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Updated European guidelines for the prevention of cardiovascular diseases. Analytic review

Frailty syndrome in patients with rheumatoid arthritis and the role of cardiovascular comorbidities

A Rare Case of Aortic Arch Anomaly with Subclavian Steal Syndrome

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Contents

Editor's Welcome

Dear colleagues!

We present the 33nd issue of the International Heart and Vascular Disease Journal that includes the leading article, original and review articles, as well as clinical case report.

The leading article section is opened by the analytic review of updated European guidelines for the prevention of cardiovascular diseases. Experts from 12 countries prepared the manuscript. The new guidelines focus on the personalized and stepwise intervention in clinical practice. Estimation of 10-year risk of cardiovascular complications with specific scales depending on age for four categories of countries with various risk is recommended. Population level approach is one of the main points in cardiovascular diseases prevention that include complex measures at the governmental and regional levels for various population segments.

The original articles section presents three articles. Authors of the article dedicated to the effective management of high blood pressure in elderly and senile patients with arterial hypotension with various combinations of medications, conclude that the development of optimal personalized treatment plans is needed considering adverse effects. The second article aimed to assess the effect of combination therapy with rosuvastatin and ezetimibe lipid parameters on lipid profile. Authors conclude that it can be recommended for the correction of lipid disturbances in patients with high or very high cardiovascular risk. The third article analyzed the incidence and clinical features of the frailty syndrome in patients with rheumatoid arthritis as well as its association with cardiovascular diseases and cardiovascular risk factors. It has been established that 40.6% of patients have frailty that is associated with older age, disorders of nutritional status, more cardiovascular diseases, and high cardiovascular risk.

The review article section present work dedicated to the issue of implementation of neural network in the risk stratification for mortality after myocardial infarction. The advantages of neural network over widely used prognostic scales are discussed. The examples of the development of such models are presented.

Clinical case report describes a rare case of aortic arch anomaly with subclavian steal syndrome. The possibilities of functional diagnostics methods of aorta and its branches anomalies are demonstrated.

The reports section presents the highlights from XI International Forum of Cardiology and Internal Medicine that was held online on 22-24 March, 2022.

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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Updated European guidelines for the prevention of cardiovascular diseases. Analytic review

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The review article presents the analysis of the main issues of updated European guidelines for the prevention of cardiovascular diseases (CVD). Previous European guidelines were dedicated to the risk stratification and the prevention of risk factors (RFs), when 2021 European Society of Cardiology guidelines on CVD prevention focuses on the personalized and stepwise intervention in clinical practice. Estimation of 10-year fatal and nonfatal CVD risk with SCORE2 is recommended in patients aged from 40 to 69 years, and SCORE-OP - for people aged ≥70 years. Four risk scales are proposed for countries depending on their risk group: low, moderate, high, very high. It is recommended to take into account not only gender and age, but also ethnicity and geographic factors during the development of prophylaxis strategy. It is also essential to personalize treatment by using stepwise method. After initial RF treatment and the achievement of RF treatment goals, the individual residual risk for recurrent CVD should be considered. The presence of comorbidities should be considered during treatment – the treatment of one pathology

should not negatively affect the course of other diseases. Lifestyle management is the key method in atherosclerosis-related CVD prevention. Population level approaches is one of the main points in CVD prevention and include complex measures at the governmental and regional levels for various population segments.

Keywords: *prophylaxis, RFs, cardiovascular diseases.*

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Cardiovascular diseases associated with atherosclerosis are the main cause of mortality worldwide. The disease burden of cancer in Europe has been increasing over the last years. However, coronary artery disease

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(CAD) and ischemic stroke are still the main causes of death [1]. According to the World Health Organization (WHO), Western Europe countries have low and medium cardiovascular risk (CVR), while countries of Eastern Europe and the former Soviet Union remain at high and very high risk that requires active interventions, including primary prevention measures [2].

Cardiovascular events prophylaxis by the reduction of cardiovascular risk is the main priority in primary prevention [3]. Previous European guidelines focused on risk stratification and RF (RF) prevention, while 2021 updated European Society of Cardiology recommendations places a strong emphasis on personalization and stepwise intervention in clinical practice [4].

Here we present the main updates on cardiovascular complications (CVC) risk assessment and the principles of preventive interventions based on analyzed clinical guidelines. According to the new guidelines, it is necessary to assess CVR not only in apparently healthy people, but also in older people with diagnosed cardiovascular diseases, as well as in people with diabetes mellitus (DM) that allows to personalize preventive measures. This approach should also be applied in patients with other diseases, including DM, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD).

The updated scale predicts not only fatal, but also non-fatal events that increases CVR numerical expressions.

For the first time non-high-density lipoprotein cholesterol instead of total cholesterol is used for the calculation of CVR, which requires the analysis of full lipid panel.

For the assessment of 10-yar CVR in people aged 40-69 years SCORE2 scale is recommended, and SCORE2-OP is recommended in people ⩾70 years. Moreover, the cut-off for CVR varies in three age categories (<50, 50-69, ⩾70 years) [5.6]. Scales are calibrated to four clusters of countries depending on CVD risk group: low, moderate, high, and very high.

It has been established that psychosomatic stress is associated with atherosclerosis-related CVD risk [7]. Social factors also play a pivotal role in the prognosis and CVD development [8].

Family history should be enquired about routinely, and a positive family history of premature CVD should be considered in CVD risk assessment [9] Current data does not support the use of genomic risk scores in CVD risk assessment in primary prevention. CVR prevalence varies in different age groups. For example, 2.5% has low CVD risk at <50 years, 5% — at 50-69 years, 7.5% - at 70 years. According to the new guidelines, patients with low CVR do not require RFs correction, patients with high CVR need correction, and in patients with very high CVR the correction of RFs is mandatory [4].

Not only gender and age, but also, ethnic, and geographic factors should be considered during the development of prophylaxis strategy.

Treatment goals also need to be personalized using a stepwise approach. The term residual risk was introduced for patients with established CVD that is defined as the risk assessed after initial lifestyle changes and RF correction [4].

One of widely discussed issues of updated guidelines is comorbidities and CVD risk. This can be explained by the fact that the number of patients with non-cardiovascular comorbidities is constantly increasing. Adverse effects of prescribed medications should be considered during treatment strategy development in patients with comorbidities. The management of comorbid diseases should be personalized and not focus on the disease separately. The updated document addresses the principles for the prevention of complications in a number of comorbidities.

Cancer and CVD have common RFs. High risk of CVC in patients with cancer can be explained not only by chemotherapy-induced cardiotoxicity, but also by the presence of RFs [10].

CKD is independent CVD RF, and CVD is the main cause of death in patients with CKD [11]. In all CKD patients, appropriate screening for CVD and changes in albuminuria monitoring is recommended. A reduction in albuminuria by approximately 30% upon starting renin-angiotensin-aldosterone system (RAAS) inhibition is associated with improved cardiovascular and kidney outcomes.

COPD is the main CVD RF including stroke and heart failure (HF) [12]. Patients with COPD tend to have atrial fibrillation (AF), ventricular tachycardia, and sudden cardiac death. All patients with COPD should be screened for CVD. Medications for COPD treatment are safe for patients with CVD.

Non-alcoholic fatty liver disease is associated with other cardiometabolic RF, therefore, screening for other cardiometabolic RFs is recommended for this group of patients.

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Migraine, especially with aura, is independent RF for ischemic stroke and CAD [13]. Vascular risk of subjects with migraine may be magnified by cigarette smoking and by the use of combined hormonal contraceptives.

Sleep duration that varies significantly up or down from the optimum of 7 h are associated with increased CV risk [4].

The risk of psychosomatic diseases increases by 2.2 times in patients with CVD that negativity affect their prognosis [14]. For the other hand, symptoms of anxiety and depression are associated with the development of CVD and with a worse prognosis in those with existing CVD (CAD, arterial hypertension (AH), AF, HF).

Preeclampsia and pregnancy-related hypertension are associated with a higher risk of CVD. Polycystic ovary syndrome confers a significant risk for future development of DM [4].

Erectile dysfunction (ED) is associated with future cardiovascular events and mortality in men of reproductive age. CVD risk should be assessed in men with ED [4].

Lifestyle change is an important point in atherosclerosis-related CVD risk prevention. Traditionally, it includes physical activity, healthy diet, and bad habits reduction [15].

Regular physical activity is the basis of CVD prevention. All adults are recommended to perform aerobic physical activity and reduce sedentary lifestyle [16].

Healthy diet reduces the risk of cardiovascular and other chronic diseases. A shift from an animal- to a more plant-based food pattern can reduce the frequency of CVD [17].

The achievement and maintenance of optimal body mass through lifestyle changes positively affect major RFs such as: blood pressure (BP), lipid and glucose metabolism. Pharmacotherapy and bariatric surgery can be recommended in high-risk individuals when lifestyle changes are ineffective [4].

Smoking cessation reduce CVD risk and is one of the key strategies in its primary and secondary prophylaxis. The following medications can be recommended: nicotine replacement therapy, varenicline, and bupropion individually or in combination [18].

Interdisciplinary approach can be recommended for the correction of psychosomatic disorders. Stress reduction and life quality improvement positively affect CVD outcomes [7].

The reduction of low-density lipoproteins (LDL) cholesterol followed by the maintenance of target level, reduces the risk of cardiovascular events. Lowering LDL cholesterol with statins, ezetimibe, and, if needed, PCSK9 inhibitors, decreases the risk of CVD proportionally to the absolute achieved reduction in LDL cholesterol [19]. When LDL cholesterol goals according to level of risk cannot be attained, LDL cholesterol should be reduced by ≥50%.

When AH is suspected, the diagnosis should be confirmed by repeated office BP measurement or 24-hour BP monitoring. Lifestyle interventions are indicated for all patients with AH and can delay the need for drug treatment or complement the BP-lowering effect during treatment. BP-lowering drug treatment is recommended in adults when office BP is ≥ 40/90 mmHg and in all adults when BP is ≥ 160/100 mmHg. BP treatment goals are lower in updated guidelines compared with previous recommendations for all patient groups, including older patients. A simple drug treatment algorithm should be used to treat most patients, based on combinations of a renin-angiotensin system (RAS) blocker with calcium channel blockers or thiazide/thiazide-like diuretics. Beta-blockers and mineralocorticoid receptor antagonists may also be used where there is a guideline-directed indication [20]. Patients with high or very high risk can be recommended with statin therapy for primary prevention. Antiplatelet therapy is indicated for secondary prevention in patients with AH.

A multifactorial approach, including lifestyle changes, is critical for patients with type 2 DM. It is known that the management of hyperglycemia reduces the risk of microvascular complications and, to a lesser extent, the risk of CVD. Glycemic targets should be relaxed in older patients. New antihyperglycemic drugs are particularly important for patients with type 2 DM with existing CVD and HF or renal failure [21].

Intensive treatment of hyperglycemia in patients with type 1 DM reduces the risk of micro- and macrovascular complications and premature mortality. The target of 6.5 - 7.5% (48-58 mmol/mol) of HbA1c is recommended. Metformin is not recommended in patients with type 1 DM to lower CVD risk. Dapagliflozin can be recommended for use in patients with type 1 DM, although it increases the risk of diabetic ketoacidosis. Other RFs reduction, in particular smoking, BP, and cholesterol levels, remains an important measure to lower CVD risk in type 1 DM.

All patients with established CVD regardless of their clinical state require mono- or dual antithrombotic therapy. The updated guidelines present new data on antithrombotic therapy schemes for atherosclerosis-related CVD risk prevention. The management of CVD RFs associated with particular disease (CAD, HF, cerebrovascular disease, peripheral artery disease) require multifactorial approach [22, 23].

Population-level approaches are important for CVD prevention. Prospective studies have shown the effectiveness of multifactorial prevention the governmental and regional levels [24]. Population-level approaches for CVD prevention include approaches to increase regular physical activity, healthy diet adherence, tobacco and alcohol use cessation. These skills should be developed from school age. Daily psychical activity at school should be practiced for at least 3 hours a week. Overall, global progress to increase physical activity has been slow, largely due to lack of awareness and investment. Adolescence is the most vulnerable period for the uptake of smoking, with lifelong consequences. Previous prevention campaigns reduced tobacco use in girls much less than in boys. High taxes on all tobacco products are the most effective policy measure to reduce smoking uptake by the young. Within the 10 voluntary targets of Word Health Organization to reach in 2025 is a 30% relative reduction in mean population salt intake. Structural measures such as: product reformulation, limitations on marketing to children, taxes on unhealthy foods, and nutrition labelling will improve healthy food choices. The measures for the reduction of harmful use of alcohol are cost-effective (increasing alcoholic beverage minimum unit pricing, restricting access to alcoholic beverages, and implementing comprehensive restrictions on advertising and the promotion of alcoholic beverages) [4].

