me; Mo; percentiles, etc.). All figures, totals and percentages should be carefully verified, and also correspond to the mention in the text. The explanatory notes are given below the table, if necessary. The footnotes must be in the following order: *, †, §, ||, ¶, #, **, †† etc.

Abbreviations should be listed in a footnote below the table in alphabetical order (for tables its list of abbreviations!).

Each first mention of a figure or table in the text is highlighted with a yellow marker. If a reference to a figure or table is included in the sentence, the full spelling of the word «figure 1», «table 1» is used; if the words are enclosed in brackets, the abbreviation is used (Fig. 1), (table. 1).

Providing the main file of the manuscript with the names of the authors or institutions is the basis for refusal to accept the manuscript for consideration.

V. The list of references.

In the form to fill in when submitting the article provides a list of cited literature (section — Literature).

Literary references are listed in the order of citation in the manuscript. The text refers to the serial number of the cited work in square brackets [1] or [1, 2]. Each link in the list is on a new line. All documents referred to in the text should be included in the list of references.

References to works that are not in the list of references and Vice versa, references to unpublished works, as well as to works of many years ago (>10 years) are not allowed. The only exceptions are rare highly informative works. Especially close attention to this item, please pay to those authors who submit "literature Review".

The bibliographic description contains the names of the authors up to three, after which, for domestic publications should indicate "et al.", for foreign — "et al." When citing articles from journals indicate in the following order the output: the name and initials of the authors, the name of the source, year, volume, number, pages (from and to). When citing articles from the collections indicate the output: name, initials, title, title of the collection, place of publication, year of publication, page (from and to).

If you want to make a quotation of the authors ' names in the text, you must specify the name of the first author with the initials, the year of work. Example design: Smith AA, et al. (2018).

With the purpose of increase of citation in the journal is the transliteration of Russian sources with the use of the official languages in the following order: the authors and the journal title is transliterated in the Latin alphabet, and the name of the article is semantic transliteration (translation into English). The name of the source where the work is published is transliterated in Latin if the source (journal) does not have an official name in English).

All Russian-language sources of literature should be presented in the transliterated version of the model given below.

The author (s) are responsible for the correctness of the data given in the references.

The list of references should correspond to the format recommended by the American National organization For information standards (national Information Standards organization — NISO), adopted by the National Library of Medicine (NLM) for databases (Library's MEDLINE/PubMed database) NLM: http://www.nlm.nih.gov/citingmedicine Oh? The names of periodicals may be abbreviated. Usually this

form of writing is accepted by the publisher; it can be found on the website of the publisher, or in the list of abbreviations Index Medicus.

Mandatory all articles DOI specified, all books ISBN. References to dissertations, patents, theses and any collections without output and ISBN are not accepted.

Examples of link design:

Article citation:

Smith A, Jones B, Clements S. Clinical translation of tissue-engineered airway. Lancet. 2008;372:1201–09. doi:10.00000/0000–0000-.

Russian-language sources with transliteration:

Bart BYa, Larina VN, Brodskyi MS, et al. Cardiac remodelling and clinical prognosis in patient with chronic heart failure and complete left bundle branch block. Russ J Cardiol. 2011;6:4–8. Russian. Барт Б. Я., Ларина В. Н., Бродский М. С., и др. Ремоделирование сердца и прогноз больных с хронической сердечной недостаточностью при наличии полной блокады левой ножки пучка Гиса. Российский кардиологический журнал. 2011;6:4–8. doi:10.15829/1560-4071-2011-6-4-8.

Book:

Shlyakhto EV, Konradi AO, Tsyrlin VA. The autonomic nervous system and hypertension. SPb.: Meditsinskoe izdatel'stvo; 2008. Russian. Шляхто Е. В., Конради А. О., Цырлин В. А. Вегетативная нервная система и артериальная гипертензия. СПб.: Медицинское издательство; 2008. ISBN 0000–0000.

Chapter:

Nichols WW, O'Rourke MF. Aging, high blood pressure and disease in humans. In: Arnold E, ed. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London/Melbourne/Auckland: Lea and Febiger; 1990. p.398–420. ISBN 0000–0000.

Russian chapter:

Diagnostics and treatment of chronic heart failure. In. National clinical guidelines 4th ed. Moscow: Silicea-Polygraf; 2011. pp.203–93. Russian Диагностика и лечение хронической сердечной недостаточности. В кн: Национальные клинические рекомендации. 4-е издание. М.: Силицея-Полиграф; 2011.сс.203–96. ISBN 0000–0000.

Webpage:

Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004)

All sources of literature are checked for correctness through the system of the Russian electronic library. Significant errors in citation or duplication of the source are the reason for the return of the manuscript to the authors for revision.

VI. Preparation of manuscript.

The author prepares the following documents to upload the manuscript to the site:

The main file Is the text of the article (the system renames it after loading, so it does not matter how it is called).

