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Journal of the Cardioprogress Foundation

Influence of the patient's age on the probability of reoperation after aortic valve neocuspidalisation surgery (Ozaki technique)

The role of SGLT-2 inhibitors in the treatment of acute decompensation of chronic heart failure: a meta-analysis of large clinical trials

Percutaneous coronary interventions in oncological patients

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International Heart and Vascular Disease Journal

Journal of the «Cardioprogress» Foundation

Volume 11, № 39, June 2023

Contents

Editor's Welcome

Dear colleagues!

We present to your attention the next, thirty-ninth issue of the International Heart and Vascular Disease Journal that includes the leading, original, review articles, and ESC Congress 2022 report as well.

The results of a clinical population study to evaluate the characteristics of aortic valve stenosis and its association with a biomarker for heart failure and atrial fibrillation are presented in the "Leading Article" section. In a study of 2380 patients aged 35–69 years, the prevalence of high-gradient aortic stenosis increased with age. Biomarkers of heart failure and atrial fibrillation were associated with aortic valve area after correcting for the presence of heart failure by history, age and sex.

Three publications are presented in the "Original Articles" section. The first article evaluates clinical and functional parameters, markers of myocardial and renal dysfunction, and the ability of multimarker models to predict adverse outcomes in patients with chronic heart failure with preserved left ventricular ejection fraction, type 2 diabetes mellitus, and chronic kidney disease. Patients with a combination of the three diseases have severe clinical, functional disorders of the cardiovascular system and carbohydrate metabolism. The model that included NT-proBNP and sST2 levels had the best prognostic value. The second article presents a retrospective study of 720 patients who underwent aortic valve neocuspidation surgery. Among the different age categories, younger age was found to be a risk factor for reoperation. The third article analyzed echocardiographic data and N-terminal brain natriuretic peptide levels during the hospital phase of treatment in patients with acute ST-elevation myocardial infarction. It was shown that high-risk patients on the GRACE scale have older age, reduced left ventricular ejection fraction, and the most severe changes in diastolic dysfunction.

Two papers are presented in the "Review Articles" section. The first article presents a systematic review of literature data to determine the impact of early prescription of sodium-glucose cotransporter type 2 inhibitors in patients with acute decompensation of chronic heart failure on the immediate prognosis, as well as the effect of therapy on reducing the level of heart failure markers at the hospital stage. The second article focuses on the problems of percutaneous coronary intervention in cancer patients. This procedure is associated with an increased risk of bleeding, in-hospital and long-term mortality, and the need for repeat revascularisation. Proper management of cancer patients with concomitant coronary artery disease can reduce the risk of periprocedural complications during revascularisation.

The Cardioprogress Foundation report presents the results of the most important clinical trials and meta-analyzes shown at the European Society of Cardiology Congress 2022.

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

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

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International medical review

Researchers compared the long-term clinical outcomes of PCI to the left circumflex artery (LCx) versus the left anterior descending artery (LAD) in a population with comparable predisposition.

Consecutive patients with symptomatic isolated de novo ostial lesions of the LCx or LAD treated with PCI were included. Patients with >40 % left main (LM) stenosis were excluded. A total of 287 consecutive patients with RIVA (n=240) or LCx (n=47) lesions treated with PCI were analyzed. After adjustment, 47 matched pairs were obtained. The mean age was 72±12 years and 82 % were male.

According to the Heart journal

Researchers in the USA studied the effect of video games on the risk of sudden death. Before the diagnosis, 1079 cardiac events were recorded in the participants. Events related to video games were found in 5 people (0.5 %). After diagnosing and treating them, 431 people were diagnosed with at least one breakthrough cardiac event.

The researchers concluded that the risk of cardiac events associated with video games is extremely low in people with hereditary diseases. The researchers note that although electronic games have a negative impact on health, the threat of sudden death should not be used to limit screen time.

According to the Journal of the American College of Cardiology

Scientists have advertised lifestyle adjustments in children and adolescents to prevent the development of obesity and reduce cardiovascular risks.

The experts noted that there has been a worldwide increase in the obesity rate in children and a decline in physical activity, leading to increased BP, dyslipidaemia and hyperglycaemia in this group. The combination of these factors causes damage to the arteries and heart.

The article details the dietary intake needed to prevent obesity. Snacking between meals should be avoided. Portion sizes should be limited, high calorie, low nutrient foods such as fruit juices, fast food should be avoided. There should be more unprocessed fruit, vegetables and cereals rich in fibre, and a lower intake of sugar and fats.

According to the European Journal of Preventive Cardiology

The researchers looked at the effect of infertility treatment on the likelihood of hospitalization for stroke after childbirth.

The incidence of hospitalization for stroke in the year after childbirth was 37 per 100,000 women who received fertility medicine and 29 per 100,000 participants who gave birth after spontaneous conception. The risk of hospitalization for stroke was 66 % higher in women who had infertility treatment. Those with haemorrhagic stroke were twice as likely to be hospitalized, and those with ischemic stroke — 55 % more likely.

The authors found that the occurrence of infertility treatment increased with the age of the women.

According to the JAMA Network Open

According to scientists, the prognosis of infective endocarditis in patients with an implanted intracardiac device is unfavourable, especially when the endocardium of the left heart is affected.

The study included 483 patients with infective endocarditis, dividing them into three groups. The first was participants with isolated infective endocarditis associated with the implanted device. The second group included patients with infective endocarditis with predominantly left heart involvement without a clear association with the implanted product. The third group included patients with infective endocarditis with predominantly left heart involvement and a clear association with the implanted device.

The removal of the device was associated with a better prognosis: the risk of death was reduced by 41 %.

According to the European Heart Journal

A group of scientists investigated the relationship between chronic liver disease and the risk of developing heart and blood vessel disease and its complications.

They assessed patients' risk of developing serious cardiovascular complications by looking at liver tests and indicators such as C-reactive protein, glycated haemoglobin, systolic blood pressure and total cholesterol.

The researchers highlighted the importance of preventing cardiovascular complications early in chronic liver disease.

According to the Journal of Hepatology

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Characteristics of aortic valve stenosis in urban population aged 35–69 years: prevalence, echocardiographic data, atrial fibrillation, biomarkers, lipoprotein(a)

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The aim of the study is to characterise the prevalence and echocardiographic (EchoCG) features of aortic valve stenosis (AVS) and to evaluate the associations of aortic valve area (AVA) with lipoprotein(a) (Lp(a)), the heart failure (HF) biomarker NT-proBNP and atrial fibrillation (AF) in an adult population.

Methods. We used data from the "Know your heart study" with a cross-sectional design, which included 2380 participants aged 35–69 years, recruited in 2015-2017. In 2328 respondents, the following were determined by EchoCG: mean pressure gradient (Gmean), mmHg, peak aortic blood flow velocity (Vmax), m/s. The presence of AS was confirmed by a ⩾15 mmHg and a Vmax at the valve ⩾2.5 m/s. In 2105 participants, AVA, cm^2 and the prevalence of severe AVS were determined by the continuous flow equation according to the criteria: AVA ⩽1.0 cm^2 and indexed AVA (iAVA) ⩽0.6 cm^2/m^2. Subtypes of AVS — high-gradient (HG) and low-gradient (LG) were distinguished according to EACI and ASE (2017) criteria. Structural and functional EchoCG parameters of the heart, disease history, biomarkers (troponin T, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), Lp(a)) were used in the analysis.

Results. The prevalence of high gradient aortic valve stenosis (HGAVS) (Gmean ⩾15 mmHg) was 0.43% (n=10), 0.2% aged 40–59 years and 1.1% aged 60–69 years (p=0.007); 0.6% in men and 0.3% in women. The prevalence of severe low gradient aortic valve stenosis (LGAVS) was 0.9% (n=18, 61% men) and all had a left ventricular ejection fraction (LVEF) >50%. The formation of concentric LV remodelling was detected in those with HGAVS, and the predominance of diastolic dysfunction was found in those with severe LGAVS. AVA value was associated with male gender (ß=0.383, p<0.001), age (ß=-0.097, p<0.001) and Lp(a) (ß=-0.048, p=0.018). In patients with severe LGAVS, NT-proBNP levels were Me 158.4 (105.4; 260.8) pg/ml and were higher than those without AVS (p=0.005). NT-proBNP correlated with iAVA and AF correlated with age, HF and AVA.

