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Comparative efficacy of pharmacological and non-pharmacological management of monomorphic right ventricular premature contractions in patients without structural heart disease

Features of acute coronary syndrome associated with anxiety and depression disorders

2025 ESC Congress HOT LINE sessions: key clinical studies

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Editor’s Welcome

Dear colleagues!

We present to your attention the forty-seventh issue of the International Heart and Vascular Disease Journal, which features leading, original, and review articles, as well as a report on key clinical studies presented during the HOT LINE sessions of the 2025 Congress of the European Society of Cardiology.

In the “Leading Article” section, an original study is presented that evaluates the effectiveness of pharmacological therapy and radiofrequency catheter ablation for the treatment of monomorphic right ventricular extrasystole, depending on the presence of predictors of arrhythmogenic cardiomyopathy in patients without structural heart abnormalities. The study included 452 patients, with a follow-up period of up to 5 years. According to the authors, among patients without structural heart abnormalities who had early monotopic right ventricular extrasystole without predictors of arrhythmogenic cardiomyopathy, Class I antiarrhythmic drugs were found to be the most effective. Meanwhile, in patients with monomorphic right ventricular extrasystole and identified predictors of arrhythmogenic cardiomyopathy, radiofrequency catheter ablation proved to be the most effective treatment approach.

The “Original Articles” section features three studies. The first article compares the levels of asymmetric dimethylarginine in patients with coronary heart disease (CHD) with and without metabolically associated fatty liver disease. The study included 50 patients diagnosed with CHD, divided into two equal groups: 25 with metabolically associated fatty liver disease and 25 without it. The results indicate the need for a personalized approach to treating patients with CHD and metabolically associated fatty liver disease, focusing on correcting metabolic disorders to reduce asymmetric dimethylarginine levels. The second article demonstrates that the use of N-terminal pro–B-type natriuretic peptide, cystatin C, and galectin-3 as part of a multifactorial model allows for more effective prediction of heart failure decompensation and cardiovascular mortality in post–COVID-19 patients with chronic heart failure with preserved ejection fraction, type 2 diabetes mellitus, and chronic kidney disease. The third study shows that arterial hypertension (AH) in patients with spondyloarthritis may present subclinically. About half of the patients who denied having AH were found to have masked hypertension, and among them, half had an abnormal circadian blood pressure pattern. The authors conclude that 24-hour blood pressure monitoring is necessary for the early detection of hypertension in patients with ankylosing spondylitis.

The “Review Articles” section includes two papers. The first article states that psychological and pharmacological interventions can have beneficial effects and should be considered for patients with acute coronary syndrome who experience depression, anxiety, and stress. Before discharge, all patients are recommended to be screened for mental disorders using validated questionnaires and referred for psychiatric consultation if necessary. The second article presents data on new lipid-lowering drugs. Bempedoic acid, an ATP-citrate lyase inhibitor, is emerging as a promising treatment option for patients with a history of statin intolerance. Icosapent ethyl, a high-dose ethyl ester of eicosapentaenoic acid, has demonstrated favorable effects on cardiovascular health.

As is traditional, the issue concludes with a brief report summarizing key clinical trials presented at the HOT LINE sessions of the 2025 European Society of Cardiology Congress.

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

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

Review of international medical news

Scientists from Scotland conducted a study showing that in patients who had suffered a myocardial infarction (MI), a three-month course of dual antiplatelet therapy produced comparable outcomes to traditional 12-month treatment. At the same time, it was associated with reduced mortality and a lower risk of bleeding.

The analysis revealed that all-cause mortality was 2.7% in the three-month treatment group and 3.4% in the 12-month group. There were no significant differences in cardiovascular mortality or non-fatal MI rates.

The authors concluded that three-month dual antiplatelet therapy after MI may be a safe alternative to the standard 12-month regimen. This approach reduces bleeding risk without compromising efficacy in preventing recurrences, which may be taken into account in future clinical guidelines.

According to ESC data

Experts have issued a scientific statement on the impact of psychological distress on outcomes in patients after myocardial infarction. The document reviews the mechanisms of these disorders, their connection with cardiovascular risk, and provides recommendations for diagnosis and management.

The analysis showed that depression, anxiety, post-traumatic stress disorder, and chronic stress after myocardial infarction significantly increase the risk of recurrent cardiovascular events and mortality. According to the SWEDEHEART registry, 21% of patients experienced persistent emotional distress, which increased the risk of cardiovascular death by 46%.

Numerous studies indicate that post-infarction depression doubles the likelihood of recurrent cardiovascular events.

According to the Circulation journal

Specialists from an international research group conducted a systematic meta-analysis of tumor necrosis factor-alpha (TNF-α) inhibitor therapy in patients with rheumatoid arthritis.

The analysis showed that TNF-α inhibitor use was associated with a significant increase in the risk of serious infections (odds ratio = 1.63). However, this therapy reduced the risk of cardiovascular events by 40% and myocardial infarction by 25%.

The authors concluded that while TNF-α inhibitor therapy in rheumatoid arthritis patients carries a high risk of infections, but may reduce the likelihood of cardiovascular events and improve metabolic syndrome parameters.

According to The Lancet journal

Researchers from France found that prescribing beta-blockers after myocardial infarction does not affect mortality, recurrence, or hospitalization rates in patients with heart failure and preserved ejection fraction.

The study included 8,500 patients with heart failure and a left ventricular ejection fraction above 40% who had experienced myocardial infarction. During 3.7 years of follow-up, adverse outcomes were observed in 316 participants in the beta-blocker group (22.5 events per 1,000 patient-years) and in 307 participants not receiving beta-blockers (21.7 events per 1,000 patient-years).

The researchers noted that when prescribing these medications to such patients, the obtained results should be taken into consideration.

According to the NEJM

Researchers from the United States analyzed the role of lipoprotein(a) as a biomarker for extracoronary atherosclerotic complications.

The analysis showed that an increase in lipoprotein(a) levels by 75 nmol/L was associated with an 18% higher risk of peripheral artery disease and a 17% higher risk of carotid artery stenosis. In patients with pre-existing peripheral artery disease, elevated lipoprotein(a) levels increased the risk of serious limb-related adverse events by 57%.

Thus, this study demonstrates that lipoprotein(a) is an important independent marker for the development and progression of extracoronary atherosclerotic disease

According to the Circulation journal

Scientists from Korea conducted a study involving 241,924 adults, which found that increasing the cumulative CVH score (Life's Essential 8) by 100 points per year between ages 30 and 40 was associated with a 34% lower risk of cardiovascular events and a 35% lower risk of kidney events in middle age.

The results suggest that maintaining a high cumulative CVH score (points × years) may serve as a valuable target for primary prevention, as achieving and maintaining good cardiovascular health earlier in life is associated with a reduced risk of premature cardiovascular and renal events in the 30–40 year age range.

According to the JAMA Cardiology

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Comparative efficacy of pharmacological and non-pharmacological management of monomorphic right ventricular premature contractions in patients without structural heart disease

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To date, antiarrhythmic medication and radiofrequency ablation (RFA) are the primary methods of right ventricular premature contractions (PVCs) management in patients without structural heart disease (SHD).

Aim of the study. The aim of the study was to evaluate the efficacy of pharmacological and non-pharmacological (RFA) strategies of monomorphic right ventricular PVCs management, depending on the identification of

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arrhythmogenic cardiomyopathy (ACM) predictors in patients without SHD.

Methods. In this study, 452 patients with high frequency of PVCs (mean 23529±561 PVCs per day) and without SHD aged 16-39 were observed. In addition to the basic parameters, such ACM predictors as the QRS complex maximum intrinsicoid deflection index, QRS complex duration, etc. were electrocardiographically assessed. The observation period was 5 years.

Results. In 95.13% of patients the early monotopic right ventricular PVCs without ACM predictors were diagnosed. No cardiovascular diseases developed in these patients, and Class I antiarrhythmic drugs were the most effective at suppressing ventricular ectopy. In this group, 15.71% of the patients declined the long-term antiarrhythmic therapy or RFA. The rest of the group continued pharmacologic therapy. In 95.28% of patients with the early monotopic right ventricular PVC without registered ACM predictors, the duration of antiarrhythmic therapy, according to the "therapeutic sufficiency" principle, was 11.1 ± 0.3 months from the beginning of the period of observation. This duration highly correlated (r = 0.89) with the observation period of patients receiving cardioprotective therapy. In 4.87% of patients with registered right ventricular PVC with ACM predictors, no effect of antiarrhythmic therapy was observed and/or clinically significant heart failure developed. These patients underwent RFA for ventricular ectopy management. In all patients of this subgroup RFA induced remission and in 85.71% of them remained free of PVC recurrence throughout the entire follow-up period.

Conclusion. Patients with the early monotopic right ventricular PVCs, without SHD and any ACM predictors treatment with Class I antiarrhythmics was the most effective, while in patients with monomorphic right ventricular PVCs and ACM predictors, RFA was the effective therapeutic option.

Keywords: Premature ventricular contractions, anti-arrhythmic therapy personalization, pharmacologic treatment, radiofrequency ablation.

Conflict of interests: none declared.

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Introduction

In patients without structural heart disease (SHD), in most cases, good prognosis of monomorphic right ventricular premature contractions (PVCs) is observed, except for the development of myocardial contractility depression in high frequency ventricular ectopy [1, 2]. Despite the use of various cardiac mapping methods, which assist with the definition of the source of premature ventricular complexes, they might be ineffective for the verification of PVCs mechanism in patients without SHD. In particular, these methods can not help to differentiate between trigger activity and re-entry mechanism [3, 4].

Prior clinical and experimental studies have shown that in most cases, early monomorphic right ventricular PVCs in patients without SHD and in the absence of electrocardiographic (ECG) predictors of arrhythmogenic cardiomyopathy, such as the duration of the ectopic QRS complex and the sinus rhythm QRS complex, their ratio, the measurement of the maximum intrinsicoid deflection index of the ectopic complex, and the variability of the corrected pre-ectopic interval assessed by its linear deviation (LD), etc., is caused by a mechanism of early afterdepolarization (EAD) and follows a predominantly benign course. Furthermore, prospective follow-up of these patients revealed no subsequent cardiovascular pathology [5].

The available literature lacks data on the comparative efficacy of pharmacological therapy versus non-pharmacological management, specifically radiofrequency catheter ablation (RFA), as well as on the natural history of early monomorphic right ventricular PVCs in patients without SHD. This is specifically for cases predominantly caused by an EAD mechanism, for instance, when antiarrhythmic drug therapy is declined to eliminate the ventricular ectopy.

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Aim of the study

The aim of the study was to evaluate the efficacy of pharmacological and non-pharmacological (RFA) strategies of monomorphic right ventricular PVCs management, depending on the identification of arrhythmogenic cardiomyopathy (ACM) predictors in patients without SHD.

Methods

A total of 452 patients without SHD, aged 16 to 39 years (mean 22.1 ± 0.1 years), with monomorphic right ventricular PVCs of IV-V gradation according to the M. Ryan classification [6], were observed.

The inclusion criteria were: documented sinus rhythm; absence of SHD, confirmed by ruling out cardiac and extracardiac diseases, electrolyte imbalances, use of medications and/or toxic products (primarily diuretics, oral contraceptives, alcohol abuse, etc.) that directly or indirectly lead to the development of ventricular arrhythmias; confirmation of the absence of SHD using various stress tests, invasive and non-invasive coronary angiography, echocardiography, and contrast-enhanced cardiac magnetic resonance imaging; presence of subjective palpitations; left ventricular ejection fraction ⩾ 54%; and provision of informed consent for participation in the study and treatment (as previously described) [5, 7].

All patients underwent general clinical examination, 24-72-hour Holter ECG monitoring, and echocardiography using a Hitachi EUB-5500 device according to standard protocols. The calculation of hemodynamic parameters, determination of the topographic localization of the premature ventricular complexes, comparison of the pre-ectopic interval (PEI) of the PVC to the QT interval of the sinus rhythm (QTsr), determination of the linear deviation (LD) of the corrected PEI (PEIcor), measurement of the QRS duration of the PVC (QRSpvc) and sinus rhythm (QRSsr), their ratio (QRSpvc/QRSsr), and the maximum intrinsicoid deflection time (MIDpvc) of the right ventricular extrasystole were performed as previously described [5, 9].

Pathological values for MIDpvc, QRSpvc duration, and the QRSpvc/QRSsr ratio were defined as ⩾ 0.5 units, ⩾ 150 ms, and ⩾ 1.5 units, respectively [2, 5]. Monotopic premature ventricular complexes were defined by an LD of the corrected PEI (PEIcor LD) of < 10 ms [3].

The selection of antiarrhythmic therapy for ventricular ectopy was based on 24-hour Holter ECG monitoring data. This included the identification of potentially effective Class I-III antiarrhythmic drugs, which were used in medium therapeutic doses [3].

The treatment protocol was initiated with Class II agents. If these were ineffective, Class I or III drugs were used. Amiodarone was employed as a last resort, if necessary. The scope and nature of antiarrhythmic drug therapy, as well as the criteria for treatment efficacy for ventricular ectopy, have been described previously [5, 6].

Pharmacological therapy followed the principle of «therapeutic sufficiency» This meant that antiarrhythmic drugs were withdrawn every 3-6 months. If PVCs recurred, the previous antiarrhythmic pharmacotherapy was reinstated. If no premature ventricular complexes were recorded, the treatment was discontinued [5, 8].

In cases where mono- or combined antiarrhythmic therapy was ineffective, or if depression of myocardial contractility developed leading to a refusal of long-term antiarrhythmic drug use, RFA became the treatment of choice for PVCs in patients without SHD [2, 3, 5].

The duration of patient follow-up after inclusion in the study was 5 years. All assessments, including patient status evaluation and ECG recording, were performed once a month. 24-hour Holter ECG monitoring was conducted no less than once every 3-4 months.

Statistical analysis

For the statistical analysis of the obtained data, the following methods were used: means and standard errors of the mean (M±m), the 95% confidence interval for the means, Student's t-test, and the x^2 test. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant. The normality of distribution for quantitative variables was assessed using the Kolmogorov-Smirnov and Gaussian tests. Linear pairwise correlation (Pearson's r) and rank correlation (Spearman's r) were employed. The association between quantitative and qualitative binary variables was evaluated using logistic regression analysis with the calculation of odds ratios (OR).

Results

Among the patients without SHD included in the study, the number of PVCs over 24 hours ranged from 11,256 to 39,798 (mean 23,529 ± 561 PVCs per day). Furthermore, 384 patients (84.96%) had ventricular ectopy accounting for 15% or more of all ventricular complexes, and 98 patients (21.68%) had non-sustained ventricular tachycardia.

The most effective drug for suppressing PVCs was etacizin in 356 patients (78.76%), allapinin in 58 (12.83%), propafenone in 23 (5.09%), Class II agents in 9 (2.00%), and sotalol in the remaining 6 patients (1.32%).

Seventy-one patients (15.71%) declined long-term antiarrhythmic drug therapy for various reasons, including the development of headaches, dizziness, diplopia, nausea, constipation or diarrhea, allergic reactions, financial constraints, etc. These patients received cardioprotective therapy, which included cardiometabolic agents such as potassium supplements and polyunsaturated fatty acids. Among them, 4 patients (5.63%) underwent RFA 6-8 months after the start of observation to eliminate ventricular ectopy due to the development of impaired pump function, which manifested as clinically overt heart failure. The remaining 381 patients (84.29%) continued antiarrhythmic medication. Of these, 18 patients (4.72%) underwent RFA 7–14 months (mean 10.8 ± 0.9 months) after initiating therapy due to the ineffectiveness of pharmacological antiarrhythmic treatment, which included the use of Class I-III drugs and their combinations.

All patients were divided into two groups. Group I consisted of 430 patients (95.13%) who used drug therapy to manage PVCs. The remaining patients were included in Group II and underwent RFA to eliminate ventricular ectopy. Group I was further divided into two subgroups. Subgroup Ia included 67 patients (15.58%) who were treated for PVCs with cardiometabolic agents only; this subgroup was used to study the «natural history» of right ventricular ectopy in patients without SHD. Subgroup Ib included 363 patients (84.42%) who received pharmacological antiarrhythmic therapy to eliminate PVCs.

All patients in subgroups Ia and Ib exhibited early monomorphic premature ventricular contractions (PVCs) without pathological values of ACM predictors. No statistically significant difference in the studied parameters was found between these subgroups (Table 1).

In Group II, all parameters reflecting ACM predictors for PVCs were significantly higher compared to subgroups Ia and Ib. No significant changes in the other studied parameters were observed between subgroups Ia and Ib when compared to Group II.

A positive clinical effect was observed in 32 patients (47.76%) of subgroup Ia within 3-9 months (mean 6.2 ± 0.5 months), and in the remaining patients within 10-23 months (mean 16.3 ± 0.8 months). In all patients of this subgroup, the PVC burden decreased by an average of 92% compared to baseline.

In 178 patients (49.04%) of subgroup Ib, the duration of antiarrhythmic therapy, guided by the principle of «therapeutic sufficiency,» ranged from 4 to 10 months (mean 6.7 ± 0.2 months) from the start of observation. For the remaining patients, it ranged from 11 to 21 months (mean 16.7 ± 0.5 months). This duration strongly correlated with the observation period of patients in subgroup Ia (r = 0.89).

In all patients of Group II, the PVCs were eliminated immediately after RFA. A positive effect from RFA was maintained throughout the entire follow-up

Table 1. **Electrocardiographic parameters of PVCs in subgroups Ia, Ib, and group II patients**

Patient groups Parameters	Subgroup Ia n = 67	Subgroup Ib n = 363	Group II n = 22
PEIpvc/QTSR, ratio	1.26±0.01 (1.18-1.36)	1.25±0.01 (1.14-1.36)	1.75±0.12 (1.22±2.32)*
LD of cor. PEI pvc, ms	8.62±0.08 (7.97-9.26)	8.61±0.01 (8.12-9.14)	82.35±10.51 (39-126)*
MIDpvc, ratio (PV ≥ 0.5)	0.41±0.01 (0.31-0.52)	0.42±0.01 (0.32-0.53)	0.58±0.01 (0.44-0.71)* †
QRS duration of PVC, ms (PV ≥ 150 ms)	137±1 (125-152)	138±1 (122-154)	179±5 (145-212)* †
QRSpvc/QRSsr, ratio (PV ≥ 1.5)	1.38±0.01 (1.24-1.53)	1.39±0.01 (1.22-1.56)	1.88±0.07 (1.46-2.23)* †
Number of PVCs per 24 hours	23787±1235 (11657-35875)	23423±531 (14856-31987)	24787±2456 (14678-36784)

Note: * — significant difference compared to subgroup Ia, ♦ — significant difference compared to subgroup Ib, † — significant difference compared to pathological values ($p < 0.05$).

