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# International Heart and Vascular Disease Journal

## Journal of the Cardioprogress Foundation

Cardiovascular diseases and risk management: the standards in diabetes mellitus 2023 (ADA recommendations). Opinion of the Russian experts

Psychotropic drugs in clinical cardiology

Clinical evaluation to identify the predictors of arrhythmogenic cardiomyopathy in patients with ventricular extrasystoles without structural heart changes. Clinical and experimental study

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# International Heart and Vascular Disease Journal

Journal of the «Cardioprogress» Foundation

Volume 11, № 40, December 2023

## Contents

# Editor's Welcome

Dear colleagues!

We present to your attention the next, fortieth issue of the International Heart and Vascular Disease Journal that includes the leading, original, review articles, and a clinical case as well.

The "Leading Article" section reflects the opinion of Russian experts on the updated guidelines of the American Diabetes Association. One of its sections is devoted to cardiovascular diseases and the risk management of cardiovascular complications. The document summarizes the key points of these recommendations with comments from leading Russian experts.

Three articles are presented in the "Original Articles" section. The first study evaluates the complex determination of predictors of the "arrhythmogenic cardiomyopathy" in patients with ventricular extrasystoles without structural heart changes to prognose the development of cardiovascular diseases in a prospective study. The work consists of two parts: experimental and clinical. Patients were followed for up to 10 years. The authors state that in patients without structural heart changes with ventricular extrasystoles, the increase in the values of the internal deviation index and QRSVE complex duration > 0.48 units and 149 m/s, respectively, determine the risk group of cardiovascular pathology formation. The second article analyzes the comorbidity of somatic diseases associated with atrial fibrillation. According to the results, the majority of patients with atrial fibrillation have other cardiovascular diseases, including hypertension, coronary heart disease, and chronic heart failure. In the study group, a combination of two and three diseases was found in more than 60 % of cases. The third article evaluated the efficacy of the hypolipidemic effect of omega-3 polyunsaturated fatty acids in coronary heart disease patients with post-infarction sclerosis and carotid artery stenosis less than 40 %. The lipid-lowering effect is also associated with improved life quality in this group of patients.

The "Review Articles" section contains an article analyzing literature data on pharmacotherapy of psychosomatic disorders in patients with cardiovascular pathology. Among neuroleptics, drugs from the group of partial agonists of dopamine receptors are proven effective due to significantly lower shortening of the QT interval. Among antidepressants, selective serotonin reuptake inhibitors have a strong cardiotropic effect without significant side effects; in turn, agomelatine proved its effectiveness in myocardial reperfusion damage by conducting a special experiment, in which its positive effect on the apoptosis reduction rate was found.

The "Clinical Case" section presents a case of cardiac complications following SARS-CoV2 infection. In this article, a young female patient with no comorbidities developed a circular myocardial infarction following coronavirus infection. Severe complications such as myomalation, inferior and anterolateral ruptures of the left ventricular wall, and hemopericardium occurred.

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

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

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# International medical review

Researchers sought to examine the relationship between high (>65 %), normal (55 – 65 %), and low (<55 %) left ventricular ejection fraction (LVEF) and long-term all-cause mortality and major adverse cardiovascular events (MACE) in women with suspected myocardial ischemia.

A total of 734 women enrolled in the Women's Ischemia Syndrome Evaluation (WISE) program were analyzed. LVEF was calculated by invasive left ventriculography. The relationship between baseline characteristics, LVEF, and outcomes was assessed. A multivariable Cox regression model was used to assess the association of LVEF with outcomes after the adjustment for known risk factors.

Low LVEF was associated with higher mortality and MACE compared to normal and high LVEF (p<0.0001).

As women are known to have relatively higher LVEF compared to men, a sex-neutral LVEF threshold continues to be used for clinical management.

*According to the Heart journal*

Researchers at a clinic in Belgium evaluated the effectiveness of artificial intelligence (AI)-based software in detecting abnormalities in left ventricular ejection fraction (LVEF) after anthracycline-based chemotherapy.

The study included 989 women without cardiovascular diseases who received anthracycline-based chemotherapy for breast cancer without metastases.

All patients were monitored by ECG and had transthoracic echocardiography before and after the treatment. The diagnostic efficiency of the developed software was evaluated on the basis of ECG registration by the values of the area under the curve (AUC) at LVEF less than 50 %.

*According to the European Journal of Preventive Cardiology*

According to a study, there is no association between the prescription of fluoroquinolones and the likelihood of aneurysm or aortic dissection. It is not recommended to avoid prescribing fluoroquinolones when clinically indicated.

Specialists evaluated the incidence of hospitalization and in-hospital mortality with a main clinical diagnosis of aortic aneurysm or aortic dissection.

The incidence rate of aortic aneurysm or dissection was higher in the cephalosporin group during the treatment period compared to the control period.

The overall incidence rate was 5.4 per 100,000 person-years in the fluoroquinolone group and 8.47 per 100,000 person-years in the third-generation cephalosporin group.

*According to the European Heart Journal*

Researchers at the US National Institutes of Health (NIH) have examined the relationship between gaining too much or too little weight during pregnancy and mortality.

They found that weight gain below recommended levels was associated with reduced diabetes-related mortality, but only in a subpopulation of women with normal pre-pregnancy weight.

A total of 46,042 women were included in the study. After 52 years of follow-up, 17,901 participants (38.9 %) had died.

*According to The Lancet journal*

A group of Chinese scientists examined the relationship between atrial fibrillation (AF) and the likelihood of developing dementia.

Compared to participants without AF, patients with this pathology had a 42 % higher risk of developing any type of dementia and a 2.06 times higher risk of vascular dementia.

The UK Biobank database was analyzed and 433,746 people without dementia at baseline were identified. AF was found in 30,601 participants.

The researchers note the importance of monitoring cognitive function in patients with atrial fibrillation in order to take timely action to reduce the risk of dementia.

*According to the JAMA Network*

Tomsk researchers have published the results of a large-scale project to find ways to effectively reduce blood glucose in animals with type 2 diabetes. They managed to find a non-medicamentous way of treating this disease.

The animals got rid of the diabetes with the help of physical training, which was correctly selected by experts for a certain period of time.

The project involved 300 experimental animals, and special equipment was made. Data analysis helped to determine the optimal time for physical training, which most effectively reduces the concentration of blood sugar.

*According to the International Journal of Molecular Science*

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# **Cardiovascular diseases and risk** management: the standards in diabetes mellitus 2023 (ADA recommendations). Opinion of the Russian experts

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In early 2023, experts from the American Diabetes Association (ADA) published the Standards of Diabetes Care document in the journal Diabetes Care, which is updated annually as new evidence accumulates. These guidelines aim to improve the diagnosis, treatment and care of patients with diabetes mellitus (DM). One of its sections is devoted to cardiovascular diseases (CVD) and management of the risk of cardiovascular complications. The main aspects of this document and the opinion of Russian experts are presented below.

**Keywords:** diabetes mellitus, cardiovascular disease, cardiovascular complications.

This article contains the extracts from the ADA recommendations. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2023. Diabetes Care 2023;46(Suppl. 1):S158-S190. https://doi.org/10.2337/dc23-S010

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## Introduction

Cardiovascular diseases (CVD), associated with atherosclerosis (coronary heart disease, cerebrovascular disease, or peripheral arterial disease) – is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). The annual cost of CVD management in patients with DM in the United States is approximately $37.3 billion [1].

Numerous studies have demonstrated the effectiveness of controlling individual cardiovascular risk factors in preventing or delaying the development of CVD in DM. In addition, simultaneous control of CVD risk factors has a greater benefit. Therefore, aggressive risk factor modification has led to a reduction in CVD morbidity and mortality in individuals with DM over the past decades [2–4].

Heart failure (HF) is recognized as one of the major causes of mortality in people with DM. Prospective studies have shown that the incidence of hospitalization for HF (adjusted for age and sex) is twice as high in people with diabetes compared to those without diabetes [5, 6].

## Cardiovascular diseases and risk management

To prevent and treat both atherosclerosis-related CVD and CHD, risk factors (RFs) should be systematically assessed at least annually in all individuals with diabetes. Important aggravating RFs include: duration of diabetes, obesity/overweight, arterial hypertension (AH), dyslipidemia, smoking, family history of CVD, chronic kidney disease (CKD), and albuminuria.

Therapy using multiple evidence-based approaches in parallel provides additional reductions in the risk of microvascular, renal, neurological and cardiovascular complications. Control of glycemia, blood pressure (BP), and lipid parameters, as well as the incorporation of specific drugs with favorable effects on cardiovascular and renal outcomes (depending on individual differences), are considered key to the overall reduction of the risk of complications of DM.

## Cardiovascular complications risk scale

The CVD risk scale (Risk Estimator Plus, USA) is a useful tool for estimating the 10-year risk of cardiovascular complications. The calculation of DM risk is included as a RF, although the duration of the DM or the presence of its complications such as albuminuria are not included. Stratification of CVD risk may help in choosing the therapy. Recently, risk scales and new cardiovascular biomarkers have been developed for risk stratification of patients for secondary prevention, but they are not yet widely used [7, 8].

## Arterial hypertension and blood pressure control

AH is common in both type 1 and type 2 DM patients and is a major RF of atherosclerotic cardiovascular disease (ACVD) and microvascular complications [9].

### *The definition of arterial hypertension*

In contrast to Russian and European guidelines, AH is defined as systolic BP ⩾130 mmHg and/or diastolic BP ⩾80 mmHg based on the average of ⩾2 measurements at ⩾2 visits, which is the definition of the American College of Cardiology and the American Heart Association [10]. In individuals with BP ⩾180/110 mmFHg and CVD, the diagnosis of AH can be made in a single visit. If the hypertension is diagnosed, BP control should be performed at every routine office visit and necessarily at home [11, 12], as it is believed that home measurements may correlate better with CVD than office measurements, also by improving adherence to antihypertensive medication [13, 14]. Separate attention is given to the detection of orthostatic hypotension, the presence of which may indicate autonomic neuropathy and require adjustment of BP target values.

### *Target blood pressure values*

The paper analyzes the underlying protocols that compared strategies of "hard" and "soft" control of systolic and diastolic BP: SPRINT (no patients with DM), STER, ACCORD BP, ADVANCE, NOT [15–19]. On the basis of these trials, the experts refer to the goal of antihypertensive therapy in patients with type 1 and type 2 DM as BP < 130/80 mmHg if it can be safely achieved, noting that there are currently no high-quality data to support these values for patients with type 1 DM. The final discussion on BP target values emphasizes the place of a personalized approach based on shared decision-making between physician and patient, with the recommendation not to lower BP <120/80 mmHg because of the risk of adverse events. This strategy is consistent with the opinion of the world's leading expert communities: American College of Cardiology and American Heart Association [9, 10], International

Society of Hypertension [11] and European Society of Cardiology [12].

### *Pregnancy and arterial hypertension*

Approaches to antihypertensive therapy in pregnant women with AH and DM are specified separately: similar to the Russian guidelines, the initiation of therapy in them is justified at BP ⩾140/90 mmHg, and the target values of BP are 110-135/85 mmHg. At the same time, there are no convincing data on the optimal lower limit, but the intensity of therapy should be reduced at BP <90/60 mmHg. This approach is supported by the International Society for the Study of Hypertension in Pregnancy, whose experts recommend a target systolic BP between 110 and 140 mmHg and a target diastolic BP between 80 and 85 mmHg [20].

Treatment with angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), and spironolactone is prohibited during pregnancy because of the risk of fetotoxicity. These drugs are also undesirable in "individuals with preserved fertile potential" who should be switched to alternative antihypertensive drugs approved for use during pregnancy, namely methyldopa, labetalol and long-acting nifedipine. Hydralazine may be considered as an emergency treatment [16]. Diuretics are not recommended for blood pressure control in pregnancy, but may be used in late pregnancy if needed to control circulatory volume [21, 22]. The American College of Obstetricians and Gynecologists also recommends 7–10 days of postpartum care, including 72 hours in the hospital, for women with gestational hypertension, pre-eclampsia, and pre-eclampsia in the setting of chronic AH. Their long-term follow-up is also warranted due to increased lifelong cardiovascular risk [23].

### *Lifestyle modification*

Lifestyle modification interventions are already recommended for people with BP > 120/80 mmHg and should be continued along with pharmacological BP correction when the AH is diagnosed. These include: weight loss, if necessary; the DASH diet, including reducing sodium (<2300 mg/day) and increasing potassium in the diet; adequate consumption of fruits and vegetables (8–10 servings per day) and non-fatty dairy products (2–3 servings per day); moderate alcohol consumption (no more than 2 servings per day for men and no more than 1 serving per day for women) [24]; and increased physical activity (at least 150 minutes of moderate-intensity aerobic exercise per week) [25].

Traditionally, it is emphasized that lifestyle modification should be discussed in conjunction with goals, taking into account the patient's capabilities, and is an important component of AH treatment due to hypotensive effect, increasing the effectiveness of some antihypertensive drugs, additive interaction with other factors of metabolic and vascular health. The use of the Internet, mobile digital platforms for more active reminders of "healthy behavior" is encouraged, which can be considered as a component of the management of patients with DM, as these interventions enhance the effectiveness of drug therapy for AH [26, 27].

### *Pharmacological correction*

In contrast to Russian and European guidelines for the treatment of AH, this document allows the monotherapy for patients with DM and AH if their BP is between 130/80-160/100 mmHg. Individuals with confirmed office BP ⩾160/100 mmHg in addition to lifestyle modification, should be prescribed with two drugs with proven efficacy in free or fixed combination in a single tablet and should be titrated in a timely manner [28-30].

In contrast to Russian and European recommendations for initial treatment of AH, renin-angiotensin-aldosterone system blockers are not prioritized. ACE inhibitors, BRAs [31, 32], thiazide-like diuretics [33] or dihydropyridine calcium channel blockers [34] can be considered as initial therapy, as all of them have been shown to reduce the risk of cardiovascular events in patients with DM. Administration of an ACE inhibitors or BRAs is suggested as the preferred strategy for the treatment of AH in patients with DM and CHD or a urinary albumin-to-creatinine ratio of 30–299 mg/g, and is strongly recommended if the ratio is greater than 300 mg/g.

However, in the absence of albuminuria, the risk of progression of renal disease is low, and ACE inhibitors, BRAs have not been shown to provide better cardioprotection than thiazide-like diuretics or dihydropyridine calcium channel blockers [35]. Thiazide-like diuretics such as chlorthalidone or indapamide are preferred by experts. In patients treated with an ACE inhibitors, BRA, or diuretic, serum creatinine levels,

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estimated glomerular filtration rate (GFR), and serum potassium levels should be monitored at least annually. Beta-blockers also have their therapeutic niche in this document: they should be prescribed in the presence of previous myocardial infarction (MI), angina pectoris, or chronic heart failure (CHF) with reduced ejection fraction, but in the absence of these conditions their effect on mortality has not been proven [36-38].

*Multiple drug therapy* is often required to achieve blood pressure targets, especially in the setting of diabetic nephropathy. However, the concomitant use of ACE inhibitors and BRAs or the combination of ACE inhibitors or BRAs with a direct renin inhibitor is contraindicated because of the lack of additional benefit in the prevention of CVD and the increased incidence of adverse events – hyperkalemia, syncope, and acute kidney injury [39-41]. Similar to the clinical guidelines of the world's leading expert communities devoted to the correction of the leading cardiovascular RFs, the need for timely intensification of antihypertensive therapy (dose titration and/or addition of another drug) to overcome therapeutic inertia and achieve target BP values is actualized.

*Dosing before bedtime*. Although previous analyses of randomized clinical trials have shown benefits of evening versus morning antihypertensive dosing [42, 43], these results have not been replicated in subsequent studies. Therefore, preferential use of antihypertensive drugs at bedtime is not currently recommended [44].

*Hyperkalemia and Acute Kidney Injury.* Treatment with ACE inhibitors and BRAs may cause acute kidney injury and hyperkalemia, while diuretics may cause hypokalemia or hyperkalemia in addition to acute kidney injury (depending on their mechanism of action) [15, 45]. Detection and treatment of these abnormalities is important because they increase the risk of CVD and death. Therefore, serum creatinine and potassium should be monitored during treatment with an ACE inhibitors, BRA, or diuretic, especially in patients with decreased GFR who are most at risk for hyperkalemia and acute kidney injury [15, 17, 45].

### *Resistant arterial hypertension*

Resistant hypertension is defined as BP ⩾140/90 mmHg despite a therapeutic strategy that includes lifestyle modification, as well as diuretics and two other antihypertensive drugs with complementary mechanisms of action at appropriate doses. That is, the guidelines do not emphasize the need for maximal drug doses. Before diagnosing resistant AH, noncompliance (e.g., due to missed doses, side effects, high cost of treatment), white-coat effect, and secondary hypertension should be excluded. Consequently, patients with secondary AH cannot be considered to have resistant AH.

To achieve BP goals in patients with DM and resistant AH, the addition of mineralocorticoid receptor antagonists (spironolactone, eplerenone) to treatment with an ACE inhibitor or BRA, a thiazide-type diuretic, and a dihydropiridine calcium channel blocker is recommended [44]. Mineralocorticoid receptor antagonists reduce albuminuria in patients with diabetic nephropathy [19, 46, 47], but the risk of hyperkalemia must be considered when adding them to a regimen that includes an ACE inhibitor or BRA. This reaffirms the importance of regular monitoring of serum creatinine and potassium levels and the need to study the long-term results of the use of mineralocorticoid receptor antagonists in the treatment of AH.

## Correction of lipid metabolism disorders

### *Basic principles of lifestyle modification in lipid metabolism disorders*

This section is based on the recommendations of the American College of Cardiology and the American Heart Association for the primary prevention of cardiovascular diseases [48]. A Mediterranean-style diet with a reduction in saturated and transfats in foods; increased intake of omega-3 fatty acids, dietary fiber, and plant stanols/sterols (e.g., oatmeal), legumes, and citrus fruits is required. Increased physical activity is also recommended to improve lipid profiles and reduce the risk of developing ACVD in people with DM.

Along with the lifestyle modification, optimization of glycemic control is recommended in patients with elevated triglycerides (⩾150 mg/dL [1.7 mmol/L]) and/or low high-density lipoprotein (HDL) cholesterol (<40 mg/dL [1.0 mmol/L] for men, < 50 mg/dL [1.3 mmol/L] for women. Glycemic control may have a beneficial effect on plasma lipid levels, particularly in patients with very high triglyceride levels and poor glycemic control.

Weight loss is recommended in obese or overweight individuals (if necessary), which, along with increased physical activity, may reduce the impact

of risk factors on the development of CVD in some patients. Dietary interventions should be tailored to each patient's age, pharmacological treatment, lipid levels, and overall health.

### *Particular features of lipid profile control different from European guidelines*

In adults with DM, it is recommended that the lipid profile of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides be measured at the time of diagnosis at the initial physical examination and at least every 5 years in patients younger than 40 years.