Conclusion. The prevalence of mild to moderately severe HGAVS according to echocardiography in the population was 0.2% at the age of 40–59 years and 1.1% at the age 60–69 years. Severe LGAVS occurred in 0.9% of participants. AVA was negatively associated with Lp(a) when corrected for sex and age. NT-proBNP and AF were associated with AVA when corrected for HF, age and sex.

Keywords: high-gradient, low-gradient aortic stenosis, population, prevalence, lipoprotein(a), N-terminal prohormone of brain natriuretic peptide (NT-proBNP).

Conflict of interest: none declared.

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Introduction

Due to an ageing population, the incidence of aortic valve stenosis (AVS) and its reconstructive surgery is increasing worldwide [1, 2]. A systematic review and meta-analysis of population-based studies conducted in European countries and North America showed that the prevalence of AVS in the elderly population (age ⩾75 years) is 12.4%, and severe AVS is present in 3.4% of elderly patients who are candidates for transcatheter aortic valve replacment (TAVR) [3]. In an epidemiological study conducted in Northern Norway (Tromsø), the prevalence of AVS was 0.2% in 50–59 year olds and 1.3% in 60–69 year olds [4]. It is noteworthy that the geographical distribution of AVS is heterogeneous. Regional clustering of AVS cases and observations of familial aggregation suggest that the genetic component contributes to the pathophysiology of AVS [5]. Researchers are currently focusing on lipoprotein(a) (Lp(a)), which is considered to be an important genetic risk factor for the development of atherosclerotic cardiovascular disease and AVS [6, 7].

In individuals with AVS, the mean pressure gradient (Gmean) often does not correspond to the aortic valve opening area (AVA), which is determined by multiple factors, both valvular (aortic valve calcification) and non-valvular (arterial stiffness), independent of flow. Of importance is the assessment of the severity of AV calcification by computed tomography (CT), which is strongly associated with the severity of AVS [8]. The AVS syndrome is heterogeneous, and low-gradient (LG) and high-gradient (HG) subtypes of AVS have been identified. Patients with "classical" LGAVS with reduced left ventricular ejection fraction (LVEF) have the worst prognosis after TAVR, including one-year

survival, compared to patients with HGAVS and "paradoxical" LGAVS with preserved LVEF [9, 10]. This phenomenon can often be misdiagnosed, leading to underestimation of symptoms and inappropriate delay of AV replacement surgery [11]. However, not all risk factors and pathophysiological features of the heterogeneous group of LG subtypes of AVS are fully understood and require further investigation. Atrial fibrillation (AF) complicates the course of AVS in 32 % of cases, often in the asymptomatic period with preserved LVEF; according to current thinking, its negative role is due to the transition from the asymptomatic stage of AVS to the symptomatic stage and to the worsening of the prognosis of patients after valve replacement [12]. Therefore, the determination of AF frequency in a population sample in different AVS subtypes seems to be relevant.

The study of HF biomarker levels, N-terminal brain natriuretic peptide (NT-proBNP) propeptide, both in relation to the severity of LV and LA remodelling and in terms of prognostic assessment of the occurrence of myocardial dysfunction after AVS surgery, is reflected in the modern literature [13]. The prospectivity of the determination of high-sensitivity cardiac troponin (hs-Tn) as a biomarker of myocardial damage, which can predict the risk of HF and other adverse cardiovascular events long before the appearance of structural and functional changes in the heart as determined by imaging techniques, has been demonstrated [14]. It is valuable in population studies with regard to the possibility of applying individual preventive measures. The prevalence of AVS and its subtypes in the population of the region (Arkhangelsk) using modern echocardiography (EchoCG) has not been determined.

The aim of the study is to characterise the prevalence and EchoCG features of AVS and to evaluate the associations of AVA with Lp(a), the HF biomarker NT-proBNP and AF in an adult population.

Methods

Data were used from the "Know your heart study" with a cross-sectional design, which included 2380 participants aged 35–69 years recruited in 2015–2017. Information on the methods of sampling and data collection are described in detail in the article by Cook S. et al [15]. The sample was formed on the basis of the anonymised database of the Federal Compulsory Medical Insurance Fund (FOMS). The database, covering four districts of the city, contained addresses of OMS-insured citizens and information on age and sex. Addresses were randomly selected and men and women aged 35–69 living there were invited to participate in the study. Inclusion criteria: living at randomly selected addresses in Arkhangelsk, aged 35–69 years. Exclusion criteria: presence of a mental illness that precludes the possibility of conducting an interview (inability to understand the questions, to answer them adequately); presence of a disability that precludes the possibility of undergoing a medical examination in a polyclinic (not able to walk); refusal to sign an informed consent form. The response rate was 68 %. Participants were given a questionnaire and 98 % underwent a medical examination at the university polyclinic. The present analyzes include 2328 participants in this study (41.4 % male) who had a set of EchoCG parameters necessary to achieve the aim of the study.

To assess AV parameters and structural and functional characteristics of the heart, we used data from transthoracic EchoCG (Vivid q, GE HealthCare) using a phased array transducer 1.5–3.6 MHz, the technique is described by Cook S. et al. [15]. LVEF according to Simpson method, %; LV stroke volume (SV), ml; SV indexed to body surface area (BSA) (iSV), ml/m^2; maximum left atrial (LA) transverse diameter, mm; LA volume (LAV), ml; LAV indexed to BSA (iLAV), min and max, ml/m^2; LV diameter in systole and in diastole, mm; LV posterior wall thickness (PWT) in systole and in diastole, mm; interventricular septal thickness (IVST) in systole and in diastole, mm; relative wall thickness (RWT); LV myocardial mass index (LVMI), g/m^2; pulmonary capillary wedging pressure (PCWP), mmHg; $E/é_{mean}$ (LV early filling velocity by transmittal Doppler/early relaxation velocity by tissue Doppler) reflecting LV filling pressure were determined and used in the analysis.

To detect AVS and assess its severity, peak aortic blood flow velocity (Vmax), m/s, and maximum and mean percutaneous pressure gradient (Gmean), mmHg, were determined. The presence of AVS was confirmed by Gmean ⩾15 mmHg and Vmax at the valve ⩾2.5 m/s.

In 2105 participants, AVA, cm^2 was determined using the continuous flow equation and the incidence of severe AVS was assessed using the criteria: AVA ⩽1.0 cm^2 and indexed AVA to BSA (iAVA) ⩽0.6 cm^2/m^2.

An attempt has been made to distinguish between four subtypes of severe AVS according to the current guidelines [16]:

Normal/preserved LVEF (pEF), HGAVS (NEF HGAVS) (pEF HGAVS): LVEF ⩾ 50 %, aortic Vmax ⩾4 m/s or Gmean ⩾ 40 mmHg, AVA ⩽ 1.0 cm^2;

Low/reduced LVEF (rEF), HGAVS (LEF HGAVS) (rEF HGAVS): LVEF<50 %, aortic Vmax ⩾4 m/s or Gmean⩾40 mmHg and AVA⩽1.0 cm^2.

Low/reduced LVEF, LGAVS ("classic" low-flow, low-gradient) (LEF LGAVS) (rEF LGAVS): LVEF<50 %, Vmax<4 m/s and G_{mean}<40 mmHg, AVA⩽1.0 cm^2, and SV ⩽35 ml/m^2.

Normal/preserved LVEF, LGAVS ("paradoxical" low-flow, low-gradient) (NEF LGAVS) (pEF LGAVS): LVEF⩾50 %, aortic Vmax<4 m/s and Gmean<40 mmHg, AVA⩽1.0 cm^2 and iAVA⩽0.6 cm^2/m^2 and SV⩽35 ml/m^2.

Information on medical history (arterial hypertension (AH), diabetes mellitus (DM), HF, AF) was obtained by questionnaire and screening examination.

