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Journal of the Cardioprogress Foundation

Key research findings presented at the 2024 ESC Congress HOTLINE sessions

The effect of pedal cadence on a cycle ergometer on blood pressure reduction in individuals with hypertension: a systematic review of randomized controlled trials

Unveiling rare hemorrhagic complications of enoxaparin therapy. A clinical case review

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CONTACT DETAILS:
Cardioprogress Foundation and Editorial Office:
Room 213, Building 2, Prospect Gostinichny 6, Moscow 127106, Russia
Editorial Office tel.: (+7) 965 236 1600
Official website: http://www.heart-vdj.com

Editorial correspondence should be sent to:
Mekhman Mamedov, Editor-in-Chief,
editor.ihvdj@gmail.com
Articles for publication should be sent to:
Anna Arteyeva, Associate Editor,
submissions.ihvdj@gmail.com

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International Heart and Vascular Disease Journal

Journal of the «Cardioprogress» Foundation

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Contents

Editor's Welcome

Dear colleagues!

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

The "Leading article" section opens with an article providing a brief overview of 34 randomized clinical trials and 4 meta-analyses presented at 12 HOT LINE scientific sessions of the 2024 Congress of the European Society of Cardiology.

The "Original Articles" section features three studies.

The first article assessed the prevalence of coronary heart disease (CHD), sleep disorders, and negative affective states in a representative sample of men aged 55–64, and investigated the probability of developing CHD in the presence of high levels of depression, hostility, vital exhaustion, and sleep disturbances. The authors found that a high level of psychosocial factors in middle-aged men was associated with the development of CHD. When designing preventive programs aimed at reducing cardiovascular risk in an open urban population, attention should be given to regulating psychological parameters. The second article explored the role of microvesicles (extracellular structures that trigger cascades of mechanisms affecting endothelial changes) of various origins in the risk of recurrent cardiovascular events (CVE) within one year after type 2 myocardial infarction (MI) in men under 45. During the acute phase of type 2 MI, CD45+ microvesicle levels were significantly higher in patients who later experienced a recurrent CVE within one year. The third article examined the clinical, echocardiographic, and laboratory characteristics of patients with chronic heart failure infected with HIV, in the context of pulmonary arterial hypertension. It was found that pulmonary arterial hypertension was present in every second patient with chronic heart failure among those infected with HIV. This group demonstrated more pronounced diastolic dysfunction, elevated plasma NT-proBNP levels, and increased total peripheral vascular resistance.

The "Review Articles" section features a single paper presenting a systematic review of randomized controlled trials examining the relationship between pedaling cadence on a cycle ergometer and blood pressure levels in individuals with arterial hypertension. A total of 199 entries were identified in the databases, but none met the inclusion criteria. This review revealed a gap in the literature regarding the effect of pedaling cadence on elevated blood pressure in individuals with arterial hypertension.

The «Clinical Case» section presents a report by specialists from Morocco. A 58-year-old man with CHD and heart failure developed a rare hemorrhagic complication — a large hematoma in the thigh muscles — during treatment with enoxaparin. The patient received conservative treatment, including blood transfusion and discontinuation of anticoagulants, which led to a favorable outcome. According to the authors, further research is needed to improve the understanding and management of such complications in thromboembolic diseases.

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

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Review of international medical news

Scientists evaluated the effectiveness of oral semaglutide in reducing the risk of cardiovascular complications in patients with type 2 diabetes (T2D). Experts analyzed data from 9,650 patients with T2D and either atherosclerotic cardiovascular disease, chronic kidney disease, or both. The average follow-up period was 47.5 months. The analysis showed that the incidence of major adverse cardiovascular events was 12.0% (3.1 events per 100 person-years) in the oral semaglutide group. In the placebo group, the rate was 13.8% (3.7 events per 100 person-years). The incidence of serious adverse events was 47.9% in the semaglutide group versus 50.3% in the placebo group. Gastrointestinal disorders occurred in 5.0% and 4.4% of patients, respectively. The authors concluded that oral semaglutide significantly reduces the risk of cardiovascular events in patients with T2D and comorbidities without increasing the incidence of serious adverse events.

According to the New England Journal of Medicine

Researchers from China assessed the effectiveness of aggressive ablation in patients with persistent atrial fibrillation (AF). They analyzed data from 3,120 patients who underwent catheter ablation for persistent AF. The study found that 66.2% of patients who received aggressive ablation had no recurrence of AF or atrial tachycardia within one year of follow-up, compared to 59.3% in the standard ablation group.

According to the EP Europace journal

According to a study conducted by U.S. scientists, patients over the age of 80 who take antihypertensive medications and maintain a systolic blood pressure (SBP) below 130 mmHg have a 26% lower risk of death from cardiovascular diseases compared to those with SBP levels of 130–160 mmHg.

The analysis demonstrated that the risk of death was 26% lower in the group with SBP <130 mmHg than in the 130–160 mmHg group. The study involved 1,593 individuals over the age of 80. During the average follow-up period, 46% of deaths were related to cardiovascular diseases.

According to the JACC

Scientists conducted a study suggesting that the high level of cardiovascular health may slow down age-related brain changes and reduce the risk of dementia.

The analysis included 10,802 participants from the Chicago Health and Aging Project (CHAP), with a mean age of 73. Cardiovascular health was assessed using the Life's Simple 7 scale, which includes physical activity, diet, body mass index, smoking status, cholesterol, blood pressure, and glycemic control.

The results showed that participants with high CVH scores (10–14 points) had lower levels of neurofilament light chain (NfL), a biomarker of axonal damage associated with neurodegeneration.

According to the JAMA Network Open

Taiwanese researchers assessed the long-term cardiovascular risks in patients who survived Stevens-Johnson syndrome or toxic epidermal necrolysis.

The analysis revealed that these patients had a 65% higher risk of stroke and a 58% higher risk of coronary heart disease compared to the control group. Furthermore, cardiovascular mortality was increased by 69% for stroke and 55% for coronary heart disease among survivors of Stevens-Johnson syndrome or toxic epidermal necrolysis.

The authors concluded that patients who had experienced these conditions remained at elevated cardiovascular mortality risk for several years after the initial illness.

According to the JAMA

A new robotic device for performing external cardiac massage has been invented in Moscow. The device allows healthcare workers to keep their hands free for other vital procedures, such as administering injections.

The apparatus can function continuously for up to 92 minutes and can be used by emergency medical teams, rescue teams, and hospitals.

The medical device has been patented and has received official registration from Roszdravnadzor, confirming its safety and efficacy.

According to the Press Service of the Mayor and Government of Moscow

Experts analyzed the association between changes in blood pressure (BP) during the first half of pregnancy and the future risk of hypertension.

Data from 175,000 women without a history of hypertension, kidney, liver, or heart disease, or preeclampsia were analyzed. The follow-up period after childbirth was 14 years.

The analysis showed that women with persistently elevated BP levels during the first 20 weeks of pregnancy were most likely to develop hypertension in the following years.

The authors concluded that BP trajectories during the first half of pregnancy can help identify a previously unrecognized risk group for developing hypertension and cardiovascular disease.

According to the Hypertension journal

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Key research findings presented at the 2024 ESC Congress HOTLINE sessions

Kanorsky S.G.[1], Mamedov M.N.[2]

[1] Kuban State Medical University of Ministry of Health Care of Russia, Krasnodar, Russia.
[2] National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia.

AUTHORS

Sergey G. Kanorsky*, MD, PhD, professor, head of the Department of Therapy department of the Federal State Budget Educational Institution of Higher Education "Kuban State Medical University" of Ministry of Health Care of Russia, Krasnodar, Russia. ORCID: 0000-0003-1510-9204

Mekhman N. Mamedov, MD, PhD, Professor, Head of the Secondary Prevention of Noncommunicable Diseases Department, National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia. ORCID: 0000-0001-7131-8049

At the 12 HOT LINE scientific sessions of the 2024 European Society of Cardiology Congress, the results of 34 randomized clinical trials and 4 meta-analyses were presented for the first time. The studies covered various fields of cardiology, including the treatment of arterial hypertension, coronary heart disease, cardiac arrhythmias, and chronic heart failure, as well as interventional and surgical procedures.

Keywords: clinical research, cardiovascular diseases, treatment, diagnostics.

Conflict of interests: none declared.

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HELIOS-B. Transthyretin amyloid cardiomyopathy is a progressive disease with a poor life prognosis. In a double-blind randomized study involving 655 patients, vutrisiran, a small interfering ribonucleic acid that blocks transthyretin synthesis in the liver when administered subcutaneously, was given at

* Corresponding author. Tel. + 7 (918) 355-8281. E-mail: kanorskysg@mail.ru

a dose of 25 mg subcutaneously (n=326) or placebo (n=329) every 12 weeks for a total of three doses. Over a 42-month follow-up period, the incidence of the primary composite endpoint—death from any cause, cardiovascular-related hospitalization, or an urgent visit for heart failure (HF) — was reduced by 28% (p=0.01) in the vutrisiran group among patients also receiving tafamidis and by 33% in the vutrisiran monotherapy group (p=0.02). Additionally, the risk of death from any cause decreased by 35% (p=0.01) compared to placebo. Treatment with vutrisiran was associated with a smaller decline in the 6-minute walk test distance (p<0.001) and a lesser deterioration in the Kansas City Cardiomyopathy Questionnaire quality-of-life score (p<0.001). The incidence of adverse events did not significantly differ between the vutrisiran and placebo groups [1].

ABYSS. The optimal duration of beta-blocker therapy after an uncomplicated myocardial infarction (MI) remains uncertain. In a multicenter, open-label randomized trial involving 3,698 patients who had suffered an MI on average 2.9 years before enrollment, with a left ventricular ejection fraction (LVEF) of at least 40% and no cardiovascular events in the previous six months, beta-blocker therapy was either discontinued (n=1,846) or continued (n=1,852). The primary composite endpoint — death, non-fatal MI, non-fatal stroke, or cardiovascular-related hospitalization—occurred in 23.8% of patients in the discontinuation group versus 21.1% in the continuation group (p=0.44 for non-inferiority) over a median follow-up of 3.0 years Discontinuing beta-blocker therapy did not improve patients' quality of life. Thus, stopping beta-blockers was not inferior to continuing their use in terms of secondary prevention of cardiovascular diseases (CVD) after MI, while quality of life did not improve in patients who discontinued these medications [2].

STOP-or-NOT. The optimal preoperative management strategy for patients taking angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) remains uncertain, leading to conflicting recommendations. Patients who had been taking ACE inhibitors (46%) or ARBs (54%) for at least three months and were scheduled for major non-cardiac surgery were randomized to either continue their medication up to the day of surgery (n=1,107) or discontinue it 48 hours before surgery (n=1,115). The primary composite endpoint — death from any cause and major postoperative complications within 28 days after surgery — occurred at a similar rate in both the continuation and discontinuation groups (p=0.85). However, intraoperative hypotension episodes were 31% more frequent in the continuation group, while rates of acute kidney injury, postoperative organ failure, hospital stay duration, and intensive care unit length of stay within 28 days after surgery did not significantly differ. Thus, in patients undergoing major non-cardiac surgeries, continuing ACE inhibitors or ARBs preoperatively was not associated with a higher rate of postoperative complications compared to discontinuing these medications before surgery [3].

BedMed and BedMed-Frail. Some studies suggested that taking antihypertensive medications at night could reduce the risk of adverse cardiovascular outcomes, but subsequent research failed to confirm this. In the open-label prospective BedMed trial, patients with hypertension (mean age 67 years) were randomized to receive medications from one of five main classes, most often as monotherapy, once daily at bedtime (n=1,677) or in the morning (n=1,680). Medication adherence was 88% for evening dosing and 97% for morning dosing over six months. After a mean follow-up of 4.6 years, the primary composite endpoint—death from any cause or hospitalization/emergency visit for stroke, acute coronary syndrome (ACS), or chronic heart failure (CHF) — occurred at similar rates in both groups (p=0.70). In the BedMed-Frail study with a similar design, elderly hypertensive patients (mean age 88 years) received medications from the same five classes, again mostly as monotherapy, once daily at bedtime (n=394) or in the morning (n=382). The sum of events for the primary endpoint was again recorded at comparable frequencies in both groups (p=0.28). According to the authors, patients taking once-daily antihypertensive medications can take them at any convenient time based on their preferences and habits. However, adherence is generally better with morning dosing.

Meta-analysis of nighttime antihypertensive medication use. A patient-level meta-analysis included data from the BedMed (n=3,357), BedMed-Frail (n=776), Hygia (n=19,168), MAPEC (n=2,201), and TIME (n=21,104) trials. The primary endpoint (all-cause mortality, MI, stroke, or worsening HF) occurred 29% less frequently in the nighttime dosing group compared to the morning dosing group, but

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this difference was not statistically significant. There were also no significant differences in safety outcomes (emergency hospitalization, bone fractures, glaucoma, cognitive impairment) between the two groups. According to the meta-analysis authors, prescribing antihypertensive therapy at night does not reduce the risk of major cardiovascular events, mortality, or affect treatment safety compared to morning dosing. Therefore, once-daily antihypertensive medications can be taken at a time that best suits the patient's preferences and circumstances. The available evidence does not support the chronotherapy concept in AH treatment.

GMRx2. Fixed-dose combinations of three or more low-dose antihypertensive agents in a single tablet show promise for initial or early hypertension treatment. In this randomized, double-blind, placebo-controlled trial, adults with hypertension (home systolic blood pressure [SBP] 130–154 mmHg after a two-week placebo run-in) were assigned in a 2:2:1 ratio to receive:

- ¼-dose combination: Telmisartan 10 mg / Amlodipine 1.25 mg / Indapamide 0.625 mg
- ½-dose combination: Telmisartan 20 mg / Amlodipine 2.5 mg / Indapamide 1.25 mg
- Placebo

The primary efficacy endpoint was the change in home SBP from randomization to week 4, while the primary safety endpoint was treatment discontinuation due to adverse events. At week 4, the placebo-adjusted mean home SBP reductions were –7.3 mmHg (¼-dose) and –8.2 mmHg (½-dose). Office SBP reductions were –8.0 mmHg (¼-dose) and –9.5 mmHg (½-dose). Blood pressure control (<140/90 mmHg) was achieved by 37% (placebo), 65% (¼-dose), and 70% (½-dose) of patients (p<0.001 vs. placebo). Treatment discontinuation due to adverse events occurred in 1.6% (placebo), 0% (¼-dose), and 5.1% (½-dose). Electrolyte disturbances were comparable across groups. This trial adds to growing real-world evidence supporting low-dose triple fixed-dose combination therapy as an effective first-line AH treatment strategy [4].

QUADRO. In a double-blind controlled study, 183 patients with an initial average office SBP of 150.3 mmHg and diastolic blood pressure (DBP) of 90.0 mmHg initially received triple fixed-dose combinations of perindopril, indapamide, and amlodipine at doses of 10/2.5/5 mg or 10/2.5/10 mg daily for 8 weeks with good tolerability. If uncontrolled BP persisted after 8 weeks (office SBP ⩾ 140 mmHg and 24-hour ambulatory SBP ⩾ 130 mmHg), patients were randomized 1:1 to either continue the same triple therapy or receive a single tablet containing perindopril, indapamide, amlodipine, and bisoprolol (10/2.5/5/5 mg or 10/2.5/10/5 mg daily) for 8 weeks. After 8 weeks, the mean office SBP in a seated position decreased by 20.67 mmHg in the quadruple therapy group and by 11.32 mmHg in the triple therapy group (adjusted difference –8.04 mmHg; p<0.0001). The quadruple therapy group also had lower mean 24-hour ambulatory SBP (–7.53 mmHg; p<0.0001) and mean office DBP in a seated position (-6.14 mmHg; p<0.0001). Office BP control (<140/90 mmHg) was achieved in 66.3% vs. 42.7% (p=0.001), ambulatory BP normalization (mean 24-hour BP <130/80 mmHg) in 51.2% vs. 20.7% (p<0.0001), and home BP normalization (<135/85 mmHg) in 60.7% vs. 25.4% of patients (p<0.0001) in the quadruple and triple therapy groups, respectively. There were no significant differences in the frequency of adverse effects between the two groups, and no serious adverse events were reported.

VERONICA-Nigeria. The study included 300 Nigerian adults with uncontrolled hypertension (mean home BP 151/97 mmHg and office BP 156/97 mmHg), who were either untreated initially or receiving a single antihypertensive drug. After randomization, patients were treated with a triple fixed-dose combination of telmisartan, amlodipine, and indapamide at doses of 10/1.25/0.625 mg, 20/2.5/1.25 mg, and 40/5/2.5 mg with accelerated titration or with standard therapy, which started with amlodipine (5 mg/day), adding losartan (50–100 mg/day), and then hydrochlorothiazide (25 mg/day). By the 6th month of treatment, the mean home SBP decreased by 31 mmHg in the fixed-dose combination group and by 26 mmHg in the standard therapy group (adjusted difference –5.8 mmHg; p<0.001). The clinic BP control rate (<140/90 mmHg) was 82% vs. 72%, and home BP control (<130/80 mmHg) was 62% vs. 28% in the fixed-dose combination group compared to the standard therapy group. None of the participants discontinued treatment due to adverse effects [5].

RESHAPE-HF2. To assess the potential benefits of interventional treatment, 505 patients with HF and moderate or severe functional mitral regurgitation were randomized into groups receiving transcatheter mitral valve reconstruction alongside guide-

line-directed medical therapy (device group; n=250) or medical therapy alone (control group; n=255). The combined rate of first/recurrent HF hospitalization or cardiovascular death over 24 months was 36% lower (p=0.002), the rate of first or recurrent HF hospitalization over 24 months was 41% lower (p=0.002), and the Kansas City Cardiomyopathy Questionnaire (KCCQ) quality of life score significantly improved (p<0.001) in the device group compared to the control group [6].

MATTERHORN. Guidelines for the treatment of patients with HF and secondary mitral regurgitation mention both transcatheter edge-to-edge repair and surgical mitral valve procedures, but randomized trial data comparing these methods have been lacking. A total of 210 patients receiving guideline-directed medical therapy were randomized to either transcatheter (intervention group) or surgical mitral valve repair or replacement (surgery group). At 1-year follow-up, the primary efficacy endpoint (composite of death, HF hospitalization, repeat mitral valve intervention, left ventricular assist device (LVAD) implantation, or stroke) occurred in 16.7% versus 22.5% of patients (p<0.001 for non-inferiority), while the composite rate of major adverse events within 30 days after the procedure was 14.9% in the intervention group versus 54.8% in the surgery group (p<0.001 for non-inferiority). Among patients with HF and secondary mitral regurgitation, transcatheter edge-to-edge repair was non-inferior to surgical mitral valve procedures regarding adverse clinical outcomes at 1 year [7].

Tri.Fr. Patients with severe symptomatic tricuspid regurgitation were randomized into a group receiving transcatheter tricuspid valve repair plus optimal medical therapy (n=152) or optimal medical therapy alone (n=148). After 1 year, improvement in NYHA functional class and overall health assessment was observed in 74.1% of patients in the interventional group versus 40.6% in the conservative treatment group. The mean overall score on the Kansas City Cardiomyopathy Questionnaire was also better in the interventional group (p<0.001). Severe or massive tricuspid regurgitation was present in 6.8% of patients in the interventional group versus 53.5% in the mediction therapy-only group (p<0.001) [8].

ASSURE DES. Patients who had received a drug-eluting stent more than a year prior to elective non-cardiac surgery were randomized to either continue aspirin monotherapy (n=462) or discontinue all antiplatelet therapy five days before surgery (n=464). Antiplatelet therapy was recommended to be resumed no later than 48 hours post-surgery if no contraindications were present. The primary endpoint—composite of all-cause death, MI, stent thrombosis, or stroke occurring between five days before and thirty days after non-cardiac surgery — was observed in 0.6% of patients in the aspirin monotherapy group and 0.9% in the antiplatelet therapy interruption group (p>0.99). No cases of stent thrombosis were recorded in either group. The rate of major bleeding did not differ significantly between groups (6.5% vs. 5.2%; p=0.39), while minor bleeding was significantly more frequent in the aspirin group (14.9% vs. 10.1%; p=0.027) [9].

SWEDEGRAFT. The "no-touch" vein harvesting technique, which leaves a small amount of surrounding tissue intact, is intended to prevent venous spasm and eliminate the need for vessel dilation during coronary artery bypass grafting (CABG). A total of 902 patients were randomized into groups undergoing either no-touch or conventional vein harvesting. The primary endpoint — graft failure (defined as occlusion or stenosis >50% based on coronary computed tomography angiography, percutaneous intervention on the venous graft, or death within two years of CABG) — was observed at 3.5 years in 19.8% of patients in the no-touch group versus 24.0% in the conventional harvesting group (p=0.15). Additionally, no significant differences were found between the groups in the composite endpoint of death, MI, or repeat revascularization (12.6% vs. 9.9%; p=0.195). However, at three months, wound complications were significantly more frequent in patients who underwent no-touch harvesting (24.7% vs. 13.8%). Two years post-surgery, leg wound-related symptoms persisted in 49.6% of patients in the no-touch group compared to 25.2% in the conventional harvesting group. Consequently, the no-touch vein harvesting technique does not surpass the conventional method in preventing venous graft occlusion or improving mid-term clinical outcomes in patients undergoing elective CABG and is associated with a higher risk of early wound complications and residual symptoms.

TIGHT K. To determine the optimal potassium level to maintain for the prevention of postoperative atrial fibrillation (AF), 1690 patients who underwent cardiac surgery and had no prior history of heart arrhythmias were randomized to receive potassium supplemen-

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tation if their serum potassium dropped below 4.5 mmol/L (strict correction group) or 3.6 mmol/L (soft correction group). The primary endpoint, clinically diagnosed and electrocardiographically confirmed new-onset AF within 120 hours post-CABG or prior to hospital discharge, occurred in 26.2% of patients in the strict correction group and 27.8% in the soft correction group. Potassium supplementation when serum potassium was below 3.6 mmol/L did not show inferior results compared to the more common practice of maintaining potassium levels above or equal to 4.5 mmol/L for preventing new-onset AF after cardiac surgery. A lower threshold for potassium supplementation was not associated with an increased risk of arrhythmias or adverse clinical outcomes [10].

NOTION-3. The benefit of percutaneous coronary intervention (PCI) in patients with stable coronary heart disease (CHD) and severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI) remains unclear. Patients with symptomatic severe aortic stenosis and at least one coronary artery stenosis with a fractional flow reserve ⩽0.80 or ⩾90% stenosis were randomized to PCI (n=227) or conservative treatment (n=228), with all undergoing TAVI. With a median follow-up time of 2 years, the primary endpoint (all-cause death, MI, or urgent revascularization) was observed in 26% of the PCI group and 36% of the conservative treatment group (p=0.04), while bleeding complications were observed in 28% and 20% of patients, respectively. These results suggest a prognostic benefit of PCI in patients with stable CHD undergoing TAVI [11].

PAUSE TAVI. One-third of patients undergoing TAVI require oral anticoagulation therapy due to comorbid conditions, and discontinuing anticoagulation during the procedure may reduce the risk of bleeding, whereas continuing it may reduce the risk of thromboembolism. In an open-label, non-inferiority trial, patients scheduled for TAVI were randomized to continue (n=431) or discontinue (n=427) oral anticoagulation during the peri-procedural period. The primary endpoint, a composite of cardiovascular death, any stroke, MI, major vascular complications, or major bleeding within 30 days of the procedure, occurred in 16.5% of patients in the continuation group and 14.8% in the discontinuation group (p=0.18 for non-inferiority). Thromboembolic complications occurred in 8.8% versus 8.2%, and bleeding complications in 31.1% versus 21.3%, respectively. Peri-procedural continuation of oral anticoagulation was not inferior to its discontinuation in terms of ischemic and hemorrhagic complications within 30 days after TAVI [12].