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period in 16 patients (72.73%) of this group. In 6 patients (27.27%), PVCs recurred 2 years after the ablation and were successfully eliminated with a repeat RFA procedure; the morphology of the recurrent premature ventricular complexes was similar to the original. Endomyocardial biopsy was performed in 8 patients (36.36%) of this group, revealing myocardial inflammatory fibrosis (myocarditic cardiosclerosis).

The positive effect of RFA highly correlated with the following ACM predictors: MID of the PVC ⩾ 0.5 units (OR = 15.4), a PVC QRS complex duration ⩾ 150 ms (OR = 12.9), and a ratio of PVC QRS to sinus rhythm QRS duration ⩾ 1.5 units (OR = 9.6).

No cardiovascular diseases were detected in any patient of Group I throughout the entire observation period.

Discussion

It is currently known that frequent monomorphic right ventricular PVCs are detected in 3% to 5% of young patients (typically under 40 years of age) without SHD, and in most cases, are typically benign [2, 3]. In patients without SHD, the indications for antiarrhythmic therapy for monomorphic PVCs are: the presence of subjective symptoms, or the detection of ventricular ectopy accounting for 15% or more of total heartbeats. If patients decline pharmacologic antiarrhythmic therapy or if it proves ineffective, RFA becomes the treatment of choice for eliminating the premature ventricular complexes [1-3].

A total of 452 patients without SHD, aged 16 to 39 years, with frequent monomorphic PVCs (mean 23,529 ± 561 PVCs per 24 hours) were observed. Early monomorphic right ventricular PVCs without predictors of ACM were recorded in 95.13% of them.

Clinical and experimental studies have shown that early monomorphic right ventricular PVCs in patients without SHD and without ACM predictors is most often caused by a mechanism of early afterdepolarization (EAD) [5].

EADs are caused by an increase in the membrane potential of cardiomyocytes to a level between –40 mV and –10 mV. This can result from, for example, inhibition or delayed inactivation of the sodium channel system, leading to the emergence of spontaneous action potentials [10, 11]. This phenomenon can be induced experimentally by various toxic agents, such as aconitine, and in humans, it may result from «oxidative stress» or other local metabolic disturbances affecting cardiomyocyte function [10, 11]. For suppressing ventricular ectopy caused by the EAD mechanism, Class I antiarrhythmic drugs are the most effective [12].

Similar findings were obtained in the present study: etacizin was the most effective drug in 78.76% of patients, allapinin in 12.83%, and propafenone in 5.09%.

For various reasons, 15.71% of patients declined long-term antiarrhythmic pharmacotherapy, while the remaining patients continued treatment with antiarrhythmic drugs.

In patients without SHD presenting with early monomorphic right ventricular PVCs, the rationale for antiarrhythmic therapy extends beyond preventing «arrhythmia-induced cardiomyopathy.» The fact that frequent ventricular ectopy itself may induce disturbances in myocardial metabolism—potentially through increased sympathetic activity, ventricular dyssynchrony, and other factors leading to stabilization of the ectopic focus, also serves as a basis for treatment [13–15].

In patients without SHD receiving cardioprotective therapy, a positive clinical effect was observed after an average of 11.8 ± 0.7 months: the PVC burden decreased by an average of 92% compared to baseline. The duration of pharmacological antiarrhythmic therapy in patients without SHD, guided by the principle of «therapeutic sufficiency,» averaged 11.1 ± 0.3 months from the start of observation. This duration strongly correlated with the observation period of patients receiving cardioprotective therapy (r = 0.89).

In patients without SHD, the occurrence of early monomorphic right ventricular PVCs without ACM predictors, typically caused by trigger mechanisms such as EAD, reflects a reversible dysfunction of cardiomyocytes [1, 5, 6]. This is supported by the results of the present study: no cardiovascular pathology was detected in these patients throughout the entire follow-up period.

In 4.87% of patients without SHD who had monomorphic PVCs with ACM predictors and who declined antiarrhythmic drug therapy, RFA was performed 6-14 months after the start of observation to eliminate ventricular ectopy due to the development of clinical heart failure and/or inefficacy of pharmacological antiarrhythmic therapy.

The immediate success rate of RFA, used, for example, when long-term antiarrhythmic drug therapy is declined or ineffective—is 80–90% [1–3], and according to some data, reaches nearly 100% [14, 15]. Similar results were obtained in the present study.

The development of monomorphic PVCs with ACM predictors in patients without SHD is likely caused by the formation of small focal areas of fibrosis or cardiosclerosis, which are usually not detected by conventional diagnostic methods. These areas may facilitate the generation of premature ventricular complexes, possibly through the induction of an ectopic focus or a re-entry mechanism [10–12]. Furthermore, previous clinical and experimental studies have shown that the identification of ACM predictors in patients without SHD with PVCs indicates an organic cause of the arrhythmia and is a risk factor for the development of cardiovascular pathology [5].

This notion is indirectly confirmed by the results of the present study. A positive effect from RFA was maintained throughout the entire follow-up period in 72.73% of patients; this outcome highly correlated with the presence of ACM predictors. An endomyocardial biopsy was performed in 36.36% of these patients, revealing myocardial fibrosis consistent with myocarditic cardiosclerosis. In 27.27% of patients, PVCs recurred 2 years after the ablation and were successfully eliminated with a repeat RFA procedure; the morphology of the recurrent premature ventricular complexes was similar to the original.

Conclusion

In 94.37% of patients without SHD who declined antiarrhythmic drug therapy for early monomorphic right ventricular PVCs, a positive clinical effect was observed after an average of 11.8 ± 0.7 months of cardioprotective therapy. In these patients, the burden of premature ventricular complexes decreased by an average of 92% compared to baseline.

In 95.28% of patients without SHD, the duration of pharmacological antiarrhythmic therapy for early monomorphic right ventricular PVCs, guided by the principle of «therapeutic sufficiency,» highly correlated with the observation period of patients receiving cardioprotective therapy ($r = 0.89$).

The presence of monomorphic PVCs with predictors of ACM in patients without SHD is a predictor of ineffective pharmacological antiarrhythmic therapy and/or the development of clinically overt heart failure. For these patients, RFA is the treatment of choice for eliminating ventricular ectopy. Following this procedure, premature ventricular complexes were eliminated and did not recur throughout the entire follow-up period in 72.73% of patients.

Conflict of interests: none declared.

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The role of metabolic disorders in the formation of asymmetric dimethylarginine levels in patients with coronary heart disease

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Aim of the study. The aim of the study was to compare levels of asymmetric dimethylarginine (ADMA) in patients with coronary heart disease (CHD) in the presence or absence of metabolic dysfunction–associated steatotic liver disease (MASLD) and assess the possible association between ADMA and metabolic disorders.

Methods. The study included 50 patients with CHD, divided into two equal groups: 25 patients with MASLD and 25 patients without MASLD. The CHD was diagnosed based on clinical, electrocardiographic, and coronarographic data. MASLD was diagnosed using liver ultrasound. ADMA levels were assessed using enzyme-linked immunosorbent assay (ELISA) of the blood serum sample.

Results. The mean age in the MASLD group was 54.2 years, and in the group without MASLD, it was 53.8 years. The mean body mass index (BMI) of patients with MASLD was significantly higher (32.8 kg/m²) than that of patients without MASLD (27.1 kg/m², $p<0.01$). Arterial hypertension was present in 80% of MASLD patients and 48% of patients without MASLD ($p<0.05$). Type 2 diabetes mellitus (T2DM) was diagnosed in 52% of MASLD patients and 20% of patients without MASLD ($p<0.05$). ADMA levels in patients with MASLD were significantly higher (165.85 ± 24.27 ng/mL) than in patients without MASLD (129.44 ± 20.22 ng/mL, $p<0.001$). Moreover, the presence of three or more metabolic criteria (e.g., obesity, arterial hyper-

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tension, and diabetes mellitus) was associated with even higher ADMA levels (190 ± 20 ng/mL).
Conclusion. The obtained data confirm the necessity of a personalized approach to treating patients with CHD and MASLD, focusing on the correction of metabolic disorders to reduce ADMA levels.
Keywords: coronary heart disease, metabolic dysfunction–associated steatotic liver disease, asymmetric dimethylarginine, endothelial dysfunction, insulin resistance

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Introduction

Coronary heart disease (CHD) remains one of the leading causes of death and disability worldwide [1]. According to the World Health Organization (WHO), cardiovascular diseases (CVDs), including CHD, account for approximately 17.9 million people yearly, making up to 32% of all deaths. CHD alone is responsible for more than 7 million deaths each year[1]. The European Society of Cardiology reports that CHD is the primary cause of death in Europe [2], accounting for 38% of all CVD-related deaths.

CVDs continue to be a leading cause of mortality and disability in Uzbekistan. According to the Ministry of Health of the Republic of Uzbekistan, circulatory system diseases account for more than 50% of total mortality[2]. Recent WHO data (Global Health Estimates, 2024 revision) indicate that the age-standardized mortality rate from all CVDs in Uzbekistan in 2021 was ≈780–800 per 100,000 population (both sexes).This is approximately 3.5 times higher than the average rate for the WHO European Region (≈220 per 100,000) and nearly twice the global average (≈250 per 100,000) [3]. There has been an increase in the incidence of CHD, hypertension, and other cardiovascular conditions. Reports from several regional cardiology centers indicate a 10–15% rise in primary incidence rates over the past 5 years [3]. Concurrently, there has been an increase in the prevalence of risk factors (RFs) such as obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome, further exacerbating the epidemiological situation[4]. Recently, researchers have increasingly focused on comorbidity of somatic diseases as a key factor affecting work capacity and prognosis in patients with cardiovascular pathology [4]. This encompasses not only pathogenetically linked disorders but also independent diseases of various organs and systems, which adversely affect the course of CVDs [5].

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a global health problem affecting up to 25% of the world's adult population [6]. Among patients with obesity and T2DM, the prevalence of MASLD reaches 70–90% [6]. Research indicates that MASLD is associated with an increased risk of cardiovascular events such as myocardial infarction (MI) and stroke, independent of conventional risk factors [7, 8]. According to the European Association for the Study of the Liver, MASLD is recognized not only as a liver disease but also as a significant cardiometabolic condition affecting the prognosis of patients with CHD [9, 10].

Contemporary studies demonstrate that MASLD increases the risk of atherosclerosis development and CHD progression through mechanisms involving systemic inflammation, oxidative stress, insulin resistance, and lipid metabolism disorders [11]. A large meta-analysis conducted by the Department of Medicine, University of Verona (Italy) revealed that patients with

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MASLD have a significantly higher risk of cardiovascular complications (CVCs), including atherosclerotic vascular lesions, compared to those without this condition [6]. Other researchers reached similar conclusions, notably the group led by S. Francque from the Department of Gastroenterology and Hepatology at the University of Antwerp (Belgium). They identified a strong association between the severity of liver fibrosis in MASLD and increased cardiovascular mortality [11]. Pathogenetically, this is attributed to systemic manifestations of metabolic dysfunction: heightened inflammatory response, activation of oxidative stress, development of insulin resistance, and progressive alterations in lipid metabolism, which collectively promote the formation and progression of atherosclerosis and CHD [4].

Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthesis, plays a key role in the development of endothelial dysfunction, which underlies atherosclerosis and CHD [12]. ADMA levels increase in the presence of MASLD, as confirmed by data from large-scale studies (NHANES and ATHEROGEN) [13]. In patients with coexisting MASLD and CHD, ADMA levels may serve as a marker of cardiovascular risk [14]. However, there is insufficient data in the scientific literature regarding its clinical significance in this patient population.

Given the global epidemic of obesity and metabolic disorders, studying the impact of MASLD on CHD progression and related biochemical markers such as ADMA is of critical importance [15]. This will enable the improvement of diagnostic, therapeutic, and preventive strategies for CVCs in this patient group [16].

The aim of the study was to compare ADMA levels in patients with CHD with and without MASLD and to assess the potential association between ADMA levels and metabolic disorders.

Methods

A pilot, open-label clinical study was conducted at the Department of Cardiometabolic Disorders of the Republican Specialized Scientific and Practical Medical Center of Cardiology from July to December 2024. The study included 50 patients with CHD, equally divided into two groups: 25 patients with MASLD and 25 without MASLD.

Inclusion Criteria:

- Confirmed diagnosis of CHD (stable exertional angina, functional class I–II)
- Age 34–70 years
- Signed informed consent

Exclusion Criteria:

- Unstable angina, acute coronary syndrome, or history of myocardial infarction.
- Chronic heart failure NYHA class III–IV or left ventricular ejection fraction <40%.
- Severe comorbidities affecting ADMA levels or endothelial function, such as chronic kidney disease (GFR <45 mL/min/1.73m^2), liver cirrhosis or severe chronic liver disease, active malignancies, significant systemic inflammatory or autoimmune disorders.
- Decompensated type 1 diabetes, uncontrolled type 2 diabetes (HbA1c >9% at enrollment, patients required treatment adjustment prior to assessment)
- Use of ADMA-affecting medications within 4 weeks prior to enrollment (e.g., high-dose L-arginine, PDE-5 inhibitors)

CHD was confirmed through clinical evaluation, electrocardiography (ECG), and coronary angiography (CAG) [2]. MASLD was diagnosed via liver ultrasound, supplemented by elastography for fibrosis staging when indicated. All participants underwent standardized laboratory testing, including complete blood count, comprehensive biochemistry panel, lipid profile, fasting glucose and insulin with HOMA-IR calculation. Serum ADMA levels were quantified using enzyme-linked immunosorbent assay (ELISA) with certified commercial kits (Beijing Solarbio Science & Technology Co., Ltd.).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software. Normally distributed data are presented as mean ± standard deviation, with between-group comparisons made using Student's t-test. For non-normally distributed data, the Mann-Whitney U test was applied. Statistical significance was defined as $p < 0.05$.

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the local ethics committee. All patients received detailed information regarding study aims and potential risks, and signed an informed consent for participation and processing of their medical data.

Results

The study included 50 patients with CHD, divided into two groups: 25 with MASLD and 25 without MASLD.

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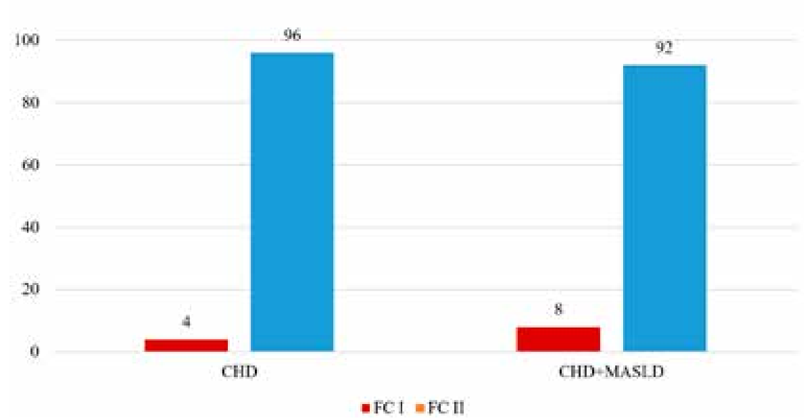

Fig. 1. Distribution of patients by angina functional class

The mean age was 54.2 years in the MASLD group and 53.8 years in the non-MASLD group, with no statistically significant difference ($p = 0.73$). Males comprised 56 % of the MASLD group and 60 % of the non-MASLD group ($p = 0.64$). All patients had stable CHD classified as Canadian Cardiovascular Society (CCS) functional class (FC) I–II (Fig. 1). CHD diagnosis was established based on medical history, ECG, and CAG when clinically indicated. Patients received guideline-directed medical therapy including antianginal agents, antiplatelet therapy, and lipid-lowering treatment. Thus, group allocation was based exclusively on MASLD status, with comparable age-sex distributions and identical CHD functional class severity between groups.

Patients with MASLD had a significantly higher mean body mass index (BMI) (32.8 kg/m²) compared to the non-MASLD group (27.1 kg/m², $p < 0.01$). Arterial hypertension (AH) was present in 80 % of MASLD patients versus 48 % in non-MASLD patients ($p < 0.05$). T2DM was diagnosed in 52 % of MASLD patients and 20 % of non-MASLD patients ($p < 0.05$). Low-density lipoprotein (LDL) levels were higher in the MASLD group (4.7 mmol/L) than in the non-MASLD group (3.1 mmol/L, $p < 0.01$) (Table 1).

Table 1. **Clinical and Metabolic Characteristics of CHD Patients Stratified by MASLD Status**

Parameter	CHD+MASLD (n=25)	CHD (n=25)	P
Mean age (years)	54.2 ± 6.1	53.8 ± 5.9	-
Male	14 (56 %)	16 (60 %)	-
BMI (kg/m²)	32.8 ± 4.2	27.1 ± 3.5	<0.01
AH (%)	80 %	48 %	<0.05
T2DM (%)	52 %	20 %	<0.05
LDL (mmol/L)	4.7 ± 0.8	3.1 ± 0.7	<0.01

ADMA levels were significantly higher in MASLD patients compared to non-MASLD patients. The mean ADMA level in the MASLD group was 165.85 ± 24.27 ng/mL, whereas the non-MASLD group showed significantly lower levels (129.44 ± 20.22 ng/mL). This difference was statistically significant ($p < 0.001$), indicating significant endothelial dysfunction in MASLD patients (Fig. 2).

Additional analysis revealed significantly higher ADMA levels in patients with a greater number of

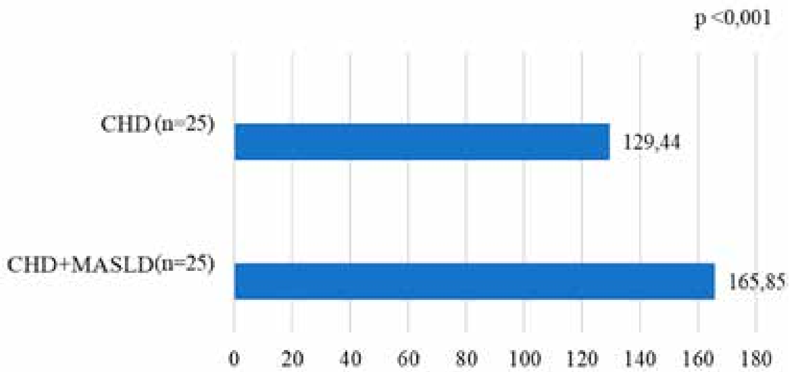

Fig. 2. ADMA levels in study groups

metabolic disorders. Patients with 1–2 metabolic criteria (e.g., hypertension and obesity) had ADMA levels of 140 ± 15 ng/mL. Those with ⩾3 criteria (e.g., obesity, type 2 diabetes, hypertension, dyslipidemia) showed substantially higher ADMA levels, averaging 190 ± 20 ng/mL ($p < 0.01$) (Table 2).

