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# International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation



Key research findings presented at  
the HOT LINE sessions of the 2025  
European Society of Cardiology  
Congress

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Amiodarone in clinical  
practice: efficacy, safety,  
precautions

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Radiofrequency  
denervation of the  
pulmonary artery trunk  
in the modulation of  
pulmonary hypertension  
in cardiovascular pathology.  
Experimental study

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# International Heart and Vascular Disease Journal

## Journal of the «Cardioprogress» Foundation

Volume 14, № 49, March 2026

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# Editor's Welcome

Dear colleagues!

We present to your attention the forty-ninth issue of the International Heart and Vascular Disease Journal, which features leading, original, and review articles.

The "Leading Article" section includes a report summarizing key findings from 40 randomized clinical trials and one meta-analysis presented at the HOT LINE sessions of the 2025 Congress of the European Society of Cardiology. The studies covered a wide range of cardiology topics, including the management of arterial hypertension, myocardial infarction, cardiac arrhythmias, heart failure, dyslipidemia, hypertrophic cardiomyopathy, optimization of antiplatelet and anticoagulant therapy, interventional and surgical procedures, and perioperative patient management.

The "Original Articles" section features four studies. The first study analyzes the clinical characteristics of 117 patients with atrial fibrillation and cardioembolic stroke, as well as their short- and long-term outcomes. This patient population demonstrated high in-hospital (35%) and 2-year (27.6%) mortality rates. The findings indicate that adherence to anticoagulant therapy significantly reduces the risk of death within 24 months after the index event. The second study is a retrospective analysis of 85 patients, identifying factors associated with poor prognosis in individuals with stable coronary heart disease. Based on these findings, the authors developed a statistically validated model for predicting the risk of mortality and nonfatal cardiovascular complications. The third study evaluates the impact of chronic heart failure (CHF) on ceruloplasmin (CP) levels in the plasma of HIV-infected patients. The study included 240 individuals with HIV infection, of whom 160 had signs of CHF. CP levels were found to be significantly decreased in patients with CHF and HIV infection. At the same time, despite generally low CP levels, an increasing trend was observed with worsening severity of CHF. A plasma CP level of 233.5 mg/L was associated with an increased likelihood of CHF with a left ventricular ejection fraction <40%. The fourth study investigates the effectiveness of radiofrequency ablation of the pulmonary artery trunk in reducing pulmonary hypertension. The evaluation was performed using immunohistochemical assessment of sympathetic denervation completeness through detection of the S-100 marker in an experimental setting. The results demonstrate that this method is effective for verifying irreversible thermal damage to autonomic nerve fibers following the intervention.

The "Review Articles" section presents a paper focused on the efficacy, safety, and precautions associated with amiodarone in clinical practice. The drug is highly effective in maintaining sinus rhythm in patients with paroxysmal and persistent atrial fibrillation, as well as in preventing life-threatening ventricular arrhythmias. However, amiodarone may cause a range of adverse effects, including thyroid dysfunction, pulmonary fibrosis, and liver injury. It also interacts with various medications, including anticoagulants, which necessitates careful monitoring to prevent complications.

We invite everybody to collaborate with the journal. Our team is 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

## Review of international medical news

German researchers assessed the effectiveness of left atrial appendage (LAA) closure compared with optimal medical therapy in high-risk patients with atrial fibrillation (AF).

The analysis included 912 patients with AF and a high risk of stroke and bleeding. Patients either underwent LAA closure or received optimal medical therapy, including direct oral anticoagulants. The primary endpoint was a composite outcome of stroke, systemic embolism, major bleeding, and cardiovascular or unexplained death over a 3-year follow-up period.

The results showed that the incidence of adverse outcomes was 16.8 per 100 patient-years in the LAA closure group versus 13.3 per 100 patient-years in the medical therapy group.

The authors concluded that LAA closure offers no advantage over optimal medical therapy in terms of major clinical outcomes in high-risk AF patients.

*According to the New England Journal of Medicine*

Researchers evaluated the prevalence of preclinical and clinical obesity and their association with cardiovascular outcomes.

Data from 502,233 adult participants from the UK Biobank were analyzed. Obesity was classified according to the new definition proposed by The Lancet Diabetes & Endocrinology Commission, taking into account functional impairment and organ dysfunction. Outcomes included stroke, heart failure, myocardial infarction, and the transition from preclinical to clinical obesity over a 12-year follow-up.

Preclinical and clinical obesity were found to be highly prevalent, affecting 31.2% and 36.6% of participants, respectively. Most individuals were classified as overweight according to WHO criteria.

The authors concluded that clinical obesity, as defined by functional criteria, is associated with a significantly higher cardiovascular risk, whereas preclinical obesity is associated with relatively lower risk.

*According to the Obesity journal*

Researchers examined the association between various mental disorders and the risk of acute coronary syndrome (ACS) and myocardial infarction (MI).

The analysis included data from 25 studies involving approximately 22 million individuals, with a mean age of 48 years. At baseline, 13% had diagnosed mental disorders, and 1% had ACS.

Post-traumatic stress disorder (PTSD) was associated with the highest risk of acute MI, with nearly a threefold increase compared to individuals without mental disorders. Anxiety disorders were associated with a 1.6-fold increased risk.

The authors concluded that anxiety, depression, sleep disorders, and especially PTSD are associated with an increased risk of ACS.

*According to the JAMA Psychiatry*

Researchers evaluated the impact of different LDL-cholesterol targets on outcomes in high-risk patients. The study included 3,048 patients aged 19 to 80 years with atherosclerotic cardiovascular disease. Participants were randomized to LDL targets of < 55 mg/dL or <70 mg/dL and followed for a median of three years.

Achieving LDL levels below 55 mg/dL reduced the risk of major cardiovascular events by 33% compared to the <70 mg/dL group.

These findings suggest that more intensive LDL reduction improves prognosis in high-risk patients.

*According to the New England Journal of Medicine*

Researchers evaluated the association between antithrombotic therapy and the risk of intracranial hemorrhage in patients with infective endocarditis (IE).

The study included 3,236 patients with confirmed left-sided IE. Patients were categorized based on therapy at diagnosis: no therapy, antiplatelet therapy, anticoagulant therapy, or combination therapy.

Intracranial hemorrhage within 30 days occurred in 5.6% of patients. The highest risk was observed in those receiving combined anticoagulant and antiplatelet therapy, which increased the risk more than threefold.

The authors concluded that anticoagulants, especially in combination with antiplatelet agents, are associated with an increased risk of intracranial hemorrhage in IE patients.

*According to the Clinical Infectious Diseases journal*

Researchers identified an association between premature menopause and increased risk of coronary heart disease (CHD) in women.

Data from 10,000 postmenopausal women across six U.S. cohorts (total population over 163,000) were analyzed.

Premature menopause was associated with a ~40% increased risk of CHD across all racial groups. Women with premature menopause also had slightly shorter CHD-free life expectancy (18 vs 19 years).

The authors concluded that premature menopause should be considered in cardiovascular risk assessment and prevention strategies.

*According to the JAMA*

# Key research findings presented at the HOT LINE sessions of the 2025 European Society of Cardiology Congress

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At the 10 HOT LINE scientific sessions of the 2025 European Society of Cardiology Congress, the results of 40 randomized clinical trials and 1 meta-analysis were presented for the first time. The studies addressed various fields of cardiology, including the treatment of arterial hypertension, myocardial infarction, cardiac arrhythmias, heart failure, dyslipidemia, and hypertrophic cardiomyopathy, as well as the improvement of antiplatelet and anticoagulant therapy, interventional and surgical procedures, and perioperative patient management.

**Keywords:** clinical trials, cardiovascular diseases, drug therapy, interventional and surgical treatment.

**Conflict of interest:** none declared.

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**POTCAST.** The study enrolled 1,200 patients at high risk of ventricular arrhythmias, with an implantable cardioverter-defibrillator (ICD), and a baseline plasma potassium level of 4.3 mmol/L or lower. Following a 1:1 randomization, patients received either treatment aimed at increasing plasma potassium levels to 4.5–5.0 mmol/L using potassium supplements, a mineralocorticoid receptor antagonist, or both, combined with dietary advice, or standard therapy. At a median follow-up of 39.6 months, a composite of primary endpoint events (documented sustained ventricular tachycardia or appropriate ICD shock, unplanned hospitalization for more than 24 hours due to arrhythmia or heart failure (HF), or death from any cause) was observed in 22.7% of patients in the high-normal potassium group compared to 29.2% in the standard therapy group ( $p=0.01$ ). The rates of hospitalization for hyperkalemia or hypokalemia were similar in both groups [1].

**AMALFI.** In a randomized trial in older adults (mean age 78 years) with a median CHA2DS2-VASc thromboembolic risk score of 4 and no history of atrial fibrillation (AF), a single continuous 14-day ambulatory electrocardiographic (ECG) monitoring was performed using an ECG patch to screen for AF and assess its prognostic benefit. The data of patients who received and mailed back the ECG monitoring patch (intervention group;  $n=2,520$ ) were compared with those receiving usual care (control group;  $n=2,520$ ). AF was detected by the patch in 4.2% of participants in the intervention group. At 2.5 years post-randomization, AF was recorded in 6.8% of patients in the intervention group and 5.4% in the control group ( $p=0.03$ ), which was associated with a 0.5-month longer duration of oral anticoagulant therapy in the former group ( $p<0.001$ ). However, the stroke incidence rates in the groups were 2.7% and 2.5%, respectively [2].

**DIGIT-HF.** The study evaluated the therapeutic efficacy of the cardiac glycoside digitoxin in patients with HF and a reduced left ventricular ejection fraction (LVEF). A total of 1,212 patients with chronic HF New York Heart Association (NYHA) functional class III or IV and an LVEF of  $\leq 40\%$ , as well as NYHA functional class II and an LVEF of  $\leq 30\%$ , were randomized in a 1:1 ratio to receive digitoxin (at an initial dose of 0.07 mg once daily) or a placebo, in addition to guideline-directed medical therapy. At a median follow-up of 36 months, the primary endpoint (death from any

cause or hospitalization for worsening HF) was recorded in 39.5% of patients in the digitoxin group and 44.1% in the placebo group ( $p=0.03$ ), with a trend toward reduced mortality (by 14%) in the cardiac glycoside group and a comparable incidence of serious adverse events (4.7% vs. 2.8% in the digitoxin and placebo groups, respectively) [3].

**DOUBLE-CHOICE.** In this study, patients with a mean age of 83 years were randomized to undergo transcatheter aortic valve implantation (TAVI) using a minimally invasive approach under isolated local anesthesia ( $n=377$ ) or the standard approach using conscious sedation ( $n=375$ ). Primary endpoint events (a composite of all-cause mortality, vascular and bleeding complications, infections requiring antibiotic therapy, and neurological disorders within 30 days) were recorded in 22.9% of patients in the minimally invasive approach group and 25.8% in the standard care group ( $p=0.003$  for non-inferiority). In patients from the local anesthesia group, the levels of anxiety, stress, pain, and discomfort during the procedure were comparatively higher [4].

**DAPA ACT HF-TIMI 68.** In a study involving patients hospitalized for HF (71.5% with LVEF  $\leq 40\%$ ), following clinical stabilization (at 24 hours to 14 days), participants were randomized to receive dapagliflozin at a dose of 10 mg/day ( $n=1,218$ ) or a placebo ( $n=1,183$ ). The primary efficacy endpoint, cardiovascular (CV) death or worsening HF within 2 months, was observed in 10.9% of patients in the dapagliflozin group and 12.7% in the placebo group ( $p=0.20$ ), while all-cause death occurred in 3.0% and 4.5% of cases, respectively. The incidence of symptomatic hypotension was 3.6% and 2.2%, and the incidence of worsening renal function was 5.9% and 4.7% for dapagliflozin and placebo, respectively. According to a pre-specified meta-analysis of DAPA ACT HF-TIMI 68 and two other trials of patients hospitalized for HF, sodium-glucose cotransporter 2 (SGLT2) inhibitors reduced the risk of CV death or worsening HF by 29% ( $p=0.012$ ) and the risk of all-cause death by 43% ( $p=0.001$ ) [5].

**VICTORIA and VICTOR.** Following the completion of the VICTORIA trial ( $n=5,050$ ), the soluble guanylate cyclase (sGC) stimulator vericiguat was approved for the treatment of worsening HF with reduced LVEF and received a Class IIb recommendation in European and North American guidelines. A subsequent trial, VICTOR ( $n=6,105$ ), evaluated the use of vericiguat

in patients with HF and reduced LVEF without a recent worsening HF event. A pre-specified pooled analysis of individual patient data from the VICTORIA and VICTOR trials was conducted to determine the impact of vericiguat on clinical outcomes. Participants in both trials received contemporary guideline-directed background HF therapy. The primary endpoint (CV death or HF hospitalization) was observed in 25.9% of the 5,579 patients in the vericiguat group and 27.9% of the 5,576 patients in the placebo group ( $p=0.0088$ ), including significant reductions in the risk of CV death (by 11%;  $p=0.020$ ) and the rate of HF hospitalization (by 8%;  $p=0.043$ ). Consequently, vericiguat can be used as an additional treatment option for selected patients with HF and reduced LVEF [6].

**ODYSSEY-HCM.** In this study, the cardiac myosin inhibitor mavacamten, approved for the treatment of adult patients with symptomatic obstructive hypertrophic cardiomyopathy, was evaluated in its non-obstructive form. Following randomization, 289 patients received mavacamten (starting dose of 5 mg/day with titration up to a maximum dose of 15 mg/day depending on LVEF) and 291 received a placebo. Over a 48-week follow-up period, no significant differences were observed for the two main endpoints: the mean change in peak oxygen consumption was 0.52 mL/kg/min in the mavacamten group and 0.05 mL/kg/min in the placebo group ( $p=0.07$ ), and the change in quality of life assessed by the 23-item Kansas City Cardiomyopathy Questionnaire was 13.1 points versus 10.4 points ( $p=0.06$ ). In patients with non-obstructive hypertrophic cardiomyopathy, mavacamten did not result in a significantly greater improvement in peak oxygen consumption or symptom reduction compared to placebo [7].

**MAPLE-HCM.** The study compared the cardiac myosin inhibitor aficamten with metoprolol in patients with obstructive hypertrophic cardiomyopathy. Following randomization, 88 patients received aficamten at a dose of 5 to 20 mg/day plus placebo, and 87 received metoprolol at a dose of 50 to 200 mg/day plus placebo. Over 24 weeks of follow-up, the change in peak oxygen consumption (primary endpoint) was 1.1 mL/kg/min in the aficamten group and -1.2 mL/kg/min in the metoprolol group ( $p<0.001$ ). Patients who received aficamten experienced significant improvements in NYHA HF functional class, quality of life assessed by the Kansas City Cardiomyopathy Questionnaire, left ventricular outflow tract gradi-

ent, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and left atrial volume index compared to those receiving metoprolol. No significant differences were observed in the left ventricular mass index or the incidence of adverse events between the two treatment groups [8].

**REBOOT-CNIC.** This open-label randomized trial compared the outcomes of contemporary treatment (coronary reperfusion and secondary prevention) in patients with ST-segment elevation or non-ST-segment elevation myocardial infarction (MI) and an LVEF  $>40\%$  receiving beta-blocker therapy ( $n=4,207$ ) versus no beta-blocker therapy ( $n=4,231$ ). At a median follow-up of 3.7 years, primary endpoint events (a composite of death from any cause, recurrent MI, or hospitalization for HF) occurred with equal frequency ( $p=0.63$ ) in both groups. There were no differences in the rates of all-cause death, recurrent MI, hospitalization for HF, or treatment safety profiles [9].

**BETAMI-DANBLOCK.** This open-label randomized trial involved patients with a prior MI and an LVEF  $\geq 40\%$  who, within 14 days after the index event, were allocated to receive long-term beta-blocker therapy ( $n=2,783$ ) or no beta-blocker therapy ( $n=2,791$ ). At a median follow-up of 3.5 years, the composite primary endpoint (death from any cause, MI, unplanned coronary revascularization, ischemic stroke, HF, or malignant ventricular arrhythmias) was observed in 14.2% of patients in the beta-blocker group and 16.3% in the no beta-blocker group ( $p=0.03$ ), with no significant differences in the rates of its individual components or therapy safety profiles between the groups. In this trial, among patients with MI and an LVEF  $\geq 40\%$ , beta-blocker therapy led to a reduced risk of death or major adverse cardiovascular events compared to no beta-blocker therapy [10].

**REBOOT/BETAMI/DANBLOCK/CAPITAL.** To conduct a meta-analysis on the impact of beta-blockers on clinical outcomes in patients with a recent (within 14 days) ST-segment elevation or non-ST-segment elevation MI, data from 1,885 participants with a mildly reduced LVEF (40–49%) and no history or signs of HF were selected from four randomized trials. The primary composite endpoint (all-cause death, new MI, or HF) was recorded 25% less frequently in the beta-blocker group compared to the no beta-blocker group ( $p=0.031$ ). There was no heterogeneity observed across the trials or between the countries where the studies were conducted. These results

allow extending the known benefits of beta-blockers in patients with MI and reduced LVEF to the subgroup with mildly reduced LVEF [11].

**REFINE ICD.** To select participants for the study, Holter ECG monitoring was performed in patients who had suffered a type 2 MI or more months prior ( $n=1,943$ ). Based on the results, 597 patients meeting the inclusion criteria (LVEF 36–50%, impaired heart rate turbulence, T-wave alternans) were identified and randomized to receive an ICD in addition to medical therapy or medical therapy alone. Another 1,053 examined individuals comprised the registry group. The risk of all-cause death was 2.01 times higher in the high-risk group included in the trial compared to the registry group. However, over a mean follow-up of 5.7 years for patients with abnormal ECG findings participating in the randomized trial, overall mortality (the primary endpoint) did not decrease in the ICD group: 24.5% vs. 21.3% in the control group ( $p=0.69$ ). Furthermore, there were no significant differences between the two study groups in the rates of CV death (8.8% vs. 7.6%), sudden cardiac death (2.6% vs. 3.8%, respectively), or non-cardiovascular death.