Environment, air pollution, and climate change issues are significant factors in CVD and other chronic disease prevention. Environmental exposure has taken on new urgency, as air pollution, in addition to its health effects, has also been ascribed as a major contributor to climate changes, notably through the burning of fossil fuels leading to increasing emissions of carbon dioxide.

Conclusion

Thus, personalized approach to CVD prevention with the implementation of CVD risk score and a stepwise treatment-intensification approach is more complex compared with general prevention strategy, however, it addresses patients' diversity and individual characteristics in clinical practice.

Principles of lifestyle changes, psychosocial factors, behavioral and biological parameters, as well as the social status of the patient should be considered during the development of individual strategy for CVD prevention and rehabilitation.

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Effective management of high blood pressure in elderly and senile patients with arterial hypotension

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Abstract

Objective *of this study was to evaluate and compare the incidence of arterial hypotension and orthostatic hypotension in elderly and senile patients with hypertension and coronary artery disease (CAD) treated with a combination of angiotensin-converting enzyme inhibitors (ACEi) and calcium channel (CCB) or beta-blockers.*

Materials and methods. *The current study included 97 female and male participants from Krasnodar region with uncontrolled hypertension and CAD. Participants were randomized into two groups. In the first group, target blood pressure (BP) was achieved with ACEi with CCB, in the second — with ACEi and beta-blockers that were administered for 12 weeks. All patients completed questionaries, had BP checked in the office and undergone 24-hour blood pressure monitoring prior to starting treatment. We also assessed the risk factors for falls according to The Morse Fall Scale (MFS), orthostatic hypotension. After 12 weeks of treatment, office BP was re-checked and 24-hour BP monitoring with systolic and diastolic hypotension time index (HTI) calculations were performed.*

Results. *After 12 weeks of treatment, statistically significant reduction of office BP readings, heart rate (HR), main 12-hour BP monitoring parameters was noted in the patients from both groups. Target BP was achieved in 41 patients from the first group and 39 patients from the second group. Reduction in the main 12-hour BP monitoring parameters didn't depend on the administered anti-hypertensive drug combination. Fall risk according to MFS was significantly lower in patients treated with amlodipine plus perindopril compared with those who took bisoprolol and perindopril (20 points vs 27 points respectively, p<0.05). Patients treated with amlodipine and perindopril lost balance in the «standing with feet together» position in 19.1 % of cases, in the «tandem» or «semi-tandem» position — in 28.6 % of cases that is lower than in the bisoprolol and perindopril group (28.3 % and 39.1 % cases respectively, p<0.05). SHTI in amlodipine and perindopril group was lower than in the bisoprolol and perindopril group during the day (16 % vs 25 %, respectively, p<0.05) and night (18 % vs 28 %, respectively, p<0.05).*

Conclusion. *According to the results of this study, further research of high blood pressure treatment risks, the effects of different pharmacologic agents and their combinations on arterial hypotension seems reasonable and is needed for the development of optimal personalized treatment plans.*

Keywords: *arterial hypertension, arterial hypotension, orthostatic arterial hypotension, 24-hour blood pressure monitoring, antihypertensive therapy, personalized therapy.*

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Arterial hypertension is one of the leading risk factors of cerebro- and cardiovascular disease leading to disability and mortality [1]. Public health and social measures increase the number of elderly and senile patients and, therefore, the prevalence of hypertension and atherosclerosis including coronary artery disease (CAD) [2].

Current clinical guidelines recommend treating hypertension in patients with CAD with the renin-angiotensin system (RAS) inhibitors such as angiotensin-converting enzyme inhibitors (ACEi), beta-blockers and calcium-channel blockers (CCB). Lower blood pressure (BP) targets are recommended for most patients. Fixed combinations of antihypertensive medications are preferred as first-line therapy [3, 4].

Mortality risk remains high in patients with CAD even with well-controlled hypertension [2]. Pathophysiology of hypertension complications in elderly and senile patients, adverse events risk stratification and possible ways to improve prognosis are still of special interest for physicians and researchers.

Frequent and prolonged hypotension and inadequate hemodynamic reaction in orthostasis are important prognostic factors in patients with arterial hypertension. The prevalence of orthostatic hypotension in general population is 6–35 %, increases with older age and peaks in elderly and senile patients [6]. According to some authors, orthostatic hypotension increases the risk of ischemic cardiovascular complications and mortality in elderly and senile patients [8]. Orthostatic hypotension plays and increasingly important role in real clinical practice. Back in 2013 in Europe evaluation of orthostatic hypotension was recommended only for a specific group of patients. By 2018, it has been implemented as a necessary part of physical exam of all patients with CVD [3]. One of the most common symptoms of orthostatic hypotension is a drug-induced vertigo that causes additional limitations to a normal everyday life and increases the risk of falls and injury [7].

Chronic biological aspects of SBP changes in older patients with hypertension should also be considered. Recent studies have identified the association between excessive daytime SBP reduction with increased risk of dementia in the elderly [9]. Moreover, the large-scale Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) has shown the benefits of 24-hour BP monitoring over office BP in cardiovascular outcomes prediction [10].

Testing for orthostatic hypotension and 24-hour blood pressure monitoring in older patients with hypertension and atherosclerosis is still insufficiently used. There are no orthostatic reactions risk calculators that would include not only patient's medical history and orthostatic testing but also chronobiologic features of 24-hor BP profile and the effects of medications. Further research and developments are needed to create optimal patient-oriented approach and safe management approaches for older hypertensive individuals as today more intensive BP control is mostly preferred.

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Materials and methods

The current study included female and male patients aged 65–85 years with uncontrolled arterial hypertension stage 1–2 (BP>140/90 mmHg while on previous antihypertensive therapy) and stable atherosclerosis.

Or study was carried out in accordance with Good Clinical Practice standards and the Declaration of Helsinki. Study protocol was approved by the local Independent Ethics Committee. Prior to participation all patients signed informed consent.

Exclusion criteria were congenital heart defects, cardiomyopathy, history of arterial revascularization, acute stroke and/or myocardial infarction in the last 6 months, diabetes, autoimmune disease, chronic disability, malignancies, and infectious disease at the moment of enrollment and inability to follow the protocol.

All patients were randomized into two groups: 1st group (n=42) included patients treated with a 5–10/5–10 of amlodipine and perindopril (Prestance, Sevier, France) in the morning; 2nd group (n=45) included patients treated with 2.5–5/5–10 of bisoprolol and perindopril (Prestilol, Sevier, France) in the morning. Patients from both groups were also administered 10–20 mg of rosuvastatin per day and 100 mg of aspirin per day.

First, we collected medical history and asked the participants to complete questionaries, initiated antihypertensive treatment and determined regular follow-ups. We performed general physical and anthropometric exams (BP, height, weight, waist and hip circumference), laboratory tests, ECG, 12-hour BP monitoring with «Petr Telegin» (BPLabVasotens, Russia) device. The patients continued with their everyday activities with BP checked every 25 minutes during the day and every 50 minutes at night. Data analysis included night (n) and day (d) SBP and DBP values, elevated SBP and DBP time index, SBP and DBP variability index and the magnitude of the morning BP elevation.

According to the study design, drug dosages were elevated if antihypertensive treatment wasn't effective enough after 4 weeks.

Secondly, 12 weeks after, we evaluated office SBP and DBP, the frequency of target BP and performed 24-hour blood pressure monitoring. Mean dosage of medications after 12 weeks of treatment were: amlodipine and perindopril — 7.2/6.7, bisoprolol and perindopril — 4.2/8.9.

Lipid lowing therapy was corrected according to the current clinical guidelines, mean dose of rosuvastatin was 15.7 in the first group and 16.2 in the second group.

We assessed the risk factors for falling according to The Morse Fall Scale (MFS). Orthostatic test (BP check after 7 minutes supine and 1–3 minutes after standing up) was used as functional testing. The test was considered positive if SBP reduced for >20 mmHg and DBP > 10 mmHg. We also assessed the presence of balance problems with the 10-second balance test. The patient was asked to hold three positions «feet together», «semitandem» and «tandem» [5].

Repeat 24-hour blood pressure monitoring was performed to assess not only the magnitude but also hypotension time index (HTI). Hypotension was identified as SBP<130 mmHg and DBP<70 mmHg. There are no strict criteria for night-time hypotension for patients >65 years so we considered SBP < 105 mmHg and DBP < 55 mmHg as low.

Statistical analysis was carried out using Statistica 10.0, StatSoft. To assess the differences between groups we used Mann–Whitney U test for independent samples and The Wilcoxon signed-rank test for dependent variables. Two and more qualitative values were compared with Chi-squared test. P<0.05 was considered statistically significant.

Results

We examined 97 male and female participants from Krasnodar region.

Clinical characteristics are presented in Table 1.

Table 1. **Clinical characteristics patients included in the study**

Parameter	Value
Age, years	76 (64–85)
Duration of hypertension, years	19 (12–24)
Body mass index, k^2	25.1 (22.5–29.6)
Office SBP, mmHg	154 (141–162)
Office DBP, mmHg	89 (78–95)
HR, beats per minutes`	69 (62–84)

Note. DBP — diastolic blood pressure; HR — heart rate; SBP — systolic blood pressure.

BP significantly reduced after 12 weeks of treatment in both groups. Target BP levels were achieved in 41 patients from the 1st group and 39 patients from the 2nd group. HR reduced more in patients from the 2nd group (p<0.05) due to the effects of beta-blockers (Table 2).

Table 2. **Blood pressure and heart rate changes after treatment**

Parameter	At baseline		After 12 weeks of treatment	
	GROUP 1 (N=42)	GROUP 2 (N=45)	GROUP 1 (N=42)	GROUP 2 (N=45)
SBP, mmHg	155 (142–165)	157 (145–168)	132 (123–137)*	135 (122–142)*
DBP, mmHg	93 (85–101)	96 (89–105)	78 (67–81) *	80 (68–84) *
HR, beats per minutes`	81 (78–85)	83 (80–86)	78 (68–82)*	65 (60–72)*

Note. DBP — diastolic blood pressure; HR — heart rate; SBP — systolic blood pressure.

Table 3. **Changes of 24-hour BP parameters after 12 weeks of treatment with amlodipine and perindopril**

Parameter	Baseline (n=42)	After 12 weeks of treatment (n=42)	Δ %
SBP 24, mmHg	156 (149–165)	130 (122–141)	— 17.4*
DBP 24, mmHg	94 (85–98)	80 (75–83.5)	— 12.8*
SBPd 24, mmHg	157 (152–166)	132 (124–142)	— 16.1*
DBPn 24, mmHg	96 (82–99)	84 (75–88)	— 8.7*
SBP TId, %	92 (78–97)	22 (19–59)	— 62.9*
DBP TId, %	87 (75–95)	19 (5–29)	— 61.4*
SBPd variation, mmHg	21 (14–25)	12 (1–19)	— 21.5*
DBPd variation, mmHg	16 (10–19)	10 (6–12.5)	— 25.9*
SBPn, mmHg	154 (132–162)	127 (117–135)	— 14.9*
DBPn, mmHg	88 (75–91)	77 (68–80)	— 13.2*
SBP TIn, %	93 (80–95)	21 (6–30)	— 59.1*
DBP TIn %	78 (68–90)	18 (3–25)	— 58.9*
SBPn variation, mmHg	20 (13–25)	14 (6–18)	— 24.5*
DBPn variation, mmHg	19 (9–22)	10 (4–13)	— 25.5*

Note. SBP — systolic blood pressure; DBP — diastolic blood pressure; TI — time index; d — day; n — night; Δ % — parameter reduction in % after 12 weeks of treatment; * — p<0.05 considered statistically significant.

Table 4. **Changes of 24-hour BP parameters after 12 weeks of treatment with bisoprolol and perindopril**

Parameter	Baseline (n=45)	After 12 weeks of treatment (n=45)	Δ %
SBP 24, mmHg	157 (150–167)	132 (125–140)	— 16.5*
DBP 24, mmHg	92 (88–94)	80 (75–83.5)	— 13.2*
SBPd 24, mmHg	159 (152–169)	135 (122–140)	— 15.1*
DBPn 24, mmHg	93 (85–96)	85 (76–85)	— 8.3*
SBP TId, %	90 (79–96)	20 (19–59)	— 64.9*
DBP TId, %	85 (77–92)	15 (31–43)	— 62.4*
SBPd variation, mmHg	20 (15–26)	14 (12–17)	— 23.4*
DBPd variation, mmHg	16.5 (11.5–20)	11 (8–13.5)	— 29.2*
SBPn, mmHg	152 (136–160)	125 (115–132)	— 15.2*
DBPn, mmHg	86 (79–89)	78 (70–81)	— 12.3*
SBP TIn, %	91 (84–96)	19 (5–27)	— 62.8*
DBP TIn %	78 (68–90)	15 (3–23)	— 61.1*
SBPn variation, mmHg	19 (14–23)	13.5 (8–17.5)	— 23.7*
DBPn variation, mmHg	18.5 (11–20)	12.5 (6.5–10)	— 24.6*

Note. SBP — systolic blood pressure; DBP — diastolic blood pressure; TI — time index; d — day; n — night; Δ % — parameter reduction in % after 12 weeks of treatment; * — p<0.05 considered statistically significant.