Additional files-Directional (accompanying) letter, Information file with the Title page, information about the authors and disclosure of conflicts of interest, files with pictures.

For more information on placing articles on the website you can read http://cardiovascular.elpub.ru/jour/announcement

VII. Copyright and publishing policy.

This section regulates the relationship between the editorial Office (Publisher) of *International heart and vascular disease journal* (the "editorial Office") and the author or group of authors who submitted their manuscript for publication in the *International heart and vascular disease journal* (the "Author").

The author, by sending the article to the Editor, agrees that the editorial Board of the journal shall be transferred to the exclusive property rights to use the manuscript (transferred to the Editorial Board of the journal material, including such protected objects of copyright as photos of the author, drawings, diagrams, tables, etc.), including the reproduction in print and on the Internet; distribution; translation into any languages of the peoples of the world; export and import of copies of the journal with the article of the Author for distribution, to bring to the public.

The editorial Board reserves the right to reduce and edit the materials of the manuscript, to carry out scientific editing, to reduce and correct articles, to change the design of graphs, drawings and tables to bring into line with the design of the journal, without changing the meaning of the information provided.

When using the article, the editors have the right to supply it with any illustrated material, advertising and allow third parties to do so.

The editorial Board has the right to assign the rights received from the Author to third parties and has the right to prohibit third parties from any use of materials published in the journal for commercial purposes.

The author guarantees that he has exclusive rights to use the submitted material. In case of violation of this guarantee and the presentation of claims to the editorial Board, the Author independently and at his own expense undertakes to settle all claims. The editorial Board is not responsible to third parties for violation of the Author's guarantees.

The Author retains the right to use the published material, its fragments and parts for personal, including scientific and teaching purposes.

The Author transfers the above rights to the Editors without limitation of their validity period, in the territory of all countries of the world without limitation, including the territory of the Russian Federation.

The rights to the manuscript are considered to be transferred By the author of the editorial Office from the moment of sending an information letter about the acceptance of the manuscript to the press.

Reprinting of materials published in the journal by other individuals and legal entities is possible only with the written permission of the editorial Board, with the obligatory indication of the journal name, number and year of publication.

The editors are not responsible for the accuracy of the information provided by the Author.

The author, sending the manuscript to the Editor, gives permission to use and process personal data.

The editorial Board reserves the right to reduce and correct the articles, to change the design of graphs, figures and tables to comply with the standard of the journal, without changing the meaning of the information provided. In case of untimely response of the author (s) to the request of the editorial Board, the editorial Board may at its discretion make changes to the article or refuse to publish.

Sending to the editor of works that have already been sent to other publications or printed in them is absolutely not allowed. The editors are not responsible for the accuracy of the information provided by the authors. Articles sent in violation of the rules of registration are not accepted by the editorial Board for consideration.

VIII. The procedure for rewiewing manuscripts

1. The manuscript should be sent in electronic form to the Editor through the website — http://www.heart-vdj.com. The manuscript should be drawn up in accordance with these requirements for scientific articles submitted for publication in the journal.

2. The author is sent a notification letter of receipt of the manuscript with the number (ID), which will be used in subsequent correspondence. The author can track the stages of work on his manuscript through the site. Since the process of bringing the manuscript to the necessary standards takes enough expert time, the payment for the initial review of the article was introduced, which the author (s) are required to carry out after the article is posted on the site.

3. The manuscript must pass the primary selection: the Editorial Board has the right to refuse publication or send comments to the article, which must be corrected by the Author before reviewing.

— checking the completeness of the manuscript: if you do not comply with the requirements of the Rules for the authors to complete the manuscript or its design, the Editors have the right to refuse to publish or in writing to require to send the missing materials or to correct the version already downloaded to the site.

— Manuscripts are checked in the "Antiplagiat" system. The originality of the manuscript should be at least 75 %. We expect manuscripts submitted for publication to be written in an original style that involves new thinking without the use of previously published text. Manuscript with originality below 75 % shall not be admissible.

4. All manuscripts submitted to the journal are sent to one of the permanent reviewers or an independent expert according to the profile of the research.

5. The review process is anonymous both for the Author and for the reviewers. The manuscript is sent to the reviewer without the names of the authors and the name of the institution.

6. The editorial Board informs the Author of the results of the review by e-mail.

7. If the reviewer makes a conclusion about the possibility of publication of the article and does not make significant corrections, the article is given to the expert on statistics and after a positive report is accepted for further work.

8. If the reviewer makes a conclusion about the possibility of publication of the article and gives instructions on the need for its correction, the Editorial Board sends the review to the Author with a proposal to take into account the recommendations of the reviewer in the preparation of a new version of the ar-

ticle or to refute them. In this case, the Author needs to make changes to the last version of the article file, which is located on the site (download file from the site, make changes and place the corrected article again, after removing the primary (uncorrected) version). The revised article is re-sent for review, and the conclusion is given that all the recommendations of the reviewer were taken into account. After receiving a positive response of the reviewer, the article is given to the expert on statistics and after a positive report is accepted for further work.