**BaxHTN.** This phase 3 trial enrolled patients with a seated systolic blood pressure (BP) ranging from 140 mmHg to 170 mmHg despite therapy with two antihypertensive drugs—uncontrolled arterial hypertension (AH)—or 3 or more drugs, including a diuretic (resistant AH). Following a two-week placebo run-in period, patients with a seated systolic BP of 135 mmHg or higher were randomized to receive the selective aldosterone synthase inhibitor baxdrostat at a dose of 1 mg ( $n=264$ ), baxdrostat at a dose of 2 mg ( $n=266$ ), or a placebo ( $n=264$ ) once daily. At 12 weeks, the change in seated systolic BP from baseline (the primary endpoint) was -14.5 mmHg with 1 mg of baxdrostat, -15.7 mmHg with 2 mg of baxdrostat, and -5.8 mmHg with placebo. The placebo-corrected difference was -8.7 mmHg for 1 mg of baxdrostat and -9.8 mmHg for 2 mg of baxdrostat ( $p<0.001$  for both comparisons). A potassium level greater than 6.0 mmol/L was recorded in 2.3% of patients in the 1 mg baxdrostat group, 3.0% in the 2 mg baxdrostat group, and 0.4% in the placebo group. In patients with uncontrolled or resistant AH, the addition of baxdrostat to background therapy resulted in a significant reduction in seated systolic BP at 12 weeks compared to placebo [12].

**KARDIA-3.** Zilebesiran is a small interfering ribonucleic acid (siRNA) that inhibits the production of angiotensinogen in the liver, thereby reducing the activity of the renin-angiotensin-aldosterone system (RAAS). This phase 2 trial enrolled adults with established CV disease or high CV risk (10-year atherosclerotic CVD risk >15%). An additional inclusion criterion was uncontrolled AH (mean office systolic BP of 140–170 mmHg and mean systolic BP of 130–170 mmHg based on 24-hour ambulatory BP monitoring for 7 days prior to randomization) despite the use of 2–4 antihypertensive drugs, including calcium channel blockers or diuretics. Participants were randomized to receive a single subcutaneous injection of zilebesiran at a dose of 300 mg ( $n=91$ ), 600 mg ( $n=91$ ), or a placebo ( $n=89$ ). During the first 3 months, antihypertensive therapy remained unchanged except for cases of systolic BP >160 mmHg or clinical indications. After 3 months, intensification of antihypertensive therapy was permitted if systolic BP remained >140 mmHg. The mean reduction in office systolic BP at 3 months (the primary endpoint) in the zilebesiran 300 mg or 600 mg groups compared to placebo was not statistically significant, amounting to 5.0 mmHg and 3.3 mmHg, and at 6 months, 3.9 mmHg and 3.6 mmHg, respectively.

**Essence-TIMI 73b.** Olezarsen is an antisense oligonucleotide that inhibits the synthesis of apolipoprotein C-III, leading to a reduction in plasma triglyceride levels. This drug was evaluated in a phase 3 randomized trial involving patients with moderate hypertriglyceridemia (triglyceride levels from 150 to 499 mg/dL) and high CV risk, or with severe hypertriglyceridemia (triglyceride levels  $\geq 500$  mg/dL), who were randomized in a 1:3 ratio to receive monthly subcutaneous injections of olezarsen at a dose of 50 mg ( $n=254$ ), olezarsen at a dose of 80 mg ( $n=766$ ), or a placebo ( $n=329$ ). After 6 months of treatment, the mean placebo-adjusted change in triglyceride levels was -58.4% in the olezarsen 50 mg group ( $p<0.001$ ) and -60.6% in the olezarsen 80 mg group ( $p<0.001$ ). The frequency of serious adverse events was similar across all study groups [13].

**VICTORION-Difference.** The study enrolled patients with hypercholesterolemia and high or very high CV risk. Participants were randomized to receive inclisiran sodium (300 mg subcutaneously;  $n=898$ ) or a placebo ( $n=872$ ) in combination with individually tailored rosuvastatin therapy until the low-den-

sity lipoprotein cholesterol (LDL-C) target was reached or at the maximum tolerated dose. On day 90, the LDL-C target level was achieved significantly more frequently in the inclisiran group compared to the control group (84.9% vs. 31.0%;  $p < 0.001$ ). The mean reduction in LDL-C from baseline to day 360 was -59.5% and -24.3% in the inclisiran and control groups, respectively ( $p < 0.001$ ). A lower proportion of participants receiving inclisiran reported muscle-related adverse events (11.9% vs. 19.2% in the control group;  $p < 0.001$ ). No new treatment safety issues were identified [14].

**DANCAVAS II.** In this study, Danish men aged 60–64 were invited to participate in screening for sub-clinical CVD based on computer-generated random numbers for comparison with a control group (1:4 ratio). Screening included assessment of coronary artery calcification, arterial aneurysms, AF, peripheral artery disease, AH, diabetes, and hypercholesterolemia. The intervention involved prescribing statins, aspirin, and observation. Of the 5,946 invitees, 62.6% ( $n=3,720$ ) attended and underwent the screening; the control group consisted of 25,322 individuals. In an intention-to-treat analysis after a median follow-up of 7.0 years, 9.3% of men in the intervention group and 9.9% in the control group died ( $p=0.169$ ). Major adverse CV events occurred in 10.2% and 10.6% ( $p=0.319$ ). Major bleeding was recorded in 6.0% and 5.1% of participants, respectively ( $p=0.007$ ), with intracranial hemorrhages occurring 23% more frequently ( $p=0.097$ ) and gastrointestinal bleeding 18% more frequently ( $p=0.014$ ) in the screening and subsequent intervention group [15].

**PERI-CRIT.** Perioperative beta-blockade reduces heart rate and the risk of MI but increases the risk of hypotension, death, and stroke. It was hypothesized that ivabradine, which selectively reduces heart rate, could prevent prognostically significant myocardial damage after non-cardiac surgery without causing hemodynamic instability. The study involved patients aged  $\geq 45$  years with atherosclerotic disease or a risk of its development who were scheduled for non-cardiac surgery. They were randomized to receive ivabradine ( $n=1,050$ ) at a dose of 5 mg twice daily for 1 hour before surgery and for 7 days, or a placebo ( $n=1,051$ ). The mean heart rate during surgery was 3.2 beats per minute lower in the ivabradine group than in the placebo group, while the mean BP during surgery did not differ between the groups. However, an elevated post-

operative cardiac troponin level in  $\geq 1$  sample above the 99th percentile of the upper reference limit within 30 days after randomization (the primary endpoint) was observed in 17.0% of patients in the ivabradine group and 15.1% in the placebo group ( $p=0.25$ ) [16].

**ABC-AF.** The biomarker-based ABC-AF-stroke score (age, NT-proBNP, and high-sensitivity troponin T, and clinical history of stroke/transient ischemic attack) provides a quantitative assessment of stroke risk both with and without oral anticoagulant treatment. Similarly, the biomarker-based ABC-AF-bleeding score (age, growth differentiation factor 15, hemoglobin, high-sensitivity troponin T, and past history of bleeding) provides a quantitative assessment of the risk of major bleeding during oral anticoagulant treatment, which can be compared with the quantitative risk of stroke. In a randomized registry-based trial involving 3,933 patients with AF (mean age 73.9 years), researchers in the intervention group obtained stroke and bleeding risk information for each patient using the ABC-AF score to support decision-making and treatment recommendations, including the choice of anticoagulant therapy. In the control group, patient management was left to the researchers' discretion, who typically followed clinical guidelines. Enrollment was terminated early due to safety concerns when, at a median follow-up of 2.6 years, 19% ( $p=0.12$ ) more primary endpoint events (stroke or death) occurred in the active group compared to the control. There were also trends toward increased risks of major bleeding (by 8%;  $p=0.50$ ), stroke (by 18%;  $p=0.44$ ), and death (by 21%;  $p=0.13$ ) in the group using the ABC-AF-stroke and ABC-AF-bleeding scores compared to the control. These findings highlight the need for prospective testing of the clinical utility of risk stratification and precision medicine tools in various clinical settings before their implementation into everyday medical practice [17].

**HI-PRO.** The optimal duration of anticoagulant therapy following venous thromboembolism (VTE) in patients with a transient provoking factor (e.g., surgery, trauma, or immobilization) and concurrent persistent risk factors remains undefined. In a randomized trial, patients with VTE following a transient provoking factor who had at least one persistent risk factor and had received at least 3 months of anticoagulant therapy were randomized to groups receiving apixaban 2.5 mg twice daily ( $n=300$ ) or a placebo ( $n=300$ ) for 12 months. During the follow-up period,

primary efficacy endpoint events (the first symptomatic VTE recurrence) were recorded in 1.3% of patients in the apixaban group and 10.0% in the placebo group ( $p<0.001$ ). Primary safety endpoint events (the first episode of major bleeding according to International Society on Thrombosis and Haemostasis criteria) occurred with comparable frequency: major bleeding was seen in 1 patient in the apixaban group and none in the placebo group; clinically relevant non-major bleeding was observed in 4.8% of patients in the apixaban group and 1.7% in the placebo group ( $p=0.06$ ). Rare fatal outcomes were not related to cardiovascular or hemorrhagic causes [18].

**SWEDEPAD 1 and 2.** These trials were conducted to evaluate the prognostic efficacy and the impact on quality of life of drug-eluting stents used in endovascular revascularization of infrainguinal arteries in patients with peripheral artery disease. The SWEDEPAD 1 project enrolled patients with chronic limb-threatening ischemia (Rutherford stages 4–6) who, after successful guidewire passage, were randomized to receive either paclitaxel-coated stents ( $n=1,206$ ) or uncoated stents ( $n=1,194$ ). At a median follow-up of 2.67 years, the incidence of the primary endpoint (ipsilateral major amputation (above the ankle)) did not differ significantly ( $p=0.61$ ), nor did all-cause mortality ( $p=0.54$ ) between the groups. Thus, in patients with chronic limb-threatening ischemia undergoing endovascular revascularization, the use of paclitaxel-coated stents did not reduce the rate of major ipsilateral amputations [19]. The SWEDEPAD 2 project involved patients with intermittent claudication (Rutherford stages 1–3) who, after successful guidewire passage, were randomized to receive either paclitaxel-coated stents ( $n=577$ ) or uncoated stents ( $n=578$ ). No difference in quality of life was observed between the groups at 1 year as assessed by the VasuQoL-6 questionnaire (the primary endpoint) ( $p=0.96$ ). All-cause mortality over a mean follow-up of 7.1 years also did not differ significantly ( $p=0.16$ ), although 5-year mortality was higher in patients randomized to the paclitaxel-coated stent group ( $p=0.010$ ). These findings do not support the routine use of expensive paclitaxel-coated stents for endovascular revascularization of infrainguinal arteries [20].

**PULSE.** The study aimed to evaluate the clinical benefit of routine coronary computed tomographic angiography (CCTA) following percutaneous coronary

intervention (PCI) for unprotected left main coronary artery stenosis. A total of 606 patients who received second-generation drug-eluting stents were examined and randomized 1:1 to undergo CCTA at 6 months (experimental group) or receive standard care (control group). At 18 months, the incidence of the composite primary endpoint (all-cause death, spontaneous MI, unstable angina, definite or probable stent thrombosis) was 11.9% in the experimental group versus 12.5% in the control group ( $p=0.80$ ). Compared to the control group, the CCTA group showed a reduced risk of spontaneous MI (0.9% vs. 4.9%;  $p=0.004$ ) and an increased risk of imaging-driven target lesion revascularization (4.9% vs. 0.3%;  $p=0.001$ ), while the rate of clinically-driven target lesion revascularization was similar (5.3% vs. 7.2%;  $p=0.32$ ) [21].

**AQUATIC.** The study included patients with chronic coronary syndrome who had undergone stent implantation more than 6 months prior to enrollment, had high atherothrombotic risk, and were receiving maintenance oral anticoagulant therapy. Following randomization, either aspirin at a dose of 100 mg ( $n=433$ ) or a placebo ( $n=439$ ) was added to the anticoagulant therapy once daily. The study was terminated early on the recommendation of an independent data and safety monitoring board after a median follow-up of 2.2 years due to an excess number of all-cause deaths in the aspirin group. The primary efficacy endpoint (a composite of CV death, MI, stroke, systemic embolism, coronary revascularization, or acute limb ischemia) was observed in 16.9% of patients in the aspirin group and 12.1% in the placebo group ( $p=0.02$ ), while all-cause death occurred in 13.4% versus 8.4% of cases, respectively ( $p=0.01$ ). The key safety indicator (major bleeding) was recorded in 10.2% of patients in the aspirin group and 3.4% in the placebo group ( $p<0.001$ ) [22].

**DUAL-ACS.** This study compared the outcomes of 3-month and 12-month dual antiplatelet therapy (DAPT) in a real-world clinical practice population, which included 5,052 patients who had suffered a type 1 MI within the previous 12 weeks and had received treatment in the form of PCI (70%), coronary artery bypass grafting (CABG) (6%), or medical therapy alone (23%). After 15 months of follow-up, the primary endpoint (all-cause death) occurred in 2.7% of patients in the 3-month DAPT group and 3.4% in the 12-month DAPT group ( $p=0.1232$ ), with no difference in the rate of CV death or non-fatal MI ( $p=0.6149$ ).

Major bleeding, whether fatal or non-fatal, was recorded in 3.2% of patients in the 3-month group and 4.0% in the 12-month DAPT group ( $p=0.0977$ ). No evidence was obtained that DAPT administered for 12 months after MI, in accordance with current guidelines, provided any additional benefit.

**OPTION-STEMI.** Patients with STEMI and multivessel disease who underwent PCI of the culprit lesion were randomized to either immediate complete revascularization (PCI of non-culprit stenoses during the index procedure;  $n=498$ ) or staged complete revascularization (PCI of remaining stenoses on a different day during the index hospitalization;  $n=496$ ). Non-culprit lesions with 50–69% diameter stenosis were assessed using fractional flow reserve (FFR). The primary endpoint (all-cause death, non-fatal MI, or any unplanned revascularization) at 1 year occurred in 13% of the immediate intervention group and 11% of the staged intervention group ( $p$  for non-inferiority = 0.24). The rates of stroke, major bleeding, and contrast-induced nephropathy did not differ significantly between the two groups. Cardiogenic shock during the index hospitalization was observed in 4% of patients in the immediate revascularization group and 2% in the staged complete revascularization group [23].

**NEO-MINDSET.** The study involved patients after successful PCI for acute coronary syndromes (ACS) who, within the first 4 days of hospitalization, were randomized to aspirin discontinuation followed by monotherapy with a potent P2Y12 inhibitor (ticagrelor or prasugrel) ( $n=1,712$ ) or DAPT (aspirin plus a potent P2Y12 inhibitor) ( $n=1,698$ ) for 12 months. During the follow-up period, primary endpoint events (all-cause death, MI, stroke, or urgent revascularization) occurred in 7.0% of patients in the monotherapy group and 5.5% in the DAPT group ( $p=0.11$  for non-inferiority). Major or clinically relevant non-major bleeding was observed in 2.0% of the monotherapy group and 4.9% of the DAPT group, while stent thrombosis occurred in 12 and 4 patients in the respective groups. Among patients who underwent successful PCI for ACS, monotherapy with a potent P2Y12 inhibitor was non-inferior to dual antiplatelet therapy in preventing the composite risk of death and ischemic events over 12 months [24].

**TAILORED-CHIP.** The study evaluated the efficacy and safety of individually tailored antiplatelet therapy with temporal modulation of platelet inhibition inten-

sity in 2,018 patients undergoing complex PCI with high-risk anatomical or clinical features. Individually tailored antiplatelet therapy with early escalation (ticagrelor 60 mg twice daily plus aspirin for 6 months) was compared with DAPT (clopidogrel plus aspirin for 12 months). PCI of the left main coronary artery was performed in 22.6% of cases, complex bifurcation PCI in 19.5%, PCI of diffuse long lesions in 84.1%, multivessel PCI in 93.7%, and PCI in medically treated diabetic patients in 36.7%. The primary endpoint (a composite of all-cause death, MI, stroke, stent thrombosis, unplanned urgent revascularization, and clinically significant Bleeding Academic Research Consortium type 2, 3, or 5 bleeding) at 12 months occurred in 10.5% of patients receiving individually tailored antiplatelet therapy and 8.8% of those receiving DAPT ( $p=0.21$ ). The frequency of major ischemic events was similar in both groups, while the rate of clinically significant bleeding at 12 months was 7.2% in the tailored therapy group and 4.8% in the DAPT group. No benefits of individually tailored antiplatelet therapy were shown for high-risk patients undergoing complex PCI [25].

**TARGET-FIRST.** The study enrolled patients who underwent successful complete coronary revascularization with modern drug-eluting stent implantation within 7 days after an MI and who completed 1 month of DAPT without ischemic complications or major bleeding. Following randomization, patients received either P2Y12 inhibitor monotherapy ( $n=961$ ) or DAPT ( $n=981$ ) for 11 months. During the follow-up period, the primary composite endpoint (all-cause death, MI, stent thrombosis, stroke, or Bleeding Academic Research Consortium type 3 or 5 bleeding) occurred in 2.1% of patients in the P2Y12 inhibitor monotherapy group and 2.2% in the DAPT group ( $p=0.02$  for non-inferiority). The major secondary endpoint (Bleeding Academic Research Consortium type 2, 3, or 5 bleeding) was observed in 2.6% of patients in the P2Y12 inhibitor monotherapy group and 5.6% in the DAPT group ( $p=0.002$  for superiority). Stent thrombosis was rare, and its incidence was identical in the compared groups [26].

**DAPT-SHOCK-AMI.** The exclusion of patients with MI complicated by cardiogenic shock from landmark antiplatelet therapy trials had left gaps in evidence, forcing clinicians to rely on extrapolations from registries and small pharmacodynamic studies, leading to heterogeneity in clinical care. This project was the

first randomized controlled trial of antiplatelet agents involving 605 patients with MI complicated by cardiogenic shock, who were randomized to receive either cangrelor (IV bolus of 30 µg/kg followed by a continuous infusion of 4 µg/kg) or ticagrelor (crushed tablets administered orally in a 180 mg loading dose, followed by a maintenance dose of 90 mg twice daily). The primary laboratory efficacy endpoint (platelet reactivity index 50% at the end of primary PCI) was achieved in 100% of patients receiving cangrelor and 22.1% of those receiving ticagrelor ( $p < 0.0001$ ). At 30 days, the clinical primary endpoint (all-cause death, MI, or stroke) was recorded in 37.6% of patients in the cangrelor group and 41.0% in the ticagrelor group ( $p$  for non-inferiority = 0.13), while the rate of major bleeding was 6.4% and 5.2%, respectively. All-cause death at 12 months occurred in 43.6% of patients in the cangrelor group compared to 49.2% in the ticagrelor group. There was a reduction in the risk of disability and total healthcare costs over 12 months for patients treated with cangrelor.