Laboratory tests included: high-sensitivity troponin T (hs-Tn), ng/mL; N-terminal propeptide of brain natriuretic peptide (NT-proBNP), pg/mL; and Lp(a), mg/dL. Hs-Tn and NT-proBNP were determined by the immunoelectrochemiluminescence method (Cobas e411 analyzer; Roche Diagnostics GmbH, Hitachi, Japan), Lp(a) by the particle amplification immunoturbidimetric assay (AU 680; Beckman Coulter chemistry system) [15].

Ethical approval. The study was performed in accordance with the standards of Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol of the "Know your heart study" was approved by the local ethical committees of the London School of Hygiene and Tropical Medicine, London, UK (protocol No. 8808, 2015) and the Russian University (protocol No. 01/01-15, 2015). All study participants signed informed voluntary consent.

Statistical analysis. Descriptive data are presented as means (M) with standard deviations (SD) or medians (Me) with quartiles (Q1; Q3). Categorical variables are presented as absolute values and percentages. Comparisons between groups for continuous variables were made using the independent samples t-test. Continuous variables with skewed distributions were analyzed by ln transformation. Comparisons between groups on categorical variables were made using the chi-squared (x2) Pearson test. Associations of continuous variables (AVA, NT-proBNP) with age and sex and a number of other indices were determined using multivariate linear regression. Results of linear regression analysis are presented as standardised β-coefficients. Associations of AVS with dichotomous characteristics (medical history) were examined using multivariate logistic regression analysis with correction for sex and age, with results presented as odds ratios (OR) with 95% confidence intervals (CI). IBM SPSS Statistics 29 software was used for statistical analysis.

Results

The prevalence of AVS according to the Gmean ⩾15 mmHg criterion in the study sample was 0.43 %. The prevalence of HGAVS (mild and moderate) was 0.6 % in men and 0.3 % in women (p=0.489). There were no individuals with severe HGAVS in this sample (Table 1). The age of participants with HGAVS in both sexes was 63.0±9.1 years compared to 53.8±9.7 years

Table 1. **Assessment of AVS frequency and severity, (n=2328)**

AVS gradation By Gmean, mmHg	Both sexes, abs. number, (%)	Males, abs. number, (%)	Females, abs. number, (%)	p	Age (years), both sexes, M±SD	p
No AVS, Gmean<15 mmHg	2318 (99.6)	958 (99.4)	1360 (99.7)	χ^2 (2) = 1.431 p=0.489	53.8±9.7	P_{1-2} 0.022 P_{1-3} 0.365
Mild AVS, Gmean 15–19 mmHg	5 (0.2)	3 (0.3)	2 (0.15)		65.5±6.8	
Moderate AVS, Gmean 20–39 mmHg	5 (0.2)	3 (0.3)	2 (0.15)		60.5±11.3	
Severe AVS, Gmean⩾40 mmHg	0 (0)	0 (0)	0 (0)		—	
Distribution of participants with AVS (Gmean ⩾15 mmHg) in different age groups						
Age groups	**Absolute number of the participants**		**AVS. abs. number, (%)**			**P**
35-39 years	222		0 (0)			x^2 (6) = 17.719 p=0.007
40-49 years	656		1 (0.2)			
50-59 years	698		1 (0.2)			
60-69 years	752		8 (1.1)			

Table 2. **Distribution of the participants by the severity of AVS assessed by AVA, (n=2105)**

AVS gradation by AVA, cm^2	Both sexes Abs. number, (%)	Females, Abs. number, (%)	Males, Abs. number, (%)	p	Age (years), both sexes, M±SD	p
No/mild AVS, AVA>1.5 cm^2	1989 (94.5)	1136 (92.4)	853 (97.37)	χ^2 (2) = 38.931 p<0.001	53.7±9.7	P_{1-2}= 0.051 P_{1-3}= 0.004
Moderate AVS, AVA 1.0–1.5 cm^2	98 (4.7)	86 (7.0)	12 (1.37)		56.1±10.6	
Severe AVS, AVA⩽1.0 cm^2	18 (0.9)	7 (0.6)	11 (1.26)		61.1±10.3	

in those without AVS, p=0.003; participants with mild stenosis were older and their age was significantly different from those without AVS (p=0.022). No differences were found in the age of participants with moderate AVS compared to those without AVS (p=0.365).

The distribution of the participants with AVS (Gmean ⩾15 mmHg) in different age groups had a significant difference (p=0.007) (Table 1).

Analyzes of the distribution of participants by aortic Vmax also showed the absence of individuals with severe HGAVS (aortic Vmax⩾4.0 m/s). We identified 10 individuals (6 men) who had mild to moderate HGAVS according to both criteria (Gmean and aortic Vmax); all 10 had pLVEF ⩾50 %.

AVA 1.0-1.5 cm^2 was detected in 4.7 % of participants, with 7 % in females and only 1.37 % in males, AVA ⩽1.0 cm^2 was detected in 0.9 % of participants, corresponding to severe AVS, the prevalence of which was higher in males 1.26 % vs. 0.6 % in females (p<0.001) (Table 2). Among those with severe AVS, males predominated with 61.1 %. The mean age was highest in individuals of both sexes with severe AVS, 61.1±10.3 years, and significantly different from that of participants without AVS (P_{1-3}=0.004).

The distribution of participants with severe AVS (AVA⩽1.0 cm^2) in different age groups was as follows: 35–39 years (n=199) — 1 participant (0.5 %), 40–49 years (n=591) — 2 people (0.3 %), 50–59 years (n=627) — 1 participant (0.2 %), 60–69 years (n=688) — 14 people (2.0 %), χ^2 (6)=27.284, p<0.001.

All participants with AVA⩽1.0 cm^2 had pEF (⩾50 %). However, Gmean and Vmax in the aorta did not meet the criteria for severe HGAVS. Gmean was 11.6±7.5 mmHg. To classify these participants into specific subtypes of severe LGAVS, SV (n=15) was also assessed, which was 24.6±7.5 ml/m^2. SV index was⩽35 ml/m^2 in 93.3 % (n=14) of participants, corresponding to severe "paradoxical" low-flow LGAVS and pEF. There were no participants with "classic" LGAVS and rEF. Three patients with LGAVS and pEF had missing SV data. One participant with severe LGAVS and SV was 36.8 ml/m^2, i.e. AVS with normal flow/LG and pEF (Appendix 1).

EchoCG parameters of individuals with HGAVS (mild and moderate) were higher than those of individuals with Gmean<15 mmHg. They had higher interventricular septal thickness in diastole (12.5±1.5 mm vs. 10.6±1.6 mm in the comparison group, p<0, 001) and LVMI (146.1±38.8 g/m^2 vs 111.6±28.7 8 g/m^2, p<0.001). LA diameter in systole (43.0±7.1 mm vs 37.3±4.5 mm, p<0.001), iLAV max (39.7±15.0 ml/m^2 vs 27.4±7.4 ml/m^2, p<0.001) were also higher. Moreover, hs-Tn concentration was higher in those with HGAVS (12.44±8.35 pg/ml vs. 7.46±5.59 pg/ml in the comparison group, p=0.002). No differences in diastolic function indices (PCWP and E/é ratio) were found between the comparison groups (Table 3).

A comparative analysis of EchoCG parameters between participants with severe LGAVS (AVA⩽1.0 cm^2) and those with AVA>1.0 cm^2 showed that this variant of AVS differed only in systolic IVST (16.6±1.9 mm vs. 15.4±2.3 mm, p=0.020) and diastolic function parameters: iLAV min (14.7±8.8 ml/m^2 vs. 11.9±4.4 ml/m^2, p=0.009), pulmonary capillary wedge pressure (14.7±4.4 vs. 11.3±3.0 mmHg, p<0.001), LV filling pressure (E/é), 10.32±3.56 vs. 7.55±2.43 in the control group, (p<0.001). The other parameters assessed were not significantly different from the group with AVA>1.0 cm^2. In contrast to HGAVS, diastolic function was significantly impaired in patients with LGAVS. Respondents with AVA⩽1.0 cm^2 also had higher hs-Tn levels (9.50±5.98 pg/ml vs. 7.46±5.35 pg/ml in the control group, p=0.027) (Table 3).