Table 2. **Analysis of ADMA Levels According to Number of Metabolic Criteria**

Study group	ADMA level (ng/mL)	P
1–2 metabolic criteria	140 ± 15	<0.01
3 and more criteria	190 ± 20	-

Discussion

This study presents the first domestic cohort analysis comparing ADMA levels in stable CHD patients stratified by MASLD status. Our findings confirm that MASLD comorbidity is associated with a pronounced elevation of this endothelial dysfunction biomarker. The observed increase (~36 ng/mL, +28 %) aligns with international studies [12]. For instance, Younossi et al. [7] reported 0.09 μmol/L higher ADMA concentrations (≈23–25 ng/mL) in biopsy-confirmed MASLD patients versus controls. Recent MASLD reviews indicate a mean excess of 0.1 μmol/L. Thus, our data demonstrate consistent manifestation of this phenomenon across diverse ethnic and geographic populations.

The causal relationship between MASLD and elevated ADMA is largely mediated by insulin resistance and chronic systemic inflammation [11]. Insulin resistance suppresses dimethylarginine dimethylaminohydrolase (DDAH) activity, the enzyme responsible for ADMA degradation, leading to its accumulation. Concurrently, proinflammatory cytokines (TNF-α, IL-6) and oxidative stress in the liver and vascular wall further inhibit DDAH while enhancing arginine methylation in proteins, thereby increasing ADMA synthesis [5].

ADMA itself competitively inhibits endothelial nitric oxide synthase, reducing nitric oxide bioavailability, enhancing vascular tone, and promoting atherogenesis. This mechanism explains the more frequent and severe coronary artery involvement in patients with combined MASLD and CHD [12].

Notably, in our cohort, ADMA levels exhibited a proportional increase with the number of metabolic disorders: patients with ⩾3 criteria showed 35 % higher values than those with 1–2 criteria. A similar gradient was demonstrated in untreated hypertensive patients (ADMA↑ ~20 %), reinforcing the concept of an ADMA-NO "metabolic cascade". Consequently, ADMA may serve as an integrative biomarker of cumulative metabolic burden on the endothelium [14]. The elevated ADMA levels observed in MASLD patients have significant clinical relevance: they enable more accurate cardiovascular risk stratification in stable CHD patients where conventional scores (SCORE2, GRACE) underestimate hepatic comorbidity impact [7]; underscore the necessity for early lifestyle modification and pharmacological management of insulin resistance to reduce ADMA and improve vascular prognosis; and function as a treatment response biomarker, where ADMA reduction during statin or combination lipid-lowering therapy correlates with atherosclerotic plaque regression [1].

As a pilot investigation, this study has inherent limitations: its single-center design and restricted sample size reduce the generalizability of findings. The single-timepoint measurement of ADMA precludes assessment of its dynamics in response to therapeutic interventions. The absence of instrumental endothelial function evaluation (flow-mediated dilation, FMD) [10] limits direct validation of ADMA as a surrogate marker. Future large-scale prospective studies employing multivariate models (incorporating ADMA + FMD + liver fibrosis indices) are needed to determine whether including ADMA enhances predictive accuracy for CVCs in MASLD patients. Furthermore, therapeutic strategies targeting ADMA reduction, such as pharmacologic DDAH activation or L-citrulline supplementation [15], remain promising yet underexplored avenues in cardiometabolic pharmacology.

Conclusion

This study demonstrated significantly higher ADMA levels in CHD patients with comorbid MASLD compared to those without MASLD. A positive correlation was observed between the number of metabolic disorders (obesity, hypertension, type 2 diabetes) and elevated ADMA concentrations, suggesting its potential role in the pathogenesis of endothelial dysfunction and CVCs. These findings support the need for a personalized approach to diagnosing and treating CHD patients that accounts for concomitant metabolic disorders, while highlighting the potential utility of ADMA as a cardiovascular risk stratification biomarker.

Conflict of interest: none declared.

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Prognostic value of selected biomarkers in comorbid patients with chronic heart failure after COVID-19

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The aim of the study was to evaluate the role of such biomarkers as N-terminal prohormone of brain natriuretic peptide (NT-proBNP), cystatin C, and galectin-3 for prediction of poor outcomes of chronic heart failure with preserved ejection fraction (HFpEF) of the left ventricle (LV) in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) with a history of COVID-19.

Methods. This study included 135 patients with HfpEF and cardiovascular disorders, T2DM, CKD, and a history of COVID-19 from more than 3 months prior to enrollment. Patients were assessed clinically, instrumentally and using laboratory methods, including NT-proBNP, cystatin C, and galectin-3 assays and echocardiography. The occurrence of heart failure (HF) decompensation and cardiovascular death (CVD) was recorded over 18 months.

Results. A multivariate regression analysis was used to build a basic model for estimation of probability of HF decompensation and CVD in patients with a history of COVID-19, HFpEF, T2DM, and CKD and included risk factors, such as rating scale of clinical state (ShOKS), stroke volume, left ventricular mass index, E/e' ratio, and NT-proBNP, which showed a high prognostic potential

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(AUC=0.856; 95% CI: 0.717–0.994; p<0.001, sensitivity 85.6%, specificity 79.2%). Adding cystatin C and galectin-3 improved prognostic properties of the resulting models (AUC=0.867; 95% CI: 0.808–0.923, p<0.001, sensitivity 86.3%, specificity 75% and AUC=0.866; 95% CI: 0.809–0.923, p<0.001, sensitivity 84.9%, specificity 83.3%, respectively). The best model was developed using levels of assessed biomarkers (AUC=0.879; 95% CI: 0.845–0.913, p<0.001, sensitivity 87.5%, specificity 88.8%).

Conclusion. Including NT-proBNP, cystatin C, and galectin-3 into a multifactorial model can improve the prediction of HF worsening and CVD in patients with a history of COVID-19, HFpEF, T2DM, and CKD.

Keywords: chronic heart failure, NT-proBNP, galectin-3, cystatin C, COVID-19, prognosis.

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Introduction

Many chronic heart failure (CHF) patients have a preserved ejection fraction (EF) of the left ventricle (LV). These patients often have arterial hypertension (AH), type 2 diabetes mellitus (T2DM), obesity, coronary heart disease (CHD), chronic kidney disease (CKD), and are elderly [1]. These comorbidities mutually exacerbate each other, regardless of their order of appearance [2].

Long-lasting impact of established risk factors (RF) in comorbid patients lead to systemic inflammation, atherosclerosis, and ischemia. Against the background of metabolic and hemodynamic disorders, associated with insulin resistance, renin angiotensin aldosterone system (RAAS) activation, elevated levels of glycation end products and adipokines, patients experience oxidative injury of cardiomyocytes, glomerular filter structures, tubular epitheliocytes, mesangial cells, accompanied by increased active transforming growth factor β production, stimulation of collagen formation and fibrosis. Structural changes in heart and kidneys result in pathologic remodeling and dysfunction. In turn, cardiorenal dysfunction leads to compensatory activation of RAAS and establishes a vicious circle [3]. Thereby, inflammation and fibrosis compose the basis of cardiorenal dysfunction formation and progression pathogenesis in patients with CHF, T2DM, and CKD. Therefore, biomarkers reflecting these processes hold promise for prognostic assessment and represent a sought-after area of research/medicine.

Cystatin C is one of well-studied markers in cardiovascular and renal disorder, which is a member of cysteine proteinase inhibitors family. Serum cystatin C levels are known to represent glomerular filtration rate (GFR) more accurately, than serum creatinine. In addition to renal dysfunction, high cystatin C concentration might be associated with inflammatory and atherogenic processes [4]. Levels of this marker were studied during the coronavirus infection pandemic (COVID-19). The meta-analysis revealed an association between high serum concentrations of this biomarker and both COVID-19 infection severity and mortality in hospitalized patients [5]. Nevertheless, the significance of cystatin C in patients after the COVID-19 infection is yet to be defined.

In the past few years, the possibility of the use of galectin-3 in patients with cardiovascular disorder, including CHF. Controversial study results preclude its recommendation as a reliable indicator of heart failure (HF). However, the use of galectin-3 in combination with gold-standard HF biomarkers (B-type natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP) might improve the prognostic assessment of adverse events [6]. The significance of galectin-3 in the pathogenesis of cardiovascular remodeling, inflammatory and autoimmune processes, and neoplasia [7]. Moreover, the increase in galectin-3-positive macrophages in renal glomeruli in T2DM is associated with level of albuminuria, progression of kidney dysfunction, and a poor prognosis [8]. For the time being, galectin-3 is considered one of the markers of fibrosis and inflammation [9].

Most studies on multiple-marker prognostic assessment were conducted before the COVID-19 pandemic, and its delayed consequences are still to be researched. It has been established that patients with CHD, AH, T2DM, CKD, and CHF fall into the category of poor COVID-19 outcomes and very high risk of cardiovascular complications [10, 11]. Despite the significant evidence base of clinical application of various biomarkers, the question of the gold-standard indicator for long-term CHF poor prognosis in patients with cardiorenal dysfunction after COVID-19 remains open [12].

Aim of the study

The aim of the study is to estimate the role of biomarkers, such as NT-proBNP, cystatin C, and galectin-3 for prognostic assessment of poor outcomes in patients with HFpEF, T2DM, CKD, and COVID-19 in medical history.

Methods

The study included 135 stable patients with HFpEF, T2DM, CKD, and a confirmed COVID-19 from 3 or more months prior to the hospitalization. All participants signed an informed consent form. The median age was 70 [62, 74]. The study included patients with CHF of I–III NYHA functional class with medical history of grade 1–2 of AH, and 85 (76.58 %) participants had CHD. The exclusion criteria were acute myocardial infarction, stroke or a transient ischemic attack for 6 months prior to the enrollment, IV NYHA functional class of CHF, hemodynamically significant cardiac abnormalities, grade 3 AH, severe renal dysfunction with estimated glomerular filtration rate (eGFR) < 25 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI) 2012, level of glycated hemoglobin (HbA1c) > 12 %. The period of observation was 18 months. NYHA functional class of CHF, clinical severity assessed by the Rating Scale of Clinical State, Kaplan-Feinstein comorbidity index, 6-minute walk test distance (6MWT), echocardiographic data (EchoCG), eGFR by the CKD-EPI 2012, urine albumin-to-creatinine ratio (uACR), serum levels of NT-proBNP, galectin-3, and cystatin C assessment. Transthoracic EchoCG with myocardial tissue Doppler imaging was carried out. Left ventricular ejection fraction was estimated with Simpson's method of disks. Diastolic function of the left ventricle was estimated using transmitral flow in pulsed-wave and tissue Doppler modes. Biomarker levels were quantitatively assessed with Enzyme-Linked Immunosorbent Assay (ELISA) with the following kits: "Biomedica NT-proBNP" (Austria), "human Galectin-3 ELISA", Bender MedSystems (Austria), "Human Cystatin C ELISA", BioVendor (Czech Republic). Additionally, a group of 21 participants (12 women and 9 men) with no signs of disease and no medical history of COVID-19 for to establish control biomarker levels. This group had a median age of 54 [49, 58] and median levels of NT-proBNP 77 [49, 91] pg/mL, galectin-3 – 2.7 [1.8, 3.6] ng/mL, cystatin C 0.781 [0.694, 0.820] mg/L.

The Inter-University Committee on ethics from 20.01.2022 (protocol № 01–22) approved the study.

Statistical analysis

Statistical data were processed using Python programming language (3.10 version, scipy, statmodels, pandas, math libraries) and MedCalc software. Descriptive statistics for group parameters included frequencies and percentages for categorical variables, and medians with interquartile ranges (Q25, Q75) for continuous variables, accounting for the distribution type. The Kolmogorov-Smirnov method was used for normality tests. Differences in proportions of a trait between groups were assessed using the proportion Z-test. Differences in medians were evaluated with the Kruskal-Wallis test. The strength of association between continuous variables was measured using Spearman's correlation, while differences between categorical variables was assessed with Fisher's exact test. The association between dichotomous and continuous variables was examined using point-biserial correlation. Risk was estimated by calculating the odds ratio and relative risk. Differences in indicators between groups were considered statistically significant at $p<0.05$. Cut-off values for the concentrations of the investigated markers, along with their sensitivity and specificity, were derived from ROC analysis. A predictive model for adverse events of the composite endpoint (CEP), including cases of cardiovascular death (CVD) and HF decompensation, was created using multivariate binary logistic regression analysis. The sensitivity and specificity of the predictive model were determined via ROC analysis.

Results

According to medical history, the median duration of CHF, AH, T2DM, and CKD was 5.0 [3.0, 8.0] years, 19 [17, 21] years, 12 [9, 17] years, and 2 [2, 3] years, respectively. Among the 85 (76.58%) patients with CHD, 49 (36.3%) had two or more affected coronary arteries, 34 (30.63%) had a history of myocardial infarction, 38 (34.23%) had undergone percutaneous coronary intervention, and 7 (6.31%) had undergone coronary artery bypass grafting. Preproliferative and proliferative stages of diabetic retinopathy were identified in 42 (31.11%) and 10 (7.41%) patients, respectively. Distal diabetic neuropathy was diagnosed in 126 (93.33%) patients, of whom 54 (40.0%) had sensorimotor neuropathy. The median Kaplan-Feinstein comorbidity index score was 15 [12, 16] points. The majority of included patients, 87 (66.44%), had NYHA FC II of CHF, 46 (34.07%) patients had NYHA FC III of CHF, and 2 (1.48%) had NYHA FC I of CHF. Key clinical, functional, and laboratory parameters are presented in Table 1.

Table 1. **Clinical, functional, and laboratory parameters, median [Q25, Q75]**

Parameter	Value
BMI, kg/m^2	31.51 [29.7, 34.41]
Waist circumference, cm	105.0 [98.5, 115.0]
ShOKS (Rating Scale of Clinical State, Russian), points	5.0 [4.0, 7.0]
6MWT (6-Minute Walk Test), m	348.0 [285.0, 395.0]
HbA1c,%	7.8 [7.1, 9.1]
Cholesterol, mmol/L	4.45 [3.78, 4.99]
Sodium, mmol/L	140.2 [139.3, 141.6]
Potassium, mmol/L	4.53 [3.91, 5.04]
Urea, mmol/L	7.17 [6.1, 9.45]
Creatinine, μmol/L	105.0 [92.0, 123.9]
Creatinine eGFR, mL/min/1,73 m^2	51.89 [39.67, 69.39]
Cystatin C, mg/L	1.54 [1.26, 2.08]
Cystatin eGFR, mL/min/1,73 m^2	39.0 [27.49, 53.03]
uACR, mg/g	150.0 [66.0, 297.0]
NT-proBNP, pg/mL	679.0 [452.0, 911.0]
Galectin-3, ng/mL	11.52 [9.4, 14.58]

All patients had concentrations of NT-proBNP, galectin-3, and cystatin C above control values. An analysis of the levels of the studied biomarkers was performed across different ranges of creatinine-based eGFR, corresponding to CKD stages 1 through 4 (Figures 1–3).

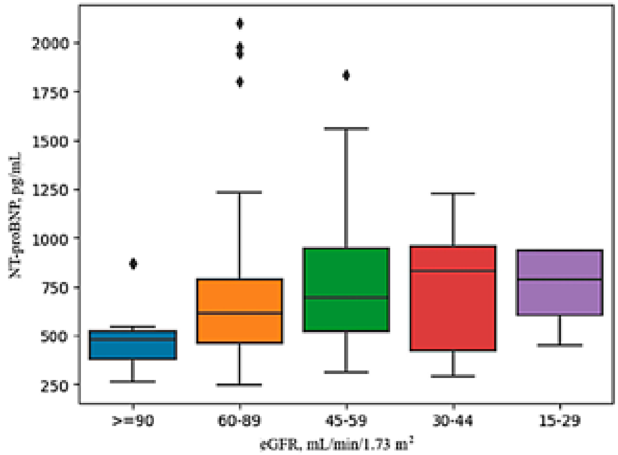


Fig. 1. NT-proBNP levels depending on eGFR, p=0.123

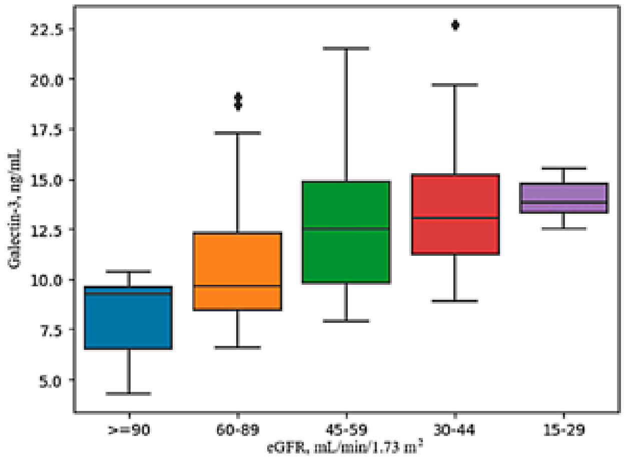
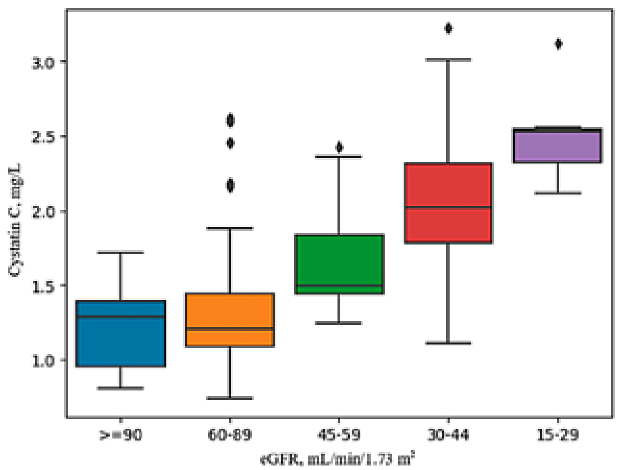


Fig. 2. Galectin-3 levels depending on eGFR, p<0.001



Unlike NT-proBNP concentration, showing no significant difference across the subgroups (p=0.123), galectin-3 and cystatin C levels increased significantly with worsening renal dysfunction (p<0.001).

Correlation analysis revealed moderate positive correlations between cystatin C level and CHF duration (r=0.325, p=0.0001), Kaplan-Feinstein comorbidity index (r=0.449, p<0.0001), Left ventricular myocardial mass index (LVMMI) (r=0.442, p<0.0001), NT-proBNP concentration (r=0.498, p<0.0001). Strong positive correlations were found between cystatin C and Creatinine levels (r=0.717, p<0.0001), Galectin-3 levels (r=0.777, p<0.0001). Significant negative correlations existed between cystatin C and 6MWT distance (r=–0.456, p<0.0001) and LVEF (r=–0.430, p<0.0001).