**ALONE-AF.** Patients included in the study had at least one non-sex-related stroke risk factor (determined by the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, mean 2.1) and no documented recurrence of atrial tachyarrhythmia for at least 1 year following catheter ablation of AF. Participants were randomized to the oral anticoagulant discontinuation group ( $n=417$ ) or the maintenance direct oral anticoagulant (DOAC) group ( $n=423$ ). At the 2-year follow-up, the primary endpoint (a composite of stroke, systemic embolism, and major bleeding) occurred in 0.3% of patients in the anticoagulation discontinuation group and 2.2% in the maintenance DOAC group ( $p=0.02$ ). Specifically, the incidence of ischemic stroke was 0.3% versus 0.8%, and major bleeding was 0% versus 1.4% in the discontinuation and maintenance groups, respectively. These results suggest that lifelong oral anticoagulation may not be necessary for all patients who have undergone successful AF ablation [27].

**BEAT-PAROX-AF.** Pulmonary vein isolation has undergone a paradigm shift with the emergence of pulsed field ablation (PFA)—a relatively simple procedure providing more tissue-selective treatment than thermal energy sources. In a study of 289 patients with symptomatic paroxysmal AF resistant to  $\geq 1$  antiarrhythmic drug, pulmonary vein isolation via PFA was compared to radiofrequency (RF) ablation using the CLOSE protocol. The primary endpoint

was the success rate (no arrhythmia recurrence lasting  $\geq 30$  seconds, cardioversion, class I/III antiarrhythmic drug use after 2 months, and repeat ablation) 12 months after a single procedure, which was 77.2% in the PFA group and 77.6% in the RF group ( $p=0.84$ ). Serious procedure-related adverse events, including unplanned or prolonged hospitalizations, were observed in 3.4% vs. 7.6% of patients in the PFA and RF groups, respectively. No deaths, permanent phrenic nerve palsies, or strokes occurred. The total procedure time was shorter with PFA (56 minutes vs. 95 minutes).

**CUVIA-PRR.** Digital twin technology allows for the precise identification of specific atrial regions that likely drive AF persistence, facilitating a personalized approach to ablation. In a study involving 304 patients with persistent AF refractory to antiarrhythmic drugs, participants were randomized to either individualized pulmonary vein isolation targeting selected phase singularity points or standard pulmonary vein isolation. At 18 months post-ablation, the rate of freedom from atrial arrhythmia recurrence was significantly higher with individualized ablation compared to the standard approach (77.9% vs. 59.5%;  $p=0.004$ ), including patients not receiving antiarrhythmic drugs (45.7% vs. 31.7%). The mean total procedure time was comparable between the two ablation strategies.

**PARACHUTE-HF.** The study enrolled patients with confirmed Chagas disease and HF with an LVEF  $\leq 40\%$  and NT-proBNP levels  $\geq 600$  pg/mL (or  $\geq 150$  pg/mL), or  $\geq 400$  pg/mL (or  $\geq 100$  pg/mL) in those hospitalized for HF within the previous 12 months. Patients were randomized to receive sacubitril/valsartan (target dose 200 mg twice daily;  $n=462$ ) or enalapril (target dose 10 mg twice daily;  $n=460$ ), added to standard therapy. At a median follow-up of 25.2 months, CV death occurred in 23.8% vs. 25.4% of participants, and the first HF hospitalization was recorded in 22.1% vs. 24.1% of patients in the sacubitril/valsartan and enalapril groups, respectively. Thus, no significant differences in clinical outcomes were found between the compared therapies, although patients in the sacubitril/valsartan group showed a more pronounced reduction in NT-proBNP levels (22.5% vs. 5.5%) at 12 weeks [28].

**HELP-MISWEDEHEART.** The study aimed to establish the effect of routine *Helicobacter pylori* screening using a urea breath test on the incidence of upper gastrointestinal bleeding in 18,466 patients hospital-

ized with MI. Upon admission, 2,284 patients during the screening period and 2,275 patients during the non-screening period reported taking proton pump inhibitors (PPIs). During the screening, 6,480 patients (70%) underwent testing, and 23.6% of them tested positive for *Helicobacter pylori*. At a median follow-up of 1.9 years, no significant difference was found in the incidence of upper gastrointestinal bleeding (the primary endpoint), which occurred in 4.1% of patients in the *Helicobacter pylori* screening group and 4.6% in the control group ( $p=0.18$ ). According to the authors, these results do not exclude a clinically significant benefit of *Helicobacter pylori* screening in MI populations with a higher prevalence of infection or in subgroups at increased risk of bleeding [29].

**Project MHYH.** This project represented a protocol for the cleaning, testing, and safety evaluation of the implantation of refurbished, used pacemakers. Export approval for such devices was obtained from the U.S. Food and Drug Administration (FDA) to countries where governments had granted permission. The study was conducted in Kenya, Mexico, Mozambique, Nigeria, Paraguay, Sierra Leone, and Venezuela in 306 patients randomized to receive either a refurbished or a new pacemaker. The infection rate within 12 months after the procedure was comparable: 1.6% with refurbished and 3.1% with new pacemakers. No device malfunctions were recorded in either group. According to the authors, this experience could be expanded, including to the use of refurbished ICDs, which are even more expensive and remain inaccessible to many patients worldwide.

**IMPACT-BP.** The study evaluated the effectiveness of home-based interventions using technology to improve BP control for AH in resource-limited rural South Africa. A total of 744 patients with uncontrolled AH were randomized into three groups: (1) standard clinic-based care (control); (2) home-based BP self-monitoring provided with blood pressure monitors, involvement of community health workers who visited patients at home for data collection and medication delivery, and remote nurse monitoring via a mobile app with decision-support functions; (3) an expanded community health worker group where monitors were equipped with cellular technology for automatic transmission of BP readings to the mobile app. At 6 months, mean systolic BP was lower in group 2 (-7.9 mmHg;  $p<0.001$ ) and group 3 (-9.1 mmHg;  $p<0.001$ ) compared to standard therapy. In the stan-

dard care group, the AH control rate at 6 months was 57.6%, compared to 76.9% and 82.8% in groups 2 and 3, respectively. In both investigated interventions, the patient retention rate in the treatment program was over 95%. According to the authors, these results serve as a clear example that equal access to medical care can be provided in disadvantaged communities, potentially improving AH control in other remote, resource-limited areas.

**NEWTON-CABG CardioLink-5.** Saphenous vein graft (SVG) occlusion following CABG remains a serious challenge. The study included patients who underwent CABG with  $\geq 2$  SVGs and were receiving moderate- or high-intensity statin therapy. Participants were randomized within 21 days after CABG to receive subcutaneous injections of evolocumab at a dose of 140 mg ( $n=389$ ) or a placebo ( $n=393$ ) every 2 weeks. At baseline, median LDL-C levels were 1.85 mmol/L and 1.86 mmol/L, with a subsequent change in LDL-C at 24 months of -52.4% vs. -4.0% in the evolocumab and placebo groups, respectively. The primary endpoint (venous graft occlusion of  $\geq 50\%$  on CCTA or clinically indicated invasive angiography) at 24 months occurred in 21.7% of grafts in the evolocumab group and 19.7% in the placebo group ( $p=0.44$ ). In patients who underwent CABG, evolocumab did not reduce the risk of venous graft restenosis 24 months after surgery, despite a significant reduction in LDL-C levels [30].

**TACSI.** In this open-label clinical trial based on cardiothoracic surgery center registries, patients after CABG for acute coronary syndrome were randomized to receive ticagrelor plus aspirin ( $n=1,104$ ) or aspirin alone ( $n=1,097$ ) for 1 year. During this follow-up period, the composite primary endpoint (death, MI, stroke, or repeat revascularization) occurred in 4.8% of patients in the ticagrelor plus aspirin group and 4.6% in the aspirin-only group ( $p=0.77$ ). The key secondary endpoint was all-cause net adverse clinical events, defined as primary endpoint events plus major bleeding, and its rate was 9.1% in the ticagrelor plus aspirin group versus 6.4% in the aspirin-only group. Major bleeding was observed in 4.9% of patients in the ticagrelor plus aspirin group and 2.0% in the aspirin monotherapy group. In patients undergoing CABG for acute coronary syndrome, adding ticagrelor to aspirin does not reduce the risk of death, MI, stroke, or repeat coronary revascularization compared with aspirin alone for 1 year [31].

**TOP-CABG.** In this study, 2,290 patients undergoing their first elective CABG with at least one saphenous vein graft were randomized to either a DAPT de-escalation group (ticagrelor 90 mg twice daily plus aspirin 100 mg once daily for 3 months, followed by placebo twice daily plus aspirin 100 mg once daily for 9 months) or a DAPT group (ticagrelor 90 mg twice daily plus aspirin 100 mg once daily for 1 year). The primary efficacy endpoint (100% occlusion of the venous graft within 1 year) was observed in 10.79% of patients in the de-escalation group and 11.19% in the group without DAPT de-escalation ( $p=0.008$  for non-inferiority). Meanwhile, clinically relevant bleeding occurred significantly less frequently in the de-escalation group (8.26% vs. 13.19% with standard DAPT;  $p<0.001$ ). According to the study authors, these results may be considered when developing future

guidelines regarding the benefits of a shorter DAPT period during the early stage following CABG.

**OPINION.** The study compared the effectiveness of surgical left atrial appendage occlusion versus no occlusion in 2,118 high-risk patients following heart valve surgery in the absence of AF. The primary endpoint event rate (ischemic stroke, transient ischemic attack, or CV death) within 1 year did not differ significantly between the groups, occurring in 6.9% of patients in the surgical left atrial appendage occlusion group and 8.2% of patients in the control group ( $p=0.25$ ). No significant differences in the incidence of bleeding were observed either. The study authors have planned to extend the patient follow-up period to 3 years.

**Conflict of interest:** none declared.

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# Cardioembolic stroke in atrial fibrillation: challenges of prevention in clinical practice

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**Objective.** The aim of this study was to analyze the clinical characteristics of patients with atrial fibrillation (AF) and cardioembolic stroke (CES), to assess the quality of primary and secondary prevention of ischemic stroke (IS) in these patients, and to evaluate their short- and long-term prognosis.

**Methods.** A retrospective analysis of the medical records of inpatients treated for CES associated with AF between January 1 and June 30, 2023, was conducted at the neurovascular department of Ryazan City Clinical Hospital No. 11. Outcomes at 6 months were evaluated via a telephone survey, while 24-month outcomes were assessed using data from the “RT MIS” medical information system utilized at the hospital.

**Results.** A group of 117 patients was studied, comprising 41 (35.0%) men and 76 (65.0%) women. The mean age of the patients was 76.3±8.9 years. The vast majority of

the patients had comorbidities, and 18% had a history of recurrent stroke. Patients with permanent AF prevailed in the study group (41.9%). The in-hospital mortality rate was 35%. Prior to admission, all patients had a high risk of thromboembolic complications (mean CHA2DS2-VASc score 5.7±1.2), but only 10 of them (8.5%) received adequate anticoagulant therapy (ACT). Telephone survey results showed that 6 months after discharge, 25% of the patients were not compliant with recommendations for oral anticoagulants. At 24 months, out of 76 patients, 21 (27.6%) had died and 30 (39.5%) had been readmitted; of those readmissions, 25 (83.3%) were due to cardiovascular diseases and 5 (16.7%) were due to recurrent IS. During the 24-month follow-up, the risk of a fatal outcome in the ACT-compliant group was 9.1 times lower compared to the non-compliant group (OR=0.109; 95% CI: 0.034–0.353, p<0.001).

**Conclusion.** Patients with CES and AF are elderly individuals with a high incidence of comorbidities and a high risk of thromboembolic complications who do not receive adequate ACT in the outpatient setting. This patient category is characterized by high in-hospital (35%) and 2-year (27.6%) mortality rates. Adherence to ACT significantly reduces the risk of a fatal outcome within 24 months after the index event.

**Keywords:** atrial fibrillation, cardioembolic stroke, ischemic stroke, anticoagulation therapy, compliance.

**Conflict of interest:** none declared.

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## Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a significantly increased risk of ischemic stroke (IS). A history of AF is present in one in five IS cases [1]. The risk of developing AF increases with age, which in turn elevates the risk of cardiovascular events, primarily acute cerebrovascular events. Given the global trend of population aging, an increase in both AF incidence and the number of strokes can be expected in the future. Cardioembolic IS in patients with AF poses a significant challenge due to its severe course and high rates of disability and mortality [2]. The administration of anticoagulant therapy (ACT) is the cornerstone of preventing thromboembolic complications (TECs) in patients with AF [3]. However, despite taking anticoagulants, approximately one-quarter of these patients develop an IS or a transient ischemic attack (TIA), which raises many questions and requires further research [4].

## Objective

The aim of this study was to analyze the baseline clinical characteristics of patients with AF and cardioembolic stroke (CES), to evaluate the quality of primary and secondary prevention of IS in these patients, and to assess their short- and long-term prognosis.

## Methods

The study was conducted at the neurovascular department of Ryazan City Clinical Hospital No. 11. The medical records of 117 inpatients with CES and AF who received inpatient treatment from January 1 to June 30, 2023 were analysed. Inclusion criteria were: age 18 years and older, men and women with AF who

had suffered a CES. Demographic and socio-economic data, prior preventive treatment, clinical characteristics, comorbidities, and the results of laboratory and instrumental tests performed in accordance with stroke treatment standards were evaluated. Six months after discharge, a telephone survey was conducted to assess adherence to ACT and possible outcomes. At 24 months, outcomes were evaluated by analyzing data from the "RT MIS" medical information system used at the hospital; data were obtained for 100% of the study participants.

## Statistical analysis

Statistical analysis was performed using StatTech v. 4.12.5 software (Stattech LLC, Russia). Continuous variables were tested for normal distribution using the Shapiro-Wilk test (for sample sizes of less than 50) or the Kolmogorov-Smirnov test (for sample sizes of more than 50). Normally distributed continuous variables were presented as the arithmetic mean (M) and standard deviation (SD). The 95% confidence interval (95% CI) was calculated to estimate the precision of the mean values. Non-normally distributed continuous data were presented as the median (Me) and the interquartile range (Q1–Q3). Categorical data were presented as absolute values and percentages. The 95% CIs for proportions were calculated using the Clopper-Pearson method. The comparison of proportions in the analysis of 2x2 contingency tables was performed using Fisher's exact test (when the minimum expected cell frequency was less than 10). The odds ratio (OR) with a 95% CI was calculated as a quantitative measure of the effect size when comparing categorical variables. Differences were considered statistically significant at  $p < 0.05$ .

## Results

The study included 117 patients: 41 (35.0%) men and 76 (65.0%) women, with a mean age of  $76.3 \pm 8.9$  years. All 117 patients suffered from arterial hypertension (AH), 89 (76.1%) had coronary heart disease (CHD), 36 (30.8%) had type 2 diabetes mellitus (DM), 25 (21.4%) had stage II–IV chronic kidney disease (CKD), and 113 (96.6%) had chronic heart failure (CHF). A history of recurrent IS was present in 18% of the patients. At the time of admission, only 46 patients (39%) were taking antihypertensive drugs, and 25 (21%) were taking lipid-lowering drugs. The in-hospital mortality rate was 35%. The main clinical and demographic characteristics of the patients are presented in Table 1.

Patients with permanent AF predominated in the study group (49 patients, 41.9%), while 39 patients (33.3%) had persistent AF, and 29 (24.8%) had paroxysmal AF. The mean CHA2DS2-VASc ( $5.7 \pm 1.2$ ) and HAS-BLED ( $2.2 \pm 0.6$ ) scores calculated prior to admission indicated that all patients required ACT; however, only 10 of them (8.5%) had been receiving the appropriate therapy in the correct dosage regimen before the cerebrovascular event occurred. The main reasons for the absence of anticoagulants in their treatment included: reluctance to take these medications (17 patients, 33.3%), high cost (13 patients, 25.5%), complaints about complications (6 patients, 11.8%), and the replacement of anticoagulants with antiplatelet agents (15 patients, 29.4%). Telephone survey results revealed that 6 months after discharge, 25% of the patients did not comply with oral

anticoagulant recommendations following their CES. At 24 months, 21 of the 76 patients (27.6%) had died, and 30 (39.5%) had been readmitted; of those readmissions, 25 (83.3%) were due to cardiovascular diseases and 5 (16.7%) were due to a recurrent IS.

ROC analysis demonstrated an association between in-hospital mortality and both the severity of the neurological deficit (NIHSS score  $> 12$  points: AUC = 0.835; 95% CI: 0.751–0.918,  $p < 0.001$ ) and the estimated glomerular filtration rate ( $< 52.3$  mL/min/1.73 m<sup>2</sup> using the CKD-EPI formula: AUC = 0.661; 95% CI: 0.561–0.760,  $p = 0.004$ ). The risk of in-hospital mortality was 4.4 times higher in patients with a history of myocardial infarction (95% CI: 1.660–11.701,  $p = 0.003$ ). Over the 24-month follow-up, the risk of a fatal outcome was 9.1-fold lower in the ACT-compliant group compared to the non-compliant group (OR = 0.109; 95% CI: 0.034–0.353,  $p < 0.001$ ).

## Discussion

Between January 1 and June 30, 2023, 117 patients received treatment for CES associated with AF at the neurovascular department of Ryazan City Clinical Hospital No. 11; the majority of these patients were elderly or senile. Women predominated among the studied cohort, which aligns with data from foreign and domestic registries. This is attributed to the longer life expectancy of women compared to men in older age groups and, consequently, a higher incidence of stroke [1, 4–6]. Maksimova M.Yu. et al. also demonstrated a predominance of female stroke survivors over males in the age group of 70 years and older [7].

All patients with AF and CES were characterized by multiple comorbidities. AH was the most prevalent concomitant pathology and a significant risk factor for both AF and stroke. Notably, the majority of the patients were not receiving necessary hypotensive therapy at the time of CES onset. Consistent with many other studies, our patient cohort showed a high prevalence of CHD, CHF, CKD, and type 2 DM [5, 8]. For 18% of the patients, the current stroke was recurrent, which substantially increases the risk of unfavorable outcomes in this patient category. Comorbidities act as risk factors for both thromboembolic and hemorrhagic complications in patients with AF, making their assessment crucial when initiating ACT.