After 12 weeks of treatment all other 24-hour BP monitoring parameters also decreased (p<0.05) (Table 3, 4). The magnitude of parameter changes didn't depend on the combination used (table 3, 4).

Patients in the amlodipine-perindopril group were at significantly lower risk of falling according to MFS compared with patients who took bisoprolol-perindopril (20 points vs 27 points, respectively, p<0.05) (Table 5).

Table 5. **Risk of falling according to The Morse Fall Scale**

Drug combinations	Points
amlodipine + perindopril (n=42)	20 (16–30)*
bisoprolol + perindopril (n=45)	27 (18–36)

Note. * – p<0.05 was considered statistically significant when comparing the frist and second groups.

Moreover, less patients in the amlodipine-perindopril group had balance defects: only 19.1 % of patients

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lost balance in «feet together» position and 28.6 % in «tandem» or «semitandem» positions compared with patients from bisoprolol-perindopril group (28.3 % and 39.1 %, respectively, p<0.05) (Table 6).

Table 6. **Prevalence of balance deficits in both groups**

Drug combinations	Balance deficits in "feet together" position, n %	Balance deficits in "tandem" and "semitandem" position, n %
amlodipine + perindopril (n=42)	8 (19.1)*	12 (28.6)*
bisoprolol + perindopril (n=45)	13 (28.3)	18 (39.1)

Note. * – p<0.05 was considered statistically significant when comparing the first and second groups.

In patients from the 2nd group BP decreased <130/70 mmHg during the daytime and < 105/55 mmHg at nighttime more compared with the 1st group. Time index of decreased SBP was significantly lower in the amlodipine-perindopril group compared with bisoprolol-amlodipine group during the day (16 % vs 25 %, respectively, p<0.05) and night (18 % vs 28 %, respectively, p<0.05). Time index of decreased DBP changes were similar (Table 7).

Discussion

Safety is one of the most important aspects of modern pharmacologic management of many diseases including hypertension. Personalized approach is usually needed to attain maximal safety. Frailty is elderly and senile patients requires careful selection of pharmacologic agents [11]. After target BP is achieved episodes of hypotension in older patients should be identified and eliminated. In frail patients with multiple comorbidities s long periods of low BP can lead to cognitive dysfunction [12] and increased risk of falling [13]. Individual features of 24-hour BP profile can't be identified during short office visits but are easily diagnosed with 24-hour BP monitoring.

According to modern clinical guidelines, a single agent, primarily, the renin-angiotensin-aldosterone system (RAAS) blockers such as ACEi and ARB, CCB and diuretics can be used in older adults for managing hypotension. However, these patients usually have multiple comorbidities such as various forms of CAD and require combination therapy.

Guidelines on hypertension present a lower BP cut-off that is significantly higher than in the definition of arterial hypotension (BP<100/60 mmHg). Therefore, some patients are in the «grey» zone between target BP according to clinical guidelines and arterial hypotension. As such, we compared the incidence of arterial hypotension (including orthostatic hypotension) and its signs: increased risk of falling according to MFS and balance deficits during functional tests in elderly and senile patients who've achieved target BP with ACEi and CCB or ACEi and beta-blockers.

After 4 weeks of antihypertensive treatment target office BP was achieved in both groups (in 95 % of patients in the first and in 93 % in the second group). The 24-hour BP monitoring showed reduction of all parameters in both groups. In the amlodipine and perindopril group patients were at a higher risk of falling according to MFS, higher incidence of balance deficits and lower prevalence of orthostatic hypotension compared with the bisoprolol and perindopril group.

These results may be possibly explained by some beneficial effects of perindopril and amlodipine in patients with chronic cerebral ischemia often seen in older patients with atherosclerosis and episodes of elevated BP. ACEi weren't associated with reduced cerebral, myocardial, or renal blood flow and their use didn't lead to reduced organ ischemia and increased collateral blood flow. Perindopril also reduces the level of angiotensin II, inhibits endothelial apoptosis, increases bradykinin and NO synthesis that have antiatherosclerotic effects [14]. CCB have anti-ischemic effects and their use isn't associated with arterial hypotension as they don't decrease normal BP. Dihydropyridine CCB don't have significant effects on carbohydrate and lipid metabolism have cerebroprotective and anti-atherosclerotic role [15].

According to our results, the prevalence of arterial hypotension and orthostatic hypotension is relatively high in older patients with hypertension and atherosclerosis. Various combinations of antihypertensive

Table 7. **Hypotension time index according to 24-hour BP monitoring**

Drug combinations	TId SBPd (%)	TId DBPd (%)	TId SBPn (%)	TId DBPn (%)
amlodipine + perindopril (n=42)	16 (5–23)*	19 (4–28)*	18 (6–25)*	24 (9–31)*
bisoprolol + perindopril (n=45)	25 (8–35)	22 (5–27)	28 (10–38)	26 (11–33)

Note. TId — time index of decreased blood pressure; SBP — systolic blood pressure; DBP — diastolic blood pressure; * – p<0.05 was considered statistically significant when comparing the frist and second groups.

agents have different effects on the development on these complications. Physicians should thoroughly choose antihypertensive treatment and use additional effectiveness control measures.

Conclusion

According to our results, high prevalence of hypotension and orthostatic hypotension in older patients with hypertension and atherosclerosis requires further research of drug-induced arterial hypotension. Not only direct antihypertensive mechanisms but also long-term effects should be considered when making any prognosis and developing personalized treatment plans.

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The state of the lipid profile in patients with hyperlipidemia during statin and combination therapy

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Abstract

Objective. *To assess the dynamics of lipid parameters in patients with hyperlipidemia during statin and combination therapy with rosuvastatin and ezetimibe.*

Materials and methods. *The lipid profiles of 120 patients aged from 45 to 65 years with primary isolated and combined dyslipidemia with very high cardiovascular risk who admitted to Kursk City Clinical Emergency Hospital. Primary hyperlipidemia and diagnosed with laboratory and morphometric parameters were analyzed. Patients with secondary hyperlipidemia according to their history were excluded from the study. All the patients from study group were diagnosed with I–II functional class of angina pectoris. Each patient was advised to follow hypolipidemic diet and prescribed with rosuvastatin for 8 weeks; in case when target parameters were not achieved, the ezetimibe was added to therapy.*

Results. *During the 8-week treatment with 10 rosuvastatin of patients with coronary heart disease (CHD) and isolated or combined hyperlipidemia the following statistically significant changes of lipid profile were detected: the decrease of total cholesterol from 30.8 % to 28 %, low-density lipoproteins (LDL) from 40 % to 31 %, atherogenic index from 42 % to 43 % and the increase of high-density lipoproteins (HDL) from 9.9 % to 11 %, respectively. At the 8th week of statin monotherapy, 35 % of patients did not achieve target levels of LDL cholesterol and were prescribed with combined therapy with the addition of 10 ezetimibe in order to decrease the level of lipids.*

Conclusion. *The combination of rosuvastatin+ezetimibe showed high effectiveness and can be recommended for the correction of lipid disturbances in patients with high or very high cardiovascular risk.*

Keywords: *hyperlipidemia, statins, ezetimibe, coronary heart disease, hypolipidemic therapy.*

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Introduction

Cardiovascular diseases (CVDs) are the main cause of death and disability among adults in the world. There is a tendency to increase of CVD morbidity due to high prevalence of modified risk factors: smoking, alcohol, obesity, arterial hypertension (AH), type 2 diabetes mellitus (T2DM), low physical activity, etc. [5]. One of the main elements in the pathogenesis and progression of CVD, especially coronary artery disease (CAD) is coronary arteries atherosclerosis caused by lipid metabolism disturbances [2, 4].

It is widely known that hypolipidemic therapy can significantly decrease the risk of cardiovascular mortality, myocardial infarction, sudden cardiac death, cerebrovascular accident. Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, which is the main enzyme in cholesterol biosynthesis, are actively used at this stage of the disease. Thus, cholesterol anabolism decreases and the number of low-density lipoproteins (LDL) receptors compensatory increases, thereby their metabolism accelerates, and the amount of antiatherogenic high density lipoproteins (HDL) rises. Thus, statins reduce the level of atherogenic and increase the level of antiatherogenic lipoproteins. Statin IV from the group of MMC–CoA reductase inhibitors that has the highest biological activity is rosuvastatin [4].

In case of insufficient effectiveness of high doses of statins, clinical guidelines for the diagnosis and management of dyslipidemias recommend to add ezetimibe to therapy scheme.

Objective

To assess the dynamics of lipid profile in patients with CAD and primary atherogenic dyslipidemia during rosuvastatin and combination therapy with rosuvastatin and ezetimibe.

Materials and methods

The study included 120 patients aged from 45 to 65 years with CAD: stable angina with verified primary atherogenic hyperlipidemia (HLP) (combined or isolated) and very high cardiovascular risk (CVR). The control group included 29 patients. Laboratory and instrumental parameters were assessed before the treatment and after 4, 8, 24, 48 weeks of pharmacotherapy and included: cardiovascular history assessment using CVD questionnaire developed by Kursk State Medical University of the Ministry of Healthcare of Russian Federation; anthropometry; biochemical profile assessment (lipid profile: total cholesterol (TC), LDL cholesterol, HDL cholesterol, triglycerides (TG), non-HDL-cholesterol, atherogenic index (AI), creatinine, urea, transaminases: alanine aminotransferase (ALT), aspartate aminotransferase (AST), 24-hour electrocardiogram (ECG) monitoring, bicycle ergometry to determine the functional class (FC) of CAD and exercise tolerance).

The main group included male patients aged from 45 to 65 years old with CAD: I–II FC of stable exertional angina with very high cardiovascular risk (TC level >5.5 mmol/l) without contraindications for ezetimibe or rosuvastatin prescription. Patients were not prescribed with statins earlier or discontinued this treatment. Written informed consent was waived from all the participants prior to the study.

Exclusion criteria were: adverse effects of the therapy: ALT or AST levels greater than two times the upper limit of normal, creatinine over 300 μmol/l, myopathies, creatine phosphokinase greater than five times the upper limit of normal, patient's refusal to participate in the research, severe comorbidities.

The study was performed in Kursk City Clinical Emergency Hospital from 2019 to 2020 years (before the COVID-19 pandemic). All the study participants were prescribed with hypolipidemic diet with the re-

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duction of calorie intake. The hypolipidemic diet was the only method of treatment in the control group and in other groups was prescribed together with pharmacotherapy, a survey was conducted to monitor diet compliance at all subsequent stages of the study.

Initially all the patients from the study group were prescribed with rosuvastatin 10, according to the medication guidelines [6]. In case when target level of LDL cholesterol (1.8 mmol/l) was not achieved by the 8 week of the study, 10 of ezetimibe was added to rosuvastatin.

Results

According to the results of the instrumental investigation all patients were diagnosed with CAD and I–II FC of stable angina. We have found concomitant diseases in clinical remission in 70.3 % of study participants (64 patients) in the study group and in 72.4 % (21 patients) in the control group. These diseases did not induce secondary HLP and did not need additional pharmacological treatment. During the assessment of risk factors, it was found that 65.8 % (79 patients) had smoked, and 58.3 % (70 patients) had low psychical activity.

Lipid profile parameters changed significantly during 8-week treatment with 10 of rosuvastatin monotherapy in patients with CAD complicated by isolated HLP: TC level decreased by 30.8 %, LDL cholesterol decreased by 40 %, non-HDL-cholesterol — by 36 %, AI — by 42 %, the level of HDL cholesterol increased by 9.9 %, that shows the effectiveness of IV generation statin in the management of isolated HLP in patients with CAD: stable angina pectoris of I–II FC (figure 1). The dynamics of TG was not statistically significant.

The following changes of lipid profile were established in patients with combined dyslipidemia during 8-week rosuvastatin therapy: TC level decreased by 28 %, LDL cholesterol decreased by 31 %, TG — by 8 %, AI — by 43 %, the level of HDL cholesterol increased by 11 %. These changes were statistically significant and are presented in table 1.