Lp(a) levels had a skewed distribution: Me 9.9 (4.8–23.8) mg/dl; percentiles: 90th, 59.2 mg/dl; 95th, 83.9 mg/dl; 99th, 129.4 mg/dl.

Univariate linear regression analysis showed that male sex was positively associated with ln-AVA (p<0.001), whereas age (p<0.001), Lp(a) (p=0.004) were negatively correlated with this index. Significant associations of Lp(a) were also maintained in multivariate linear regression (p=0.018) after correction for sex and age (Table 4).

In participants with severe LGAVS, the NT-proBNP concentration was 158.4 (105.4–260.8) pg/ml. In 61 % of participants, NT-proBNP was >125 pg/ml, consis-

Table 3. **Echocardiographic parameters and hs-Tn levels in responders with high-gradient (G_{mean}≥15 mmHg) and low-gradient (AVA≤1.0 cm²) AVS, both sexes**

Parameter	HGAVS		p	LGAVS		p
	G_{mean}≥15 mmHg	G_{mean}<15 mmHg		AVA≤1.0 mm²	AVA>1.0 mm²	
	M±SD			M ± SD		
Mean pressure gradient, mmHg	17.7±2.0* 23.9±6.2#	3.7±1.4	<0.001	11.6±7.5	3.7±1.5	<0.001
AVA, cm²	1.2±0.3	2.4±0.6	<0.001	0.9±0.1	2.4±0.6	<0.001
LA diameter in systole, mm	43.0±7.1	37.3±4.5	<0.001	39.1±4.2	37.3±4.5	0.083
LA volume, ml	33.1±11.7	22.5± 9.5	0.002	26.3±14.5	22.3±9.2	0.069
LA volume index (min), ml/m²	17.2±5.6	12.0±4.7	0.002	14.7±8.8	11.9±4.4	0.009
LA volume index (max)**, ml/m²	39.7±15.0	27.4±7.6	<0.001	31.3±12.0	27.4±7.4	0.071
LVEF, %	57.0±4.3	56.7±5.9	0.926	56.1±4.1	56.8±5.9	0.620
LV diameter in systole, mm	31.3±3.2	30.9±4.1	0.789	30.1±5.1	30.9±4.1	0.428
LV diameter in diastole, mm	52.9±5.3	50.4±4.6	0.086	50.4±5.6	50.3±4.6	0.970
LV posterior wall thickness in systole, mm	16.1±2.2	13.9±2.5	0.002	13.4±2.1	13.9±2.5	0.419
LV posterior wall thickness in diastole, mm	9.8±1.2	8.6±1.4	0.011	8.7±1.4	8.7±1.4	0.788
Interventricular septal thickness in systole, mm	17.5±1.7	15.4±2.3	0.002	16.6±1.9	15.4±2.3	0.020
Interventricular septal thickness in diastole, mm	12.5±1.5	10.6±1.6	<0.001	10.6±1.6	10.9±1.0	0.479
LV relative wall thickness	0.42±0.05	0.38±0.05	0.025	0.39±0.05	0.38±0.06	0.479
LV myocardial mass index, g/m²	146.1±38.8	111.6 ±28.7	<0.001	117.3±26.8	111.6±28.6	0.394
LV filling pressure, E/é	8.45±2.25	7.48±2.43	0.294	10.32±3.56	7.55±2.43	<0.001
Pulmonary capillary wedge pressure, mmHg	12.4±2.2	11.2±3.0	0.294	14.7±4.4	11.3±3.0	<0.001
hs-Tn*, ng/l	12.44±8.35	7.46±5.59	0.002	9.50±5.98	7.46±5.35	0.027

Note. * — When comparing groups, the variable was included in the analysis in ln-transformed form, ** — in individuals with mild AVS, # — in individuals with moderate AVS.

Table 4. **Relationship between AVA (cm²) and lipoprotein(a), sex and age**

Parameter	Univariate analysis*		Multivariate analysis**	
	β	p	β	p
Lipoprotein(a)***	−0.063	0.004	−0.048	0.018
Age	−0.100	<0.001	−0.097	<0.001
Sex, males — 1, females — 0	0.384	<0.001	0.383	<0.001

Note. *— one-factor linear regression; ** — multiple linear regression; *** — the parameter is used in ln-transformed form.

Table 5. **Relationships between ln-NT-proBNP and indexed AVA, HF, sex and age**

Parameter	Multivariate analysis*	
	β	p
iAVA, cm/m²	−0.065	0.001
History of HF (1 — present, 2 — none)	−0.070	<0.001
Age, years	0.398	<0.001
Sex, female.	0.175	<0.001

Note. * — multiple linear regression.

Table 6. **Relationship between AF and the different degrees of AVS**

AVS	AF		Total
	Yes Abs. number, (%)	No Abs. number, (%)	
AVS, defined by AVA*			
Mild/none (AVA >1.5 cm²)	33 (1.7 %)	1950 (98.3 %)	1983 (100 %)
Moderate (AVA 1.0–1.5 cm²)	3 (3.1 %)	95 (96.9 %)	98 (100 %)
Severe (AVA <1.0 cm²)	3 (16.7 %)	15 (83.3 %)	18 (100 %)
Total	39 (1.9 %)	2060 (98.1 %)	2099 (100 %)
AVS, defined by Gmean#			
No AVA stenosis, G_{mean} <15 mmHg	43 (1.9 %)	2266 (98.1 %)	2309 (100 %)
Mild AVA stenosis, G_{mean} 15–19 mmHg	2 (40 %)	3 (60 %)	5 (100 %)
Moderate AVA stenosis, G_{mean} 20–39 mmHg	2 (40 %)	3 (60 %)	5 (100 %)
Total	47 (2.0 %)	2272 (98.0 %)	2319 (100 %)

Note. * — χ^2 (2) = 22,607; p<0,001; # — χ^2 (2) = 72,934; p<0,001.

tent with HF. There was a significant difference in the mean ln-NT-proBNP concentration in participants with different degrees of AVS. The ln-NT-proBNP level was highest in the group with severe AVS (5.18±0.78) and differed significantly from the group with no/mild AVS: 4.40±0.02 (p=0.005), and the latter group differed significantly from the group with moderate AVS: ln-NT-proBNP 4.40±0.02 vs. 4.71±0.10 (p=0.014).

A significant negative correlation of ln-NT-proBNP with iAVA was shown (p=0.001) when adjusted for the presence of HF history, sex and age (Table 5).

The frequency of AF was 16.7 % in participants with severe LGAVS and 40 % in those with HGAVS (Table 6).

Table 7. **Associations of AF with medical history, AVA, age and sex**

Parameter	OR*	95 % CI OR	p	OR adjusted**	95 % CI OR adjusted	p
Age, years	0,92	0,89–0,96	<0,001	0,95	0,91–0,99	0,019
Sex, male	1,05	0,58–1,89	0,880	—	—	
AH	0,31	0,16–0,61	0,001	—	—	
DM	0,43	0,20–0,94	0,034	—	—	
HF	0,17	0,09–0,31	<0,001	0,24	0,12–0,47	<0,001
AVA***, cm^2	1,89	1,65–14,98	0,004	3,76	1,23–11,47	0,020

Note. * — one-factor linear regression; ** — multiple linear regression; *** — the parameter is used in ln-transformed form.

In the univariate logistic regression models, AF was significantly associated with age (p<0.001), history, AH (p=0.001), DM (p=0.034), HF (p<0.001) and ln-AVA (p=0.004). In the multivariate model (Table 7), significant associations of AF with age, history of HF and ln-AVA remained (OR=3.76, p=0.020).

Discussion

In the «Know your heart» study, the prevalence of HGAVS was 0.2 % in the age group of 40–59 years and 1.1 % in the age group of 60–69 years, which is comparable to data from an epidemiological study conducted in northern Norway (Tromsø) using the same assessment criterion, Gmean ⩾15 mmHg. In the Tromsø study, the prevalence of AVS was 0.2 % in the 50–59 year age group and 1.3 % in the 60–69 year age group [4]. In the series of population-based studies by Nkomo V. T. et al, the prevalence of AVS was closely related to age, with an OR of 2.5 (95 % CI 2.0–3.1) for each 10-year increase in age [18].