RHEIA. In a first-ever trial, only female patients (n=443) with severe aortic stenosis (either high or low gradient) were randomized 1:1 to TAVI using a third-generation balloon system (Edwards Sapien, Sapien Ultra) with femoral artery access or surgical aortic valve replacement (Edwards Magna Ease, Intuityn Livanova Perceval). Over a 1-year period, the primary endpoint (a composite of all-cause death, stroke, rehospitalization due to valve- or procedure-related symptoms, or worsening heart failure) occurred in 8.9% of patients in the TAVI group versus 15.6% in the surgery group (p=0.03). The main reasons for these differences were fewer rehospitalizations due to valve- or procedure-related symptoms or worsening HF (4.8% vs. 11.4%; p=0.02), fewer cases of atrial fibrillation (3.3% vs. 28.8%; p<0.001), and shorter hospital stays (4 days vs. 9). However, the rate of pacemaker implantation was higher in the TAVI group (8.8%) compared to the surgical group (2.9%; p=0.01). The valves implanted via TAVI had higher mean pressure gradients (p<0.001) and smaller effective orifice areas (p<0.001) at 1 month and 1 year, and a higher frequency of mild paravascular aortic regurgitation (15.5% vs. 2.4%; p<0.001) compared to those replaced surgically. This is the first study to compare TAVI with surgical aortic valve replacement specifically in women, laying the foundation for future specialized studies in women in cardiovascular surgery.

STEEER-AF. This study was conducted in 70 centers across six European countries as part of a targeted educational program aimed at improving adherence to Class I and III guidelines for the treatment of AF, with a particular focus on stroke prevention, sinus rhythm control, and the integration of medical care. The participating centers were randomized to receive the educational program or to continue the usual practice. A total of 1732 patients were included, and their treatments were surveyed. Initially, adherence to all Class I or III recommendations was 61.0% for stroke prevention and 21.0% for sinus rhythm control, both of which were much lower than expected. After the educational intervention, with a median follow-up of 7.7 months, there was a significant impact on rhythm control but no effect on stroke prevention. The adherence rate for rhythm control increased from 20.5% to 22.9% in the control group and from 21.4%

to 33.9% in the experimental group, showing a much larger effect of the educational program. Adherence to stroke prevention guidelines increased from 58.6% to 60.9% in the control group and from 63.4% to 67.5% in the experimental group, indicating no significant differences between the groups.

OCEANIC AF. Stroke prevention in patients with AF using direct oral anticoagulants (DOACs) is associated with an increased risk of bleeding, which limits their use. Asundexian, an activated factor XI inhibitor, is an oral anticoagulant that may prevent strokes with a lower risk of bleeding. In a phase 3 study, patients with AF (mean CHA2DS2-VASc score 4.3 ± 1.3) were randomized to receive asundexian at a dose of 50 mg once daily (n=7415) or standard treatment with apixaban (n=7395). The primary objectives were to determine if asundexian was at least non-inferior to apixaban in preventing stroke or systemic embolism and whether asundexian was superior to apixaban in terms of major bleeding. The study was prematurely terminated on the recommendation of an independent data monitoring committee. Stroke or systemic embolism occurred in 1.3% of patients assigned to asundexian and 0.4% in the apixaban group (relative risk (RR) 3.79), while major bleeding occurred in 0.2% and 0.7%, respectively (RR 0.32). The hypothesis that asundexian would have comparable efficacy and superior safety compared to apixaban was not confirmed [13].

EPIC-CAD. Patients with AF (mean CHA2DS2-VASc score 4.3) and stable CHD were randomized to receive either edoxaban monotherapy (n=524) or dual antithrombotic therapy with edoxaban and an antiplatelet agent (n=516). After 12 months, the primary endpoint (all-cause death, MI, stroke, systemic embolism, unplanned urgent revascularization, and major or clinically significant minor bleeding) occurred in 6.8% of the edoxaban monotherapy group and 16.2% in the dual therapy group (p<0.001). The cumulative rate of major ischemic events was similar between the groups. Major or clinically significant minor bleeding occurred in 4.7% of patients in the edoxaban monotherapy group and 14.2% in the dual therapy group. The results support current clinical guidelines recommending anticoagulant monotherapy for patients with AF and stable CHD [14].

FINEARTS-HF. In a double-blind trial, patients with HF and LVEF ⩾40% were randomized to receive finerenone at maximum doses of 20 mg or 40 mg once daily (n=3003) or placebo (n=2998) in addition to standard therapy. Over a median follow-up of 32 months, the primary endpoint (unplanned hospitalization or urgent visit due to HF and cardiovascular death) occurred 16% less frequently in the finerenone group compared to the placebo group (p=0.007), with 18% fewer cases of HF worsening (p=0.006) and 7% fewer cardiovascular deaths. The finerenone group had a higher risk of hyperkalemia but a lower risk of hypokalemia [15].

MRAs in Heart Failure. A pre-specified meta-analysis at the individual patient level included data from the RALES (spironolactone) and EMPHASIS-HF (eplerenone) trials, which involved patients with HF and reduced LVEF, as well as from the TOPCAT (spironolactone) and FINEARTS-HF (finerenone) trials, which included patients with HF and mildly reduced or preserved LVEF. A total of 13,846 patients were included across these four studies. Mineralocorticoid receptor antagonists (MRAs) reduced the risk of cardiovascular death or hospitalization due to heart failure by 23%. The risk of the composite event was reduced by 34% in patients with HF and reduced LVEF and by 13% in those with HF and mildly reduced or preserved LVEF. Specifically, hospitalization for HF was reduced by 37% and 18%, cardiovascular death by 28% and 8%, and all-cause mortality by 27% and 6% in patients with HF with reduced and mildly reduced or preserved LVEF, respectively. Treatment with MRAs increased the risk of hyperkalemia by 2.27 times and reduced the risk of hypokalemia (<3.5 mmol/L) by 49% [16].

FINE-HEART. Cardiovascular-renal-metabolic syndrome is a new category that links CVD, chronic kidney disease (CKD), and diabetes mellitus (DM). The nonsteroidal mineralocorticoid receptor antagonist finerenone was studied in three randomized prospective clinical trials in patients with cardiovascular-renal-metabolic syndrome: FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF, involving a total of 18,991 patients. Over a median follow-up of 2.9 years, the primary endpoint of the meta-analysis—cardiovascular death—occurred in 4.4% of patients receiving finerenone and in 5.0% of those receiving placebo (p=0.076). All-cause mortality occurred in 11.0% of the finerenone group and in 12.0% of the placebo group (p=0.027). Finerenone also significantly reduced the risk of hospitalization for heart failure by 17% (p<0.001) and the composite kidney outcome by

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20% (p<0.001). Although this pooled analysis did not demonstrate a significant reduction in cardiovascular mortality, treatment with finerenone was associated with a significantly lower risk of all-cause death, adverse cardiovascular, and renal outcomes [17].

SENIOR-RITA. In a prospective study, 1,518 patients with non-ST elevation myocardial infarction (NSTEMI) aged ≥75 years (mean age 82 years) were randomized 1:1 to receive an invasive strategy — coronary angiography and revascularization plus the best available medical therapy (n=753) — or a conservative strategy — best available medical therapy alone (n=765). Over a median follow-up of 4.1 years, the primary endpoint (the composite of cardiovascular death or non-fatal MI) was observed in 25.6% of patients in the invasive strategy group and 26.3% in the conservative strategy group (p=0.53). Cardiovascular death occurred in 15.8% of patients in the invasive strategy group and 14.2% in the conservative strategy group, while non-fatal MI occurred in 11.7% and 15.0% of patients, respectively. Complications from the invasive procedure occurred in less than 1% of patients. In elderly patients, an invasive strategy for treating NSTEMI did not significantly reduce the total risk of cardiovascular death or non-fatal MI compared to a conservative strategy [18].

EARTH-STEMI. A meta-analysis using databases such as PubMed, Embase, and Cochrane was conducted to analyze individual patient data from 7 randomized clinical trials involving patients aged ≥75 years with STEMI. These studies compared complete revascularization (n=816) with revascularization of only the infarction-related artery (n=917). Complete revascularization, compared with selective revascularization, significantly reduced the risk of the primary endpoint (death, MI, or revascularization due to ischemia) by 22% over a follow-up period of up to 4 years, but not over the maximum follow-up period (–17%). Additionally, complete revascularization significantly (by 24%) reduced the risk of cardiovascular death or MI during the maximum follow-up period. There was no difference in long-term mortality between the groups receiving complete and partial revascularization [19].

SCOFF. Currently, the recommended fasting before a cardiology procedure with conscious sedation involves 6 hours of fasting from solid food and 2 hours from liquids, which is not based on research evidence. Patients scheduled for coronary angiography, PCI, or implantation of electronic devices were randomized 1:1 into groups with the recommended fasting (n=358) or without fasting (n=358). The primary endpoint (the composite of aspiration pneumonia, hypotension, hyperglycemia, and hypoglycemia) occurred in 19.1% of patients in the fasting group and in 12.0% in the non-fasting group. The non-fasting group had better patient satisfaction scores. There were no significant differences in the need for non-invasive and invasive mechanical ventilation, ICU admissions, rehospitalization, pneumonia, and 30-day mortality. These results support the cancellation of fasting requirements for patients undergoing cardiology procedures (such as catheterization) that require conscious sedation [20].

STROKESTOP II. In a randomized mass screening program for AF among 75–76-year-old residents of Stockholm, Sweden, the goal was to determine whether an invitation for screening would reduce the risk of thromboembolic events compared to a control group that was not invited for screening. Of the 6,843 invited individuals, 49% accepted the invitation. For participants with no known AF, the levels of N-terminal pro-B-type natriuretic peptide were analyzed to stratify them into high-risk (≥125 ng/L) and low-risk (<125 ng/L) groups. The low-risk group (40%) underwent a single episode of screening with a one-channel electrocardiogram (EKG), while the high-risk group (60%) underwent more intensive home screening (4 times a day for 2 weeks) with EKG registration using a portable one-channel device. AF was newly diagnosed in 2.4% of all participants. With a median follow-up time of 5 years, there were no differences in the risk of stroke or systemic embolism between the intervention group (including those who attended the screening and those who were invited but did not attend) and the control group. The risk of stroke or systemic embolism was 41% lower in the low-risk group compared to the control group. In the high-risk group, the likelihood of developing new AF over 5 years was more than twice as high, and the risk of ischemic stroke or systemic embolism was 57% higher compared to the low-risk group.

GUARD-AF. Using the Zio XT monitor, which is adhesive and placed on the skin, continuous EKG monitoring was conducted for 14 days to answer whether detecting AF in elderly individuals with previously undiagnosed arrhythmia would reduce stroke incidence compared to usual treatment. A total of 11,905 partic-

ipants were randomized into screening or usual care groups. There was a 52% increase in new AF diagnoses, an increase in the use of oral anticoagulants without a rise in hospitalization for bleeding, but no significant reduction in hospitalizations for any stroke compared to usual care over a maximum follow-up of 2.5 years. The researchers cautioned that their results should not be considered final due to early termination of the study because of the COVID-19 pandemic and fewer clinical events than expected.

MIRACLE-AF. This study involved 1,039 patients aged ⩾65 years with AF from rural clinics in China. The clinics were randomized to receive either telemedicine-integrated care (intervention group) or extended usual care (control group). Treatment in both groups was provided by doctors who underwent additional training in comprehensive care based on the principles of Atrial Fibrillation Better Care (ABC). However, only the intervention group had access to the telemedicine platform. After 1 year, 33% of patients in the intervention group and 8.8% in the control group met all three ABC criteria, and after 3 years, 42% and 10%, respectively. Over 3 years, the combined primary endpoint (cardiovascular death, any stroke, hospitalization due to worsening heart failure or acute coronary syndrome, and emergency visits due to AF) was 36% lower in the intervention group compared to the control group. Specifically, the risk of cardiovascular death was 50% lower in the intervention group, and the risks of any stroke and hospitalization due to worsening heart failure or acute coronary syndrome were 36% and 31% lower, respectively, compared to the control group. Telemedicine for AF care in rural settings was found to be an effective and feasible strategy that could be scaled in areas with limited access to healthcare.

SHAM-PVI. There have been concerns that pulmonary vein isolation for AF could have a strong placebo effect, but no double-blind randomized clinical trials have been conducted on this issue. To determine whether pulmonary vein isolation is more effective than a sham procedure, patients with symptomatic paroxysmal or persistent AF were randomized to either cryoablation (n=64) or sham procedure using diaphragmatic nerve stimulation (n=62). AF burden was assessed at 6 months using an implantable loop recorder. The absolute mean reduction in AF burden from baseline to 6 months was 60.31% in the ablation group and 35.0% in the sham procedure group ($p<0.001$). In the ablation group, patients showed a significant advantage in the overall impact of AF on quality of life and general health according to the Short Form scale [21].

SUPPRESS-AF. This study involved 1,347 patients with persistent AF undergoing their first catheter ablation. Among them, 343 patients (25.5%) were found to have low-voltage areas in the left atrium ⩾5 cm^2 and were randomized 1:1 to receive either ablation of low-voltage areas in addition to the standard procedure (n=170) or standard pulmonary vein isolation (n=171, control). Recurrences of arrhythmia were monitored using 24-hour continuous EKG at 6 and 12 months after ablation, along with twice-daily home EKG recording for 1 year. The primary endpoint, recurrence of AF or atrial tachycardia within a year without antiarrhythmic drug prophylaxis, was found in 61% of the patients in the additional ablation group and 50% in the standard treatment group, as well as 63% versus 55%, respectively, when antiarrhythmic drugs were used. However, in the subgroup with left atrial dilation (diameter ⩾45 mm), the additional ablation of low-voltage areas reduced the recurrence of AF by 40%. The rate of serious complications, such as stroke, was very low and comparable between groups (1.7% versus 1.8%, respectively). The study suggested that ablation targeting low-voltage areas in the left atrium in addition to standard pulmonary vein isolation should be considered only in cases of significant left atrial dilation.

CRABL-HF. In the first randomized trial comparing radiofrequency catheter ablation (n=55) and cryoballoon catheter ablation (n=55) in patients with heart failure with reduced ejection fraction (HFrEF) and AF, continuous outpatient EKG monitoring was provided for patients with implanted electronic devices to record AF episodes. For patients without implanted devices, ambulatory ECG was recorded twice daily for 1 year following a 90-day blinded period after the procedure. After 1 year, no significant differences were found in the frequency of episodes of atrial tachyarrhythmias lasting 30 seconds or longer, observed in 21.8% of patients in the radiofrequency group and 22.2% in the cryoballoon group. The cryoballoon procedure was significantly faster (median time of 101 vs. 165 minutes) and required less infusion volume during the ablation, reducing the risk of worsening heart failure. No significant differences were found in the overall safety profile of the two ablation methods

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(1 case of arteriovenous fistula in the radiofrequency group and 1 case of retroperitoneal hematoma in the cryoballoon group). There were no reports of worsening heart failure, symptomatic cerebral infarcts, transient ischemic attacks, pulmonary vein stenosis, atrioesophageal fistulas, or procedure-related deaths. Over 1 year, there were no differences in the total complication rate, including death from any cause or hospitalization for HF between the two groups, nor in quality of life as measured by the AFEQT questionnaire. The study concluded that the simpler cryoballoon ablation procedure is justified for treating AF in most patients with HFrEF.

OCCUPI. Patients with anatomically complex atherosclerotic coronary artery lesions requiring PCI with drug-eluting stents were randomized 1:1 to receive control with optical coherence tomography (n=803) or standard angiographic control (n=801). Over a 1-year follow-up, the combined primary endpoint (cardiac death, MI, stent thrombosis, and revascularization of the target artery) occurred 38% less frequently in the optical coherence tomography control group, including a 64% reduction in the risk of spontaneous MI or revascularization of the target artery.

INFINITY-SWEDEHEART. The bioadaptor is a new implant designed to restore hemodynamic modulation of the artery, providing cyclic pulsation, vasomotion, and adaptive remodeling, unlocking and supporting the artery dynamically. Patients with ACS (76.6% of cases) or stable CHD, with indications for PCI and three lesions suitable for implantation of one device at each lesion site, were randomized to receive the DynamX bioadaptor (n=1201) or the modern zotarolimus-eluting stent Resolute Onyx and Onyx Trustar (n=1198). After 12 months of follow-up, the primary endpoint — cardiovascular death, MI in the target artery zone, or revascularization of the target artery due to ischemia — occurred in 2.4% vs. 2.8% of patients in the bioadaptor and standard stent groups ($p<0.0001$ for non-inferiority), with device thrombosis (safety endpoint) occurring in 0.7% vs. 0.5%, with no significant difference between the groups [22].

REC-CAGEFREE I. Patients with uncomplicated CHD and indications for PCI were randomized 1:1 to balloon angioplasty with paclitaxel-coated balloons with the option for emergency stenting due to unsatisfactory results (n=1133) or implantation of second-generation sirolimus-eluting stents (n=1139). Over 24 months of follow-up, the events of the combined primary endpoint (cardiovascular death, MI in the target artery zone, or clinically and physiologically justified revascularization of the target artery) occurred in 6.4% of patients in the angioplasty group and 3.4% in the stent implantation group, meaning the non-inferiority criterion for angioplasty was not met. Based on these results, in patients with uncomplicated CHD, modern stent implantation should remain the preferred treatment method [23].

PROTEUS. The use of artificial intelligence (AI) in cardiovascular imaging has the potential to improve clinical decision-making in the treatment of cardiovascular diseases. However, no prior prospective randomized controlled trials have evaluated its impact on cardiovascular outcomes. This study assessed whether AI-based decision-making is at least as effective as standard decision-making in selecting patients for invasive coronary angiography after stress echocardiography. In the randomized trial, 2341 patients who underwent stress echocardiography were assigned to receive clinical decision-making using AI (intervention) or standard methods (control). The primary endpoint was appropriate referral for coronary angiography, with true positive results defined as severe ischemic disease requiring revascularization in patients referred for invasive angiography, and false negatives as acute coronary events within 6 months. Decision-making using AI did not show superiority compared to the clinical approach in selecting patients for coronary angiography. Among the referrals for angiography, 34 out of 49 were correct in the intervention group, and 27 out of 36 were correct in the control group. Of patients who should have been referred for angiography and subsequently experienced ischemic events, 19 were in the AI group and 22 in the control group, with no statistically significant difference. The predictive accuracy of the logistic model (AUROC) for the intervention did not meet the "non-inferiority" criterion in the intervention group compared to the control group. Since AI-based decision-making in stress echocardiography did not meet the non-inferiority endpoint, it cannot yet be considered as a primary approach for clinical decision-making [24].

RAPIDxAI. In a randomized trial, the impact of AI-based decision support (intervention group) on cardiovascular disease outcomes was evaluated compared to usual care (control group) over 12 months in 14,131 patients with suspected cardiac pain and myocardial

injury in the emergency department. After 6 months, the use of AI-based decision support in the emergency department did not significantly improve treatment to enhance cardiovascular outcomes. There were no significant differences in the primary endpoint events (cardiovascular death, MI, and unplanned re-hospitalization for cardiovascular disease) between the intervention group (26.0%) and the control group (26.4%) (p=0.606). In patients discharged from the emergency department with the AI-based decision support system, the likelihood of death or MI within 30 days was slightly lower than for those receiving usual care (0.86% vs. 1.1%; p<0.001 for non-inferiority). The study did not identify increased risks with the implementation of AI-based clinical decision support, confirming its safety.

WESTCOR-POC. A total of 1494 consecutive patients with symptoms suggesting ACS who were admitted to the emergency department were randomized to either rapid (8-minute) cardiac troponin testing or standard testing in a central laboratory. In each group, the results of 0-hour and 1-hour troponin tests were compared. The median length of stay in the emergency department was 174 minutes in the rapid testing group compared to 180 minutes in the standard testing group. However, in patients who were seen earlier (within 60 minutes), rapid testing reduced the length of stay by 15 minutes (147 vs. 162 minutes). In patients with non-ST elevation ACS, rapid testing reduced emergency department stay by 43 minutes compared to standard testing (average 137 vs. 180 minutes), and high-risk patients were transferred to the cardiology department more quickly. The sum of adverse outcomes such as death, MI, and urgent revascularization within 30 days was similar in both rapid and standard testing groups (11.4% vs. 9.4%, respectively).

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References

1. Fontana M, Berk JL., Gillmore JD, et al.; HELIOS-B Trial Investigators. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. N Engl J Med. 2025;392:33-44. DOI: 10.1056/NEJMoa2409134
2. Silvain J, Cayla G, Ferrari E, et al.; ABYSS Investigators of the ACTION Study Group. Beta-Blocker Interruption or Continuation after Myocardial Infarction. N Engl J Med. 2024;391(14):1277-1286. DOI: 10.1056/NEJMoa2404204
3. Legrand M, Falcone J, Cholley B, et al.; Stop-or-Not Trial Group. Continuation vs Discontinuation of Renin-Angiotensin System Inhibitors Before Major Noncardiac Surgery: The Stop-or-Not Randomized Clinical Trial. JAMA. 2024;332(12):970-978. DOI: 10.1001/jama.2024.17123
4. Rodgers A, Salam A, Schutte AE, et al. Efficacy and Safety of a Novel Low-Dose Triple Single-Pill Combination Compared With Placebo for Initial Treatment of Hypertension. J Am Coll Cardiol. 2024;84(24):2393-2403. DOI: 10.1016/j.jacc.2024.08.025
5. Ojji DB., Salam A, Sani MU, et al. Low-Dose Triple-Pill vs Standard-Care Protocols for Hypertension Treatment in Nigeria: A Randomized Clinical Trial. JAMA. 2024;332(13):1070-1079. DOI: 10.1001/jama.2024.18080
6. Anker SD., Friede T, von Bardeleben RS, et al.; RESHAPE-HF2 Investigators. Transcatheter Valve Repair in Heart Failure with Moderate to Severe Mitral Regurgitation. N Engl J Med. 2024;391(19):1799-1809. DOI: 10.1056/NEJMoa2314328
7. Baldus S, Doenst T, Pfister R, et al.; MATTERHORN Investigators. Transcatheter Repair versus Mitral-Valve Surgery for Secondary Mitral Regurgitation. N Engl J Med. 2024;391(19):1787-1798. DOI: 10.1056/NEJMoa2408739
8. Donal E, Dreyfus J, Leurent G, et al.; Tri-Fr Investigators. Transcatheter Edge-to-Edge Repair for Severe Isolated Tricuspid Regurgitation: The Tri.Fr Randomized Clinical Trial. JAMA. 2024 Nov 27. DOI: 10.1001/jama.2024.21189.
9. Kang DY, Lee SH, Lee SW, et al.; ASSURE DES Investigators. Aspirin Monotherapy vs No Antiplatelet Therapy in Stable Patients With Coronary Stents Undergoing Low-to-Intermediate Risk Noncardiac Surgery. J Am Coll Cardiol. 2024;84(24):2380-2389. DOI: 10.1016/j.jacc.2024.08.024
10. O'Brien B, Campbell NG, Allen E, et al.; TIGHT K investigators. Potassium Supplementation and Prevention of Atrial Fibrillation After Cardiac Surgery: The TIGHT K Randomized Clinical Trial. JAMA. 2024;332(12):979-988. DOI: 10.1001/jama.2024.17888
11. Lønborg J, Jabbari R, Sabbah M, et al.; NOTION-3 Study Group. PCI in Patients Undergoing Transcatheter Aortic-Valve Implantation. N Engl J Med. 2024;391(23):2189-2200. DOI: 10.1056/NEJMoa2401513
12. van Ginkel DJ, Bor WL, Aarts HM, et al; POPular PAUSE TAVI Investigators. Continuation versus Interruption of Oral Anticoagulation during TAVI. N Engl J Med. 2024 Aug 31. DOI: 10.1056/NEJMoa2407794.
13. Piccini JP, Patel MR., Steffel J, et al.; OCEANIC-AF Steering Committee and Investigators. Asundexian versus Apixaban in

Patients with Atrial Fibrillation. N Engl J Med. 2024 Sep 1. DOI: 10.1056/NEJMoa2407105.