Despite high effectiveness of 8-week treatment with rosuvastatin (10), 35 % of patients did not reach target level of LDL cholesterol that was used as the cut-off point for the assessment of lipid-lowering treatment effectiveness. These patients were prescribed with combined therapy of the ezetimibe (10) and rosuvastatin.

By 48 week of treatment patients with isolated HLP who were prescribed with rosuvastatin+ezetimibe showed additional decrease of TC by 20 %, LDL cholesterol — by 24 %, HDL cholesterol by 27 %, AI by 30 % and the increase of HDL cholesterol by 4.6 % that can be seen from table 2.

The level of TC decreased by 14.5 %, TG by 11.2 %, LDL cholesterol by 21.5 % and the change of HDL cholesterol was not statistically significant — 4.5 % in patients with CAD complicated by combined HLP after 48 weeks of lipid-lowering treatment with two various mechanisms of action. Due to changes in the lipid transport system, the level of AI decreased by 35.3 % and non-HDL cholesterol — by 22.7 %.

One of the study objectives was to evaluate the change in the level of TC by the end of the study compared with baseline after the treatment with rosuvastatin + ezetimibe in patients with combined and isolated primary dyslipidemia. The effectiveness of combination therapy was 5.6 % higher in terms of TC levels in patients with isolated dyslipidemia that can be seen from Fig. 2.

Discussion

Ezetimibe is hypolipidemic medication that inhibit intestinal absorption of cholesterol, which has shown its safety, efficacy, and good tolerability in domestic and foreign studies [3]. Ezetimibe interacts with the NPC1L1 protein, transmembrane cholesterol transporter, that inhibits the absorption of cholesterol in the intestine and from bile acids, and does not affect the absorption of other fat-soluble substances. In response to the decrease of cholesterol that enters the liver, LDL hepatocytes cholesterol receptors activate and their blood clearance increase [5]. For decades, ezetimibe has been considered as an alternative to statins in case of intolerance. Later it was approved as adjunctive treatment to statin therapy when target levels of lipids haven't been achieved [1].

Literature data allow to assess the effectiveness of treatment with statin (primary simvastatin) and NPC1L1 inhibitor (ENHANCE, SEAS, SHARP, IMPROVE-IT) [3]. This therapy involves two mechanisms that determine cholesterol blood level- its synthesis in the liver and absorption in the intestine, therefore, an additional decrease of LDL cholesterol that plays key role in the development and progression of atherosclerosis, varies between 18–25 % [1, 3].

However, studies that performed long-term monitoring (within a year) of the lipid profile in patients with combination therapy with rosuvastatin + ezetimibe

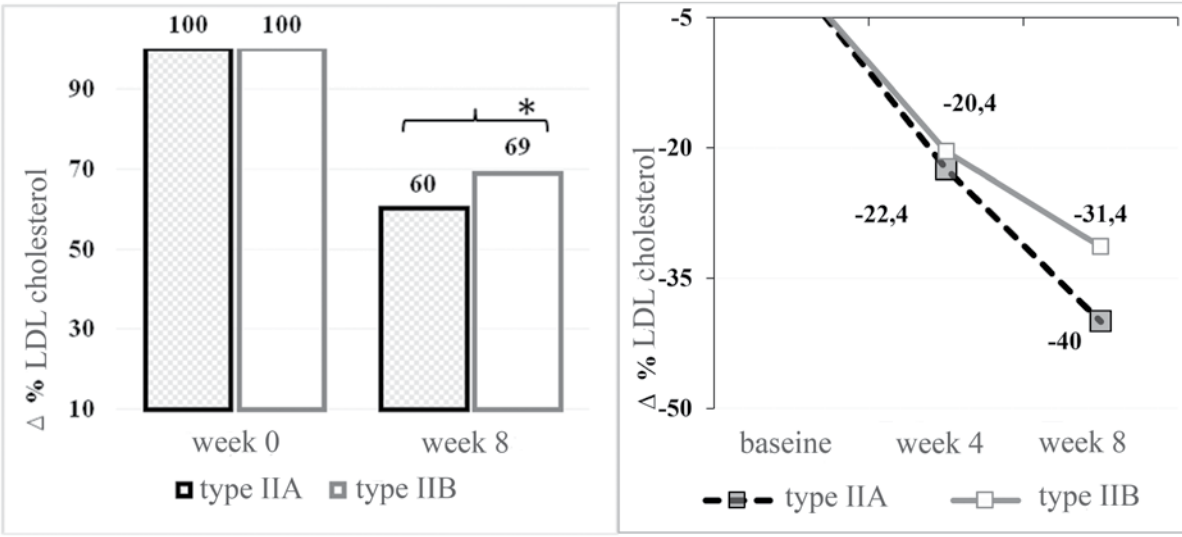

Figure 1. The dynamics of LDL cholesterol at the 8th week of rosuvastatin monotherapy (10 mg/day) in patients with CAD and HLP. Comment. *Changes are statistically significant (p<0.05).

Table 1. **The dynamics of lipid profile in patients with CAD and combined dyslipidemia during 8-week rosuvastatin monotherapy (10)**

Therapy time points	N	Lipid profile parameters, mmol/l		The change of lipid parameters compared with baseline (%)	p-value (Wilcoxon test)
		Median	Interquartile range		
Total cholesterol					<0.001*
Week 0	46	6.10	5.90–6.45		
Week 4	46	5.33	4.36–5.57	−11.62	<0.001
Week 8	46	4.38	3.75–4.60	−28.19	<0.001
LDL cholesterol					<0.001*
Week 0	46	4.27	3.95–4.60		
Week 4	46	3.40	2.41–3.59	−20.37	<0.001
Week 8	46	2.93	1.99–3.49	−31.38	<0.001
HDL cholesterol					0.037
Week 0	46	1.01	0.93–1.10		
Week 4	46	1.06	1.00–1.17	4.95	0.063
Week 8	46	1.12	1.10–1.20	10.89	0.026
Triglycerides					0.05
Week 0	46	1.84	1.78–1.91		
Week 4	46	1.77	1.71–1.82	−3.80	0.063
Week 8	46	1.70	1.60–1.77	−7.61	0.042
Non-HDL-cholesterol					<0.001*
Week 0	46	5.10	4.70–5.44		
Week 4	46	4.17	3.21–4.24	−18.24	0.025
Week 8	46	3.21	2.45–3.39	−37.06	0.022
Atherogenic index					<0.001*
Week 0	46	5.09	4.54 — 5.76		
Week 4	46	3.96	2.63–3.81	−21.11	0.040
Week 8	46	2.91	1.85–3.54	−42.83	0.031

Note. * – differences are significant at p<0.05.

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Table 2. **The dynamics of lipid profile in patients with CAD and isolated dyslipidemia during 48-week combination therapy**

Therapy time points	N	Lipid profile parameters, mmol/l		The change of lipid parameters compared with baseline (%)	p-value (Wilcoxon test)
		Median	Interquartile range		
Total cholesterol					0.019*
Week 8	10	5.76	5.33–6.10		
Week 24	10	5.1	4.89–5.34	–11.45	0.005
Week 48	10	4.60	3.90–4.86	–20.13	0.003
LDL cholesterol					0.022*
Week 8	10	3.96	3.22–4.10		
Week 24	10	3.57	3.06–3.85	–9.85	0.004
Week 48	10	3.01	2.93–3.45	–23.98	0.004
HDL cholesterol					0.449*
Week 8	10	1.09	1.06–1.20		
Week 24	10	1.12	1.10–1.22	2.75	0.241
Week 48	10	1.14	1.10–1.24	4.58	0.018
Triglycerides					0.549*
Week 8	10	1.53	1.30–1.59		
Week 24	10	1.43	1.21–1.60	–6.54	0.100
Week 48	10	1.42	1.17–1.59	–6.58	0.647
Non-HDL-cholesterol					0.022*
Week 8	10	4.51	4.05–4.89		
Week 24	10	3.90	3.75–4.10	–13.52	0.002
Week 48	10	3.29	2.98–3.49	–27.05	0.003
Atherogenic index					0.009*
Week 8	10	4.18	3.85–4.50		
Week 24	10	3.41	3.18–3.76	–18.42	0.031
Week 48	10	2.92	1.48–2.21	–30.14	0.012

Note. * — differences are significant at p<0.05.

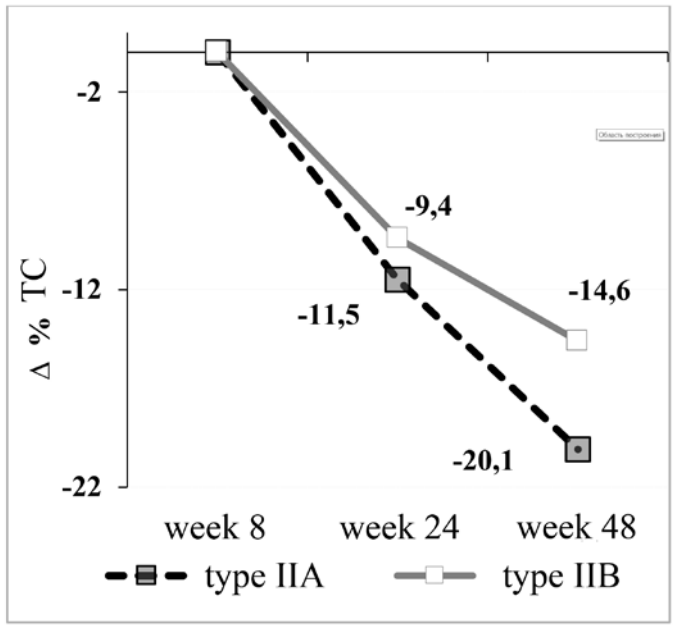

Figure 2. The dynamics of non-HDL-cholesterol by 48 week of combination therapy in patients with CAD and atherogenic HLP.

are scarce. Therefore, there is the need for studies of various statins and ezetimibe combinations that will allow to identify the most effective treatment.

Our study assessed the effectiveness of rosuvastatin + ezetimibe therapy in patients with isolated and combined dyslipidemia that was higher in patients with isolated HLP.

Conclusion

The addition of ezetimibe to the treatment of atherogenic HLP in patients with CAD: I–II FC of stable angina in case when target level of LDL cholesterol has not been achieved led to the improvement of lipid profile parameters. Such results expand the possibilities of primary and secondary prevention of atherosclerosis progression in patients with high cardiovascular risk.

Conflict of interest: None declared.

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Frailty syndrome in patients with rheumatoid arthritis and the role of cardiovascular comorbidities

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Abstract

The objective of the current study was to assess the incidence and clinical features of the frailty syndrome in patients with rheumatoid arthritis (RA) as well as the role of cardiovascular disease (CVD) and cardiovascular disk factors.

Materials and methods. *Our study included 101 patients (86 women and 15 men) aged 45–81 years with confirmed RA of 8 [3; 15] year duration. Frailty syndrome was diagnosed based on the phenotype of frailty developed by Fried LP, et al (2001). We performed electrocardiography (ECG), echocardiography (echo), assessed the risk of CV mortality according to the SCORE scale, CV risk factors, the Health Assessment Questionnaire-Disability Index (HAQ-DI) functional status, nutritional status, dementia screening and calculated Charlson Comorbidity Index.*

Results. *Of all the 101 patients with RA, 41 were frail (40.6 %), 56 (55.4 %) were prefrail and 4 were not frail (4.0 %). Compared with prefrail patients, frail individuals were older (p=0.002) and had higher disease activity (p=0.03) and stage (p=0.003) of RA based on X-ray studies, were in more pain according to the visual analogue scale (VAS) (p=0.001) and had more limitations of their everyday activity according to HAQ-DI (p=0.002). In frail patients wrist dynamometry values (p=0.001) were lower and 4 m walking test time was higher (p=0.004) compared with prefrail. Frail patients were also more prone to unmotivated weight loss (p<0.001), fatigue (p<0.001) and lack of physical activity (p<0.001). However, they were at a lower risk of malnutrition (p<0.001). Frail patients with RA had higher prevalence of CVD (chronic heart failure, coronary artery disease) (p=0.008), and more pronounce left ventricular hypertrophy (p=0.004). Frail patients had higher 10-year cardiovascular mortality risk according to SCORE scale (p=0.02). The majority of these individuals were at a very high risk despite lower levels of total cholesterol compared with prefrail participants (p=0.009). Key cardiovascular risk factors in frail patients were older age, arterial hypertension, and lack of physical activity, in prefrail –hypertension and obesity.*

Conclusion. *The overall prevalence of frailty in patients with RA was 40.6 %. It is associated with older age, more severe RA, disorders of nutritional status, more everyday life limitations, CVD, and high CV risk.*

Keywords: *frailty, prefrailty, rheumatoid arthritis, cardiovascular disease.*

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Introduction

Frailty (senile asthenia) is a syndrome defined as an increased susceptibility to negative environmental factors and associated with loss of ability to self-care and adverse health outcomes [1, 2]. It's initial stage is prefrailty (preasthenia) that can further progress to frailty in the absence of any preventive measures. Frailty syndrome has emerged as a new challenge for internal medicine and is considered a consequence of age-related changes and multimorbidity. Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology characterized by a chronic erosive arthritis and systemic inflammation that causes early disability and reduction of life span [3]. RA can possibly cause accelerated aging and frailty in younger patients. According to some studies, frail patients are at a higher risk of cardiovascular disease (CVD) compared with healthy individuals [4]. On the other hand, chronic inflammation in RA accelerates atherogenesis and increases the risk of CVD [5]. As such, severe CVD is associated with frailty in RA and, at the same time, patients with RA at a higher risk of severe CV complications. Research on frailty syndrome in RA is sparse [6–10] and clinical features and the role of CVD in frail RA patients are not well studied.