In younger individuals with a longer disease course (e.g., type 1 DM onset at a young age), more frequent lipid profile monitoring may be appropriate. The lipidogram should be checked immediately before starting statin therapy. Once the patient starts taking statins, LDL cholesterol levels should be assessed 4–12 weeks after initiation of therapy (in Russian and European guidelines, after 4–8 weeks of therapy), as well as after each dose change and on an individual basis (e.g., to monitor drug absorption and efficacy). If LDL cholesterol levels do not change despite medication, clinical evaluation is recommended to determine the need for and timing of lipid profile measurements. The highly variable LDL cholesterol-lowering response to statins is poorly understood in individual patients. Clinicians should attempt to adjust doses or find alternatives to statins when side effects occur. There is an evidence of benefit even of the very low doses of statins, much lower than those usually recommended.

### *Treatment with statins for primary prevention*

This section is presented according to the guidelines of American endocrinologists [49–51]. For people with diabetes aged 40–75 years without ACVD, it is recommended to use moderate-intensity statin therapy in addition to lifestyle changes (in contrast to the Russian and European recommendations, risk levels and risk scales are not used, but division into age groups). For people with diabetes aged 20–39 years with additional ACVD RFs, it is recommended to start statin therapy in addition to lifestyle changes.

For people with DM aged 40–75 years at increased risk of CVD, including those with one or more ACVD RFs, it is recommended that high-intensity statin therapy be used to reduce LDL cholesterol by ≥ 50 % of baseline and achieve a target LDL cholesterol level of <1.8 mmol/L.

For people with DM aged 40–75 years who are at increased cardiovascular risk, especially those with multiple ACVD RFs and LDL cholesterol levels ≥1.8 mmol/L, the addition of ezetimibe or the proprotein convertase inhibitor subtilisin/kexin type 9 (PCSK9) to the maximum tolerated dose of a statin may be appropriate. In patients with DM older than 75 years who are already receiving statin therapy, it is reasonable to continue such treatment. In people with DM older than 75 years, it may be appropriate to initiate moderate-intensity statin therapy after discussing the potential benefits and risks. Statin therapy is contraindicated during pregnancy.

### *Statin treatment for secondary prevention*

High-intensity statin therapy should be added to lifestyle interventions for people of all ages with DM and ACVD.

High-intensity statin therapy is recommended for people with DM and ACVD to reduce LDL cholesterol by ≥50 % from baseline and achieve a target LDL cholesterol level of <1.4 mmol/L. The addition of ezetimibe or a PCSK9 inhibitor with proven efficacy is recommended if this goal is not achieved with the maximum tolerated dose of a statin.

People who cannot tolerate the maximum doses of statins should be prescribed the maximum tolerated doses of these drugs.

Accordingly, statins are the drugs of choice for LDL cholesterol lowering and cardioprotection: high-intensity statin therapy reduces LDL cholesterol by approximately ≥50 % and moderate-intensity statin therapy reduces LDL cholesterol by 30–49 % (Table 1). Treatment with low-dose statins is not usually recommended for people with DM, but sometimes it is the only possible dose of statins that a patient can tolerate. In patients who cannot tolerate statin therapy at the desired intensity, the maximum tolerated dose of statins should be used.

Moderate-intensity statin therapy is recommended for primary prevention in patients aged ≥40 years, although high-intensity therapy should be considered in the context of additional ACVD risk factors. Because it is often difficult in clinical practice to establish baseline LDL cholesterol levels prior to initiating statin therapy, it is recommended that these patients focus

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*Table 1*

**Lowering cholesterol levels with statin therapy**

| High-intensity statin therapy (reduces LDL cholesterol by ⩾ 50 %) | Moderate-intensity statin therapy (reduces LDL cholesterol by 30 – 49 %) |
|---|---|
| Atorvastatin 40 – 80 mg | Atorvastatin 10 – 20 mg |
| Rosuvastatin 20 – 40 mg | Rosuvastatin 5 – 10 mg |
| | Simvastatin 20 – 40 mg |
| | Pitavastatin 1 – 4 mg |

on a target LDL cholesterol level of <1.8 mmol/L rather than a percentage reduction in LDL cholesterol. In these individuals, it may also be appropriate to add ezetimibe or a PCSK9 inhibitor to maximally tolerated statin therapy if needed to reduce LDL cholesterol by ⩾ 50 % and achieve the recommended target LDL cholesterol level of <1.8 mmol/L. Moderate intensity statin therapy is recommended for people with DM aged ⩾ 75 years. However, in this population, the risk-benefit ratio of treatment should be regularly reassessed and the dose reduced if necessary.

### *Recommendations for age group under 40 years and/or with type 1 diabetes mellitus*

Patients younger than 40 years of age have a lower risk of developing CVD over a 10-year period, but they have a high lifetime risk of developing CVD and MI, stroke, or death from CVD. It is recommended that people younger than 40 years of age and/or those with type 1 DM with other comorbidities discuss the relative benefits and risks of treatment with their physician and consider the use of moderate-intensity statin therapy [52].

### *Patients with atherosclerotic cardiovascular diseases*

High-intensity statin therapy is recommended for all people with DM and ACVD to reduce LDL cholesterol by ⩾50 % of baseline and achieve a target LDL cholesterol level of <1.4 mmol/L. If this goal is not achieved with maximally tolerated statin therapy, the addition of ezetimibe or a PCSK9 inhibitor is recommended. Evidence supporting progressively lower LDL cholesterol targets in people with DM and established CVD comes from several large randomized trials evaluating the benefits of adding non-statin drugs to statin therapy. Each study found a significant benefit in the reduction of ACVD events that was directly related to the degree of further reduction in LDL cholesterol. These large trials included significant numbers of participants with DM and prespecified rates of cardiovascular outcomes in people with and without DM. The decision to add a non-statin drug should be made after the physician and patient have discussed the benefits, safety, and costs of combination therapy [53–56].

### *Combination therapy to lower low-density lipoprotein cholesterol levels*

Overall, the addition of ezetimibe resulted in a relative reduction of 6.4 % and an absolute reduction of 2 % in the risk of major adverse cardiovascular events (atherosclerotic cardiovascular events), according to the guideline authors. The magnitude of the benefit was directly proportional to the change in LDL cholesterol, which averaged 1.8 mmol/L in the statin group and 1.4 mmol/L in the combination therapy group. In patients with DM (27 % of study participants), the combination of moderate-intensity doses of simvastatin (40 mg) and ezetimibe (10 mg) showed a significant reduction in the risk of major adverse cardiovascular events, with an absolute risk reduction of 5 % and a relative risk reduction of 14 % compared with simvastatin monotherapy at a dose of 40 mg.

The effect of PCSK9 inhibition on the ACVD outcomes identified in these guidelines was evaluated in the FOURIER trial, which enrolled 27564 high-risk patients with prior ACVD who were on maximum tolerated doses of statins. Evolocumab reduced LDL cholesterol levels by 59 %. At a median follow-up of 2.2 years, the combined outcome of CVD death, MI, stroke, angina hospitalization or revascularization was reported in 11.3 % of patients compared to 9.8 % in the placebo and evolocumab groups (15 % relative risk reduction; p<0.001). The composite of cardiovascular death, MI or stroke was reduced by 20 % (p<0.001). Importantly, similar benefits were observed in a pre-specified subgroup of people with DM comprising 11031 patients (40 % of the study population).

In another study, ODYSSEY OUTCOMES, 18924 patients (28.8 % of whom had DM) with a recent acute coronary syndrome were randomized to receive the PCSK9 inhibitor alirocumab or placebo every 2 weeks on top of maximum tolerated statin therapy. The

dose of alirocumab was titrated from 75 to 150 mg to achieve LDL cholesterol levels of 25 to 50 mg/dL. At a median follow-up of 2.8 years, the combination of alirocumab and statins resulted in a greater absolute reduction in the incidence of the primary endpoint in people with DM (by 2.3%) than in people with pre-diabetes (by 1.2%) or normoglycemia (by 1.2%).

In addition to monoclonal antibodies targeting PCSK9, a small interfering RNA therapy, inclisiran, has been developed and has recently become available in the United States and Russia. Treatment with inclisiran involves less frequent dosing compared to monoclonal antibodies and has been administered at day 1, day 90 and every 6 months in studies. In the ORION-10 study, 47.5% of patients in the inclisiran group and 42.4% of patients in the placebo group, and in the ORION-11 study, 36.5% and 33.7% of patients, respectively, had DM. A prespecified cardiovascular endpoint, which includes death from heart attack, cardiac arrest, non-fatal MI or stroke, was observed in 7.4% of patients in the inclisiran group and 10.2% of patients in the placebo group in ORION-10 and 7.8% and 10.3%, respectively, in ORION-11.

Severe hypertriglyceridemia (fasting triglyceride levels ≥5 mmol/L and especially >10 mmol/L) requires pharmacologic therapy (fibrates and/or fish oil – omega-3 polyunsaturated fatty acids) and reduction of dietary fat to reduce the risk of acute pancreatitis. Moderate to high intensity statin therapy should also be used when indicated to reduce the risk of cardiovascular events. In people with moderate hypertriglyceridemia, lifestyle modification, treatment of secondary risk factors, and avoidance of medications that may increase triglyceride levels are recommended [57].

### *Management of patients with hypertriglyceridemia*

The REDUCE-IT trial enrolled 8179 adults receiving statin therapy with moderately elevated triglyceride levels (1.4–4.9 mmol/L, median baseline 2.16 mmol/L) who had established CVD (secondary prevention) or DM plus at least one other CVD risk factor (primary prevention) [58]. Patients were randomized to receive icosapentetil (omega-3 polyunsaturated fatty acid) at a dose of 4 g/day (2 g twice daily with meals) versus placebo. A 25% relative risk reduction ($p<0.001$) was achieved for the primary endpoint consisting of CVD death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina. This risk reduction while taking icosapentetil was observed in people with or without DM. The combination of cardiovascular death, non-fatal MI or non-fatal stroke was reduced by 26% ($p<0.001$). It should be noted that similar data on the efficacy of other omega-3 polyunsaturated fatty acids are not available, and the results of the REDUCE-IT study should not be extrapolated to other products.

Combination therapy with statins and fibrates does not improve ACVD outcomes and is generally not recommended (in contrast to Russian and European recommendations). Combination therapy (statins and fibrates) is associated with an increased risk of abnormal transaminase levels, myopathy, and rhabdomyolysis. The risk of rhabdomyolysis is greater with higher doses of statins and renal failure and appears to be higher when statins are combined with gemfibrozil (compared with fenofibrate).

### *Risk of diabetes mellitus when using statins*

Although the use of statins is associated with the risk of developing DM, the reduction in the incidence of cardiovascular events with statins far outweighs the risk of DM, even in patients at the highest risk of developing DM. A meta-analysis of 13 randomized trials of statins involving 91,140 participants showed that the odds ratio for a new diagnosis of DM was 1.09, meaning that, on average, treatment with statins for 4 years in 255 patients resulted in one additional case of DM while preventing 5.4 vascular events in these 255 patients [59].

Concerns that statins or other hypolipidemic agents may cause cognitive dysfunction or dementia are not currently supported by evidence and should not prevent their use in individuals with DM and high risk of the ACVD [60].

## The use of antiplatelet drugs

There is a large base of evidence that the benefits of using aspirin for secondary prevention in people with documented CVD far outweigh the risks [61]. Aspirin has been shown to be effective in reducing CVD and mortality in high-risk patients with a history of MI or stroke (secondary prevention) [62].

There is currently no convincing evidence to support the use of a specific dose of aspirin. However, the average daily doses used in most clinical trials in patients with DM ranged from 50 to 650 mg, but were

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usually in the range of 100 – 325 mg/day. Consequently, the lowest possible dose of aspirin is appropriate to reduce side effects, primarily the risk of major bleeding [63]. For patients with DM and high/very high cardiovascular risk, European experts recommend the use of aspirin at a dose of 75 – 100 mg/day [62].

In the ADAPTABLE trial involving patients with confirmed CVD, 38 % of whom had DM, there were no significant differences in the incidence of cardiovascular events or major bleeding between patients treated with 81 mg or 325 mg of aspirin daily [64].

Although platelet dysfunction is present in individuals with DM, it is unclear what effect, if any, this finding has on the dose of aspirin required for cardioprotection in DM. There are many alternative pathways of platelet activation that are independent of thromboxane A2 and therefore unaffected by aspirin [65]. "Aspirin resistance" has been described in DM using a variety of ex vivo and in vitro methods (platelet aggregometry, thromboxane B2 measurement) [66], but impaired response to aspirin in DM patients has not been confirmed in other studies [67]. It has been shown that more frequent aspirin dosing may reduce platelet reactivity in people with DM [68]; however, these observations alone are not sufficient to recommend the use of higher doses of aspirin in this group at this time. A meta-analysis hypothesized that the efficacy of low-dose aspirin is reduced in individuals with a body weight >70 kg [69]. However, the ASCEND trial found a benefit of low-dose aspirin in individuals of this weight, contradicting this hypothesis [70]. According to the ADA guidelines, aspirin doses of 75 – 162 mg/day are optimal [71].

Thus, aspirin therapy at a dose of 75 – 162 mg/day should be used as a secondary prevention strategy in patients with a history of DM and ACVD [71].

In recent years, other antiplatelet agents, particularly clopidogrel, have been studied as alternatives to aspirin [12]. However, there is evidence that clopidogrel is less effective than aspirin in patients with DM [73].

At the same time, clopidogrel at a dose of 75 mg/day is recommended in documented aspirin allergy in patients with DM and ACVD [71].

The use of dual antiplatelet therapy has an undoubted advantage over aspirin monotherapy in patients with acute coronary syndrome and percutaneous coronary intervention. Thus, the use of a P2Y12 receptor antagonist in combination with aspirin is reasonable for at least 1 year in patients who have had an acute coronary syndrome and may provide benefit beyond this period.

Trial results support the use of either ticagrelor or clopidogrel if percutaneous coronary intervention was not performed, and clopidogrel, ticagrelor, or prasugrel if it was performed [74]. In patients with DM and a history of MI (1–3 years old), the addition of ticagrelor to aspirin significantly reduced the risk of recurrent ischemic events, including cardiovascular death and death due to CHD [75]. Similarly, the addition of ticagrelor to aspirin reduced the risk of ischemic cardiovascular events compared with aspirin alone in subjects with DM and stable CHD [76, 77]. However, a higher incidence of major bleeding, including intracranial hemorrhage, was observed with dual antiplatelet therapy, which requires a more balanced approach (careful consideration of bleeding risk) 1 year after acute coronary syndrome.

Therefore, the ADA expert recommendation that dual antiplatelet therapy (low-dose aspirin plus a P2Y12 receptor inhibitor) is reasonable for 1 year after acute coronary syndrome and may be of benefit beyond this period seems most reasonable [71].

The net clinical benefit (effect on the sum of ischemic and hemorrhagic complications) is higher with ticagrelor therapy in patients with a history of percutaneous coronary intervention, whereas no such benefit is observed in patients without such intervention [77].

In this context, according to the ADA Expert Recommendation, individuals with a history of coronary intervention, high coronary risk, and low bleeding risk should consider long-term dual antiplatelet therapy to prevent major adverse cardiovascular events [71].

However, early discontinuation of aspirin compared with continuing dual antiplatelet therapy after coronary stenting may reduce the risk of bleeding without a corresponding increase in the risk of mortality and ischemic events, as shown in an analysis of a cohort of patients with DM included in the TWILIGHT trial and in a recent meta-analysis [78, 79].

In recent years, a combination of aspirin and low-dose rivaroxaban has been considered as a pharmacological approach to reduce cardiovascular risk in individuals with stable coronary heart disease and/or peripheral arterial disease. In the COMPASS trial, which enrolled 27,395 patients with documented CHD and/or PAD, aspirin 100 mg once daily plus ri-

varoxaban 2.5 mg twice daily was superior to aspirin 100 mg once daily plus placebo in reducing the risk of cardiovascular ischemic events, including major adverse limb ischemic events. The absolute benefit of combination therapy was greater in a group of 10,341 study participants with DM [80, 81]. A similar treatment strategy was evaluated in the VOYAGER PAD Vascular Outcomes Study [82], in which 6564 patients with PAD undergoing revascularization were randomized to rivaroxaban (2.5 mg twice daily) plus aspirin or placebo plus aspirin. In the rivaroxaban group, there was a significant reduction in the incidence of ischemic cardiovascular complications, including major adverse events in the lower extremities. However, there was an increased risk of major bleeding when rivaroxaban was added to aspirin therapy in both COMPASS and VOYAGER PAD. These data suggest that patients should be carefully selected for combination therapy with aspirin and rivaroxaban, as supported by the following ADA expert recommendation.

In individuals with stable coronary and/or peripheral arterial disease and low risk of bleeding, combination therapy with aspirin plus low-dose rivaroxaban should be considered to prevent severe limb and cardiac ischemic events [71].

Current evidence precludes the recommendation of aspirin and other antiplatelet agents for primary prevention in individuals at low risk of CVD (e.g., men and women aged <50 years with DM without other major CVD risk factors), because the risk of bleeding is likely to outweigh the small benefit [83]. Previous randomized controlled trials of aspirin in people with DM have consistently failed to demonstrate a significant reduction in CVD risk. This calls into question the efficacy of aspirin for primary prevention in people with DM, although some sex differences have been suggested [84-86].

In the ASCEND trial, which included 15,480 participants with DM but without documented CVD, patients were randomized to receive aspirin at a dose of 100 mg daily or placebo [70]. The primary efficacy endpoints were: vascular death, MI, or stroke/transient ischemic attack. During a mean follow-up of 7.4 years, there was a significant 12% reduction in the rate of the primary efficacy endpoint (p=0.01), but there was a significant 1.3-fold increase in the rate of major bleeding in the aspirin group (p=0.003), and this increase was associated with gastrointestinal and other extracranial bleeding. No significant differences in outcomes were observed according to sex, body weight, duration of DM, and baseline CVD risk. Two other large randomized trials of aspirin for primary prevention in people without DM (ARRIVE) [87] and in elderly patients (ASPREE) [88], which included 11% of patients with DM, found no benefit of aspirin with respect to the primary efficacy endpoint of increased risk of bleeding.

Analysis of the available data may suggest that aspirin has a moderate effect on ischemic vascular events, with an absolute reduction in their incidence depending on the risk of CVD. The main adverse effect of aspirin is an increased risk of gastrointestinal bleeding, which may reach 5 cases per 1000 patients per year in real-world practice. However, in adults with a CVD risk > 1% per year, the number of cases prevented by aspirin is equal to the number of drug-induced bleeding events, although these complications do not have the same impact on long-term health [89].

Therefore, the use of aspirin for primary prevention of CVD should be carefully justified and is generally not recommended. Aspirin may be considered in the context of high cardiovascular risk with low bleeding risk [90–93], but generally not in the elderly. In people over 70 years of age (with or without DM), the risks of aspirin use appear to outweigh the benefits [70, 88]. Aspirin use is generally contraindicated in patients under 21 years of age because of the associated risk of Reye's syndrome. The willingness of patients to take aspirin long-term should also be considered [94].

In this context, the recommendation of the ADA experts that aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in patients with DM at increased cardiovascular risk, after a comprehensive discussion with the patient about the benefits compared with a comparable increased risk of bleeding, is justified [71].