Galectin-3 concentration correlated with T2DM duration (r=0.371, p<0.0001), HF duration (r=0.323, p=0.00013), Kaplan-Feinstein comorbidity index (r=0.429, p<0.0001), 6MWT distance (r=-0.417, p<0.0001), uACR level (r=0.345, p<0.0001), Creatinine level (r=0.603, p<0.0001), eGFR (r=-0.490, p<0.0001), LVEF (r=-0.363, p<0.0001), LVMMI (r=0.361, p<0.0001), E/e′ ratio (r=0.519, p<0.0001), NT-proBNP level (r=0.533, p<0.0001). As the analysis reveals, markers reflecting diverse processes within the complex pathogenesis of CHF in comorbid patients, and parameters of functional status, target organ damage severity, and duration of risk factor exposure, are closely associated.

Using point-biserial correlation, a significant association was established between the severity of prior COVID-19 and levels of the studied biomarkers: NT-proBNP (r=0.238, p=0.005), galectin-3 (r=0.371, p<0.0001), and cystatin C (r=0.279, p=0.001). The stronger correlation of prior COVID-19 severity with galectin-3 concentration may be attributed to patients' initially more severe clinical status or consequences of the infectious process.

During the period of observation, CEP events occurred in 54 patients (40%): 3 (2.2%) patients died from cardiovascular causes, 23 (17.03%) patients were hospitalized due to CHF decompensation, 28 (20.74%) patients required outpatient medication adjustment for worsening HF symptoms. Assessment of CEP cases revealed that adverse outcomes occured more frequently in patients with higher baseline functional impairment, higher Kaplan-Feinstein comorbidity index (16.0 points [15.0, 18.0] compared to 14.0 points [11.0, 15.0] in patients without CEP, p<0.001; Table 2), more pronounced cardiorenal dysfunction. Moreover, 41 patients (75.93%) who experienced CEP had a CHF hospitalization within the 12 months prior to the study, compared to 28 patients (34.57%) in the non-CEP subgroup, p<0.001.

Table 2. **Baseline characteristics of patients stratified by composite endpoint occurrence**

Parameter	No CEP (n=81)	CEP (n=54)	p-value
Age, years	70 (61; 73)	71 (65; 75)	0.16
Male, n (%)	33 (40.74)	31 (57.41)	0.04
CHF duration, years	4 (2; 6)	7 (5; 12)	<0.001
T2DM duration, years	10 (9; 17)	14 (11; 19)	0.002
CKD duration, years	2 (1; 3)	3 (2; 4)	<0.001
BMI, kg/m^2	31.38 (29.94; 34.09)	31.51 (29.07; 35.02)	0.59
ShOKS, points	5 (4; 6)	7 (6; 8)	<0.001
6MWT, m	380 (325; 405)	290 (269; 365)	<0.001
Creatinine, μmol	98.0 (82.5; 122.0)	108.7 (96.0; 134.0)	0.003
uACR, mg/g	122.3 (66.0; 263.0)	263.0 (75.0; 526.0)	0.007
NT-proBNP, pg/mL	512 (410; 746)	897 (690; 1112.0)	<0.001
galectin-3, ng/mL	10.5 (8.74; 12.3)	14.94 (11.4; 17.01)	<0.001
Cystatin C, mg/L	1.4 (1.16; 1.79)	2.02 (1.53; 2.41)	<0.001
Comorbidities, n (%)			
CHD	57 (70.37)		
Myocardial infarction in medical history	16 (19.75)	46 (85.19)	0.04
Atrial fibrillation	21 (25.93)	25 (46.3)	0.001
Obstructive sleep apnea		29 (53.7)	0.001
	3 (3.7)	7 (12.96)	0.04
LVEF, %	54 (52; 57)	53 (51; 56)	0.03
Left atrial volume index, mL/m^2	34.67 (34.17; 35.6)	36.96 (35.1; 45.26)	<0.001
LVMMI, g/m^2	139.25 (116.96; 153.45)	151.03 (132.53; 164.19)	0.001
E/e`	14.18 (10.6; 15.6)	16.48 (15.26; 17.79)	<0.001

When assessing the prognostic significance of NT-proBNP, cystatin C, and galectin-3, the markers were tested in ROC analysis. The area under the

Table 3. **Prognostic characteristics of investigated markers in univariate analysis**

Parameter	AUC	95%CI	Threshold	Sensitivity, %	Specificity, %	p
NT-proBNP, pg/mL	0.787	0.633–0.942	897.0	82.5	73	<0.001
Cystatin C, mg/L	0.788	0.634–0.945	1.683	83.3	73.6	<0.001
galectin-3, ng/mL	0.791	0.637–0.949	13.08	84.1	72.7	<0.001

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curve (AUC) was 0.787, 0.788, and 0.791, respectively. Marker levels above established cut-off values – NT-proBNP: 897 pg/mL (relative risk (RR) = 4.523, 95% confidence interval (CI): 3.277–5.77; p<0.001), cystatin C: 1.683 mg/L (RR=6.428, 95% CI: 5.735–7.122; p<0.001), galectin-3: 13.08 ng/mL (RR=3.214, 95% CI: 2.103–4.325; p<0.001) identified patients as having an elevated CEP risk (Table 3).
Using multivariate logistic regression analysis, baseline mathematical Model 1 was constructed to predict the probability of HF decompensation and CVD, incorporating the ShOKS score, stroke volume (SV), LVMMI, E/e′ ratio, and NT-proBNP concentration (Table 4). The resulting model demonstrated high prognostic value (AUC = 0.856; 95% CI: 0.717–0.994; p<0.001; sensitivity 85.6%, specificity 79.2%) (Fig. 4).

Table 4. **Risk factors for HF decompensation in multivariate regression models (Models 1, 2)**

Parameter	Model 1 (AUC=0.856; p<0.001)		Model 2 (AUC=0.867; p<0.001)	
	OR (95%CI)	p-value	OR (95%CI)	p-value
NT-proBNP	1.01 (1.00–1.02)	0.001	1.01 (1.00–1.02)	<0.001
ShOKS	1.06 (0.77–1.46)	0.335	1.01 (0.72–1.41)	0.933
SV (Stroke volume)	0.98 (0.94–1.02)	0.929	0.99 (0.95–1.03)	0.73
LVMMI	0.96 (0.94–0.99)	0.045	0.96 (0.93–0.99)	0.01
E/e`	1.14 (0.97–1.34)	0.194	1.09 (0.91–1.29)	0.311
Cystatin C	No data	No data	2.52 (0.78–8.09)	0.199

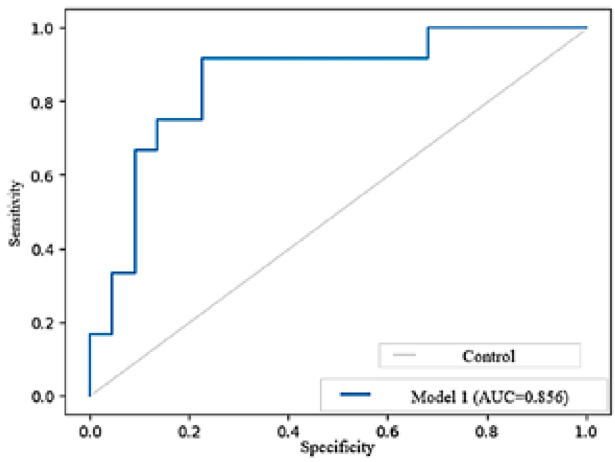

Fig. 4. ROC curve for baseline Model 1 including NT-proBNP

When assessing the prognostic capability of the studied biomarkers, cystatin C and galectin-3 concentrations were sequentially added to the baseline model and the performance of the resulting models was analyzed. Incorporating cystatin C into the original model (Model 2) improved the prognostic properties of Model 1, increasing the area under the ROC curve (AUC=0.867; 95% CI: 0.808–0.923, p<0.001; sensitivity 86.3%, specificity 75%) (Fig. 5, Table 4).

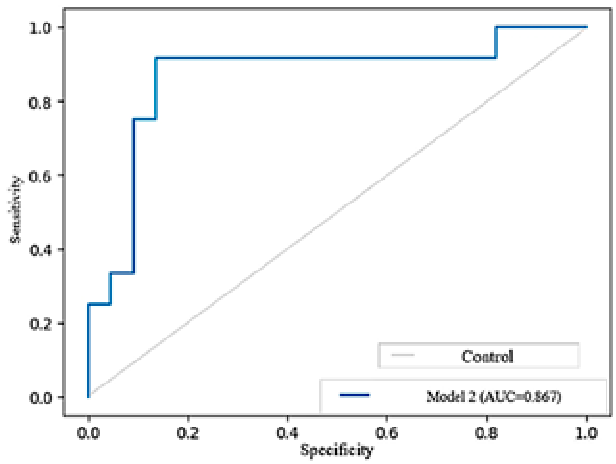

Fig. 5. ROC curve for Model 2 including NT-proBNP and cystatin C

Model 3, which included galectin-3 concentration (AUC=0.866; 95% CI: 0.809–0.923, p<0.001; sensitivity 84.9%, specificity 83.3%), demonstrated a larger AUC compared to baseline Model 1 but did not significantly differ in prognostic significance from the model containing cystatin C (Fig. 6, Table 5).

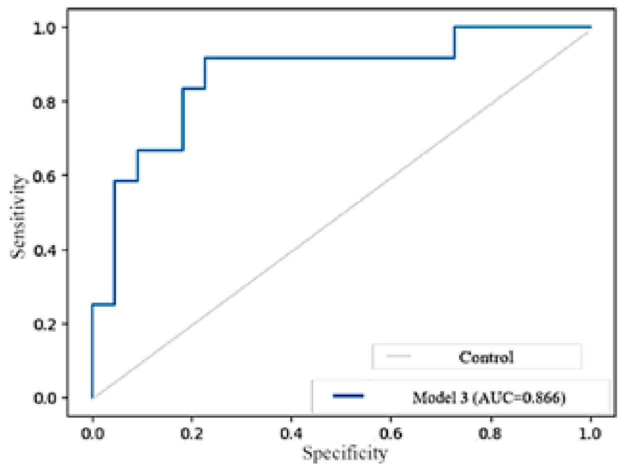

Fig. 6. ROC curve for Model 3 including NT-proBNP and galectin-3

The inclusion of all studied biomarkers further improved the predictive properties of the model (AUC=0.879; 95% CI: 0.845–0.913, p<0.001; sensitivity 87.5%, specificity 88.8%) (Fig. 7, Table 5).
Thus, compared to the baseline model incorporating NT-proBNP concentration, the addition of cystatin C

Table 5. **Risk factors for HF decompensation in multivariate regression models (Models 3, 4)**

Parameter	Model 3 (AUC=0.866; p<0.001)		Model 4 (AUC=0.879; p<0.001)	
	OR (95%CI)	p-value	OR (95%CI)	p-value
NT-proBNP	1.01 (1.00–1.02)	0.01	1.01 (1.0–1.02)	0.004
ShOKS	1.07 (0.77–1.49)	0.647	1.01 (0.7–1.43)	0.966
SV	0.98 (0.94–1.02)	0.516	0.99 (0.95–1.03)	0.74
LVMMI	0.96 (0.93–0.99)	0.016	0.96 (0.94–0.99)	0.021
E/e`	1.08 (0.9–1.3)	0.363	0.99 (0.83–1.18)	0.965
Galectin-3	1.1 (0.92–1.31)	0.26	1.14 (0.92–1.4)	0.21
Cystatin C	No data	No data	1.47 (0.35–6.13)	0.592

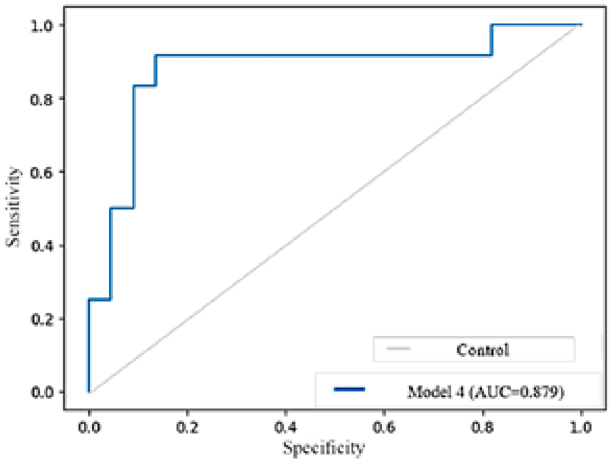

Fig. 7. ROC curve for Model 4 including NT-proBNP, cystatin C, and galectin-3

and/or galectin-3 enhances the predictive capability for assessing the risk of HF decompensation and CVD in post-COVID-19 patients with HFpEF, T2DM, and CKD.

Discussion

The comprehensive algorithm for HF patients' diagnosis and treatment efficacy evaluation involves the use of biomarkers and EchoCG data. Extensive evidence has established NT-proBNP as a reference-standard biomarker in HF [13]. Study results confirmed the reasonably high prognostic value of NT-proBNP (ROC AUC=0.787; 95% CI 0.633–0.942, p<0.001) in HFpEF patients with cardiovascular disease, T2DM, CKD, and a history of COVID-19. The biomarker was a significant predictor in the multivariate model (p=0.001).

Given the scarcity of studies evaluating long-term prognosis using markers reflecting different aspects of HFpEF pathogenesis in patients with T2DM and CKD after COVID-19, this work investigated the prognostic influence of established markers such as cystatin C and galectin-3 in comorbid HFpEF patients.

The study revealed correlations of varying strength between cystatin C levels and cardiac structural and functional parameters, indicating a close connection of cardiorenal dysfunction in HFpEF and CKD patients. The observed increase in cystatin C concentration corresponding to declining eGFR levels and severity of prior COVID-19 likely reflects more severe renal impairment and inflammation. In previous studies, cystatin C has proven to be an ideal marker for GFR, with its levels also associated with acute kidney injury and inflammatory status severity during the COVID-19 pandemic [4, 14, 15]. Elevated cystatin C in COVID-19 patients alongside reduced GFR may result from its involvement in the release of cytokines such as tumor necrosis factor-α (TNF-α), interleukin-12 (IL-12), interleukin-10 (IL-10), and nitric oxide (NO) [16]. Cystatin C activates the inducible isoform of nitric oxide synthase (iNOS), which generates higher NO concentrations compared to endothelial NOS (eNOS) and neuronal NOS (nNOS) during local and systemic inflammatory responses. This leads to the formation of highly reactive derivatives that cause irreversible alterations in intracellular structures and cellular apoptosis. This process represents one of the pathophysiological mechanisms underlying cytokine storm development and severe COVID-19 progression [17–19].

In prognostic assessment, cystatin C demonstrated predictive capability for the CEP development comparable to NT-proBNP. The established cystatin C cut-off value of ≥1.683 mg/L in the univariable model identified high-risk individuals for HF decompensation and CVD among clinically stable HFpEF patients with T2DM and CKD after COVID-19. Adding this biomarker to baseline parameters, which included NT-proBNP, improved prediction accuracy. Previous studies associated cystatin C levels >0.80–1.6 mg/L with increased mortality risk [20–22]. The higher cut-off value observed in this study may reflect the more severe clinical profile of our patient cohort.

In this study, galectin-3, being a biomarker of inflammation and fibrosis, exhibited correlations with T2DM duration, HF duration, patient comorbidity burden and functional status, left ventricular remodeling and diastolic dysfunction parameters, NT-proBNP levels, renal dysfunction markers (ACR, creatinine, and eGFR). Prolonged systemic exposure to risk factors evidently activates proinflammatory processes, oxidative stress, and fibrosis in target organs, leading to progressive functional decline. Similar but stronger correlations were reported in a Turkish study of HFpEF patients, where galectin-3 correlated with NT-proBNP (r=0.90, p<0.0001), left atrial volume index (r=0.75, p=0.0001), LVMMI (r=0.86, p=0.0001), E/e' ratio (r=0.80, p=0.0001) [23]. A weaker galectin-3/NT-proBNP correlation (r=0.21, p=0.048) was observed in another HFpEF cohort [24]. Association between galectin-3 and LV diastolic dysfunction was documented in HFpEF patients with ST-segment elevation myocardial infarction as well [25]. The observed link between galectin-3 and renal impairment severity aligns with prior research [8]. Impaired renal clearance, particularly in patients with kidney dysfunction, is presumed to contribute to elevated galectin-3 in HF [26].

In this study, a galectin-3 level ≥13.08 ng/mL (sensitivity 84.1%, specificity 72.7%, p<0.001) was associated with increased risk of the CEP. Previous studies also established statistically significant associations between galectin-3 and mortality in CHF patients [27]. Elevated galectin-3 levels were linked to worse outcomes regardless of treatment or NT-proBNP concentration [28]. Furthermore, in patients from CHF-risk groups, galectin-3 independently predicted HF development and 10-year mortality [29].

Model 4, which incorporated NT-proBNP, cystatin C, and galectin-3 in addition to baseline parameters, demonstrated the strongest predictive performance. Multimarker risk assessment for HF decompensation and CVD enhanced model performance, increasing the ROC AUC to 0.879 (p<0.001). Thus, biomarkers reflecting core pathophysiological mechanisms of cardiorenal interactions in post-COVID-19 HFpEF patients with T2DM and CKD enable precise identification of high-risk individuals, facilitating timely therapeutic management for subclinical disease control and prevention of potential complications.

Conclusion

Analysis of this HFpEF cohort with T2DM and CKD demonstrated that measuring cystatin C and galectin-3 alongside NT-proBNP enhances risk stratification, addressing the urgent unmet need for more precise prediction tools for HF decompensation and CVD in comorbid post-COVID-19 patients. These findings reveal the potential clinical utility of inflammation and fibrosis biomarkers in comorbid HFpEF populations. Prospectively, serial monitoring of cystatin C and galectin-3, particularly, in post-COVID patients, combined with multimarker assessment would provide refined prognostic insights and enable therapy efficacy evaluation. Extended follow-up of comorbid HFpEF patients using biomarkers reflecting diverse pathophysiological pathways, alongside developing specialized diagnostic and prognostic panels, may facilitate timely treatment correction. The stronger association between galectin-3 levels and COVID-19 severity warrants further investigation for objectively assessing post-infectious sequelae in critically ill patients.

Conflict of interest: none declared.

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Clinical significance of 24-hour blood pressure monitoring in patients with ankylosing spondylitis

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The aim of the study was to determine the clinical significance of 24-hour ambulatory blood pressure monitoring (ABPM) in patients with ankylosing spondylitis (AS).

Methods. A cross-sectional, single-center study included 47 men with a confirmed diagnosis of AS, aged 18 to 60 years (mean age 42.51 ± 6.04 years), with a mean disease duration of 17.26 ± 9.03 years. All patients were divided into two groups depending on the presence of hypertension based on office blood pressure (BP) measurement. AS activity was assessed using BASDAI and ASDAS–CRP indices. ABPM was performed in all patients.