Patients with permanent AF prevailed in our cohort, which is consistent with findings by Melekhov A.V. et

**Table 1. Clinical characteristics of patients with AF and CES**

Variable	Patients included in the study	
	Number	%
Urban/rural, %	62/55	53/47
Employed/Unemployed, %	5/112	4.3/95.7
Disability, %	10	8.5
Active smokers, %	8	6.8
Alcohol abuse, %	4	3.4
Obese, %	48	41
BMI, kg/m <sup>2</sup>	29.1±6.5	
Brachiocephalic arteries atherosclerosis (50%/50–70% stenosis)	89/41	76.1/35.0
NIHSS score	10.6±7.2	
Total cholesterol, mmol/L	5.1±1.4	
Triglycerides, mmol/L	1.31±0.9	
Glucose, mmol/L	6.7±2.7	
Creatinine, mmol/L	105.5±63	
Glomerular filtration rate, mL/min/1.73 m <sup>2</sup>	56.2±17.1	

al., despite the risk of stroke being approximately equal for permanent and paroxysmal forms of AF. This may be explained by the fact that stroke is often the first clinical manifestation of previously undiagnosed AF. Therefore, the true prevalence of paroxysmal AF among patients with IS remains underestimated [1].

Prior to developing a CES, all patients had absolute indications for ACT due to a high risk of TECs; however, only a third of them were taking anticoagulants, and the vast majority of those did not adhere to the proper dosing regimen. A similar situation was described by Sokolov A.V. et al [9]. According to foreign authors, approximately 30% of patients with AF exhibit poor adherence to ACT [10]. An analysis of the reasons for the lack of direct oral anticoagulants (DOACs) in the treatment regimens of CES patients revealed that the overwhelming majority discontinued the drugs on their own due to low awareness of their condition and a lack of motivation. A survey by Potpara T.S. et al. demonstrated that even after a detailed explanation of the risk factors and benefits of therapy, 12% of patients would still refuse to take anticoagulants; the main reasons for refusal were fear of bleeding and underestimation of stroke risk [11]. The high cost of DOACs is another significant barrier to therapy; in our study, 25.5% of patients cited this as an issue.

Data regarding a history of stroke and adherence to ACT are controversial. On one hand, due to post-stroke cognitive impairment, patients often forget to take their medications or fail to recognize the need for therapy, as demonstrated by Tiili P. et al [12]. On the other hand, Luger S. et al. reported high adherence (>90%) to ACT during the first year after a stroke [13]. In our study, 75% of the patients adhered to ACT recommendations following a CES, which is significantly higher than the percentage of patients taking

DOACs for primary TEC prevention. This is likely due to an increased awareness of the problem by both the patients and their relatives. Among all IS subtypes, CES is associated with the highest acute in-hospital mortality and a rather poor long-term prognosis. In a study by Arboix A. et al., in-hospital mortality for CES was 27.3%, compared to 0.8% for lacunar and 21.7% for atherothrombotic strokes [14]. In-hospital mortality in our sample was even higher (35%), which can be attributed to insufficient control of cardiovascular risk factors at the pre-hospital stage and delayed hospital admission. Regarding long-term prognosis, several authors report that the 24-month mortality rate for AF patients after a CES ranges from 30% to 50%, with the lack of adequate ACT being the leading modifiable risk factor [10, 14, 15]. In our cohort, the 2-year mortality rate was 27.6%, and adherence to ACT significantly reduced this risk.

## Conclusion

Patients who experience a CES associated with AF form a particularly vulnerable cohort of elderly individuals with multiple comorbidities, which results in a high risk of recurrent thromboembolic events. Adequate ACT prior to the cerebrovascular event is received by only 8.5% of patients; however, even after suffering a CES, only 75% of them remain compliant with the prescribed direct oral anticoagulant regimen. CES in patients with AF is characterized by high rates of in-hospital mortality (35%), 2-year mortality (27.6%), hospital readmissions (39.5%), and recurrent IS (16.7%). Uninterrupted ACT reduces the risk of a fatal outcome within 24 months of the index event by a factor of 9.1.

**Conflict of interest:** none declared.

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# Predicting mortality and non-fatal cardiovascular events in patients with stable coronary heart disease

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**Objective.** The aim of the study was to identify the factors, associated with poor prognosis in patients with stable coronary heart disease (CHD), and to build a statistically validated model for predicting the risk of mortality and non-fatal cardiovascular events (CVEs) in patients with stable CHD.

**Methods.** This retrospective observational cohort study included 85 patients, admitted to the Dagestan Center of Cardiology and Cardiovascular Surgery for planned inpatient treatment from 01.01.2015 to 31.12.2017 and with a diagnosis of stable exertional angina. The data were collected from patients' medical records and their long-term outcomes were consequently verified. Simultaneously, a telephone contact was established with enrolled patients to ascertain vital status and to record cardiovascular events. The patients were invited for reassessment, which included clinical and anamnestic data, laboratory and instrumental diagnostics. For the prognostic model,

binary logistic regression was used to evaluate the impact of certain factors on the probability of adverse outcomes development.

**Results.** Over the 4-year period of observation, 5.9% (5 people) of 85 patients died. In 84.7% (72 patients) of all cases, admission due to CHD worsening was registered. In 15.3% of patients (13 people), the primary composite endpoint, which included all-cause mortality and CVE development, was reached.

The prognostic model for evaluation of probability of reaching the primary endpoint, depending on the influence of variable factors was built. The most significant factors included: hematocrit, echocardiographic left atrial volume, and coronographic chronic occlusion of the left circumflex artery. The obtained model was proven statistically significant ( $p < 0.001$ ), and had high sensitivity (85.7%) and specificity (97.4%).

**Conclusion.** In this study, certain factors that contribute to the risk of death and non-fatal CVEs in patients with stable CHD were identified. This allowed for the development of a prognostic model to estimate these risks and facilitate the further implementation of secondary prevention measures in clinical practice.

**Keywords:** coronary heart disease, stable exertional angina, cardiovascular events, life expectancy, survival.

**Conflict of interest:** None declared.

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## Introduction

According to the World Health Organization, cardiovascular diseases (CVDs) remain one of the leading causes of mortality worldwide, despite continuing advances in diagnosis and treatment [1]. Statistical data indicate that CVD mortality in the Republic of Dagestan (RD) rose from 203.1 in 2018 to 208.4 per 100,000 population in 2022 [2]. Mortality from coronary heart disease (CHD) accounted for 23.8% of all-cause deaths and, specifically, 54.2% of CVD deaths, placing it first among CVDs in Russia in 2022 [2]. Between 2019 and 2022, CHD mortality in Russia increased from 301.4 to 307.4 per 100,000 population, representing a growth rate of 2.0%. Furthermore, during the first two years of the COVID-19 pandemic, a sharp increase in mortality was observed (from 347.3 in 2020 to 348.1 per 100,000 population in 2021) compared with 2019 [3]. An analysis of age-standardized CHD mortality across 45 countries demonstrated that the Russian Federation belongs to the group of countries with high CHD mortality, and that the burden of CHD in Russia exceeds that of economically developed nations [4].

CVD mortality ranks first in the overall mortality structure in the RD, accounting for 40.6%<sup>1</sup> in 2024. Between 2016 and 2019<sup>2</sup>, CVD mortality in the RD declined gradually by 5.3%, from 209.4 to 198.7 per 100,000 population. However, in 2020, against the backdrop of the COVID-19 pandemic, CVD mortality spiked sharply to 244.4 per 100,000 population, which may be attributed to constraints in the organizational and methodological work on cause-of-death analysis across nosological groups during the pandemic. Over

the period from 2020 to 2024, CVD mortality in the RD declined from 244.4 to 191.8 per 100,000 population. The highest CVD mortality rates were recorded in the highland districts of the RD, where older age groups predominate. It should be noted that CHD has remained the primary driver of high CVD mortality over the past decade, accounting for 58.4% in 2024<sup>1</sup>.

Stable exertional angina is the most frequently diagnosed form of CHD. It is characterized by a relatively predictable pattern of ischemic chest pain that occurs with physical exertion or emotional stress and is rapidly relieved by rest [5].

Patients with stable angina are at elevated risk of subsequent myocardial infarction or sudden cardiac death due to rupture of an unstable atherosclerotic plaque. The mean annual event rate is approximately 2% [5].

Although modern treatment strategies substantially improve the prognosis of patients with stable CHD, individualized risk stratification for adverse outcomes in this population remains an important clinical challenge. A key trend in contemporary medicine in general, and in cardiology in particular, is the shift toward personalized medicine, which requires precise risk stratification based on each patient's individual characteristics. However, existing prognostic scores are frequently limited either by a narrow set of parameters or by insufficient adaptation to real-world clinical practice.

In this context, predicting mortality and non-fatal cardiovascular events (CVEs) in patients with stable CHD using clinical, anamnestic, laboratory, and instrumental data routinely available in clinical prac-

<sup>1</sup> Resolution of the Government of the Republic of Dagestan On approval of the regional program of the Republic of Dagestan "Optimal medical rehabilitation for health restoration in the Republic of Dagestan" dated June 30, 2025 № 219.

<sup>2</sup> Resolution of the Government of the Republic of Dagestan On Amendments to the State Program of the Republic of Dagestan "Combating Cardiovascular Diseases" dated June 30, 2021 № 159.

tice represents a task of both scientific and practical importance.

### Objective

The aim of this study was to identify factors associated with poor prognosis in patients with stable CHD and to develop a statistically validated prognostic model for mortality and non-fatal CVE risk based on clinical and anamnestic data available at initial hospitalization.

### Methods

This retrospective, observational, cohort study enrolled 85 patients who underwent planned inpatient treatment between 01.01.2015 and 31.12.2017 with a diagnosis of CHD with stable exertional angina at the Dagestan Center of Cardiology and Cardiovascular Surgery (DCCVS). Data were collected from medical records archived at the DCCVS for the above period, followed by verification of long-term outcomes. Telephone contact was established with enrolled patients to ascertain vital status and to record cardiovascular events. Patients were invited to the DCCVS for a follow-up assessment comprising clinical and anamnestic data collection and laboratory and instrumental investigations (complete blood count, biochemical blood panel, lipid profile, electrocardiography, echocardiography).

#### Inclusion criteria

Inclusion criteria: planned hospitalization at the DCCVS from 01.01.2015 to 31.12.2017 with a diagnosis of stable exertional angina; residence within the RD; coronary angiography (CAG) performed during the index hospitalization; availability of a medical record in the hospital archive containing clinical, anamnestic, and laboratory/instrumental data at the time of the index hospitalization.

#### Exclusion criteria

Exclusion criteria: refusal to participate in the study; diagnosis of acute myocardial infarction or unstable angina at admission or within one month prior to the index hospitalization; emergency CAG or percutaneous coronary intervention performed within the first 24 hours of admission; residence outside the RD; relocation outside the RD; absence of CAG data at the index hospitalization; absence of a medical record in the hospital archive; presence of an active malignancy at the time of index hospitalization.

The study identified factors associated with adverse outcomes in patients with stable CHD, assessed the incidence of the primary composite endpoint (PCE)—defined as all-cause death or non-fatal CVE (myocardial infarction, stroke, or transient ischemic attack)—and developed a statistically validated model for predicting PCE risk based on clinical and anamnestic data available at the index hospitalization.

PCE components observed in the study population were: 5 deaths, 2 myocardial infarctions, 3 strokes, and 3 transient ischemic attacks.

The study was conducted in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. The Ethics Committee of Dagestan State Medical University of the Ministry of Health of the Russian Federation approved the study protocol. Written informed consent was obtained from all participants prior to enrollment.

### Statistical analysis

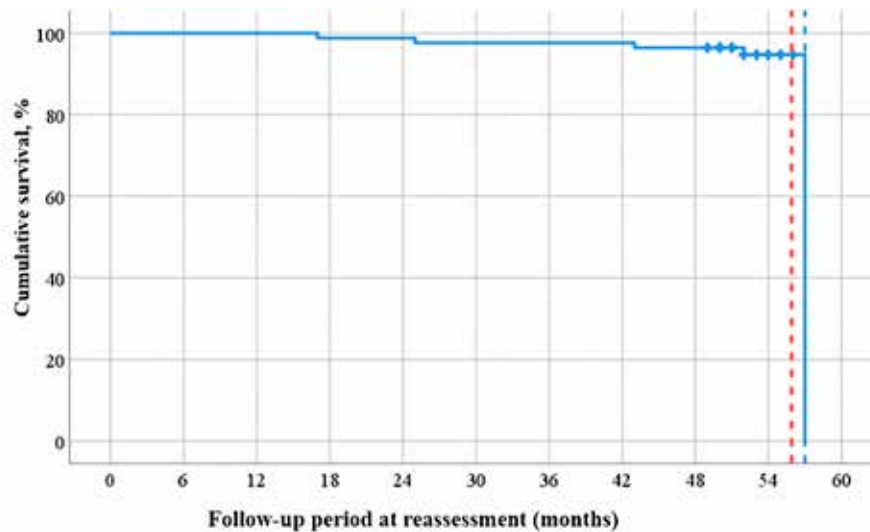
Statistical analysis was performed using IBM SPSS Statistics, version 26. The null hypothesis served as the basis for significance testing, with a p-value of <0.05 considered statistically significant. A binary logistic regression model with stepwise backward elimination (Wald method) was used to identify independent predictors of PCE. Model quality was assessed, and sensitivity and specificity were calculated by constructing receiver operating characteristic (ROC) curves with determination of the area under the curve (AUC).

### Results

The study included 85 patients: 62 men (72.9%) and 23 women (27.1%). Mean age at index hospitalization was  $58.55 \pm 8.5$  years (95% CI: 56.39–60.71) in men and  $61.96 \pm 8.6$  years (95% CI: 58.23–65.69) in women. At the time of follow-up assessment, mean age was  $62.84 \pm 8.6$  years (95% CI: 60.58–65.11) in men and  $66.36 \pm 8.9$  years (95% CI: 62.38–70.35) in women.

Patients were followed for 4 years. During this period, all-cause mortality was 5.9% (5 patients): 1 woman (1.7%) and 4 men (6.7%). The mean age at death among men was  $63 \pm 7.26$  years (95% CI: 51.45–74.55); the female decedent was 66 years old.

The Kaplan-Meier survival curve (Fig. 1) depicts the timing of deaths in the study population. Survival analysis yielded a mean survival time of  $55.9 \pm 0.69$  months (95% CI: 54.54–57.26 months). The median



**Fig. 1.** Kaplan-Meier curve, characterizing the survival of the patients with stable CHD (months)

survival time, corresponding to the estimated time to death in at least 50% of patients, was 57 months.

Among the causes of death, 2 cases were classified as sudden cardiac death (40% of decedents), 2 deaths were attributable to concomitant malignancies, and the cause of death could not be established in 1 patient (20% of decedents).

The incidence of deaths and CVEs as a proportion of the total study population (n=85) and per 1,000 patient-years over the follow-up period is presented in Table 1.

**Table 1. Incidence of deaths and CVEs recorded during 4 years of follow-up in the study population, (n=85)**

Event	Number of recorded events		Event frequency to 1000 patient-years
	n	%	
Death	5	5.9 %	21.4
Myocardial infarction	2	2.4 %	6.1
Stroke	3	3.5 %	9.3
Transient ischemic attack	3	3.5 %	9.1

During the 4-year follow-up, 84.7% of patients (72) required repeated hospitalizations due to CHD progression.

**Table 2. Comparison of PCE rates by presence of echocardiographic ventricular dilatation, chronic LCx occlusion, and PDA stenosis on CAG at index hospitalization**

Risk factor	PCE rate				OR	95 % CI	p
	Factor present		Factor absent				
	n	%	n	%			
Echocardiographic ventricular dilatation	5	33.3	7	10.3	4.36	1.15–16.45	0.036*
Chronic LCx occlusion on CAG	3	50	10	12.8	6.8	1.2–38.45	0.045*
PDA stenosis on CAG	4	50	9	12.7	6.89	1.46–32.53	0.022*

**Note \***—statistically significant difference (p<0.05).

The PCE was reached in 15.3% of patients (n=13).

The Kaplan-Meier curve (Fig. 2) shows the time to PCE. Event-free survival analysis yielded a mean time to PCE of 52.62 ± 1.42 months (95% CI: 49.83–55.40 months). The median time to PCE, corresponding to the estimated time at which at least 50% of patients would have reached the endpoint, was 57 months.

Univariate analysis identified echocardiographic ventricular dilatation, chronic occlusion of the left circumflex artery (LCx) on CAG, and stenosis of the posterior descending artery (PDA) on CAG as factors with the greatest statistically significant impact on the odds of PCE (Table 2).

PCE rates were significantly higher in patients with echocardiographic ventricular dilatation versus those without (p=0.036), in patients with chronic LCx occlusion on CAG versus those without (p=0.045), and in patients with PDA stenosis on CAG versus those without (p=0.022). The odds of PCE were 4.36-fold higher with ventricular dilatation (95% CI: 1.15–16.45), 6.8-fold higher with chronic LCx occlusion (95% CI: 1.20–38.45), and 6.89-fold higher with PDA stenosis (95% CI: 1.46–32.53). The associations between PCE and

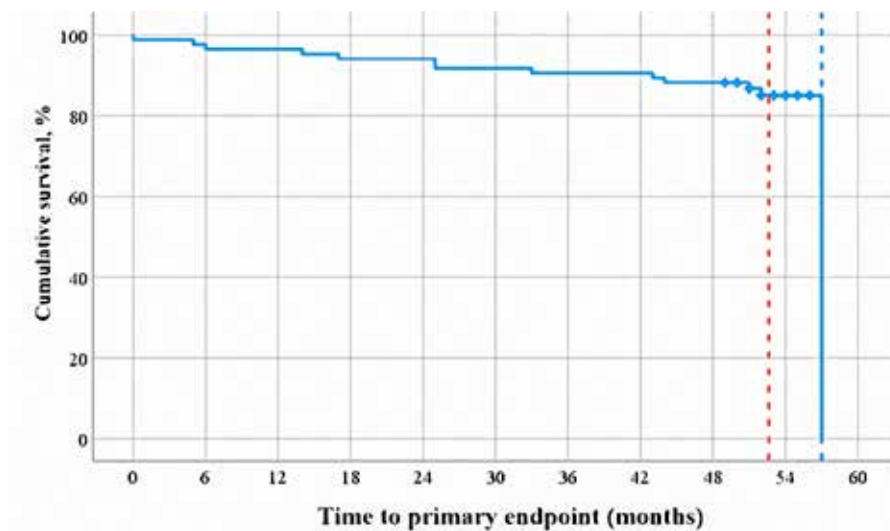


Fig. 2. Kaplan-Meier curve, characterizing reaching of the PCE over the period of observation (months)

each of these three factors were moderate (Cramér's  $V=0.252, 0.265, \text{ and } 0.304$ , respectively).