The objective of this study was to investigate the incidence and clinical features of frailty syndrome in RA patients and its association with CVD and CV risk factors.

Material and methods

The study protocol was approved by the local Ethics Committee. Informed consents were obtained from all patients prior to participation.

The study included 101 patients (86 women and 15 men) with RA diagnosis according to the ACR/EULAR, 2010 criteria, aged 45–81 years (median of age was 60 years [52; 66])., who were hospitalized to Ivanovo City Hospital № 4 and Ivanovo Regional Clinical Hospital, Ivanovo, Russia. Of all patients, 50 were 60 years of age or younger. The duration of illness was from 0.5 to 40 years (median 8 years [3; 15]) and 15 patients had RA for <1 year)

Most patients (82.2 %) had seropositive RA with moderate activity (DA28, ESR 4.6 [3.7; 5.5]), stage II categorized by radiologic criteria (40.6 %), III functional class (60.4 %). 73 patients (72.3 %) were treated with methotrexate (15 [10; 20] mg/week), 19 (18.8 %) with leflunomide 20. Some patients were administered methotrexate (15 patients) or leflunomide (4 patients) together with biologic drugs. Others were administered hydroxychloroquine and sulfasalazine. 79.2 % of patients took >5 mg of corticosteroids for a prolonged period of time (>3 months). Cumulative dose of steroids was 1475 [300; 10000] mg.

Frailty syndrome was diagnosed according to Fried L. P. et al. (2001) phenotype model that included the following criteria:

Unintentional weight loss ≥4.5 kg in prior year.

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Poor endurance and energy (Fatigue Assessment Scale, FAS) (FAS≥22 points) [11].

Slowness when walking 4 m based on time to walk 4 m, male: ≥7 sec for ≤1.73 m height and ≥6 sec for >1.73 height; female: ≥7 sec for ≤1.59 m and ≥6 sec for >1.59 m.

Low grip strength measured with DK-25 dynamometer (kg-hand grip power, kgp). For men, low grip strength was considered ≤29 kgp for BMI≤24 k^2, ≤30 kgp for BMI 24.1–28 k^2, ≤32 kgp for BMI>28 k^2. For women: ≤23 kgp for BMI ≤17 k^2, ≤17.3 for BMI 23.1–26 k^2, ≤18 kgp for BMI 26.1–29 k^2, ≤21 kgp for BMI >29 k^2.

Low physical activity according to Physical Activity Questionnaire (IPAQ): for 18–39 years — <21 points, 40–65 years — <14 points, >65 years — <7 points [12].

If three or more criteria were present the patient was considered frail, one-two criteria — prefrail, none — nonfrail [13].

Nutritional status was determined using the Mini Nutrition Assessment (MNA) form: normal (≥25 points), risk of malnutrition (17–23.5 points), malnutrition (<17 points) (Guigoz Y et al., 1994). We also assessed the intensity of pain using a Visual Analogue Scale (VAS) and Health Assessment Questionnaire Disability Index (HAQ) (Bruce B. et al., 2003). We examined cardiovascular system: ECG, echocardiography, lipid profile, calculated BMI. 10-year cardiovascular mortality risk was calculated with SCORE (Systematic Coronary Risk Evaluation) scale modified by the European antirheumatic league [14]; SCORE risk was multiplied by 1.5. 10-year mortality risk was evaluated with Charlson comorbidity index (Charlson M. E. et al., 1987).

Statistical analysis was performed with Statistica 6.0 software. Results are presented as median (Me) and quartiles [Q25; Q75]. Quantitative variables were compared with non-parametric Mann–Whitney U test. Qualitative variables were compared with Chi-squared test. Correlation analysis was performed with Spearman's correlation coefficient (r). $p<0.05$ was considered statistically significant.

Results

Frailty was diagnosed in 41 patients (40.6 %), prefrailty in 56 (55.4 %) patients and 4 patients were nonfrail (4.0 %).

Frail patients were older than prefrail (Table 1). However, 14 frail patients were younger than 60 years (44–59 years). Older frail patients had higher RA activity according to DAS28 mostly due to higher levels of C-reactive protein (CRP) and worse subjective evaluation of health. More frail patients had stage III RA, III functional class. Frail patients had more intensive pain according to VAS and more loss of functional activity according to HAQ-DI.

Diagnostic criteria were also different in the study groups. Frail patients had lower values of dynamometry of the right (3 [3; 8] kgp and 8 [5; 13] kgp, p=0.001) and left wrist (4 [2.5; 7] kgp and 6.5 [4; 10] kgp, p=0.025), needed more time to walk 4 m (6.3 [5.0; 8.6] sec and 4.4 [3.4; 5.3] sec, p=0.004), more frequently lost weight unintentionally (28 vs 8 people, χ^2=29.582, p<0.001), had poor endurance and energy (39 vs 27 people, χ^2= 23.953, p<0.001) and had reduced physical activity (19 vs 0, χ^2 = 32.273, p<0.001) Reduced physical activity was associated with lower functional status according to HAQ-DI (r=0.51, p<0.05). Malnutrition risk due to reduced consumption of protein, vitamins and minerals with the same caloric intake was present in the majority of frail patients (27 vs 16, χ^2= 13.332, p<0.001).

Frail patients had higher 10-year mortality risk according to Charlson index (0 [0; 53.0]% and 53 [21; 77]%, p=0.004) due to higher comorbidity burden and older age. Comorbidities present in frail and prefrail

Table 1. **Comparison of frail and prefrail patients according to RA clinical parameters**

Parameters	Frail (n=41) Me [Q25; Q75]	Prefrail (n=56) Me [Q25; Q75]	p
Age, years	63 [55; 69]	57 [49; 65]	0.002
CRP, mg/dl	10.4 [3.2; 30.3]	7.3 [2.0; 23.1]	0.020
VAS, мм	70 [45; 88]	40 [20; 50]	0.001
DAS28 according to CPR	5.0 [4.2; 5.9]	4.4 [3.7; 4.9]	0.003
III radiographic stage, abs.	15	6	0.003
III functional calss, abs.	30	29	0.020
Pain visual self-assessment, mm	70 [50; 80]	50 [30; 60]	0.001
HAQ	2.125 [1.625; 2.5]	1.0 [0.375; 1.625]	0.002
HAQ-DI, abs.	25	6	0.035

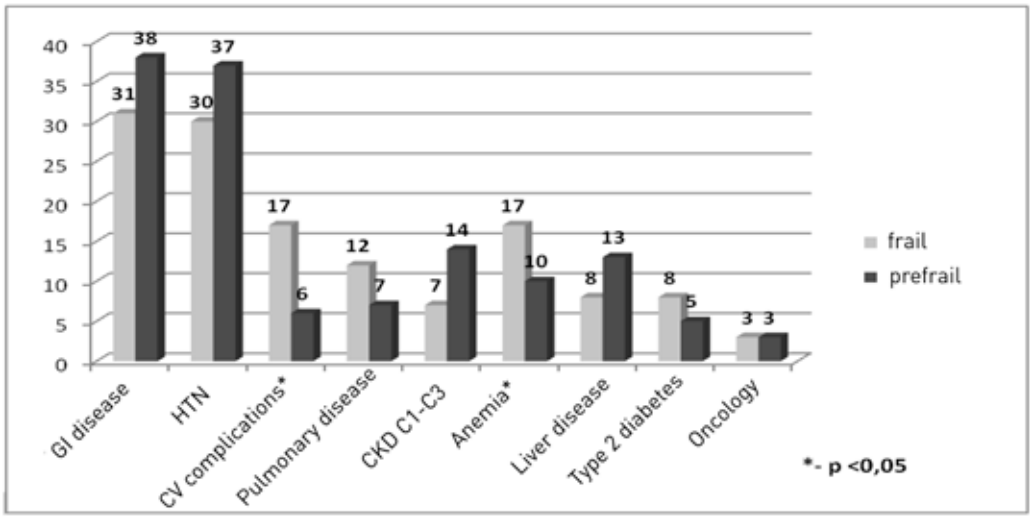

Figure 1. Comorbidities in frail and prefrail RA patients

patients are presented in Figure 1. The majority of patients from both groups had gastrointestinal diseases such as chronic gastroduodenitis, gastric and duodenal ulcers (75.6 % vs 67.9 %, p>0.05), and arterial hypertension (73.2 % vs 66.1 %, p>0.05). More frail patients had light anemia (41.5 % vs 17.9 %; p=0.025), probably due to higher RA activity.

Frail patients had higher prevalence of CVD (41.5 % vs 10.7 %, p=0.008) compared with nonfrail. CVD comorbidities in frail and prefrail RA patients are presented in Figure 2. Congestive heart failure (CHF) was the most prevalent CVD in all patients and was present in most frail patients compared with prefrail (34.1 % vs 7.1 %, p=0.010).

Frail paints had higher 10-year CV mortality according to SCORE (p=0.020). More frail patients were at a very high risk (≥10.0 %) of CV mortality compared with nonfrail (21 vs 17, p=0.04).

SCORE values correlated with age (r=0.67 and r=0.78, p<0.05), hypertension (r=0.43 and r=0.55, p<0.05), CVD (r=0.77 and r=0.58, p<0.05), CHF stage (r=0.60 and r=0.68, p<0.05), Charlson comorbidity index (r=0.70 and r=0.69, p<0.05) and was negatively associated with left ventricular ejection fraction (LVEF) (r=–0.50 and r=–0.64, p<0.05). In many prefrail patients SCORE risk correlated with LV myocardial mass index) (r=0.49, p=0.010), CRP (r=0.35, p=0.010), and was higher in slower patients (r=0.40, p=0.025) and lower dynamometry values (r=-0.34, p=0.005).

CV risk factors and some CV functional parameters in frail and prefrail RA patients are presented in Table 2.