Results. Low AS activity was observed in 2 (4.3 %) patients, moderate in 20 (42.6 %), and high in 25 (53.2 %). A normal circadian BP profile ("dipper" type) was found in 16 (34 %) patients, while impaired circadian BP regulation was observed in 31 (66 %). No significant differences were identified between the two groups regarding the prevalence of abnormal BP profiles ($p = 0.547$). The duration of AS was significantly longer in patients with arterial hypertension (AH) (both previously diagnosed and newly detected by ABPM) compared with those without AH according to ABPM data ($p = 0.035$). Masked AH, as revealed by ABPM, was found in 10 (43.5 %) patients from

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the second group; among them, 5 (50 %) also had an impaired circadian BP profile.

Conclusion. Arterial hypertension in patients with spondyloarthritis may remain subclinical. Nearly half of the patients who denied having AH were found to have masked hypertension, and half of them exhibited abnormal circadian BP profiles. These findings underscore the necessity of ABPM for the early detection of hypertension in patients with AS.

Keywords: spondyloarthritis, ankylosing spondylitis, arterial hypertension, masked arterial hypertension, circadian blood pressure profile, cardiovascular comorbidity.

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Introduction

Cardiovascular diseases (CVD) have been the leading cause of mortality worldwide for many years [1].

The development of CVD is promoted by risk factors (RF), which are classified into non-modifiable (sex, age, race, genetics, etc.) and modifiable ones (smoking, physical inactivity, arterial hypertension (AH), dyslipidemia, obesity, diabetes mellitus, etc.) [2].

A pooled analysis of data from 112 cohort studies conducted in 34 countries including 1,518,028 participants demonstrated that modifiable RF account for about 50 % of CVD burden in the general population. Among them, AH is the most significant [2].

Among patients with rheumatic diseases (RD), CVD also rank first in the structure of mortality, while the risk of their development substantially exceeds that in the general population [3]. This is explained by the higher prevalence of traditional RF as well as factors associated with chronic inflammation itself [4].

According to the largest cross-sectional observational study of comorbidities and RF in patients with spondyloarthritis (SpA) (COMOSPA), cardiovascular RF are highly prevalent in this group, with AH being the most common [5].

Ankylosing spondylitis (AS) is a chronic inflammatory disease from the SpA group, characterized by obligatory involvement of the sacroiliac joints and/or spine, potentially progressing to ankylosis, with frequent involvement of entheses and peripheral joints [6]. The disease mainly affects young, working-age individuals, gradually leading to disability. The development of AH and, consequently, the acceleration of CVD reduce working capacity and significantly impair quality of life in this patient population.

Diagnosis of AH includes office blood pressure (BP) measurement and ambulatory blood pressure monitoring (ABPM).

Depending on the circadian BP profile, patients with AH can be divided into four groups. A normal profile is the “dipper” type, characterized by a 10–20 % decrease in nocturnal BP compared with daytime values. Other profiles — non-dipper, night-picker, and over-dipper — are associated with an increased risk of cardiovascular complications [7].

ABPM also allows for the detection of masked hypertension (MH), which is diagnosed in patients with normal BP values measured in a clinical setting but elevated BP outside the clinic. MH was first described more than 20 years ago and immediately became a subject of scientific interest [8]. Over the years, it has been shown that the risk of complications in MH is higher than in normotensive individuals and comparable to the risk of fatal cardiovascular events in manifest AH [9].

In the general population, the prevalence of MH is 8.5–16.6 % [10]. In RA it reaches 38.7 % [11]. However, no such studies have been conducted in patients with AS, and thus the value of ABPM in this population remains undefined.

The aim of the study was to determine the clinical significance of 24-hour ABPM in patients with ankylosing AS.

Methods

A cross-sectional single-center study included 47 men with a confirmed diagnosis of AS (according to the New York criteria, 1984 [12]) who were treated in the rheumatology department of the Saratov Regional Clinical Hospital. The mean age of patients was 42.51 ± 6.04 years, and the mean duration of AS was 17.26 ± 9.03 years. Low AS activity was observed in 2 patients (4.3 %), moderate in 20 patients (42.5 %), and high in 25 patients (53.2 %).

All patients were divided into two groups depending on the presence of AH: Group 1 included patients with established AH (n = 24, 51.1 %), and Group 2 included patients in whom hypertension had not been previously diagnosed based on office BP measurement (n = 23, 48.9 %). Patients in Group 1 were receiving adequate antihypertensive therapy at a stable dose for at least two weeks, maintaining BP within target values. The groups were comparable in age and AS activity (p > 0.05).

AS activity was assessed using the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS–CRP (Ankylosing Spondylitis Disease Activity Score) [12]. ABPM was performed using the BPLab device (LLC "Petr Telegin," Russia).

Exclusion criteria were the presence of other RD besides AS, thyroid dysfunction, previous myocardial infarction or stroke, as well as any comorbid pathology in the acute phase.

The main limitation of the study was the relatively small sample size, which did not allow us to establish associations between AS severity and the frequency of MH, as well as gender differences. The study had no sources of funding.

Statistical analysis

Statistical analysis was performed using StatTech v.4.8.11 software (developer – StatTech LLC, Russia).

Quantitative variables were assessed for normality using the Shapiro–Wilk test.

Quantitative variables with distributions consistent with normality were described using arithmetic means (M) and standard deviations (SD). The boundaries of the 95 % confidence interval (95 % CI) were provided as a measure of representativeness for mean values.

If the distribution of quantitative variables deviated from normality, the data were described using the median (Me) and lower and upper quartiles (Q1–Q3).

Categorical data were described using absolute values and percentages. The 95 % CI for proportions was calculated using the Clopper–Pearson method.

Comparison of two groups for a quantitative variable with normally distributed data and equal variances was performed using Student's t-test; in the case of unequal variances, Welch's t-test was applied.

Comparison of two groups for a quantitative variable with a non-normal distribution was carried out using the Mann–Whitney U-test.

Comparison of proportions in 2×2 contingency tables was performed using Fisher's exact test (when the minimum expected frequency was less than 10). As a quantitative measure of effect when comparing relative indicators, odds ratios (OR) with 95 % CI were calculated. In cases of zero cell frequencies in contingency tables, the odds ratio was calculated with the Haldane–Anscombe correction.

Comparison of proportions in multi-way contingency tables was carried out using Pearson's χ^2 test.

Differences were considered statistically significant at $p < 0.05$.

All participants were thoroughly informed and provided written informed consent. All procedures were approved by the Ethics Committee of Saratov State Medical University named after V.I. Razumovsky, Ministry of Health of Russia.

Results

The characteristics of the examined patients are presented in Table 1. The groups did not differ in terms

Table 1. **Clinical characteristics of patients with AS depending on the presence of AH**

Parameters	Group 1 (AS + AH), n=24	Group 2 (AS with no AH), n=23	p
Age, M (SD)	44.08 (6.68)	40.87 (4.92)	0.068
Disease duration, M (SD)	19.96 (8.93)	14.43 (8.43)	0.035*
CRP, Me [IQR]	7.35 [3.30; 24.50]	15.00 [3.90; 28.65]	0.595
Low activity, abs. (%)	0 (0.0 %)	2 (8.7 %)	0.310
Moderate activity, abs. (%)	10 (41.7 %)	10 (43.5 %)	
High activity, abs. (%)	14 (58.3 %)	11 (47.8 %)	
Continuous NSAID therapy	23 (95.8 %)	22 (95.7 %)	1.000
DMARD thearapy	10 (43.5 %)	10 (41.7 %)	1.000
Biologic agents therapy	9 (37.5 %)	4 (17.4 %)	0.193
GC use	18 (75 %)	13 (56.5 %)	0.227

Note. * — the differences are statistically significant (p<0.05)

Table 2. **ABPM parameters in patients with AS depending on the initial presence of AH**

Parameters	Group 1 (AS + AH), n=24	Group 2 (AS with no AH), n=23	p
Mean daytime SBP, M (SD), mmHg	133.96 (12.50)	125.74 (15.17)	0.048*
Mean daytime DBP, M (SD), mmHg	85.67 (8.11)	84.78 (11.18)	0.759
Mean nighttime SBP, M (SD), mmHg	125.33 (17.86)	113.30 (16.86)	0.022*
Mean nighttime DBP, M (SD), mmHg	78.21 (12.07)	75.52 (10.89)	0.428
Impaired circadian BP profile	17 (70.8%)	14 (60.9%)	0.547
Mean heart rate, M (SD), bpm	72.79 (11.60)	71.91 (10.06)	0.783

Note. * — the differences are statistically significant ($p<0.05$)

of age or AS activity; however, patients in Group 1 had a longer disease duration ($p < 0.035$).

No significant differences were found between the groups in terms of C-reactive protein (CRP) levels or AS activity. The number of patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs) on a regular basis, as well as those on disease-modifying antirheumatic drugs (DMARDs) or biologic agents, also did not differ significantly between the groups.

The results of ambulatory blood pressure monitoring (ABPM) in the examined patients are presented in Table 2.

According to ABPM, a normal circadian BP profile ("dipper" type) was identified in 16 patients (34%), while an abnormal circadian BP profile was observed in 31 patients (66%). Among these, the "non-dipper" profile was found in 22 patients (71%), the "over-dipper" profile in 3 patients (9.7%), and the "night-picker" profile in 6 patients (19.3%). There were no significant differences between the two groups in the frequency of abnormal circadian BP profiles ($p = 0.547$).

Mean systolic BP (SBP) was significantly higher in Group 1 during both daytime ($p = 0.048$) and nighttime ($p = 0.022$). No significant differences between the groups were observed in mean diastolic BP (DBP), either during the day ($p = 0.759$) or at night ($p = 0.428$).

MH according to ABPM data was detected in 10 patients (43.5%) in Group 2, of whom 5 patients (50%) had an abnormal circadian BP profile.

Discussion

The increased prevalence of CVDs in patients with RDs may be explained by a combination of traditional RFs with inflammation, oxidative stress, and the use of DMARDs, biologic agents, glucocorticoids (GCs), and NSAIDs [4, 13].

In the search for an association between CRP levels and the development of AH, a cohort of 20,525 female health professionals in the United States aged over 45 years with normotension at baseline was followed for a mean of 7.8 years, with incident hypertension cases recorded. In adjusted models, an increase in baseline CRP by 1 SD was associated with an adjusted relative risk of developing AH of 1.14, suggesting that enhanced inflammation clearly preceded the clinical manifestation of elevated blood pressure [14]. The fact that AH appears to be associated with autoimmune inflammation underscores the need to investigate its coexistence with various RDs.

In the present study, it was found that patients with longer disease duration of AS more frequently had AH, while nearly every second patient with AS who denied having hypertension was found to have MH. This likely makes a significant contribution to the increased incidence of CVD in this patient population.

The prevalence of MH in AS is considerably higher than in the general population and higher than in patients with rheumatoid arthritis (Table 3).

Table 3. **Frequency of MH in different population groups**

Group	Frequency of MH
General population, n=7700	8.5–16.6%
Patients with RA, n=31	38.7%
Patients with AS, n=23	43.5%

Thus, there is a strong tendency toward studying the BP profile in patients with RDs, and the results obtained highlight the problem of underdiagnosis of AH as one of the key contributors to the elevated CVD risk in this nosological group.

It is noteworthy that AH is a modifiable RF and therefore may serve as a successful target for interventions aimed at preventing CVD and mortality. Consequently, performing ABPM in patients with AS is essential for the timely detection and management of AH.

Conclusion

SpA are a group of diseases with a proven cardiovascular risk. AH in patients with AS may remain subclinical. Almost half of the patients who denied having AH were found to have MH, and among them, half had an abnormal circadian blood pressure profile. This highlights the necessity of ABPM for the early detection of hypertension in patients with AS, since timely diagnosis will allow optimization of therapy and thereby delay the development of CVD in this population.

Further studies are needed to clarify the role of MH in cardiovascular risk stratification not only in patients with AS but also in those with other RDs.

Conflict of interests: none declared.

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Features of acute coronary syndrome associated with anxiety and depression disorders

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Cardiovascular Diseases (CVDs) are a leading cause of death, with the highest mortality rates observed during exacerbations of Coronary heart disease (CHD). A high incidence of affective disorders has been demonstrated in patients after acute coronary syndrome (ACS), both in the inpatient and outpatient settings.
The aim of this review is to present and analyze data from national and international studies on the features of ACS, associated with anxiety and depression disorders, published between 2016 and 2024.
Methods. The review was prepared using materials from peer-reviewed articles published on PubMed, eLIBRARY.RU, cyberleninka.ru, and the other resources from 2016 to 2024 were used.
Results. Along with well-established cardiovascular risk factors (RFs), such as arterial hypertension,

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smoking, and obesity, stress, anxiety, and depression are also recognized as risk factors. Due to hemodynamic disturbances in ACS, ischemic brain injuries may occur. These can lead to severe conditions, such as vascular delirium, as well as less severe disorders manifesting as cognitive impairment, sleep disorders, anxiety and/or depression.

Conclusion. To date, there are no clear, joint cardiology and psychiatry guidelines on diagnosis and management of psychiatric disorders in patients with ACS. Psychological and pharmacological interventions can have a positive effect and should be considered for ACS patients with depression, anxiety, and stress. Prior to discharge, all patients should be screened for mental disorders using validated questionnaires and, if necessary, a psychiatric consultation.

Keywords: Acute coronary syndrome, myocardial infarction, stress, anxiety, depression, risk factors, delirium, sudden cardiac death, antidepressants.

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Introduction

Cardiovascular diseases (CVDs) remain a leading cause of death, with the highest mortality rates observed during exacerbations of coronary heart disease (CHD) [1]. A high incidence of affective disorders has been demonstrated in patients after acute coronary syndrome (ACS), both in the inpatient and outpatient settings [2, 3]. Experts of the European Society of Cardiology (ESC) and the American Heart Association have noted an increasing impact of psychosocial factors, such as stress, depression, and anxiety on the development and progression of CVDs [4-6]. Due to hemodynamic disturbances in ACS, ischemic brain injuries may occur. These can lead to severe conditions, such as vascular delirium, as well as less severe disorders manifesting as cognitive impairment, sleep disorders, anxiety and/or depression [7-9].

The aim of this review is to present and analyze data from national and international studies on the features of ACS, associated with anxiety and depression disorders, published between 2016 and 2024.

Methods

The review was prepared using materials from peer-reviewed articles published between 2016 and 2024 on databases such as PubMed, eLIBRARY.RU, CyberLeninka, and other relevant scientific platforms.

Results

Along with well-established cardiovascular risk factors (RFs), such as arterial hypertension, smoking, and obesity, stress, anxiety, and depression are also recognized as risk factors [10]. However, to date, there are no clear, joint cardiology and psychiatry guidelines on diagnosis and management of psychiatric disorders in patients with ACS. Thus, an update to the ESC guidelines on ACS from 2023 [10] contains only one paragraph dedicated to mixed anxiety–depressive disorder (MADD) in ACS (13.2.4. Psychological considerations), reflecting the correlation between depression, anxiety, and stress and worse outcomes. Psychological and pharmacological interventions may have a positive effect and should be considered for ACS patients with depression, anxiety, and stress. Prior to discharge, all patients should be screened for mental disorders using validated questionnaires and, if necessary, a psychiatric consultation [5, 10].

The incidence of stress, anxiety and depression disorders in cardiovascular disease

The meta-analysis of 15 international clinical studies revealed that anxiety, depression, and psychosocial stress was associated with a 28% CVD risk increase [11]. MADD was most frequently observed in patients after acute myocardial infarction (AMI), with chronic heart failure (CHF), after cerebral strokes, in patients with atrial fibrillation (AF), as well as following advanced treatment procedures: coronary artery bypass graft (CABG) surgeries and implantations of cardioverter-defibrillators [12-14]. Chronic depression symptoms were identified in 65% of individuals with AMI, with every fifth of them diagnosed with an MADD [15]. According to research data [16], in patients with AMI, symptoms of anxiety, depression, and post-traumatic stress disorder (PTSD) occur in 9–60%, 11–20%, and 12–19% of cases, respectively. Stress, anxiety, and depression precede the development of AMI in 6–25% of cases [17]. Thus, ESC experts concluded the negative impact of anxiety, depression, and PTSD in patients with CVDs [18]. Derisi M.M. et al. mention in their work a 25.55% increase in the frequency of mental disorders among patients with coronary heart disease (CHD) from 2000 to 2021 compared to the period 1984–2000 [19]. Stress, anxiety, and depression are found in 58%, 33%, and 31% of patients with CVD, respectively [20, 21].

Stress, anxiety, depression, and the risk of adverse cardiovascular complications

A meta-analysis of 17 prospective studies, which analyzed the condition of 39,038 patients with ACS, found a 25% increased risk of adverse cardiovascular events (CV events) in patients with ACS associated with anxiety. However, after adjustment for depression, anxiety was not statistically significantly associated with mortality risk (p=0.37) [22]. Possible reasons for the link between depression and increased frequency of adverse CV events included lack of adherence to a healthy lifestyle (smoking, low physical activity, etc.), medication and rehabilitation non-adherence. ACS can cause post-traumatic stress, and PTSD triggered by ACS, in turn, can increase the risk of subsequent adverse CV events and mortality in patients. Clinically significant symptoms of ACS-induced PTSD are associated with a doubling of the risk of death and/or ACS recurrence (relative risk 2.00; 95% confidence interval (CI) 1.69–2.37) in patients with ACS who have clinically significant PTSD symptoms compared to patients without PTSD symptoms [22].

Mujkanovic J. et al. studied all cases of death among residents of Denmark aged 18 to 90 years in 2010 by analyzing death certificates and autopsy protocols: out of 4.3 million residents, the authors analyzed 45,703 death cases, of which 6,002 were caused by sudden cardiac death (SCD) [23]. The incidence of SCD was 1.79–6.45 times higher among patients with mental disorders than in the general population and was statistically significantly dependent on age ($p < 0.001$ in all age groups). In analyzing all death certificates and autopsy reports, the authors paid special attention to the medications that had been prescribed to the deceased[1].

Delirium and adverse outcomes in acute myocardial infarction

Delirium is an acute condition characterized by confusion, acute disturbances in attention, consciousness, or thinking, developing over several hours or days due to an underlying illness or medication side effects. Delirium cannot be explained by an alternative diagnosis or a comatose state [24].

Forms, key signs, and symptoms of delirium

There are three forms of delirium: hypoactive, hyperactive, and mixed. The key signs and symptoms of delirium include impaired attention (97%), long-term memory deterioration (89%), short-term memory deterioration (88%), disorientation (76%), reduced visuospatial abilities (87%), speech disturbances (57%), and disturbances of perception (50%) [25]. The Montreal Cognitive Assessment (MoCA) and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) are used for the detection of delirium. The incidence of delirium in patients with AMI ranges from 1.4% to 11%. Delirium not only prolongs hospitalization but also increases in-hospital mortality by 1.4–1.9 times [26, 27].