In our sample of participants, mild and moderate HGAVS were detected; there was no severe HGAVS in individuals under 70 years of age. Moderate AVS, defined by an AVA of 1.0–1.5 cm^2, was found in 4.7 % of participants and severe (low-grade) in 0.9 %. The incidence of severe LGAVS was 10 times higher in the 60–69 years age group compared to the 40–49 and 50–59 years groups and was 2.0 %. Participants with LGAVS require reassessment and additional diagnostic techniques, particularly determination of the extent of AV calcinosis by CT scan [17]. Snir A. D. et al. analyzed a large EchoCG database [2] and found that of 192060 patients with native AV, 12013 patients (6.3 %) had severe AVS. Of these, 5601 (46.6 %) had severe high-gradient AVS, whereas 6412 (53.4 %) had severe low-gradient AVS. In 2561 patients with low gradient who had data on SV and/or LVEF, the prevalence of different subgroups of AVS was estimated in them, which were LGAVS and pEF 19.2 %, "paradoxical" (low flow, LG, pEF) 20.8 %, "classical" (low flow, LG, rEF) severe AVS 13.3 %. It should be noted that the average age of the participants in the sample was 75 years.

HGAVS and severe LGAVS in the age group we analyzed (35–69 years) was more common in men, but among participants with AVA of 1.0–1.5 cm^2 corresponding to moderate AVS, 87.8 % were women. Although the literature suggests that women with AVS have several distinctive characteristics compared to men [19], gender differences in the prevalence and developmental features of AVS were not considered in our article. We also concluded that male gender was positively associated with AVA, while the age was negatively associated.

Lp(a) is a new risk factor for AVS [7, 20]. Its high level is associated with both microcalcification and macrocalcification of AV, especially in relatively young healthy people (45–54 years) [7]. We also obtained a negative association of Lp(a) with AVA in the 35–69 years age group, which remained significant after adjustment for sex and age. Lp(a) is very rarely evaluated in routine clinical practice in Russia. According to the European Atherosclerosis Society document [7], it is recommended to check Lp(a) concentration at least once in adults; multiple testing is of potential value in familial hypercholesterolaemia, as well as in a family or individual history of (very) high Lp(a) levels or premature CVD.

Characteristics of HGAVS include significant structural changes in the LV and LA myocardium, the development of concentric remodelling (tendency to higher mean RWT) and LV hypertrophy, and higher levels of hs-Tn. A circulating biomarker, hs-Tn, is now considered a highly sensitive indicator of myocardial damage, increased apoptosis, low-grade systemic inflammation and fibrosis formation, as the small increase in hs-Tn independently predicts the occurrence of HF, other adverse events and higher mortality [14]. Structural changes of the LV and LA myocardium in individuals with severe "paradoxical"

LGAVS were less severe, and less high levels of hs-Tn were observed. However, these individuals showed signs of diastolic dysfunction and high levels of NT-proBNP, suggesting the presence of latent HFpEF. "Paradoxical" low-flow LGAVS shares many pathophysiological and clinical similarities with HFpEF [21, 22]. The prevalence of this AVS subtype increases with age, and is more common in women and individuals with the presence of concomitant systemic AH. This variant of AVS is also characterised by restrictive physiology, the development of fibrosis, resulting in markedly reduced LV pumping function and hence SV, despite the preserved LVEF. In the analyzed sample, presumably 0.9 % of participants had "paradoxical" low-flow, LGAVS. Severe "paradoxical" LGAVS is characterised by a high prevalence of AF, chronic HF and reduced survival, while AV replacement is associated with improved survival. These findings have implications for the evaluation and subsequent treatment of severe LGAVS, as older adults with a high number of comorbid conditions are the candidates for TAVR [22].

Severe AVS with normal flow/low gradient and pEF can be assumed in one study participant. According to the literature, early surgical AV replacement and surveillance and conservative treatment strategy show similar survival in symptomatic patients with similar subtype of AVS [23]. Vigilant surveillance with timely surgical intervention should be considered as the optimal management tactic.

One of the serious complications of AVS is atrial fibrillation, which, according to modern concepts, is primarily a consequence of the development of LA stiffness, changes in its longitudinal deformation and contributes to the worsening of haemodynamics, clinical symptoms and prognosis [12]. In our study, atrial fibrillation was present in 40 % cases of HGAVS and 16.7 % of severe LGAVS cases. In a multivariate logistic regression model, age, history of HF and AVA were found to be associated with AF. In 2022, Ahn Y. et al [24] presented factors associated with major cardiac and cerebrovascular events after surgical AV replacement in a scientific report. Those were: AF before surgery, high NT-proBNP level, "classic" LGAVS, smaller aortic root size. It was shown that all-cause mortality during 3-year follow-up after surgical valve replacement was significantly higher in patients with "classic" LGAVS (33.3 %) compared with HGAVS (13 %) and "paradoxical" LGAVS (14.5 %) [24]. The prognostic value of a high NT-proBNP concentration before AV surgery (more than 2000 pg/ml) is also suggested by the publications by Russian authors [13].

Thus, understanding the prevalence, severity and subtypes of AVS in the population, evaluating EchoCG and CT parameters of AV, determining functional and structural remodelling of the heart and clinical characteristics of AVS will allow competent selection for different types of aortic valve replacement and prediction of outcomes (complications and survival) after interventions, especially in the elderly.

Study limitations. The «Know your heart» study included participants aged 35–69 years, whereas the incidence of AVS in the elderly population increases significantly after the age of 75 years. The prevalence of aortic valve stenosis is low according to population-based studies, so the groups for analysing the characteristics of HGVAS and LGAVS were small, limiting the statistical power of the study to identify associations between the variables studied.

Conclusion

The prevalence of mild to moderate HGAVS and EF >50 % by echocardiography in the population aged 35–69 years was 0.43 % and increased with age (0.2 % in 40–59 years and 1.1 % in 60–69 years). There were no cases of severe HGAVS. Severe LGAVS and LVEF > 50 % occurred in 0.9 % of participants. Males predom-

Appendix 1

Parameters of a participant with a severe LGAVS with normal flow/LG and preserved LVEF

Parameter	Factual data
Sex, age	Female, 69 years
Anthropometric data	Height 151 cm, weight 58.8 kg, BSA — 1.54 m^2, (the woman is of a «small size»).
Comorbidities, (from questionnaire data)	AH, AF, CHD with angina rpisodes, chronic kidney disease, osteoarthritis, depression
EchoCG parameters	**Aortic valve:** AVA — 0,94 cm^2, iAVA — 0,61 cm^2/m^2, Gmean — 4,4 mmHg, Vmax 1,55 — m/s, and SV — 36,8 ml/m^2. **LA:** diameter — 48,9 mm, LAV — 65,5 ml, iLAV — 42,4, ml/m^2; **LV:** severe LV hypertrophy — LVMI — 142 g/m^2; LVEF — 56 %. **Diastolic dysfunction:** PCWP — 21,6 mmHg, E/é ratio — 15,7;
Biomarkers	NT-proBNP — 263 pg/ml, hs-Tn — 8,55 ng/l

inated among participants with HGAVS and severe LGAVS.

AVA was independently negatively associated with Lp(a) after THE adjustment for sex and age. AF occurred in 40 % of participants with HGAVS and 16.7 % of participants with severe LGAVS and LVEF >50 %. AF and NT-proBNP were independently associated with AVA in a population-based sample after adjustment for HF history, sex and age.

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Characteristics of heart failure and the predictors of adverse outcomes in patients with cardiovascular pathology, type 2 diabetes mellitus and chronic kidney disease

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The aim of the study was to evaluate clinical and functional parameters, markers of myocardial and renal dysfunction, and the potential of multimarker models for predicting adverse outcomes in patients with chronic heart failure with preserved left ventricular ejection fraction (HFpEF) with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD).