However, in multivariate analysis, chronic LCx occlusion on CAG emerged as the sole statistically significant independent predictor, associated with a marked increase in the odds of PCE (OR  $\approx 67.8$ ;  $p=0.034$ ) (Table 3).

Table 3. Association between model predictors and PCE probability

Factors	Change in odds with factor present		p
	OR	95% CI	
Hematocrit level on CBC (%)	1.502	0.979-2.305	0.063
LA volume on Echo (mL)	0.854	0.728-1.002	0.053
Chronic LCx occlusion on CAG	67.791	1.387-3313.552	0.034*

Note \*—statistically significant impact of a factor ( $p<0.05$ )

Using binary logistic regression, we developed a prognostic model for the probability of PCE in patients with stable CHD based on clinical and anamnestic data available at the index hospitalization. The relationship is described by equation (1):

$$P = 1 / (1 + e^{-z}) \times 100 \%$$

$$z = -11.016 + 0.407 \times X_{\text{HEMAT}} - 0.158 \times X_{\text{LAV}} + 4.216 \times X_{\text{OCCL.LCX}} \quad (1),$$

where  $P$ —probability of PCE (%);  $X_{\text{HEMAT}}$  = hematocrit level on CBC (%);  $X_{\text{LAV}}$  = left atrial volume on Echo (mL);  $X_{\text{OCCL.LCX}}$  = chronic LCx occlusion on CAG (0 = absent, 1 = present).

The regression model was statistically significant ( $p<0.001$ ). Based on the Nagelkerke  $R^2$ , model (1) accounted for 60.2% of the factors determining the probability of PCE.

Based on regression coefficients, hematocrit level and chronic LCx occlusion on CAG were positively associated with PCE probability, whereas echocardiographic left atrial (LA) volume was inversely associated. A 1% increase in hematocrit increased the odds of PCE 1.502-fold (95% CI: 0.979–2.305); chronic LCx occlusion on CAG increased the odds 67.791-fold (95% CI: 1.387–3313.552); a 1 mL increase in LA volume, conversely, decreased the odds 1.171-fold (OR=0.854; 95% CI: 0.728–1.002) (Table 3).

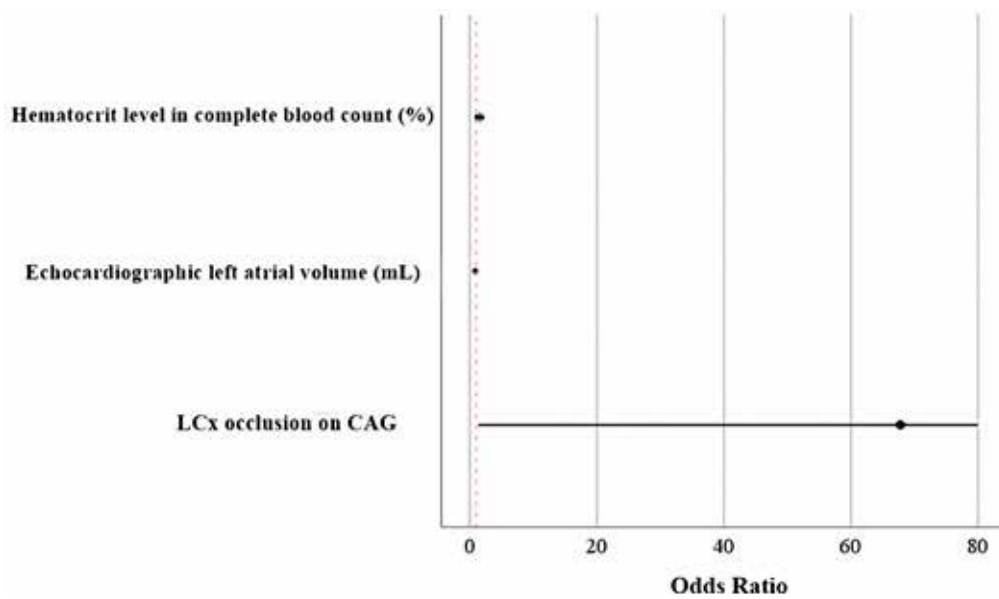
Although the contributions of hematocrit and LA volume did not reach strict statistical significance, both variables were retained in the prognostic model as clinically relevant parameters.

Figure 3 presents the OR values with 95% CI for the factors included in model (1).

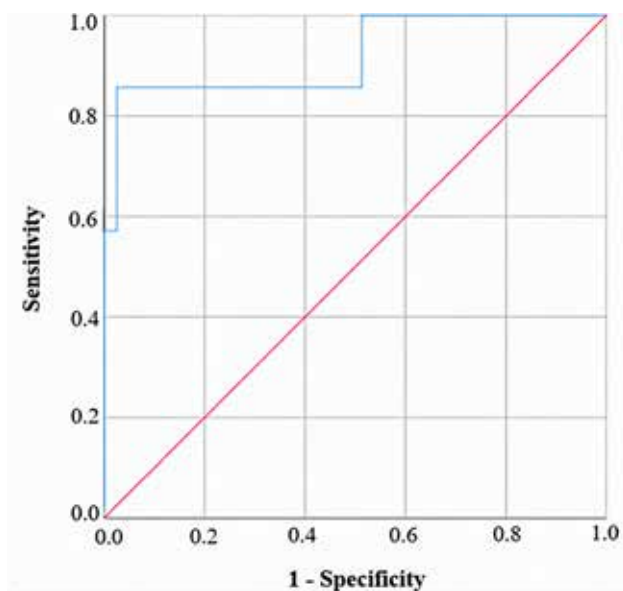
The threshold value of logistic function  $P$  was determined by ROC curve analysis. The resulting curve is presented in Figure 4.

The area under the ROC curve for the relationship between predicted PCE probability in stable CHD patients and the logistic regression function values was  $0.92 \pm 0.07$  (95% CI: 0.78–1.00). The model was statistically significant ( $p<0.001$ ).

The cut-off value of function  $P$  (1) was 50.9%. Values of  $P > 50.9\%$  indicated high risk of PCE; values of  $P < 50.9\%$  indicated low risk. At this threshold, model sensitivity was 85.7% and specificity was 97.4%.



**Fig. 3.** Values of OR with 95 % CI for the studied factors, contributing to the reaching the PCE in patients with stable CHD



**Fig. 4.** ROC curve showing the performance of the prognostic model (1) in predicting the probability of the PCE in patients with stable CHD

## Discussion

The overall mortality of 5.9%, corresponding to 21.4 deaths per 1,000 patient-years, is broadly consistent with mortality rates reported in comparable studies, such as the PROGNQZ IBS study [6], which enrolled patients with similar clinical characteristics.

The Framingham Heart Study reported 2-year rates of acute myocardial infarction and cardiovascular mortality of 6.2% and 3.8%, respectively, in women and 14.3% and 5.5% in men among patients with stable angina [7].

Well-established adverse prognostic factors in stable CHD include advanced age, severe angina, significant myocardial ischemia, extensive coronary atherosclerosis, proximal plaque localization, multivessel disease, severe chronic heart failure, tachycardia, severe depression, poor socioeconomic conditions, comorbidities such as chronic kidney disease, pulmonary disease, malignancy, and peripheral or cerebrovascular disease, as well as traditional cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus [DM], smoking, obesity, etc.) [8, 9]. A relationship between survival in stable CHD patients and the extent of coronary atherosclerosis, degree of luminal narrowing, and anatomical distribution of stenoses has also been established [9]. According to the SCORE risk charts, the 10-year risk of cardiovascular mortality is approximately 4-fold higher in CHD patients aged 50 to 65 years, independent of other risk factors [10, 11].

The CLARICOR trial, which evaluated the predictive value of standard clinical parameters routinely available during outpatient visits for stable CHD patients presenting without new cardiac complaints, found that in univariate analysis smoking, DM, prior myocardial infarction, and use of calcium channel blockers, ACE inhibitors, long-acting nitrates, diuretics, cardiac glycosides, statins, high-sensitivity C-reactive protein, and reduced GFR were all significant predictors of the composite outcome comprising acute myocardial infarction, unstable angina, cerebrovascular disease, and all-cause mortality ( $p < 0.05$ ). In multivariate

analysis, independent predictors of the composite outcome in stable CHD patients were smoking, DM, GFR, and use of long-acting nitrates and cardiac glycosides [12].

Comorbidity is a critical determinant of both the clinical course of stable CHD and long-term patient survival. Among CHD patients with comorbid conditions, those with concomitant chronic obstructive pulmonary disease (COPD) constitute a particularly important subgroup. Population-based data indicate that CHD patients with COPD face a 2- to 3-fold increase in the risk of cardiovascular death. Several studies have demonstrated that the leading cause of mortality in COPD patients is not respiratory failure but complications of coronary insufficiency [13].

Notably, several comorbidities—including COPD, bronchial asthma, and chronic kidney disease stages 3–5—that were associated with significantly increased PCE risk in prior studies such as PROGNOLIBS [8] did not demonstrate a statistically significant effect on PCE in our analysis, which may reflect the limited sample size and the low prevalence of these conditions in our cohort.

Our findings confirm the central role of coronary anatomy in predicting mortality and non-fatal CVEs in patients with stable CHD. Specifically, chronic LCx occlusion emerged as one of the most powerful independent predictors of adverse outcomes in our cohort. These results are consistent with established understanding of the prognostic significance of the location and severity of coronary atherosclerotic lesions in stable CHD [6].

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The inclusion of laboratory and echocardiographic parameters (hematocrit level, echocardiographic LA volume) in our prognostic model reflects the multifactorial nature of outcome prediction and underscores the need for comprehensive risk assessment of mortality and CVEs in patients with stable CHD.

## Conclusion

This study identified key factors associated with increased risk of death and CVEs in patients with stable CHD in the RD and enabled the development of a prognostic model based on clinical and instrumental parameters. The resulting model demonstrated high diagnostic accuracy and predictive precision.

The study results allow identification of patients at high risk of death and CVEs among those with stable CHD, thereby facilitating personalized treatment decisions and selection of patients who would benefit most from advanced therapeutic interventions. Furthermore, the findings provide a basis for optimizing secondary prevention of stable CHD in the RD healthcare system, enabling more rational and targeted allocation of public health resources.

## Limitations of the study

The study was conducted with a limited number of patients (n=85) with a diagnosis of stable exertional angina. An additional limitation is the single-center study design.

**Conflict of interest:** none declared.

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# Changes in ceruloplasmin levels in chronic heart failure in patients with HIV Infection

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Ceruloplasmin (CP) is an important plasma antioxidant and a weak acute-phase reactant, and this is why its assessment allows evaluation of the level of antioxidant defence and the activity of the inflammatory process in the body.

**Objective.** To evaluate the effect of chronic heart failure (CHF) on ceruloplasmin plasma levels in HIV-infected patients.

**Methods.** A total of 240 HIV-infected patients were examined, 160 of them had signs of CHF. CP levels were measured in the plasma of all CHF patients and 30 healthy volunteers using RANDOX reagent kits on a biochemical

analyser. The diagnosis of CHF was confirmed in accordance with the 2020 Clinical Guidelines of the Russian Society of Cardiology.

**Results.** The CP plasma level in healthy volunteers was  $388.9 \pm 18.7$  mg/L. The CP level in HIV-infected patients with CHF was significantly below the reference range: 137.0 [102.0; 155.5] mg/L. CP levels increased in the presence of chronic kidney disease and anaemia. The threshold CP level for the development of CHF with reduced ejection fraction was 233.5 mg/L (sensitivity 99%, specificity 90%).

**Conclusion.** CP plasma levels are significantly reduced in HIV-infected patients with CHF. Even against a background of low CP values, a tendency for CP to increase with worsening CHF severity is preserved. A plasma CP level of 233.5 mg/L increases the probability of CHF with Ejection Fraction (EF) < 40%. In patients with reduced left ventricular ejection fraction or NT-proBNP  $\geq$  1500 pg/mL, CP levels are somewhat elevated but remain below the reference limits. CP levels increase in the presence of chronic kidney disease and anaemia.

**Keywords:** HIV infection, chronic heart failure, ceruloplasmin, chronic kidney disease, anaemia, inflammation.

**Conflict of interest:** none declared.

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## Introduction

Ceruloplasmin (CP) is a copper-containing glycoprotein with ferroxidase activity, particularly essential for iron metabolism, as it facilitates the conversion of ferrous iron ( $\text{Fe}^{2+}$ ) to ferric iron ( $\text{Fe}^{3+}$ ), enabling its binding to transferrin [1]. Elevated CP levels following clinical recovery of patients with inflammatory diseases indicate an incomplete resolution of the inflammatory process [2]. The Human Immunodeficiency Virus (HIV) causes a multitude of metabolic disorders, including significant alterations in iron metabolism, which contributes to the development of complications including anaemia and oxidative stress [1].

Oxidative stress poses a serious problem in HIV infection, as it promotes cell and tissue damage, inflammation, and disease progression. CP neutralises free radicals, thereby protecting against oxidative stress and demonstrating its potent antioxidant properties [3].

## Objective

The aim of the study was to evaluate the effect of CP levels on the clinical and functional status of HIV-infected patients.

## Methods.

A total of 240 HIV-infected patients were examined at the State Budgetary Healthcare Institution "City Clinical Hospital named after M.A. Tverie" in Perm, 160 of them were diagnosed with chronic heart failure (CHF). To establish the normal CP plasma concentrations, its levels were measured in 30 healthy volunteers (donors at the blood transfusion station). CP plasma levels were analysed in 160 HIV-infected CHF patients. Plasma CP concentrations were deter-

mined using RANDOX (United Kingdom) reagent kits on the Clima MC-15 biochemical analyser.

To confirm the diagnosis of CHF, all patients underwent echocardiography using the VIVID T8 system (USA), plasma N-terminal pro-natriuretic peptide (NT-proBNP) levels were measured, and clinical assessment was performed using the Clinical Status Assessment Scale modified by V.Yu. Mareev (SHOKS) [4] and the Six-Minute Walk Test (6MWT). NT-proBNP was determined using Vektor-Best (Russia) reagent kits on the Immulite 1000 immunoassay analyser (USA). A total peripheral resistance (TPR) level of 210 kPa·s/L or higher was considered elevated, as it was previously established by our group [5]. Alcohol dependence was diagnosed using the AUDIT questionnaire, with a score of 20 or more [6].

Inclusion criteria: diagnosis of CHF in an HIV-infected patient and signed voluntary informed consent to participate in the study. Patients with oncological pathology, severe valvular heart disease, pregnant women, individuals under 18 years of age, and patients with tuberculosis were excluded.

The study design complied with the requirements of the Declaration of Helsinki and GCP, and was approved by the Ethics Committee of Perm State Medical University named after Academician E.A. Wagner.

## Statistical analysis

Statistical analysis was performed using Statistica 13 (Russia) and SPSS 26 (USA) software. The normality of distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. In all of cases, quantitative variables had a non-normal distribution and are presented as median with upper and lower quartiles. Binary variables are presented as absolute

numbers and percentages. The Mann–Whitney test, chi-squared ( $\chi^2$ ) test, and ROC analysis were used.

## Results

The CP level in healthy volunteers was  $388.9 \pm 18.7$  mg/L [Patent No. 2362998]. According to reference materials, the normal plasma CP value is 200–600 mg/L [7]. CP serum levels were analysed in CHF patients infected with HIV ( $n=160$ ). The mean CP level was  $137.0$  [102.0; 155.5] mg/L, which is substantially below the reference values.

CP levels were analysed in the group of HIV-infected CHF patients across subgroups defined by key features determining CHF severity (table 1).

It was found that CP levels were significantly reduced in CHF with reduced EF and at plasma NT-proBNP levels  $\geq 1500$  pg/mL. An interesting association was found between elevated CP serum levels and subsequent death within 2 months of study enrolment. No significant differences were found for the remaining parameters.

ROC analysis was performed between serum CP levels and the presence of CHF with reduced EF  $< 40\%$ , and significant results were obtained ( $p=0.036$ ), with an area under the ROC curve of  $0.940 \pm 0.034$  [95% CI: 0.874–1.000]. The threshold CP value for the development of CHF with reduced EF was  $233.5$  mg/L (sensitivity 99%, specificity 90%). Thus, a serum CP level of  $233.5$  mg/L might indicate a very high probability of CHF with reduced EF in an HIV-infected patient. A search was conducted for differences between features depending on the presence of a threshold CP value of  $233.5$  mg/L.

Group 1 comprised patients with CP levels at or above the threshold. Group 2 comprised patients who did not reach the threshold CP level (table 2).

At threshold and above CP levels, fewer steps were completed during the 6MWT, which may indicate a greater clinically significant reduction in exercise tolerance. Left ventricular end-diastolic volume (EDV) was higher, and LVH was more frequent in the group with threshold and above CP values.

The ratio of peak velocities of early transmitral blood flow and early diastolic mitral annular motion ( $E/e'$ ) was higher in the group with threshold CP values. This group also had a higher prevalence of patients with reduced LVEF, PAH, and enlarged LA volume. TPR was higher in Group 1 patients.

At threshold and above CP levels, higher serum cystatin C concentrations and lower GFR values were observed. The latter indicates an association between CP and renal glomerular function. The level of growth stimulation expressed gene 2 (ST2), encoded by the ST2 gene (also known as suppression of tumorigenicity 2), differed significantly between groups, with higher values in the higher-CP group. ST2 is a modern, highly sensitive CHF biomarker, and its concentration increase is associated with worsening CHF severity [8]. The proportion of patients with elevated NT-proBNP  $\geq 1500$  pg/mL was higher in the group with threshold and elevated CP, while NT-proBNP plasma levels did not differ significantly between groups.