Risk factors for delirium development

Predisposing factors for delirium include: advanced age, male sex, central nervous system disorders (dementia, stroke, Parkinson's disease), visual or hearing impairments, alcohol intoxication, immobilization, and alcoholism accompanied by dehydration [24, 25, 27].

Initiating factors for delirium development include: use and/or withdrawal of narcotic, toxic, and other psychotropic substances; severe acute illness; urinary tract infection; hypoxemia; hyponatremia; shock; anemia; pain syndrome; bladder catheterization; surgical interventions; admission to the intensive care unit (ICU); and a high number of medical procedures. Pharmacological risk factors for delirium development include: narcotic analgesics (primarily morphine); psychotropic drugs (benzodiazepines, tri-

[1] Mujkanovic J, Warming PE, Kessing LV et al. Use of antidepressant medication linked to substantial increase in risk of sudden cardiac death. https://www.escardio.org/The-ESC/Press-Office/Press-releases/Use-of-antidepressant-medication-linked-to-substantial-increase-in-risk-of-sudden-cardiac-death

cyclic antidepressants, haloperidol, phenothiazines, Belladonna-derived drugs, antiparkinsonian agents); drugs with anticholinergic activity; certain antibiotics; codeine; cimetidine; captopril; dipyridamole; hypothiazide; digoxin; furosemide; isosorbide dinitrate; nifedipine; prednisolone; theophylline; and other drugs such as antihistamines, laxatives, non-steroidal anti-inflammatory drugs, H2-histamine receptor blockers, and anticoagulants.

The incidence of delirium can range from 5.7% in AMI patients admitted to the ICU to 40% in patients who have undergone open-heart surgery. Delirium, as a clinical manifestation of acute brain dysfunction syndrome occurring against the background of myocardial infarction (MI), is a serious complication of the underlying disease with an unfavorable prognosis.

Efficacy and safety of antipsychotic drugs in patients with delirium and myocardial Infarction

The efficacy and safety of antipsychotic drugs (neuroleptics) in patients with delirium and MI have not been sufficiently studied to date. An analysis of nine observational studies found that the odds of developing AMI were 1.88 times higher (odds ratio [OR] 1.88, 95% CI 1.39, 2.54) in users of antipsychotics compared to individuals who did not take antipsychotics. A subgroup analysis revealed an OR of 2.48 (95% CI 1.66, 3.69) among patients with schizophrenia and an OR of 2.64 (95% CI 2.48, 2.81) among short-term (<30 days) antipsychotics users. The authors of this meta-analysis confirm an increased risk of MI in users of antipsychotic drugs, demonstrating an elevated and more pronounced risk of AMI in short-term users [28]. In a number of studies, male sex, a diagnosis of schizophrenia, and antipsychotic exposure periods of < 60 days were associated with a higher risk of MI [29]. In a large nationwide cohort of patients admitted to the hospital, Park Y. et al. found a slight increase in the risk of death within one week of initiating treatment with haloperidol compared to atypical antipsychotics [30]. The increased risk was noted within the first four days and was no longer apparent by the 5th day of observation. These findings are consistent with a large body of data from previous outpatient studies demonstrating a higher risk of mortality associated with the initiation of typical versus atypical antipsychotics [30]. The results of this study suggest that atypical antipsychotics may be a less harmful treatment option for elderly patients with AMI [30].

Conclusion

CHD and mental disorders are leading causes of morbidity and mortality not only in Russia but worldwide. Due to the high prevalence of depression and mortality from MI and CHD globally, the observed association between depression, MI, and SCD has significant public health implications. Psychological and pharmacological interventions may have a positive effect and should be considered for patients with ACS associated with depression, anxiety, and stress. Prior to discharge, all patients should be screened for mental disorders using validated questionnaires and, if necessary, a psychiatric consultation. The timely detection, treatment, and prevention of anxiety and depression can significantly reduce the risk of MI and SCD. However, to date, there are conflicting data regarding the efficacy and safety of antipsychotic drugs in patients with AMI and delirium. In the future, there is a critical need to develop national guidelines for the diagnosis and treatment of comorbid mental disorders in patients with CVD for cardiologists, internists, general practitioners, psychiatrists, and other specialists.

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Modern trends in hypolipidemic therapy

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Despite treatment with statins, patients with excessive levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides have a relatively high risk of developing complications from cardiovascular diseases (CVDs).

For the past ten years, research of various hypolipidemic medications has been in constant development. Hypolipidemic medication is applied for treatment of patients with statin intolerance or inability to reach the recommended LDL-C level.

Inclisiran is a small interfering ribonucleic acid, targeted at the proprotein convertase subtilisin/kexin type 9 (PCSK9), exerts effects similar to monoclonal antibodies against PCSK9. Bempedoic acid, an ATP-citrate lyase enzyme inhibitor, is nowadays considered a promising option of statin-intolerant patients' treatment. Pemafibrate, an agonist of the peroxisome proliferator-activated receptor alpha, had demonstrated an exceptional risk/benefit ratio during the phase 2 of the clinical trials, nevertheless, the phase 3 was terminated due to ineffectiveness shown by the late interim analysis. High doses of icosapent ethyl, the ethylic ester of eicosapentaenoic acid, has a beneficial effect on the cardiovascular system.

For the time being, there still are not enough data on the use of novel medications for the primary prevention of CVDs. For faster integration into clinical practice, safety and effectiveness of these methods, as well as cost-efficiency, have to be demonstrated by the randomized study of cardiovascular outcomes.

Keywords: Monoclonal antibodies to proprotein convertase subtilisin/kexin 9, inclisiran, bempedoic acid, pemafibrate, eicosapentaenoic acid, docosahexaenoic acid.

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Introduction

Cardiovascular diseases (CVDs) are a leading cause of mortality not only in Russia, but worldwide as well [1]. In 2022 alone, CVDs caused 831 557 deaths in the Russian Federation. The mortality from neoplasia was almost 3 times lower. Most deaths were associated with complications of coronary heart disease (CHD) (54.2% of all deaths) and cerebrovascular disease (29.2% of all deaths). These diseases are commonly caused by atherosclerosis, which is strongly associated with dyslipidemia[1].

The goal of hypolipidemic therapy is to reduce the risk of developing atherosclerotic CVDs, most commonly caused by elevated levels of low-density lipoprotein cholesterol (LDL-C). Statins are the first-line drugs for treating hypercholesterolemia. For patients at high risk of CVD, with familial hypercholesterolemia (FH), or with type 2 diabetes mellitus (T2DM), it is recommended to achieve a target LDL-C level of < 1.8 mmol/L and reduce it by ≥50% from the baseline [2]. Nevertheless, the persisting risk of CVDs demonstrates an ongoing clinical need for the development and implementation of medications that effectively lower the blood levels of atherogenic particles [3].

Sufficient data on the efficacy of novel lipid-lowering drugs and their potential for clinical application have been accumulated in the literature. This review includes an analysis of new hypolipidemic drugs that affect blood levels of LDL and triglycerides (TG).

Methods

All material for this review was compiled from peer-reviewed articles published over the past 10 years on platforms such as PubMed, eLIBRARY.RU, cyberleninka.ru and other research databases. This time frame was selected as it encompasses the publication of key clinical studies on the subject. Search terms included "hypolipidemic therapy," "PCSK9 inhibitors," "inclisiran," and "bempedoic acid."
Studies or articles that did not meet quality standards were excluded.

Results

LDL-C-lowering drugs

A number of clinical and genetic studies have demonstrated that LDL particles cause CVDs, and that reducing CVD risk is dependent on lowering blood LDL-C levels [4].

Inhibition of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) with monoclonal antibodies

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a liver enzyme that binds to LDL-C receptors on hepatocyte membranes and reduces their expression. As a result of its action, the level of LDL-C in the plasma increases.

Evolocumab and alirocumab are monoclonal antibodies that inhibit this enzyme. These antibodies reduce the concentration of PCSK9 in the blood plasma, leading to increased expression of LDL-C receptors and, consequently, a decrease in blood LDL-C levels. PCSK9 inhibitors also reduce TG and lipoprotein(a) levels while simultaneously increasing apolipoprotein A-I (apoA-I) levels [5].

Evolocumab is indicated for patients with heterozygous and homozygous FH. It can be used as monotherapy or in combination for patients already on statin therapy who are not achieving their target LDL-C levels. This drug is also recommended for patients with statin intolerance [6, 7]. In patients with homozygous familial hypercholesterolemia, evolocumab reduced plasma LDL-C levels by 31% [8]. The cardiovascular outcomes study FOURIER (Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) confirmed the feasibility of using evolocumab for hyperlipidemia. This study followed 27,564 patients with a plasma LDL-C level ≥ 1.8 mmol/L or non-high-density lipoprotein cholesterol (non-HDL-C) ≥2.6 mmol/L, who had atherosclerotic changes in various vascular beds and were concurrently receiving treatment with statins and ezetimibe. According to the results of this study, adding evolocumab to therapy reduced LDL-C levels by 59% from 2.4 mmol/L to 0.78 mmol/L, and the risk of CVD was reduced by 15% (hazard ratio (HR) = 0.85; 95% confidence interval (CI): 0.79-0.92, p <0.001) [9, 10].

[1] Federal State Statistics Service (Rosstat) «Demographic Yearbook of Russia 2023» https://rosstat.gov.ru/folder/210/document/13207

In the prospective, randomized, double-blind, placebo-controlled EVOPACS study, serum LDL-C levels were measured in 308 patients hospitalized with acute coronary syndrome (ACS) and elevated LDL-C levels, who had been on statin therapy for at least 4 weeks prior to hospitalization (LDL-C ≥1.8 mmol/L with high-intensity statin therapy; ≥2.3 mmol/L with low- or moderate-intensity statin therapy; or ≥3.2 mmol/L in patients taking statins inconsistently). Patients were randomized 1:1 to receive either evolocumab 420 mg subcutaneously or placebo in the hospital and for an additional 4 weeks after discharge (totaling 8 weeks), in addition to atorvastatin 40 mg therapy. The mean LDL-C level decreased from 3.61 to 0.79 mmol/L at week 8 in the evolocumab group and from 3.42 to 2.06 mmol/L in the placebo group; the difference in the mean percentage change from baseline was ~40.7% (95% CI: 45.2 to 36.2%; p < 0.001). An LDL-C level of <1.8 mmol/L was achieved at week 8 in 95.7% of patients in the evolocumab group compared to 37.6% in the placebo group, confirming the feasibility of using evolocumab [11].

The benefits of PCSK9 inhibitor drugs are also demonstrated by the results of the multicenter, double-blind, placebo-controlled, randomized clinical trial GLAGOV [10]. The study included 968 patients aged 18 years and older with specific clinical indications identified during coronary angiography. Specifically, they had at least one epicardial coronary stenosis obstructing 20% or more of the vessel lumen. Furthermore, these patients had a target vessel that could be visualized and whose obstruction did not exceed 50%. At the start of the study, patients were on stable-dose statin therapy for at least 4 weeks and had an LDL-C level of ≥2.1 mmol/L or between 1.6 and 2.1 mmol/L with one major or three minor risk factors for CVD. Major risk factors included: non-coronary atherosclerotic vascular disease, myocardial infarction (MI), or hospitalization for unstable angina within the previous 2 years, as well as type 2 diabetes. Minor risk factors included: smoking, hypertension, low high-density lipoprotein cholesterol (HDL-C) levels, family history of early coronary heart disease, high-sensitivity C-reactive protein (hs-CRP) level ≥0.2 mmol/L, or age ≥50 years for men and ≥55 years for women. The study patients were randomized to receive monthly subcutaneous injections of either evolocumab 420 mg (484 patients) or placebo (484 patients) for 76 weeks, in addition to statins. The primary efficacy measure was the change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasound (IVUS). Secondary efficacy measures were the change in total atheroma volume (TAV) and the percentage of patients with plaque regression.

The safety and tolerability of evolocumab were also assessed. Among the 968 patients treated, lower LDL-C levels were achieved in the evolocumab group: 2.41 mmol/L in the placebo group versus 0.95 mmol/L in the evolocumab group, with a between-group difference of −1.46 mmol/L (95% CI: −1.55 to −1.38 mmol/L; p < 0.001). The primary efficacy parameter, PAV, increased by 0.05% with placebo and decreased by 0.95% with evolocumab — a difference of −1.0% (95% CI: −1.8% to -0.64%; p < 0.001). The secondary efficacy parameter, TAV, decreased by 0.9 mm^3 with placebo and by 5.8 mm^3 with evolocumab, a difference of −4.9 mm^3 (95% CI: −7.3 to −2.5 mm^3; p < 0.001). Evolocumab induced plaque regression in a greater percentage of patients than placebo: 64.3% vs. 47.3%, a difference of 17.0% (95% CI: 10.4 to 23.6%); for PAV: 61.5% vs. 48.9%, a difference of 12.5% (95% CI: 5.9 to 19.2%; p < 0.001); for TAV, p < 0.001. Thus, it can be concluded that the combination of evolocumab and statins promotes the regression of atherosclerotic plaques in patients with coronary heart disease, as confirmed by IVUS data [12].

The efficacy and safety of another drug in this class, alirocumab, in patients with high cardiovascular risk and uncontrolled hypercholesterolemia despite maximally tolerated statin doses, were established in the multicenter, double-blind, randomized, placebo-controlled study ODYSSEY COMBO II. This study included 720 patients with confirmed CVD and elevated LDL-C ≥1.8 mmol/L, or without confirmed CVD history but with high cardiovascular risk and LDL-C ≥ 2.6 mmol/L, despite maximum statin doses (rosuvastatin 20/40 mg, atorvastatin 40/80 mg, or simvastatin 80 mg) used for more than 1 year. Patients were randomized into 2 groups. The first group received alirocumab 75 mg subcutaneously every 2 weeks (plus oral placebo tablets). The second group received oral ezetimibe 10 mg daily (plus subcutaneous placebo injections) on top of statin therapy. At week 24, the mean reduction in LDL-C from baseline was 50.6 ± 1.4% for alirocumab versus 20.7 ± 1.9% for ezetimibe (difference 29.8 ± 2.3%; p<0.0001); 77.0% of patients receiving alirocumab and 45.6% of patients receiv-

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ing ezetimibe achieved LDL-C levels <1.8 mmol/L ($p<0.0001$). The mean achieved LDL-C level at week 24 was 1.3 ± 0.04 mmol/L for alirocumab and 2.1 ± 0.05 mmol/L for ezetimibe and was maintained until week 52. Alirocumab was generally well-tolerated, with no signs of an excess of treatment-emergent adverse events observed [13].

The efficacy of long-term (78 weeks) treatment with alirocumab was demonstrated in two multicenter, randomized, double-blind, placebo-controlled studies, ODYSSEY FH I (486 patients) and FH II (249 patients), in patients with heterozygous familial hypercholesterolemia (HeFH) and inadequate LDL-C control despite maximally tolerated statin therapy (rosuvastatin 20–40 mg, atorvastatin 40–80 mg, or simvastatin 80 mg) with or without other lipid-lowering drugs for at least 4 weeks prior to the study (6 weeks for fenofibrate; other fibrates such as clofibrate, gemfibrozil, bezafibrate, ciprofibrate, except fenofibrate, were not permitted). Patients with HeFH without a history of cardiovascular events, as well as patients who had experienced MI or ischemic stroke, were included in the study if their LDL-C level did not reach the target value, according to current guidelines, for primary (≥2.6 mmol/L) or secondary (≥1.8 mmol/L) prevention respectively. Study patients were randomized in a 2:1 ratio to receive alirocumab 75 mg every 2 weeks or placebo. The alirocumab dose was blindly increased to 150 mg at week 12 if the patient's LDL-C level at week 8 was ≥1.8 mmol/L. Throughout the study, patients continued taking statins and other lipid-lowering medications. The mean LDL-C level decreased from a baseline of 3.7 mmol/L to 1.8 mmol/L after treatment (–57.9% compared to placebo) at week 24 in patients randomized to the alirocumab group in the ODYSSEY FH I study, and from 3.5 mmol/L to 1.8 mmol/L (–51.4% compared to placebo) in the ODYSSEY FH II study ($p < 0.0001$). This reduction was maintained until week 78. An LDL-C level of <1.8 mmol/L (regardless of cardiovascular risk) was achieved at week 24 by 59.8% and 68.2% of patients receiving alirocumab in the ODYSSEY FH I and FH II studies, respectively [14].

The multicenter, randomized, double-blind, placebo-controlled study ODYSSEY OUTCOMES demonstrated an improvement in cardiovascular outcomes after ACS in 18,924 patients receiving high-intensity statin therapy with the addition of 75 mg alirocumab. At baseline, the mean LDL-C level in the study patients was 2.38 ± 0.80 mmol/L. In the alirocumab group, the mean LDL-C level at 4 months, 12 months, and 48 months after randomization was 1.0 mmol/L, 1.2 mmol/L, and 1.7 mmol/L respectively; in the placebo group, the mean LDL-C level at 4 months, 12 months, and 48 months after randomization was 2.4 mmol/L, 2.5 mmol/L, and 2.7 mmol/L respectively. In an analysis conducted in the alirocumab group (which excluded values measured after alirocumab discontinuation and after blinded substitution of alirocumab with placebo), the mean LDL-C level at 4 months, 12 months, and 48 months was 0.98 mmol/L, 1.1 mmol/L, and 1.4 mmol/L respectively; these levels were on average 62.7%, 61.0%, and 54.7% lower than the corresponding levels in the placebo group. The primary composite endpoint (PCE) included: death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. The median follow-up duration was 2.8 years. A PCE event occurred in 903 patients (9.5%) in the alirocumab group and 1052 patients (11.1%) in the placebo group (HR = 0.85; 95% CI: 0.78–0.93; $p < 0.001$). A total of 334 patients (3.5%) died in the alirocumab group and 392 patients (4.1%) in the placebo group (HR = 0.85; 95% CI: 0.73–0.98). Thus, it can be concluded that alirocumab is capable of not only reducing LDL-C levels but also reducing the risk of cardiovascular complications and death in patients after ACS [15].

The effect of alirocumab on coronary artery atherosclerosis in patients who underwent percutaneous coronary intervention (PCI) for acute MI was studied in the recently conducted multicenter, double-blind, placebo-controlled, randomized clinical trial PACMAN-AMI. In this study, 300 patients who underwent PCI for acute MI (participant enrollment: from May 9, 2017, to October 7, 2020; final follow-up: October 13, 2021) were randomized to receive 150 mg of alirocumab (148 patients) subcutaneously every two weeks or placebo (152 patients). Treatment began less than 24 hours after urgent PCI and was administered for 52 weeks in addition to high-intensity statin therapy (rosuvastatin 20 mg). At 52 weeks, the mean change in PAV was –2.13% with alirocumab versus –0.92% with placebo, a difference of –1.21% (95% CI: –1.78% to –0.65%; $p < 0.001$). The mean change in minimal fibrous cap thickness was 62.67 μm with alirocumab versus 33.19 μm with placebo, a difference of 29.65 μm (95% CI: 11.75–47.55; p =

0.001) [16]. Thus, in patients with acute MI, the addition of alirocumab to high-intensity statin therapy, compared with placebo, led to significantly greater regression of coronary plaque at 52 weeks.