## Specifics of managing patients with diabetes mellitus and cardiovascular diseases

### *Cardiologic testing*

Candidates for advanced or invasive cardiac testing are DM patients who have: 1) typical or atypical cardiac symptoms, and 2) resting electrocardiogram

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(ECG) abnormalities. A stress ECG with or without echocardiographic imaging may be used as an initial test. In adults with DM aged ≥40 years, measurement of coronary artery calcium is also appropriate for cardiovascular risk assessment. Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with DM in whom abnormal resting ECG changes preclude exercise testing (e.g., left bundle branch block or ST-T abnormalities). Pharmacologic stress echocardiography or nuclear imaging may also be used in detrained individuals who require exercise testing.

### *Screening of asymptomatic patients*

The screening of asymptomatic patients at high risk for ACVD is not recommended [95], partially because these patients should already be receiving intensive medical therapy, a treatment that provides similar benefits to invasive revascularization [96, 97]. In prospective studies, coronary calcium measurement has been hypothesized to be an independent predictor of cardiovascular complications in people with DM, superior to the assessment used in the UKPDS and Framingham study populations [98-100]. However, a randomized observational study demonstrated a lack of clinical benefit from routine screening of asymptomatic individuals with type 2 DM and a normal ECG [101]. Despite imaging evidence of impaired myocardial perfusion in more than one in five patients, the incidence of adverse cardiac outcomes was similar in screened and unscreened patients. Therefore, non-selective screening is not cost-effective. Studies have shown that a risk factor-based approach to the initial diagnostic evaluation and follow-up of patients with CHD does not help to determine which people with type 2 DM will have silent myocardial ischemia on screening tests [102, 103].

Any benefit of newer noninvasive coronary artery disease screening modalities, such as CT calcinosis assessment and computed tomographic angiography, in asymptomatic people with DM remains uncertain in terms of identifying patient subgroups for different treatment strategies. Asymptomatic people with DM and a higher burden of coronary heart disease are at higher risk of future cardiac events [98, 104, 105], and additional imaging tests may provide justification for intensification of treatment and/or lead to informed patient decision making, readiness to initiate therapy, and active participation in therapy. While screening methods for coronary artery pathology, such as coronary calcium scoring, may improve cardiovascular risk assessment in people with type 2 DM [106], their routine use is associated with radiation exposure and may lead to unnecessary invasive testing, such as coronary angiography, and revascularization procedures. The final balance of benefits, costs, and risks of this approach in asymptomatic patients remains controversial, especially in the current setting of aggressive control of ACVD risk factors.

### *Lifestyle modification and pharmacotherapy*

Intensive lifestyle modifications, focusing on weight loss by reducing caloric intake and increasing physical activity, as in the Look AHEAD trial, can be considered to improve glycemic control, maintain fitness, and correct some ACVD risk factors [107]. Patients at increased risk of ACVD should take statins, ACE inhibitors or BRAs if they have AH, and possibly aspirin if there are no contraindications to these drugs. Because of the clear benefits of ACE inhibitors or BRAs in people with DM, kidney disease, or AH, these drugs are recommended for BP lowering in people with established ACVD (especially CHD) [108-110]. In people with type 2 DM and CHD, treatment with finerenone should be considered to reduce the risk of adverse cardiovascular outcomes and progression of CHD [111-114]. Beta-blockers should be used in people with angina pectoris or CHF with reduced ejection fraction and within 3 years of MI in patients with preserved left ventricular ejection fraction [115, 116].

### *Glucose-lowering therapy and cardiovascular outcomes*

In 2008, the U.S. Food and Drug Administration (FDA) issued a directive for drug manufacturers to evaluate cardiovascular outcomes in studies of all new type 2 diabetes medications due to concerns about increased cardiovascular risk. Previously approved drugs for the treatment of type 2 DM were not subject to such a safety assessment. Recently published studies have provided additional data on cardiovascular and renal outcomes in people with type 2 DM and cardiovascular disease or high cardiovascular risk (Tables 2, 3).

Studies of cardiovascular outcomes with all dipeptidyl peptidase-4 inhibitors have failed to show a cardiovascular benefit of these drugs compared with placebo. The CAROLINA trial showed similar efficacy

*Table 2*

**Trial results, regarding the cardiovascular safety of SGLT-2 inhibitors**

| Trial | EMPA-REG OUTCOME (n=7020) | CANVAS Program (n=10 142) | DECLARE-TIMI 58 (n=17 160) | CREDENCE (n=4401) | DAPA-CKD (n=4304; T2DM n = 2906) | VERTIS CV (n=8246) |
|---|---|---|---|---|---|---|
| Intervention | Empagliflozin/ placebo | Canagliflozin/ placebo | Dapagliflozin/ placebo | Canagliflozin/ placebo | Dapagliflozin/ placebo | Ertugliflozin/ placebo |
| Started/Ended | 2010/2015 | 2009/2017 | 2013/2018 | 2017/2019 | 2017/2020 | 2013/2020 |
| Primary endpoint | 3-component MACE 0.86 (0.74 – 0.99) | 3-component MACE 0.86 (0.75 – 0.97) | 3-component MACE 0.93 (0.84 – 1.03) Cardiovascular death or hospitalization due to HF 0.83 (0.73 – 0.95) | Terminal CKD. Creatinine doubling or death due to renal or cardiovascular outcomes 0.70 (0.59 – 0.82) | ≥50 % GFR reduction. Terminal CKD. Creatinine doubling or death due to renal or cardiovascular outcomes 0.61 (0.51 – 0.72) | 3-component MACE 0.97 (0.85 – 1.11) |
| Cardiovascular death | 0.62 (0.49 – 0.77) | 0.87 (0.72 – 1.06) | 0.98 (0.82 – 1.17) | 0.78 (0.61 – 1.00) | 0.81 (0.58 – 1.12) | 0.92 (0.77 – 1.11) |
| Myocardial infarction | 0.87 (0.70 – 1.09) | 0.89 (0.73 – 1.09) | 0.89 (0.77 – 1.01) | – | – | 1.04 (0.86 – 1.26) |
| Stroke | 1.18 (0.89 – 1.56) | 0.87 (0.69 – 1.09) | 1.01 (0.84 – 1.21) | – | – | 1.06 (0.82 – 1.37) |
| Hospitalization due to HF | 0.65 (0.50 – 0.85) | 0.67 (0.52 – 0.87) | 0.73 (0.61 – 0.88) | 0.61 (0.47 – 0.80) | – | 0.70 (0.54 – 0.90) |
| Hospitalization due to unstable angina | 0.99 (0.74 – 1.34) | – | – | – | – | – |
| All-cause mortality | 0.68 (0.57 – 0.82) | 0.87 (0.74 – 1.01) | 0.93 (0.82 – 1.04) | 0.83 (0.68 – 1.02) | 0.69 (0.53 – 0.88) | 0.93 (0.80 – 1.08) |

*Table 3*

**Trial results, regarding the cardiovascular safety of SGLT-2 inhibitors in HF patients with preserved and reduced left ventricular ejection fraction**

| Trial | DAPA-HF (n=4744; 1983 with T2DM) | EMPEROR-Reduced (n=3730; 1856 with T2DM) | EMPEROR-Preserved (n=5988; 2938 with T2DM) | DELIVER (n=6263; 2807 with T2DM) |
|---|---|---|---|---|
| Intervention | Dapagliflozin/ placebo | Empagliflozin/ placebo | Empagliflozin/ placebo | Dapagliflozin/ placebo |
| Inclusion criteria | NYHA class II – IV HF and LVEF ≤40 %, with or without T2DM | NYHA class II – IV HF and LVEF ≤40 %, with or without T2DM | NYHA class II – IV HF and LVEF ≤40 %, with or without T2DM | NYHA class II – IV HF and LVEF ≤40 %, with or without T2DM |
| Started/Ended | 2017/2019 | 2017/2020 | 2017/2020 | 2018/2022 |
| Primary endpoint | HF decompensation or cardiovascular death 0.74 (0.65 – 0.85) | Cardiovascular death or hospitalization due to HF 0.75 (0.65 – 0.86) | Cardiovascular death or hospitalization due to HF 0.79 (0.69 – 0.90) | HF decompensation or cardiovascular death 0.82 (0.73 – 0.92) |
| Secondary endpoint | Cardiovascular death или Hospitalization due to HF 0.75 (0.65 – 0.85) | All hospitalizations due to HF 0.70 (0.58 – 0.85) Average decrease in GFR 1.73 (1.10 – 2.37) | All hospitalizations due to HF (first and repeated) 0.73 (0.61 – 0.88) GFR decrease level ( – 1.25 vs – 2.62 ml/ min/1.73m$^2$; p<0.001) | Total number of cases of HF decompensation and cardiovascular death 0.77 (0.67 – 0.89) Changes in KCCQ TSS after 8 months 1.11 (1.03 – 1.21) Average change 2.4 (1.5 – 3.4) All-cause mortality 0.94 (0.83 – 1.07) |
| Cardiovascular death | 0.82 (0.69 – 0.98) | 0.92 (0.75 – 1.12) | 0.91 (0.76 – 1.09) | 0.88 (0.74 – 1.05) |
| Hospitalization due to HF | 0.70 (0.59 – 0.83) | 0.69 (0.59 – 0.81) | 0.73 (0.61 – 0.88) | 0.77 (0.67 – 0.89) |
| All-cause mortality | 0.83 (0.71 – 0.97) | 0.92 (0.77 – 1.10) | 1.00 (0.87 – 1.15) | 0.94 (0.83 – 1.07) |

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of the DPP-4 inhibitor linagliptin and the sulfonylurea derivative glimepiride in influencing cardiovascular outcomes, despite a lower incidence of hypoglycemia in the linagliptin treatment group [117]. However, trials of other new treatments for type 2 DM have had mixed results.

### *Studies of sodium-glucose cotransporter type 2 inhibitors*

In the randomized EMPA-REG OUTCOME trial in patients with type 2 DM and cardiovascular diseases, the sodium-glucose cotransporter type 2 (SGLT-2) inhibitor empagliflozin reduced the risk of the adverse outcomes (MI, stroke, and cardiovascular death) by 14% (p=0.04) and cardiovascular mortality by 38% (p<0.001) compared to placebo [118]. Results from CANVAS, a research program on the SGLT-2 inhibitor canagliflozin, showed a significant reduction in the risk of the adverse outcomes (cardiovascular death, MI or stroke) compared with placebo. However, there was an increased risk of lower limb amputation in the canagliflozin group [119]. In the CREDENCE study in patients with type 2 DM and CKD, the canagliflozin group had a reduced risk of sum of end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes compared with placebo. In this study, there was no significant increase in lower extremity amputations, fractures, acute renal failure or hyperkalemia with canagliflozin compared to placebo. However, an increased risk of diabetic ketoacidosis was observed in the canagliflozin group compared to placebo [120]. The results of the randomized DECLARE-TIMI 58 trial in patients with type 2 DM with documented ACVD (40% of participants) or multiple risk factors met the defined criteria of no less efficacy than placebo with respect to major adverse cardiovascular events, but did not show a reduction in their incidence. The reduced risk of cardiovascular death or hospitalization for HF decompensation in the dapagliflozin group compared with placebo reflected a lower incidence of hospitalization due to HF, with no difference in the risk of cardiovascular death between groups [121]. In the DAPA-CKD study in patients with or without CKD and type 2 DM, the risk of the composite of adverse outcomes (sustained reduction in GFR of at least 50%, end-stage CKD, or death from renal or cardiovascular causes) was significantly reduced in the dapagliflozin group compared with the placebo group [122]. In the VERTIS CV study, the SGLT-2 inhibitor ertugliflozin was equivalent to placebo in its effect on the risk of major adverse cardiovascular outcomes in patients with type 2 DM and documented ACVD. In addition, ertugliflozin reduced the risk of hospitalization due to HF, which is consistent with findings from studies of other SGLT-2 inhibitors [123]. The SGLT-1 and SGLT-2 inhibitor sotagliflozin, which is not currently approved by the FDA in the United States, reduced the cumulative incidence of adverse events (death from cardiovascular causes, hospitalization, or need for acute HF decompensation treatment) in the SCORED trial in people with type 2 DM, CKD, and other cardiovascular risk factors. Side effects of sotagliflozin were similar to those observed with other SGLT-2 inhibitors, but included an increased incidence of diarrhea associated with SGLT-1 inhibition [124].

### *Studies of glucagon-like peptide-1 receptor agonists*

In large randomized trials involving patients with type 2 DM, the glucagon-like peptide-1 (GLP-1) receptor agonists liraglutide in LEADER [125], semaglutide in SUSTAIN-6 [126], and dulaglutide in REWIND [127] were shown to reduce the risk of cardiovascular death, non-fatal MI, or non-fatal stroke compared with placebo. The oral form of semaglutide in the randomized PIONEER trial [128], albiglutide in Harmony Outcomes [129], lixisenatide in ELIXA [130], and exenatide in EXSCEL [131] were not superior to placebo in affecting the sum of these adverse outcomes. Currently, the treatment with SGLT-2 inhibitors (empagliflozin, canagliflozin, dapagliflozin) and GLP-1 receptor agonists (liraglutide, semaglutide, and dulaglutide) can significantly reduce the risk of cardiovascular events in people with type 2 DM. According to meta-analyses, drugs in these two classes can comparably reduce the risk of major adverse cardiovascular complications in people with type 2 DM and known ACVD [132, 133]. SGLT-2 inhibitors also reduce the risk of hospitalization due to HF decompensation and progression of kidney disease in people with known ACVD or its multiple risk factors or CKD with albuminuria [134, 135]. Therefore, in patients with type 2 DM and ACVD, multiple risk factors for ACVD, or diabetic nephropathy, SGLT-2 inhibitors with proven efficacy are recommended to reduce the risk of major adverse cardiovascular events and/or hospitalization due to HF decompensation. In type 2 DM patients with

ACVD or multiple ACVD risk factors, GLP-1 receptor agonists with proven efficacy are recommended to reduce the risk of major adverse cardiovascular events. The combined use of SGLT-2 inhibitors and GLP-1 receptor agonists may provide additional improvements in cardiovascular and renal outcomes [136].

### *Glucose-lowering therapy and heart failure*

The common co-occurrence of type 2 DM and HF is characterized by increased morbidity and mortality, requiring appropriate choice of glucose-lowering agents to improve outcomes. Thiazolidinediones increase the risk of developing HF and should be avoided in people with symptomatic HF [137]. Observational studies in people with type 2 DM and HF have not shown a negative effect of metformin on the outcomes [138]. Despite the lack of relevant randomized trials, metformin can be used to treat hyperglycemia in people with stable HF as long as renal function remains within the recommended range for its use. The dipeptidyl peptidase-4 inhibitor saxagliptin increased the risk of hospitalization due to HF decompensation compared with placebo in the randomized SAVOR-TIMI 53 trial [139]. However, other drugs in this class in cardiovascular outcomes trials – alogliptin in EXAMINE, sitagliptin in TECOS, and linagliptin in CARMELINA – did not have this effect [137]. Trials of the GLP-1 receptor agonists lixisenatide, liraglutide, semaglutide, exenatide, albiglutide, and dulaglutide did not show an increased risk of hospitalization for HF compared to placebo [137].

The use of SGLT-2 inhibitors in patients with type 2 DM was associated with a reduced incidence of hospitalization due to HF compared with placebo in the randomized trials of empagliflozin (EMRA-REG OUTCOME) [118], canagliflozin (CANVAS) [119] and dapagliflozin (DECLARE-TIMI 58) [121]. In patients with New York Heart Association (NYHA) class II – IV CHF and an ejection fraction ⩽40 %, dapagliflozin in the DAPA-HF trial [140] and empagliflozin in the EMPEROR-Reduced trial [141] reduced the risk of cardiovascular death or hospitalization due to CHF decompensation compared with placebo. In patients with NYHA class II – IV CH and an ejection fraction > 40 %, empagliflozin in the randomized EMPEROR-Preserved trial [142] and dapagliflozin in the DELIVER significantly reduced the risk of cardiovascular death or hospitalization due to HF [143]. Approximately half of the participants in these trials had DM, but the presence of DM did not affect the reported outcomes. A meta-analysis of these four trials of SGLT-2 inhibitors, supplemented by the SOLOIST-WHF data using sotagliflozin, showed a reduced risk of cardiovascular death or hospitalization due to HF, cardiovascular death, first hospitalization due to HF, and all-cause mortality in a wide range of patients with HF, supporting their emerging role as first-line therapy for HF regardless of ejection fraction and concomitant therapy [144].

In patients with type 2 DM and diagnosed HF with reduced (<40 %), moderately reduced (41 – 49 %), or preserved (⩾50 %) ejection fraction, treatment with SGLT-2 inhibitors is recommended to reduce the risk of HF progression and cardiovascular death because of their proven benefit in this patient population. In addition, SGLT-2 inhibitors are recommended in this patient population to reduce symptoms and physical limitations and to improve quality of life [145-147]. The observed benefits likely represent a class effect of SGLT-2 inhibitors, are not related to glycemic lowering, and are similar in patients with and without type 2 DM and HF.

### *Finerenone in patients with type 2 diabetes mellitus and chronic kidney disease*

People with DM have an increased risk of CKD, which also increases the cardiovascular risk. The selective nonsteroidal mineralocorticoid receptor antagonist finerenone improved CKD outcomes in the randomized FIDELIO-DKD trial in people with stage 3 or 4 CKD, severe albuminuria, and type 2 DM [148]. In the FIGARO-DKD trial in patients with diabetic nephtopathy receiving maximal renin-angiotensin system blocker therapy, finerenone reduced the risk of cardiovascular death, non-fatal MI, non-fatal stroke or hospitalization due to HF compared with placebo [111]. In a pooled analysis of FIDELITY, the improvement in cardiovascular and renal outcomes in patients with type 2 DM and CKD under the effect of finerenone was confirmed [113]. Therefore, in people with type 2 DM and CKD with albuminuria who are receiving maximally tolerated doses of ACE inhibitors or ARBs, the addition of finerenone should be considered to improve cardiovascular outcomes and reduce the risk of CKD progression.

### *Features of the clinical use of drugs*

In people with type 2 DM and a high risk of ACVD, HF, or CKD, therapy with SGLT-2 inhibitors and/or GLP-1 receptor agonists should be used as part of a comprehensive approach to reduce the risk of adverse cardiovascular and renal outcomes. Drugs of these classes should be included in therapy regimens regardless of the need for additional glycemic correction and the use of metformin. SGLT-2 inhibitors or agonists of GLP-1 receptors in combination with drugs for the treatment of AH, dyslipidemia, hyperglycemia, antiplatelet therapy will provide additional improvement of the of patients` prognosis. Therefore, their use should be initiated in people with diagnosed cardiovascular or renal disease who may subsequently be diagnosed with DM, as cardioprotective agents are appropriate to use from the start of DM treatment. The addition of SGLT-2 inhibitors or GLP-1 receptor agonists to therapy for long-term DM may be more challenging, especially if patients are already receiving complex glucose-lowering therapy. In such a case, treatment with SGLT-2 inhibitors or GLP-1 receptor agonists may require replacement of some or all of the previously prescribed glucose-lowering medications to minimize the risk of hypoglycemia and other adverse effects and to reduce treatment costs. Close collaboration between primary care physicians and specialists can help facilitate this adjustment of therapy and improve outcomes in people with type 2 DM who are at high risk for complications.