14. Cho MS, Kang DY, Ahn JM, et al.; EPIC-CAD Investigators. Edoxaban Antithrombotic Therapy for Atrial Fibrillation and Stable Coronary Artery Disease. N Engl J Med. 2024 Sep 1. DOI: 10.1056/NEJMoa2407362.
15. Solomon SD, McMurray JJV, Vaduganathan M, et al.; FINEARTS-HF Committees and Investigators. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2024;391(16):1475-1485. DOI: 10.1056/NEJMoa2407107
16. Jhund PS, Talebi A, Henderson AD, et al. Mineralocorticoid receptor antagonists in heart failure: an individual patient level meta-analysis. Lancet. 2024;404(10458):1119-1131. DOI: 10.1016/S0140-6736(24)01733-1
17. Vaduganathan M, Filippatos G, Claggett BL, et al. Finerenone in heart failure and chronic kidney disease with type 2 diabetes: FINE-HEART pooled analysis of cardiovascular, kidney and mortality outcomes. Nat Med. 2024;30(12):3758-3764. DOI: 10.1038/s41591-024-03264-4
18. Kunadian V, Mossop H, Shields C, et al.; British Heart Foundation SENIOR-RITA Trial Team and Investigators. Invasive Treatment Strategy for Older Patients with Myocardial Infarction. N Engl J Med. 2024;391(18):1673-1684. DOI: 10.1056/NEJMoa2407791
19. Campo G, Böhm F, Engstrøm T, et al. Complete Versus Culprit-Only Revascularization in Older Patients With ST-Segment-Elevation Myocardial Infarction: An Individual Patient Meta-Analysis. Circulation. 2024;150(19):1508-1516. DOI: 10.1161/CIRCULATIONAHA.124.071493
20. Ferreira D, Hardy J, Meere W, et al. Fasting vs. no fasting prior to catheterization laboratory procedures: the SCOFF trial. Eur Heart J. 2024;45(47):4990-4998. DOI: 10.1093/eurheartj/ehae573
21. Dulai R, Sulke N, Freemantle N, et al. Pulmonary Vein Isolation vs Sham Intervention in Symptomatic Atrial Fibrillation: The SHAM-PVI Randomized Clinical Trial. JAMA. 2024;332(14):1165-73. DOI: 10.1001/jama.2024.17921
22. Erlinge D, Andersson J, Fröbert O, et al. Bioadaptor implant versus contemporary drug-eluting stent in percutaneous coronary interventions in Sweden (INFINITY-SWEDEHEART): a single-blind, non-inferiority, registry-based, randomised controlled trial. Lancet. 2024;404(10464):1750-1759. DOI: 10.1016/S0140-6736(24)02227-X
23. Gao C, He X, Ouyang F, et al.; REC-CAGEFREE I Investigators. Drug-coated balloon angioplasty with rescue stenting versus intended stenting for the treatment of patients with de novo coronary artery lesions (REC-CAGEFREE I): an open-label, randomised, non-inferiority trial. Lancet. 2024;404(10457):1040-1050. DOI: 10.1016/S0140-6736(24)01594-0
24. Upton R, Akerman AP, Marwick TH et al.; for the PROTEUS Investigators. PROTEUS: A Prospective RCT Evaluating Use of AI in Stress Echocardiography. NEJM AI 2024;1(11) Oct 18 DOI: 10.1056/AIoa2400865

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Associations of the prevalence of coronary heart disease and psychosocial risk factors in middle-aged men from an open urban population

Kayumova M. M.[1], Gafarov V. V.[2], Bessonova M. I.[1], Troshina I. A.[3], Gorbunova T.Yu.[1], Akimov A. M.[1], Novosyolov A. V.[1], Lebedev E. V.[1], Akimova E. V.[1]

[1] Tyumen Cardiology Research Center, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia.
[2] Institute of Therapy and Preventive Medicine — Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Novosibirsk, Russia.
[3] Tyumen State Medical University, Tyumen, Russia.

AUTHORS

Marina M. Kayumova*, MD, PhD, Senior researcher of the Laboratory of Epidemiology and Prevention of Cardiovascular Diseases, Tyumen Cardiology Research Center, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia. ORCID: 0000-0001-5326-119X

Valery V. Gafarov, MD, PhD, Professor, Honored Scientist of the Russian Federation, Head of the Laboratory of Psychological and Sociological Problems of Therapeutic Diseases, Institute of Therapy and Preventive Medicine — Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Novosibirsk, Russia. ORCID: 0000-0001-5701-7856

Marina I. Bessonova, MD, PhD, Researcher of the Laboratory of Epidemiology and Prevention of Cardiovascular Diseases, Tyumen Cardiology Research Center, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia. ORCID: 0000-0002-2686-3715

Irina A. Troshina, MD, PhD, Professor, Head of the Department of Hospital Therapy, Tyumen State Medical University, Tyumen, Russia. ORCID: 0000-0002-8702-3883

Tatiana Yu. Gorbunova, MD, PhD, cardiologist, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia. ORCID: 0009-0008-7207-4937

* Corresponding author. Tel.: +7 (905) 823-2837. E-mail: kayumova@infarkta.net

Aleksandr M. Akimov, Candidate of Social Sciences, Senior researcher of the Laboratory of Epidemiology and Prevention of Cardiovascular Diseases, Tyumen Cardiology Research Center, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia. ORCID: 0000-0001-5152-8460
Antov V. Novosyolov, Junior researcher of the Laboratory of Epidemiology and Prevention of Cardiovascular Diseases, Tyumen Cardiology Research Center, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia. ORCID: 0000-0003-4101-6079
Egor V. Lebedev, Junior researcher of the Laboratory of Epidemiology and Prevention of Cardiovascular Diseases, Tyumen Cardiology Research Center, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia. ORCID: 0000-0001-6222-0445
Ekaterina V. Akimova, MD, PhD, Head researcher of the Laboratory of Epidemiology and Prevention of Cardiovascular Diseases, Tyumen Cardiology Research Center, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia. ORCID: 0000-0002-9961-5616

The aim of the study is to determine the prevalence of coronary heart disease (CHD), sleep disorders, and negative affective states among men aged 55–64 years in an open urban population and to assess the likelihood of developing CHD with high levels of depression, hostility, vital exhaustion, and sleep disorders.

Methods. A cross-sectional study with an 85.0% response rate was conducted on a representative sample of men aged 25–64 years in the city of Tyumen (n=1000). Standard epidemiological methods were used to determine the prevalence of CHD. High levels of depression, hostility, vital exhaustion, and sleep disorders among middle-aged individuals (55–64 years) were identified using algorithms from the WHO MONICA-MOPSY questionnaire.

Results. With a lower prevalence of high levels of depression in the open population and its increase among middle-aged men, the highest likelihood of developing definite CHD (DCHD) and CHD according to extended epidemiological criteria was observed in the general population, with a tendency to decrease in the sixth decade of life. In the presence of high levels of hostility at the age of 55–64 years, the likelihood of developing CHD and DCHD increased by 2 and 5 times, respectively. In the same age category, with a significant increase in vital exhaustion relative to the general population indicator, the likelihood of developing CHD with high levels of vital exhaustion was lower than in the general population, while the likelihood of developing DCHD increased by 12.5 times with its twofold increase in the general population. Among men aged 55–64 years, with a significant increase in sleep disorders, the likelihood of developing CHD in the presence of sleep disorders did not differ significantly from the general population indicator, but there was a twofold increase in the likelihood of developing DCHD.

Conclusion. Thus, the analysis of identifying psychosocial risk factors in middle-aged men and the associations of their high levels with the development of CHD appears necessary for use in forming preventive programs aimed at reducing high cardiovascular risk in an open urban population. These programs should primarily focus on regulating psychological parameters.

Keywords: open population, epidemiologic study, psychosocial factors, coronary heart disease.

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Introduction

According to the results of the WHO-MONICA project, conventional risk factors (RFs) explain only 50% of the occurrence of cardiovascular diseases (CVDs) [1, 2]. It has now been proven that psychosocial factors (PSFs) can be one of the reasons for the negative trend in the deterioration of population health and contribute significantly to the morbidity and mortality from coronary heart disease (CHD) [3–5]. Results from large epidemiological studies have shown that PSFs and

their components (sleep disorders and negative affective states), such as depression, hostility, and vital exhaustion (VE), are associated with a high risk of developing CHD [6–8]. Analysis of literature data has demonstrated a significant prevalence of PSFs, particularly negative affective states, primarily among middle-aged individuals [9–11]. However, PSFs may play a decisive role in shaping the unfavorable epidemiological situation regarding CVDs and mortality from them in Russian populations in recent decades, while the role of non-conventional risk factors (RFs) in relation to CVDs remains insufficiently studied [12–14]. The relationships between high levels of PSFs and the prevalence of CHD in Siberia are understudied and require scientific justification [1, 9]. At the same time, assessing the needs and demands of the population regarding preventive measures, taking into account its psychosocial characteristics, is the basis for developing a concept for the quality of medical and preventive care in healthcare [11, 12].

The aim of the study is to determine the prevalence of coronary heart disease (CHD), sleep disorders, and negative affective states among men aged 55–64 years in an open urban population and to assess the likelihood of developing CHD with high levels of depression, hostility, VE, and sleep disorders.

Methods

A cross-sectional study with an 85.0% response rate was conducted on a representative sample of men aged 25–64 years, selected randomly from electoral lists in Tyumen, totaling 1000 individuals, distributed equally across four decades of life by quartiles (budget topics No. NIOKTR: 122020300112–4 and NIIPM No. FWNR-2024–0002). For the analysis within this study, one decade of life — the age category of 55–64 years — was taken. The inclusion criteria for the population study were: 1) male sex; 2) age groups 25–64 years and 55–64 years; 3) permanent residents of Tyumen. The exclusion criteria for the population study were: 1) female sex; 2) age categories other than 25–64 years and 55–64 years; 3) migrants, military personnel, and prisoners.

Based on the processing of electrocardiograms using the Minnesota Code (MC) and analysis of the WHO questionnaire on exertional angina, an epidemiological diagnosis of CHD was established: 1) according to strict criteria — "definite" CHD (DCHD); 2) according to non-strict criteria — "possible" CHD (PCHD). In accordance with the MC, strict and non-strict criteria for CHD together defined CHD according to extended epidemiological criteria. Depression (D), hostility (H), vital exhaustion (VE), and sleep disorders (SD) were assessed using scales for depression, hostility, vital exhaustion, and sleep disorders, aligned with the WHO MONICA-MOPSY program algorithm [1].

Written informed consent was obtained from each participant for participation in the cardiac screening. The cardiac screening protocol was approved by the ethics committee of the Tyumen Cardiology Research Center.

Statistical Analysis

Statistical analysis was performed using the IBM STATISTICA 21.0 software package. To assess the significance of differences between sample proportions in two groups, Pearson's chi-square test (χ^2) was used. The critical significance level for testing statistical hypotheses was set at $p < 0.05$, taking into account the degrees of freedom.

Age standardization of all studied indicators was performed using the direct method. In cases where the number of participants in any subgroup was less than 10 or exactly equal to 0, comparisons were recalculated using Fisher's exact test. Associations of high levels of PSFs with the prevalence of CHD, its "definite" and "possible" forms, were determined by calculating odds ratios (OR) and their 95% confidence intervals (CI). In each case, the statistical significance of the OR was assessed based on the 95% CI values. If the CI included 1, meaning its upper limit was > 1 and the lower limit was < 1, it was concluded that there was no statistically significant association between the factor and the outcome at a significance level of $p < 0.05$.

Results

In the open population of a moderately urbanized city in Western Siberia (Tyumen), among men aged 25–64 years, the results of cardiac screening demonstrated a high prevalence of CHD according to extended epidemiological criteria (12.4%). The age-standardized prevalence of DCHD was 6.6%, and PCHD was 5.7%. Among men aged 55–64 years, the prevalence of CHD according to extended epidemiological criteria was significantly higher than the age-standardized indicator (33.2% vs. 12.4%, $p < 0.001$). The prevalence of DCHD and PCHD in men aged 55–64 years also showed statistically significant differences compared

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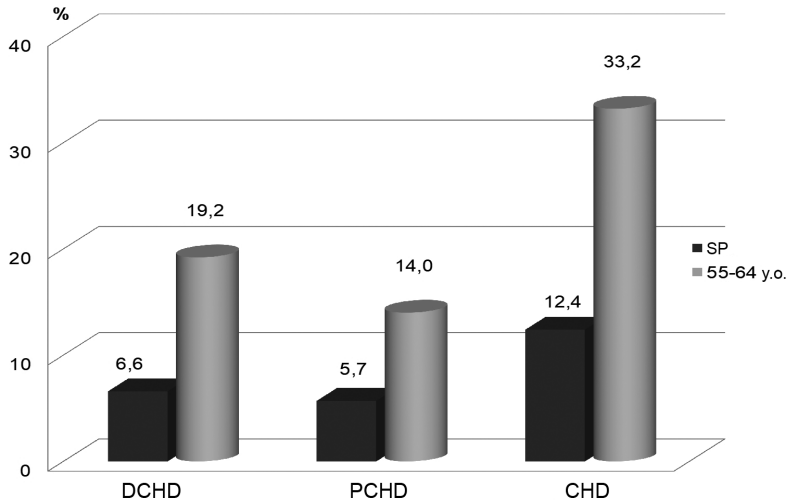

Fig. 1. Prevalence of CHD in middle-aged men, %

to their frequency in the general population (19.2% vs. 6.6%; 14.0% vs. 5.7%, p < 0.001) (Fig. 1).

Figure 2 presents the prevalence of high levels of PSFs in the general male population aged 25–64 years (SP – age-standardized parameter) and the age category of 55–64 years in a comparative aspect. For each of the studied variables, a trend toward an increase in the 55–64 age group relative to the SP was observed, with statistically significant differences for high levels of depression (4.6% vs. 14.6%, p < 0.001), VE (15.9% vs. 31.3%, p < 0.001), and sleep disorders (9.5% vs. 17.3%, p = 0.0081). The highest prevalence of high levels of PSFs, both in the open population and among middle-aged men, was observed for high levels of hostility, while the lowest was for high levels of depression (Fig. 2).

An assessment of the odds of developing different forms of CHD in the age category of 55–64 years and in the general population, depending on high levels of PSFs in men, was conducted.

Thus, with a high level of depression, the likelihood of developing CHD according to extended epidemiological criteria in the general population increased by 21.07 times (OR 21.07 with 95% CI 41.26; 10.76, p < 0.05), and the likelihood of developing DCHD increased by 39.84 times (OR 39.84 with 95% CI 80.90; 19.61, p < 0.05). At the same time, the likelihood of developing PCHD did not differ between high and low levels of depression (p > 0.05). Among men aged 55–64 years, compared to the age-standardized indicator, the likelihood of developing CHD according to extended epidemiological criteria in the general population with a high level of depression increased significantly less — by 14.51 times (OR 14.51 with 95% CI 39.52; 5.33, p < 0.05), as did the likelihood of developing DCHD — by 29.33 times (OR 29.33 with 95% CI 82.11; 10.48, p < 0.05). Similarly to the situation in the gen-

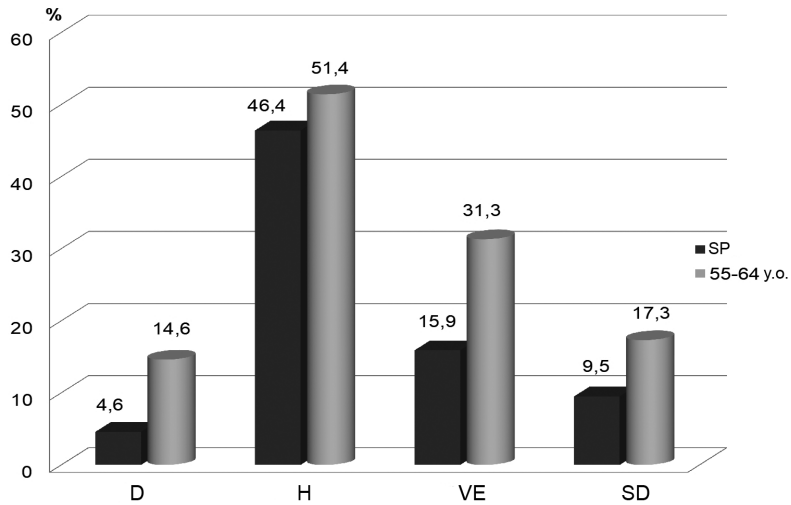

Fig. 2. High levels of PSF in middle-aged men, %

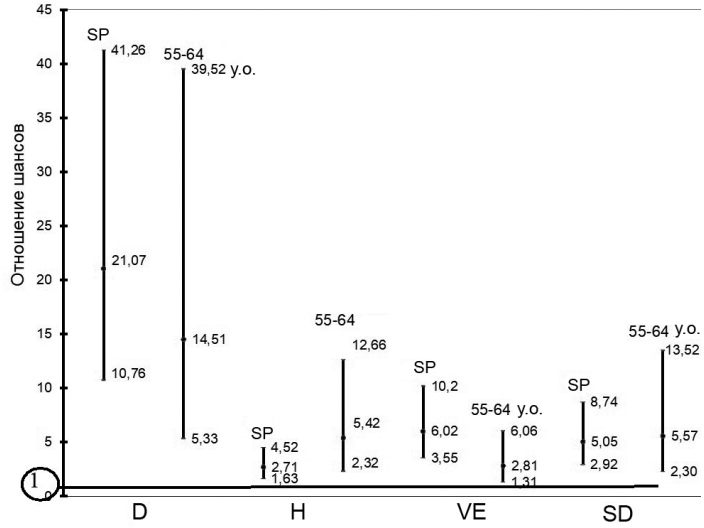

Fig. 3. The odds ratio of developing CHD at high PSF levels

eral population, the likelihood of developing PCHD did not differ between high and low levels of depression in men aged 55–64 years (p > 0.05) (Fig. 3, 4).

With a high level of hostility, statistically significant differences in the likelihood of developing CHD according to extended epidemiological criteria in the general population were maintained, although it was significantly lower (OR 2.71 with 95% CI 4.52; 1.63, p < 0.05). A similar trend was observed for the likelihood of developing DCHD (OR 4.65 with 95% CI 10.12; 2.14, p < 0.05). The likelihood of developing PCHD did not differ between high and low levels of hostility (p > 0.05). In the age group of 55–64 years, compared to the SP, the likelihood of developing CHD according to extended epidemiological criteria in the general population with a high level of hostility was significantly higher (OR 5.42 with 95% CI 12.66; 2.32, p < 0.05). At the same time, the likelihood of developing DCHD in the 55–64 age group with a high level of hostility increased by 25.85 times, with statistical significance in the OR calculation (OR 25.85 with 95% CI 202.60; 3.30, p < 0.05). Similarly to the situation in the general population, the likelihood of developing PCHD did not significantly differ between high and low levels of hostility in the 55–64 age group (p > 0.05).

With a high level of VE, the likelihood of developing CHD according to extended epidemiological criteria in the general population increased by 6.02 times (OR 6.02 with 95% CI 10.20; 3.55, p < 0.05), and the likelihood of developing DCHD increased by 14.11 times (OR 14.11 with 95% CI 31.67; 6.29, p < 0.05). At the same time, the likelihood of developing PCHD did not differ between high and low levels of VE (p > 0.05). Among men aged 55–64 years, compared to the SP, the likelihood of developing CHD according to extended epidemiological criteria in the general population

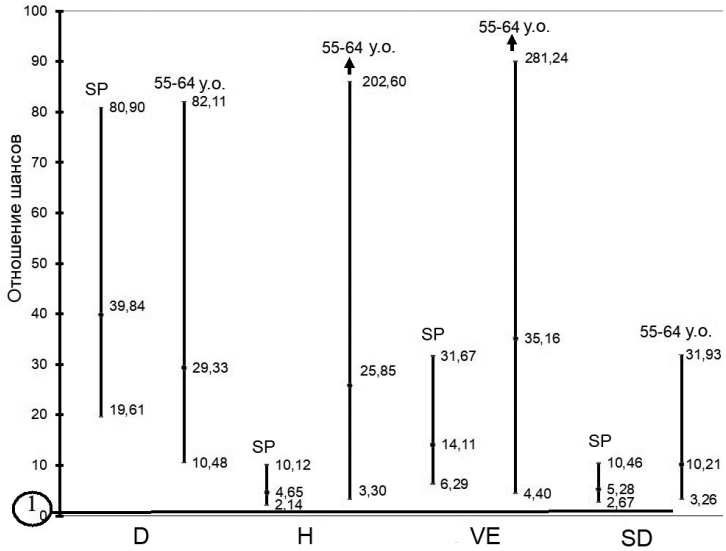

Fig. 4. The odds ratio of developing DCHD at high PSF levels

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with a high level of VE increased significantly less — by 2.81 times (OR 2.81 with 95% CI 6.06; 1.31, $p < 0.05$). However, the likelihood of developing DCHD in the 55–64 age group with a high level of VE increased by 35.16 times (OR 35.16 with 95% CI 281.24; 4.40, $p < 0.05$). The likelihood of developing PCHD did not differ between high and low levels of VE in the 55–64 age group ($p > 0.05$).

With sleep disorders (SD), the likelihood of developing CHD according to extended epidemiological criteria in the general population increased by 5.05 times (OR 5.05 with 95% CI 8.74; 2.92, $p < 0.05$), the likelihood of developing DCHD increased by 5.28 times (OR 5.28 with 95% CI 10.46; 2.67, $p < 0.05$), and the likelihood of developing PCHD increased by 3.13 times (OR 3.13 with 95% CI 6.65; 1.47, $p < 0.05$). Among men aged 55–64 years, compared to the SP, the likelihood of developing CHD according to extended epidemiological criteria in the general population with SD increased by 5.75 times (OR 5.75 with 95% CI 13.52; 2.30, $p < 0.05$), and the likelihood of developing DCHD increased by 10.21 times (OR 10.21 with 95% CI 31.93; 3.48, $p < 0.05$). At the same time, the likelihood of developing PCHD did not differ between the presence and absence of SD in middle-aged men ($p > 0.05$).

Discussion

When using epidemiological criteria to define CHD in the presence of PSFs, the odds of CHD detection were higher, with the highest likelihood observed for the "definite" form of CHD and the lowest for the "possible" form of CHD. The results regarding the prevalence of PSFs are comparable to data from Novosibirsk and Tomsk studies, which were conducted using the same protocol as this study. A comparative analysis with data from Novosibirsk researchers shows that in the Tyumen population, a high level of depression predominated among middle-aged men, likely influenced by factors of chronic social stress prevalent in this age category [9, 13]. The adverse effects of depressive disorders on the development of CVDs may be mediated through platelet mechanisms. Increased susceptibility to platelet activation and the secretion of their products are considered one of the most important links in the pathogenesis, explaining the vulnerability of individuals with such conditions to developing cardiovascular pathology. As a result, theoretical assumptions about the significance of negative affective disorders in the development and progression of CVDs have a material basis [15–16]. In the presence of a high level of depression among men aged 25–64 years in Tyumen, the prevalence of CHD increased more than 20-fold.