Considering current clinical guidelines, PCSK9 inhibitors should be prescribed to patients receiving therapy with statins and ezetimibe at maximally tolerated doses, who have a high risk of CVD and a plasma LDL-C level ≥1.8 mmol/L [2].

With subcutaneous administration of alirocumab at doses of 75 and 150 mg and evolocumab at a dose of 140 mg every 2 weeks to patients with atherosclerotic CVD on background statin therapy, a 60% reduction in LDL-C level and a 15% reduction in the risk of CVD complications were observed [2].

PCSK9 inhibition via RNA interference

Inclisiran is a small interfering RNA that inhibits the synthesis of the PCSK9 protein in hepatocytes. The effect of this drug lasts longer than that of other lipid-lowering agents [17].

In the ORION-9 study evaluating the effect of inclisiran treatment on LDL-C levels in HeFH, which included 482 patients with HeFH and a baseline plasma LDL-C level ≥2.6 mmol/L on statin therapy, inclisiran sodium at a dose of 300 mg (equivalent to 284 mg of inclisiran free acid) was administered on days 1, 90, 270, and 450. The mean baseline LDL-C level was 4.0 ± 1.4 mmol/L. On day 510, inclisiran reduced plasma LDL-C levels by 47.9%. The mean absolute change in LDL-C level from baseline on day 510 was a reduction of 1.5 mmol/L (95% CI: −1.7 to −1.4 mmol/L) in the inclisiran group and an increase of 0.3 mmol/L (95% CI: 0.1 to 0.4 mmol/L) in the placebo group, with a between-group difference of 1.8 mmol/L (95% CI: −2.0 to −1.6 mmol/L; $p < 0.001$). A higher frequency of injection site reactions was noted in the inclisiran group compared to the placebo group (17.0% vs. 1.7%). Most adverse events were assessed as mild, with no serious complications identified [18].

In the ORION-10 study, which involved a total of 1561 patients with atherosclerotic CVD such as coronary heart disease, peripheral artery atherosclerosis, etc., a dose of 284 mg of inclisiran (as the free acid) was administered on days 1, 90, 270, and 450. The mean baseline LDL-C level was 2.71 ± 0.99 mmol/L. On day 510, inclisiran reduced plasma LDL-C levels by 52.3% (95% CI: 48.8 to 55.7%). The absolute change in LDL-C level on day 510 was −0.05 mmol/L in the placebo group and −1.45 mmol/L in the inclisiran group, with a between-group difference of −1.40 mmol/L (95% CI: −1.48 to −1.32 mmol/L; $p < 0.001$). The percentage change on day 510 was 13.5% with placebo and −69.8% with inclisiran, representing a between-group difference of -83.3% (95% CI: −89.3% to −77.3%; $p < 0.001$) [19].

Russian clinical guidelines approve inclisiran for subcutaneous administration at 284 mg, with a regimen of three doses in the first year and two doses annually thereafter [2].

Bempedoic Acid

ATP-citrate lyase (ACLY) catalyzes the ATP-dependent conversion of citrate and coenzyme A (CoA) into oxaloacetate and acetyl-CoA. Acetyl-CoA, a precursor of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), is crucial for cholesterol biosynthesis. Thus, inhibition of ACLY leads to reduced levels of acetyl-CoA and cholesterol synthesis [20].

Bempedoic acid (BA) is a prodrug that acts as a selective ACLY antagonist after activation by acyl-CoA synthetase-1. Since this enzyme is primarily expressed in the liver, BA has minimal impact on other body tissues, particularly skeletal muscle. Unlike statins, patients treated with BA exhibited a lower incidence of myopathy, rhabdomyolysis, or other muscle-related adverse effects [20]. Among the most common side effects are increased plasma uric acid levels and the development of gout [21].

In addition to lowering LDL-C levels, BA also affects the level of high-sensitivity C-reactive protein (hs-CRP) [22].

The CLEAR Harmony and CLEAR Wisdom studies investigated the effect of BA therapy on cholesterol levels, involving 2230 and 779 patients, respectively, with atherosclerotic CVD and familial hypercholesterolemia and a plasma LDL-C level ≥1.8 mmol/L despite maximally tolerated statin therapy, with BA added to their regimen. Plasma LDL-C levels decreased by approximately 18%. In the CLEAR Harmony study, the baseline LDL-C was ≥1.8 mmol/L, while in CLEAR Wisdom, the mean baseline LDL-C was 3.1 ± 0.98 mmol/L. In CLEAR Harmony, at 12 weeks of BA therapy, the mean LDL-C level decreased by 0.5 mmol/L. Treatment with BA led to a significantly greater reduction in LDL-C levels compared to

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the placebo group, both at week 12 ($p < 0.001$) and week 24 ($p < 0.001$). In the CLEAR Wisdom study, at week 12, BA reduced LDL-C significantly more than placebo (–15.1% vs. +2.4%, respectively; $p < 0.001$). The mean LDL-C level at week 12 was 2.5 mmol/L in the BA group compared to 3.9 mmol/L in the placebo group [20, 23].

While the aforementioned studies assessed the efficacy of BA as an add-on lipid-lowering therapy in patients on maximum statin therapy, the CLEAR Serenity study included 345 patients with hypercholesterolemia and a history of intolerance to at least two statins (one statin at the lowest available dose). Patients were randomized 2:1 to receive oral BA 180 mg or placebo once a day for 24 weeks. At baseline, the mean LDL-C level was 4.08 ± 1.03 mmol/L, non-HDL-C was 4.99 ± 1.16 mmol/L, mean total cholesterol was 6.32 ± 1.2 mmol/L, apolipoprotein B (apoB) was 3.66 ± 0.81 mmol/L, and the median hs-CRP was 0.03 μmol/L (Q1-Q3: 0.01-0.05 μmol/L). BA treatment significantly reduced LDL-C from baseline to week 12 (placebo-corrected difference, –21.4% [95% CI: –25.1% to –17.7%]; $p < 0.001$). Significant reductions in BA group compared to placebo were also observed for non-HDL-C (–17.9%), total cholesterol (–14.8%), apoB (–15.0%), and hs-CRP (–24.3%); ($p < 0.001$ for all comparisons). BA was well-tolerated and safe. The most common muscle-related adverse event was myalgia, observed in 4.7% and 7.2% of patients receiving BA and placebo, respectively. This study expanded the evidence for the long-term use of BA in patients with statin intolerance [24].

BA affects blood levels of urea nitrogen, uric acid, and creatinine, increasing their levels. The drug also led to a decrease in hemoglobin levels. The incidence of gout was higher in the BA group compared to the placebo group (1.6 per 100 person-years vs. 0.5 per 100 person-years). The incidence of new-onset diabetes/hyperglycemia was lower in the BA group compared to the placebo group (4.7 per 100 vs. 6.4 per 100) [21].

The use of BA for the primary prevention of CVD was evaluated in the double-blind, randomized, placebo-controlled cardiovascular outcomes trial CLEAR Outcomes, involving 13,970 patients at high CVD risk, with statin intolerance, and an LDL-C level ≥2.59 mmol/L, who received BA (180 mg/day). Among the 13,970 patients included, 4,206 (30%) met the criteria for primary CVD prevention; of these, 2,100 were randomized to the BA treatment group and 2,106 to the placebo group. The mean LDL-C level was 3.69 mmol/L, mean HDL-C was 1.32 mmol/L, median TG was 4.19 mmol/L, and median hs-CRP was 0.06 mmol/L. Compared to placebo, BA reduced LDL-C by 21.3% after 6 months of treatment and reduced hs-CRP by 21.5% after 12 months of treatment. In the subgroup of high-risk CVD patients, the use of BA for primary CVD prevention was associated with a reduced incidence of major cardiovascular events. Specifically, BA reduced the risk of major adverse cardiovascular events by 13% (HR = 0.87; 95% CI 0.79–0.96; $p = 0.004$) [25, 26].

Thus, BA has become a long-awaited pharmacological alternative for lowering LDL-C levels both in patients not achieving target LDL-C levels on maximally tolerated statin therapy and in patients with statin intolerance. BA can be prescribed as monotherapy or as an add-on to treatment with maximally tolerated doses of statins and ezetimibe in patients who have not reached their target LDL-C level.

Agents for reducing triglyceride levels

Epidemiological and clinical studies clearly demonstrate a correlation between CVD risk and plasma TG levels. However, TGs play a secondary role in the formation of atherosclerotic plaques and are not directly involved in their development, as they can be broken down by most cells in the body. Consequently, TGs are not a direct cause of atherosclerosis. Nevertheless, recent attention has focused on the causal relationship between TGs, triglyceride-rich lipoproteins (TRLs), and their remnants in the risk of developing atherosclerosis. Genetic, epidemiological, and clinical studies suggest a causal link between TRLs and their remnants and an increased risk of atherosclerosis, and this dyslipidemia may be an independent risk factor for adverse cardiovascular events. Specifically, in patients with obesity, metabolic syndrome, diabetes, and chronic kidney disease, abnormal levels of TRLs and their remnants significantly increase the risk of developing atherosclerosis and CVD. The accumulation of excessively synthesized TRLs in the plasma, impaired function of enzymes involved in TRL lipolysis, and disrupted hepatic clearance of cholesterol-rich TRL remnants can lead to the deposition of TRLs and their remnants in the arteries, promoting the formation of foam cells and arterial wall inflammation. Thus, understanding the pathogenesis of

TRL-induced atherosclerosis and implementing targeted treatment may slow the progression of atherosclerosis, thereby reducing the morbidity and mortality from CVD, particularly coronary heart disease resulting from coronary artery atherosclerosis [27].

According to American clinical guidelines, omega-3 fatty acids or fibrates are prescribed to patients with hypertriglyceridemia for the prevention of pancreatitis [28]. European clinical guidelines recommend prescribing omega-3 polyunsaturated fatty acids in combination with statins for patients with elevated blood TG levels between 1.5 and 5.6 mmol/L [29].

Pemafibrate

Fibrates are TG-lowering drugs that act as agonists of the peroxisome proliferator-activated receptor alpha (PPARα). These receptors are located on the membranes of hepatocytes, platelets, macrophages, as well as muscle, heart, kidney, and adipose tissue cells. Upon activation, PPARα receptors stimulate or suppress genes responsible for metabolic processes in the body. A meta-analysis demonstrated that fibrates reduce the risk of CVD in a subgroup of patients with high baseline plasma TG levels [30].

Drugs in this class include: pemafibrate, bezafibrate, gemfibrozil, and fenofibrate.

Pemafibrate is the first selective PPARα receptor agonist. Its activity exceeds that of fenofibrate, or more precisely its active form (fenofibric acid), by more than 2500 times. Pemafibrate demonstrates 2500 times greater affinity than fenofibric acid (the active metabolite of fenofibrate) for human PPAR-α, with over 5000 times greater affinity for PPAR-α than for PPAR-γ or -δ, thus requiring much lower doses and consequently limiting adverse effects [31].

The efficacy and safety of add-on therapy with pemafibrate for treating residual hypertriglyceridemia despite statin treatment were evaluated in a multicenter, randomized, double-blind, placebo-controlled, parallel-group, comparative clinical study on Japanese patients. The study included 751 patients with dyslipidemia who were taking pitavastatin. They were randomized into four groups of 188 patients each, assigned to receive either placebo or pemafibrate at doses of 0.1, 0.2, or 0.4 mg/day. These patients had residual dyslipidemia with mean fasting TG levels between 3.9 mmol/L and 4.3 mmol/L despite pitavastatin treatment, while the mean LDL-C level ranged from 3.0 mmol/L to 3.2 mmol/L. Treatment continued for 12 weeks. Results from this first study showed that TG levels decreased significantly by approximately 50% from baseline to week 12 in all combination therapy groups, whereas no significant changes were observed in the pitavastatin monotherapy group. A dose-dependent reduction in TG levels was confirmed, and the decrease in TG levels from baseline to week 12 was statistically significant ($p<0.001$) in all pemafibrate combination therapy groups compared to the pitavastatin monotherapy group [32].

The incidence of adverse events and adverse drug reactions in the pemafibrate combination therapy groups was comparable to that in the statin monotherapy groups, without any significant findings in the study [32].

The efficacy and safety of pemafibrate were also convincingly demonstrated among patients in a European randomized, double-blind, placebo-controlled Phase II study. The study included 408 patients who had been taking a stable dose of a statin (except pravastatin, lovastatin, or fluvastatin) for at least 12 weeks prior to the study and continued taking the same statin at an unchanged dosage throughout the study. At enrollment, the observed patients had fasting TG levels between 1.97 mmol/L and 5.65 mmol/L, HDL-C concentrations of ≤1.30 mmol/L for men and ≤1.43 mmol/L for women, and LDL-C concentrations not exceeding target values by more than 0.259 mmol/L. Patients were randomized to placebo or one of the following pemafibrate dosing regimens: 0.05 mg twice daily, 0.1 mg twice daily, 0.2 mg twice daily, 0.1 mg once daily, 0.2 mg once daily, or 0.4 mg once dailyRandomized patients received two tablets in the morning and two in the evening for 12 weeks. The tablets contained either the investigational drug (at doses of 0.05 mg, 0.1 mg, or 0.2 mg per tablet) or a matching placebo. Study results showed that pemafibrate reduced TG levels at any dosage ($p<0.001$), with the greatest placebo-adjusted reduction from baseline to week 12 observed in the 0.2 mg twice-daily regimen group (54.4%). A significant increase in HDL-C levels, ranging from 7.4% to 12.9%, was also observed at all dosages except 0.1 mg once daily ($p<0.05$). A significant increase in LDL-C levels, ranging from 9.2% to 20.5%, was observed at all dosages except 0.05 mg twice daily ($p<0.05$). Pemafibrate was safe and generally well-tolerated. However, some patients exhibited a minor increase in serum creatinine and homocysteine concentrations [33].

Omega-3 Fatty Acid formulations

Omega-3 polyunsaturated fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which exert their effects indirectly through the activation of peroxisome proliferator-activated receptors (PPAR). By reducing the concentration of very-low-density lipoproteins, they lower triglyceride levels in the blood plasma [34].

Although omega-3 fatty acids are recommended for patients with severe hypertriglyceridemia in addition to statin therapy, the benefits of this approach for both primary and secondary prevention of CVD have not been confirmed by most conducted studies [34, 35].

For example, the multicenter, randomized, double-blind, placebo-controlled REDUCE-IT trial involved 8,179 patients with elevated plasma TG levels (1.69 to 5.63 mmol/L), LDL-C levels (1.06 to 2.59 mmol/L), and a history of atherosclerotic CVD or diabetes, who were receiving stable statin therapy for at least 4 weeks prior to the study. Patients were randomly assigned to groups receiving 2 grams of icosapent ethyl (an ethyl ester of eicosapentaenoic acid — an omega-3 polyunsaturated fatty acid ethyl ester) twice daily (total daily dose of 4 g) or placebo. Patients were followed for a median of 4.9 years. The primary composite endpoint was a combination of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. A key secondary endpoint (KSE) was the composite of cardiovascular death, nonfatal MI, or nonfatal stroke. PCE events occurred in 17.2% of patients in the icosapent ethyl (IE) group compared to 22.0% in the placebo group (HR=0.75; 95% CI: 0.68–0.83; p<0.001); corresponding rates for the KSE were 11.2% and 14.8% (HR=0.74; 95% CI: 0.65–0.83; p<0.001). The incidence of additional ischemic endpoints was significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death — 4.3% vs. 5.2% (HR=0.80; 95% CI: 0.66–0.98; p=0.03). A greater number of patients in the icosapent ethyl group were hospitalized for atrial fibrillation or flutter compared to the placebo group (3.1% vs. 2.1%, p=0.004). Serious bleeding events were observed in 2.7% of patients in the icosapent ethyl group and 2.1% in the placebo group (p=0.06) [36].

The effect of icosapent ethyl on the progression of coronary atherosclerosis in patients with elevated TG levels on statin therapy was studied in the randomized, double-blind, placebo-controlled EVAPORATE trial. This study included 80 patients aged 30 to 85 years with diagnosed coronary atherosclerosis (≥20% stenosis in one coronary artery by invasive coronary angiography or coronary computed tomography angiography (CCTA)), elevated fasting TG (1.52-5.63 mmol/L), and LDL-C levels from ≥1.04 to ≤2.98 mmol/L, who were on stable statin therapy (with or without ezetimibe), and adhering to a diet and exercise regimen for ≥4 weeks prior to the study. All patients followed a low-cholesterol diet and continued their current statin therapy during the study. Patients were randomized 1:1 to receive IE 4 g/day or mineral oil as a placebo to assess the rate of plaque volume progression via CCTA. Patients underwent interim scanning at 9 months and final scanning at 18 months using CCTA. The predefined PCE was the change in plaque volume at 18 months between the IE and placebo groups. The study results showed a significant reduction in the PCE, as IE reduced plaque volume by 17%, while in the placebo group, plaque volume more than doubled (+109%) (p=0.0061). Significant differences in progression rates between the IE and placebo groups were also observed at the end of the study, including volumes of fibrous and fibrofatty plaques, which regressed in the IE group and progressed in the placebo group (p<0.01 for all). However, no statistically significant differences were found in the main lipid parameters (total cholesterol, LDL-C, HDL-C, and TG) from baseline to follow-up with either therapy [37].

However, opposing results were obtained in the randomized, double-blind, placebo-controlled, event-driven STRENGTH trial, which evaluated the long-term outcomes of risk reduction with omega-3 carboxylic acids in patients at high cardiovascular risk with hypertriglyceridemia on statin therapy [38, 39]. This drug is an omega-3 fatty acid formulation that undergoes an additional manufacturing step of hydrolyzing and distilling ethyl esters into omega-3 free fatty acids (omega-3 carboxylic acids) with a 75% concentration of EPA and DHA. Given its free fatty acid formulation, the drug does not require hydrolysis by pancreatic lipase, unlike conventional omega-3 ethyl esters, to enhance intestinal absorption. This higher bioavailability is supported by its lack of dependence on dietary fat content.