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# **Clinical evaluation to identify the predictors** of arrhythmogenic cardiomyopathy in patients with ventricular extrasystoles without structural heart changes. Clinical and experimental study

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The aim of the study was to evaluate the complex determination of predictors of "arrhythmogenic cardiomyopathy" in patients with ventricular extrasystoles (VE) without structural heart changes to predict the development of cardiovascular diseases in a prospective study.

**Methods.** Experimental study. Rats were used to model VE by the mechanism of early postdepolarization (aconitine arrhythmia), rabbits — for delayed postdepolarization (barium chloride-induced arrhythmia), and dogs — for re-entry peroxide arrhythmia. In the electrocardiogram (ECG), in addition to the conventional parameters, the pre-excitation interval, its variability and the index of intrinsic deviation of VE (IDVEi) were analyzed.

**Clinical study.** We observed 412 patients without structural changes of the heart aged from 16 to 43 years (mean 28.4±0.8 years), and the number of VEs per day of observation ranged from 6157 to 37254 (mean 19706±656 VEs). The same parameters were determined by the ECG as in experimental arrhythmias: they were calculated separately for mono- and polymorphic left- and right ventricular extrasystoles (LVE and RVE). The duration of patient follow-up was up to 10 years.

**Results.** In the modeling of ventricular arrhythmias by the mechanism of delayed postdepolarization, polymorphic VE, early postdepolarization — early monomorphic VE, re-entry — early and late monomorphic VE were registered. In the animals with the modeling of arrhythmia by the mechanism of re-entry IDVEi was significantly higher in comparison with VE caused by the mechanisms of early and delayed postdepolarization. The main predictors of "arrhythmogenic cardiomyopathy" in patients without structural changes of the heart with VE, which determine the development of organic heart pathology, such as coronary heart disease (CHD) and mitral valve prolapse (MVP), are IDVEi and $QRS_{VE}$ complex duration. Increased values of these parameters (>0.42 units and 148 m/s, respectively), characterize the risk group of cardiovascular pathology formation.

The development of CHD in patients without structural heart changes with VE highly correlated with IDVEi ⩾ 0.56 units, duration of $QRS_{VE}$ complex ⩾157 m/s in monomorphic LVE, use of class III drugs. The development of MVP in these patients highly correlated with duration of $QRS_{VE}$ complex ⩾ 159 m/s in polymorphic VE, efficacy of class I drugs and to a lesser extent of the class III drugs.

**Conclusion.** In patients without structural heart changes with VE, the increase in IDVEi values and QRSVE complex duration > 0.48 units and 149 m/s, respectively, determine the risk group of cardiovascular pathology formation. In patients without structural heart changes with VE, the development of CHD highly correlated with IDVEi ⩾0.56 units, QRSVE complex duration ⩾157 m/s in monomorphic LVE, and MVP — with QRSVE complex duration ⩾159 m/s in polymorphic VE.

**Keywords:** ventricular extrasystoles, predictors of the development of organic heart pathology in patients without structural heart changes.

**Conflict of interests:** none declared.

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## Introduction

It is now known that despite the benign course of ventricular extrasystoles (VE) in patients without structural heart disease, frequent ventricular ectopy may contribute to the development of left ventricular dysfunction manifested by clinical symptoms of heart failure, and suppression of premature ventricular complexes usually leads to improvement in cardiac function [1, 2]. In most cases, it is relatively harmless, but VE may be one and only manifestation of the onset of various diseases, particularly of the cardiovascular system, such as coronary heart disease (CHD), mitral valve prolapse (MVP), etc. [1, 2]. In these patients, various predictors are used to assess the risk of "arrhythmogenic cardiomyopathy". Most often, the number of premature ventricular contractions per day of observation is determined (for example, more than 15% of premature ventricular ectopias from all cardiac contractions, including the number of paired, grouped VEs and/or ventricular complexes that constitute unstable ventricular tachycardia [2, 3]). Also, the duration of the QRS complex in VE and sinus rhythm ($QRS_{VE}$ and QRSsr), the index of internal deviation of VEs (IDVEi) are sometimes taken into account. The duration of the corrected premature ventricular ectopic interval (PEIVEc), its variability, e.g. by determining the linear deviation (LD) of PEIVEc have also been used in clinical practice [1, 3]. Hypothetically, it

is possible to assume that in experimental modeling of VE it is possible to estimate the frequency of detection and significance of predictors of the occurrence of "arrhythmogenic cardiomyopathy" depending on the mechanism of development of induced ventricular arrhythmia. In the available literature no information was found on the possibility of using the predictors of "arrhythmogenic cardiomyopathy" in patients with VE without structural heart changes (including those depending on the mechanism of its development) to predict the development of cardiovascular diseases.

**The aim of the study** was to evaluate the complex determination of predictors of "arrhythmogenic cardiomyopathy" in patients with ventricular extrasystoles (VE) without structural heart changes to predict the development of cardiovascular diseases in a prospective study.

## Methods

### *Experimental study*

Experiments were performed on 11 Wistar rats (male and female, body weight 180-240 g), 12 rabbits and 14 mongrel dogs weighing 1.2–2.4 kg (average — 1.7±1.4 kg) and 5.5-12.3 kg (average — 9.2±1.3 kg). The choice of experimental arrhythmias was made taking into account the electrophysiological mechanisms involved in their formation. Arrhythmias with the mechanism of early postdepolarization were modeled with aconitine, delayed postdepolarization — with barium chloride, re-entry — with hydrogen peroxide [4].

In rats, the early postdepolarization mechanism was modeled by intravenous injection of aconitine hydrobromide at a dose of 10.0 μg/kg, and in rabbits, the delayed postdepolarization mechanism was modeled by intravenous injection of barium chloride at a dose of 5 mg/kg [4]. In dogs, after removal of the pericardium under hexenal anesthesia, ventricular arrhythmias were modeled in the open heart by injection of arrhythmogen (0.3% hydrogen peroxide) into the ventricular myocardium [4]. After hydrogen peroxide injection, vascular damage is first observed with the subsequent development of "oxidative stress" of cadiomyocytes [4-6] and the occurrence first of VE due to the mechanism of early postdepolarization [7] and then, with further membrane hyperpolarization and prolongation of action potential duration — to re-entry [4, 8]. In all dogs, the mechanism of arrhythmia development was assessed by excitation conduction mapping [8]. Electrograms and electrocardiograms (ECG) in standard and augmented leads were recorded on a digital electrocardiograph "Poly-Spectrum" (Neurosoft, Ivanovo). On ECG, after modeling of each ventricular arrhythmia, we calculated PEIVEc and its LD separately for left and right ventricular extrasystoles (LVE and RVE). We also calculated the ratio of PEIVE to QT of sinus rhythm (QTsr.), IDVEi, defined as the ratio of the time from the onset of the premature ventricular contraction to the apex of the maximum R or S wave of the premature ventricular complex to the duration of $QRS_{VE}$ [4, 9, 10].

### *Clinical study*

412 patients aged 16 to 43 years (mean — 28.4±0.8 years) were observed. Inclusion criteria: absence of structural cardiac changes, presence of sinus rhythm, detection of class IV-V VE according to Rayn M. (1985) classification [1], subjective sensation of arrhythmia, LVEF ⩾ 54%, chronic heart failure class I–II according to NYHA [1, 9], informed patient consent for research and treatment. The study was approved by the local ethics committee.

The absence of structural cardiac changes was confirmed after exclusion of cardiac and extracardiac diseases, electrolyte disorders, use of medications and/or toxic products (mainly diuretics, oral contraceptives, alcohol abuse, etc.) that independently or indirectly led to the development of VE, as well as other exclusion criteria. Those included the use of various stress tests, invasive and noninvasive coronary angiography, and contrast-enhanced magnetic resonance imaging, which were described earlier [1, 9].

In addition to a general clinical examination, all patients underwent ECG monitoring (1–3 days) and echocardiographic examination with the Hitachi EUB-5500 according to generally accepted methods. Calculation of hemodynamic parameters such as LVEF, etc. and determination of the localization of premature ventricular complexes have been described previously [8–10]. In addition, PEIVEc and its LD separately for LVE and RVE, the ratio of PEIVE to QTsr, IDVEi, $QRS_{VE}$ complex duration were calculated as in the experimental study.

In the first stage, all patients were treated primarily with cardioprotective therapy, including potassium supplements, sedatives, polyunsaturated fatty acids, etc., to eliminate VE. [1, 9], and if there was no effect, the choice of differentiated antiarrhythmic therapy

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*Table 1*

**ECG parameters of VEs induced in the experiment (M±m, 95% confidence interval of mean values in parentheses)**

| Parameters | Early postdepolarization (aconitine arrhythmia), n = 11 | Delayed postdepolarization (barium chloride-induced arrhythmia), n = 12 | Early postdepolarization (peroxide arrhythmia), n = 14 | Re-entry (peroxide arrhythmia) n = 14 |
|---|---|---|---|---|
| PEIVE/QTsr, units | 1.11±0.02 (1.03–1.18) | 1.83±0.16* (1.36–2.28) | 1.12±0.02 (1.04–1.21) | 1.78±0.17* (1.14–2.28) |
| LDcPEVEi, ms | 1.71±0.03 (1.64–1.83) | 42.12±3.69* (25.05–58.14) | 1.73±0.06 (1.55–1.92) | 39.33±3.17* (24.82–54.93) |
| IDVEi, units | 0.29±0.02 (0.25–0.34) | 0.31±0.02 (0.22–0.38) | 0.32±0.03 (0.24–0.42) | 0.66±0.02* (0.58–0.72) |
| QRSVE/QRSsr | 1.36±0.03 (1.25–1.44) | 1.37±0.03 (1.27–1.48) | 1.31±0.03 (1.21–1.43) | 1.91±0.09* (1.56–2.23) |

**Note.** * — reliable difference of parameters in comparison with VE caused by the mechanism of early postrepolarization (at $p < 0.05$).

for VE was based on screening tests with antiarrhythmic drugs of classes I-III used in average therapeutic doses [9]. Class II drugs were used first, and if they were ineffective, class I or III drugs were used, with amiodarone used last if necessary. The antiarrhythmic drugs of choice were metoprolol at 50–100 mg/day, propranolol at 80–160 mg/day, carvedilol at 25-50 mg/day, and lappaconitine hydrobromide (Allapinin) at 50–75 mg/day, diethylaminopropionylethoxycarbonylaminophenothiazine (etacizine) — 100–150 mg/day, sotalol — 160–240 mg/day, propafenone (propanorm) — 300–600 mg/day, amiodarone — 600–800 mg/day. In the absence of effect of monotherapy, the combined therapy was used instead. Daily ECG monitoring was performed before and after antiarrhythmic therapy, and the criterion of positive effect was reduction of the number of extrasystoles by 75% or more in comparison with their initial number, as well as elimination of paired and group extrasystoles [1, 2].

For statistical processing of the obtained data we used mean values and error of mean values (M±m), standard deviation (σ), 95% CI of mean values, Student's t-test, $\chi^2$ criteria, ($p<0.05$ values were considered as statistically significant). The normality of the distribution of the studied quantitative parameters was checked using the Kolmogorov-Smirnov test and ±3σ rule (Gaussian distribution), Pearson's and Spearman's linear pairwise and rank correlations (r) (for nonparametric parameters) were used, respectively. The comparison of two binary variables was assessed using the logistic regression method with determination of the odds ratio (OR) using the computer program "Statistica", version 11.0.

The study was performed in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki.

## Results

### *Experimental study*

Polymorphic LVE or RVE were registered in modeling of barium chloride-induced arrhythmia, in aconitine arrhythmia — early monomorphic LVE or RVE, in re-entry peroxide arrhythmia — first early, then early and late monomorphic LVE. Development of unstable VT was observed in all animals with aconitine arrhythmia modeling, in 6 (42.86%) of 14 dogs with re-entry peroxide arrhythmia. In animals with barium chloride-induced arrhythmia modeling, PEIVE/QTsr and LDPEIVEc values were significantly greater compared to aconitine arrhythmia, whereas all indices studied were significantly greater when VE was induced by the re-entry mechanism compared with ventricular ectopy induced by the early postdepolarization mechanism caused by aconitine and hydrogen peroxide administration. There were no significant changes in the other parameters studied (Table 1).

### *Clinical study*

In 412 patients without structural heart changes, the number of premature ventricular contractions per day of observation ranged from 6157 to 37254 (mean — 19706±656 VEs). In 166 patients (40.29%) the development of cardiovascular or gastrointestinal diseases was observed during 1–10 years after the first examination (main group), and in the rest of the patients during this period of observation there were no structural changes of the heart at the first and subsequent examinations, as well as cardiovascular system diseases and pathology of other organs and systems (comparison group). Various clinical forms of CHD were detected in 41 (24.70%) patients of the main group, 11 (26.83%) of them had myocardial infarction, and in 22 (73.33%) of 30 patients the diagno-

*Table 2*

**Characteristics of ventricular extrasystole and efficacy of antiarrhythmic therapy in patients without structural heart changes**

| Parameters \ Patients group | Comparison group, n = 246 | Main group, n = 166 | | |
|---|---|---|---|---|
| | | CHD, n = 41 | MVP, n = 15 | GI diseases, n = 110 |
| Number of VEs from 6,000 to 15,000/day | 115(46.75 %) | 27(65.85 %) | 8(53.33 %) | 56(50.91 %) |
| Number of VEs more than 15000/day | 131(53.25 %) | 14(34.15 %) | 7(46.67 %) | 54(49.09 %) |
| Monomorphic LVE | 5(2.03 %) | 38(92.68 %)* | — | --- |
| Polymorphic LVE | 10(4.07 %) | — | 9(60 %)* | 34(30.91 %)* |
| Monomorphic RVE | 215(87.40 %) | 3(7.32 %)* | --- | --- |
| Polymorphic RVE | 16(6.50 %) | --- | 6(40 %)* | 76(69.09 %)* |
| Class II drugs | 24(9.76 %) | 4(9.76 %) | — | 14(12.73 %) |
| Ethacizin | 176(71.54 %) | — | — | — |
| Propafenone | 42(17.07 %) | — | 10(66.67 %)* | — |
| Allapinin | 4(1.63 %) | — | — | 85(77.27%)* |
| Sotalol | — | 32(78.05 %) | 5(33.33%) | 11(10 %) |
| Amiodarone | — | 5(12.19 %) | — | — |

**Note.** * — reliable difference of parameters with the comparison group (at $p < 0.05$), dash — parameters were not registered.

sis was confirmed by coronary angiography (clinically significant stenosis of coronary arteries was detected), 15 (9.04%) had MVP, 16 (9.64%) had peptic ulcer disease, 58 (34.94%) had gastroesophageal reflux disease, 22 (13.25%) had hyperacid gastritis type "B", and the rest had hiatal hernia.

In the control group, monomorphic RVE was more common (87.40%), and class I drugs were most effective in treating ventricular ectopy. In patients with the development of CHD, monomorphic LVE and, less frequently, monomorphic RVE were significantly more common than in the comparison group, and class III drugs were most effective for the treatment of premature ventricular complexes. In patients with MVP, polymorphic LVE and RVE were significantly more frequent compared with the control group, with a positive clinical effect of VE treatment with class I drugs. In patients with formation of gastrointestinal tract pathology, polymorphic LVE and RVE were significantly more frequently registered in comparison with the control group with the highest efficacy of ventricular ectopia elimination by class I drugs with vagolytic activity. There was no significant difference in other studied parameters of the main group in comparison with the control group (Table 2).

In the comparison group, the ratio of PEIVE of monomorphic VE to QTsr were ⩽1.35 units, LDcPEVEi — ⩽10 m/s, the values of IDVEi and duration of $QRS_{VE}$ complex did not exceed 0.42 units and 148 m/s, respectively, while polymorphic ventricular ectopy in these patients was characterized by significantly higher variability of PEIVEc, and other ECG parameters were not significantly different in comparison with monomorphic extraordinary ventricular complexes. In case of CHD, all ECG parameters of monomorphic VE, including IDVEi, $QRS_{VE}$ complex duration, were significantly greater compared with similar ectopy in the control group. In patients with MVP, the duration of $QRS_{VE}$ complex of polymorphic VE was significantly longer compared with similar premature ventricular depolarization in the control group, while no significant difference was found in other studied parameters. In patients with gastrointestinal pathology, ECG signs of polymorphic VE were not significantly different from similar ectopy in the control group (Table 3).

In the comparison group, ECG signs of monomorphic LVE and RVE highly correlated with similar parameters characteristic of modeling ventricular ectopy by the mechanism of early postdepolarization ($r = 0.92$), and polymorphic — with delayed postdepolarization ($r = 0.94$). In patients without structural heart changes with subsequent CHD formation, ECG parameters of monomorphic LVE corresponded to experimental arrhythmias induced by the re-entry mechanism ($r = 0.96$), and in the cases of MVP and gastrointestinal pathology, ECG parameters of polymorphic LVE and RVE highly correlated with experimental arrhythmias induced by the delayed postdepolarization mechanism ($r = 0.92$ and $r = 0.96$, respectively).

In patients without cardiac and extracardiac pathology, control of VE, mainly due to the mechanism of early repolarization, highly correlated with the

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*Table 3*

**ECG parameters of VE in patients without structural heart changes (M±m, 95% confidence interval of mean values in parentheses)**

| Patients groups / Parameters | Comparison group, n = 246 | Main group, n = 166 | | |
|---|---|---|---|---|
| | | CHD, n = 41 | MVP, n = 15 | GI diseases, n = 110 |
| PEIVE/QTsr, units | 1.27±0.01 (1.18-1.35) / 1.74±0.11† (1.23-2.19) | 1.79±0.07* (1.34-2.24) / — | — / 1.66±0.11 (1.22-2.04) | — / 1.68±0.05 (1.18-2.15) |
| LDPEIVEc, ms | 9.21±0.08 (8.11-10.02) / 82.53±2.31† (50.81-115.67) | 85.37±6.58* (44.12-121.36) / — | — / 72.54±9.18 (37.11-105.14) | — / 83.45±4.28 (42.16-123.57) |
| IDVEi, units | 0.35±0.01 (0.24-0.42) / 0.36±0.02 (0.27-0.46) | 0.67±0.02* (0.56-0.78) / — | — / 0.34±0.02 (0.28-0.42) | — / 0.37±0.01 (0.26-0.48) |
| QRSVE complex duration, ms | 134±1 (125-148) / 138±1 (133-146) | 185±4* (157-210) / — | — / 189±8* (159-226) | — / 137±1 (129-144) |

**Note.** * — reliable difference of parameters with the comparison group, † — with monomorphic VE (at $p < 0.05$); above the isoline are the parameters characterizing monomorphic VE, below — polymorphic VE, dash — parameters were not registered.

use of class I drugs, represented mainly by etacizine (OR = 11.7). Development of CHD was highly correlated with IDVEi ⩾0.56 units (OR = 12.9), $QRS_{VE}$ complex duration ⩾157 m/s (OR = 9.8), monomorphic VE due to re-entry mechanism, using class III drugs (OR = 8.1). The development of MVP highly correlated with the duration of the $QRS_{VE}$ complex ⩾159 m/s (OR = 10.7) in polymorphic VE due to the mechanism of delayed postdepolarization, the efficacy of class I drugs represented by propafenone (OR = 6.2) and, to a lesser extent, class III drugs (OR = 1.6). The formation of GI pathology highly correlated with polymorphic VE caused by the mechanism of delayed postdepolarization (OR = 4.1) and the use of class I drugs, represented mainly by allapinin (OR = 10.2).