## Discussion

CP is the main copper-containing glycoprotein of the blood, binding up to 95% of plasma copper and ap-

Table 1. Plasma CP levels (mg/L) compared by features determining CHF severity in HIV-infected patients

Comparison parameter	CP level in subgroup with feature present	CP level in subgroup with feature absent	p
Male sex, n (%)	135.5 [102.0; 146.0]	143.0 [102.5; 237.5]	0.131
LVEF $< 40\%$ , n (%)	272.0 [267.0; 277.0]	130.0 [97.0; 143.0]	0.038
Diastolic dysfunction of LV (DDL), n (%)	139.0 [110.5; 132.5]	115.5 [95.5; 138.0]	0.083
$\uparrow$ TPR, n (%)	161.0 [101.0; 186.0]	110.5 [99.0; 139.0]	0.887
$\uparrow$ Left atrial volume index, n (%)	126.0 [105.0; 147.0]	138.0 [97.0; 139.0]	0.650
Pulmonary arterial hypertension (PAH), n (%)	137.0 [115.0; 147.0]	113.0 [99.0; 139.0]	0.756
Smoking, n (%)	134.0 [95.0; 153.0]	137.0 [134.0; 158.0]	0.126
Alcohol dependence, n (%)	115.0 [90.0; 153.0]	137.0 [106.0; 158.0]	0.291
Coronary heart disease, n (%)	142.0 [128.5; 150.0]	135.5 [97.0; 161.0]	0.229
NT-proBNP $> 1500$ pg/mL, n (%)	193.5 [150.0; 250.5]	155.0 [108.0; 190.0]	0.048
Death within 2 months of study inclusion, n (%)	267.0 [153.0; 277.0]	134.0 [99.0; 147.0]	0.031
Chronic kidney disease, n (%)	212.0 [147.0; 277.0]	123.0 [97.0; 128.0]	0.044
Antiretroviral therapy, n (%)	110.5 [90.0; 139.0]	138.0 [105.0; 164.0]	0.123
Anaemia, n (%)	139.0 [117.5; 161.0]	73.5 [42.3; 97.0]	0.025
Thrombocytopaenia, n (%)	135.5 [97.0; 150.0]	133.5 [105.0; 164.0]	0.223

**Table 2. Differences in characteristics by threshold CP level of 233.5 mg/L in HIV-infected CHF**

Parameter	CP ≥233.5 mg/L, n=36	CP < 233.5 mg/L, n=124	p
Clinical and anamnestic parameters			
Age, years	35.5 [30.0; 44.0]	36.0 [32.0; 40.0]	0.886
CHF functional class	2 [1; 3]	1 [1; 2]	0.055
6MWT, m	300.0 [250.0; 320.0]	440.0 [350.0; 500.0]	<0.001
SHOKS score	5.0 [4.0; 7.5]	5.0 [4.0; 7.0]	0.361
Viral hepatitis B, C, or both, n (%)			
Echocardiographic parameters			
LVEF < 40%, n (%)	11 [30.5]	1 [0.8]	<0.001
LVEF, %	49.0 [37.0; 63.0]	54.0 [46.0; 64.0]	0.432
DDL, n (%)	16 [100]	63 [34.7]	0.501
LV myocardial mass index, g/m <sup>2</sup>	89.0 [77.0; 120.5]	119.0 [99.0; 105.0]	0.067
LVH, n (%)	13 [36.1]	71 [57.2]	0.025
LV end-diastolic volume, mL	79.0 [44.0; 92.0]	102.0 [83.0; 113.0]	0.038
LV end-systolic volume, mL	30.0 [23.0; 47.0]	38.0 [32.0; 54.0]	0.383
Left atrial (LA) volume, mL	30.8 [24.7; 61.9]	31.6 [26.0; 45.4]	0.834
TPR, kPa·s/L	442.3 [321.4; 552.9]	238.3 [173.7; 355.2]	0.033
Enlarged LA volume, n (%)	22 [61.1]	49 [39.5]	0.021
PAH, n (%)	25 [69.4]	53 [42.7]	0.004
Mean pulmonary artery pressure, mmHg	17.0 [11.0; 33.0]	16.0 [14.0; 33.0]	0.922
E/e'	3.8 [2.6; 5.6]	6.9 [5.2; 9.9]	0.031
Laboratory parameters			
Transferrin, mg/dL	138.4 [83.8; 172]	92.1 [48.7; 127.0]	0.136
Ferritin, µg/L	152.0 [85.0; 256.0]	119.9 [65.9; 325.2]	0.559
Uric acid, µmol/L	87.2 [45.3; 184.7]	106.3 [61.1; 178.7]	0.799
Cystatin C, mg/L	4.97 [4.0; 5.2]	1.7 [1.27; 4.0]	<0.001
GFR, mL/min/1.73m <sup>2</sup>	32.0 [10.0; 38.0]	41.0 [12.0; 59.0]	<0.001
NT-proBNP, pg/mL	392.0 [159.1; 1635.7]	364.8 [256.1; 801.9]	0.885
NT-proBNP > 1500 pg/mL; n (%)	19 [52.8]	15 [12.1]	<0.001
CP, mg/L	257.5 [239.0; 285.0]	135.5 [101.0; 162.0]	<0.001
ST2, pg/mL	104.6 [100.0; 110.2]	91.4 [77.9; 148.4]	<0.001

proximately 3% of total body copper. It functions as a “scavenger” of superoxide radicals, serving as an important antioxidant and acute-phase protein [9].

CP exhibits significant antioxidant properties, protecting cells from oxidative stress. It scavenges reactive oxygen species free radicals, including superoxide radicals, thereby preventing oxidative damage to cellular components. This is particularly important in inflammatory processes, where elevated free radical levels cause extensive tissue damage [1]. CP reduces platelet pro-aggregant properties, decreasing the activity of the inflammatory process [10].

The majority of CP is synthesised by hepatocytes, and a smaller fraction is made by lung epithelial cells [11]. In our study, many patients had hepatocellular insufficiency with frequent comorbidity with viral hepatitis, which explains the reduced CP levels observed across almost the entire patient cohort. Hepatocellular insufficiency, particularly in the context of hepatic fibrosis, is known to be accompanied by a marked decrease in CP levels [12]. In CHF, and

especially CHF with reduced EF, CP concentrations increase [13], which was also observed in our study — even against a background of initially low values, a rise in CP was noted with reduced EF.

We previously developed a non-invasive method for diagnosing the completion of the inflammatory process in the necrosis zone in myocardial infarction, and identified a link between CP concentration and CHF severity in myocardial infarction [14], where the relationship between CP and heart failure, as well as the increase in CP concentration with worsening CHF, were first demonstrated. In the present study, CP levels were reduced below reference values in all HIV-infected patients with CHF, however, a rise in CP was noted with reduced LVEF, as well as with elevated NT-proBNP ≥ 1500 pg/mL. Severe CHF with NT-proBNP ≥ 1500 pg/mL is accompanied by more intense inflammatory activity in HIV-infected patients [15].

CP is a contradictory agent. On the one hand, the ferroxidase properties of CP manifest as antioxidant activity through inhibition of free radicals, the abil-

ity to “capture and quench” superoxide anion radicals, and prevention of erythrocyte haemolysis. On the other hand, oxidative stress may substantially enhance the oxidase properties of CP as an acute-phase reactant [10]. According to the literature, CP levels exhibit divergent trends in various viral infections. An increase in CP activity has been described in post-COVID syndrome, explained by deficiency of copper and iron required for oxidative phosphorylation and cellular respiration [16]. Severe herpesvirus infection in the acute and remission stages is accompanied by a slight elevation in blood CP levels [17]. Severe influenza is associated with CP suppression, explained by a marked reduction in antioxidant defence. CP concentrations in plasma and cerebrospinal fluid were studied in HIV-infected patients in the context of cerebral disorders, when high CP levels were associated with pronounced cognitive impairment [18]. In unstable atherosclerotic plaques, outside of acute coronary syndrome, blood CP concentrations were reduced [19]. There are data indicating elevated blood CP concentrations in atherosclerosis, angina pectoris, and aortic aneurysm [20]. CP plasma levels may decrease following coronary artery bypass grafting [21]. The complexity of

evaluating the role of CP in mechanisms of oxidative stress lies in the possible manifestation of both its ferroxidase and oxidase properties. CP is an extracellular antioxidant and under normal conditions inhibits approximately 50% of blood lipid peroxidation products [22].

Thus, the obtained data demonstrate the complex and ambiguous role of CP in the pathogenesis of CHF in HIV-infected patients, where its level reflects the interplay between oxidative stress, inflammation, hepatic and renal dysfunction.

## Conclusion

Plasma CP levels are markedly reduced in HIV-infected patients with CHF. This is attributable to suppression of antioxidant defence in the context of HIV infection, tissue hypoxia promoted by CHF, and hepatocellular insufficiency. Even against a background of low CP values, a tendency for CP to increase with worsening CHF severity is preserved. A plasma CP level  $\geq 233.5$  mg/L increases the probability of CHF with EF  $< 40\%$  and NT-proBNP  $> 1500$  pg/mL.

**Conflict of interest:** none declared.

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# Radiofrequency denervation of the pulmonary artery trunk in the modulation of pulmonary hypertension in cardiovascular pathology. Experimental study

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In recent years, radiofrequency ablation (RFA) of the pulmonary artery (PA) trunk has been successfully applied in patients with cardiac pathology complicated by severe pulmonary hypertension (PH), demonstrating high effectiveness in improving quality of life and prognosis. At the same time, the question of objectifying the mechanisms of action of PA trunk RFA and its hemodynamic/clinical efficacy remains under discussion, which served as the basis for this experimental study.

The aim of the study is to substantiate the effectiveness of PA trunk RFA in reducing pulmonary hypertension using immunohistochemical assessment of the completeness of sympathetic denervation by determining the S-100 marker under experimental conditions.

**Methods.** The study included 30 pulmonary artery trunks obtained from individuals who died of non-cardiac causes, aged 31 to 65 years. Immunohistochemical staining for the S-100 protein was performed.

**Results.** In sections of pulmonary artery trunks subjected to RFA, nerve fibers did not stain for S-100, which indicates the destruction of autonomic nerve fibers in the pulmonary trunk.

**Conclusion.** Immunohistochemical staining for S-100 is a valid method for verifying irreversible thermal damage to autonomic nerve fibers in the pulmonary artery trunk as a result of RFA.

**Keywords:** radiofrequency ablation, pulmonary hypertension, autonomic nerve fibers, pulmonary trunk, immunohistochemistry, S-100.

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## Introduction

Cardiovascular diseases continue to rank among the leading causes of mortality worldwide. According to the Ministry of Health of the Russian Federation, in 2024 approximately 45% of all deaths in the country were associated with heart and vascular diseases [1]. According to the World Health Organization, cardiovascular diseases claim the lives of nearly 17.9 million people annually [1]. The prevalence of mitral valve disease reaches 8%, and its numerous complications require an individualized surgical approach [2–4]. Pulmonary hypertension (PH) often accompanies many cardiac and pulmonary diseases, as well as autoimmune disorders [3]. In PH, there is a progressive increase in pressure within the pulmonary artery system, leading to right ventricular heart failure and premature death [4]. The pathogenesis of the disease is associated with endothelial dysfunction, characterized by increased production of vasoconstrictors (thromboxane, endothelin-1) and decreased production of vasodilators (NO, prostacyclin), resulting in vascular wall remodeling manifested by reduced elasticity, vascular obliteration, and reduction of the pulmonary vascular bed [2].

In recent years, in a number of cardiac surgery centers in Russia and abroad, radiofrequency denervation (RFD) of the pulmonary artery (PA) trunk has

been performed simultaneously with surgical correction of acquired mitral valve disease [3, 4]. It has been shown that this procedure allows for an additional reduction in mean pulmonary artery pressure [4] compared to isolated correction of mitral valve disease, thereby improving long-term prognosis in this severe category of cardiac surgical patients [5, 6]. In addition to its effectiveness, RFA of the PA trunk has demonstrated safety in clinical studies [7–9]. Besides the minimally invasive catheter-based endovascular RFA procedure, it is often performed during surgical correction of mitral valve disease in patients complicated by atrial fibrillation. The essence of the method lies in creating circular sympathetic denervation, i.e., RFA of ganglionated plexuses of the PA trunk and its orifices, using a specialized clamp-destruction device [10–11]. An informative method for assessing the degree of PA denervation and, consequently, the effectiveness of the procedure is immunohistochemical analysis using polyclonal antibodies to the S-100 protein. The S-100 protein is a low-molecular-weight calcium-binding protein that serves as a sensitive marker of nerve tissue damage [8].

As a result of RFA, structural changes occur in the pulmonary artery tissues, including the sympathetic

fibers located on its surface that exert a vasoconstrictive effect on intrapulmonary vessels [2]. Complete capture and irreversible thermal damage of sympathetic fibers may lead to total desympathization of the pulmonary vascular bed and a sustained reduction in pulmonary artery pressure in the postoperative period.

The aim of the study is to substantiate the effectiveness of PA trunk RFA in reducing pulmonary hypertension through immunohistochemical assessment of the completeness of sympathetic denervation by determining the S-100 marker under experimental conditions.

**Methods.** A total of 30 pulmonary artery trunks obtained during planned autopsies from individuals who died of non-cardiac causes, aged 31 to 65 years, were studied. The material was collected no later than 6 hours after death.

For PA denervation, a radiofrequency generator ("Angio Lab") operating at a frequency of 440 kHz was used, with adjustable exposure time ranging from a few seconds to several minutes and power output from 5 to 120 W. In the experiment, a power setting of 10 W was applied until a circular coagulation line appeared in the RFA area, indicating complete visual damage to the entire wall of the PA trunk. To study the topography of autonomic nerve fibers, five randomly selected pulmonary artery trunks were used as controls for comparison with PA trunks treated with RFA. Samples of pulmonary artery trunks were fixed in 10% neutral buffered formalin, and paraffin blocks were prepared according to a standard protocol. Immunohistochemical staining of the PA wall for the S-100 protein was performed using a Leica Bond MAX immunostainer and polyclonal antibodies to S-100, which provide high staining sensitivity. Nuclear counterstaining was performed with hematoxylin and eosin [9]. Analysis of the obtained histological material was carried out using a Leica DM 4000 microscope with Leica Application Suite 3.8 morphometry.

### Statistical analysis

For primary data processing, systematization, and summarization, methods of descriptive and variation statistics were used. As a quantitative measure, the relative area ( $\mu\text{m}^2$ ) of nerve fibers ( $S_{\text{rel}}$ ) was used, defined as the ratio of the mean area of stained nerve fibers within the field of view to the total area of the field of view. For each pulmonary artery trunk, 5 sec-

tions were examined with 10 fields of view each, and the arithmetic mean value was calculated. The data are presented as median values (Me) with  $\pm 95\%$  confidence interval. Differences between two independent groups were determined using a nonparametric method with the Mann-Whitney U test. Differences between groups were considered statistically significant at  $p < 0.05$ .

### Results

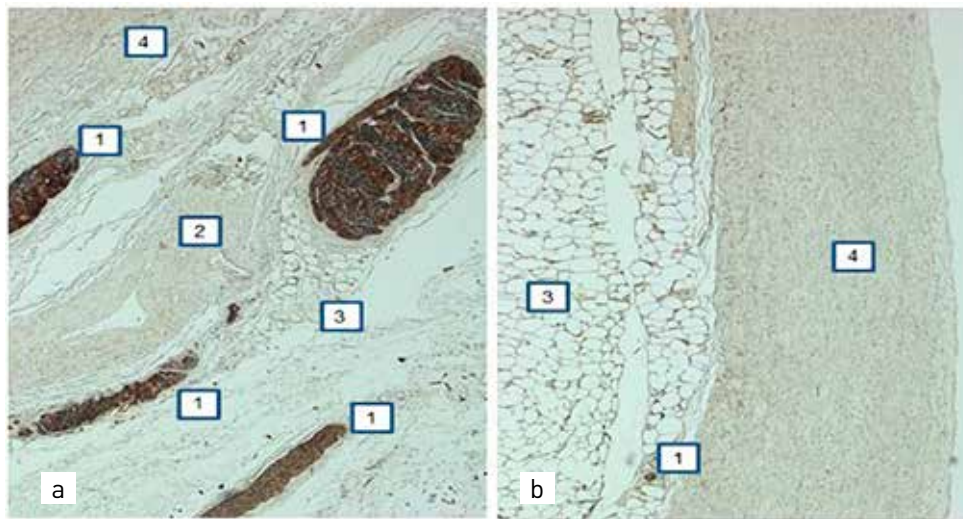
In immunohistochemical examination for the S-100 protein, intact autonomic nerve fibers within the nerve trunk stain intensely in sepia shades (Fig. 1a). They appear as oval structures located adjacent to the vasa vasorum at the boundary between the adipose tissue surrounding the pulmonary trunk and its wall. The membranes of adipocytes and the fibrillar structures of the vasa vasorum and the pulmonary trunk stain in sepia tones less intensely than the autonomic nerve trunks.

Pulmonary artery trunk segments subjected to RFD do not demonstrate immunohistochemical staining for the S-100 protein (Fig. 1b). The sections reveal basophilically stained cell nuclei, as well as shadow-like remnants of the vasa vasorum and adjacent autonomic nerve trunks. The fibrillar structure of the walls of the vasa vasorum and the pulmonary trunk is not visualized. Circular areas of expanded empty space are observed around the nerve trunks, apparently formed by water vapor during the RFA process. A single nerve fiber is identified within the structure of the vasa vasorum in the adventitial layer of the pulmonary artery (Fig. 1b).

The observed changes are similar to those seen in thermal injury. The absence of characteristic immunohistochemical staining for the S-100 protein is likely associated with thermal coagulation of proteins in the RFD zone of the pulmonary artery. It is evident that proteins lose both their native structure and antigenic properties under these conditions, which prevents staining with antibodies to the marker protein [8].

A comparative assessment of the RFD results revealed a statistically significant difference in the Srel parameter between the left lateral margin of the pulmonary trunk and the anteroposterior wall of the pulmonary trunk (Table 1): 5.72% and 0.99%, respectively ( $p < 0.05$ ).

It is known that the extracardiac plexus of the heart is involved in the innervation of other organs of the



**Fig. 1.** Anterior wall of the pulmonary trunk. Immunohistochemical staining, magnification  $\times 200$ :

a) 1 – nerve fiber, 2 – vasa vasorum, 3 – adipose tissue, 4 – wall of the pulmonary trunk,

b) 1 – a single nerve fiber within the structure of the vasa vasorum in the adventitial layer of the pulmonary artery, 3 – adipose tissue, 4 – wall of the pulmonary trunk

**Table 1. Relative area of stained nerve trunks ( $S_{rel}$ )**

Parameter	Left lateral margin of the pulmonary trunk	Anterior and posterior walls of the pulmonary trunk
$S_{rel}$	5.72 % (95 % CI 4.27–8.95)	0.99 % (95 % CI 0.48–0.93)

thoracic cavity, including the pulmonary trunk, PA, and lungs. The innervation of the heart, aorta, and pulmonary trunk is carried out by branches of the cervical sympathetic ganglia. Two cardiac plexuses are distinguished: superficial and deep. The superficial cardiac plexus is located between the aortic arch and the pulmonary trunk. It receives cardiac nerves from the left superior cervical sympathetic ganglion and the left superior cervical cardiac branch of the vagus nerve. The deep cardiac plexus is located posterior to the aortic arch, adjacent to the tracheal bifurcation. It is formed by all other branches of the cervical sympathetic ganglia: the right superior cervical, the middle, and the stellate ganglia.