The study included 13,086 patients aged ⩾18 years who had been on a stable diet and taking statins for at least 4 weeks prior to the study initiation, with confirmed:

- LDL-C level < 2.59 mmol/L; however, subjects were also eligible for participation if their LDL-C level was ⩾ 2.59 mmol/L, provided they were receiving high-intensity or maximally tolerated statin therapy, with or without ezetimibe;
- Atherogenic dyslipidemia, defined as TG levels ⩾ 2.03 mmol/L and < 5.650 mmol/L and HDL-C < 1.09 mmol/L for men or < 1.22 mmol/L for women, measured after an overnight fast;
- High risk of future cardiovascular events.

The mean age of the studied patients was 62.5 ± 9.0 years. The cohort included 35% women and 65% men; 70% of all patients also had diabetes. The median LDL-C level was 1.94 mmol/L, the median TG level was 2.71 mmol/L, the median HDL-C level was 0.93 mmol/L, and the median hs-CRP level was 0.05 mmol/L.

Patients who met all inclusion criteria and voluntarily agreed to participate were randomized in a 1:1 ratio to receive either the study drug at 4 g/day or a corresponding placebo (corn oil). The study duration was 5 years.

The PCE was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina. KSEs included:

- The composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina in patients with established cardiovascular disease at baseline;
- The composite of cardiovascular death, nonfatal MI, and nonfatal stroke in the entire cohort and in patients with established cardiovascular disease at baseline;
- The composite of cardiac death, nonfatal MI, coronary revascularization, and hospitalization for unstable angina in the entire cohort and in patients with established cardiovascular disease at baseline;
- Cardiovascular death in the entire cohort and in patients with established cardiovascular disease at baseline;
- All-cause mortality in the entire cohort and in patients with established cardiovascular disease at baseline.

Prespecified tertiary efficacy endpoints (TCE) included newly diagnosed atrial fibrillation, thrombotic complications, and newly diagnosed heart failure. Changes in lipid levels, inflammatory markers, and EPA/DHA levels were also prespecified efficacy parameters. A retrospective analysis examined the association between plasma and erythrocyte EPA/DHA concentrations and the incidence of cardiovascular events [38, 39].

The study was terminated prematurely after 1,384 patients experienced a PCE, based on an interim analysis of the study results that indicated a low probability of clinical benefit for Epanova compared to the corn oil placebo. Of the 13,078 treated patients, 12,633 (96.6%) completed the study with confirmed PCE status. The PCE occurred in 785 patients (12.0%) receiving Epanova compared to 795 patients (12.2%) receiving placebo (HR = 0.99; 95% CI: 0.90–1.09; p = 0.84). The Epanova group had a higher incidence (24.7%) of gastrointestinal adverse effects (diarrhea, nausea, dyspepsia, and abdominal discomfort) compared to patients receiving placebo (14.7%) [38, 39].

Among patients at high cardiovascular risk taking statins, the addition of the omega-3 carboxylic acid formulation to usual background therapy did not lead to a significant change in the composite outcome of major adverse cardiovascular events compared to corn oil-based placebo. These results do not support the use of this specific omega-3 fatty acid formulation for reducing the incidence of major cardiovascular events in high-risk patients [38, 39].

Conclusion

Hypolipidemic therapy is primarily conducted to reduce the risk of CVDs. Statins have established themselves as first-line drugs for lowering plasma levels of LDL-C, a well-known risk factor for CVD. However, even with optimal statin therapy, a significant residual cardiovascular risk persists. Consequently, new drugs with mechanisms different from statins that lower LDL-C levels, as well as new targets beyond LDL-C for intervention to reduce the risk of atherosclerosis progression, are undoubtedly necessary.

Modern physicians have at their disposal a wide array of hypolipidemic drug classes with diverse mechanisms of action, the efficacy and safety of which have been demonstrated in large, randomized, placebo-controlled trials. Consequently, for patients with dyslipidemia and atherosclerotic CVD who fail to achieve their target lipid profile on maximally tolerated statin therapy or in statin-intolerant patients, a broad selection of alternative hypolipidemic agents is now available. It is crucial to emphasize, nonetheless, that statins remain the first-line therapy for initiating lipid-lowering treatment.

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2025 ESC Congress HOT LINE sessions: key clinical studies

At the 2025 European Congress of Cardiology, the results of 42 international multicenter clinical trials were presented in the HOT LINE sessions. The studies addressed various areas of cardiology, including arterial hypertension, coronary heart disease, atrial fibrillation, lipid-lowering therapy, pharmacotherapy for heart failure, intensive care in cardiology, and healthcare management in cardiology. New texts for five clinical guidelines were also presented. A summary report presents the results of the most interesting studies.

Keywords: clinical trials, meta-analyses, clinical guidelines, cardiovascular diseases.

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From August 29 to September 1, 2025, the regular Congress of the European Society of Cardiology was held in Madrid (Spain), combined this year with the World Congress of Cardiology. The main theme of the event was "Global Health: Cardiology Without Borders".

Congress participants reviewed 5 new texts of clinical guidelines:

- for the treatment of valvular heart diseases;
- for the treatment of myocarditis and pericarditis;
- for the treatment of cardiovascular diseases in pregnancy;
- targeted update of the 2019 guidelines for the treatment of dyslipidemia;
- consensus statement on mental health and cardiovascular diseases.

The full texts of these documents are available online at https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines.

The results of 42 specially selected clinical studies were reported for the first time at 10 HOT LINE scientific sessions. The studies were devoted to various areas of cardiology, including the management of patients with cardiac arrhythmias, chronic heart failure, hypertrophic cardiomyopathy, dyslipidemia, arterial hypertension, after myocardial infarction, coronary revascularization, venous thromboembolism, in the perioperative period.

The most interesting studies are summarized below.

The **POTCAST** study involved 1200 patients with a high risk of ventricular arrhythmias — with an implantable cardioverter defibrillator — and with an initial plasma potassium level of 4.3 mmol/l or lower. After randomization in a 1:1 ratio, treatment was administered to increase plasma potassium levels to 4.5–5.0 mmol/l using potassium supplements, a mineralocorticoid receptor antagonist, or both plus dietary advice, or standard care. At a median follow-up of 39.6 months, the composite of the primary endpoint events (documented sustained ventricular tachycardia or corresponding cardioverter-defibrillator shock, unplanned hospitalization for more than 24 hours for arrhythmia or heart failure, or death from any cause) occurred in 22.7% of patients in the high-normal potassium group compared with 29.2% in the standard care group (p=0.01). The rate of hospitalization for hyperkalemia or hypokalemia was similar in both groups.

The therapeutic efficacy of the cardiac glycoside digitoxin in patients with heart failure and reduced ejection fraction was assessed in the **DIGIT-HF** study. A total of 1,212 patients with New York Heart Association functional class III or IV chronic heart failure with a left ventricular ejection fraction of 40% or less, or functional class II with a left ventricular ejection fraction of 30% or less were randomized in a 1:1 ratio to receive digitoxin (at an initial dose of 0.07 mg once daily) or placebo in addition to drug therapy prescribed in accordance with current clinical guidelines. At a median follow-up of 36 months, the primary endpoint (death from any cause or hospitalization for worsening heart failure) occurred in 39.5% of patients in the digitoxin group and 44.1% in the placebo group (p=0.03), with a trend toward a reduction in mortality (by 14%) in the cardiac glycoside group and a comparable incidence of serious adverse events (4.7% versus 2.8% of cases in the digitoxin and placebo groups, respectively).

Following the completion of the **VICTORIA** study (n=5050), the soluble guanylate cyclase stimulator vericiguat was approved for the treatment of advanced heart failure with reduced ejection fraction and received a Class IIb recommendation in European and North American guidelines. The subsequent VICTOR study (n=6,105) evaluated vericiguat in patients with heart failure with reduced ejection fraction without recent worsening. A pre-specified pooled analysis of patient-level data from the **VICTORIA and VICTOR** studies was conducted to determine the effect of vericiguat on clinical outcomes. Participants in both studies received current background heart failure therapy according to guidelines. The primary endpoint of cardiovascular death or hospitalization for heart failure occurred in 25.9% of 5,579 patients in the vericiguat group and 27.9% of 5,576 patients in the placebo group (p=0.0088), including significant reductions in the risk of cardiovascular death (by 11%; p=0.020) and hospitalization for heart failure (by 8%; p=0.043). Therefore, vericiguat may be used as an additional treatment option for selected patients with heart failure with reduced ejection fraction.

In the **ODYSSEY-HCM** study, the cardiac myosin inhibitor mavacamten, approved for the treatment of adult patients with symptomatic obstructive hypertrophic cardiomyopathy, was evaluated in the non-obstructive form. After randomization, 289 patients received mavacamten (starting dose of 5 mg/day adjusted to a maximum dose of 15 mg/day depending on left ventricular ejection fraction) and 291 received placebo. Over a 48-week follow-up period, there were no significant differences in the two primary endpoints: the mean change in peak oxygen consumption was 0.52 ml/kg/min in the mavacamten group and 0.05 ml/kg/min in the placebo group (p=0.07), and the change in quality of life according to the 23-item Kansas City Cardiomyopathy Questionnaire was 13.1 points versus 10.4 points (p=0.06). In patients with non-obstructive hypertrophic cardiomyopathy, mavacamten did not lead to a significantly greater improvement in peak oxygen consumption or reduction in symptoms compared with placebo.

The cardiac myosin inhibitor aficamten was compared with metoprolol in patients with obstructive hypertrophic cardiomyopathy in the MAPLE-HCM trial. After randomization, 88 patients received aficamten at a dose of 5 to 20 mg/day plus placebo, and 87 received metoprolol at a dose of 50 to 200 mg/day plus placebo. During 24 weeks of observation, the change in peak oxygen consumption (the primary endpoint) was 1.1 ml/kg/min in the aficamten group and –1.2 ml/kg/min in the metoprolol group (p<0.001). Patients receiving aficamten had significant improvements in New York Heart Association functional class, Kansas City Cardiomyopathy Questionnaire quality of life, left ventricular outflow tract pressure gradient, N-terminal pre-brain natriuretic peptide level, and left atrial volume index compared with patients receiving metoprolol. There were no significant differences in left ventricular mass index or adverse event rates between the two treatment groups.

The open-label, randomized **REBOOT-CNIC** trial compared the results of contemporary treatment (coronary reperfusion and secondary prevention) in patients with ST-segment elevation myocardial infarction and left ventricular ejection fraction greater than 40% with beta-blocker therapy (n=4207) versus no therapy (n=4231). With a median follow-up of 3.7 years, the primary endpoint (a composite of death from any cause, reinfarction, or hospitalization for heart failure) occurred at equal rates (p=0.63) in the

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two groups; there was no difference in the rates of death from any cause, reinfarction, hospitalization for heart failure, or safety outcomes.

The open-label, randomized **BETAMI–DANBLOCK** study included patients with a history of myocardial infarction and a left ventricular ejection fraction of at least 40% who were randomized within 14 days of the event to receive long-term beta-blocker therapy (n=2,783) or no beta-blocker therapy (n=2,791). At a median follow-up of 3.5 years, the combined primary endpoint (death from any cause, myocardial infarction, unplanned coronary revascularization, ischemic stroke, heart failure, or malignant ventricular arrhythmia) occurred in 14.2% of patients in the beta-blocker group and 16.3% in the no-beta-blocker group (p=0.03), with no significant differences in the incidence of individual components or safety parameters between the groups. In this study, in patients with myocardial infarction and a left ventricular ejection fraction of at least 40%, beta-blocker therapy resulted in a reduced risk of death or major adverse cardiovascular events compared with no beta-blocker therapy.

The phase 3 BaxHTN study enrolled patients with sitting systolic blood pressure 140 mmHg to less than 170 mmHg despite treatment with two antihypertensive agents (uncontrolled hypertension) or three or more such agents (resistant hypertension), including a diuretic. After a 2-week placebo run-in period, patients with sitting systolic blood pressure 135 mmHg or greater were randomized to receive the selective aldosterone synthase inhibitor baxdrostat 1 mg (n=264), baxdrostat 2 mg (n=266), or placebo (n=264) once daily. After 12 weeks, the change from baseline in sitting systolic blood pressure (primary endpoint) was -14.5 mmHg. with 1 mg baxdrostat, –15.7 mmHg with 2 mg baxdrostat, and –5.8 mmHg with placebo. The placebo-corrected difference was –8.7 mmHg with 1 mg baxdrostat and –9.8 mmHg with 2 mg baxdrostat (p<0.001 for both comparisons). Potassium levels greater than 6.0 mmol/L were recorded in 2.3% of patients in the 1 mg baxdrostat group, 3.0% in the 2 mg baxdrostat group, and 0.4% in the placebo group. In patients with uncontrolled or resistant hypertension, the addition of baxdrostat to background therapy resulted in a significant reduction in sitting systolic blood pressure after 12 weeks compared with placebo.

Olezarsen is an antisense oligonucleotide that inhibits the synthesis of apolipoprotein C-III, resulting in lower plasma triglyceride levels. The drug was evaluated in the randomized phase 3 Essence–TIMI 73b study in patients with moderate hypertriglyceridemia (triglycerides 150 to 499 mg/dL) and increased cardiovascular risk or severe hypertriglyceridemia (triglycerides ≥500 mg/dL) who were randomized 1:3 to receive monthly subcutaneous administration of olezarsen 50 mg (n=254), olezarsen 80 mg (n=766), or placebo (n=329). After 6 months of treatment, the mean change in triglyceride levels adjusted for placebo was –58.4% in the olezarsen 50 mg group (p<0.001) and –60.6% in the olezarsen 80 mg group (p<0.001). The incidence of serious adverse events was similar in all study groups.

The optimal duration of anticoagulation after venous thromboembolism in patients with a transient precipitating event (e.g., surgery, trauma, or immobilization) and concomitant persistent risk factors has not been determined. In the randomized HI-PRO study, patients with VTE following a transient trigger, at least 1 persistent risk factor, and receiving anticoagulation for at least 3 months were randomized to receive apixaban 2.5 mg twice daily (n=300) or placebo (n=300) for 12 months. During the follow-up period, the primary efficacy endpoint (first symptomatic recurrence of VTE) occurred in 1.3% of patients in the apixaban group and 10.0% in the placebo group (p<0.001). The primary safety endpoint (first major bleeding event according to the International Society on Thrombosis and Haemostasis criteria) occurred with comparable frequency: major bleeding occurred in 1 patient in the apixaban group and in no patients in the placebo group, minor clinically significant bleeding was observed in 4.8% of patients in the apixaban group and in 1.7% in the placebo group (p=0.06). Rare fatal outcomes were not associated with cardiovascular or hemorrhagic causes.

The **AQUATIC** study included patients with chronic coronary syndrome who had a stent implanted more than 6 months before inclusion in the study, had a high atherothrombotic risk and received continuous oral anticoagulant therapy. After randomization, once-daily aspirin 100 mg (n=433) or placebo (n=439) was administered in addition to anticoagulants. The study was terminated early on the recommendation of an independent data and safety monitoring board after a median follow-up of 2.2 years due to excess death from any cause in the aspirin group. The primary efficacy endpoint (a composite of cardiovascular death, myocardial infarction, stroke, systemic embolism, coronary revascularization, or acute limb ischemia) occurred in 16.9% of patients in the aspirin group and in 12.1% in the placebo group (p=0.02), and death from any cause occurred in 13.4% versus 8.4% of cases, respectively (p=0.01). The key safety indicator (major bleeding) was recorded in 10.2% of patients in the aspirin group and in 3.4% in the placebo group (p<0.001).

The **NEO-MINDSET** study enrolled patients after successful percutaneous coronary intervention for acute coronary syndromes who were randomized within the first 4 days of hospitalization to stop aspirin and then receive monotherapy with a potent P2Y12 inhibitor (ticagrelor or prasugrel) (n=1712) or dual antiplatelet therapy (aspirin and a potent P2Y12 inhibitor) (n=1698) for 12 months. During this follow-up period, the primary end point events (death from any cause, myocardial infarction, stroke, or urgent revascularization) occurred in 7.0% of patients in the monotherapy group and 5.5% in the dual antiplatelet therapy group (p=0.11 for noninferiority). Major or clinically relevant non-major bleeding occurred in 2.0% of patients in the monotherapy group and 4.9% of patients in the dual antiplatelet therapy group, and stent thrombosis occurred in 12 and 4 patients in the matched groups, respectively. Among patients who underwent successful percutaneous coronary intervention for acute coronary syndrome, monotherapy with a potent P2Y12 receptor inhibitor was non-inferior to dual antiplatelet therapy in preventing the combined risk of death and ischemic events at 12 months.

The **TARGET-FIRST** trial included patients who had successfully undergone complete coronary revascularization with implantation of advanced drug-eluting stents within 7 days of myocardial infarction and who completed 1 month of dual antiplatelet therapy without ischemic complications or major bleeding. After randomization, patients were assigned to receive either P2Y12 receptor inhibitor monotherapy (n=961) or dual antiplatelet therapy (n=981) for 11 months. During follow-up, the primary composite endpoint (death from any cause, myocardial infarction, stent thrombosis, stroke, or major bleeding type 3 or 5 according to the Bleeding Academic Research Consortium definition) occurred in 2.1% of patients in the P2Y12 receptor inhibitor monotherapy group and 2.2% of patients in the dual antiplatelet therapy group (p=0.02 for noninferiority). The primary secondary endpoint (Bleeding Academic Research Consortium type 2, 3, or 5 bleeding) occurred in 2.6% of patients in the P2Y12 receptor inhibitor monotherapy group and 5.6% in the dual antiplatelet therapy group (p=0.002 for superiority). Stent thrombosis was rare and its incidence was similar in both groups.

In this open-label, registry-based, cardiothoracic surgery center-based clinical trial, TACSI, patients undergoing coronary artery bypass grafting for acute coronary syndrome were randomized to receive ticagrelor and aspirin (n=1104) or aspirin alone (n=1097) for 1 year. During this follow-up period, the combined primary endpoint event (death, myocardial infarction, stroke, or repeat revascularization) occurred in 4.8% of patients in the ticagrelor plus aspirin group and 4.6% in the aspirin alone group (p=0.77). The key secondary endpoint was all adverse clinical outcomes, defined as the primary endpoint events plus major bleeding, and its incidence was 9.1% of cases in the ticagrelor plus aspirin group versus 6.4% in the aspirin alone group. Major bleeding occurred in 4.9% of patients in the ticagrelor plus aspirin group and 2.0% in the aspirin alone group. In patients undergoing coronary artery bypass grafting for acute coronary syndrome, adding ticagrelor to aspirin does not reduce the risk of death, myocardial infarction, stroke, or repeat coronary revascularization compared with aspirin alone for 1 year.

The next congress of the European Society of Cardiology is scheduled to be held in Munich, Germany, from 28 to 31 August 2026.

The material was prepared by **Professor Kanorsky S.G.** (Krasnodar, Russia), edited by **Professor Mamedov M.N. (Moscow, Russia).**

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.

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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.

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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.

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

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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.

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Webpage:

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