## Discussion

Currently, classical genetics has shown that the heritability of various cardiovascular diseases, such as CHD and other pathologies, is approximately 40% [1]. The presence of various risk factors or their association in apparently healthy patients leads to a local disturbance of cardiomyocyte metabolism and may cause the development of VE. In the absence of structural heart disease, cardiac or extracardiac pathology, the course of VE is usually considered benign according to the classification of Bigger B. (1984) [1]. These patients are likely to develop "arrhythmogenic cardiomyopathy", and in addition to estimating the number of premature ventricular complexes, the presence of such predictors as increased duration of the $QRS_{VE}$ complex, PEIVEc and its variability, IDVEi, etc. are determined [1, 3]. On the other hand, in patients without structural heart disease with VE, the presence of predictors inducing the development of "arrhythmogenic cardiomyopathy" may become the first symptoms of "arrhythmic form" of the beginning of the formation of various clinical forms of CHD, myocarditis, cardiomyopathy, MVP or other pathology [1].

In experimental modeling of VE, the informative value of predictors of arrhythmogenic cardiomyopathy depends on the mechanism of development of induced ventricular ectopy. VE with the mechanism of early postdepolarization was modeled with aconitine, delayed postdepolarization — with barium chloride, early postdepolarization and re-entry — with hydrogen peroxide [4, 8]. In modeling of barium chloride-induced arrhythmia, polymorphic VE was recorded, in aconitine arrhythmia — early monomorphic VE, in re-entry peroxide arrhythmia — first early, then early and late monomorphic LVE. In animals with arrhythmia modeled by re-entry mechanism, IDVEi was significantly greater compared to VE caused by early and late postdepolarization mechanisms, as well as PEIVE/QTcr ratio and LDcPEVEi values were greater compared to ventricular ectopy caused by early postdepolarization mechanism.

Aconitine depresses or delays the inactivation of the sodium channel system, artificially increasing the membrane potential to a level between –40 mV and –10 mV, which leads to the emergence of spontaneous action potentials by the mechanism of early postdepolarization [1, 11]. The same phenomenon can occur in human myocardium: under the influence of aconitine or "oxidative stress" it depolarizes and spontaneously activates [1, 7, 11]. The appearance of delayed postdepolarizations is preceded by hyperpolarization of the cell membrane in the range of — 60–70 mV with the subsequent appearance of a premature action potential when the threshold of subthreshold excitation is reached [11]. In addition, their development requires an increase in the concentration of calcium ions in cardiomyocytes. VEs caused by early and delayed postdepolarization are associated with less hyperpolarization of cell membranes compared to arrhythmias caused by the re-entry mechanism, reflecting the potentially reversible nature of cardiomyocyte dysfunction [11]. Further increase of membrane hyperpolarization due to deeper metabolic disturbances leading to prolongation of action potential duration, as well as decrease of outward and inward currents, (especially when L-type cardiomyocyte calcium channels are damaged) may provoke an increase of heterogeneity of repolarization. Such areas usually show unidirectional and/or frequency-dependent conduction block and Wenckebach phenomenom, which is characteristic of VE caused by the re-entry mechanism [1, 11].

166 (40,29 %) out of 412 patients without structural changes of the heart had cardiovascular or GI diseases in the first ten years after the first examination, and the rest had no structural changes of the heart at the first and subsequent examinations, as well as cardiovascular diseases and pathology of other organs and systems. In 41 (24,70 %) out of 166 patients of the main group various clinical forms of CHD, in 15 (9,04 %) — MVP, and in the rest — GI diseases represented by peptic ulcer, gastroesophageal reflux disease, hyperacid gastritis type "B", hiatal hernia were found.

In patients without detected cardiac and extracardiac pathology during the whole period of observation, the ECG-signs of monomorphic LVE and RVE highly correlated with similar indices characteristic for modeling of experimental ventricular ectopy by the mechanism of early postdepolarization (r = 0.92), and polymorphic — by the delayed postdepolarization (r = 0.94). In them, the PEIVE ratios of monomorphic VE to QTsr were ⩽1.35 units, LDcPEVEi — ⩽10 m/s, values of IDVEi and duration of $QRS_{VE}$ complex did not exceed 0.48 units and 149 m/s, respectively, while polymorphic ventricular ectopy in these patients was characterized by a significantly higher variability of PEIVEc. Other ECG parameters were not significantly different in comparison with monomorphic premature ventricular complexes. In these patients, the positive effect of VE elimination highly correlated with the use of class I drugs, mainly represented by etacizine (OR = 11.7).

Apparently, in patients without cardiovascular and extracardiac pathology, the occurrence of VE due to the mechanisms of early and delayed postdepolarization is associated with less hyperpolarization of cell membranes compared to re-entry, which probably reflects the reversible nature of cardiomyocyte dysfunction caused by local metabolic changes [1, 11]. In these patients, ventricular arrhythmias usually resolve as cardiomyocyte function normalizes [1, 9, 11].

In patients without structural heart changes with subsequent CHD formation, ECG parameters of monomorphic VE corresponded to experimental arrhythmias induced by re-entry mechanism (r = 0.96), and in patients with MVP and GI pathology, ECG parameters of polymorphic LVE and RVE highly correlated with experimental arrhythmias induced by delayed postdepolarization mechanism (r = 0.92 and r = 0.96, respectively).

CHD development highly correlated with IDVEi ⩾0.56 units (OR = 12.9), $QRS_{VE}$ complex duration ⩾157 m/s (OR = 9.8), monomorphic VE with class III drugs (OR = 8.1).

Increased values of IDVEi and $QRS_{VE}$ complex duration in monomorphic VE probably determine its epicardial or intramural localization, in which slow depolarization from the epicardium to the endocardium is observed [10]. The occurrence of epicardial or intramural VE is associated with occlusion of small branches of epicardial arteries with the formation of small foci of fibrosis or "mute" myocardial ischemia, which are not verified by conventional methods of investigation [1], but represent an organic anatomical substrate of re-entry loop formation [11]. It should be noted that the efficacy of class III antiarrhythmic drugs indirectly confirms the presence of ventricular arrhythmias caused by the re-entry mechanism [1, 8,

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11]. On the other hand, in patients with acute CHD, a high risk of fatal arrhythmias in the first 72 hours (up to 80%) from the onset of the disease was found for LDPEIc <10 m/s not only for monomorphic, but also polymorphic LVE and RVE. This is probably due to the mosaic nature of myocardial damage with the appearance of zones of ischemia, damage and necrosis with the occurrence of ventricular arrhythmias with different mechanisms of their development and unpredictable course [8].

The development of MVP highly correlated with the duration of $QRS_{VE}$ complex ≥159 m/s of polymorphic VE (OR = 10.7), and the efficacy of class I drugs represented by propafenone (OR = 6.2) and to a lesser extent — class III (OR = 1.6).

VE in patients without structural changes of the heart with localization in the papillary muscles of the mitral valve, less often in the tricuspid valve or in the mitral annulus, LV outflow tract, may induce the development of non-myxomatous MVP due to superficial fibrosis of the mitral valve leaflets, thinning and/or chordal elongation [1, 2, 10]. These patients may have LVE and/or RVE with $QRS_{VE}$ complex duration >150 m/s, and radiofrequency ablation is indicated when class I drugs are ineffective [1, 2].

The development of GI pathology highly correlated with polymorphic VE (OR = 4.1) and with the use of class I drugs for the treatment of VE, represented mainly by allapinin (OR = 10.2).

The occurrence of VE in patients without structural heart changes and subsequent development of GI pathology is associated with excessive vagal influence on the heart as a result of functional dyspepsia [1, 9]. This is indirectly confirmed by the results of the present study: in these patients, the positive clinical effect of therapy was achieved mainly by the use of class I drugs with vagolytic effect.

## Conclusion

When modeling ventricular arrhythmias by the mechanism of delayed postdepolarization, polymorphic VE were registered; in early postdepolarization — early monomorphic VE; in re-entry — early and late monomorphic LVE. In animals with modeling of arrhythmia by the mechanism of re-entry, there is significantly higher IDVEi in comparison with VE caused by the mechanisms of early and delayed postdepolarization. In patients with VE without structural changes of the heart the increase of IDVEi values and $QRS_{VE}$ complex duration ≥0.48 units and ≥149 m/s, respectively, in addition to estimation of the number of ventricular ectopias per day of observation, determine the risk group of cardiovascular system pathology. The development of CHD in patients without structural heart changes with VE highly correlated with IDVEi ≥0.56 units, $QRS_{VE}$ complex duration ≥157 m/s monomorphic LVE, and the use of class III drugs. The development of MVP correlated with $QRS_{VE}$ complex duration ≥159 m/s of polymorphic VE, the effectiveness of class I drugs, and to a lesser extent with class III drugs.

**Conflict of interests:** none declared.

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# **Identification of comorbid pathology** in patients with atrial fibrillation

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**The aim of the study** is to determine the incidence of comorbid diseases in associated with atrial fibrillation (AF).
**Methods.** The one-phase study included 134 patients (72 men and 62 women) with a confirmed diagnosis of atrial fibrillation. Patients underwent anthropometric examination (height, weight, body mass index), blood pressure (BP) measurement, resting electrocardiography, Doppler echocardiography, ultrasonography. Thyroid hormonal status (free T3, free T4, thyroid stimulating hormone, anti-TG, and antibodies to thyroperoxidase) was also examined. Thyroid hormones were analyzed by enzyme-linked immunosorbent assay using Bio Screen MS-500 (USA).
**Results.** The distribution of atrial fibrillation by form was as follows: paroxysmal form was registered in 26 (19.4%) patients, persistent — in 7 (5.2%), long-term persistent — in 19 (14.2%), and permanent — in 79 (59.0%). Arterial hypertension (AH) was detected in 81 patients (60.4%) with AF, chronic heart failure (CHF) in 82.8%, type 2 diabetes mellitus in 26 (19.4%), and coronary heart disease (CHD) in 42 (31.3%). Ischemic stroke was registered in 9 (6.7%) patients with a history of AF.
One somatic comorbidity was found in 25 (18.8%) patients, two in 40 (29.3%), three in 44 (32.8%), four in 19 (14.5%), and five in 6 (4.6%).
Approximately 80% of patients with AF were at high risk for stroke and thromboembolic complications without anticoagulant therapy.
**Conclusion.** The majority of AF patients are diagnosed with other cardiovascular diseases, including AH, CHD and CHF. In the surveyed group, a combination of two and three diseases was detected in more than 60% of cases.
**Keywords:** atrial fibrillation, comorbidity, somatic diseases.

**Conflict of interests:** none declared.

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## Introduction

Atrial fibrillation (AF) is the most common type of supraventricular arrhythmia, causing serious hemodynamic disturbances and complications. Despite some progress in the treatment of AF, this type of arrhythmia remains one of the leading causes of stroke, chronic heart failure (CHF) and sudden cardiac death. In addition, the incidence of this condition is expected to increase in the coming years [1].

The prevalence of AF worldwide is 3 % in the population over 20 years of age [2, 3]. In Europe and the USA, one in four middle-aged people is at high risk of developing AF. It should be noted that the prevalence of AF in the elderly is increasing, including in the presence of comorbidities — arterial hypertension (AH), coronary heart disease (CHD), heart failure (HF), obesity, diabetes mellitus (DM), thyroid pathology, chronic kidney disease (CKD) [1-4].

AF has both a symptomatic and asymptomatic course. Latent asymptomatic AF can lead to serious complications such as stroke and death [5]. Population screening with resting ECG to detect asymptomatic AF, especially in the elderly and those with AF-related diseases, is recommended [5].

Prevention, early detection and appropriate correction of risk factors leading to AF and other comorbidities play an important role in the management of AF and its complications [6, 7]. The most common comorbidities include CHD, CHF, AH, cardiomyopathies, chronic obstructive pulmonary disease, thyroid pathology, DM and others. In most cases, the average number of comorbidities in patients with AF is 3–4 [1]. These diseases can act both as the primary cause of AF and as comorbidities, and thus pathogenetically contribute to the progression of AF, reduce the quality of life of patients, and increase the risk of complications and sudden cardiac death [8, 9].

**The aim of the study** was to determine the incidence of comorbid conditions associated with AF of non-valvular genesis.

## Methods

The one-phase cohort clinical study included 134 patients (72 males and 62 females) aged 18 years and older (mean age 62.8 years; 95 % confidence interval (CI) — 60.9; 64.6) with various forms of AF who were being followed as inpatients and outpatients at the Mirgasimov Republican Clinical Hospital. The presence of atrial fibrillation was documented according to the data of 12-lead electrocardiographic (ECG) series, including during ECG Holter monitoring. According to AF classification, 29 patients (21.6 %) of 134 patients were diagnosed with paroxysmal AF, 7 patients (5.2 %) with persistent AF, 19 patients (14.2 %) with long-term persistent AF, and 79 patients (59.0 %) with permanent AF, including 16 patients (11.9 %) with first-time AF.

All patients were divided into 3 groups according to the ECG variant of AF: Group 1–29 patients with paroxysmal AF, Group 2–26 patients with persistent and long-term persistent AF, and Group 3–79 patients with permanent AF. Complex clinical. instrumental and laboratory investigations revealed the presence of various comorbid diseases and clinical conditions (Table 1). AH was found to be the most common pathology associated with AF among the patients studied. Among 81 patients with AH (60.4 %; 95 % CI — 52.14, 68.76), stage I (uncomplicated) was found in 22 patients, stage II (asymptomatic) in 36 patients, and stage III (complicated) in 23 patients.

*Table 1*

**Clinical characteristics of the examined patients**

| Criteria | Group 1 (n=29) | Group 2 (n=26) | Group 3 (n=79) |
|---|---|---|---|
| Males/females, n | 20 / 9 | 16 / 10 | 42 / 37 |
| Age, years | 50.3 (48.4; 56.3) | 56.6 (52.8; 60.3) | 65.8 (56.1; 68.2) |
| History of myocardial infarction, n / % | 2 / 6.9 | 3 / 11.5 | 11 / 13.9 |
| History of stroke, n / % | — | 2 / 7.7 | 7 / 8.9 |
| Type 2 DM, n / % | 4 / 13.8 | 5 / 19.2 | 17 / 21.5 |
| AH, n / % | 16 / 55.2 | 17 / 65.4 | 48 / 60.8 |
| CHF, functional classes II–IV, n / % | 12 / 41.4 | 20 /76.9 | 79 /100.0 |
| Anemia (Hb <110 g/l), n / % | 2 / 6.9 | 2 / 7.7 | 13 / 13.9 |
| Obesity, classes 1–3, n / % | 6 / 20.7 | 5/ 19.2 | 12 / 15.2 |
| Left ventricle hypertrophy, n / % | 11 / 37.9 | 13 / 50.0 | 40 / 50.6 |
| CKD, stages 2-3 | 13 / 17.3 | 8 / 17.0 | 21 / 17.2 |

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Exclusion criteria were: congenital and/or acquired valvular heart disease; isolated atrial fibrillation; patients who underwent catheter radiofrequency ablation of the pulmonary vein orifices; clinically and laboratory confirmed hypo- and hyperthyroidism; use of drugs affecting thyroid function; refusal to participate in the study.

Patients underwent the following examinations: clinical examination, anthropometric measurements (height and weight were measured, body mass index was calculated), blood pressure (BP) measurement, resting ECG in 12 standard leads, Doppler echocardiography, ultrasound examination of the thyroid gland and internal organs. Doppler echocardiographic data were used to calculate structural and functional parameters of the heart: heart chambers dimensions, wall thickness, global systolic function, left ventricle myocardial mass index (LVMI). In case of sinus rhythm, i.e. in paroxysmal and persistent atrial fibrillation, LV diastolic function was assessed.

The European Heart Rhythm Association (EHRA) scale was used to assess the clinical severity of atrial fibrillation. Thyroid hormonal status was assessed (free T3, free T4, TSH, anti-TG and antibodies to thyroperoxidase). The analysis of thyroid hormones was performed by enzyme immunoassay on the Bio Screen MS-500 device (USA) with the reagent of Chema LLC (Moscow).

To assess the comorbidity of somatic diseases, the verified diseases registered in medical documents were taken into account. AH was confirmed in the presence of BP ⩾140/90 mmHg in two consecutive clinical visits and in patients receiving adequate doses of antihypertensive drugs, according to the recommendations of the European Society of Cardiology/European Society of Hypertension 2018 (ESC/ESH-2018) [10]. The diagnosis of type 2 DM was verified according to the criteria of the American Diabetes Association [11]. CHF, its phenotypes and functional classes were determined on the basis of clinical and instrumental parameters (symptoms, LV ejection fraction parameters) according to the recommendations of the European Society of Cardiology [12].

The $CHA_2DS_2$-VASc score was calculated to decide on the prescription of anticoagulant therapy for each patient [1].

## Statistical analysis

Statistical analysis was performed using standard Microsoft Excel software. During the statistical analysis of the material, the minimum, maximum and mean values of the sample, the standard deviation and the error of the mean were determined. The normality of the distribution of the variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The Student's t-test was calculated. The 95% CI of fractions was calculated using an online calculator according to the Wilson method. The CI of means for 95% probability was also determined. Calculations were performed using the Confidence Limits for Mean Calculator. For small samples, the significance of differences was determined using the Mann-Whitney U-test.

Reliability of differences between proportions was calculated using Pearson's chi-squared test ($\chi^2$) and Fisher's exact test. Calculations for these methods were performed online using the MEDCALC calculator. Differences were considered statistically significant at $p<0.05$.

## Results

Of 134 patients with AF, 28 patients were in class I, 32 patients were in class IIa, 56 patients were in class IIb, and 18 patients were in class III according to the EHRA scale. When evaluating the frequency of comorbid diseases associated with AF, it was shown that in 19.4% of cases (95% CI 73.88; 87.32) there was type 2 DM, in 23 patients — 17.2% (95% CI 10.76; 23.57) — abdominal obesity of varying severity. In 42 patients — 31.3% (95% CI 23.46; 39.23) — various clinical forms of CHD were diagnosed, including 16 patients (11.9%) with a history of myocardial infarction. In addition, 111 patients — 82.8% (95% CI 73.88; 87.32) were diagnosed with CHF, including 29 patients — 21.6% (95% CI 18.45; 35.25) of II FC, 59 patients — 44% (95% CI 45.20; 64.06) of III FC, and 23 patients — 17.2% (95% CI 11.16; 25.88) of IV FC.

When assessing the predictive role of different clinical conditions associated with AF, some peculiarities were revealed. There was a difference in the severity (stage) of CHF depending on the ECG variant of AF. In patients with permanent AF (group 3), cases of congestive CHF were predominant, whereas in patients with paroxysmal and/or persistent AF (groups 1 and 2), cases of early CHF were predominant: 83.5% vs. 50% ($\chi^2$=13.28; p=0.0003). However, in patients with uncomplicated stages of AH, paroxysmal and/or persistent AF was significantly more common than permanent AF: 76.4% vs. 49.4% ($\chi^2$=13.28; p=0.0017).