Methods. The study included 246 patients with HFpEF and T2DM, including 122 males and 124 females. The study participants were divided into two groups. The first group included 168 patients with HFpEF with T2DM and CKD, and the second group included 78 patients with HFpEF with T2DM without CKD. Follow-up period was 18 months. The combined endpoint of the study was patients' death from cardiovascular causes, hospitalization due to decompensation of chronic heart failure, or outpatient visits due to worsening heart failure symptoms. Clinical and functional parameters, quality of life, echocardiographic parameters, renal function, NT-proBNP, sST2, galectin-3, cystatin C concentrations were evaluated in all patients.

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Statistical data processing was performed using the Python programming language (version 3.10, sklearn, scipy, statmodels libraries) and R (version 4.2.2).

Results. Patients in group 1 had a longer course of DM (p<0.001) and chronic heart failure (CHF) (p=0.01), higher body mass index, waist circumference (p<0.001), lower indices of exercise tolerance (p<0.001) and quality of life (p<0.001) compared to patients in group 2. Patients with CKD had multivessel coronary artery disease (p<0.001) more frequently and a more severe course of DM. More patients in this group had a history of myocardial infarction (p<0.001), stroke (p<0.001) and aortocoronary bypass surgery (p=0.04). More severe haemodynamic disturbances, severity of left ventricle remodeling in patients with renal impairment corresponded to higher levels of the biomarkers studied. Different correlations between the parameters of renal dysfunction and indicators of the structural and functional state of the heart, cardiac biomarkers, were found. A higher degree of correlation from moderate to high was found with the calculated glomerular filtration rate than with the degree of albuminuria. The predictive models for the decompensation of heart failure using the markers of cardiac and renal dysfunction obtained by multivariate analysis were of high quality. The area under the curve (AUC) in the ROC analysis in model 1 with NT-proBNP concentration was 0.822 (95% CI: 0.677-0.967; p<0.001). In model 2 with NT-proBNP and sST2 — AUC = 0.942 (95% CI: 0. 876-1.0; p<0.001); in model 3 with NT-proBNP and galectin-3 — AUC = 0.869 (95% CI: 0.738-0.982; p<0.001); in model 4 with NT-proBNP and cystatin C — AUC=0.862 (95% CI: 0.736-0.992; p<0.001);

Conclusion. Patients with HFpEF, T2DM and CKD have more severe clinical and functional disorders of the cardiovascular system and carbohydrate metabolism than HFpEF patients without CKD. Evaluation of NT-proBNP, sST2, galectin-3, cystatin C levels allows the differentiation of stable patients with HFpEF with T2DM and CKD and those with the high risk of heart failure decompensation. The model including NT-proBNP and sST2 levels had the best prognostic value.

Keywords: chronic heart failure with preserved ejection fraction, diabetes mellitus, chronic kidney disease, NT-proBNP, sST2, galectin-3, cystatin C.

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Introduction

Chronic kidney disease (CKD) often occurs in patients with chronic heart failure with preserved ejection fraction (HFpEF) in combination with type 2 diabetes mellitus (DM) and has an unfavourable impact on prognosis. To date, biomarkers have played an important role in the diagnosis, severity assessment and prognosis of chronic heart failure (CHF). However, there is variability in the levels of some markers in CHF patients with comorbidities, which may affect their diagnostic significance [1]. Therefore, it is necessary to further investigate the influence of renal dysfunction on the course of CHF and to evaluate the role of biomarkers in predicting adverse outcomes in patients with type 2 DM and CHF in order to select their optimal combination.

The prevalence of NYHA functional class (FC) I–IV CHF in the European part of the Russian Federation (RF) is approximately 7.0%. Approximately half of all patients with CHF have preserved left ventricular ejection fraction (LVEF) [2]. Arterial hypertension (AH) and coronary heart disease (CHD) remain the main causes of the development of heart failure (HF). However, the role of DM in the development of HF has increased from 10.6% in 1998 to 16.6% in 2017 [3]. This is associated, among other things, with a steady increase in new cases of DM both in our country and worldwide. Despite significant progress in risk factor modification, diagnosis and treatment of carbohydrate metabolism disorders, the number of people with diabetes aged 20–79 years will exceed 537 million by the end of 2021 and, according to the International Diabetes Federation, will increase to 643 million by 2030 and to 783 million by 2045. In the Russian Federation, 4.9 million people (3.34% of the population) are registered as having diabetes, of whom 91.8% (4.5 million) are type 2 DM patients. The actual number of patients is almost twice as high as

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the official statistics, which is confirmed by the results of the NATION study [4].

DM may be the underlying cause of myocardial damage and the subsequent development of HF. According to the Framingham study, the risk of developing HF in patients with type 2 DM aged 45–74 years is more than twice as high in men and five times as high in women as in patients without DM. It not only increases the likelihood of HF, but also worsens its course, with an almost twofold increase in the number of hospitalizations associated with CHF decompensation compared with patients without DM, regardless of LVEF [5].

The development of HFpEF is closely associated not only with type 2 DM, AH, but also with CKD. Persistent renal dysfunction may occur in patients with CHF secondary to the progression of HF and/or long-term diabetes or as a result of common cardiometabolic risk factors [6]. Renal pathology, regardless of its cause and mechanism of development, is common in patients with HF [7]. Increased attention to the diagnosis and treatment of CKD is due to the unfavourable impact of renal dysfunction on prognosis. A large-scale systematic review showed a 33.7 % increase in deaths over a ten-year period (2007–2017) associated with CKD, and these rates were higher than those for cancer (+25.4 %), cardiovascular disease (CVD) (+21.1 %) and comparable to those for DM (+34.7 %) [8]. Renal dysfunction leads to increased mortality in all CHF subtypes, but more so in HFpEF patients [9]. The severity of myocardial dysfunction and mortality rates increase in parallel with the stage of CKD [10].

The pathogenetic model for the development and progression of HFpEF in patients with cardiovascular disease, type 2 DM and CKD includes systemic inflammatory and metabolic disorders with the development of endothelial dysfunction, left ventricular (LV) hypertrophy, oxidative stress and myocardial fibrosis, leading to diastolic and systolic cardiac dysfunction [11]. Symptoms of diastolic dysfunction in patients with DM and CKD are often non-specific, making early detection of CHF difficult and the diagnosis of HFpEF challenging [12]. The lack of accurate indicators to detect HFpEF in groups of patients with different phenotypes requires further investigation of the influence of renal dysfunction on the course of CHF to improve diagnosis and therapeutic efficacy.

Clinical guidelines include B-type natriuretic peptide (BNP) and N-terminal BNP peptide (NT-proBNP) as "reference" diagnostic biomarkers for CHF. However, NT-proBNP may not reflect all pathogenetic aspects of the course of CHF. In addition, the results of studies show variability in the levels of this biomarker in patients with DM, CKD and obesity [1]. More informative in this regard is the cardiac marker soluble ST2 (sST2) — a member of the interleukin-1 receptor family, which shows the least intra- and inter-individual variability and reflects the degree of severity of fibrotic processes and pathological remodelling of the heart. The level of sST2 provides independent prognostic information in addition to clinical data and other biomarkers such as high-sensitivity troponin (hsTn), cystatin C and NT-proBNP in patients with CHF and renal failure [13].

In recent years, much attention has been paid to the study of galectin-3 in patients with cardiovascular pathology. This biomarker is of particular interest for HF diagnosis and outcome prediction because its level is stable during rapid haemodynamic changes. Galectin-3 stimulates fibroblast activation and may be involved in the development of cardiac fibrosis, processes of pathological ventricular remodelling and renal dysfunction, which is very important in patients with CHF, type 2 diabetes and CKD [13].

Despite the established association of galectin-3 with CKD, cystatin C is considered to be a more accurate indicator of renal dysfunction [15]. It is not only a sensitive indicator of glomerular filtration rate (GFR), capable of diagnosing early stages of renal disorders, but also a highly effective prognostic marker of cardiovascular complications (CVC), clinically the most significant for coronary risk stratification when used in combination with other biomarkers. Since the diagnostic and prognostic value of a single biomarker at a given time point in a comorbid patient is limited, they should be combined and monitored for optimal diagnostic and clinical effect [16].