The results of this study regarding the higher level of hostility and the significant increase in the likelihood of developing CHD among middle-aged men are consistent with data from a Finnish study, where similar findings were reported. Currently, many researchers believe that hostility (as one of the key components of Type A personality) has a greater influence on the onset of the disease and acute triggering factors (spasm, thrombosis, plaque rupture) and a lesser influence on vascular atherosclerosis. Thus, hostility may provoke acute coronary spasm and serve as a reliable prognostic marker for the development of myocardial infarction (MI) in general population groups, although its role as a prognostic marker for the progression of atherosclerosis and, consequently, the development of arterial hypertension (AH) and stroke remains undefined [10].

Population patterns regarding PSFs in a moderately urbanized Siberian city (Tyumen) are also concerning, particularly the high prevalence of VE among middle-aged men — for men, the vulnerable age period for high levels of VE in the population was the 55–64 age group. According to the data from this study, results from the male population of Novosibirsk showed that the proportion of individuals with CHD was significantly higher in the presence of VE than without it. This effect is amplified, as shown by both Tyumen and Novosibirsk studies, by a significant predominance in this group of other negative affective states, sleep disorders, low education levels, and unskilled heavy physical labor [17, 18].

In the open population of Tyumen, the standardized prevalence of sleep disorders among men aged 25–64 years was high but comparable to the results obtained in the male population of Novosibirsk [1]. According to a number of researchers, sleep disorders are a sign of vital exhaustion, depression, anxiety, and, accordingly, a predictor of the development of cardiovascular pathology [12]. When sleep quality decreases, its primary function as a restorative process is disrupted, preventing the body from fully adapting to changing external and internal conditions, ultimately leading to the development of cardiovascular pathology [19]. Assessing self-reported sleep quality allows for the evaluation of the population frequency of

sleep disorders, identification of sleep-related problems in various population groups, and identification of groups at increased risk of developing CVDs. High levels of sleep disorders in the Tyumen male population aged 25–64 years were 5 times more common in men with CHD than in men without CHD; the same pattern was observed for men with DCHD. In individuals with PCHD, reduced sleep quality was detected 3 times more often than in the general population. This situation is likely natural, as, according to the literature, the vast majority of patients with chronic sleep disorders attribute their ailments to life circumstances, most often citing personal problems. In older adults, sleep disorders arise due to general dissatisfaction with life, fear of death, and negative attitudes toward aging. Our findings are supported by data from other researchers regarding sleep disorders as a predictor of CVDs — arterial AH, MI, and stroke. Numerous experimental, clinical, and epidemiological studies have shown associations between sleep disorders and both negative affective states and the development of CHD. It has been demonstrated that anxiety-depressive syndrome manifests as increased cortical activation, contributing to a state of dysfunctional arousal, which leads to difficulty falling asleep and maintaining sleep [19, 20]. The close relationship between sleep disorders and negative affective states is confirmed by global epidemiological studies, which show that sleep problems appear earlier than other manifestations of these states. This is why subjective sleep assessment is of great importance for predicting the future development of depression and VE [1].

Conclusion

In the open population of Tyumen, among men aged 55–64 years with high levels of PSFs (depression, hostility, vital exhaustion, sleep disorders), an increase in the odds of developing definite CHD and CHD according to extended epidemiological criteria was observed.

The analysis of identifying PSFs in middle-aged men and the associations of their high levels with the development of CHD appears necessary for use in forming preventive programs aimed at reducing high cardiovascular risk in an open urban population. These programs should primarily focus on regulating psychological parameters.

Conflict of interests: none declared.

References

1. Gafarov VV, Akimova EV, Trubacheva IA et al. The contribution of psychosocial factors to survival, the risk of developing cardiovascular diseases among people 25–64 years old in Siberia (Novosibirsk, Tyumen, Tomsk): results of cross-sectional and cohort studies 1981–2020. Atherosclerosis. 2024; 20(4): 397–412. Russian. DOI: 10.52727/2078-256X-2024-20-4-397-412
2. Duarte Junior MA, Pintos CS, Martínez-Gómez D et al. Lifestyle behaviors, social and economic disadvantages, and all-cause and cardiovascular mortality: results from the US National Health Interview Survey. Front Public Health. 2024 Feb 28;12:1297060. DOI: 10.3389/fpubh.2024.1297060
3. Curry SJ, Krist AH, Owens DK et al. US Preventive Services Task Force. Risk Assessment for Cardiovascular Disease with Nontraditional Risk Factors: US Preventive Services Task Force Recommendation Statement. J. Am Med Assoc. 2018;320(3):272–280. DOI: 10.1001/jama.2018.8359
4. De Hert M, Detraux J, Vancampfort D. The intriguing relationship between coronary heart disease and mental disorders. Dialogues Clin. Neurosci. 2018; 20(1): 31–40. DOI: 10.31887/DCNS.2018.20.1/mdehert
5. Cocchio S, Baldovin T, Furlan P et al. Is depression a real risk factor for acute myocardial infarction mortality? A retrospective cohort study. BMC Psychiatry. 2019;19:2–8. DOI: 10.1186/s12888-019-2113-8
6. Arrebola-Moreno M, Petrova D, Garrido D et al. Psychosocial markers of pre-hospital decision delay and psychological distress in acute coronary syndrome patients. Br J Health Psychol. 2020; 25(2):305–323. DOI: 10.1111/bjhp.12408
7. Mamedov MN Dynamics of risk factors and cardiovascular diseases: analytical review of international and Russian data for 2017. International Heart and Vascular Disease Journal. 2018;6(19):32–37. Russian.
8. Yao B-C., Meng L-B., Hao M–L., et al. Chronic stress: a critical risk factor for atherosclerosis. J. Int. Med. Res. 2019;47 (4):1429–1440. DOI:10.1177/0300060519826820
9. Akimova EV, Gafarov VV, Gakova EI et al. Relationship between depression and coronary artery disease in an open female and male population of a middle-urbanized city of Western Siberia. Cardiovascular therapy and prevention. 2021;20(2):2557. Russian. DOI: 10.15829/1728-8800-2021-2557
10. Akimova EV, Bessonova MI, Kayumova MM, Akimov AM The risk of cardiovascular disease development depending on psychosocial factors from the perspective of hostility research: gender aspect. International Heart and Vascular Disease

Journal. 2022;10(35):5–12. Russian. DOI: 10.24412/2311-1623-2022-35-5-12

11. Pogosova NV, Boytsov SA, Oganov RG et al. Clinical-Epidemiological Program of Studying Psychosocial Risk Factors in Cardiological Practice in Patients With Arterial Hypertension and Ischemic Heart Disease: First Results of a Multicenter Study in Russia. Cardiology. 2018;58(9):47–58. Russian. DOI: 10.18087/cardio.2018.9.10171
12. Gomanova LI, Balanova YuA, Kutsenko VA et al. Psycho-emotional stress as a risk factor for the development of non-communicable diseases. The Russian Journal of Preventive Medicine. 2023;26(8):114–120. Russian. DOI: 10.17116/profmed20236081114
13. Kayumova MM, Bessonova MI, Gafarov VV et al. Associations of depression with parameters of attitude towards medical care in an open urban population, gender aspect. Vrach. 2023;34(8):48–53. Russian. DOI: 10.29296/25877305-2023-08-09
14. Chinnaiyan K. Role of stress management for cardiovascular disease prevention. Curr Opin Cardiol. 2019; 34 (5): 531–535. DOI:10.1097/HCO.0000000000000649
15. Mamedov MN, Mitchenko EI, Serpitis P, et al. Updated European recommendations for the prevention of cardiovascular diseases. Analytical review. International Journal of Heart and Vascular Diseases. 2022;10(33):4–11. Russian. DOI: 10.24412/2311-1623-2022-33-4-11
16. Souilhol C, Canic J, Fragiadaki M, et al. Endothelial responses to shear stress in atherosclerosis: a novel role for developmental genes. Nat Rev Cardiol. 2020;17(1):52–63. DOI:10.1038/s41569-019-0239-5
17. Gafarov VV, Voevoda MI, Gromova EA, et al. Cardiovascular diseases and vital exhaustion: a prospective study in Russia/Siberia (WHO MONICA program-psychosocial). Russian Journal of Cardiology. 2016;4:115–123. Russian. DOI: 10.15829/1560-4071-2016-4-eng-115-123
18. Pester MS, Gonzalez A, Schmaus J. et al. Sex differences in the association of vital exhaustion with regional fat deposition and subclinical cardiovascular disease risk. J Psychosom Res. 2022; 157: 110785. DOI: 10.1016/j.jpsychores.2022.110785
19. Yakupov EZ, Troshinalu V Anxiety, insomnia, depression — in conjunction with or opposite to functional disorders. Journal of Neurology and Psychiatry. S. S. Korsakov. 2016;116(5): 119–124. Russian. DOI:10.17116/jnevro201611651119-124
20. De Hert M, Detraux J, Vancampfort D The intriguing relationship between coronary heart disease and mental disorders. Dialogues Clin. Neurosci. 2018;20(1):31–40. DOI: 10.31887/DCNS.2018.20.1/mdehert

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Prediction of recurrent cardiovascular events within the first year after a type 2 acute myocardial infarction in men under 45 years of age

Gorbacheva N.S.[1], Veselovskaya N.G.[2], Nikolaeva M.G.[2,3], Momot A.P.[2,3], Gorbacheva P.A.[2]

[1] Regional Clinical Hospital of Emergency Medical Care No. 2, Barnaul, Russia.
[2] Altai State Medical University, Barnaul, Russia.
[3] National Medical Research Center for Hematology, Altai branch, Barnaul, Russia.

AUTHORS

Natalia S. Gorbacheva,* Head of Cardiology Department, Regional Clinical Hospital of Emergency Medical Care No. 2, Barnaul, Russia. ORCID: 0000-0002-0188-3234

Nadezhda G. Veselovskaya, MD, PhD, Professor of the Department of Cardiology and Cardiovascular Surgery, Altai State Medical University, Barnaul, Russia. ORCID: 0000-0001-8654-7020

Marina G. Nikolaeva, MD, PhD, Professor of the Department of Obstetrics and Gynecology with a course of hemostasis, Altai State Medical University, National Medical Research Center for Hematology, Altai branch, Senior Medical Officer, Barnaul, Russia. ORCID: 0000-0001-9459-5698

Andrey P. Momot, MD, PhD, Professor, Head of the Department of Hematology, Altai State Medical University, Director of National Medical Research Center for Hematology, Altai branch, Barnaul, Russia. ORCID: 0000-0001-8953-3759

Polina A. Gorbacheva, 5th year student, Institute of Clinical Medicine, Altai State Medical University, Barnaul, Russia. ORCID:0009-0006-8480-3397

In recent years, cardiovascular diseases (CVD) have remained among the top three causes of mortality and disability worldwide. In this regard, the search for and study of risk factors, identification of pathogenetic mechanisms underlying cardiovascular complications, and improvement of primary and secondary prevention methods continue. Currently, there is emerging evidence on important components of the hemostatic system, including extracellular formations of various sizes — microvesicles of different or-

* Corresponding author. Tel. +7 (906) 945-2853. E-mail: Natalya-gorbacheva-1974@mail.ru

igins. Research into their role in the pathogenesis of acute arterial thromboses is ongoing. Microvesicles (EVs) are extracellular structures that trigger a cascade of mechanisms affecting changes in the vascular endothelium.

The aim of the study is to investigate the role of microvesicles of different origins in the risk of recurrent cardiovascular events within 1 year after a type 2 acute myocardial infarction (AMI) in men under 45 years of age.

Methods. The study included young men under 45 years of age with type 2 AMI, confirmed by coronary angiography and elevated markers of myocardial injury. The control group consisted of young men under 45 years of age without chronic diseases. The main group consisted of 60 patients, the control group included 30 healthy volunteers. The study investigated microvesicles of platelet (CD41+), endothelial (CD31+ — platelet endothelial adhesion molecule), and leukocyte origin (CD45+) in peripheral blood. To determine the quantity of microvesicles, venous blood samples were examined using 0.32% sodium citrate anticoagulant and processed within 2 hours after blood collection. The samples were processed through sequential centrifugation. All measurements were performed on a CytoFlex flow cytometer (Beckman Coulter, USA) equipped with three lasers: Red (638 nm), Blue (488 nm), and Violet (405 nm). Extracellular vesicles were separated by diameter, and measurements were taken for unstained samples to set positive gates. Subsequently, the material was stained, mixed again, and measured after diluting the sample 100 times using phosphate-buffered saline (PBS x10, Bio-Rad). In each analysis, 1 million events were recorded at a flow rate of 60 µl/min. For statistical processing, the parameter of the number of events (extracellular events) per 1 µl was used.

Results. While studying microvesicles, it was found that the levels of CD31+ EVs (endothelial) and CD45+ EVs (leukocyte-derived) were comparable in healthy volunteers and patients with type 2 AMI under 45 years of age. A decrease in the expression of CD31+ EVs by the endothelial glycocalyx was observed, which may indicate its consumption. A difference was observed in the number of CD45+ EVs in patients with recurrent cardiovascular events (CVE) within one year, while during a CVE episode, the number of CD31+ EVs decreased.

Conclusion. During the acute phase of type 2 AMI, the level of CD45+ EVs was statistically significantly higher in patients who subsequently experienced recurrent CVEs within one year.

Keywords: type 2 acute myocardial infarction, microvesicles, cardiovascular complications, risk factors, hemostasis, recurrent cardiovascular events

Conflict of interests: none declared.

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Introduction

In recent years, cardiovascular diseases (CVD) have remained among the top three causes of mortality and disability worldwide. This has led to ongoing research into risk factors (RF), the identification of pathogenetic mechanisms underlying cardiovascular complications (CVC), and the improvement of primary and secondary prevention methods [1–3].

Currently, traditional RFs for CVD (hypertension, obesity, smoking, alcohol consumption, dyslipidemia, diabetes mellitus) and non-traditional RFs (gender, age) have been extensively studied [4–6]. The persistent trend in CVD morbidity and mortality highlights the need to explore potential causes and new RFs [7].

In recent decades, factors related to vascular-platelet and coagulation hemostasis, the fibrinolytic system (coagulation factors II and XIII), and microvesicles (EVs) of various origins have been actively studied in the context of arterial thrombosis risk in young patients without traditional atherosclerosis RFs [8, 9]. Previously, EVs were studied in oncology, obstetrics and gynecology, and wound surface surgery, with emerging evidence of their role in cardiology. As is known, microvesicles (EVs), which are extracellular formations, trigger a cascade of mechanisms causing changes in the vascular endothelium, thereby contributing to thromboembolic complications [10–12].

Moreover, imbalances in the hemostatic system are influenced by gene polymorphisms and comorbid somatic diseases, which can lead to acute vascular events [13, 14].

During acute myocardial infarction (AMI), blood cells and endothelial cells release EVs, the quantity of which can be measured in peripheral blood [15].

It can be hypothesized that changes in the concentration of EVs of various origins after AMI may underlie recurrent cardiovascular events (CVE). EVs have also been shown to actively participate in angiogenesis and myocardial remodeling [16, 17].

To date, the functions of exogenous EVs derived from cultured pluripotent cells in vitro have been sufficiently studied, but there is limited data on the functions of endogenous EVs in type 2 AMI. Theoretical insights into the potential role of EVs of various origins in the development of type 2 AMI and early complications after vascular events have provided the basis for their investigation in a cohort of young men with type 2 AMI and early recurrent CVEs.

The aim of the study is to investigate the role of microvesicles of different origins in the risk of recurrent cardiovascular events within 1 year after a type 2 AMI in men under 45 years of age

Methods

The study was conducted at the Altai Regional Cardiological Dispensary in Barnaul. Laboratory diagnostic tests and flow cytometry were performed in the hemostasis laboratory of the Regional Clinical Hospital of Emergency Medical Care No. 2.

To determine the quantity of microvesicles, venous blood samples were examined using 0.32% sodium citrate anticoagulant and processed within 2 hours after blood collection. The samples were processed through sequential centrifugation. All measurements were performed on a CytoFlex flow cytometer (Beckman Coulter, USA) equipped with three lasers: Red (638 nm), Blue (488 nm), and Violet (405 nm). Extracellular vesicles were separated by diameter, and measurements were taken for unstained samples to set positive gates. Subsequently, the material was stained, mixed again, and measured after diluting the sample 100 times using phosphate-buffered saline (PBS x10, Bio-Rad). In each analysis, 1 million events were recorded at a flow rate of 60 µl/min, ensuring that no objects larger than 1000 nm were present in the analyzed area. For statistical processing, the parameter of the number of events (extracellular events) per 1 µl was used.

The study included 90 men under 45 years of age (41.5±1.5 years), of whom 30 were healthy volunteers and 60 were diagnosed with type 2 AMI with ST-segment elevation without comorbidities. The diagnosis of type 2 AMI was established based on coronary angiography data, which showed no atherosclerotic lesions in the coronary arteries, and an elevated concentration of troponin I in peripheral blood. All patients admitted with AMI were assessed for traditional RFs of AMI, coagulation hemostasis, and the fibrinolytic system. Blood serum analysis was also performed to determine microvesicles (EVs) of various origins using flow cytometry.

Prospective follow-up was conducted for 1 year from the time of patient inclusion in the study. Adverse CVEs included recurrent AMI, death, and acute cerebrovascular accident (stroke).

In our study, microvesicles of platelet (CD41+), endothelial (CD31+ — platelet endothelial adhesion molecule), and leukocyte origin (CD45+) in peripheral blood were investigated.

Limitations of the study included a relatively small cohort of patients (60 individuals) with type 2 AMI without atherosclerotic lesions, and limited data in the literature on microvesicles and their role in arterial thromboses.

Inclusion criteria: Men with type 2 AMI under 45 years of age, signed informed consent, elevated markers of myocardial injury, and absence of stenotic lesions according to coronary angiography.

Exclusion criteria: Female sex and men over 45 years of age; presence of severe comorbidities (chronic obstructive pulmonary disease, liver or kidney failure, oncological diseases); previously diagnosed type 1 or type 2 diabetes mellitus; history of stroke; post-infarction cardiosclerosis; cardiac arrhythmias and conduction disorders (atrial fibrillation, atrioventricular or sinoatrial block).

Statistical analysis

Statistical processing and graphical representation of data were performed using computer programs MedCalc 20.0.27 and Statistica 12.0 (StatSoft).

To assess the influence of the studied factors and indicators, the method of multiple binary logistic regression was used. Based on stepwise analysis, several factors (predictors) statistically significantly influencing the outcome ($p < 0.05$) were included in the regression model, with one of the study indicators being EVs. To compare two independent groups regarding quantitative characteristics, the Nagelkerke

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coefficient was used. The obtained data are presented as the arithmetic mean (M) and standard deviation (SD), with differences considered statistically significant at $p < 0.05$.

Results

While analyzing traditional RFs, the mean values of the body mass index (BMI) were obtained: 26.76±3.36 kg/m² in the control group and 31.29±14.00 kg/m² in the main group. In the subgroup with CVE, the BMI was 30.4±4.6 kg/m², and in the subgroup without CVE, it was 30.8±6.2 kg/m², showing no significant difference between the comparison groups.

The total cholesterol (TC) level in the main group was 6.71±1.23 mmol/L, while in the control group, it was 4.78±1.34 mmol/L. When comparing TC results in the subgroup with CVE (6.89±2.1 mmol/L) and without CVE (6.34±1.6 mmol/L), no significant differences were found between these groups.

During the study, platelet-derived EVs (CD41+) in blood plasma were determined in both groups. Comparative analysis of blood plasma in patients from the main and control groups revealed a concentration of 953.65±164 per μL in the main group and 1005.3±98.7 per μL in the control group. In the subgroup of type 2 AMI with CVE, the concentration of CD41+ EVs was 892±95.4 per μL, and without CVE, it was 934.8±76.5 per μL. Comparative analysis between the groups showed no significant differences (p=0.965) (Fig. 1).

While analyzing leukocyte-derived microvesicles (CD45+), their concentration in the control group was 2267.9±1104.43 per μL, and in the main group, it was 2486.91±1003.56 per μL, also showing no significant difference between the comparison groups (p=0.568) (Fig. 2).

In the analysis of endothelial-derived EVs (CD31+), their concentration in the control group was 123.061±72.8 per μL, and in the main group, it was 87.43±62.55 per μL. In the type 2 AMI subgroup with CVE, the concentration of CD31+ EVs was 118.14±87.12 per μL, and without CVE, it was 102.56±73.35 per μL.

A decrease in their concentration was observed in the type 2 AMI patient group, which was likely due to the binding of CD31+ to blood cells and the endothelial glycocalyx (a consumption mechanism) (Fig. 3).

While evaluating CD31+ EVs as predictors of recurrent CVEs after 1 year using ROC analysis, the sensitivity was 48.1%, and the specificity was 72.7%, indicating a good quality of the predictive model for recurrent CVEs based on CD45+ EV levels (Fig. 4).

According to the regression analysis model, a statistically significant influence of microvesicles (CD41+ EVs, CD31+ EVs, and CD45+ EVs) on the dependent variable — the likelihood of CVE development — was identified (χ^2=128.7; p<0.001). It was also shown that these predictors determine the outcome (dependent

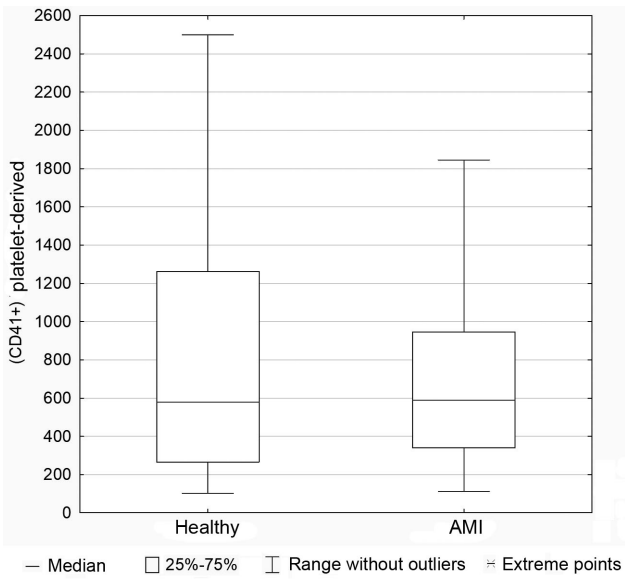

Fig. 1. CD41+ EVs in the comparison group of healthy men and patients with type 2 AMI

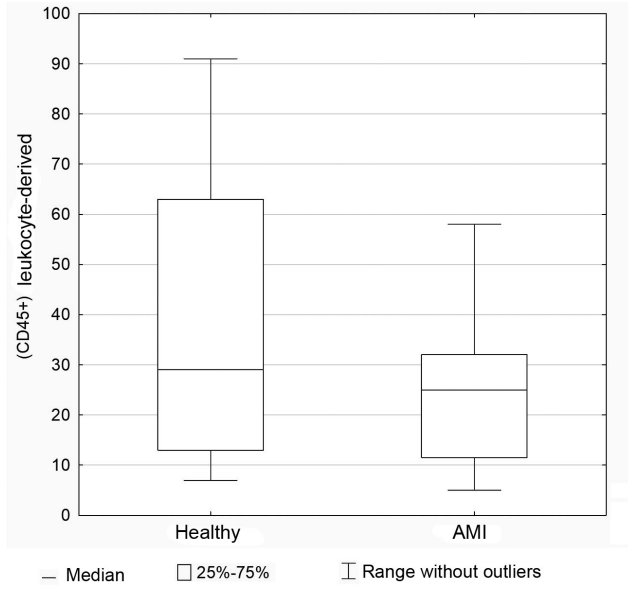

Fig. 2. CD45+ EVs in the comparison group of healthy men and patients with type 2 AMI

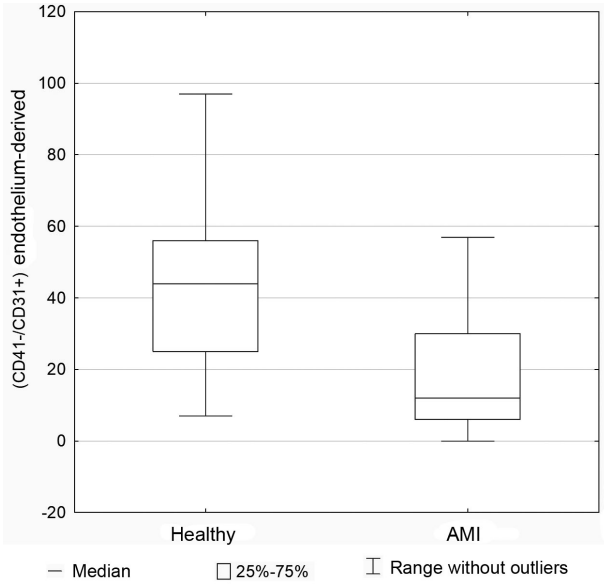

Fig. 3. CD31+ EVs in the comparison group of healthy men and patients with type 2 AMI

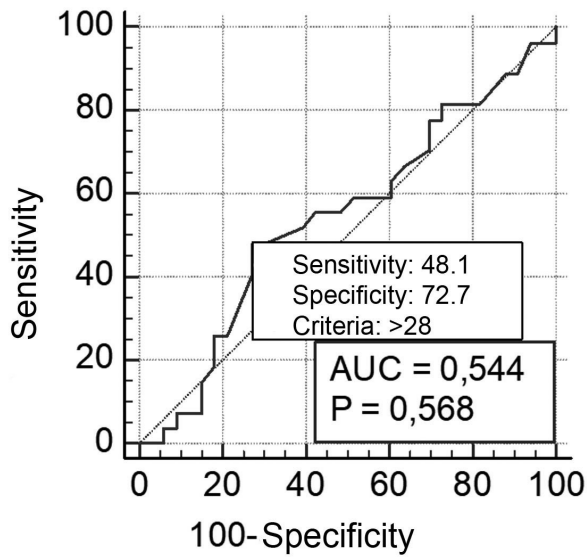

Fig. 4. ROC-curve of EVs CD 45+

variable) by 40.9%. Thus, the obtained data indicate the need for further research into microvesicles in the risk of CVE development, especially in young individuals.