This implies that the presence of AH without associated clinical conditions is a risk factor for paroxysmal and/or persistent AF, whereas CHF, especially stages III–IV, is usually correlated with persistent AF.

It was also revealed that the incidence of CKD did not differ significantly between groups, although it was more frequent in group 3. However, a comparative evaluation of the estimated value of the glomerular filtration rate determined by the CKD-EPI formula revealed a significant difference between the 1-2nd and the 3rd groups. As it is known, the detection rate of cardiovascular diseases, including atrial fibrillation, increases with the age of the population. Therefore, the mean age in the group of patients with paroxysmal AF was significantly lower than in the group of patients with permanent AF: 50.3 (48.4; 56.3) and 65.8 (56.1; 68.2) years, respectively (p <0.001).

It should be noted that when comparing the functional status of patients with AF, i.e. taking into account the AF severity class according to EHRA, similar trends were obtained both depending on the ECG variant of AF. Analysis of the obtained data revealed the presence of at least one comorbid pathology in all patients with AF (table 2). Thus, 25 (18.8%) patients had one, 40 (29.3%) — two, 44 (32.8%) — three, 19 (14.5%) — four and 6 patients (4.6%) — five comorbidities. In addition, it was shown that the age of patients with 4–5 comorbidities was significantly higher than the age of patients with 1–2 comorbidities (p<0.05).

In the group of patients with 1–2 comorbidities, AH was detected significantly more often than in patients with 4 ($\chi^2$=8.05; p=0.005) and 5 comorbidities ($\chi^2$=3.90; p=0.048). This indicates that AH is the most common comorbid condition, especially in relatively young patients with paroxysmal AF, and is a predictor of arrhythmia development. The main markers of atrial electrical vulnerability ("arrhythmogenic readiness") are considered to be hypertensive cardiac remodeling, manifested by LV diastolic dysfunction and increased left atrial volume, P-wave dispersion and shortened refractory period [9].

In the group of patients with 5 comorbidities, CHF, especially FC III–IV, was found in all 6 patients (100.0%), also characterized by the predominance of the permanent form of AF. On the contrary, the frequency of CHF was significantly lower in patients with 1–2 comorbidities. This may be explained by the fact that in patients with permanent AF, the development of CHF with signs of fluid retention in the body is more likely to be a manifestation of tachysystolic dilated cardiomyopathy caused by AF.

To determine the risk of stroke and thromboembolic complications in patients with AF before prescribing anticoagulant therapy, the CHA2DS2-VASc score was calculated, according to which the patients were divided into 3 groups: low-risk patients — 14.5%, intermediate-risk patients — 11.6%, and high-risk patients — 73.9% (table 3).

*Table 2*

**The prevalence of comorbid pathology combinations in patients with AF (n / %)**

| Parameters | Number of comorbidities | | | |
|---|---|---|---|---|
| | 1–2 (n = 65) | 3 (n = 44) | 4 (n = 19) | 5 (n = 6) |
| Age, years | 51.3 (46.2; 50.7) | 55.9 (53.8; 60.5) | 63.1 (54.0; 67.8) | 65.8 (58.7; 68.4) |
| Stage 1–3 AH, (n = 81) | 47 (72.3) | 25 (56.8) | 7 (36.8) | 2 (33.3) |
| CHD, (n = 41) | 8 (12.3) | 16 (36.4) | 12 (63.2) | 6 (100.0) |
| Type 2 DM, (n = 26) | 10 (15.4) | 8 (18.2) | 6 (31.5) | 2 (33.3) |
| Obesity, classes 1–3, (n = 23) | 12 (18.5) | 7 (15.9) | 3 (15.8) | 1 (16.7) |
| CHF, stages II–IV, (n = 111) | 52 (80.0) | 35 (79.6) | 18 (94.7) | 6 (100.0) |
| Paroxysmal AF, (n = 29) | 15 (23.1) | 10 (22.7) | 3 (15.8) | 1 (16.7) |
| Persistent AF, (n = 26) | 9 (13.9) | 9 (20.5) | 5 (26.3) | 3 (50.0) |
| Permanent AF, (n = 79) | 30 (46.2) | 27 (61.4) | 16 (84.2) | 6 (100.0) |

*Table 3*

**Risk of stroke and thromboembolism, history of stroke, and anticoagulant therapy in patients with AF**

| CHA2DS2VASc | | | History of stroke | Anticoagulant therapy | |
|---|---|---|---|---|---|
| Low risk | Intermediate risk | High risk | 9 (6.7%) | Recieved | Did not recieve |
| 19 (14.5%) | 15 (11.6%) | 100 (73.9%) | | 32 (23.9%) | 102 (76.1%) |

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It should be noted that 9 patients (6.7%) had a history of ischemic stroke. Anticoagulant therapy was used in 32 (23.9%) patients and not used in 102 (76.1%) patients. Overall, 22.4% of patients were treated with warfarin and only 1.5% with rivaroxaban.

## Discussion

The single-stage study is dedicated to the investigation of somatic comorbidity in patients with different forms of AF. The relevance of this problem is due to the high risk of hemodynamic disorders and thromboembolic complications in AF [13, 14]. The most serious of these is ischemic stroke. In 20–30% of patients with a history of ischemic stroke, atrial fibrillation is found in the acute phase of the disease or after hospitalization [15-16]. In addition, vascular dementia and impaired quality of life due to cognitive impairment are common in patients with AF [17–18]. Stroke in AF is more likely to be disabling and fatal compared to other causes. Anticoagulant therapy is prescribed to reduce the risk of stroke/thromboembolism. The $CHA_2DS_2VASc$ scale is widely used to choose therapy. If the $CHA_2DS_2VASc$ score is > 1 in men and > 2 in women, the likelihood of thromboembolic complications increases, indicating the use of oral anticoagulants.

In our study, oral anticoagulant therapy was indicated for almost all patients, but in real clinical practice, in most cases, they were not prescribed or, when prescribed, patient compliance was low. In particular, 30 patients were prescribed warfarin as anticoagulant therapy, but the international normalized ratio recommended for its efficacy and safety was not always determined. New oral anticoagulants, which are safer than warfarin and do not require regular laboratory testing, were prescribed in only 1.5% of cases.

In patients with AH, the presence of AF significantly increases the risk of stroke and also increases the risk of CHF. At the same time, high blood pressure can increase the likelihood of stroke and hemorrhagic complications and lead to arrhythmia recurrence [19].

CHF is known to be one of the most common comorbidities in patients with AF. The development of AF in patients with CHF is associated with the presence of common pathophysiological mechanisms (structural remodeling, activation of neurohormonal mechanisms) and risk factors [20, 21]. The most severe hemodynamic disorder is tachycardia-induced cardiomyopathy, which is characterized by an unfavorable prognosis. On the other hand, patients with AF and CHF comorbidity have been shown to have a worse prognosis and increased risk of cardiovascular mortality, regardless of LV ejection fraction [22].

The presence of common risk factors of type 2 DM and AF also increases the frequency of their comorbidity. In recent years, type 2 DM has been recognized as a potential risk factor for the development of AF, which has been confirmed by numerous studies. For example, patients with diabetes were found to have a 39% higher risk of developing AF compared to those without diabetes [23]. Control of glycemic status is also important, with inadequate control increasing the risk of AF [24, 25].

In the present study, one in three patients had a combination of two or three somatic diseases. The most common combination was AF with AH and CHF. At present, one in six patients with AF has a combination of AH, CHD and CHF. Therefore, it can be assumed that AF is detected at all stages of the cardiovascular continuum, which increases the risk of complications.

## Conclusion

The majority of AF patients have comorbid cardiovascular diseases, including AH, CHD and CHF. In the cohort studied, a combination of two and three diseases was found in more than 60% of cases. Approximately 80% of AF patients were at high risk for stroke and thromboembolic complications without anticoagulant therapy.

Early detection of comorbidities and complex therapy, including anticoagulant therapy, may reduce the risk of AF or its progression or the development of complications, thereby improving the quality of life and prognosis of patients with AF.

**Conflict of interests:** none declared.

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# Hypolipidemic effect of $\omega_3$-polyunsaturated fatty acids in coronary heart disease and carotid atherosclerosis

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**The aim of the study** was to evaluate the efficacy of hypolipidemic action of $\omega_3$-polyunsaturated fatty acids in patients suffering from coronary heart disease (CHD) with postinfarction cardiosclerosis (PICS) and atherosclerotic lesions of carotid arteries up to 40%.

**Methods.** The study included 90 participants with CHD, PICS, atherosclerotic stenosis <40%, and laboratory-confirmed dyslipidemia. Patients of the main group were prescribed $\omega_3$-polyunsaturated fatty acids ($\omega_3$-PUFA) in addition to the baseline therapy. The study was conducted at the Kursk City Clinical Emergency Hospital from December 2022 to May 2023. Laboratory and instrumental diagnostics were performed at 4-week intervals, including ECG, duplex scanning of the brachiocephalic arteries, complete blood count, urinalysis, biochemical blood analysis with the determination of the patient's lipid profile. Before and after the start of therapy, patients were surveyed using the SF-36 questionnaire. Data were statistically processed by calculating Student's criterion with Bonferroni correction for independent and dependent variables.

**Results.** At the end of the 24th week of the study, the target hypolipidemic effect was registered in 26.6% of patients with type IV hyperlipidemia (HL) and 35.3% — with type IIB HL, optimal values of high-density lipoprotein cholesterol (HDL–C) (>1.0 mmol/l) were achieved in 17.5% of patients with type IV HL and in 21.3% — with type IIB HL. According to the SF-36 questionnaire, 57.2% of those studied showed positive changes in physical health after being treated with $\omega_3$-PUFA.

**Conclusion.** As a result of the study, it was found that $\omega_3$-PUFAs have a hypolipidemic effect in patients with

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CHD (PICS, dyslipidemia and carotid atherosclerosis) and improve the quality of life of the patients.

**Keywords:** coronary heart disease, carotid atherosclerosis, $\omega_3$ polyunsaturated fatty acids, postinfarction cardiosclerosis, hyperlipidemia.

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## Introduction

Cardiovascular diseases (CVD) remain the leading cause of mortality and disability in the adult population in all countries [1, 2]. In the Russian Federation, cerebral vascular pathology ranks second in the structure of mortality from cardiovascular diseases [3]. The search for new approaches to the therapy of cardiological patients is a key aspect in reducing cardiovascular mortality and improving the quality of life.

Lipid metabolism disorders are considered to be the main link in the development and progression of arterial atherosclerosis, increasing the risk of cardiovascular events [4, 5]. In the Russian Federation, there is a high prevalence of atherogenic dyslipidemia, according to data from the ESSE-RF epidemiological study [2]. Carotid artery stenosis is a consequence of arterial lesions with atherosclerotic plaque. Carotid artery stenosis >50 % is associated with up to 36 % probability of ischemic stroke. If the stenosis is < 50 %, additional evaluation to determine the morphologic appearance of the atherosclerotic plaque is indicated because unstable atheroma is the leading cause of embolic stroke [6].

Hypolipidemic therapy is aimed at preventing cardiovascular complications and further progression of atherosclerosis. Drugs with pleiotropic effects are of some interest, as they reliably increase the life expectancy of patients. Preparations from the group of $\omega_3$-polyunsaturated fatty acids ($\omega_3$-PUFA) have not only hypolipidemic action, but also reduce platelet aggregation, have anti-inflammatory effect [5], potentiate antioxidant effect of high-density lipoproteins (HDL–C) [7], which can be used to correct dyslipidemia in patients with carotid atherosclerosis and prevent the development of organic brain lesions.

**The aim of the study** was to evaluate the the hypolipidemic effect of Omacor in CHD patients with postinfarction cardiosclerosis (PICS) and atherosclerotic stenosis < 40 %.

## Methods

The study included 90 men aged 51 to 59 years (M = 54.5 years) with a diagnosis of CHD (PICS) with hyperlipidemia (HL) type IIB (combined HL) and type IV (hereditary triglyceridemia) according to Fredrickson and instrumentally confirmed atherosclerotic stenosis of the carotid arteries up to 40 %. General, laboratory and instrumental examinations of the patients were performed before and every 4 weeks during the study, including medical history, anthropometry, and the measurement of blood pressure (BP). Complete blood count and urine analysis, blood biochemistry with determination of lipid fractions (total cholesterol (TC), low-density lipoprotein (LDL–C) and high-density lipoprotein (HDL–C), triglycerides (TG), atherogenic index (AI) and glucose level), Holter monitoring, ultrasound duplex scanning of brachiocephalic arteries (BCAUS) were also performed, as well as the consultation with a neurologist. Patients' quality of life was assessed before pharmacological intervention and after four months of therapy using the SF-36 questionnaire.

**Inclusion criteria:** male sex, age of patients from 51 to 59 years, confirmed diagnosis of CHD: stable angina, functional class II–III (FC), PICS, instrumentally confirmed atherosclerotic stenosis of carotid arteries up to 40 %, proven dyslipidemia (TG>1.77 mmol/L, TC>5.0 mmol/L, LDL–C>3.0 mmol/L), absence of contraindications to the prescription of $\omega_3$-PUFA. Informed and voluntary consent was obtained from all patients to participate in the study. The study was conducted at the Kursk City Clinical Emergency Hospital from December 2022 to May 2023.

Cardiac patients were excluded from the study based on the following criteria: contraindications to $\omega_3$-PUFA prescription, unstable angina pectoris, stable angina pectoris FC IV, valvular disease, II–III degree atrioventricular block, carotid stenosis > 40 %, circulatory insufficiency above stage IIA, history

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of stroke, diabetes mellitus (DM), thyroid disease, symptomatic AH, side effects of treatment, refusal of observation.

All study participants were prescribed baseline therapy (β-adrenoblockers, statins, antiplateletes, angiotensin-converting enzyme inhibitors) with individual selection of drug dosages according to clinical guidelines for the treatment of CHD [8]. Patients in the control group (20 patients) were prescribed baseline therapy only. The main group (70 patients) was prescribed Omacor (PATHEON SOFTGELS, B.V., The Netherlands) at a dosage of 1 g per day instead of statins in addition to basic pharmacotherapy. To evaluate the effect on TG levels, the dosage was increased according to the drug's instructions (4 g/day). Hypolipidemic therapy was carried out for 24 weeks.

Data were statistically processed using the STATISTICA 12.0 (StatSoft Inc.). Student's criterion with Bonferroni correction was calculated for dependent and independent variables. Differences were considered statistically significant at $p<0.05$.

## Results

Baseline lipid metabolism values were comparable in all randomized groups taking into account the phenotype of dyslipidemia: mean values of TC — 7.53±0.59 mmol/l (type IIB) and 4.98±0.31 mmol/l (type IV), TG in patients with type IIB HL — 3.36±0.9 mmol/l, with type IV — 4.2±0.98 mmol/l. At the 8th week of the study in patients with type IIB HL, who were included in the control group, there was a decrease in TC by 23.5% and LDL–C by 22.4%; there was an increase in HDL–C by 18.6% ($p<0.05$). Among patients with type IV dyslipidemia who took only baseline therapy, there was a significant decrease in TC by 22.7%, LDL–C by 30.3%, TG by 31.7% ($p<0.05$), an increase in HDL–C by 18.6% ($p<0.01$), which contributed to a significant decrease in AI by 32.1%. Pharmacologic intervention was continued. By week 16, optimal lipid profile values were achieved in 13.4% of patients with type IV dyslipidemia and in 39.4% of patients with combined HL. The optimal values of the lipid profile were taken as the indicators presented in the national guidelines for the diagnosis of correction of lipid metabolism disorders: TC<5.0 mmol/l, TG<1.7 mmol/l, LDL–C <1.4 mmol/l, HDL–C>1.0 mmol/l [9]. Further lipid profile values did not change significantly. The overall lipid-lowering effect of baseline therapy is presented in Figure 1.

In patients with CHD, PICS, atherosclerotic stenosis of carotid arteries < 40% and type IIB HL who underwent 8-week treatment with $\omega_3$-PUFA the following changes in lipid metabolism parameters were observed: the level of TC decreased by 18.2%; also the level of LDL–C — by 19.2% and TG — by 35.5%. At the same time, HDL–C increased by 20.8% ($p<0.01$) and AI decreased by 36.5% ($p<0.05$). In patients with type IV HL, the following changes were observed af-

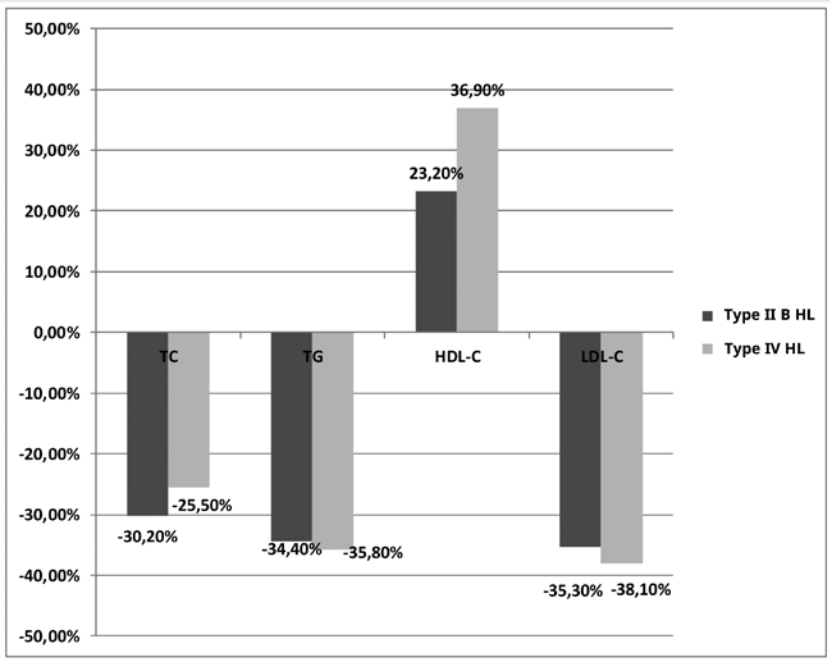


**Fig. 1.** Degree of decrease in lipid fractions of the control group by the end of the 24th week of the study

*Table 1.* **Changes in lipidogram by 24 weeks of treatment with Omacor (4 g/day) in CHD patients with type IIB and IV HL**

| HL type | TC, mmol/L | TG, mmol/L | LDL–C, mmol/L | HDL–C, mmol/L | AI |
|---|---|---|---|---|---|
| Prior to pharmacologic intervention | | | | | |
| IIB type | 8.25±1.2 | 3.3±0.98 | 5.16±1.16 | 0.77±0.19 | 8.82±2.84 |
| IV type | 4.98±0.52 | 4.0±1.25 | 1.97±0.5 | 1.03±0.29 | 3.9±2.4 |
| 8 weeks | | | | | |
| IIB type | 6.75±1.1* | 2.13±0.6* | 4.17±1.08* | 0.93±0.22* | 5.6±2* |
| IV type | 4.82±0.52 | 2.46±0.77* | 1.96±0.48 | 1.21±0.3* | 2.94±2 |
| 16 weeks | | | | | |
| IIB type | 6.0±1.0* | 2.1±0.5* | 4.15±1.0** | 0.94±0.24** | 5.5±2* |
| IV type | 4.8±0.53 | 2.42±0.75* | 1.92±0.48* | 1.28±0.32* | 2.92±2.1* |
| 24 weeks | | | | | |
| IIB type | 5.8±0.9* | 2.0±0.7* | 4.1±1.0** | 0.95±0.21** | 5.3±2* |
| IV type | 4.75±0.65* | 2.33±0.88** | 1.91±0.46* | 1.31±0.54** | 2.77±2.4* |

**Note.** * — p<0,05, ** — p<0,01 compared to pre-treatment values.

ter 8 weeks of treatment with $\omega_3$-PUFA: TG levels decreased significantly — by 38.5%, HDL–C increased by 17.5%. At the same time, AI decreased by 24.6%.