Thus, the wide prevalence of CKD, type 2 DM and their unfavourable impact on the prognosis of HFpEF patients necessitate further study of the pathogenetic features of the course of HF in the population of comorbid patients using polymarker evaluation and determination of the optimal marker for predicting HF decompensation for timely correction of therapy.

The aim of the study

To evaluate clinical and functional parameters, markers of myocardial and renal dysfunction, and the po-

tential of multimarker models for predicting adverse outcomes in patients with HFpEF, type 2 DM and CKD.

Methods

The study was approved by the Inter-University Ethical Committee. The study included 246 stable patients with type 2 DM, including 122 men (49.6%) and 124 women (50.4%). The median (Me) age of the participants was 70 years and the interquartile range (Q1; Q3) was (62; 73). All patients were diagnosed with HFpEF with clinical manifestations of CHF I–III FC according to NYHA criteria. HFpEF was diagnosed according to the clinical recommendations on chronic heart failure of the Ministry of Health of the Russian Federation from 2018 [2]. The study participants were divided into two groups. Group 1 included 168 HFpEF patients with type 2 DM and CKD, group 2 included 78 HFpEF patients with type 2 DM without CKD. All patients suffered from AH of stage 1–2. CHD was confirmed in 180 patients (73.17%). 71 patients had a history of atrial fibrillation (AF): 28 had paroxysmal form and 43 had persistent form. The majority of participants were in NYHA class II FC. The median LVEF was 55.5% (52; 58). Patients with acute myocardial infarction, stroke or transient ischemic attack within 6 months prior to inclusion in the study, patients with CHF IV FC, haemodynamically significant heart defects (above moderate) were excluded. Patients with grade 3 AH, with marked impairment of renal function and a calculated GFR (cGFR) < 25 ml/min/1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI) 2012, glycated haemoglobin (HbA1c) level above 12%, and no informed consent to participate in the study were also excluded. The follow-up period was 18 months. The combined endpoint (CEP) in the study included patients dying of cardiovascular cause, hospitalization due to CHF decompensation or outpatient visit to a health care facility due to worsening of CHF symptoms. All patients underwent clinical and laboratory examination with assessment of NYHA CHF FC, Clinical Status Scale (CSS), Charlson and Kaplan-Feinstein comorbidity indices [17], distance in the six-minute walk test (6MWT) [2], quality of life using the Kansas Cardiomyopathy Questionnaire (KCQ) [18] and Minnesota Heart Failure Quality of Life Questionnaire (MLHFQ) [2]. Echocardiography (ECHO-CG) data [1], HbA1c levels, renal impairment (cGFR using the CKD-EPI creatinine-cystatin C formula (2012) and urinary albumin-to-creatinine ratio (ACR) [19], biomarkers of cardiac and renal dysfunction: NT-proBNP, sST2, galectin-3, cystatin C were also assessed.

Transthoracic ECHO-CG was performed on a Samsung HS70A device using tissue myocardial dopplerography. LV systolic function was measured using the disc method (Simpson method). LV diastolic function was assessed in case of sinus rhythm by the indices of transmitral blood flow in pulse-wave mode: peak velocity of early diastolic filling (E) and peak velocity of late diastolic filling of the left ventricle (A), their ratio (E/A). In tissue doppler mode — velocity of early diastolic motion of septal and lateral parts of the mitral valve fibrous ring with calculation of average velocity (e`) and ratio (E/e`) were assessed.

Biomarker concentrations were quantified by enzyme-linked immunosorbent assay (sandwich) using the following kits: "Biomedica NT-proBNP" (Austria), "Presage® ST2 Assay Critical Diagnostics" (USA), "human Galectin-3 ELISA", Bender MedSystems (Austria), Cystatin C — "Human Cystatin C ELISA", BioVendor (Czech Republic).

Statistical analysis

Statistical data processing was performed using Python (version 3.10, sklearn, scipy, statmodels libraries) and R (version 4.2.2) programming languages. Main group indicators were described using fractions for categorical traits and mean with standard deviation (M±SD) for normal distribution or medians (Me) with interquartile range (25^{th} and 75^{th} percentiles) for continuous variables for other distribution. Normality of distribution was confirmed using the Kolmogorov-Smirnov method. Differences between proportions of a trait in different groups were assessed using the two-proportion Z-test, between medians — using the Kraskell-Wallace test. Spearman correlation was used to assess the closeness of the relationship between continuous variables, Fisher's exact test was used between categorical variables. The relationship between dichotomous and continuous variables was investigated using point-biserial correlation. Risk was assessed by calculating the odds ratio and relative risk. Differences between groups were considered statistically significant at $p<0.05$. Multivariate analysis by binary logistic regression with stepwise exclusion of features depending on their contribution to the model was performed to create a model of CEP prediction. In the multivariate analysis, continuous

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indicators were standardised (reduced to the 0–1 interval). The quality of prognostic models was determined using ROC analysis.

The results

The main clinical and demographic characteristics of the participants are shown in Table 1. As shown in the

Table 1. **Demographic and clinical characteristics of the patients**

Parameter	1 group HFpEF, Type 2 DM with CKD, n=168	2 group HFpEF, Type 2 DM without CKD, n=78	p
Age, years	70 (61; 74)	67 (64; 72)	0.78
Females, n (%)	85 (50.59)	39 (50.0)	0.86
Duration of CHF, years	5.0 (3; 8)	3.5 (2; 7)	0.01
Duration of DM, years	12 (9; 17)	5 (5; 8)	<0.001
BMI, kg/m^2	31.64 (29.72; 34.89)	29.29 (25.83; 31.63)	<0.001
Waist circumference, cm	107.0 (98.5; 117.0)	98.5 (91.0; 105.0)	<0.001
CHF FC according to NYHA, n(%) I II III	 4 (2.38) 118 (70.24) 46 (27.38)	 16 (20.51) 62 (79.49) 0 (0)	 <0.001 0.13 <0.001
CSS, average score	5.0 (4; 6)	4.0 (3; 6)	<0.001
6MWT, minutes	365.0 (290; 403)	402.5 (380; 420)	<0.001
KCCQ, score	57.29 (48.59; 63.96)	66.95 (64.58; 70.94)	<0.001
MLHFQ, score	41.0 (35; 51)	25.0 (22; 29)	<0.001
HbA1c,%	7.9 (7.1; 9.1)	7.1 (6.7; 7.1)	<0.001
Creatinine, μmol/l	102.0 (85.0; 118.4)	80.15 (73.1; 89.0)	<0.001
Cystatin C, mg/l	1.46 (1.17; 1.95)	1.09 (0.87; 1.12)	<0.001
cGFR with creatinine and cystatin, ml/min/1.73 m^2	46.98 (35.58;67.35)	73.81 (66.07; 84.55)	<0.001
NT-proBNP, pg/ml	589.0 (423; 890)	335.0 (251; 462)	<0.001
sST2, ng/ml	33.92 (30.8; 37.45)	29.1 (26.7; 30.84)	<0.001
Galectin-3, ng/ml	10.8 (8.9; 13.8)	7.15 (5.9; 8.2)	<0.001
Comorbidities, n (%) CHD History of MI PCI CABG History of stroke AF COPD BA	 125 (74.4) 46 (27.38) 57 (33.93) 9 (5.36) 29 (17.26) 55 (32.74) 10 (6.02) 7 (4.22)	 55 (70.51) 8 (10.26) 24 (30.77) 0 (0.0) 0 (0.0) 16 (20.51) 8 (10.26) 8 (10.26)	 0.52 <0.001 0.62 0.04 <0.001 0.05 0.23 0.06
CA atherosclerosis, n (%) 1 CA 2 CA 3 or more	 9 (5.42) 30 (17.85) 27 (16.27)	 16 (20.51) 8 (10.26) 0 (0.0)	 <0.001 0.12 <0.001
Charlson index	6 (5; 7)	4 (3; 5)	<0.001
Kaplan-Feinstein index	15.0 (12; 16)	10.0 (8; 13)	<0.001
Hospitalization due to CHF in the previous 12 months, n (%)	73 (43.45)	8 (10.26)	<0.001
Treatment, n (%) ACEi (ARB) Diuretics Beta-blockers MRA CCB Antiplateletes Anticoagulants Statins	 168 (100) 164 (97.62) 153 (91.07) 89 (52.97) 98 (58.33) 119 (70.83) 51 (30.36) 164 (97.61)	 63 (80.77) 61 (78.21) 47 (60.26) 8 (10.26) 55 (70.51) 46 (58.97) 16 (20.51) 78 (100.0)	 <0.001 <0.001 <0.001 <0.001 0.07 0.07 0.11 0.17
DM treatment, n (%) Peroral drugs Peroral drugs+insulins	 168 (100.0) 84 (50.0)	 78 (100.0) 7 (8.97)	 n/a <0.001
Distal neuropathy, n (%) Sensory Motor Sensorimotor	 93 (55.36) 1 (0.59) 58 (34.52)	 39 (50.0) 0 (0.0) 0 (0.0)	 0.43 0.49 <0.001
Retinopathy, n (%) Non-proliferative, n (%) Pre-proliferative, n (%) Proliferative, n (%)	 105 (62.5) 53 (31.93) 10 (5.95)	 70 (89.74) 8 (10.26) 0 (0.0)	 <0.001 <0.001 0.03