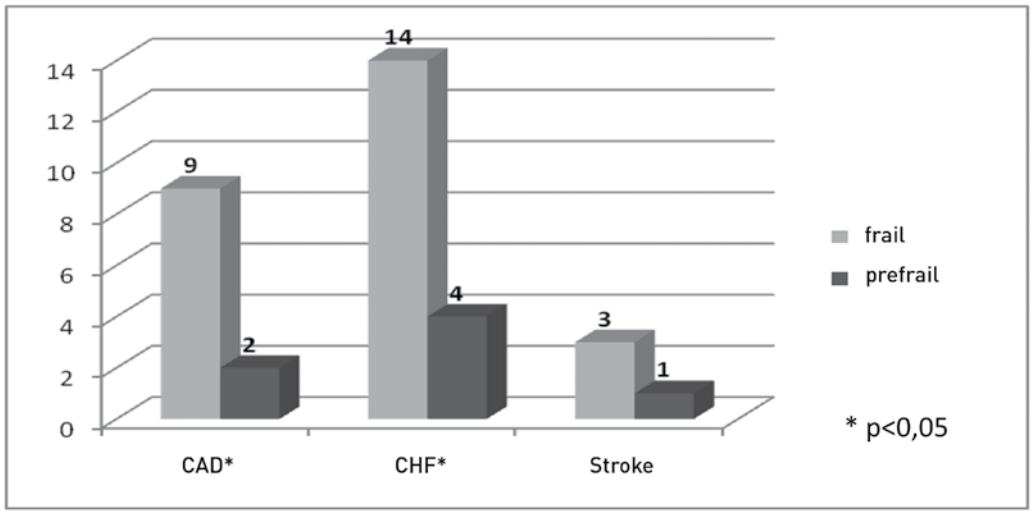

Figure 2. Cardiovascular disease in frail and prefrail patients RA

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Table 2. **Cardiovascular risk factors in frail and prefrail patients with RA**

Parameters	Frail (n=41) Me [Q25; Q75]	Prefrail (n=56) Me [Q25; Q75]	p
BMI, k^2	27.0 [23.6; 31.4]	27.4 [24.9; 31.9]	1.005
Overweight, abs	8	20	0.060
Obesity, abs.	14	21	0.085
Lack of physical activity, abs.	19*	0	0.003
Smokers. abs.	7	9	1.000
Alcohol misuse, abs.	2	0	0.070
Total cholesterol, mmol/l	4.5 [4.0; 5.4]*	5.2 [4.7; 6.0]	0.009
LDL, mmol/l	2.5 [2.2; 3.1]	3.0 [2.8; 3.4]	1.035
HDL, mmol/l	1.6 [1.2; 2.0]	1.3 [1.2; 1.7]	0.900
Hyperuricemia, abs.	3	7	0.550
SBP, mmHg	140 [130; 150]	140 [130; 150]	0.060
LVMM, ^{2}	136 [125; 164]*	120 [108; 132]	0.004
LVEF, %	58 [56; 64]	61 [58; 64]	1.150

Note. *BMI — body mass index (k^2); LDL — low-density lipoproteins (mmol/l); HDL — high-density lipoproteins (mmol/l); SBP — systolic blood pressure (mmHg); LVMM — left ventricular myocardial mass (^{2}); LVEF — left ventricular ejection fraction (%).*

Independently from the frailty phenotype most patients in both groups were overweight or obese; higher BMI values were identified in frail individuals with low physical activity (r=0.38, p=0.010). Frailty was also associated with lower total cholesterol levels (TC), unintentional weight loss (r=-0.34, p=0.005). Higher levels of TC in frailty were seen in younger individuals (r=-0.38, p=0.008) with normal nutritional status (r=0.55, p=0.002) and lower CRP (r=-0.54, p=0.040). In prefrail patients, low-density lipoprotein levels (LDL) correlated with systolic BP (r=0.73, p=0.020) and normal nutritional status (r=0.48, p=0.025). Irrespectively from baseline BP frail patients had higher LV myocardium mass index. In both groups this parameter correlated with Charlson comorbidity index (r=0.40 in frail, r=0.47 in prefrail, p=0.001). Hypertension in prefrail patients correlated with 4 m walking time (r=0.38, p=0.005).

Discussion

In accordance with the results of our previous studies that used L.P. Fried phenotype model [13], frailty syndrome was often seen in patients with RA including those younger than 60 years [6, 8]. As in our previous research, frailty prevalence in RA (40.6 %) was significantly higher than in other geriatric patients — 4–11 % [8]. In our study, prevalence of frailty was, however, higher than in the foreign studies — 15.0–23.4 % [6–9]. These differences can be due to enrollement of older patients with higher RA activity and CVD comorbidity burden. The prevalence of prefrailty was 55.4 % in RA patients, which is similar to that of patients without RA (40–55 %) [6, 13]. According to our results, frailty in RA is associated with older age, higher disease stage and activity and severe functional limitations. Frail RA patients have more motor deficits such as decreased hand drip strength, walking speed, less physical activity, and poor nutrition. Functional deficits in patients enrolled in our study are similar to the results of Andrews J. S., et al. (2017).

Frail patients with RA have higher burden of CV comorbidities that, probably, play a role in the development of this syndrome. The most prevalent comorbidities were one associated with atherosclerosis: coronary artery disease and CHF. Myocardial inflammation is also an important factor of CHF development in RA. Lack of physical activity and hypertension were the key risk factors in frail RA patients; hypertension and obesity — in prefrail. The majority of frail patients with RA had very high risk of CV mortality according to SCORE. At the same time, CV mortality in these patients wasn't associated with hypercholesterinemia. This phenomenon can be defined as «lipid paradox"»described by Myasoedova E., et al. (2011). Lipids can be paradoxically associated with CV mortality risk in RA in the presence of increased levels of proinflammatory markers when lower levels of LDL are associated with higher risk of CV mortality [15]. According to our results, CV mortality risk in frail RA patients is higher in individuals with higher disease activity and levels of CRP compared with prefrail patients. It can be supposed that an increase of anti-inflammatory cytokines that is seen both in active RA and in the presence of severe comorbidities causes LV myocardial remodeling (hypertrophy) in frail patients with RA compared with prefrail.

Limitations of this study include a small sample and an absence of control group that would include nonfrail patients with RA. However, our study was the first in Russia to describe the problem of frailty in RA. Moreover, we were the first to investigate the association between CVD and frailty in RA.

Conclusion

The prevalence of frailty and prefrailty is 40.6 % and 55.4 % in patients with RA. It can be present event in patients younger than 60 years. Prefrailty progression into frailty is associated with older age, higher disease activity and radiographic stage of RA and high burden of CV comorbidity and nutritional deficits. Frail RA patients have more physical deficits such as reduced hand grip strength, walking speed and lower functional status according to HAQ-DI. Frail RA patients also have higher burden of CV comorbidity and higher values of an absolute 10-year CV mortality risk according to SCORE with a tendency to lower levels of cholesterol ("lipid paradox" phenomenon). CV risk factors in frail patients include older age, hypertension, and lack of physical activity, in prefrail patients — hypertension and obesity.

Conflict of interest: none declared.

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The implementation of neural network in the risk stratification for mortality in myocardial infarction survivors

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Abstract

The review article is dedicated to the issue of the implementation of neural network in the risk stratification for mortality after myocardial infarction. The advantages of neural network over widely used prognostic scales are discussed. The examples of the development of such models are presented.

Keywords: *myocardial infarction, risk stratification, machine learning, neural network.*

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Introduction

Machine learning is computational process that uses input data to achieve the certain goal, not by directly programming the desired result [1]. Such algorithms are used to build systems that automatically improve through experience. The process of adaptation, when input data and desired result are inserted into the program, is called learning. Then algorithm is modified not only due to produce with the learning data, but also based on new data [2].

Artificial neural networks in cardiology, textual data analysis

The quality of machine learning model primally depends on the sample size that is used for learning [1]. In medical science the largest samples with patient's characteristics are data registers [1].

For the quality control of machine learning most scientists prefer to use the results of the logistic regression or TIMI and GRACE scales [3,4]. The main advantage of machine learning is wider range of data that is used for prognosing. Widely used scales are outdated and cannot provide modern patients with high quality prognosis due to changes in approaches to antiplatelet therapy prescription, the use of drug-eluting stents, and the possibility of modifying samples that are used for learning over time. Another advantage of machine learning is that such models can consider regional features and, as the result, provide better forecast compared with scales developed in other regions [5].

Artificial neural networks for the prognosis of outcomes in patients with myocardial infarction

Sherazi et al. developed prediction model based on data from Korea Acute Myocardial Infarction (MI) Registry (KAMIR) in 2020 [6]. Patients who failed to follow up after hospital and patients who died during hospital admission were excluded from the study [7]. Thus, sample size was 8227 patients including 395 deaths after hospital discharge.

Study subjects were then subdivided into training and testing data sets with the ratio of 80 % to 20 %, respectively. One of the most significant limitations of the study was no division of the outcomes into cardiac and non-cardiac mortality. The following variables were used for the mortality prediction model: demographical, clinical, biochemical parameters, Killip classification class and lesion type [8], echocardiographic parameters, the presence of concomitant diseases, medication characteristics of patients; angiographic, echocardiographic parameters, results of percutaneous coronary intervention (PCI), PCI stent types. Four different machine learning models were developed based on the following algorithms: gradient boosting machine (GBM), generalized linear model (GLM), deep neural network (DNN), random forest (RF) [9]. After the training process, the results of machine learning–based mortality prediction models were compared with GRACE scale [4]. The GBM and DNN models had the AUC of 0.898 and 0.898, respectively, that was superior to GRACE. D'Ascenzo et al. performed the study where aimed to predict three outcomes: all-cause death, recurrent acute myocardial infarction, and major bleeding after acute myocardial infarction [10]. Study participants were obtained from two registries: the BleeMACS registry (n=15 401) [11] that included patients from North and South America, Europe, and Asia, and the RENAMI registry (n=4425) that included patients from Europe [12]. The data from two registers were combined and then randomized. The next step was the random split of cohort into two datasets: training (80 %) cohort, and testing (20 %) (internal validation) cohort. The main feature of this study was the use of internal validation group as the control group. The external validation cohort included 3444 patients from the European SECURITY randomized controlled trial [13], 1465 patients from two prospective registries from the University of Ferrara [14], and 1537 patients from the Clinical Governance in Patients with ACS project of the Fondazione IRCSS [15]. Such approach allows to exclude overfitting error when running the model. Overfitting happens when a model learns the detail and noise in the training data to the extent that it negatively impacts the performance of the model on new data [16]. Patients were described with clinical data and medication characteristics and angiographic data. Several machine learning algorithms were

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tested during model development, and the adaptive boosting algorithm was the most successful learning model. The final model was called PRAISE risk score and can be used as online calculator [17]. The prediction results for one year mortality show high quality prognostic value for developed model [18]. Data are presented in table 1.

Table 1. **The quality of PRAISE risk score predictoin**

Outcome predictions	AUC	CI
Prediction quality in training cohort		
All-cause mortality	0.91	0.90–0.92
Recurrent acute myocardial infarction	0.88	0.86–0.89
Bleeding	0.87	0.85–0.88
Prediction quality in internal validation cohort		
All-cause mortality	0.82	0.78–0.85
Recurrent acute myocardial infarction	0.74	0.70–0.78
Bleeding	0.70	0.66–0.75
Prediction quality in external validation cohort		
All-cause mortality	0.92	0.90–0.93
Recurrent acute myocardial infarction	0.81	0.66–0.85
Bleeding	0.86	0.82–0.89

Comment. AUC — area under curve (площадь под кривой); CI — confidence interval.

Conclusion

Neural network can effectively predict mortality during one year follow-up in patients after myocardial infarction and can be used as promising direction in prevention of adverse cardiovascular events. Machine learning needs to be developed and implemented into practice both in world and domestic medicine, since high-quality prediction of mortality risks allows practitioners to identify high-risk patients and, as the result, prevent their deaths.

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A Rare Case of Aortic Arch Anomaly with Subclavian Steal Syndrome

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This paper discusses a rare case of aortic arch anomaly with subclavian steal syndrome. The images of our diagnostic findings are presented and compared with findings in healthy individuals.

Key words: *aortic arch anomaly, subclavian steal syndrome, functional diagnostics, blood pressure.*

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Introduction

Aortic arch anomaly is a rare form of cardiovascular system (CVS) congenital disorders [1–3]. Subclavian steal syndrome (SSS) is an occlusion or stenosis of the subclavian artery (SA) causing retrograde flow in the vertebral artery (VA) and vertebrobasilar insufficiency (VBI) [4, 5]. In this paper we present a clinical case of SSS due to aortic arch anomaly that was diagnosed with non-invasive procedures.

Case report

A 53-year female with a history of diffuse systemic scleroderma with sclerodactyly, hyperpigmentation, telangiectasia, tightening of the mouth area, Raynaud's phenomenon, achalasia, and fibrosing alveolitis. She had stage 0–1 dyspnea and a history of pneumonitis.

The patient's complaints at admission and during hospital stay were typical for systemic scleroderma.

The patient has had systemic scleroderma for over 20 years. She's been previously treated with cytostatics, systemic glucocorticoids, antifibrates, vascular agents, calcium-containing agents, and peripheral vasodilators. The patient wasn't adherent to the recommended treatment altering the dose or timing of a medication. For over 9 years there were signs of bilateral interstitial lung disease.

The patient has been overweight for many years. For the last 5 years she has been diagnosed with Cushing syndrome. The patient underwent menopause at age 42. She was diagnosed with osteoporosis due to menopause and glucocorticoid treatment 3 years ago. Her blood pressure (BP) was usually within normal limits with rare elevations up to 130/90 mmHg. The patient denied having a history of stroke, coronary artery disease (CAD), or diabetes.

Physical exam findings matched the clinical diagnosis. Excessive accumulation of adipose tissue in the abdominal region was noted. Body mass index (BMI) was 31.2 k^2. Body temperature, oxygen saturation, respiration rate, and heart rate were within normal limits during the hospital stay. BP was always checked at the left arm and normal. Evaluation and clinical management were performed according to current guidelines and standard algorithms for systemic scleroderma management. Laboratory and instrumental findings also confirmed the clinical diagnosis. Electrocardiography and echocardiography (Echo-CG) [6] revealed no abnormalities. 6-minute walking test was 430 m.