Discussion

In recent decades, CVDs have maintained their leading position in morbidity, mortality, and disability. According to the published Global Burden of Disease (GBD) report on December 11, 2023, the mortality rate from coronary heart disease (CHD) is 108.8 deaths per 100,000 people. Statistics show that 1 million people die annually from CVDs in Russia[1]. AMI is one of the forms of cardiovascular catastrophes. According to statistics, the number of patients with AMI is increasing annually, with a trend toward younger patients. Among young people aged 20–24 years in Russia, mortality from AMI increased by 82% from 2018 to 2023, and among those aged 30–35 years, it increased by 63% [18]. The prevalence of AMI in men is almost 5 times higher than in women[2].

Based on statistical data, young men with type 2 AMI, who show an increased incidence of CVCs after acute coronary events, are of particular interest. This patient group remains understudied.

According to epidemiological studies, traditional RFs have been well studied [4–6], but non-traditional risk factors, such as indicators of coagulation hemostasis (factor II [18], factor XIII [19]), and EVs [11], which were previously studied in oncological processes [20], gynecological pathology [21], and obstetrics [22], have a profound and significant impact.

In our study, among the numerous types of microvesicles, CD45+ EVs, CD31+ EVs, and CD41+ EVs, which have tropism for the vascular wall, were selected.

CD45+ EVs initiate signaling events through their C-terminal PTPase domain, leading to endothelial-mesenchymal transition — a dynamic process in which endothelial cells acquire mesenchymal properties that promote vascular remodeling and tissue proliferation. Comparative analysis revealed that elevated levels of CD45+ EVs in patients with recurrent CVEs may indicate a primary excessive inflammatory response.

CD31+ EVs activation is associated with signaling events that trigger the anti-atherogenic production of NO by the endothelium, causing vasodilation mediated by CD31+ EVs. Additionally, CD31+ EVs are important for switching cellular phenotypes necessary for accelerating wound healing after the inflammation phase.

A decrease in the concentration of CD31+ EVs was observed in the type 2 AMI patient group, likely due to

[1] Morbidity of the population by major classes of diseases in 2000-2023. Federal State Statistics Service (Rosstat). — (Data from the Russian Ministry of Health, calculated by Rosstat) 29.11.2024 Russian

[2] Bichurin D.R., Atmaikina O.V., Cherepanova O.A. Cardiovascular diseases. regional aspect., O.A. International Scientific Research Journal. 2023. 8 (134). Russian DOI: 10.23670/IRJ.2023.134.103

the binding of CD31+ to blood cells and the endothelial glycocalyx (a consumption mechanism).

CD41+ EVs are the most numerous and coagulation-active, accounting for about 70–90% of the total EVs in blood plasma. They affect the vascular endothelium, inducing changes by transferring arachidonic acid to endothelial cells and enhancing platelet adhesion due to the presence of collagen-binding receptor proteins in their composition [23].

Thus, for a comprehensive assessment of RFs for recurrent CVEs in patients after a first-time AMI, along with traditional RFs, it is necessary to evaluate hemostatic system indicators to predict complications and select secondary prevention methods.

Conclusion

Thus, the study of microvesicles revealed that the levels of CD31+ EVs (endothelial) and CD45+ EVs (leukocyte-derived) were comparable in healthy volunteers and patients with type 2 AMI under 45 years of age. A decrease in the expression of CD31+ EVs by the endothelial glycocalyx was observed, which may indicate a consumption mechanism. During the acute phase of type 2 AMI, the level of CD45+ EVs was statistically significantly higher in patients who subsequently experienced recurrent CVEs within one year.

Further research in this direction will contribute to understanding the mechanisms of arterial thromboses and early CVEs in young patients, as well as identifying high-risk groups in combination with genetic testing for thrombogenic mutations. This will enable the development of individualized preventive programs, potentially including adjustments to antiplatelet/anticoagulant therapy.

Conflict of interests: none declared.

References

1. Baghdasaryan P, Natarajan B, Nalbandian M, Varadarajan P, Pai RG. Myocardial Infarction with Nonobstructive Coronary Artery Disease-Definition, Etiopathogenesis, Diagnosis, and Management. Int J Angiol. 2021 Mar 3;33(4):211–221. DOI: 10.1055/s-0041-1724040
2. Pedersen LR, Frestad D, Michelsen MM et al. Risk Factors for Myocardial Infarction in Women and Men: A Review of the Current Literature. Curr Pharm Des. 2016;22(25):3835–52. DOI : 10.2174/1381612822666160309115318
3. Lisowska A, Makarewicz-Wujec M, Filipiak KJ. Risk factors, prognosis, and secondary prevention of myocardial infarction in young adults in Poland. Kardiol Pol. 2016;74(10):1148–1153. DOI: 10.5603/KP.a 2016.0098
4. Kotseva K, Wood D, De Bacquer D et al.; EUROASPIRE Investigators. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol. 2016 Apr;23(6):636–48. DOI: 10.1177/2047487315569401
5. Mozaffarian S, Etemad K, Aghaali M et al. Short and Long-Term Survival Rates Following Myocardial Infarction and Its Predictive Factors: A Study Using National Registry Data. J Tehran Heart Cent. 2021 Apr;16(2):68–74. DOI: 10.18502/jthc.v16i2.7387
6. Galimzyanov AF, Galiullin AN, Galiullin DA et al. Medical and social problems of managing risk factors for cardiovascular diseases leading to morbidity, disability and mortality of the population. Emergency medical services. 2023. 3: 7–10. Russian. DOI: 10.24884/2072-6716-2023-24-3-51-58
7. Lee JC, Zdrojewski T, Pencina MJ et al. Population Effect of Differences in Cholesterol Guidelines in Eastern Europe and the United States. JAMA Cardiol. 2016 Sep 1;1(6):700–7. DOI: 10.1111/dme.12542
8. Ratajczak MZ, Ratajczak J. Leukemogenesis occurs in a microenvironment enriched by extracellular microvesicles/exosomes: recent discoveries and questions to be answered. Leukemia. 2024 Apr;38(4):692–698. DOI: 10.1038/s41375-024-02188-9
9. Navarro S, Stegner D, Nieswandt B et al. Temporal Roles of Platelet and Coagulation Pathways in Collagen- and Tissue Factor-Induced Thrombus Formation. Int J Mol Sci. 2021 Dec 29;23(1):358. DOI: 10.3390/ijms23010358
10. Alkarithi G, Duval C, Shi Y et al. Thrombus Structural Composition in Cardiovascular Disease. Arterioscler Thromb Vasc Biol. 2021 Sep;41(9):2370–2383. DOI: 10.1161/ATVBAHA.120.315754
11. Sadowski M, Ząbczyk M, Undas A Coronary thrombus composition: links with inflammation, platelet and endothelial markers. Atherosclerosis. 2014 Dec;237(2):555–61. DOI: 10.1016/j.atherosclerosis.2014.10.020
12. Ratajczak MZ, Ratajczak J Extracellular microvesicles/exosomes: discovery, disbelief, acceptance, and the future? Leukemia. 2020 Dec;34(12):3126–3135. DOI: 10.1038/s41375-020-01041-z
13. Ståhl AL, Johansson K, Mossberg M et al. Exosomes and microvesicles in normal physiology, pathophysiology, and renal diseases. Pediatr Nephrol. 2019 Jan;34(1):11–30. DOI: 10.1007/s00467-017-3816-z

14. Yusuf S, Hawken S, Ounpuu S et al.; INTERHEART Study Investigators. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet. 2005 Nov 5;366(9497):1640–9. DOI: 10.1016/S0140-6736(05)67663-5
15. Kletukhina SK, Gomzikova MO Multiplex analysis of cancer cells treated with induced mesenchymal stem cell membrane vesicles. Genes & Cells. 2024. 19(4): 441–452. Russian (. DOI: 10.17816/gc609563
16. Khandagale A, Lindahl B, Lind SB et al. Plasma-derived extracellular vesicles from myocardial infarction patients inhibits tumor necrosis factor-alpha induced cardiac cell death. Curr Res Transl Med. 2022 May;70(2):103323. DOI: 10.1016/j.retram.2021.103323
17. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020 Feb 7;367(6478): 6977. DOI: 10.1126/science.aau
18. Zeidan RK, Farah R, Chahine MN et al. Prevalence and correlates of coronary heart disease: first population-based study in Lebanon. Vasc Health Risk Manag. 2016 Mar 17;12:75–84. DOI: 10.2147/VHRM.S97252
19. Pircher J, Czermak T, Ehrlich A, et al. Cathelicidins prime platelets to mediate arterial thrombosis and tissue inflammation. Nat Commun. 2018; 9:1523. DOI: 10.1038/s41467-018-03925-2
20. Pieters M., Philippou H., Undas A. et al. Subcommittee on Factor XIII and Fibrinogen, and the Subcommittee on Fibrinolysis An international study on the feasibility of a standardized combined plasma clot turbidity and lysis assay: Communication from the SSC of the ISTH. J. Thromb. Haemost. 2018; 16:1007–1012. DOI: 10.1111/jth.14002
21. Bitsadze V.O., Sluchanchuk E. V., Solopova A. G. et al. The role of the microenvironment in tumor growth and spread. Obstetrics, Gynecology, and Reproduction. 2024;18(1):96–111. Russian. DOI: 10.17749/2313-7347/ob.gyn
22. Kajdos M, Szymanski J, Jerczynska H et al. Microvesicles released from ectopic endometrial foci as a potential biomarker of endometriosis. Ginekol Pol. 2023;94(10):780–791. DOI: 10.5603/ GP.a 2022.0096
23. Aharon A., Brenner B. Microvesicles and thrombosis in obstetric-gynecological complications. Obstetrics, Gynecology and Reproduction. 2016;10(1):5–10. DOI: 10.17749/2313-7347.2015.10.1.005-010

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Certain characteristics of chronic heart failure and pulmonary arterial hypertension in HIV-positive patients

Goryacheva O.G., Zubarev M.A.

Perm State Medical University named after E. A. Wagner of the Ministry of Healthcare of the Russian Federation, Perm, Russia.

AUTHORS

Olga G. Goryacheva, MD, PhD, Associate Professor, Department of the Polyclinic Therapy, Perm State Medical University named after E. A. Wagner (PSMU) of the Ministry of Healthcare of the Russian Federation, Perm, Russia. ORCID 0000-0002-3336-229X

Mikhail A. Zubarev, MD, PhD, Honorary Professor, Department of Propedeutics of Internal Medicine, Perm State Medical University named after E. A. Wagner (PSMU) of the Ministry of Healthcare of the Russian Federation, Perm, Russia. ORCID 0009-0002-0909-742X

Pulmonary arterial hypertension (PAH) occurs in up to 36.5% of HIV-infected individuals and contributes to the development of pulmonary complications.

The aim of the study is to investigate the clinical, echocardiographic, and laboratory characteristics of patients with chronic heart failure (CHF) and HIV infection in the presence of PAH.

Methods. This study complied with the Declaration of Helsinki and was designed as a screening, cross-sectional, one-time clinical study. A total of 160 patients with HIV infection and CHF were examined, of whom 50% were diagnosed with PAH. The diagnosis of PAH was confirmed via echocardiography by determining a mean pulmonary artery pressure of ≥25 mmHg.

Results. Among the PAH patients with the background of CHF and HIV infection, there was a predominance of smokers and individuals who abused alcohol. These patients also had a higher prevalence of atrial fibrillation in their medical history. Diastolic dysfunction (DD), left ventricular hypertrophy, and left atrial dilation were more frequently observed in the PAH group. Tricuspid annular plane systolic excursion (TAPSE) was lower, while total peripheral vascular resistance (TPR) was higher in patients with PAH. Serum iron and transferrin levels were lower, and NT-proBNP levels were higher in CHF patients with HIV infection and PAH.

Among HIV-infected patients with CHF, the odds of developing PAH were 2.38 times higher (95% CI: 1.238–4.584, p=0.010), while the risk of developing CHF in HIV-infected individuals with PAH was 1.63 times higher (95% CI: 1.090–2.45). For those diagnosed with heart failure with reduced ejection fraction (HFrEF <40%), the odds of diagnosing PAH increased 4.89 times (95% CI: 1.009–23.736;

* Corresponding author. Tel. +7 (982) 452 7679. E-mail: o.goryacheva@mail.ru

p=0.047), and the risk of developing HFrEF in the presence of PAH rose 1.77 times (95% CI: 1.250–2.530).

Conclusion. The prevalence of PAH among HIV-infected patients with CHF is 50%. In this context, DD is more pronounced, patients with HFrEF are more common, NT-proBNP levels and TPR are higher. DD, HFrEF, left atrial dilatation, chronic kidney disease, pericardial effusion, and pleural effusion contribute to the development of PAH in HIV-infected individuals.

Keywords: HIV infection, chronic heart failure, pulmonary arterial hypertension, arterial stiffness, health status.

Conflict of interests: none declared.

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Introduction

Pulmonary arterial hypertension (PAH) is one of the most common vascular complications of HIV infection. PAH is present in up to 36.5% of HIV-infected individuals and contributes to the development of pulmonary damage [1].

The pathogenesis of PAH in HIV infection involves both the direct impact of the virus on the endothelium of the pulmonary artery and its branches, as well as indirect mechanisms due to secondary causes — such as the development of valvular heart disease, chronic heart failure (CHF), ongoing inflammatory processes, and the effects of certain components of antiretroviral therapy (ART).

The aim of the study is to investigate the clinical, echocardiographic, and laboratory characteristics of patients with CHF and HIV infection in the presence of PAH.

Methods

240 HIV-infected patients were examined ϕt the State Budgetary Healthcare Institution "City Clinical Hospital named after M.A. Tverye" in Perm. Of these, 160 patients were diagnosed with CHF, and 80 patients with CHF were found to have PAH, accounting for 50%.

The inclusion criteria for this study were: confirmed diagnosis of CHF in an HIV-infected patient and signed informed consent for participation in the study. Exclusion criteria included the presence of oncological diseases, deviant behavior, and severe valvular heart defects. The study was screening, cross-sectional, single-time-point, and clinical in nature, and was conducted in accordance with the Declaration of Helsinki.

The diagnosis of CHF was established based on an elevated plasma level of N-terminal pro–brain natriuretic peptide (NT-proBNP) above 125 pg/mL, echocardiographic (EchoCG) findings, and a combination of clinical symptoms, according to the 2020 clinical guidelines for the diagnosis and treatment of CHF [2].

Among patients with CHF, PAH was diagnosed using echocardiography on a VIVID T8 device (GE Healthcare, USA) following the methods recommended by the European and American Societies of Echocardiography [3, 4]. PAH diagnosis was based on measuring mean pulmonary artery pressure (mPAP) via the acceleration time to ejection time ratio (AT/ET) in the right ventricular outflow tract. Measurements were taken using pulsed-wave Doppler mode, and mPAP was calculated using a standard AT/ET ratio chart [4, 5]. PAH was diagnosed when mPAP was ≥25 mmHg at rest, in line with current clinical recommendations [6].

Arterial wall stiffness was assessed by calculating total peripheral vascular resistance (TPR) based on hemodynamic parameters:

$$TPR = mBP \times 60 / CO, \quad \text{in kPa·s/L}$$

Where mBP = mean blood pressure (mmHg), CO = cardiac output (L/min), and 60 is a conversion factor to seconds.

CO was calculated as:

$$CO = SV \times HR$$

Where SV = stroke volume, HR = heart rate.

mBP was calculated using the formula:

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$$mBP = ((SBP - DBP)/3 + DBP) \times 0.133,$$

Where SBP = systolic blood pressure (mmHg), DBP = diastolic blood pressure (mmHg), and 0.133 is the conversion factor to kPa.

$$SV = (EDV – ESV)/1000$$

Where EDV = end-diastolic volume (mL), ESV = end-systolic volume (mL), and 1000 is the conversion factor to liters.

PAH in HIV infection is classified under category 1.4.2 – "PAH associated with HIV infection." Measuring pulmonary capillary wedge pressure using a Swan–Ganz catheter was technically unavailable.

The Tei index was calculated using the formula:

$$Tei\ Index = (IVCT + IVRT) / ET$$

Where IVCT = isovolumic contraction time, IVRT = isovolumic relaxation time, and ET = ejection time.

Time intervals were measured using pulsed-wave and tissue Doppler modes by evaluating the peak velocity of the lateral and medial portions of the mitral annulus in the apical view. To minimize the influence of heart rate, the Tei index was measured over several cardiac cycles and the mean value was used.

Statistical Analysis

The statistical analysis of the study results was carried out using Statistika 13 (Russia) and SPSS 36 (USA). Normality of distribution was assessed using the Kolmogorov–Smirnov test. Comparisons of quantitative variables that did not follow a normal distribution were performed using the Mann–Whitney U-test. Categorical variables were compared using Pearson's chi-square (χ^2) test. Correlation analysis was conducted using Spearman's rank correlation method. To determine the predictive value of the studied variables, ROC analysis and calculation of odds ratios (ORs) and relative risks (RRs) were used.

Results

Among the 160 HIV-infected patients with CHF, 80 individuals (50%) were diagnosed with PAH. Table 1 presents the main clinical and anamnestic characteristics of HIV-infected patients with CHF and PAH in comparison to those without PAH.

The obtained results indicate a significant predominance of smokers and patients with alcohol abuse in the PAH group. AF in medical history was more frequently observed in patients with PAH. The percentage of smokers in the entire cohort of HIV-infected patients with CHF was 76.2%. In the PAH subgroup, the percentage of smokers was significantly higher, reaching 91.2%.

Table 1. **Main clinical and anamnestic differences depending on the presence of PAH in patients with CHF and HIV infection**

Parameter	PAH, n=80	No PAH, n=80	p
Males, n (%)	46 (57.5)	24 (30.0)	0.414
Age, years	36.0 [33.5; 40.0]	37.0 [35.0; 39.0]	0.718
6MWT, m	400.0 [350.0;450.0]	350.0 [300.0; 400.0]	0.325
ShOKS, score	6.0 [4.5; 7.5]	5.0 [4.0; 7.0]	0.046
FC of CHF	2.0 [2.0; 3.0]	2.0 [2.0; 3.0]	0.850
BMI, kg/m^2	20.0 [18.5; 22.9]	20.0 [17.9; 21.7]	0.481
Smoking, n (%)	73 (91.2)	49 (61.2)	<0.001
Alcohol abuse, n (%)	54 (67.5)	39 (48.7)	0.016
CHD, n (%)	14 (17.5)	24 (30)	0.063
PICS, n (%)	3 (3.75)	1(1.25)	0.311
Diabetes mellitus, n (%)	5 (6.25)	3 (3.75)	0.468
Atrial fibrillation (AF), n (%)	5 (6.25)	0 (0)	0.023
Ventricular arrhythmias, n (%)	36 (45)	27 (33.7)	0.145
Ascites, n (%)	17 (21.2)	19 (23.7)	0.705
Hydropericardium, n (%)	10 (12.5)	1 (1.25)	0.004
ART, n (%)	10 (12.5)	17 (21.25)	0.139
Anemia, n (%)	64 (80)	66 (82.5)	0.685
Thrombocytopenia, n (%)	48 (60)	42 (52.5)	0.339
Pancytopenia, n (%)	30 (37.5)	33 (41.2)	0.627

Table 2. **Main EchoCG data depending on the presence of PAH in patients with CHF and HIV infection**

Parameter	PAH, n=80	No PAH, n=80	p
LVEF, %	55.0 [46.0; 65.0]	60.0 [50.0; 67.0]	0.043
EF<40%, n (%)	9 (11.25)	2 (2.5)	0.028
LV E/A	1.22 [0.95; 1.72]	1.2 [0.9; 1.6]	0.989
E/e'	9.14 [5.6; 18.3]	6.1 [4.9; 10.3]	0.104
Tei index	0.56 [0.48; 0.7]	0.5 [0.38; 0.63]	0.049
LVMI, г/м^2	132.0[99.6; 184.0]	148.0[115.5; 167.5]	0.759
LVH, n (%)	51 (63.7)	32 (40.0)	0.002
LA volume, mm^3	43.0[30.5; 58.5]	31.8 [28.4; 42.0]	0.009
MPAP, mmHg	30.4 [25.6; 43.5]	13.7 [10.0; 15.5]	<0.001
LV EDV/BA, mm^3/m^2	54.3 [43.3; 64.5]	61.5 [51.6; 76.0]	0.343
LV ESV/BA, mm^3/m^2	21.8 [17.5; 31.0]	19.1 [15.9; 28.5]	0.140
LA volume/BA, mm^3/m^2	24.2 [16.9; 34.1]	18.9 [15.9; 26.5]	0.025
LVDD, n (%)	70 (87.5)	28 (35)	<0.001
Tortuosity of the CCA, n (%)	26 (32.5)	12 (15.0)	0.009
TVR, kPa·s/L	219.5 [175.0; 289.8]	191.1 [129.2; 227.2]	0.048
Elevated TPR, n (%)	37 (46.2)	14 (17.5)	<0.001
TAPSE, mm	15.0 [11.0; 20.0]	26.0 [20.0; 35.0]	0.024

Note. E/A – the ratio of the peak maximum velocity of early filling of the left ventricle to the peak maximum velocity of late filling of the left ventricle; E/e' – the ratio of the peak maximum velocity of early filling of the left ventricle to the early diastolic velocity of the movement of the fibrous ring; TAPSE – the systolic excursion of the tricuspid valve fibrous ring.

Table 2 presents the main EchoCG findings depending on the presence of PAH in patients with CHF and HIV infection. According to our data, patients with PAH had lower left ventricular ejection fraction (LVEF) values compared to patients without PAH.