Thus, with $\omega_3$-PUFA pharmacotherapy, lipid profile target values were achieved in 17.6% of type IV HL CHD patients with verified carotid atherosclerosis and in 23.5% — with type IIB HL (p<0.05), leading to continuation of pharmacological correction.

In patients with type IIB HL, a 36.4% reduction in TG levels was observed after 16 weeks of $\omega_3$-PUFA treatment. LDL–C levels decreased by 19.6%. At the same time, HDL–C increased by 22.1% (p<0.01). After 16 weeks of therapy in comorbid patients with type IV HL, a significant decrease in TG levels was observed — by 39.5%, HDL–C increased by 24.3% (Table 1).

By the end of week 24 of the study, patients with type IV HL on $\omega_3$-PUFA therapy had a 27.2% increase in HDL–C (p<0.01). In patients with type IIB HL, there was a decrease in TG by 39.4% (p<0.05), a decrease in LDL–C by 20.5% (p<0.01) and an increase in HDL–C by 23.4% (p<0.01). Optimal lipid profile values were achieved in 26.6% of patients with type IV HL and 35.3% of patients with type IIB HL (Figure 2). Thus, the addition of $\omega_3$-PUFA to baseline therapy allows for a more pronounced hypotriglyceridemic effect.

Based on the SF-36 questionnaire, positive changes in physical health were observed in 57.2% of subjects when $\omega_3$-PUFAs were added to baseine therapy. Social activity increased in 18.1% of patients (p<0.05). The majority of respondents noted a reduction in the impact of pain syndrome on the quality of life. The

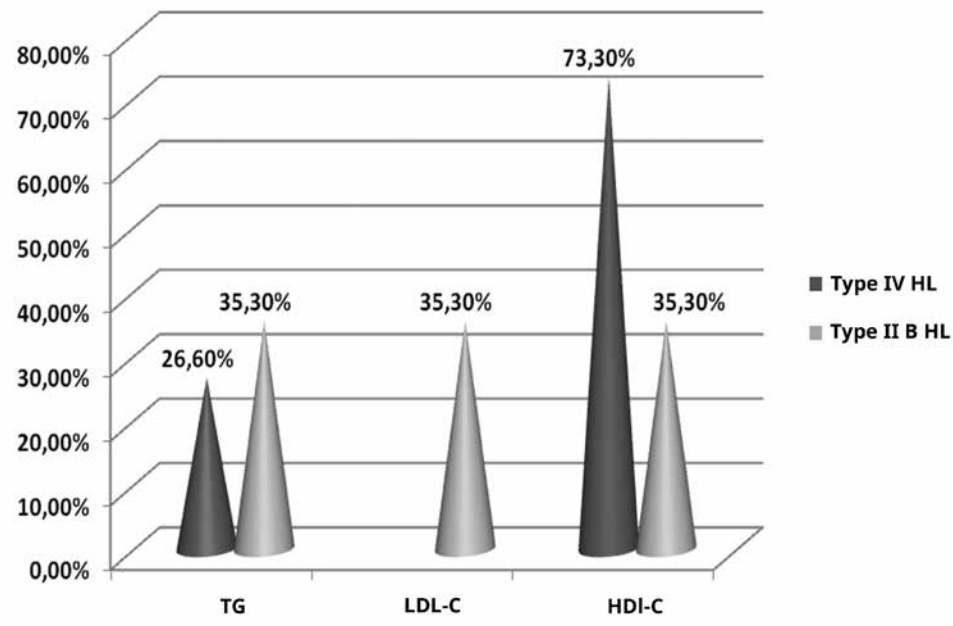


**Fig. 2.** Number of patients who achieved optimal lipid profile values by week 24 of $\omega_3$-PUFA therapy

increase in vitality scale indices together with positive changes in psychological health confirms the improvement of life quality in patients with PICS, type IIB and IV HL, and atherosclerotic stenosis of carotid arteries <40 % when $\omega_3$-PUFA were added.

## Discussion

Under the activity of enzymes, $\omega_3$-PUFAs are metabolized to prostaglandins, thromboxanes, leukotrienes, and nitro fatty acids, which have vasodilatory, anti-aggregatory, and anti-inflammatory effects [5]. In addition, $\omega_3$-PUFAs improve vascular endothelial function [7] by stimulating endothelial nitric oxide synthase [10].

Special attention should be paid to the hypolipidemic effect of $\omega_3$-PUFAs. The Framingham epidemiological study demonstrated that a TG level above 1.7 mmol/L significantly increases the risk of cardiovascular complications [1]. $\omega_3$-PUFAs have mainly a triglyceride-lowering effect due to stimulation of beta-oxidation of free fatty acids and inhibition of TG synthesis in the liver, which decreases their concentration. It is known that in addition to lipid-lowering effects, the use of $\omega_3$-PUFA leads to the stabilization of atherosclerotic plaque. Randomized studies have shown that the use of $\omega_3$-PUFAs reduces macrophage infiltration of the atherosclerotic plaque coating in carotid arteries [5].

$\omega_3$-PUFA supplements have been studied in a number of randomized, placebo-controlled clinical trials. The most convincing evidence base for the efficacy of this pharmacological group is represented by two studies: GISSI-prevenzion, which included people who had suffered a myocardial infarction, and GISSI-HF, which included patients with chronic heart failure. These studies show a significant reduction in cardiovascular mortality in these nosologies after administration of $\omega_3$-PUFA [10]. The efficacy of $\omega_3$-PUFAs in the prevention of cardiovascular complications was not proven in the ORIGIN trial, which included patients with type 2 DM [5]. However, the REDUCE-IT clinical trial, which was conducted in patients with a history of CVD or type 2 diabetes, showed a significant reduction in cardiovascular events and mortality in the groups taking $\omega_3$-PUFA at a dose of 4 mg per day [1, 11].

The study by Skulas-Ray A.C. et al [12] showed that the hypotriglyceridemic effect of the combination of eicosapentaenoic and docosahexaenoic fatty acids (4 g per day) in patients with high baseline TG levels is effective both as monotherapy and in combination with other hypolipidemic drugs [13]. A meta-analysis by Khan S. U. et al. (38 studies, 149051 patients) showed that $\omega_3$-PUFAs reduce cardiovascular mortality and improve patient prognosis [14].

The use of $\omega_3$-PUFAs is associated with a lower risk of dementia [15], which may be due to the angioprotective effects of this pharmacological group on cerebral blood vessels [7].

## Conclusion

Thus, the addition of $\omega_3$-PUFA to the baseline therapy is reasonable for the correction of lipid metabolism disorders in patients with CHD, PICS combined with carotid atherosclerosis, as it allows to improve the quality of life of patients and achieve additional reduction of triglyceride levels.

The pleiotropic effect of $\omega_3$-PUFA expands the possibilities of lipid-lowering therapy in comorbid patients. Numerous studies confirm the safety and efficacy of adding $\omega_3$-PUFA supplements to the main therapy in patients with different levels of cardiovascular risk. The use of these drugs may become an effective way of secondary prevention of cardiovascular mortality in the Russian Federation.

**Conflict of interests**: none declared.

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# **Psychotropic drugs** in clinical cardiology

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This review article notes that the new generation of antidepressants — selective serotonin reuptake inhibitors and melatonin derivatives — do not have the side effects characteristic of tricyclic antidepressants and can be used in the treatment of patients with cardiovascular pathology in combination with depression. The causes and incidence of QT interval prolongation associated with the use of antidepressants are described. Numerous somatotropic and behavioral effects of tricyclic antidepressants have been demonstrated due to their effects on several receptor groups: α1-adrenoceptors, serotonin, muscarinic, and histamine H1 receptors. We searched PubMed, Embase, Web of Science, eLIBRARY and Google Scholar databases for the use of psychotropic drugs in cardiology practice, giving priority to systematic reviews, randomized clinical trials, supplemented by several cohort studies and the descriptions of some experiments. The data of comparative evaluation of modern antidepressants depending on pharmacological effects and development of adverse events are presented. The above-mentioned drugs, unlike traditional antidepressants, are acceptable for treatment of comorbid depressive disorders in patients with cardiovascular diseases. Proven efficacy among antidepressants are escitalopram, paroxetine, which have a strong cardiotropic effect, and agomelatine, which has proven efficacy in myocardial ischaemia–reperfusion injury.

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**Keywords:** antidepressants, SSRIs, neuroleptics, arrhythmias, arterial hypertension, QT interval prolongation, agomelatine, escitalopram, paroxetine.

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## Introduction

In the clinical practice of a cardiologist, it is not uncommon to encounter depressive disorders as concomitant pathologies of the underlying cardiac disease, the correction of which requires the use of special drugs (antidepressants, sedatives, nootropics). Depression and cardiovascular diseases are related. In recent years, evidence has emerged that depression is an independent risk factor for coronary heart disease (CHD) [1-3]. The results of studies in recent years indicate that depression is present in 10–65% of patients hospitalized for acute coronary syndrome (ACS). Of these, 22% have depressive episodes of moderate to severe degree [4]. In general, most researchers agree that the presence of anxiety-depressive disorders in ACS patients is associated with higher rates of future cardiac complications. Several studies have shown that the risk of a new cardiovascular event or death in these patients is 1.36 times higher than in patients with myocardial infarction (MI) without depression [5].

According to the currently accepted concept, mild to moderate depression in cardiac patients can be treated by a cardiologist or general practitioner [6]. This has become possible due to the emergence in recent years of a number of new highly effective antidepressants that, unlike the classical tricyclic antidepressants (amitriptyline, etc.), do not have pronounced behavioral toxicity and negative side effects on the cardiovascular system.

## Neuroleptics

The use of neuroleptics in cardiology is not fully studied, but individual trials have reported their cardiotropic effects. A meta-analysis of clinical trials of 20 antipsychotics showed that lurazidone and partial dopamine agonists (brexpiprazole and aripiprazole) were less likely to cause QT prolongation, whereas

*Table 1.* **Causes and frequency of the QT prolongation**

| Mechanisms of action | Frequency of QT interval prolongation (absolute number of reports) | |
|---|---|---|
| Neuroleptics | | |
| Direct and indirect antagonistic effect on IKr, inhibitory effect on cytochrome P450 system (CYP 1A2, CYP 2D6, CYP 3A4). | Haloperidol | 16 |
| | Ziprasidone | 11 |
| | Quetiapine | 30 |
| | Clozapine | 12 |
| | Olanzapine | 22 |
| | Risperidone | 17 |
| | Sertindole | 1 |
| | Sulpiride | 13 |
| | Thioridazine | 2 |
| | Chlorpromazine | 3 |
| Antidepressants | | |
| Direct antagonistic effect on IKr, inhibitory effect on cytochrome P450 system (CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, CYP 3A4). | Amitriptyline | 8 |
| | Doxepin | 2 |
| | Desipramine | — |
| | Imipramine | 3 |
| | Clomipramine | 5 |
| | Fluoxetine | 16 |
| | Sertraline | 18 |
| | Paroxetine | 5 |

sertindole, amisulpride, and ziprasidone were more frequently associated with this adverse effect [7]. A positive correlation was also found between the risk of reporting QT prolongation and hERG channel affinity. According to the new clinical guidelines of 2021, neuroleptics, especially the group of atypical antipsychotics, are widely used in the treatment of depressive disorders and schizophrenia as long-term antidepressant therapy. In a recent publication Ostroumova O.D. presents a systematized psychotropic drugs according to their effect on the QT interval (Table 1) [8].

Improvement of autonomic function in response to antipsychotic pharmacotherapy in patients with schizophrenia, psychosis and additional cardiovascular risk has been demonstrated [9]. Cardiorespiratory coupling was observed to strengthen with antipsychotic administration, and the effect of heart rate on respiratory rate increased from day 1 to day 3 of the study.

## Antidepressants

This type of drugs is much more widespread in clinical practice and has a greater impact on the cardiovascular system among other neurotropic drugs. Most of the research works mention the significant advantage of antidepressants from the group of selective serotonin reuptake inhibitors (SSRIs) over tricyclic antidepressants. A summary table of the pharmacodynamics and pharmacokinetics of modern antidepressants with side effects (Table 2) is presented below [10–13].

Many somatotropic and behavioral effects of tricyclic antidepressants are related to their non-selectivity — their influence on several groups of CNS receptors (α1-adrenergic receptors, serotonin, muscarinic, and histamine H1-receptors) (Table 3) [14–20].

Tricyclic antidepressants have a pronounced effect on prolongation of PQ, QT intervals, atrial-ventricular QRS complex, especially in patients with initial arrhythmia. Reflectory tachycardia is also one of the side effects that limits the use of tricyclic antidepressants in cardiological practice. Many somatotropic and behavioral effects of tricyclic antidepressants are related to their non-selectivity — their influence on several groups of CNS receptors (α1-adrenergic receptors, serotonin, muscarinic and histamine H1-receptors). SSRIs are selective and lack the side effects of tricyclic antidepressants (Table 4) [21].

One of the retrospective studies on the use of modern antidepressants in cardiological practice found that SSRI antidepressants were used for more than 3 days when treating main cardiovascular diseases [22]. The safe use of antidepressants was proved by their effect on the cardiac conduction system, which

*Table 2.* **Pharmacodynamics, pharmacokinetics and side effects of modern antidepressants**

| Mechanism of action, doses, toxicity, and effect on weight gain of modern antidepressants | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Drugs | Initial doses, (mg/day) | Standart doses, (mg/day) | Overdose lethality | Side effects | | | | | | |
| | | | | Insomnia and agitation | Sedation | Hypotension | Anticholinergic effects | Nausea and gastrointestinal disturbances | Sexual dysfunction | Weight gain |
| SSRIs | | | | | | | | | | |
| Fluoxetine | 20 | 20-40 | Low | Moderate | No or mild | No or mild | No or mild | Moderate | Moderate | No |
| Paroxetine | 20 | 20-40 | Low | Moderate | No or mild | No or mild | Mild | Moderate | Moderate | Moderate |
| Sertraline | 50 | 50-150 | Low | Moderate | No or mild | No or mild | No or mild | Moderate | Moderate | Mild |
| Fluvoxamine | 50 | 100-250 | Low | Moderate | No or mild | No or mild | No or mild | Moderate | Moderate | Mild |
| Citalopram | 20 | 20-40 | Low | Moderate | No or mild | No or mild | No or mild | Moderate | Moderate | Mild |
| Escitalopram | 10 | 10-20 | Low | Moderate | No or mild | No or mild | No or mild | Moderate | Moderate | Mild |
| Reboxetine | 4-8 | 8-12 | Low | Mild | No or mild | No or mild | No or mild | Mild | Mild | No or mild |
| Venlafaxine | 75 | 150 | Moderate | Mild | No or mild | No orMild | No or mild | Moderate | Moderate | No or mild |
| Desvenlafaxine | 50 | 100 | Low | Mild | No or mild | No or mild | No or mild | Mild | Mild | No or mild |
| Duloxetine | 30 | 60-120 | Low | Mild | Mild | Moderate | No or mild | Mild | Mild | No or mild |
| NSSRIs | 100 | 200 | Low | Mild | Mild | No or mild | No or mild | No or mild | No or mild | No or mild |
| NSSRIs | | | | | | | | | | |
| Desipramine | 25-50 | 100-300 | High | Mild | No or mild | Moderate | Mild | No or mild | Mild | Mild |
| Nortriptyline | 25-50 | 75-200 | High | Mild | Mild | Mild | Mild | No or mild | Mild | Mild |
| Maprotiline | 75 | 75-200 | High | Mild | No or mild | Mild | Mild | No or mild | Mild | Moderate |

*Table 3.* **Extent of inhibition of monoamine receptors and transporters by antidepressants**

| Drugs | Norepinephrine transporter | Serotonin transporter | A1-adrenoreceptor | H1-histamine receptor | Muscarinic receptor | Serotonin receptor (5-HT-2A) |
|---|---|---|---|---|---|---|
| TCAs | | | | | | |
| Amitriptyline | ++ | +++ | +++ | +++ | +++ | +++ |
| Clomipramine | ++ | +++ | ++ | +++ | ++ | +++ |
| Doxepin | ++ | + | +++ | +++ | +++ | ++ |
| Imipramine | ++ | +++ | ++ | ++ | ++ | ++ |
| Nortriptyline | +++ | +++ | ++ | ++ | ++ | ++ |
| Opipramol | + | + | — | +++ | — | + |
| Trimipramine | + | + | ++ | +++ | +++ | ++ |
| Mirtazapine | + | — | — | ++ | — | +++ |
| SSRIs | | | | | | |
| Duloxetine | ++ | ++ | — | — | — | — |
| Venlafaxine | ++ | ++ | — | — | — | — |
| Citalopram | — | +++ | — | — | — | — |
| Sertraline | — | +++ | — | — | — | — |
| Paroxetine | — | +++ | — | — | + | — |
| Other antidepressants | | | | | | |
| Agomelatine | — | — | — | — | — | — |
| Bupropion | ++ | — | — | — | — | — |
| Vortioxetine | — | + | — | — | — | + |

**Note.** – — no inhibition; + — mild inhibition; ++ — moderate inhibition; +++ — strong inhibition.

*Table 4.* **Values of inhibition constant (Ki) (nmol/L) in TCAs and comparison of drugs by two criteria — inhibition of reuptake and antagonism toward postsynaptic receptors**

| Drugs | Reuptake inhibition | | | Antagonism towards postsynaptic receptors | | |
|---|---|---|---|---|---|---|
| | 5-HT | NA | H1 | A1 | M2 | 5 HT-2A |
| Mirtazapine | >10000 | 4600 | 0.14 | 500 | 670 | 16 |
| Mianserin | >4000 | 71 | 0,4 | 34 | 820 | 7 |
| Doxepin | 68 | 29,5 | 0,24 | 24 | 83 | 25 |
| Amitriptyline | 20 | 50 | 1 | 27 | 18 | 29 |
| Imipramine | 7 | 60 | 40 | 32 | 46 | 80 |
| Clomipramine | 0,14 | 54 | 15 | 32 | 25 | 35 |
| Nortriptyline | 100 | 10 | 6.3 | 55 | 37 | 44 |
| Dothiepin | 78 | 70 | 4 | 400 | 38 | 260 |
| Desipramine | 18 | 0,83 | 110 | 100 | 100 | 280 |
| Reboxetine | 58 | 7.2 | 310 | >1000 | >1000 | >1000 |

was evaluated by the dynamics of the QT interval on the ECG, systolic and diastolic blood pressure (SBD and DBP), heart rate and hemorrhagic complications. Data obtained for periods of 3, 6 and 8 days were analyzed. The result confirmed the high cardiological safety of new generation antidepressants, no clinically significant changes of QT interval on ECG were detected during regular treatment. Analysis of the dynamics of blood pressure and heart rate in patients also revealed no significant differences in these parameters before, as well as 3, 6–8 days after the administration of these drugs. No cases of hemorrhagic complications were observed.