In this study, the following cardiac plexuses are considered, which cover the regions of the pulmonary trunk subjected to RFA 1) the anterior left plexus, which descends from the left surface of the pulmonary trunk onto the anterior wall of the left ventricle; 2) the anterior right plexus, which descends from the right surface of the pulmonary trunk and the ascending aorta onto the posterior wall of the right ventricle.

Thus, according to the above data, sympathetic innervation of the selected area is provided by branches

of the superficial cardiac plexus, which exert a vasoconstrictive effect on the pulmonary vessels and are located along the lateral surfaces of the pulmonary trunk. In addition, localized RFA applied to the lateral walls of the pulmonary trunk, closer to the site of bifurcation, is unlikely to have a significant effect on bronchial smooth muscle tone, since parasympathetic innervation of the lungs is provided by the parasympathetic plexus (branches of the vagus nerve) located at the pulmonary hilum.

## Discussion

It should be noted that one of the promising directions in endovascular surgery is the use of RFA technology for interventional procedures in various cardiovascular diseases. This includes well-established catheter ablation for severe cardiac arrhythmias [12]. In addition, renal sympathetic denervation has long been used in clinical practice for patients with refractory arterial hypertension, demonstrating good antihypertensive efficacy and improved prognosis [13].

In this context, RFA of the pulmonary trunk and the PA orifices has also demonstrated high efficacy and safety in patients with severe PH undergoing surgical correction of valvular heart disease, including cases complicated by atrial fibrillation [2, 11]. According to other researchers, the efficacy and safety of RFD of the pulmonary trunk and PA orifices in severe PH have been confirmed based on histological examina-

tion of autopsy material [9]. This method represents an effective and safe approach for denervation of sympathetic plexuses located in the adventitial layer of the pulmonary artery. Histological examination of the adventitia of the pulmonary trunk and PA orifices subjected to circular RFA confirms the effectiveness of RFD, demonstrated by a 16% reduction in the mean specific area of nerve endings compared to tissues not exposed to the procedure. It has been shown that RFA of sympathetic nerve fibers of the pulmonary trunk enables effective and long-term control of pulmonary artery pressure in patients with valvular heart disease [2, 3].

In the present study, the effectiveness of RFD is described using quantitative analysis of the relative area of stained nerve endings. This method helps to avoid subjectivity in assessing the degree of damage induced by PA RFA. The use of the relative area of stained nerve fibers as a parameter reduces morphometric measurement errors associated with tissue changes during fixation and paraffin embedding. As a result of RFD, pulmonary artery trunk segments subjected to the procedure do not

exhibit immunohistochemical staining for the S-100 protein. The described changes in the pulmonary artery correspond to the pattern of thermal injury, indicating a persistent effect of sympathetic denervation.

## Conclusion

Immunohistochemical staining for the S-100 protein is a reliable method for verifying irreversible thermal damage to autonomic nerve fibers in the pulmonary artery trunk as a result of PA RFD. This approach can be used to assess the effectiveness of PA denervation. The identified histotopographic patterns of autonomic nerve fibers in the adventitial layer of the human pulmonary artery should be taken into account when performing surgical interventions, including PA RFD in clinical practice.

Thus, immunohistochemical examination for the S-100 protein is an informative tool for evaluating the effectiveness of PA trunk RFD and thereby confirms the pathophysiological mechanism of this procedure.

**Conflict of interests:** none declared.

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# Amiodarone in clinical practice: efficacy, safety, precautions

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Amiodarone, an iodinated benzofuran derivative with properties of Class I, II, III, and IV antiarrhythmic agents, is a commonly prescribed antiarrhythmic drug used for the treatment of supraventricular and ventricular cardiac arrhythmias. Effective use of this agent, given its serious and potentially hazardous adverse effects, requires an understanding of the risk-benefit balance to ensure treatment safety. Amiodarone is most effective as a means of maintaining sinus rhythm in patients with paroxysmal and

persistent atrial fibrillation, for prevention of life-threatening ventricular arrhythmias. The drug has a complex pharmacokinetic profile, a large volume of distribution, and a long half-life, which leads to persistence of its effects after discontinuation. Amiodarone may cause various adverse effects, including thyroid dysfunction, pulmonary fibrosis, and hepatic injury. It interacts with various drugs, including anticoagulants, requiring careful monitoring to prevent complications. In this context,

current perspectives on oral and intravenous amiodarone administration methods, indications, contraindications, recommended doses, drug interactions, adverse effects, and monitoring protocols during long-term treatment with this antiarrhythmic drug are of particular relevance.

**Keywords:** amiodarone, management of cardiac arrhythmias, supraventricular arrhythmias, ventricular arrhythmias, drug interactions, adverse effects.

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## Introduction

Amiodarone was originally synthesised in 1961 at Labaz Laboratories (Belgium) by chemists Tondeur and Binon. They were developing drugs from the extract of the plant *Khella* (*Ammi visnaga*), widely distributed in North Africa [1]. Due to its coronary-dilating and antiadrenergic effects and reduction of myocardial oxygen demand, amiodarone was initially recommended for the treatment of angina pectoris. However, its long-term efficacy proved inferior to that of beta-blockers and calcium channel blockers.

In the 1970s, Charlier R et al. first identified the antiarrhythmic effect of amiodarone in animal experiments, which was confirmed in numerous experimental and clinical studies demonstrating blockade of potassium channels and, to a lesser extent, sodium and calcium channels of cardiomyocyte membranes [1-3]. A comprehensive analysis of the antiarrhythmic effects of amiodarone led Vaughan Williams E.M. to classifying it as a Class III antiarrhythmic agent [1]. However, amiodarone also possesses properties of Class I, II, and IV antiarrhythmics, the combination of which partly explains its exceptional clinical efficacy [1]. Amiodarone causes modest coronary and peripheral vasodilation, which compensates for the potential negative inotropic effect [1-3]. The high antiarrhythmic efficacy of amiodarone is combined with frequently observed negative adverse reactions and complications affecting various organs and systems. In this context, questions regarding the benefit-risk balance of amiodarone use, practical measures to prevent complications, and recommendations for patient monitoring to ensure treatment efficacy and safety remain relevant.

## Objective

The aim of this study was to provide an updated, comprehensive review of indications, contraindications,

recommended dosages, drug interactions, adverse effects, and principles of patient monitoring when using amiodarone.

## Methods

An analysis of scientific publications presented in the Medline, PubMed, elibrary.ru, ncbi.nlm.nih.gov, and researchgate.net databases and web resources over the period 2012–2025 was conducted. Inclusion criteria were results of randomised studies, systematic reviews, and original papers. Exclusion criteria were studies without clearly formulated conclusions or with contradictory results.

## Basic pharmacological properties of amiodarone

In terms of its chemical structure, amiodarone is an iodinated benzofuran derivative. Each tablet (200 mg) contains 75 mg of iodine. The pharmacokinetics of amiodarone has distinctive features associated with its high lipophilicity, large volume of distribution, and slow tissue accumulation. The bioavailability of the drug after oral administration is 30–80%, and simultaneous ingestion with a fatty meal increases intestinal absorption 2.4–3.8-fold compared with fasting [2, 3]. Following oral administration, intravascular distribution continues for approximately 24 hours, and the degree of plasma protein binding is 95%. Over the subsequent days, amiodarone accumulates in almost all tissues, predominantly adipose tissue, as well as the liver, lungs, spleen, and cornea. The therapeutic effect of amiodarone typically develops one week after initiation of therapy (from several days to 2 weeks) [4, 5]. With continuous oral administration, for example for more than 4 weeks, when a tissue depot has been established, the half-life may reach 50–60 days. After discontinuation of prolonged therapy, amiodarone is detectable in plasma for up to 9

months. The possibility of pharmacodynamic effects persisting for 10–30 days after discontinuation should be taken into account [4, 5].

The relatively prolonged saturation period for amiodarone is due to its slow tissue accumulation until the state of equilibrium is achieved. A sustained therapeutic effect with oral administration is observed at a cumulative dose of approximately 10 grams [2, 3]. For saturation, amiodarone is typically administered at 600–800 mg per day in 2–3 or 4 doses; high loading doses (800–1200 mg/day in 2–3 doses) can accelerate the onset of therapeutic effect [3–5].

Amiodarone is metabolised in the liver [4, 5]. In the human body, amiodarone is converted to the active metabolite mono-N-desethylamiodarone, which may potentiate the antiarrhythmic effect of the parent compound [3, 5]. Renal excretion plays a minor role in elimination; therefore, dose adjustment is not required in patients with renal insufficiency [3]. After a single intravenous administration of 300 mg amiodarone, the half-life is approximately 4 hours, with two to three times daily oral dosing at 400–600 mg, the half-life is 1–2 days [3–5]. The complete antiarrhythmic effect of amiodarone on ventricular and supraventricular arrhythmias can be assessed after a plateau effect is reached, approximately 8–10 weeks after initiation of therapy [5–7]. There is no clear correlation between plasma amiodarone or metabolite concentrations and positive clinical effect in arrhythmia treatment, however, at plasma concentrations exceeding 2.5 mg/L, various adverse effects may be observed [5, 6]. No specific studies on optimal maintenance dosing have been conducted. In clinical practice, the maintenance dose is usually 200 mg/day, much less commonly 400 mg/day. Reports of efficacy at lower doses (e.g. 100 mg/day) have been published [6, 7].

Administration of amiodarone results in blockade of Na<sup>+</sup> and Ca<sup>2+</sup> channels of cardiomyocyte membranes, as well as beta-adrenoceptors, thereby producing effects characteristic of Class I, IV, and non-selective Class II agents respectively [8]. The basis of amiodarone's antiarrhythmic action is blockade of K<sup>+</sup> channel ionic current, which is a Class III effect [9]. QT interval prolongation results from prolongation of phases 2 and 3 of the action potential, achieved through blockade of L-type Ca<sup>2+</sup> channels and K<sup>+</sup> channels [1, 10]. Amiodarone decreases sinus node automaticity, slows sinoatrial, atrial, and atrioventricular conduction without affecting ventricular con-

duction, increases refractory periods, reduces atrial and ventricular myocardial excitability, prolongs the refractory period of the atrioventricular node, slows conduction and increases the duration of the refractory period in accessory atrioventricular pathways [8].

One of the potential mechanisms of the antiarrhythmic efficacy of amiodarone may be its ability to inhibit the conversion of thyroxine to triiodothyronine [11]. Administration of the drug may be accompanied by a slight increase in thyroid-stimulating hormone (TSH) levels and a decrease in thyroxine levels, however, these hormonal changes are usually not accompanied by significant clinical symptoms [10, 11].

### **Clinical use of amiodarone**

Amiodarone has been used in clinical practice since the 1960s. Currently, the proportion of amiodarone prescriptions in the structure of pharmacological antiarrhythmic therapy is 24.1% in the USA, 34.5% in Western Europe, and reaches 73.8% in Latin America [6, 7].

Indications for amiodarone administration are outlined in various clinical guidelines for the treatment of ventricular and supraventricular cardiac arrhythmias [12–16] and are presented below.

#### ***Suppression of ventricular ectopic activity in patients with and without structural heart disease***

Amiodarone as monotherapy and in combination with beta-blockers is an effective antiarrhythmic agent for the treatment of ventricular arrhythmias in patients with and without structural heart disease. However, its use is associated with a high risk of extracardiac toxicity. Therefore, amiodarone is typically used when other antiarrhythmic agents are ineffective or cannot be used. The usual regimen is oral amiodarone 200 mg 2–3 times daily for 3–4 weeks, then, after reaching a cumulative dose of 10 grams, treatment is continued at 200 mg once daily 5–7 days per week.

#### ***Termination of paroxysmal tachycardia and tachyarrhythmia episodes***

Intravenous amiodarone is administered into central veins via catheter, as prolonged infusion into peripheral veins may cause phlebitis. When administering into peripheral veins, 20 mL of 0.9% sodium chloride solution should be immediately infused rapidly following injection.

Intravenous amiodarone is recommended for termination of ventricular tachycardia (VT) paroxysms not causing haemodynamic instability. Intravenous amiodarone is recommended for the treatment of polymorphic VT or ventricular fibrillation (VF) associated with acute coronary syndromes. Amiodarone may suppress these life-threatening arrhythmias refractory to electrical cardioversion. Thus, in VT or VF after three unsuccessful defibrillator shocks, intravenous bolus administration of 300 mg amiodarone is recommended, continued during cardiopulmonary resuscitation, to increase the efficacy of electrical shocks and prevent recurrence of life-threatening arrhythmias upon restoration of sinus rhythm. An additional 150 mg amiodarone is recommended after 5 unsuccessful defibrillator shocks. Upon successful treatment, subsequent infusion of amiodarone at 1 mg/min for 6 hours, then 0.5 mg/min for 18 hours is advisable.

For termination of polymorphic VT and supraventricular paroxysmal tachycardia with high ventricular rate, particularly in the context of Wolff–Parkinson–White (WPW) syndrome without haemodynamic compromise, intravenous amiodarone 5 mg/kg over 20 minutes is used. For termination of non-sustained VT with haemodynamic compromise, intravenous bolus administration of 300 mg amiodarone is the method of choice.

Amiodarone is indicated for pharmacological cardioversion of paroxysmal and persistent atrial fibrillation or atrial flutter, including in patients with clinical manifestations of chronic heart failure with reduced Left Ventricular Ejection Fraction (LVEF) <40%. The necessary conditions for such therapy are the absence of haemodynamic instability and anticoagulant therapy. The initial dose of amiodarone is 300 mg intravenously over 30–60 minutes, supplemented if necessary by intravenous infusion of 900–1200 mg over 24 hours. Subsequently, if the arrhythmia does not terminate, oral amiodarone 200 mg three times daily for 4 weeks is recommended until a cumulative dose of approximately 10 grams is reached. It should be noted that oral loading doses of amiodarone represent an adequate and effective alternative to intravenous administration. The expected time to sinus rhythm restoration varies from 8–12 hours (44% of cases) to several days, and the cumulative efficacy of therapy may reach 92%. Although the pharmacological approach is generally less effective than electrical

cardioversion, it avoids cardiac trauma and does not require patient sedation. Amiodarone administration prior to elective electrical cardioversion can increase its efficacy.

### ***Prevention of recurrence of paroxysmal tachycardias and tachyarrhythmias***

For VT and VF, the oral loading dose is 600–1200 mg/day for 8–10 days. The subsequent maintenance dose may be higher, ranging from 200 to 400 mg/day.

For supraventricular paroxysmal tachycardias, amiodarone is prescribed when antiarrhythmic agents of other classes are ineffective or contraindicated. Oral amiodarone 200 mg three times daily for 3–4 weeks is recommended. Upon reaching a cumulative dose of approximately 10 grams, a maintenance dose of 200 mg/day 5–7 days per week is used.

For documented episodes of sustained supraventricular paroxysmal tachycardia in patients with WPW syndrome, amiodarone use is analogous to that in other supraventricular tachycardias.

Amiodarone is the most effective drug for preventing recurrence of atrial fibrillation/flutter. It is recommended for prevention of recurrent symptomatic atrial fibrillation (AF) in patients with heart failure and moderately reduced or reduced LVEF. The amiodarone dosing regimen in such cases is analogous to that for prevention of other supraventricular tachyarrhythmias.

In patients who have undergone cardiac surgery, amiodarone is an effective agent for prevention of postoperative AF [17, 18].

### ***Prevention of sudden cardiac death in high-risk patients***

In patients with structural heart disease (coronary heart disease, dilated, hypertrophic, restrictive, or arrhythmogenic right ventricular cardiomyopathy, haemodynamically significant valvular and congenital heart defects, and marked left ventricular hypertrophy), the risk of sudden cardiac death (SCD) depends on the character of ventricular ectopic activity and the degree of left ventricular dysfunction. The presence of frequent ventricular ectopy (>10 per hour), multiple forms of ventricular ectopic activity (paired ventricular extrasystoles, non-sustained VT), and/or reduced LVEF (<40% on echocardiography) in patients with structural heart disease is associated with increased

SCD risk. Amiodarone monotherapy or its combination with beta-blockers represents the most effective pharmacotherapy for ventricular arrhythmias in patients with structural heart disease, a method of primary and secondary SCD prevention, and the only pharmacological alternative to an implantable cardioverter-defibrillator (ICD). Such treatment reduces the frequency of both life-saving and inappropriate ICD discharges, extending device service life and improving patient quality of life. It is indicated when ICD implantation is impossible for economic reasons.

### ***Amiodarone and radiofrequency catheter ablation***

Currently, radiofrequency catheter ablation (RCA) is one of the primary methods for treating frequent ventricular ectopy and tachyarrhythmias, including supraventricular tachycardias, atrial flutter or AF, and VT in patients with and without structural heart disease [12-16]. With prolonged amiodarone use (1 month or more) prior to RCA, it should be discontinued 1.5–2 months before the procedure, except for planned radiofrequency isolation of pulmonary vein ostia in AF patients.

After one or two intravenous amiodarone doses of 150–300 mg, RCA should be performed after 1–2 days (i.e. 5–7 half-lives; after intravenous administration of 300 mg, the half-life is approximately 4 hours). After two or three oral doses of 400–600 mg, RCA should be performed 1–2 weeks after discontinuation. Before planned ablation, all antiarrhythmic drugs except amiodarone are discontinued for a period calculated as 5–7 half-lives.

Amiodarone administration after RCA performed for ventricular or supraventricular arrhythmias prevents early recurrences, and with prolonged use, late recurrences of arrhythmia [7].

### **Adverse effects of amiodarone**

The World Health Organization classifies the frequency of adverse effects as follows: very common  $\geq 1/10$ ; common  $\geq 1/100$  to  $< 1/10$ ; uncommon  $\geq 1/1000$  to  $< 1/100$ ; rare  $\geq 1/10,000$  to  $< 1/1000$ ; very rare  $< 1/10,000$ . With amiodarone treatment, a number of adverse effects occur very commonly or commonly [19].