Despite the fact that the E/e' ratio did not significantly differ between the groups, the Tei index showed higher values in the PAH group. Additionally, the number of patients with LVDD was higher in the PAH group. LVH and increased LA volume were more common in the PAH group.

Vascular wall stiffness was increased in PAH, reflecting damage to the vascular endothelium. The index of vascular wall stiffness, TVR, was higher in the PAH group, and the number of patients with elevated TVR in the PAH group was greater than in the group without PAH. On this background, pathological tortuosity of the carotid arteries was more often observed in patients with PAH. TAPSE values were significantly lower in the PAH group.

Table 3 presents the main laboratory parameters of the patients under study. The serum transferrin and iron levels were lower in the PAH patients. The number of patients with low transferrin and serum iron levels was higher in the PAH group. Since all patients had heart failure, the NT-proBNP levels did not differ significantly between the groups, but were elevated in all cases. Laboratory results showed lower transferrin and serum iron levels in patients with PAH. The number of patients with low transferrin levels was greater in the PAH group. The number of patients with NT-proBNP levels >300 pg/mL was higher in the PAH group. Serum urea and uric acid concentrations were higher in the PAH group compared to the group without PAH.

A correlation analysis was conducted between mPAP and several indicators that showed differences in the group comparisons. A statistically significant weak correlation ($p<0.05$) was found between mPAP and transferrin levels (r=0.175), serum iron (r=0.206), NT-proBNP (r=0.239), LVEF (r=-0.229), Tei index (r=0.257), TVR (r=0.228), E/e' (r=0.162), urea (r=0.258), and uric acid (r=0.259) according to the Cheddock scale.

An odds and risk ratio analysis was conducted regarding the development of PAH, considering factors that likely influence its occurrence. The findings revealed that, in HIV-infected individuals diagnosed with CHF, the odds of developing PAH increased by 2.38 times (95% CI 1.238-4.584, p=0.010), while the risk of developing CHF in the presence of PAH in HIV-infected individuals increased by 1.63 times (95% CI 1.090-2.45).

When LVEF<40% was detected in HIV-infected individuals, the chances of diagnosing PAH increased 4.89 times (95% CI 1.009–23.736; p=0.047), while the risks of LVEF <40% in HIV-infected individuals with PAH increased 1.77 times (95% CI 1.250-2.530).

Table 3. **Main laboratory parameters based on the presence of PAH in patients with CHF and HIV infection**

Parameter	PAH, n=80	No PAH, n=80	p
Transferrin, mg/dL	72.9 [44.2; 145.1]	91.7 [77.5; 120.7]	0.004
Low transferrin, n (%)	69 (86.2)	37 (46.2)	<0.001
Ferritin, μg/L	116.4 [61.9; 300.0]	172.8 [59.1; 570.5]	0.290
Low ferritin, n (%)	19 (23.7)	14 (17.5)	0.328
Uric acid, μmol/L	131.3 [75.2; 217.0]	111.5 [42.25; 221.7]	0.006
Serum iron, μmol/L	2.0 [1.1; 4.45]	3.5 [1.35; 7.0]	0.013
Low serum iron, n (%)	62 (77.5)	36 (45)	<0.001
NT-proBNP, pg/mL	509.4 [312.4; 1376.7]	513.1 [243.1; 1553.5]	0.263
NT-proBNP > 300 pg/mL, n (%)	62 (77.5)	25 (31.2)	<0.001
Serum CRP, mg/L	13.0 [5.3; 57.0]	24.0 [6.9; 53]	0.825
Urea, mmol/L	6.8 [4.3; 14.0]	3.8 [2.8; 9.6]	0.013
Sodium, mmol/L	141.7 [137.5; 144.0]	140.0 [137.0; 142.0]	0.279
Potassium, mmol/L	4.15 [3.6; 4.5]	3.8 [3.6; 4.4]	0.246
Creatinine, μmol/L	102.5 [77.5; 170.0]	92.5 [57.0; 142.0]	0.130
eGFR, mL/min/1.73m^2	74.0 [39.0; 96.5]	85.5 [41.0; 119.0]	0.116
CKD, n (%)	26 (32.5)	14 (17.5)	0.762
Fibrinogen, g/L	4.0 [3.0; 4.5]	3.5 [3.0; 5.0]	0.946
ESR, mm/h	42.0 [20.0; 61.0]	37.0 [21.0; 47.0]	0.399
CD-4 T-lymphocytes	200.0 [66.0; 300.0]	200.0 [21.0; 375.0]	0.863
Hemoglobin, g/L	92.0 [37.5; 111.0]	99.0 [75.0; 110.0]	0.579
Platelets, x10^9/L	138.0 [95.0; 228.0]	119.0 [68.0; 220.0]	0.380
Erythrocytes, x10^{12}/L	3.5 [2.8; 3.8]	3.2 [3.0; 3.3]	0.592

In the case of CKD in HIV-infected individuals, the risk of developing PAH was 2.18 times higher (95% CI= 1.047-4.536; p=0.044), while the risk of CKD in the presence of PAH increased by 1.46 times (95% CI=1.044-2.057).

The detection of pleural effusion in HIV-infected individuals increased the odds of developing PAH by 2.92 times (95% CI=1.224-6.996; p=0.019). PAH increased the risks of developing pleural effusion by 1.64 times (95% CI 0.298-1.172).

Hydropericardium in HIV-infected individuals increased the odds of developing PAH by 5.625 times (95% CI=1.242–25.492), while PAH increased the risks of developing pericardial effusion by 2.42 times (95% CI 1.124–5.208). The presence of LV diastolic dysfunction (DDLV) increased the odds of developing PAH by 3.18 times (95% CI 1.64–6.16). An increase in the volume of the LA increased the odds of developing PAH by 1.91 times (95% CI 1.04-3.54).

Discussion

The diagnosis of PAH is confirmed when mPAP is 25 mmHg or higher, however, patients with mPAP between 21 and 24 mmHg are also considered to be at risk [7]. The mean pulmonary artery pressure in healthy individuals is 14.0±3.3 mmHg [8]. The prevalence of PAH among the entire cohort of HIV-infected individuals, according to the US registry data, is 36.5%, with the proportion of truly HIV-associated PAH being 3.92%, and the rest of the cases being classified as idiopathic PAH [1]. Among the patients participating in our study, the proportion of PAH was exactly 50%, with all patients also having CHF in addition to HIV infection. There is insufficient data in the literature on the prevalence of PAH in patients with CHF and HIV infection.

Smoking is a risk factor for the development of cardiovascular diseases, which can further complicate the development of CHF [9]. Among HIV-infected patients with CHF, according to our data, 76.2% are smokers. Despite the fact that smoking was not identified as a factor influencing the development of PAH in the American HIV registry [1], our study shows that a significantly higher percentage of smokers is present in the PAH group. It is possible that the development of bronchial obstruction syndrome in smoking HIV-infected patients also contributes to the development of PAH, which does not diminish the significance of smoking as an risk factors for PAH development, as it can occur through several pathophysiological mechanisms.

The impact of alcohol on the development of PAH in HIV-infected individuals was found to be insignificant according to the American registry data [1], while in our study, this factor was significantly more prevalent in the group of patients with PAH and CHF+HIV

compared to the group with CHF+HIV without PAH. This can be attributed to the additional impact of the cardiotoxic effects of alcohol on the cardiovascular system of HIV-infected patients, as it is known that alcohol affects not only cardiomyocytes but also the endothelium, and PAH is one of the manifestations of alcoholic endothelial dysfunction [10, 11]. According to the literature, alcohol dependence is a trigger for the development of PAH [12].

HIV infection increases the likelihood of developing AF to the same or even a greater extent compared to traditional risk factors such as diabetes and hypertension [13]. In our study, cases of AF were recorded only in PAH patients with the background of CHF and HIV. In contrast, no cases of AF were registered in the group of patients with CHF and HIV without PAH. This suggests a possible association between PAH and AF in HIV-infected individuals. This may be facilitated by the prevalence of LA dilation in HIV-infected patients with PAH.

Pericardial effusion was more frequently observed in patients with PAH. It is known that the appearance of pericardial effusion in patients with PAH is an indicator of the development of right-sided heart failure [14]. This was confirmed in our study, as the group with PAH had a significantly reduced systolic excursion of the tricuspid valve fibrous ring, indicating the development of right-sided heart failure.

Lower values of LVEF in the PAH group suggest that in HIV-infected patients with CHF, PAH develops as a result of left-sided heart failure due to pulmonary venous congestion, the overcoming of the Kitaev reflex, and further elevation of pressure in the pulmonary artery system, as described in the work of Rosenkranz et al. in 2016 [15].

The Tei myocardial index was higher in the PAH group. Unlike the E/e' ratio, which increases with LVDD, the Tei index increases not only with left heart dysfunction but also with right heart dysfunction [16]. It is likely that the development of right-sided heart diastolic dysfunction, as a result of PAH, contributes to the increase in the Tei index in HIV-infected patients with CHF.

The LA volume was larger in patients with PAH, which can be explained by the development of PAH due to left heart failure and hypertension in the pulmonary veins. LVH was more common in PAH, similarly serving as a sign of left heart failure, which is the cause of PAH.

The increased tortuosity of the carotid arteries can be explained by the effects of endothelial dysfunction and elevated arterial pressure. The arterial stiffness indicator – TVR – was higher in the PAH group, probably due to the more pronounced endothelial damage in both circulations and the inflammatory syndrome associated with HIV infection in CHF patients [17].

Transferrin, unlike ferritin, is found in the blood plasma, and its concentration decreases not only in anemia but also in CHF, with a reduction of 20% or more being an unfavorable factor for CHF [18]. A decrease in transferrin levels in HIV-infected patients with PAH against the background of CHF can be interpreted as an unfavorable sign, as this is accompanied by an increase in plasma NT-proBNP levels – a marker for diagnosing and assessing the severity of CHF.

An elevated level of uric acid in HIV-infected patients signals significant endothelial dysfunction [19]. In our study, the serum uric acid level in PAH patients was significantly higher, along with higher TVR values, which supports the hypothesis about the relationship between uric acid and endothelial dysfunction in HIV-infected individuals.

An increase in blood urea concentration in PAH patients indirectly indicates the formation of a cardiorenal syndrome against the background of total endothelial dysfunction in HIV-infected patients with CHF. It is known that urea in HIV-infected individuals is a sensitive marker of acute kidney injury and tubulointerstitial damage [20].

The prognostic significance of some markers is presented for the first time. The chances of developing PAH in HIV-infected patients increase by 2.38 times with the development of CHF, by 4.89 times with a decrease in LVEF<40%, by 2.18 times with the development of CKD, and by 5.65 times with the detection of pleural effusion. On the other hand, the diagnosis of PAH in HIV-infected individuals increases the risks of developing CHF by 1.63 times, HFrEF by 1.77 times, CKD by 1.46 times, and the risks of developing pericardial effusion by 2.46 times.

Undoubtedly, the method of right heart catheterization using the Swan-Ganz catheter must be used to diagnose PAH, but echocardiography, even with slightly lower specificity, has sufficient sensitivity and, most importantly, is non-invasive [21].

Conclusion

The prevalence of PAH in HIV-infected patients with CHF is 50%. In the presence of PAH, patients with CHF and HIV exhibit more pronounced manifestations of diastolic dysfunction, and patients with reduced LVEF are more frequently observed, with higher levels of plasma NT-proBNP and TVR values. Diastolic dysfunction, HFrEF, increased LA volume, CKD, pericardial effusion, and pleural effusion contribute to the development of PAH in HIV-infected individuals.

Conflict of interests: none declared.

References

1. Kolaitis NA, Lammi M, Mazimba S, et al. HIV-associated Pulmonary Arterial Hypertension: A Report from the Pulmonary Hypertension Association Registry. Am J Respir Crit Care Med. 2022; 205(9):1121-1124. DOI: 10.1164/rccm.202111-2481LE
2. Tereshchenko SN, Galyavich AS, Uskach TM and others. Chronic heart failure. Clinical guidelines 2020. Russian Journal of Cardiology. 2020. 25(11): 311-374. Russian. DOI: 10.15829/1560-4071-2020-4083
3. Lang RM, Badano LP, Tsang W et al. American Society of Echocardiography; European Association of Echocardiography. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. Eur Heart J Cardiovasc Imaging. 2012 Jan;13(1):1-46. DOI: 10.1093/ehjci/jer316
4. Bazylev VV, Babakov RM, Bartosh FL et al. Comparative analysis of echocardiographic acceleration time and the ratio of acceleration time to total left ventricular ejection time with catheterization parameters in assessing the severity of aortic stenosis in patients with Normal flow High Gradient. Medical imaging. 2022;26(2):91-100. Russian DOI: 10.24835/1607-0763-1006
5. Rybakova MK, Mitkov VV, Baldin DG Echocardiography from M.K. Rybakova: manual: with the DVD-ROM attachment "Echocardiography from M.K. Rybakova". 2nd ed. M. : Publishing house "Vidar-M", 2018. 600 p. Russian
6. Avdeev SN, Barbarash OL, Bautin AE Pulmonary hypertension, including chronic thromboembolic pulmonary hypertension. Clinical guidelines 2020. Russian Journal of Cardiology. 2021. 26(12): 198-267.Russian. DOI: 10.15829/1560-4071-2021-4683
7. Hoeper MM, Bogaard HJ, Condliffe R et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D42-50. DOI: 10.1016/j.jacc.2013.10.032
8. Beshay S, Sahay S, Humbert M. Evaluation and management of pulmonary arterial hypertension. Respir Med. 2020 Sep;171:106099. DOI: 10.1016/j.rmed.2020.106099
9. Boytsov SA, Pogosova NV, Ansheles AA and others. Cardiovascular prevention 2022. Russian national guidelines. Russian Journal of Cardiology. 2023;28(5):5452. Russian. DOI: 10.15829/1560-4071-2023-5452
10. Williams EC, Hahn JA, Saitz R et al. Alcohol Use and Human Immunodeficiency Virus (HIV) Infection: Current Knowledge, Implications, and Future Directions. Alcohol Clin Exp Res. 2016; 40(10):2056-2072. DOI:10.1111/acer.13204
11. Goryacheva OG, Terekhina NA, Terekhin GA The effect of alcohol dependence on the course of chronic heart failure in patients with HIV infection. Ural Medical Journal. 2023; 22 (6): 104-111. Russian. DOI: 10.52420/2071-5943-2023-22-6-104-112
12. Donovan MK, Abdel-Rahman AA. Ethanol-induced lung and cardiac right ventricular inflammation and remodeling underlie progression to pulmonary arterial hypertension. Alcohol Clin Exp Res (Hoboken). 2024;48(7):1250-1260. doi: 10.1111/acer.15341.
13. Park DY, An S, Romero ME et al. Incidence and risk factors of atrial fibrillation and atrial arrhythmias in people living with HIV: a systematic review and meta-analysis. J Interv Card Electrophysiol. 2022;65(1):183-191. DOI: 10.1007/s10840-022-01233-w
14. Movsisyan GA, Arkhipova OA, Korobkova IZ et al. A clinical case of the use of ambrisentan as part of combination therapy in a severe patient with idiopathic pulmonary hypertension. Eurasian Journal of Cardiology. 2017 25; 2: 52-57. Russian
15. Rosenkranz S, Gibbs JS, Wachter R et al. Left ventricular heart failure and pulmonary hypertension. Eur Heart J. 2016;37(12):942-54. DOI: 10.1093/eurheartj/ehv512
16. Askin L, Yuce Eİ, Tanriverdi O. Myocardial performance index and cardiovascular diseases. Echocardiography. 2023;40(7):720-725. DOI: 10.1111/echo.15628
17. Arildsen H, Sørensen KE, Ingerslev JM et al. Endothelial dysfunction, increased inflammation, and activated coagulation in HIV-infected patients improve after initiation of highly active antiretroviral therapy. HIV Med. 2013;14(1):1-9. DOI: 10.1111/j.1468-1293.2012.01027.x
18. Campodonico J, Nicoli F, Motta I et al. Prognostic role of transferrin saturation in heart failure patients. Eur J Prev Cardiol. 2021;28(15):1639-1646. DOI: 10.1093/eurjpc/zwaa112
19. Pirro M, Bianconi V, Schiaroli E et al. Elevated serum uric acid levels are associated with endothelial dysfunction in HIV patients receiving highly-active antiretroviral therapy. Atherosclerosis. 2018; 272:101-107. DOI: 10.1016/j.atherosclerosis.2018.03.031.
20. Ikegwuonu I, Mercy N, Perpetua N, et al. The effect of highly active antiretroviral therapy on the urea and creatinine of HIV/

AIDS patients in Enugu Southeast of Nigeria. International Journal of Science and Research Archive. 2023. 9(2): 979-985. DOI: 10.30574/ijsra.2023.9.2.0681

21. Dong TX, Zhu Q, Wang ST et al. Diagnostic and prognostic value of echocardiography in pulmonary hypertension: an umbrella review of systematic reviews and meta-analyses. BMC Pulm Med. 2023;23(1):253. DOI: 10.1186/s12890-023-02552-y

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The effect of pedal cadence on a cycle ergometer on blood pressure reduction in individuals with hypertension: a systematic review of randomized controlled trials

Antonov A.G.[1,2], Miroshnikov A.B.[1], Rybakova P.D.[1,2], Smolensky A.V.[1]

[1] The Russian University of Sport (GTSOLIFK), Moscow, Russia.
[2] Center for Sports Innovative Technologies and Training of National Teams of the Moscow City Sports Department, Moscow, Russia.

AUTHORS

Alexey G. Antonov, Analyst, Department of Sports Nutritionology, Center for Sports Innovative Technologies and Training of National Teams of the Moscow City Sports Department, PhD student, Department of Sports Medicine, The Russian University of Sport (GTSOLIFK), Moscow. Russia. ORCID: 0000-0002-3409-4485
Alexander B. Miroshnikov, Doctor of Biological Sciences, Associate Professor, Professor, Department of Sports Medicine, The Russian University of Sport (GTSOLIFK), Moscow. Russia. ORCID: 0000-0002-4030-0302
Polina D. Rybakova*, Analyst, Department of Sports Nutritionology, Center for Sports Innovative Technologies and Training of National Teams of the Moscow City Sports Department, PhD student, Department of Sports Medicine, The Russian University of Sport (GTSOLIFK), Moscow. Russia. ORCID: 0000-0003-1165-6518
Andrey V. Smolensky, MD, PhD, Professor, Head of the Department of Sports Medicine, The Russian University of Sport (GTSOLIFK), Moscow. Russia. ORCID: 0000-0001-5663-9936

Aerobic exercise (walking, swimming, bicycling, etc.) is an important component of lifestyle modification for the prevention and control of arterial hypertension (AH).

The aim of this study was to conduct a systematic review of randomized controlled trials (RCTs) to investigate the relationship between pedal cadence on a cycle ergometer and blood pressure (BP) levels in individuals with hypertension (AH).

Methods. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Literature searches were performed in the following databases: PubMed, MedNar, Cochrane Library, Epistemonikos, and eLibrary. No restrictions on date or language were applied.

Results. A total of 199 records were identified across the databases. However, none of the studies met the inclusion criteria. As a result of a systematic search in multiple electronic databases (PubMed, MedNar, Cochrane Library, Epistemonikos, and eLibrary) without date or language restrictions, the review did not identify any RCTs

* Corresponding author. Tel. +7 (495) 788-1111. E-mail: rybakova.poly@yandex.ru

investigating the potential impact of different pedal cadences on BP in individuals with AH.
Conclusion. We consider it appropriate to publish our findings, as this study has identified a gap in the literature regarding the relationship between pedal cadence and elevated BP in individuals with AH.
Keywords: pedal cadence, cycling cadence, cycle ergometry, hypertension, cardiovascular diseases.

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Introduction

Hypertension (AH) is one of the leading causes of cardiovascular disease (CVD) mortality. Currently, approximately 1.4 billion people worldwide suffer from AH [1]. AH is a multifactorial condition and can be caused by factors such as low physical activity (LPA), consumption of high-sodium foods, obesity, alcohol consumption, and smoking [2].

The non-pharmacological effects of physical exercise can contribute to hemodynamic changes, increased nitric oxide production, and alterations in peripheral arterial resistance [3]. LPA promotes the development of chronic diseases. Physical activity programs and dietary monitoring are essential as part of disease prevention. Acute responses to exercise typically lead to an increase in heart rate (HR), vasodilation due to enhanced nitric oxide synthesis, increased blood flow [4], and improved absorption of energy substrates [5].

In the theory and practice of secondary AH prevention, significant attention is given to aerobic activity. Long-term chronic responses to exercise contribute to adaptations such as reduced resting HR, associated decreases in blood pressure (BP) [6], and improved cardiac function [7]. Current guidelines recommend physical exercise as part of both primary and secondary CVD prevention [8]. While variables such as exercise volume and intensity have been studied [6], the literature has paid little attention to the effects of different pedal cadences (PC) on a bicycle/cycle ergometer in the prevention and treatment of AH. Systematic physiological responses to exercise are directly influenced by the intensity, duration, and frequency of the activity.

An analysis of existing challenges within the context of modern scientific literature, as well as inquiries from specialists in sports medicine, clinical practice, and therapeutic exercise, highlights the relevance and importance of this topic, necessitating further in-depth study.

The present study aims to conduct a comprehensive analysis of data obtained through a search for randomized controlled trials. The objective of the analysis is to determine the relationship between pedal cadence on a cycle ergometer and BP levels in individuals with AH.

Methods

The study was conducted at The Russian University of Sport (GTSOLIFK), Department of Sports Medicine (Moscow). This systematic review and data analysis were performed in strict accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria, which establish standards for reporting systematic reviews and meta-analyses [9].

The study protocol was developed in full compliance with PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) requirements, which regulate reporting standards for systematic review and meta-analysis protocols [10]. The protocol was registered before the information search began and was not modified at any stage of the study, either during or after its completion. The protocol registration was conducted in the international database protocols.io[1].

During the study planning phase, it was decided to include only randomized controlled trials (RCTs) in the analysis.