Hildebrandt V., Dumenil K. et al. conducted a study on BP changes after the administration of a new generation antidepressant in a psychiatric institution [23]. This is an observational single-center analytical retrospective cohort study with additional data collection on patient stays between 2013 and 2015. Patients were divided into two groups — antidepressant treatment (which they took during their hospitalization) and control (no antidepressant). Blood pressure measurements were taken over a 30-day period. Of the 1241 patients, 124 were in the treatment group and 1117 in the control group. The mean age was 56, 80 ± 0.54 years (37 to 79 years). Increased

SBP was associated with baseline SBP variability and BMI. Assessment of DBP showed an association with baseline elevated DBP, BMI, and the presence of a history of bipolar disorder. There was no significant difference in BP change over time between the treated and control groups at 30 days. This result is reassuring with regard to the early development of arterial hypertension after antidepressant administration. Among antidepressants, citalopram has been found to have a greater effect on QT interval prolongation than other SSRIs, although the clinical significance of this prolongation remains unclear [24]. In a recent study evaluating the effect of escitalopram, a less pronounced effect on the myocardial conduction system was found (with citalopram — QT reached up to +0.04 sec to baseline (QT — 0.35 sec), respectively up to 0.39 sec). And in patients who were older than 60 years and took citalopram in 20 mg dosage — QT prolongation was up to 0.42 sec. Escitalopram administration was associated with QT interval prolongation in average up to 0.35 sec, $p < 0.05$. In addition, this study proved that taking ziprasidone at a dose of 160 mg daily led to QT prolongation up to 0.46 sec in 188 patients. While aripiprazole, which is a representative of the same group, was the safest and practically did not lead to QT interval prolongation (0.35 sec, $p<0.05$.).

In an experimental study, paroxetine was shown to have a beneficial effect on myocardial remodeling by blocking the interaction of GRK2 and ADRB1 in AH [25]. The expression of GRK2 and ADRB1 in peripheral blood mononuclear cells was found to be positively associated with the blood pressure level in AH patients and with the expression of these genes in the myocardium. In vitro data showed their direct interaction, and genetic depletion of GRK2 blocks epinephrine-induced activation of hypertrophic and fibrotic genes in cardiomyocytes. In vivo treatment with paroxetine reduced AH-induced cardiac hypertrophy, dysfunction and fibrosis in animal models. This drug was found to suppress sympathetic overload and increase the sensitivity of adrenergic receptors to catecholamines. Concomitant administration of paroxetine with metoprolol enhances BP and HR reduction and activates reverse myocardial remodeling in the experiment with spontaneous hypertension.

A recent study describes the cardioprotective use of agomelatine in myocardial reperfusion injury [26, 27]. Agomelatine is a melatonin receptor agonist and a serotonin receptor antagonist. To study the effect of agomelatine on myocardial reperfusion injury, an experimental model was used that was subjected to 30 minutes of ischemia followed by 120 minutes of reperfusion; agomelatine (10, 20, or 40 mg/kg) was administered intraperitoneally 1 hour before cardiac isolation. Agomelatine (20 mg/kg and 40 mg/kg) significantly improved cardiac function, attenuated pathological changes in ischemic myocardium, reduced infarction size, and decreased creatine kinase-MB and lactate dehydrogenase release.

## Conclusion

Thus, unlike traditional antidepressants, the presented drugs are acceptable for the treatment of comorbid depressive disorders in patients with cardiovascular diseases. Brexpiprazole and aripiprazole (drugs from the group of partial agonists of dopamine receptors) have proven efficacy in the treatment of depressive disorders in patients with remodeled myocardium due to significantly lower shortening of the QT interval. Escitalopram and paroxetine have a pronounced cardiotropic effect practically without significant side effects; Agomelatine, on the other hand, proved its efficacy in myocardial reperfusion damage by the experiment in which an inhibitory effect on the apoptosis rate was found.

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# **COVID-19 and myocardial infarction** with myomalation. A clinical case report

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This article presents a case of the development of antero-inferior myocardial infarction, myomalation, apex wall rupture and hemopericardium following SARS-CoV2 infection.
**The clinical case.** Patient T.E., 36 years old, was admitted to hospital on 15.05.2023 with the diagnosis: "New coronavirus infection of severe degree. Acute myocardial infarction". She had no complaints on admission. From the medical history: she became ill three weeks before the hospitalisation, when the weakness appeared, body temperature increased to 37.3 °C. She took non-steroidal anti-inflammatory drugs with a temporary improvement. For several days the body temperature reached up to 38.4 °C. In the evening of 14.05.2023 the patient noted a transient substernal discomfort at rest. 15.05.2023 — the patient's condition worsened, pressing substernal pain had appeared, that led to an ambulance call. Electrocardiogram (ECG) data: abnormal Q-wave in leads II, III, aVF and V2-V6. In the same leads there were the ST segment elevation and the inversion of the T-wave. Blood pressure (BP) — 105/76 mmHg. The NEWS2 score is 9 points. PCR test for coronavirus is positive. Chest computed tomography (CT) scan: CT evidence of viral interstitial pneumonia — CT-3 (73 % of lung tissue lesions). Despite the initiated treatment, the patient died. The autopsy revealed signs of viral pneumonia. Karyolysis and the accumulation of blood between myocytes were found in the heart. The myocardium was circularly flaccid; there was a slit-shaped irregular defect with the disruption of myocardial integrity in the area of the inferior and anterolateral wall of the left ventricle (LV).
**Conclusion.** In the case presented, a young patient without comorbidities developed an anterior-inferior MI after SARS-CoV-2 infection. Severe complications occurred — myomalation, inferior and anterolateral LV wall ruptures and hemopericardium.

**Keywords:** COVID-19, thrombosis, coronary arteries, myocardial wall rupture, hemopericardium.

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## Introduction

The most prominent clinical manifestation of COVID 19 is pulmonary damage. However, after infection with **SARS-CoV-2**, the hematopoietic system is primarily affected and coagulopathy occurs, which plays an important role in the pathogenesis and clinical manifestations of the disease [1–3]. When secondary activation of the coagulation system occurs during severe infection, endogenous anticoagulant mechanisms cannot be controlled and acute generalized inflammatory reaction leads to endothelial vascular dysfunction, resulting in generalized thrombosis and tissue ischemia.

The incidence of cardiovascular complications after **SARS-CoV-2** infection ranges from 5 to 38% in hospitalized patients [3–5]. These include the development of acute heart failure due to acute coronary syndrome, myocardial infarction (MI), myocarditis, arrhythmias [2, 3]. COVID-19 infection affects important pathways of biochemical regulation of the heart, such as ACE2 signal transduction pathway, fibrinogen pathway, redox homeostasis, leads to destabilization and rupture of atherosclerotic plaques, exacerbates myocardial damage and dysfunction [6, 7]. Myocardial damage without direct plaque rupture can also occur due to cytokine storm, hypoxic state, coronary spasm, endothelial or vascular dysfunction [8–10]. Despite the emerging trend of decreasing cases of COVID-19, the problem continues to persist, MI in COVID-19 cases remains one of the debated issues in the medical scientific community. Due to the relevance of the problem, we present a case of development of circular myocardial infarction, myomalation, rupture of the inferior anterolateral LV wall and hemopericardium after SARS-CoV2 infection.

## Clinical case

Patient T.E., 36 years old, on 15.05.2023 was hospitalized for several hours at the Republican Cardiology Dispensary of the Ministry of Health of Chuvashia in the ICU. She was admitted for the diagnosing and treatment of COVID-19 coronavirus infection and its complications. She had no complaints on admission. From the medical history: she became ill three weeks before the hospitalisation, when the weakness appeared, body temperature increased to 37.3 °C. She took non-steroidal anti-inflammatory drugs (NSAID) and analgetics with a temporary improvement. For several days the body temperature reached up to 38.4 °C, the patient continued the intake of antipyretics with mild improvement. In the evening (14.05.2023) she noticed transient discomfort behind the sternum at rest. In the morning (15.05.2023) the patient's condition worsened, the substernal pressing pain appeared, she took NSAIDs — with no effect. In the evening (15.05.2023), due to persisting symptoms, called an ambulance and was admitted to the Republican Cardiology Dispensary.

**Known diseases:** according to the outpatient card — no chronic diseases of internal organs. The patient rarely sought medical help.

**Physical examination:** Medical state is critical. Consciousness is clear. Emotionally stable. Normosthenic physique. Superficial and deep sensitivity are preserved. Skin: cyanotic color. Visible mucous membranes are pale pink. Peripheral lymph nodes are not enlarged. Cardiovascular system: Blood pressure — 105/76 mmHg. Heart sounds are muffled. Respiratory system: respiratory rate — 24 per minute. Breathing is noisy, auscultation — small bubbling rales in the lower parts of the lungs. Urination and excretion are normal. The NEWS2 score is 9 points.

## Laboratory and instrumental diagnostics

*Complete blood count:* Leukocytes: $25.3 \times 10^9$/l, Lymphocytes: 2%, Monocytes: 5%. Coagulation testing: D-dimer: 19.95 mcg/mL, APTT: 64.1 sec, fibrinogen: 17.9 g/L, troponin T: 2.1 ng/mL. PCR test for coronavirus infection was positive.

*ECG data:* abnormal Q-wave in leads II, III, aVF and V2-V6. In the same leads there were the ST segment elevation and the inversion of the T-wave.

*Chest CT scan:* CT evidence of viral interstitial pneumonia — CT-3 (73% of lung tissue lesions).

Despite the initiated treatment (IV nitrates, antibiotics, antiplateletes, loop diuretics, ventilator), preparation for CAG and PCI, sudden death occurred.

*The immediate cause of death* was pulmonary and cardiac failure due to COVID-associated pneumonitis, alveolitis and circulatory MI.

Final clinical diagnosis:

**Main diagnosis:** 1. New coronavirus infection, virus identified, severe degree. 2. Acute ST-Elevation Myocardial Infarction with Q-waves.

**Complications:** Viral interstitial pneumonia. Stage 3 respiratory failure. Acute cardiovascular failure.

Sectional examination of respiratory organs revealed the following changes: lungs with areas of

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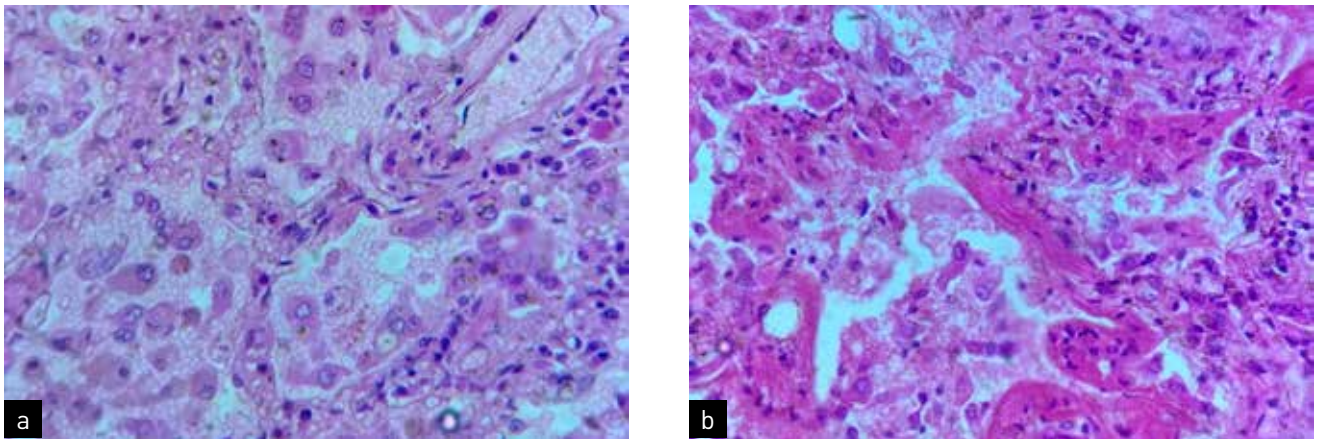


**Fig. 1.** Microscopic picture: a — inflammatory exudate in the lumen of alveoli, denudation of basal membranes; b — edematous fluid in the lumen of alveoli, hyaline membranes along the contour of alveoli. Hematoxylin and eosin staining, x900

uneven compaction, heavy, airless, red on section. Histological examination revealed dilated full blood vessels with perivascular sclerosis. Alveoli are unevenly distributed, their lumen is filled with serous exudate, in some places — with admixture of erythrocytes, sloughed alveolocytes and macrophages, on the walls of some of them there are deposits of homogeneous pink masses in the shape of "crescents" in the form of hyaline membranes (Fig. 1). Edematous fluid is present in the lumen of some alveoli. The interalveolar septa are thickened and sclerosed, irregularly hemorrhagic.

The following changes in the cardiovascular system were noted: in the area of the apex the myocardium is circularly flaccid with merging areas of red color, there is a slit-shaped irregularly defect with myocardial rupture in the area of the inferior and anterolateral wall of LV, myocardium at the edges of the slit is red. In the same zone there is an area of softening up to 2.6×2.7×1.2 cm. In the lumen of the anterior interventricular branch, thrombotic masses with dense adherence to the intima of the vessel are seen. Histological examination: epicardium with moderate amount of adipose tissue underneath. There is blood statis in capillaries, interstitial edema. Transverse striation of cardiomyocytes is lost, deformation and karyolysis are observed in them. Clusters of polymorphonuclear leukocytes are detected along the periphery of necrosis, forming a demarcation zone between necrotized and intact tissue (Fig. 2 a). Blood accumulation between myocytes was noted (Fig. 2 b). The result of virological examination of sectioned material (lung tissue) (Laboratory of Virological Research and Diagnostics Center of Hygiene and Epidemiology of the Chuvash Republic): SARS-CoV-2 coronavirus RNA was detected in lung, heart.

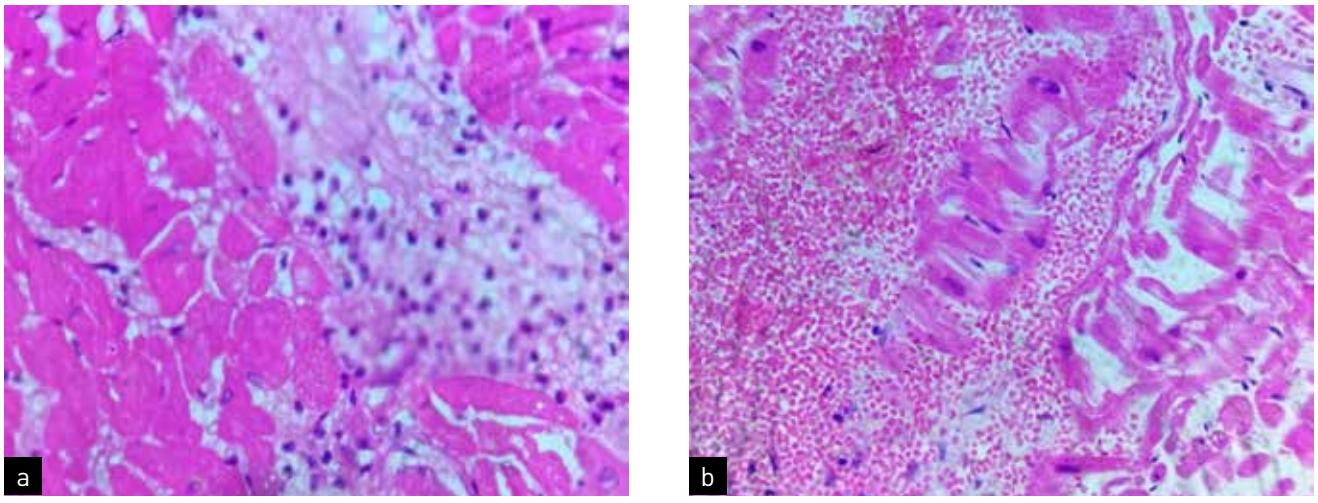


**Fig. 2.** Microscopic picture: a — areas of cardiomyocyte necrosis; b — accumulation of blood between myocytes. Hematoxylin and eosin staining, x900

**Pathologic diagnosis (comorbid):**

**Main diagnosis (comorbid):** 1. New coronavirus infection COVID-19, SARS-CoV-2 coronavirus RNA detected. 2. Acute circular myocardial infarction.

**Complications:** Viral interstitial pneumonia. Acute respiratory distress syndrome. Pulmonary edema. Rupture of the outer wall in the region of the apex. Myomalation. Hemopericardium.

## Discussion

Cardiac damage after SARS-COV-2 infection is based on:

1) Vasoconstriction (due to increased angiotensin II concentration after angiotensin-converting enzyme II receptors are blocked by the virus).

2) Hypoxic state due to respiratory failure.

3) Myocardial infarction (type 1 and 2 — the ischemia due to increased myocardial oxygen demand or decreased coronary blood flow, e.g. coronary artery spasm, embolism, hypotension).

4) Due to acute viral myocarditis and "cytokine storm".

5) Thrombosis due to Covid-associated coagulopathy [9].

Thus, under the influence of SARS-COV-2, angiotensin II concentration is increased and angiotensin 1–7, which has cardioprotective properties, is decreased [8]. Angiotensin II, in turn, exerts vasoconstrictive and proatherosclerotic effects [7–9]. In addition, TNF-$\alpha$ expression is increased and the local and systemic inflammatory process is enhanced, leading to further myocardial damage [6–9]. Respiratory failure and generalized inflammatory process cause a mismatch between oxygen consumption and delivery to tissues with the development of hypoxia, which leads to excessive intracellular calcium accumulation and then to myocardial cell apoptosis and myocardial damage [6–8]. Direct intracellular penetration of SARS-COV-2 can also induce cardiomyocyte necrosis and myocardial destruction [6–9].

In the presented case, circular MI developed in a young patient without comorbid pathology after SARS-CoV-2 infection. There were severe complications — myomalation, ruptures of the inferior and anterolateral LV wall and hemopericardium.

## Conclusion

Based on the pathological study, it was revealed that the patient's death was due to bicausal pathology represented by the main nosologies — COVID-associated pneumonitis, alveolitis with the development of acute respiratory distress syndrome and acute circular myocardial infarction. Severe complications occurred — myomalation, inferior and anterolateral LV wall ruptures and hemopericardium.

**Conflict of interests:** none declared.

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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.

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.

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

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

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

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

**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.

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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.

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

**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/ictrp/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.

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

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

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

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

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

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

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

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

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**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.

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**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.

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

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

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

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

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*Book:*

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

*Chapter:*

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

*Russian chapter:*

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

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**VII. Copyright and publishing policy.**

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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.

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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.

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**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

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

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