The presence of obesity, BP elevation episodes, dyslipidemia, long-term use of glucocorticoids with Cushing syndrome necessitated carotid artery duplex scan for cardiovascular disease (CVD) risk stratification. Carotid artery duplex showed normal blood flow in the common carotid (CCA), external carotid (ECA), and internal carotid arteries (ICA). Blood flow linear velocity (BFLV) was also normal without significant asymmetry (Table 1). Intima-media ratios (IMR) of the right and left CCA were normal (0.9 mm on the right and 0.99 mm on the left). Thickness and echo density were even, layers well-differentiated. However, we found that left and right CCA arised from the common trunk with 7.4 mm diameter and 8.0 length from aortic arch (Figures 1, 2). Left subclavian artery (LSCA) was 7.6 mm in diameter and had normal location (started from the aortic arch) and angle with aortic arch; BFLV was 96 cec. Right subclavian artery (RSCA) was 5.0 mm in diameter, but we couldn't determine its origin. It probable arised from the posterior wall of the descending aorta. RSCA turned out to be collateral with reduced systolic BFLV (46 cec) and no phases (Figures 3b). It normally should have high amplitude and three phases (Figure 3a). Right extracranial vertebral artery had retrograde flow; left — antegrade flow (Figure 4).

Table 1. **Extracranial carotid artery duplex scan parameters**
(GE Vivid S70 Ultrasound Machine with GE 11L–D Linear Probe, 1–6 MHz)*

Vessel	Right BFLV				Left BFLV			
	PS, CEC	DIAST, CEC	RI	D, MM	PS, CEC	DIAST, CEC	RI	D, MM
CCA	78	19	0.75	6.8	99	20	0.80	6.4
ICA	64	24	0.61	4.4	68	21	0.68	4.5
ECA	—**	—	—	3.5	—	—	—	4.5
VA	73	11	0.85	4.0	54	15	0.72	4.9

Note. *— reference values were determined according to critical parameters specific for this pathology [7]. ** — no clinical significance. BFLV — blood flow linear velocity, CCA — common carotid artery, d, mm — vessel diameter; Diast, cec — diastolic velocity; ECA — external carotid artery, ICA — internal carotid artery, Ps, cec — peak systolic velocity; RI — resistive index; VA — vertebral artery.

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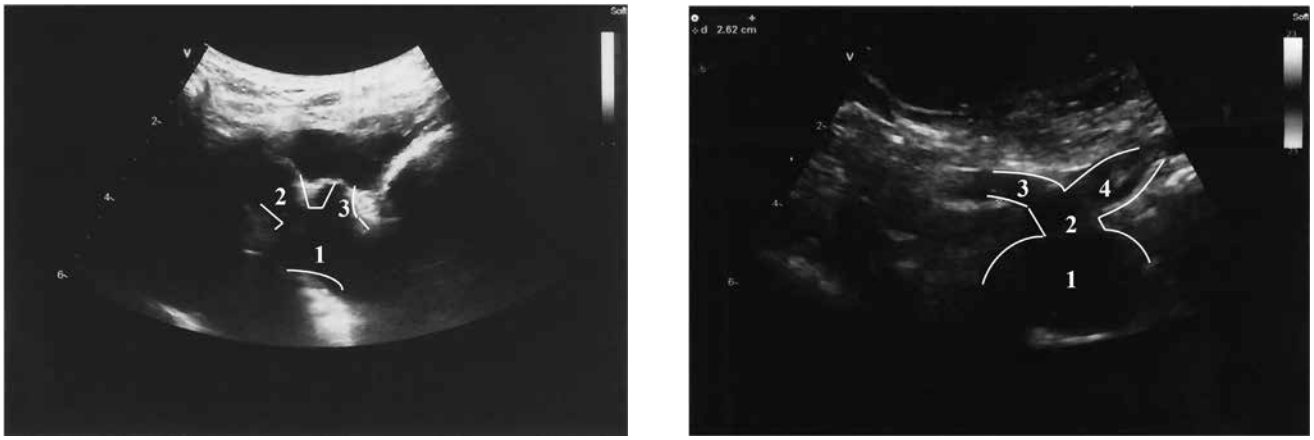
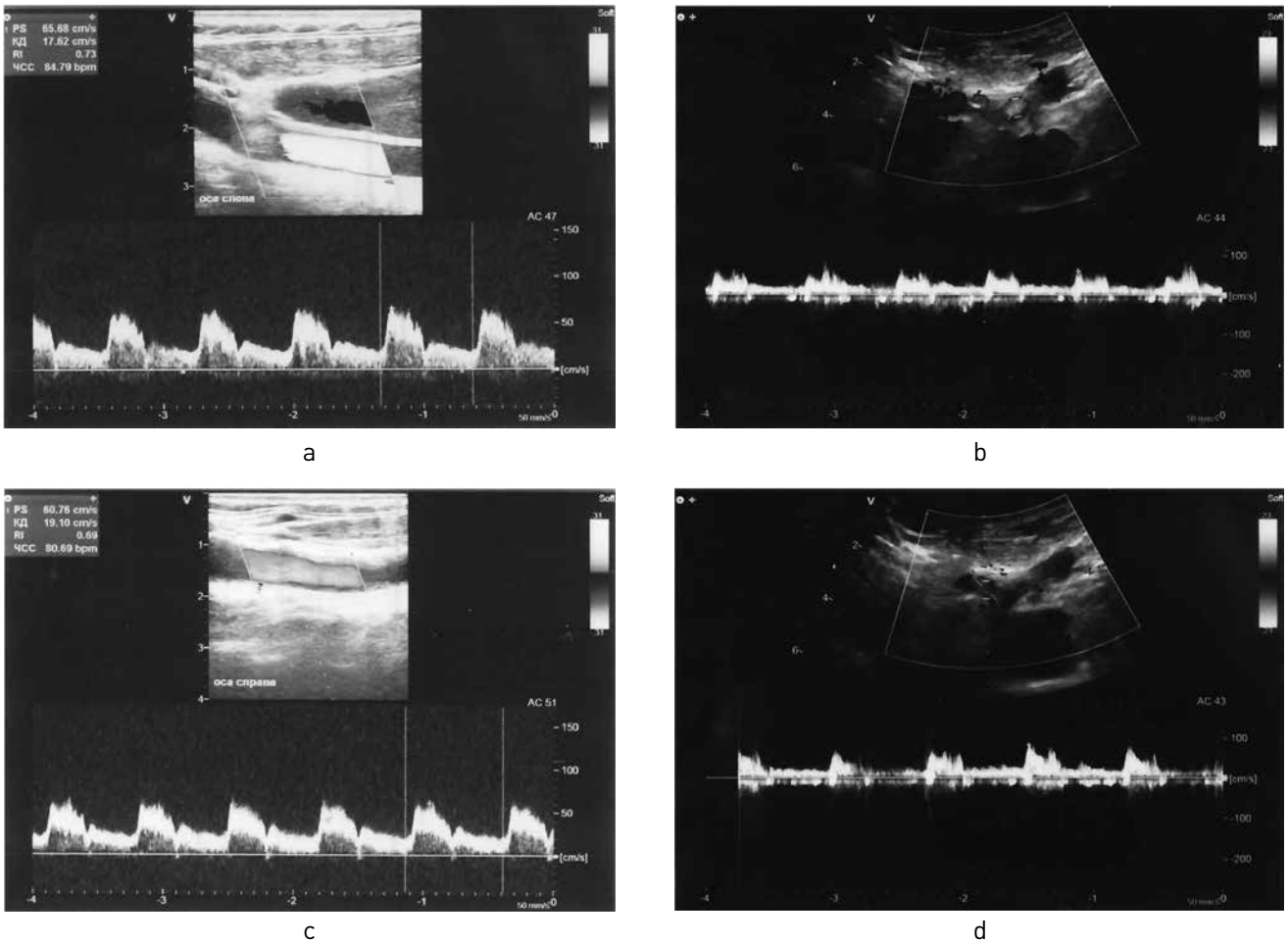


a b

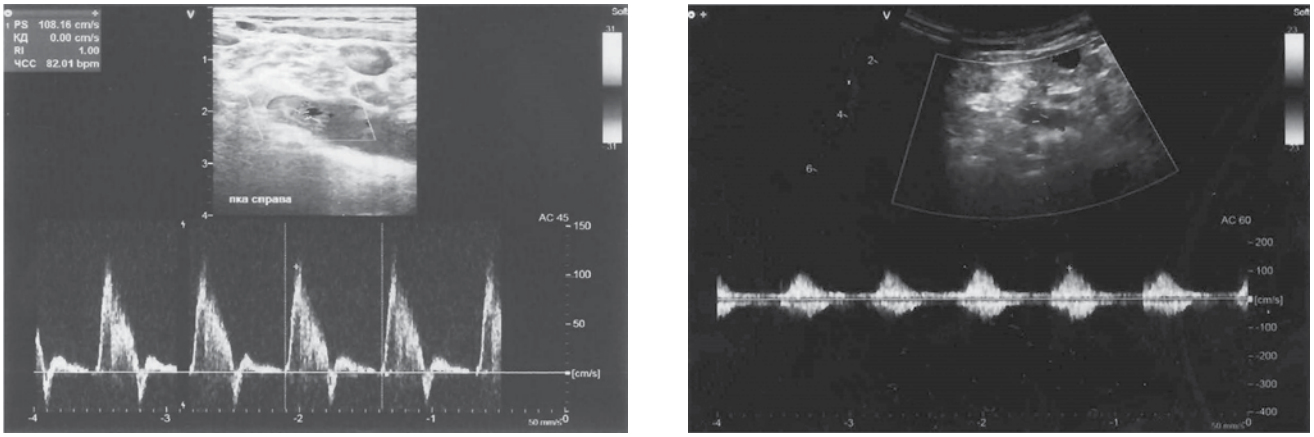
Figure 1. Carotid artery duplex scans showing aortic arch in: a — a healthy individual (1-aortic arch, 2 — brachiocephalic trunk, 3 — left CCA); b –aortic arch anomaly (1 — aortic arch, 2 — common trunk of the right and left CCA, 3 — right CCA, 4 — left CCA) (further from here — scans are compared with images from a healthy female patient of the same age).



a b

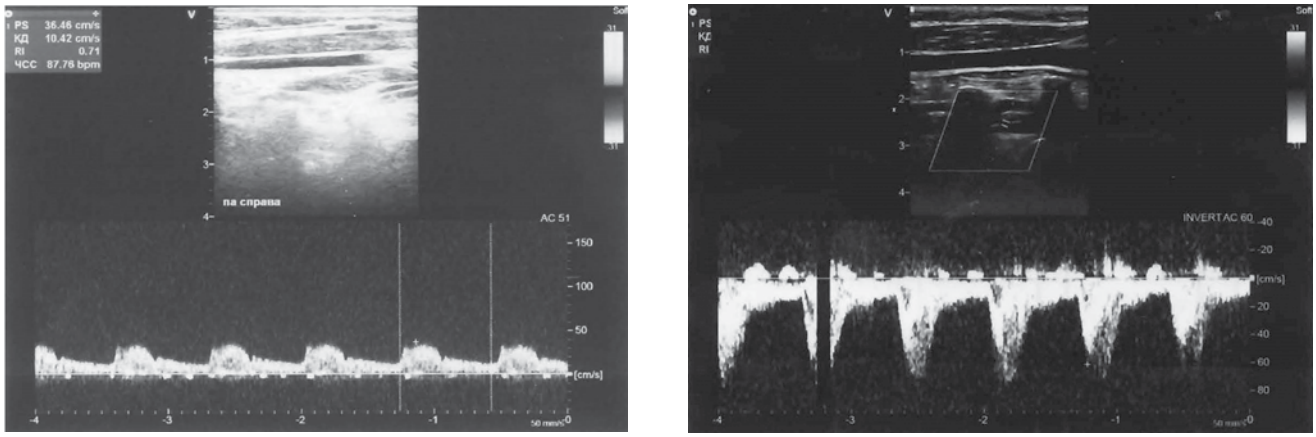
c d

Figure 2. Blood flow in the common carotid arteries (CCA): a — left CCA in a healthy individual; b — left CCA in our patient; c — right CCA in a healthy individual; d — right CCA in our patient



a b

Figure 3. Blood flow in the right subclavian artery: a — in a healthy individual; b — in subclavian steal syndrome



a b

Figure 4. Blood flow in the right vertebral artery in extracranial carotid artery duplex scan: a — in a normal individual; b — in subclavian steal syndrome (retrograde flow)

Therefore, we found an aortic arch branch anomaly: both CCA originated form a single trunk (truncus arteriosus) with aberrant (most-probably, left-sided) RSCA from the posterior wall of the descending aorta with a complete right subclavian steal syndrome.