[1] DOI: dx.doi.org/10.17504/protocols.io.ewov19p6ylr2/v1

Table. **Databases and search queries**

Database	Search query
PubMed	(((((“cadence”[All Fields] OR “cadences”[All Fields] OR “cadency”[All Fields] OR ((“foot”[MeSH Terms] OR “foot”[All Fields] OR “pedal”[All Fields] OR “pedaled”[All Fields] OR “pedaling”[All Fields] OR “pedalled”[All Fields] OR “pedalling»”All Fields] OR “pedals”[All Fields]) AND (“rotate”[All Fields] OR “rotated”[All Fields] OR “rotates”[All Fields] OR “rotating”[All Fields] OR “rotation”[MeSH Terms] OR “rotation”[All Fields] OR “rotations”[All Fields] OR “rotational”[All Fields] OR “rotator”[All Fields] OR “rotators”[All Fields]) AND (“epidemiology”[MeSH Subheading] OR “epidemiology”[All Fields] OR “frequency”[All Fields] OR “epidemiology”[MeSH Terms] OR “frequence”[All Fields] OR “frequences”[All Fields] OR “frequencies”[All Fields]))) AND (“bicycle”[All Fields] OR “bicycled”[All Fields] OR “bicycles”[All Fields] OR “bicycling”[MeSH Terms] OR “bicycling”[All Fields]) AND ((“bicycling”[MeSH Terms] OR “bicycling”[All Fields] OR “cycling”[All Fields] OR “cycle”[All Fields] OR “cycle s”[All Fields] OR “cycled”[All Fields] OR “cycles”[All Fields] OR “cyclings”[All Fields]) AND (“ergometer”[All Fields] OR “ergometers”[All Fields])) AND (“hypertension”[MeSH Terms] OR “hypertension”[All Fields] OR (“high”[All Fields] AND “blood”[All Fields] AND “pressure”[All Fields]) OR “high blood pressure”[All Fields])) OR (“hypertense”[All Fields] OR “hypertension”[MeSH Terms] OR “hypertension”[All Fields] OR “hypertension s”[All Fields] OR “hypertensions”[All Fields] OR “hypertensive”[All Fields] OR “hypertensive s”[All Fields] OR “hypertensives”[All Fields])) NOT ((“healthies”[All Fields] OR “healthy”[All Fields]) AND (“adult”[MeSH Terms] OR “adult”[All Fields] OR “adults”[All Fields] OR “adult s”[All Fields]))) AND ((“filter”[All Fields] OR “filter s”[All Fields] OR “filtered”[All Fields] OR “filtering”[All Fields] OR “filterings”[All Fields] OR “filters”[All Fields]) AND (“randomized controlled trial”[Publication Type] OR “randomized controlled trials as topic”[MeSH Terms] OR “randomized controlled trial”[All Fields] OR “randomised controlled trial”[All Fields]))) AND (randomizedcontrolledtrial[Filter])
Epistemonikos	(title:(cadence) OR abstract:(cadence)) OR (title:(cadence) OR abstract:(cadence)) OR (title:(pedal rotation frequency) OR abstract:(pedal rotation frequency)) AND (title:(bicycle) OR abstract:(bicycle)) OR (title:(cycle ergometer) OR abstract:(cycle ergometer)) AND (title:(high blood pressure) OR abstract:(high blood pressure)) OR (title:(hypertension) OR abstract:(hypertension)) NOT (title:(healthy adults) OR abstract:(healthy adults))
Cochrane Library	(cadence):ti,ab,kw AND (cycle ergometer):ti,ab,kw AND (hypertension):ti,ab,kw
MedNar	Full Record: cadence OR pedal rotation frequency AND bicycle OR cycle ergometer AND high blood pressure OR hypertension
Elibrary	(cadence, pedal speed, bicycle ergometer, hypertension, hypertension, high blood pressure)

Search Strategy. The literature search was conducted as part of a comprehensive analysis covering publications in all languages without restrictions on the publication date. The search methodology followed the PRESS (Peer Review of Electronic Search Strategies) guidelines [11] and included the following electronic databases: “PubMed,” “MedNar,” “Cochrane Library,” “Epistemonikos,” and “eLibrary.” The keywords (search queries) are presented in the table.

• Following the recommendations of Benzies et al., a search for “gray” literature was conducted in the electronic archive SportRχiv to deepen the study on this topic [12]. Studies identified through the electronic search underwent manual screening to detect additional potentially relevant data.

• The inclusion criteria for studies in the systematic review were based on the PICOS framework [13]: P (Population) – individuals over 18 years old with elevated BP or AH; I (Intervention) – performance of exercise protocols (long-term and short-term) on a cycle ergometer with varying PC; C (Comparison) – comparison with a control group or pre-intervention baseline; O (Outcomes) – Changes in BP; S (Study) – RCTs.

• **Exclusion criteria:** (a) PC was not specified; (b) The intervention was not limited to cycle ergometer exercise; (c) Participants were normotensive.

• *Study selection procedure:* Two researchers, Antonov A.G. and Rybakova P.D., independently and in parallel screened article titles and abstracts from electronic databases to determine eligibility based on the inclusion/exclusion criteria. Duplicate articles and those not meeting the set criteria were excluded from further review. Any discrepancies in the selection process were resolved through discussion and consensus between the researchers. If necessary, a third expert, Miroshnikov A.B., was consulted for the final decision.

• *Data extraction procedure.* After the final selection of studies, Antonov A.G. and Rybakova P.D. independently and in parallel extracted data from the full texts of RCTs according to the predefined inclusion/exclusion criteria. Any disagreements regarding data extraction were resolved through discussion and consensus. If necessary, a third expert, Miroshnikov A.B., was involved to reach a final decision. According to McHugh, inter-rater agreement (kappa coefficient) ranged from 0.53, which is considered weak, to 1.00, which is close to perfect [14].

• **Study Results.** The database search identified 199 potentially relevant sources. The study scheme, illustrating the empty review process, is presented in Figure 1. The absence of studies meeting the inclusion criteria prevented statistical data analysis.

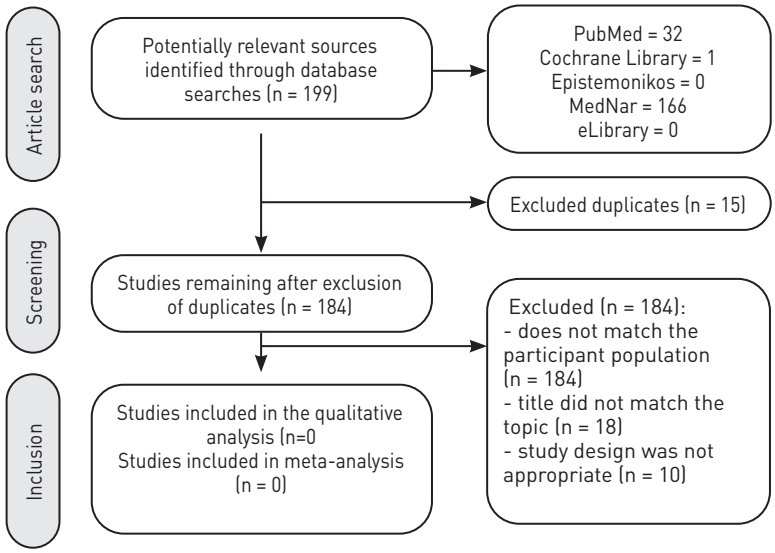

Fig. 1. Block diagram PRISMA

Nevertheless, the work adhered to the "Synthesis Without Meta-analysis in Systematic Reviews" (SWiM) guidelines [15]. Additionally, the risk of systematic bias was not assessed. Based on the currently available data, this systematic review appears to be the first study investigating the relationship between PC and BP in individuals with elevated BP and AH.

Discussion

The systematic search conducted across five electronic databases covering healthcare, physical education, and sports — without temporal or linguistic restrictions— did not identify any RCTs examining the effects of different PC on BP in individuals with AH. Empty reviews, such as this one, play a crucial role in emphasizing the need for systematic analysis of current issues. They highlight gaps in existing scientific literature, demonstrate the current level of evidence, and indicate areas where further research is necessary [16, 17].

The impact of aerobic exercise protocols on BP in individuals with AH is well-documented in the global literature [6]. A 2023 meta-analysis compared two aerobic exercise modalities—high-intensity interval training (HIIT) and continuous aerobic training—finding that HIIT had a greater BP-lowering effect than continuous aerobic workouts [18]. Additionally, a 2024 meta-analysis suggests that sprint interval training (SIT) is an effective intervention for reducing BP in adults. This type of training represents a practical and feasible alternative to moderate-intensity continuous training while providing additional health benefits such as improved cardiovascular endurance and enhanced metabolic function [19].

For instance, a 2024 RCT involving competitive cyclists examined three tests with different PC rates (60, 90, and 120 rpm) while maintaining identical power output. The results indicated that at 120 rpm, the higher speed required a faster cycle of muscle contraction and relaxation, potentially increasing reliance on glycolytic fast-twitch muscle fibers, which are designed for rapid and powerful contractions [20]. The possible mechanisms underlying the benefits of HIIT and SIT with high PC include the recruitment of high-threshold muscle fibers, which triggers a cascade of physiological processes that enhance the oxidative potential of glycolytic fibers. This, in turn, increases nitric oxide production, leading to antihypertensive effects and improved aerobic capacity [21].

Although current international guidelines recommend cycling as an aerobic exercise for the prevention and treatment of AH [8], they do not specify the optimal PC for achieving the best outcomes. It is likely that different PC rates may have distinct effects on BP, underscoring the need for RCTs in this area.

Conclusion

The systematic review aimed at assessing the impact of PC on BP in individuals with AH has revealed a significant gap in the available evidence. A thorough search of leading electronic databases using an extensive set of keywords failed to identify any RCTs that met the specified inclusion criteria. Consequently, there are currently no direct pieces of evidence link-

ing PC effects to BP changes in individuals with AH. This result is important in itself, as it highlights the lack of high-quality evidence in this research area. It underscores the need for further scientific efforts to obtain reliable data. It is essential to emphasize that the absence of RCTs does not equate to a complete lack of information on this issue but rather indicates the necessity of conducting additional research to establish solid evidence.

Conflict of interests: none declared.

References

1. Al-Makki A, DiPette D, Whelton PK, et al. Hypertension Pharmacological Treatment in Adults: A World Health Organization Guideline Executive Summary. Hypertension. 2022; 79(1): 293-301. DOI: 10.1161/HYPERTENSIONAHA.121.18192
2. Channon KM. Exercise and cardiovascular health: New routes to reap more rewards. Cardiovasc. Res. 2020; 116: 56–58. DOI: 10.1093/cvr/cvz264
3. Hanssen H, Boardman H, Deiseroth A, et al. Personalized exercise prescription in the prevention and treatment of arterial hypertension: a Consensus Document from the European Association of Preventive Cardiology (EAPC) and the ESC Council on Hypertension. Eur J Prev Cardiol. 2022; 29(1): 205-215. DOI: 10.1093/eurjpc/zwaa141
4. Oral O. Nitric oxide and its role in exercise physiology. J Sports Med Phys Fitness. 2021;61(9): 1208-1211. DOI: 10.23736/S0022-4707.21.11640-8
5. Picard M, McEwen BS, et al. An energetic view of stress: Focus on mitochondria. Front. Neuroendocrinol. 2018; 49: 72-85. DOI: 10.1016/j.yfrne.2018.01.001
6. Edwards JJ, Deenmamode AHP, Griffiths M, et al. Exercise training and resting blood pressure: a large-scale pairwise and network meta-analysis of randomised controlled trials. Br J Sports Med. 2023; 57(20): 1317-1326. DOI: 10.1136/bjsports-2022-106503
7. Paluch AE, Boyer WR, Franklin BA, et al. Resistance Exercise Training in Individuals With and Without Cardiovascular Disease: 2023 Update: A Scientific Statement From the American Heart Association. Circulation. 2024;149(3):e217-e231. DOI: 10.1161/CIR.0000000000001189
8. Kreutz R, Brunström M, Burnier M, et al. 2024 European Society of Hypertension clinical practice guidelines for the management of arterial hypertension. Eur J Intern Med. 2024; 126: 1-15. DOI: 10.1016/j.ejim.2024.05.033
9. Dickson K, Yeung CA. PRISMA 2020 updated guideline. Br Dent J. 2022; 232(11): 760-761. DOI: 10.1038/s41415-022-4359-7
10. Shamseer L, Moher D, Clarke M, et al. PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015; 350: g7647. DOI: 10.1136/bmj.g7647
11. McGowan J, Sampson M, Salzwedel DM, et al. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016; 75: 40-6. DOI: 10.1016/j.jclinepi.2016.01.021
12. Benzies KM, Premji S, Hayden KA. State-of-the-evidence reviews: advantages and challenges of including grey literature. Worldviews Evid Based Nurs. 2006; 3(2): 55-61. DOI: 10.1111/j.1741-6787.2006.00051.x
13. Amir-Behghadami M, Janati Population A. Intervention, Comparison, Outcomes and Study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews. Emerg Med J. 2020; №37(6): 387. DOI: 10.1136/emermed-2020-209567
14. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012; 22(3): 276-82. DOI: 10.11613/BM.2012.031
15. Campbell M, McKenzie J, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ. 2020; 368: l6890 DOI: 10.1136/bmj.l6890
16. Gray R. Empty systematic reviews: Identifying gaps in knowledge or a waste of time and effort?. Nurse Author & Editor. 2021; 31: 42-44. DOI: 10.1111/nae2.23
17. Slyer JT. Unanswered questions: implications of an empty review. JBI Database System Rev Implement Rep. 2016; 14(6): 1-2. DOI: 10.11124/JBISRIR-2016-002934
18. Oliveira GH, Okawa RTP, Simões CF, et al. Effects of High-Intensity Interval Training on Central Blood Pressure: A Systematic Review and Meta-Analysis. Arq Bras Cardiol. 2023; 120(4): e20220398. DOI: 10.36660/abc.20220398
19. Liang W, Liu C, Yan X, et al. The impact of sprint interval training versus moderate intensity continuous training on blood pressure and cardiorespiratory health in adults: a systematic review and meta-analysis. PeerJ. 2024; 12: e17064. DOI: 10.7717/peerj.17064
20. Dunst AK, Hesse C, Ueberschär O. Understanding optimal cadence dynamics: a systematic analysis of the power-velocity relationship in track cyclists with increasing exercise intensity. Front Physiol. 2024; 15: 1343601. DOI: 10.3389/fphys.2024.1343601
21. Kazeminia M, Daneshkhah A, Jalali R, et al. The Effect of Exercise on the Older Adult's Blood Pressure Suffering Hypertension: Systematic Review and Meta-Analysis on Clinical Trial Studies. International journal of hypertension. 2020; 2020: 2786120. DOI: 10.1155/2020/2786120

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Unveiling rare hemorrhagic complications of enoxaparin therapy. A clinical case review

Abdalani B.[1], Moufid O.[1], Abdellah B.[1], Habbal R.[1,2]

[1] Department of cardiology P37, Ibn Rochd University Hospital, Casablanca, Morocco.
[2] Faculty of Medicine and Pharmacy, Hassan II university of Casablanca, Casablanca, Morocco.

AUTHORS

Abdalani Badr*, MD, Department of Cardiology, Ibn Rochd Hospital, Casablanca, Morocco. ORCID: 0009-0003-5010-2179 Moufid Omar, MD, Department of Cardiology, Ibn Rochd Hospital, Casablanca, Morocco.
Moufid Omar, MD, Department of Cardiology, Ibn Rochd Hospital, Casablanca, Morocco.
Boucetta Abdellah, MD, Department of Cardiology, Ibn Rochd Hospital, Casablanca, Morocco.
Habbal R., Professor, MD, Head of the Department of Cardiology, Ibn Rochd Hospital, Casablanca, Morocco.

Background. Enoxaparin sodium, a low molecular weight heparin, is widely used for prophylaxis and treatment of thrombotic diseases. Despite its efficacy, enoxaparin can lead to complications, including hemorrhagic events.

Case presentation. We present a case of a 58-year-old man with ischemic heart disease and heart failure who developed a rare hemorrhagic complication—an extensive thigh muscle hematoma—while on enoxaparin therapy. The patient was managed conservatively with blood transfusion and discontinuation of anticoagulation, resulting in favorable outcomes.

Conclusions. This case underscores the importance of understanding the risks associated with enoxaparin therapy and highlights the need for individualized patient management strategies. Furthermore, it emphasizes the significance of interdisciplinary collaboration in addressing rare complications to optimize patient care. Further research is warranted to enhance our understanding and management of such complications in thromboembolic disorders.

Key words: Enoxaparin, soft muscles hematoma, complications, management.

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* Corresponding author. E-mail: abdalanibadr@gmail.com

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Background

Enoxaparin sodium is an injectable anticoagulant belonging to the low molecular weight heparin (LMWH) class, which are one of the most used anticoagulants, they are acting by inhibition of the final common pathway of the coagulation cascade [1]. Enoxaparin is characterized by a high ratio of anti-Xa to anti-IIa activity, a more regular release of tissue factor pathway inhibitor, weaker platelet interactions, and less inhibition of bone formation, distinguishing it from unfractionated heparin (UFH) [2]. Its use expanded widely since its introduction in 1995 for thrombotic disease prophylaxis, encompassing both curative treatment of venous and arterial thromboembolic disease [3]. However, like any medication, enoxaparin has contraindications such as renal insufficiency, and it may elicit adverse effects, notably bleeding, a formidable complication whose severity varies depending on its origin and the patient's clinical condition. Our case represents one of the hemorrhagic complications of enoxaparin, albeit rare, particularly due to its unusual localization.

Case presentation

Clinical findings

A 58-year-old man with modifiable cardiovascular risk factors, including a 5-year history of type 2 diabetes treated with rapid-acting insulin and chronic smoking cessation two months prior to admission, presented to the emergency department with worsening dyspnea that exacerbated at rest, accompanied by orthopnea evolving over the course of a week. Past medical history revealed treatment for ischemic heart disease over the past four years, initially manifesting as a basal ST-elevation myocardial infarction (STEMI) necessitating revascularization through angioplasty with active stenting of the middle anterior interventricular artery, proximal circumflex artery, and distal right coronary artery. Subsequent follow-up indicated a left ventricular ejection fraction (LVEF) of 25%, with frequent ventricular extrasystoles managed pharmacologically. Additionally, the patient had undergone surgical intervention for an open leg fracture five years prior, utilizing external fixator osteosynthesis.

The patient's medical regimen included treatment for heart failure with reduced ejection fraction (HFrEF), comprising high-dose diuretics (Furosemide 500 mg/day), Spironolactone 25 mg/day, a converting enzyme inhibitor (Ramipril 1.25 mg/day), aspirin 75 mg/day, statin (Simvastatin 20 mg/day), and an antiarrhythmic agent (Amiodarone 200 mg/day). However, the patient reported non-adherence to prescribed medications and discontinued therapy upon symptomatic improvement.

Symptoms of heart failure began approximately two months prior to presentation, initially manifesting as New York Heart Association (NYHA) class III exertional dyspnea with lower limb edema and no other associated symptoms. Progression of symptoms over the preceding week was characterized by worsening dyspnea at rest and orthopnea, exacerbation of edema to generalized edematous syndrome, and onset of productive cough, prompting medical consultation. Upon admission to the cardiac intensive care unit, the patient was noted to be drowsy and confused, with a Glasgow Coma Scale score of 14/15, hemodynamically stable with a blood pressure of 140/90 mmHg, heart rate of 103 bpm, respiratory rate of 34 breaths per minute, oxygen saturation of 82% on room air, capillary glucose level of 1.89 g/L, exhibiting cyanosis of the extremities, and weighing 99 kg (Body mass index: 35 kg/m²).Cardiovascular examination revealed a systolic heart murmur of mitral regurgitation, a displaced apex beat, palpable and regular peripheral pulses, and signs of acute heart failure including jugular venous distension, dependent edema reaching the root of the thigh with hydrocele formation, low-to-moderate ascites, facial edema, and crackles audible up to the apex.

Pleuropulmonary examination revealed diffuse wheezing with localized rhonchi in the right basithoracic region, while abdominal examination was unremarkable apart from ascites. Electrocardiography demonstrated regular sinus rhythm, prolonged PR interval, anteroseptal Q waves, isoelectric ST segments, inverted T waves in lateral and inferior leads, and low QRS voltage in peripheral leads, along with frequent ventricular extrasystoles. Transthoracic echocardiography (TTE) identified uncertainty regarding the presence of an apical thrombus measuring 29 x 22 mm (Figure 1), with comprehensive findings outlined in the accompanying table I.

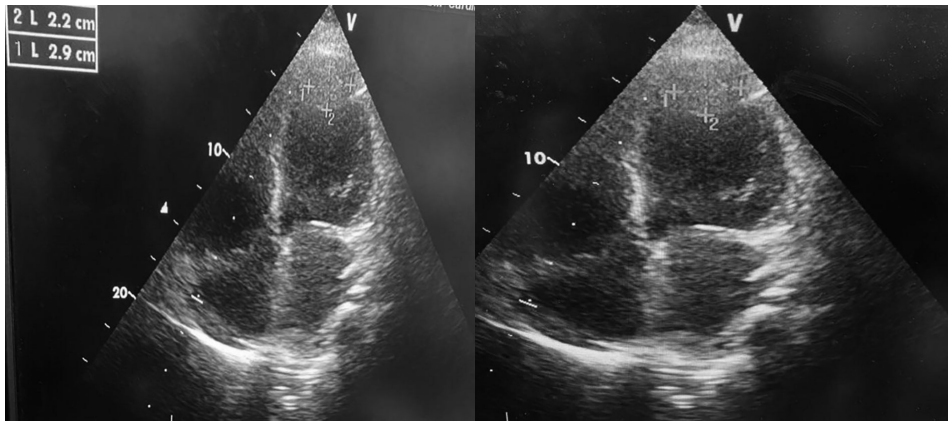

Fig. 1. The echocardiogram revealed an uncertain apical thrombus measuring 22 by 29 millimeters in the apical four-chamber view

Transthoracic Echocardiography findings

Table I: TTE findings at the admission

Left Ventricle	Dilated and non-hypertrophied, exhibiting global hypokinesia with a large apical akinesia. LVEF measured at 10–15%. Notably, there are apical thrombi measuring 29 × 22 mm
Mitral Valve	Demonstrates a merged type with high left ventricular filling pressure (LVFP).
Left Atrium	Dilated, without evidence of thrombus formation.
Right Atrium	Also dilated, with no evidence of thrombus
Mitral Valve	Presents of moderate mitral regurgitation without stenosis.
Aortic Valve	Tricuspid without evidence of leakage or stenosis.
Right Ventricle	Dilated with longitudinal systolic dysfunction.
Tricuspid Valve	Exhibits laminar tricuspid regurgitation, with estimated pulmonary artery systolic pressure (PAPS) of 74+15 = 89 mmHg
Pericardium	No effusion observed.
Inferior Vena Cava	Expanded to 32 mm, indicating non-compliance.
Aorta	Appears to be of normal caliber in the segments explored.

Additional Diagnostic Findings

Holter-ECG: Revealed rare supraventricular extrasystoles without significant ventricular response. However, frequent ventricular extrasystoles were noted at a rate of 50 per hour, with a load estimated at 1.65%. These extrasystoles were monomorphic and distributed throughout the day, including 16 bigeminy occurrences, 3 episodes of quadrigeminy, and 18 episodes of trigeminy. Notably, there was a burst of transient ventricular non-sustained tachycardia (TVNS) lasting 2800 ms at 6:00 p.m., and a rapid idioventricular rhythm (RIVA) reaching 123 bpm at 11:55 p.m.

Venous Doppler Ultrasound of Lower Limbs: No evidence of deep vein thrombosis detected. **Abdominal Ultrasound:** Demonstrated ascites without any significant abnormalities noted in renal or vesical structures.

Renal-Vesical Ultrasound: Showed normal-sized, evenly contoured, and fairly well-differentiated kidneys, with no dilatation of the excretory cavities.