9. If the reviewer makes a conclusion about the impossibility of publication of the article. The author of the reviewed work is given the opportunity to read the text of the review, if he does not agree with the conclusions of the reviewer. In case of disagreement with the opinion of the reviewer, the Author has the right to provide a reasoned response to the Editor. The article can be sent for re-review or for approval to the editorial Board. The editorial Board or its authorized editor shall send its response to the Author.

10. All manuscripts that have been reviewed and evaluated by an expert in statistics are submitted to the editorial Board, which decides on the publication. After the decision on the admission of article for publication, the Editorial office inserts the publication of the article in terms of publications. Information about the annual (thematic) plan of publications is placed on the website of the journal.

11. The decision to publish a manuscript is made solely on the basis of its significance, originality, clarity of presentation and compliance of the research topic with the direction of the journal. Reports on studies in which negative results are obtained or the provisions of previously published articles are challenged are considered on General grounds.

12. Original reviews are kept in the Editorial office for 5 years from the date of publication.

13. In case of a decision to refuse to publish an article, its archive copy remains in the electronic system of the editorial Board, but access to it by editors or reviewers is closed.

IX. The manner of publication of manuscripts

1. According to the requirements of the Higher attestation Commission, the journal provides priority for post-graduate and doctoral works, the period of their publication depends on the expected date of protection, which the authors must specify in the primary documents attached to the manuscript.

2. Each issue of the journal is formed by a separate Executive editor appointed by the editor-in-Chief and/or editorial Board. It is the responsibility of the editor-in-charge to select high-quality articles for publication, and he can be guided by both thematic principles and a separate scientific direction.

3. All selected articles are submitted to the scientific editor and proofreader. After creating the layout of the article and editing it, the article will be available to the Author through the site. At this stage, it will be possible to send comments on the text of the article. The author is obliged to send his / her consent to the publication or his / her comments within the established time specified in the cover letter.

4. The editorial office does not send the author's copy by mail or PDF of the article by e-mail, access to the published numbers is open.

Subscription to the printed version is carried out by half a year (through subscription agencies).

X. After the publication in the journal

1. Information on publication is distributed in the following scientific citation databases: Russian science citation index, CYBERLENINKA and others. The article is assigned a DOI index and the full text is publicly available on the journal's website.

2. Information about the publication of the issue is distributed by mailing of The Cardioprogress Foundation and in social networks.

3. We expect the authors of the articles to actively make efforts to bring the results of their research to the public, namely: to have a personal page on the Internet (personal page), to monitor and update your profile ORCID and RecsearcherID, to involve colleagues in their work through social networks.

XI. Revocation or correction of articles

The full text of the journal's policy on Revocation and correction of articles is available in the information section on the website. The editors follow COPE Recommendations issued by the Committee on publishing ethics (COPE) — http://www.publicationethics.org.uk. in cases:

Editors of journals should consider the opinion of the publication, if:

they have clear evidence of the unreliability of the information published, either as a result of conscious actions (for example, falsification of data), or due to good faith errors (for example, errors in calculations or experiments); the findings have been previously published in another publication and there is no proper reference, authorization and justification for re-publication (i.e. duplicate publication).); it is plagiarism; describes unethical research.

Editors of journals should consider the concerns, if:

they received information about the authors ' inappropriate actions, but there is no clear evidence of such behavior; there are arguments that the results of the work are unreliable, and the institution in which the authors work is not going to find out the truth; they believe that the investigation into the alleged violations committed by the authors in connection with the publication has either not been or will not be fair, impartial and convincing; the authors ' violations are being investigated, but the results are not expected soon enough.

Journal editors should consider making amendments if:

a small part of the rest of the high-quality publication is unreliable (especially because of conscientious errors); the list of authors / sponsors contains errors (i.e., it does not contain someone who is worthy to be an author, or a person who does not meet the authorship criteria).

In most cases, a review is not appropriate if:

authorship needs to be changed, but there is no reason to doubt the validity of the findings.

XII. Position E-log backup (if journal is no longer published)

The purpose of backup is to prevent loss of information in case of hardware, software, critical and crisis situations, etc.

Information of the following main categories is subject to backup: — personal information of authors (personal directories on file servers); — pdf of published articles; — information about literary links to the article in the DOI system.

All this information is publicly available in The system of the Russian citation index on the website of the Electronic library www.elibrary.ru

XIII. Journal subscription

Information on subscriptions is available on the journal website in the section "Subscription":

XIV. Journal subscription

The name of the journal in English is International heart and vascular disease journal.

Official sites where information about the journal is placed:

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