#### ***Very common and common adverse effects***

Amiodarone treatment is often or very often accompanied by gastrointestinal disorders, including nau-

sea, vomiting (in 10–25% of cases), dysgeusia (dulling or loss of taste sensation), decreased appetite, epigastric heaviness, and constipation, usually occurring during the loading dose phase and resolving after dose reduction [19]. At the start of amiodarone therapy, particularly within 24–72 hours of intravenous administration, a moderate increase in serum transaminase levels occurs in 15–30% of cases, with subsequent decrease upon dose reduction [4, 20, 21]. In the event of jaundice and/or acute hepatic failure (0.5–1% of cases), amiodarone should be discontinued [20]. This form of toxicity is predominantly associated with hepatocellular injury rather than cholestasis [21]. The exact mechanism of hepatotoxicity resulting from intravenous amiodarone administration remains unknown. Reports indicate that subsequent oral amiodarone administration did not aggravate hepatic injury [22]. The main metabolic pathways of amiodarone involve CYP450 enzymes (CYP3A4 and CYP2C8), and the primary metabolite mono-N-desethylamiodarone is a potential factor of mitochondrial hepatotoxicity; this effect is dose-dependent [23].

Each amiodarone tablet (200 mg) contains approximately 75 mg iodine. With amiodarone doses of 200–600 mg/day, the patient receives 6 to 18 mg of free iodine daily, which is 50 times the optimal daily iodine intake [24, 25]. Deiodination of amiodarone releases a large amount of iodine, which can impair thyroid function, causing hypothyroidism (in 5–20% of treated patients) or thyrotoxicosis (in 1–5% of cases) in predisposed individuals. Not only excess iodine, but amiodarone itself or its metabolite may cause thyroid dysfunction through direct cytotoxicity toward thyroid cells [1, 4, 10, 11]. In addition, amiodarone impairs peripheral conversion of thyroxine to triiodothyronine, which may lead to elevated triiodothyronine levels. Subclinical hypothyroidism is the most common thyroid disorder induced by amiodarone [24]. Hypothyroidism may develop weeks, months, or years after initiation of therapy, serum TSH initially increases but then decreases, often to baseline, and discontinuation of amiodarone is not required [24, 25]. When amiodarone is prescribed for life-threatening indications and hypothyroidism develops, it is not discontinued; levothyroxine is prescribed as indicated to replace thyroid hormone deficiency. Normalisation of serum TSH is the criterion of effective hypothyroidism treatment [26, 27].

A more serious complication is amiodarone-induced thyrotoxicosis, which occurs in two types [24, 25, 28, 29]. Type 1 develops in patients with pre-existing thyroid changes (nodular or diffuse-nodular goitre, diffuse toxic goitre, etc.) and develops as iodine-induced thyrotoxicosis [24, 25]. It is more common in iodine-deficient areas [28, 29]. Type 2 thyrotoxicosis represents destructive thyroiditis with thyroid cell destruction due to the toxic action of amiodarone itself, not only the iodine it contains, and lasts 1–3 months [24, 25]. Destruction of thyroid cells is accompanied by release of increased quantities of thyroid hormones into the bloodstream [11, 28, 29]. For differential diagnosis, in addition to medical history and thyroid ultrasound (detection of nodules, determination of gland volume), radioactive iodine uptake testing is used. In Type 1 thyrotoxicosis, areas of increased isotope uptake may be identified, while in Type 2, uptake is normal or reduced [11]. Treatment approaches for these two types differ. Development of thyrotoxicosis usually requires amiodarone discontinuation, however, this decision is made individually for each patient based on the balance of arrhythmia severity and clinical manifestations of thyrotoxicosis. For Type 1 thyrotoxicosis, antithyroid drugs are prescribed (sometimes in combination with corticosteroids); surgical treatment is performed if drug therapy is ineffective. For Type 2 thyrotoxicosis, corticosteroids are used (prednisolone 30–40 mg/day) [30].

Amiodarone use is associated with dose-dependent bradycardia and a moderate, usually transient, reduction in blood pressure. In cases of overdose or excessively rapid intravenous amiodarone administration, pronounced hypotension and cardiovascular collapse have been reported [1, 4, 5]. Amiodarone therapy is associated with expected QT interval prolongation on the electrocardiogram [1, 4, 5, 29]. A QTc duration exceeding 500 ms is associated with an increased risk of torsade de pointes ventricular tachycardia [1, 4, 5]. Although criteria for QTc prolongation have been proposed, the definitive threshold indicating QTc prolongation without proarrhythmic risk remains undefined [29]. It should be noted that moderate QT prolongation of less than 500 ms in asymptomatic patients is not necessarily dangerous and is, in essence, associated with the anticipated pharmacological effect of amiodarone [1, 9]. The drug exerts a pronounced clinical effect in treating various types of cardiac arrhythmias through prolongation of ac-

tion potential duration, and this prolongation should be interpreted not as an adverse side effect but as a manifestation of the drug's mechanism of action [1, 9, 10].

In 25–75% of cases during amiodarone treatment, increased ocular light sensitivity and photosensitisation develop [1, 10, 29]. In approximately 10% of cases, greyish or bluish skin pigmentation may be observed, which slowly disappears over 10–24 months after drug discontinuation [29]. For this reason, patients should avoid sun exposure and ultraviolet radiation in general [1, 29]. Preventive measures include limiting sun exposure and using broad-spectrum sunscreens containing zinc oxide or titanium dioxide [20, 29].

Corneal microdeposits consisting of complex lipids occur in virtually all patients receiving amiodarone. They are usually confined to the area beneath the pupil, do not require treatment discontinuation, and disappear after drug withdrawal, however, they can occasionally cause visual disturbances such as coloured halos under bright light or blurred vision [20, 29].

In approximately 30% of patients, amiodarone causes motor or mixed peripheral neuropathies and/or myopathies, tremor or other extrapyramidal symptoms, cerebellar ataxia, sleep disturbances, benign intracranial hypertension (pseudotumour cerebri) accompanied by headache, and nightmares; all are reversible after drug discontinuation [20, 29].

### ***Uncommon adverse effects***

A proarrhythmic effect rarely develops with amiodarone use (less than 1% of cases) [1–4]. This may be attributable to amiodarone possessing properties of antiarrhythmic agents of all four classes. Although QT prolongation occurs, torsade de pointes tachycardia develops very rarely, and prolonged use does not lead to an increase in proarrhythmic effect frequency [1, 2, 4, 29]. At the same time, amiodarone causes atrioventricular conduction disorders of varying degrees and sinus node dysfunction: from sinoatrial block to sinus arrest. In individual cases, prolonged administration may lead to progression of chronic heart failure [1, 2, 4, 5]. Therefore, patients receiving long-term amiodarone therapy, particularly at doses exceeding 200 mg/day, require careful monitoring for both cardiac and extracardiac adverse effects [1, 4, 29].

The most severe extracardiac adverse effect is the development of respiratory pathology in the form of

interstitial lung disease or toxic alveolitis, obliterative bronchiolitis with pneumonia, and pleuritis. Less common are acute respiratory distress syndrome (ARDS) and pulmonary haemorrhage, arising from direct toxic drug effects (amiodarone-induced pulmonary toxicity) or immune mechanisms [31, 32]. Amiodarone-induced pulmonary toxicity typically presents as interstitial pneumonitis and fibrosis, developing subacutely or chronically in approximately 1% of cases. Usually by this time the patient has been receiving amiodarone for several months or years at doses exceeding 200 mg/day; however, in patients with pre-existing chronic pulmonary pathology, toxic lung injury may develop considerably faster. The disease manifests as progressive dyspnoea, dry cough, general malaise, fever, and rarely pleuritic chest pain, weight loss, and very rarely haemoptysis. Mortality from amiodarone-induced pulmonary toxicity may reach 20% or more. It should be distinguished from the non-hazardous, usually asymptomatic, effect of amiodarone on the lungs, termed lipid pneumonia [32]. The mechanism by which amiodarone causes pulmonary toxicity is not fully understood, however, some authors believe it is due to a synergistic effect of amiodarone and angiotensin II on T-cell accumulation and induction of alveolar epithelial cell apoptosis [33, 34]. Amiodarone and its metabolites cause mitochondrial dysfunction and may exert both direct cytotoxic effects and indirect effects through activation of free radical production. The drug inhibits phospholipase A, resulting in accumulation of phospholipids as lamellar bodies in lysosomes of lung cells (alveolar macrophages, type II alveolar cells), leading to inflammation and pneumocyte damage and structural changes in the lungs [33, 34]. In amiodarone-induced pulmonary toxicity, discontinuation of amiodarone alone is of limited efficacy; prolonged glucocorticosteroid therapy is required to resolve extensive pulmonary lesions with hypoxaemia. Prednisolone at 40–60 mg/day (0.5–1 mg/kg/day) for 4–12 months with gradual dose reduction is usually prescribed [20, 29, 33, 34]. Preventive measures for amiodarone-induced pulmonary toxicity include use of the minimum effective amiodarone dose (100–200 mg/day), which is associated with a total incidence of pulmonary adverse effects of no more than 1% per year [20, 31, 32].

Amiodarone-induced optic neuropathy or optic neuritis occurs in approximately 1% of patients, char-

acterised by gradual loss of vision, bilateral involvement, and prolonged resolution after drug discontinuation. However, a direct causal relationship between amiodarone and optic neuropathy remains unclear [35].

### ***Rare and very rare adverse effects***

The frequency of these adverse effects is so low that only individual case reports or reviews thereof have been published. A direct link between amiodarone use and these adverse effects is not always convincingly established.

Reports exist of erythema during radiotherapy [29, 35], alopecia [20, 29], secondary vasculitis [36], haemolytic and aplastic anaemia, thrombocytopenia [37], epididymitis [38], erectile dysfunction [20, 29], renal injury with elevated creatinine [20, 21, 29], hepatic steatosis, pseudoalcoholic hepatitis, liver cirrhosis with chronic hepatic failure [20, 29, 39], acute pancreatitis, and dry oral mucosa [20, 29, 40].

### **Contraindications to amiodarone use**

Like almost any drug, amiodarone has contraindications [1, 10, 26, 29]. The principal ones are:

- hypersensitivity/allergy to iodine and/or allergy to amiodarone, iodine, or any other component of the drug;
- sick sinus syndrome, sinus bradycardia, sinoatrial block in the absence of an implanted pacemaker (risk of sinus arrest), second- or third-degree atrioventricular block in the absence of an implanted pacemaker;
- hypokalaemia, hypomagnesaemia;
- congenital or acquired QT interval prolongation;
- concomitant use of drugs that prolong the QT interval and may cause polymorphic torsade de pointes ventricular tachycardia;
- thyroid dysfunction (hypothyroidism, hyperthyroidism);
- interstitial lung disease;
- pregnancy, lactation;
- age under 18 years.

### **Drug Interactions of Amiodarone**

Drug interactions of amiodarone must be considered, first and foremost, to ensure treatment safety [1, 10, 20, 26, 29]. In this context, the list of the main QT-prolonging drugs should be remembered, due to the risk of torsade de pointes VT:

- antiarrhythmic drugs (quinidine, hydroquinidine, disopyramide, procainamide, dofetilide, ibutilide, bretylium tosylate, dronedarone, sotalol);
- drugs for psychiatric disorders (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine, fluphenazine, amisulpride, sultopride, sulpiride, tiapride, droperidol, haloperidol, sertindole, pimozide);
- antidepressants (tricyclic antidepressants, citalopram, escitalopram);
- antibacterial agents (levofloxacin, moxifloxacin, sparfloxacin, ciprofloxacin, erythromycin, azithromycin, clarithromycin, roxithromycin, spiramycin, co-trimoxazole);
- antifungal agents (voriconazole, itraconazole, ketoconazole, fluconazole);
- antimalarials (quinine, chloroquine, mefloquine, halofantrine, lumefantrine);
- antiprotozoal agents (pentamidine);
- anticancer agents (vandetanib, arsenic trioxide, oxaliplatin);
- antiemetics (domperidone, ondansetron);
- gastrointestinal motility agents (cisapride);
- antiallergic agents (mizolastine, astemizole, terfenadine);
- other agents (difemanil methylsulphate, bepridil).

Combined therapy of amiodarone with verapamil or diltiazem (risk of pronounced bradycardia and atrioventricular conduction disorders) or stimulant laxatives (risk of hypokalaemia with increased ventricular proarrhythmic risk) should not be recommended.

Careful monitoring to prevent adverse effects is required when amiodarone is used concomitantly with certain drugs [13, 14]:

- with beta-blockers (regular ECG recording at least once weekly during dose titration, followed by 24-hour ECG monitoring at least once every 3–4 months, due to the risk of pronounced bradycardia and atrioventricular conduction disorders);
- with agents causing hypokalaemia, including diuretics, corticosteroids (glucocorticoids, mineralocorticoids), tetracosactide, amphotericin B, due to the risk of ventricular arrhythmias. Efforts to prevent hypokalaemia are required;
- with oral anticoagulants warfarin and dabigatran, due to potentiation of their effect and increased bleeding risk. Frequent monitoring of anticoagulant

efficacy with possible dose adjustment during and after amiodarone therapy is required;

- with cardiac glycosides, due to the risk of pronounced bradycardia and atrioventricular conduction disorders. Clinical, electrocardiographic, and laboratory monitoring (including plasma digoxin levels where possible) is required; dose reduction of cardiac glycosides may be necessary;
- with the anticonvulsant phenytoin, as elevated plasma phenytoin levels and neurological adverse effects may occur. Clinical monitoring, phenytoin dose reduction upon signs of overdose, and plasma phenytoin measurements are required;
- with drugs metabolised via the CYP3A4 isoenzyme (cyclosporine, fentanyl, lidocaine, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine, simvastatin). Amiodarone increases their concentrations, requiring dose reduction upon toxic and/or potentiated pharmacodynamic effects;
- with flecainide, as elevated plasma flecainide levels requiring dose reduction may occur;
- with general anaesthetic agents. Complications may range from atropine-refractory bradycardia, arterial hypotension, and conduction disorders with reduced cardiac output, to severe respiratory complications (ARDS in adults);
- with clonidine, guanfacine, cholinesterase inhibitors (donepezil, galantamine, rivastigmine, tacrine, ambenonium chloride, pyridostigmine, neostigmine), pilocarpine, which in combination with amiodarone increase the risk of pronounced bradycardia;
- with cimetidine, HIV protease inhibitors, dextromethorphan, sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, which increase amiodarone plasma concentrations [41];
- with orlistat, clopidogrel, rifampicin, and St John's Wort preparations, a predictable decrease in amiodarone and its active metabolite concentrations is expected, which may reduce its efficacy.

### **Baseline and ongoing monitoring of amiodarone therapy**

Before initiating amiodarone therapy, the physician should have information on all diseases and special conditions in the patient, including current or past pulmonary, hepatic, cardiac, and thyroid pathology, current or planned pregnancy, and breastfeeding. Before initiating therapy, chest radiography should be

performed, thyroid function should be assessed via plasma hormone levels, hepatic function via transaminase activity, and plasma electrolyte concentrations. Dynamic monitoring of changes in a range of indicators and organ functions of the patient forms the basis of amiodarone treatment safety [1, 10, 20, 26, 29].

During amiodarone treatment, an ECG should be recorded at least once every 3 months (monitoring of QT interval duration). QT interval prolongation of no more than 450 ms or no more than 25% above baseline is considered acceptable. Although these changes do not represent toxic drug effects, they require monitoring for possible dose adjustment and proarrhythmic risk assessment. In the event of first-degree atrioventricular block, enhanced patient observation is required. In the event of second- or third-degree atrioventricular or sinoatrial block, or bifascicular intraventricular block, amiodarone should be discontinued.

Regular measurement of hepatic transaminase levels is recommended. If their activity exceeds the upper limit of normal by 3-fold or more, amiodarone dose reduction or discontinuation is necessary.

Annual chest radiography, spirometry every 6 months, monitoring of plasma thyroxine and triiodothyronine levels, and ophthalmological review to detect ocular pathology are recommended. In the absence of clinical signs of thyroid dysfunction or visual disturbances, amiodarone treatment should not be discontinued.

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## Review Article

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# Author Guidelines

Manuscript publication rules  
in the International heart and vascular disease journal

Edit from December, 2021

Disclaimer: The rules came into effect from December 2021. 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](mailto: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 has not been previously published contains a full disclosure of the conflict of interest all authors meet the criteria of authorship, it was read and approved 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 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.

**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!**

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.).

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.

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.

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.

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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.

**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:

**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.<sup>1</sup>, Kontsevaya A.V.<sup>1</sup>, Konstantinov V.V.<sup>1</sup>, Artamonova G.V.<sup>2</sup>, Galaganova T.M.<sup>3</sup>,...

<sup>1</sup>FGBU State research center of preventive medicine of the Ministry of health of Russia, Moscow;

<sup>2</sup>FGBU Research Institute of complex problems of cardiovascular diseases SB RAMS, Kemerovo;

<sup>3</sup>RD VPO North Ossetian state medical Academy, Vladikavkaz;..., Russia.

**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.

**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.

**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.).

**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.

**Information on overlapping publications (if available).**

**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.

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**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 comparative control group, studies the interaction between inter-

ventions to improve health or the results obtained. The world health organization offers the primary register: International Clinical Trials Registry Platform (ICTRP) ([www.who.int/ictcp/network/primary/en/index.html](http://www.who.int/ictcp/network/primary/en/index.html)). The clinical study is considered to be reliable in a group of more than 20 patients.

**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. Manuscript submission 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:

Article title

Summary with key words

List of abbreviations

Text

Acknowledgements (if any)

List of references

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  $>$ ,  $<$ ,  $\pm$ ,  $=$ ,  $+$ ,  $-$  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](http://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 ( $M \pm m$ ;  $M \pm SD$ ;  $Me$ ;  $Mo$ ; 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).

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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).

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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, Brodskiy 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*. 3<sup>rd</sup> 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 4<sup>th</sup> 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)

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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 reviewing manuscripts**

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.

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.

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 "Anti-plagiat" 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.

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.

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.

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

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.

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.

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.

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.

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.

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

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**

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 protec-

tion, which the authors must specify in the primary documents attached to the manuscript.

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.

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

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

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

#### **X. After the publication in the journal**

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

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

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

#### **XI. Revocation or correction of articles**

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

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

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

**Editors of journals should consider the concerns, if:**

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

**Journal editors should consider making amendments if:**

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

**In most cases, a review is not appropriate if:**

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

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

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

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

All this information is publicly available in The system of the Russian citation index on the website of the Electronic library [www.elibrary.ru](http://www.elibrary.ru)

**XIII. Journal subscription**

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

**XIV. Journal subscription**

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

Official sites where information about the journal is placed:

<http://www.heart-vdj.com>

On the reception of the articles, making decisions about publication, reviews — [mmamedov@mail.ru](mailto:mmamedov@mail.ru)

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

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Files with a letter of transmittal and General information have been prepared for upload to the site.

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