In order to visualize vertebral intracranial blood flow, we performed transcranial doppler (TCD) ultrasound. The results are presented in Table 2. SSS was confirmed with retrograde blood flow in the right vertebral artery (Figure 5), antegrade blood flow in the left vertebral artery, increased BFLV in both vertebral arteries.

Suprasternal view echocardiogram was performed to determine the anatomy of branches of aortic arch (Figure 6). Right and left CCA originate from a single trunk. LSCA arises to the left from the common trunk. Blood flow was normal in all arteries. Brachiocephalic trunk wasn't found in the typical lo-

Table 2. **TCD parameters (GE Vivid S70 Ultrasound Machine with M5Sc-D probe)**

Parameter	Vertebral artery			Main artery	
	NORMAL*	RESULT		NORMAL*	RESULT
	LEFT, RIGHT	LEFT	RIGHT		
VPs, cec	56.3±7.8	81	97	59.5±17.0	98
VPd, cec	27.0±5.3	22	19	29.2±8.4	40
RI	0.52±0.16	0.82	0.87	0.49±0.12	0.54
Flow direction	ANTEGRADE	ANTEGRADE	RETROGRADE	—	—

Note. *— age-related reference range [8]; RI — resistive index, TCD — transcranial doppler, VPd, cec — diastolic velocity, VPs, cec — peak systolic velocity.

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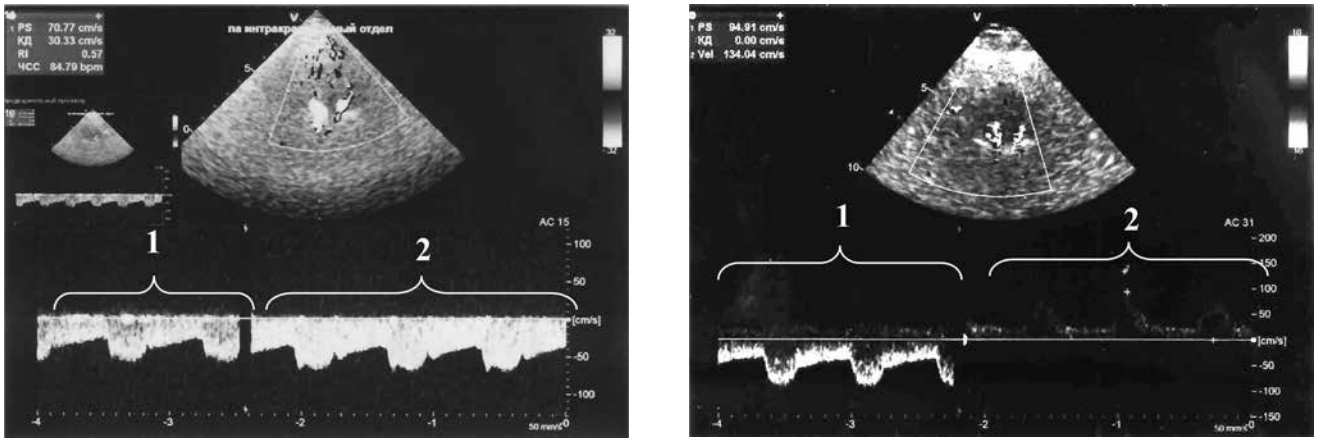
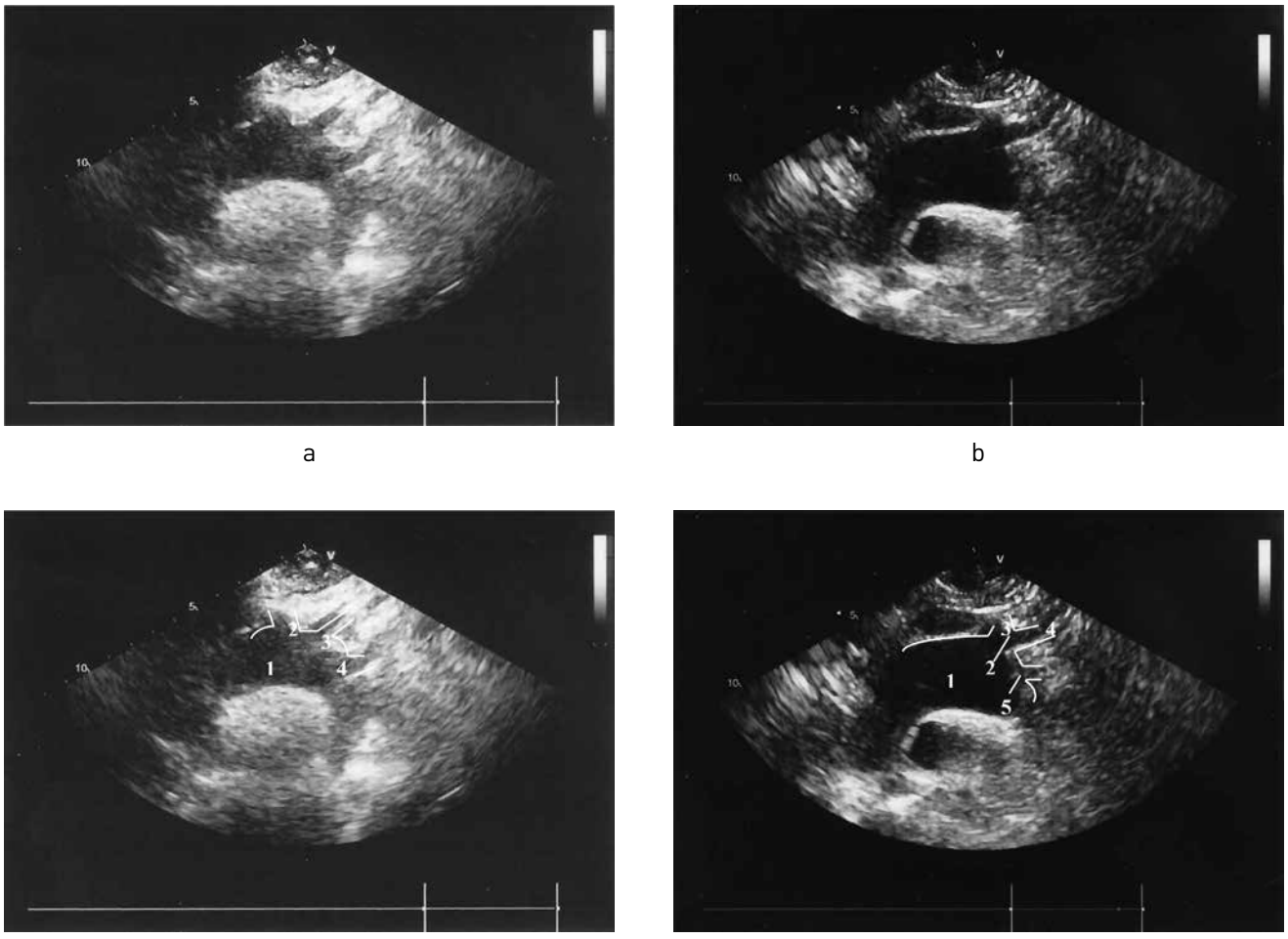


a b

Figure 5. Blood flow in the vertebral artery in transcranial doppler ultrasound on the extracranial level on the left (1) and right (2): a — in a healthy individual; b — in subclavian steal syndrome



a b

c g

Figure 6. Suprasternal view echocardiograms showing aortic arch branches: a, c — in a healthy individual (1-aortic arch, 2 — brachiocephalic trunk, 3 — left CCA, 4 — LSCA); b, g — in our patient (1 — aortic arch, 2 — common trunk of the right and left CCA, 3 — right CCA, 4 — left CCA, 5 — LSCA)

cation. RSCA wasn't visualized due to right internal jugular vein.

Discussion

This case report describes the abilities of functional diagnostics. Although the anomaly described was congenital, it was only first discovered at the age of 53. Detailed review of the patient's medical history didn't reveal any complaints specific for SSS such as any signs of vertebrobasilar insufficiency. We then checked BP on both arms simultaneously: BP on the right arm was lower (90/50 mmHg) then on the left arm (130/80 mmHg) after taking 5 mg/day of amlodipine. We couldn't determine whether BP was previously checked only on one hand and if so, which one, or on both hands, and how were the measurements evaluated. If BP difference was determined at the first place, the sequence of diagnostic evaluations would've been different. Differential diagnosis also included atherosclerosis and Takayasu disease.

As for the further management, the patient will require cardiovascular surgery consultation, regular BP monitoring and review of the medications that may affect BP on the left arm.

Conclusion

Vertebrobasilar system anatomy variations are well-described and are usually diagnosed using the invasive procedures [3, 4]. This case report demonstrates that congenital aortic arch anomalies can be diagnosed with non-invasive techniques.

Conflict of interest: none declared.

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XI International Forum of Cardiology and Internal Medicine highlights

The annual International Forum took place on 22-24 March, 2022. The forum has been working since 2011, and in last two years, due to the epidemiological situation, the event was held online. The new format provided additional opportunities, thus, many health care professionals from the various federal subjects of Russian Federation and CIS countries could participate.

At the solemn opening of the International Forum, the president of the Cardioprogress Foundation, doctor of medical sciences, professor Mamedov M.N. spoke about the history and the creation of the Forum as well as about its development course over the last 11 years. The main goals and objectives of this important scientific and educational event were identified.

According to the analysis of the Scientific Committee, 110 professionals applied for oral presentations and lectures from various cities of Russian Federation and CIS countries in 2022. The final scientific program included 86 reports. The program was independent and mainly focused on academic works – gave preference to the works of domestic and foreign clinicians and scientific researchers. This event contributes to the development of clinical science in the Russian federal subjects and CIS countries.

The scientific program consisted of 18 symposia, including: a plenary session, a round table, 4 clinical lectures, 6 symposia of regional medical schools, 3 joint symposia with the CIS countries, and 3 thematic symposia. This year, experts from Belarus, Kazakhstan, Uzbekistan, Kyrgyzstan and the USA made presentations. The program focused of actual cardiological and internal diseases issues, such as: atherosclerosis, coronary syndrome, coronary artery disease, the implementation high technology, cardio-oncology, chronic obstructive pulmonary disease, connective tissue dysplasia, gastrointestinal tract diseases, nephrology, cognitive impairment and family medicine. A separate symposium and lectures were devoted to coronavirus infection. By the decision of the Scientific Committee of the International Forum, recordings of all reports will be posted on Cardioprogress Foundation website and will be available for 365 days.

Traditionally, the collection of scientific papers presented at the Forum was published. This year it included 74 articles and abstracts dedicated to cardiovascular and other internal diseases. The papers were reviewed independently by three experts and were highly appreciated. The collection received an international book qualification number for citation. The book is in the public domain of the Cardioprogress Foundation official website and soon will be placed in the e-library electronic database.

Registration and participation in the Forum were free. About 700 physicians and researchers joined the Forum. All registered users will receive a certificate of participation.

The Organizing Committee of the International Forum hope that this event will help the participants to systematize and acquire new knowledge in the treatment and prevention of cardiovascular and other internal diseases, as well as will improve the efficacy of their daily practice.

Information support was provided by leading cardiological journals, specialized Internet resources and all-Russian social networks.

The next XII International Forum of Cardiology and Internal Medicine will be held in March 2023 in Moscow. Detailed information on the Forum and other scientific events is available on the official website of the Cardioprogress Foundation: www.cardioprogress.ru.

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http://www.heart-vdj.com

Author Guidelines

Manuscript publication rules
in the International heart and vascular disease journal

Disclaimer: Edition of rules come into force since November, 2018. The rules describe the conditions of publication of manuscripts (articles) through the site http://www.heart-vdj.com. The editorial Board is ready to answer questions and help authors by e-mail: submissions.ihvdj@gmail.com.

The *International heart and vascular disease journal* has been published since 2013. It is official journal of the Cardioprogress Foundation. The target audience of this peer-reviewed journal is cardiologists and internal disease specialists. The journal is primarily focused on questions of epidemiology, prevention, and cardiac pharmacotherapy. It also publishes lectures and literature reviews on various problems of modern cardiology, reports on new diagnostic methods, and other information which is important for the practitioners.

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.

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http://www.heart-vdj.com

On the reception of the articles, making decisions about publication, reviews — mmamedov@mail.ru

On organizational issues (working with the site, subscription) — editor.ihvdj@gmail.com

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