Chest X-ray: Revealed cardiomegaly with hilar overload

Table II: Biological findings at the admission

Biological Check-up: (Table II)

Hemoglobin: 10.3 g/dL (microcytic hypochromic anemia)
Leukocytes: 5460/mm³
Neutrophils: 4430/mm³
Lymphocytes: 520/mm³
Platelets: 179000/mm³
Prothrombin Time (PT): 57%
Activated Partial Thromboplastin Time (aPTT): 34.2 seconds
Fibrinogen: 2.89 g/L
D-Dimers : 560 mg/mL
Urea: 1.61 g/L
Creatinine: 22 mg/L
Creatinine Clearance: 33 ml/min/1.73 m²
Sodium (Na+): 138 mmol/L
Potassium (K+): 4.4 mmol/L
Calcium (Ca++): 8.5 mg/dL
Magnesium (Mg++): 1.31 mg/dL
Plasmatic Protein: 71 g/L
C-Reactive Protein (CRP): 9.9 mg/L
Ferritin: 36.6 µg/mL
Aspartate Aminotransferase (ASAT): 26 IU/L
Alanine Aminotransferase (ALAT): 15 IU/L
Hemoglobin A1C (HbA1C): 8.5%
Creatine Phosphokinase (CPK): 238 IU/L
Lactate Dehydrogenase (LDH): 593 IU/L
Troponin I (us): 0.023 ng/mL
Thyroid-Stimulating Hormone (TSH): 1.28 mIU/L
Cytobacteriological Examination of Urine: Sterile

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Cytobacteriological Examination of Urine: Sterile

Therapeutic Management

- Positioning.
- Half-seated position to optimize respiratory mechanics and alleviate dyspnea.
- Non-Invasive Ventilation: One-hour sessions every four hours to assist with respiratory support and improve oxygenation.
- Nebulization: Nebulized treatments administered once every four hours to relieve bronchospasm and facilitate airway clearance.
- Oxygen Therapy: High-concentration oxygen therapy delivered via mask until respiratory status improves, ensuring adequate oxygenation.
- Diuretics: Furosemide: 500 mg intravenous initially with subsequent boluses of 120 mg every six hours (totaling 1g/day) to reduce fluid overload and alleviate symptoms of congestive heart failure.
- Hydrochlorothiazide: 25 mg orally once daily for additional diuresis.
- Dobutamine was introduced at a dosage of 2.5 µg/kg/min to enhance diuresis, following the CARESS protocol, subsequent to the placement of a central venous catheter in the right femoral vein between the 2nd and 5th day.
- Potassium Management: Potassium supplementation titrated based on serum potassium levels to prevent hypokalemia associated with diuretic therapy.
- Antiplatelet Therapy: Aspirin: 75 mg orally once daily for antiplatelet effects to reduce the risk of thrombotic events.
- Anticoagulation: Enoxaparin: 0.9 ml (90 mg adjusted to the patient's weight) subcutaneously twice daily (0,9 mg/kg/12h), indicated in light of the following findings: suspicion of intraventricular left thrombus, potentially exacerbated by significant apical akinesia and impaired ejection fraction within the context of ischemic cardiomyopathy.
- Lipid-Lowering Therapy: Simvastatin: 20 mg orally once daily to manage dyslipidemia and reduce cardiovascular risk.
- Antiarrhythmic Therapy: Amiodarone: 200 mg orally once daily for rhythm control in the setting of frequent ventricular extrasystoles.
- ACE Inhibitor: Ramipril: 1.25 mg orally once daily for its beneficial effects in heart failure management.
- Antibiotic Therapy: Amoxicillin-Clavulanic Acid: 1g intravenous every eight hours for ten days to treat possible underlying infection.
- Iron Supplementation: Iron Injection: 1000 mg intravenous for the management of microcytic hypochromic anemia.
- Chronic Obstructive Pulmonary Disease (COPD) Management: Implementation of appropriate pharmacological and non-pharmacological measures to manage COPD exacerbation.
- Hygienic and Dietary Measures.

Clinical Progression and Management

On the seventh day of hospitalization which is the seventh day of enoxaparin therapy, the patient presented with severe pain localized to the superior-internal aspect of the left thigh, accompanied by clinical findings of a palpable, tender ecchymosis (Figure 2). Despite these symptoms, the patient remained hemodynamically stable. Laboratory investigation revealed a notable decline in hemoglobin levels, indicative of worsening anemia with a recorded value of 6.1 g/dL, the PT was low at 45%, aPTT was at 47 seconds (1,6 Normal value) and the anti-Xa activity was high (1,2 UI/mL). Soft tissue ultrasound examination delineated the presence of hematomas within the deep muscular loge of the medial thigh muscle group. Consequently, anticoagulant therapy was promptly ceased. Consultation with the vascular surgery team ensued, leading to the performance of arterial and venous doppler ultrasound assessments of the lower limbs, revealing an absence of discernible vascular lesions (Figure 3). Furthermore, an abdominal ultrasound was conducted to assess for the presence of peritoneal or retroperitoneal hemorrhage, yielding negative findings for hematoma formation. Subsequently, a collective decision was made to pursue conservative management strategies, encompassing the implementation of the RICE protocol (Rest, Ice, Compression, Elevation), alongside anti-edematous and analgesic therapies. Additionally, the patient received a transfusion of 2 units of packed red blood cells to address the exacerbation of anemia. The administration of protamine was omitted due to the hemodynamically stable condition of the patient, who exhibited favorable response to alternative therapeutic interventions. Additionally, the presence of renal insufficiency posed a risk of

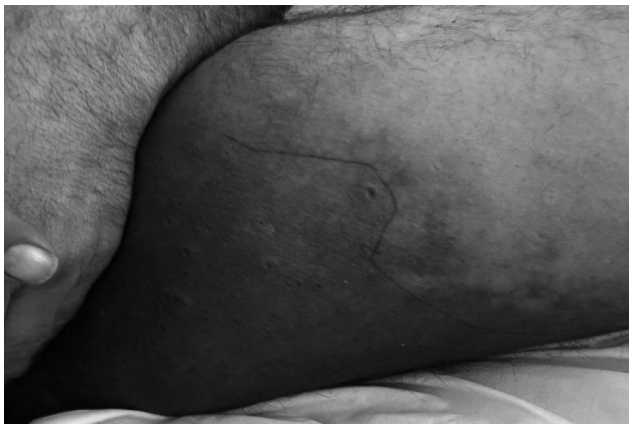

Fig. 2. Image demonstrating significant extension of the hematoma.

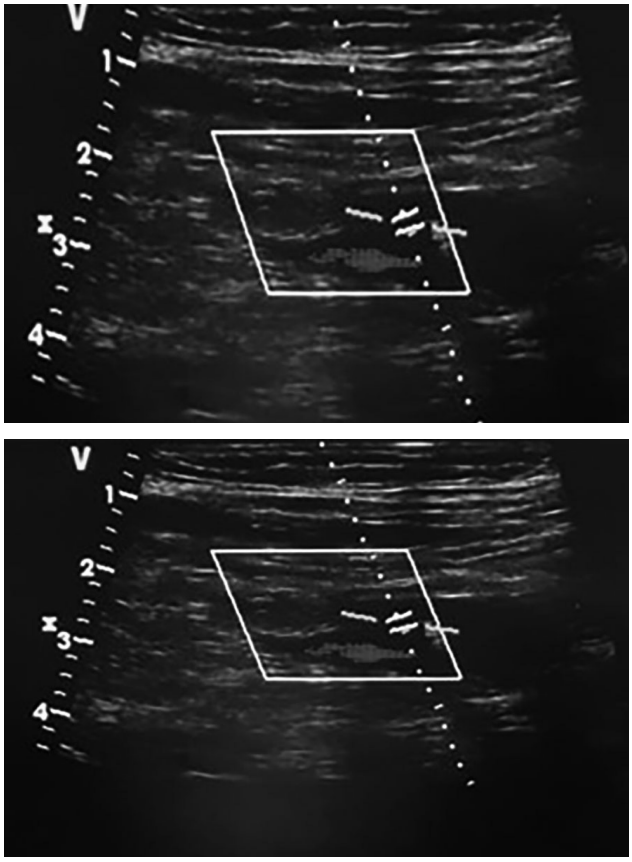

Fig. 3. Vascular Doppler imaging reveals no vascular lesions adjacent to the hematoma.

exacerbating renal filtration rate and consequently worsening cardiac decompensation.

Subsequent Progress

Substantial clinical amelioration was observed, marked by diminished pain severity and reduction in hematoma dimensions, as verified by both clinical evaluation and ultrasonographic imaging conducted on the second day following treatment initiation. Hemoglobin levels were meticulously monitored, demonstrating a controlled rise to 9.2 g/dL upon evaluation. Continuation of vigilant clinical and hematological surveillance ensured maintenance of stable hemoglobin levels, which eventually reached 11 g/dL. On the 10th day of hospitalization, a Transthoracic echocardiography revealed complete resolution of the previously identified apical thrombus, prompting the definitive cessation of anticoagulant therapy.

A transthoracic echocardiogram is performed following the stabilization of the patient on the 14th day of hospitalization, confirming the absence of an intracardiac thrombus, prompting the definitive cessation of anticoagulant therapy.

Subsequent to these positive developments, the patient was discharged from the hospital after 15 days of comprehensive treatment for heart failure, with effective management of decompensation and ongoing monitoring of the evolving hematoma. Follow-up consultations were arranged at regular intervals of 7 days, 15 days, and subsequent intervals, during which favorable clinical progress and regression of the hematoma were consistently observed on ultrasound imaging, and without any thrombus visualized in the TTE.

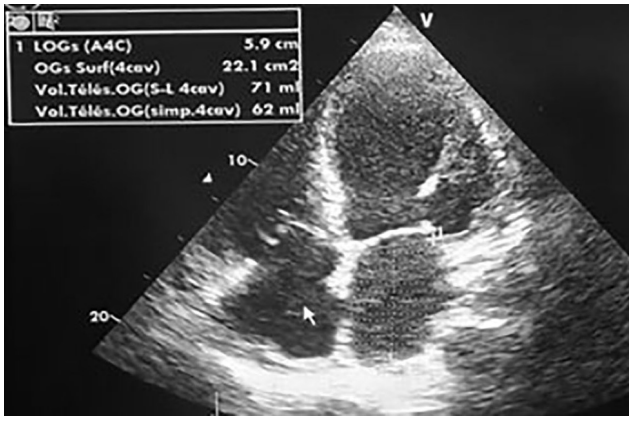

Fig. 4. Four-chamber echocardiographic view confirming the absence of an intracardiac thrombus.

Discussion

Enoxaparin stands as a prevalent choice among prescribed anticoagulant therapies, ranking second only to UFH during the acute phase of coronary syndrome [4].

Enoxaparin, a depolymerized derivative of heparin, shares structural similarities with UFH, comprising glycosaminoglycans. Its composition fea-

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tures polysaccharide chains composed of alternating D-glucosamine and uronic acid residues [5]. Enoxaparin's anticoagulant effect is mediated by interaction with antithrombin III, which inactivates serine proteases such as factors IIa (thrombin), IXa and Xa, thus indirectly inhibiting the conversion of prothrombin to thrombin and reducing thrombin-mediated conversion of fibrinogen to fibrin, thus preventing clot formation [4]. Intracardiac thrombus represents a common indication for LMWH anticoagulation, as observed in the case of our patient.

Intracardiac thrombi are a complication of severe left ventricular dysfunction at the stage of heart failure with LV ejection fraction < 40%, and differ in location, type and size, thus being responsible for other thromboembolic events (stroke) and thus a high mortality [6]. The etiologies of intracardiac thrombi are multiple, dominated by ischemic heart disease, dilated cardiomyopathy, mitral stenosis, mechanical prosthesis thrombosis, cardiac amyloidosis and also other systemic causes such as Bechet's disease, thrombophilia, antiphospholipid antibody syndrome and systemic lupus erythematosus [6-8]. Diagnosis is based on thrombus visualization by transthoracic or transesophageal echocardiography, the latter proving superior in terms of positive thrombus diagnosis, or cardiac MRI [9, 10]. Left ventricular thrombi are generally located in the apical region and do not infiltrate the ventricular wall. Morphologically, thrombi may be laminar or protruding, smooth or irregular in shape. They are generally contiguous with areas of non-contracted myocardium. The appearance of a left ventricular thrombus on CT is variable and depends on the age of the thrombus [11]. In the present case study, an ambiguous apical thrombus was identified through TTE. This observation was correlated with ischemic heart disease and a diminished ejection fraction of 15%.

Intracardiac thrombi are treated with anticoagulant therapy, whether injectable in the acute phase (LMWH, UFH or fondaparinux), vitamin K antagonists or direct oral anticoagulants, with anticoagulation management differing according to several parameters [12, 13]. In our clinical investigation, the decision to utilize LMWH was predicated upon the patient's precarious clinical condition. Anticipating the need for invasive hemorrhagic interventions, specifically central venous catheterization for vasopressor drug delivery, LMWH or UFH were deemed advantageous due to their facilitation of such procedures and obviation of the necessity for continuous anticoagulation monitoring [14].

Anticoagulation with Enoxaparin requires weight-based dose adjustment to avoid bleeding complications. A therapeutic dose has been successfully used in a morbidly obese patient at a weight-based dose of 0.85 mg/kg subcutaneously every 12 hours without the need for further adjustments [15]. A systematic literature review identified eight studies that evaluated the therapeutic dosing of enoxaparin in patients with a BMI ⩾ 40 kg/m^2 or > 100 kg and determined that patients with reduced dosing (0.75–0.85 mg/kg) achieved target anti-Xa levels in 66% of cases, compared with 43% of cases with full weight-based dosing (⩾ 0.95 mg/kg), and that the use of reduced weight-based enoxaparin dosing (0.75–0.85 mg/kg) may enable a greater number of obese patients with BMI ⩾ 40 kg/m2 or body weight > 100 kg to achieve target anti-Xa levels than with a full weight-based dose [16]. Although another study suggests that administration of enoxaparin to morbidly obese patients (up to 175 kg) with doses capped at 150 mg was not associated with an increase in the incidence of bleeding [17]. In our case, with a BMI of 35 kg/m², a dosage of 0.9 mg/kg subcutaneously every 12 hours was selected.

Hemorrhagic complications of enoxaparin are highly variable in terms of location and life-threatening severity, and may arise despite the implementation of preventive anticoagulation measures [18]. Mortality due to spontaneous muscle hematomas on anticoagulants can reach 25% [14].

Spontaneous muscle hematomas (SMH) as a complication of anticoagulation are a rarely described entity, accounting for just 0.6% of all cases [19]. They are classically associated with anticoagulant treatment and generally may occur in three distinct anatomical regions: the anterior abdominal musculature, the posterior abdominal musculature and the gluteal muscles. But they can also affect the lumbar and iliac muscles, with hemodynamic repercussions [20, 21].

Clinical symptomatology is highly variable, ranging from simple localized pain, with clinical examination revealing localized tenderness in the area of the hematoma, to hemodynamic instability if the bleeding is active and abundant, with general signs such as tachycardia and hypotension [14, 19].

Biologically, anemia may manifest, the severity of which correlates with the extent of bleeding [14, 19].

Radiological diagnosis is based on ultrasonography, which is the basic diagnostic tool, and CT, MRI or sometimes angiography of the lower limbs in search of arterial lesions [18, 19, 22, 33].

There is no consensus guiding the management of spontaneous muscle hematomas due to anticoagulation. Case studies published in this field find that the basis of treatment is analgesia, treatment of predisposing conditions and discontinuation of anticoagulation [14].

Conservative treatment is a therapeutic option. In the acute phase, it consists of pain relief and hematoma control, based on the RICE protocol (rest, ice, compression, elevation) [24, 25]. Ice will result in vasoconstriction, limiting hematoma extension, compression to act on intramuscular blood flow, and elevation to reduce swelling by modifying the pressure gradient to increase limb drainage [26].

The need for a blood transfusion must be assessed on the basis of the patient's hemodynamic status and comorbidities, it is not indicated systematically [23].

Reversing the anticoagulant effects in cases of bleeding can pose challenges. Protamine administration may be considered for patients experiencing bleeding episodes, as it offers partial reversal of the effects of LMWH [14].

If the SMH is large or uncontrollable, surgery involving incision and drainage of the hematoma, or surgical excision and drainage, remains an effective treatment option [23]. Another therapeutic avenue for managing active hemorrhage involves interventional procedures such as percutaneous transcatheter arterial embolization (PTAE), which aims to occlude the bleeding vessel [18].

In our patient's case, a conservative therapeutic strategy was implemented, comprising blood transfusion and unequivocal discontinuation of anticoagulant therapy, in conjunction with analgesic administration and strict adherence to the RICE protocol (rest, ice, compression, elevation). Case management was characterized by scrupulous oversight, contributing to a favorable clinical trajectory for the patient.

Conclusions

In conclusion, the management of venous thromboembolic disease and its associated complications necessitates a multifaceted approach grounded in evidence-based practices and patient-tailored interventions. The utilization of anticoagulation therapy, such as enoxaparin, underscores the delicate balance between thromboprophylaxis and the risk of hemorrhagic complications, especially in patients with complex medical backgrounds. Through a thorough understanding of the pathophysiology and risk factors involved, coupled with vigilant monitoring and judicious dosing adjustments, clinicians can optimize patient outcomes while mitigating adverse events. Additionally, the recognition and prompt management of rare complications like spontaneous muscle hematomas highlight the importance of interdisciplinary collaboration and individualized patient care. Moving forward, further research and clinical experience will continue to refine our approach to anticoagulant therapy, ultimately enhancing patient safety and quality of care in the management of thromboembolic disorders.

References

1. Mulloy B, Hogwood J, Gray E, Lever R, Page CP. Pharmacology of Heparin and Related Drugs. Pharmacol Rev. 2016;68(1):76-141. DOI:10.1124/pr.115.011247
2. Damiani A, De Menezes Caceres V, Roberts G, Coddo J, Scarfo N, Willliams DB, et al. A Clinical Practice-Based Comparison of Conventional and Individualized Dosing Strategies for Therapeutic Enoxaparin. Pharmacol Res Perspect. 2025;13(1):e70039. DOI: 10.1002/prp2.70039
3. Hoffmann P, Keller F. Increased major bleeding risk in patients with kidney dysfunction receiving enoxaparin: a meta-analysis. Eur J Clin Pharmacol. 2012;68(5):757-765. DOI: 10.1007/s00228-011-1149-6
4. Imbalzano E, Orlando L, Dattilo G, Gigliotti De Fazio M, Camporese G, Russo V, et al. Update on the Pharmacological Actions of Enoxaparin in Nonsurgical Patients. Medicina (Kaunas). 2024;60(1):156. DOI: 10.3390/medicina60010156
5. Gates RS, Lollar DI, Collier BR, Smith J, Faulks ER, Gillen JR. Enoxaparin titrated by anti-Xa levels reduces venous thromboembolism in trauma patients. Journal of Trauma and Acute Care Surgery. 2022;92(1):93-97. DOI: 10.1097/TA.0000000000003418
6. McCarthy CP, Murphy S, Venkateswaran RV, et al. Left Ventricular Thrombus. Journal of the American College of Cardiology. 2019;73(15):2007-2009. DOI: 10.1016/j.jacc.2019.01.031

7. Nya F, Abdou A, Bamous M, et al. Pseudotumeur cardiaque révélant une maladie de Behçet. Pan Afr Med J. 2017;26. DOI:10.11604/pamj.2017.26.151.11478
8. Dhibar DP, Sahu KK, Varma SC, et al. Intra-cardiac thrombus in antiphospholipid antibody syndrome: An unusual cause of fever of unknown origin with review of literature. Journal of Cardiology Cases. 2016;14(5):153-156. DOI:10.1016/j.jccase.2016.07.005
9. Chang P, Xiao J, Hu Z, Kwan AC, Fan Z. Imaging of left heart intracardiac thrombus: clinical needs, current imaging, and emerging cardiac magnetic resonance techniques. Ther Adv Cardiovasc Dis. 2022;16:17539447221107737. DOI: 10.1177/17539447221107737
10. Zhai M, Huang L, Liang L, et al. Clinical characteristics of patients with heart failure and intracardiac thrombus. Front Cardiovasc Med. 2022;9:934160. DOI:10.3389/fcvm.2022.934160
11. Pradhan A, Bhandari M, Vishwakarma P, et al. Anticoagulation for Left Ventricle Thrombus – Case Series and Literature Review for Use of Direct Oral Anticoagulants. JCDD. 2023;10(2):41. DOI:10.3390/jcdd10020041
12. Zhou Y, Logan K. Rectus sheath hematoma associated with commencement of therapeutic low molecular weight heparin injections: a case report. J Med Case Rep. 2022;16(1):87. DOI: 10.1186/s13256-022-03318-6
13. Hanni CM, Wilhelm SM, Korkis B, Petrovitch EA, Tsilimingras KV, McConachie SM. Therapeutic Enoxaparin in the Morbidly Obese Patient: A Case Report and Review of the Literature. Hosp Pharm. 2019;54(6):371-377. DOI:10.1177/0018578718802839
14. Chilbert MR, Zammit K, Ahmed U, et al. A systematic review of therapeutic enoxaparin dosing in obesity. J Thromb Thrombolysis. 2024;57(4):587-597. DOI:10.1007/s11239-024-02951-w.
15. Czupryn MJ, Exline C. Dosing of Enoxaparin in Morbidly Obese Patients: A Retrospective Cohort. Hosp Pharm. 2018;53(5):331-337. DOI: 10.1177/0018578718757518
16. Mackiewicz-Milewska M, Cisowska-Adamiak M, Szymkuć-Bukowska I, et al. Intramuscular Hematomas in Patients Receiving Prophylaxis or Anticoagulant Treatment after Spinal Cord Injury (SCI) – A Rare Complication: Description of Seven Cases and a Literature Analysis. Biomedicines. 2023;11(4):1142. DOI:10.3390/biomedicines11041142
17. Dohan A, Darnige L, Sapoval M, Pellerin O. Spontaneous soft tissue hematomas. Diagnostic and Interventional Imaging. 2015;96(7-8):789-796. DOI:10.1016/j.diii.2015.03.014
18. Abedini L, Mehrabi S, Hosseinpour R, Jahantab MB, Salehi V, Yavari Barhaghtalab MJ. Non-penetrating traumatic psoas muscle hematoma presenting with gross hematuria: a case report. Int J Emerg Med. 2021;14(1):20. DOI:10.1186/s12245-021-00345-w
19. Mackiewicz-Milewska M, Sakwińska K, Cisowska-Adamiak M, Szymkuć-Bukowska I, Ratuszek-Sadowska D, Mackiewicz-Nartowicz H. Bleeding into the Abdominal and Ilio-Lumbar Muscles – A Rare Complication in the Course of COVID-19: Analysis of Four Cases and a Literature Review. JCM. 2022;11(16):4712. DOI:10.3390/jcm11164712
20. Zhu Y, Wang C, Xu C, Liu J. Case Report: Spontaneous Intramural Hematoma of the Colon Secondary to Low Molecular Weight Heparin Therapy. Front Pharmacol. 2021;12:598661. DOI:10.3389/fphar.2021.598661
21. Mendes D, Penedones A, Martins M, Cavadas S, Alves C, Batel-Marques F. Rectus sheath hematoma in patients receiving subcutaneous enoxaparin: A case series of five patients. Clin Case Rep. 2020;8(12):3432-3439. DOI: 10.1002/ccr3.3427
22. Hotfiel T, Seil R, Bily W, Bloch W, Gokeler A, Krifter RM, et al. Nonoperative treatment of muscle injuries – recommendations from the GOTS expert meeting. J Experimental Orthopaedics. 2018;5(1):24. DOI: 10.1186/s40634-018-0139-3
23. Das S, Prakash S, Singh S, Shaikh O, Balasubramanian G. Spontaneous Rectus Sheath Hematoma. Cureus. 2023; 15(8):e44138. DOI: 10.7759/cureus.44138
24. Bisciotti GN, Volpi P, Amato M, Alberti G, Allegra F, Aprato A, et al. Italian consensus conference on guidelines for conservative treatment on lower limb muscle injuries in athlete. BMJ Open Sport Exerc Med. 2018;4(1):e000323. DOI: 10.1136/bmjsem-2017-000323
25. Kary JM. Diagnosis and management of quadriceps strains and contusions. Curr Rev Musculoskelet Med. 2010;3(1-4):26-31. DOI:10.1007/s12178-010-9064-5
26. Stainsby BE, Piper SL, Gringmuth R. Management approaches to acute muscular strain and hematoma in National level soccer players: a report of two cases. J Can Chiropr Assoc. 2012 Dec;56(4):262-8.

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Author Guidelines

Manuscript publication rules
in the International heart and vascular disease journal

Edit from December, 2021

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

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VIII. The procedure for rewiewing manuscripts

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

IX. The manner of publication of manuscripts

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

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

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

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X. After the publication in the journal

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

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

XIII. Journal subscription

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

XIV. Journal subscription

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

Official sites where information about the journal is placed:

http://www.heart-vdj.com

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

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

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