table, patients in the observation groups were comparable in age and sex (p=0.78; p=0.86). However, patients with CKD were older: the median age was 70 years (61; 74) vs 67 years (64; 72) in the comparison group. Patients in group 1 had higher body mass index (BMI) and waist circumference (p<0.001), higher comorbidity indices (Kaplan-Feinstein, Charlson index) (p<0.001), more severe stages of diabetic neuropathy (p<0.001) and retinopathy (p=0.03), and were more likely to require combined glucose-lowering therapy (p<0.001). They also had a longer duration of DM (p<0.001) and CHF (p=0.01). Multivessel coronary disease was more common in patients with CKD (p<0.001). More patients in this group had a history of myocardial infarction (p<0.001), stroke (p<0.001) and aortocoronary bypass surgery (p=0.04). The majority of patients (73.17%) in the observation groups were in FC 2. At the same time, the group with CKD had higher CSS scores (p<0.001), about 27% of patients had III FC and patients with I FC were less frequent (p<0.001). The lower functional status of patients with CKD was objectively confirmed by the shorter distance travelled in 6MWT (p<0.001). Quality of life assessment showed a significant decrease in patients with renal dysfunction compared to patients without CKD both by the KSSQ and MLHFQ scores (p<0.001). Patients with CKD had more severe impairment of carbon metabolism (p<0.001). Thus, HFpEF, type 2 DM patients with CKD compared to patients without CKD had longer duration of DM and CHF, more severe clinical condition, unfavourable course of CHD and DM, low indices of exercise tolerance and quality of life.

Patients with renal impairment had, as expected, higher systolic and diastolic blood pressure (BP) values (p<0.001) and a greater degree of cardiac damage (Table 2). According to the algorithm for the instrumental diagnosis of HFpEF, functional and structural indices were assessed by ECHO-CG in all participants: left atrial volume (LAV), E/è, left ventricular wall thickness, left ventricular myocardial mass (LVMM), LVMM index (LVMMI), left atrial volume index (LAVI) and relative left ventricular wall thickness index (RLWTI) were calculated. Most patients had increased E and decreased A, with a median E/A ratio of 1.3 (0.78; 1.5). More severe diastolic dysfunction up to the development of the "restrictive" type was more common in patients with CKD. Increases in LAV size, LVMM, and in their indices were observed in patients of both observation groups, but were more significant in patients with CKD. The change in LV geometry was characterised by an increase in RLWTI with a median of 0.51 (0.48; 0.54). The RLWTI was significantly higher in the first group, indicating more severe concentric LV remodelling in patients with renal impairment (see Table 2).

Data analysis showed increased concentrations of markers of cardiac dysfunction in the observation groups, but the medians of the parameters studied prevailed in patients with CKD (p<0.001) and corresponded to the severity of remodelling and the degree of LV diastolic dysfunction. In patients with CKD, the median levels of creatinine, cystatin C and cGFR were significantly different from those in the control group. At the same time, the levels of NT-proBNP, sST2,

Table 2. **Hemodynamic and structural-functional parameters of the left heart chambers**

Parameter	1 group HFpEF, Type 2 DM с CKD, n=168	2 group HFpEF, Type 2 DM без CKD, n=78	p
HR, b/min	74,5 (68; 79)	65,0 (63; 70)	<0,001
SBP, mmHg	144,0 (138,0; 150,0)	130,0 (130,0; 140,0)	<0,001
DBP, mmHg	90,0 (82; 90)	82,5 (80; 85)	<0,001
LV EDVI, ml/m^2	60,48 (54,55; 68,67)	58,13 (53,39; 60,93)	<0,001
LV EDVI, ml/m^2	21,31 (17,45;25,89)	19,2 (18,24; 21,25)	<0,001
LV EF, %	55,0 (52; 58)	56 (55; 57)	<0,001
LAVI, ml/m^2	35,07 (34,35; 36,91)	34,35 (34,11; 34,6)	<0,001
LV EDD, cm	5,1 (4,8; 5,2)	4,8 (4,8; 5,0)	<0,001
LV ESD, cm	3,3 (3,0; 3,5)	3,1 (3,1; 3,2)	<0,001
RLWTI	0,52 (0,48; 0,55)	0,51 (0,48; 0,52)	0,01
LVMM, g	276,44 (239,86; 306,81)	233,75 (204,99; 255,46)	<0,001
LVMMI, g/m^2	137,41 (116,96; 155,81)	113,81 (104,87; 129,65)	<0,001
E/A	1,4 (1,1;1,6)	1,19 (0,75;1,38)	<0,001
E/è	15,1 (11,38;16,57)	11,77 (9,24;13,22)	<0,001

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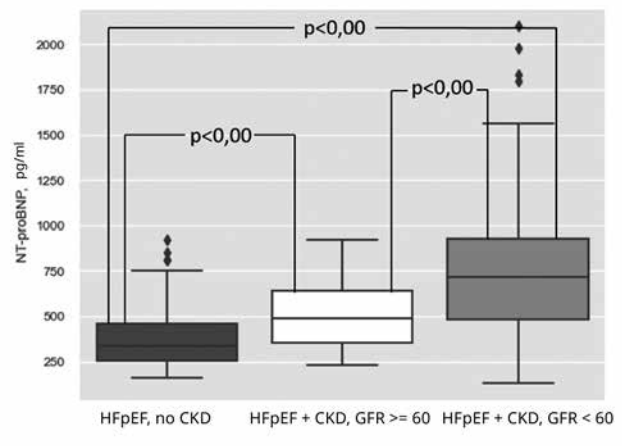

Fig. 1. NT-proBNP values in patients with HFpEF, Type 2 DM without CKD and with CKD in GFR ⩾ 60 ml/min/1,73 м^2 and GFR < 60 ml/min/1.73 м^2 groups

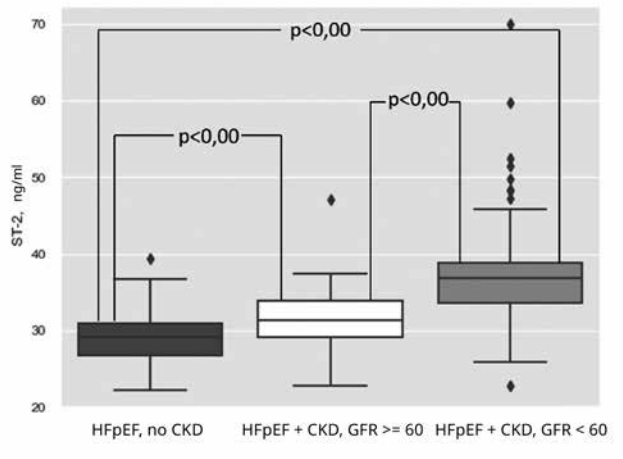

Fig. 2. sST2 values in patients with HFpEF, Type 2 DM without CKD and with CKD in GFR ⩾ 60 ml/min/1,73 м^2 and GFR < 60 ml/min/1.73 м^2 groups

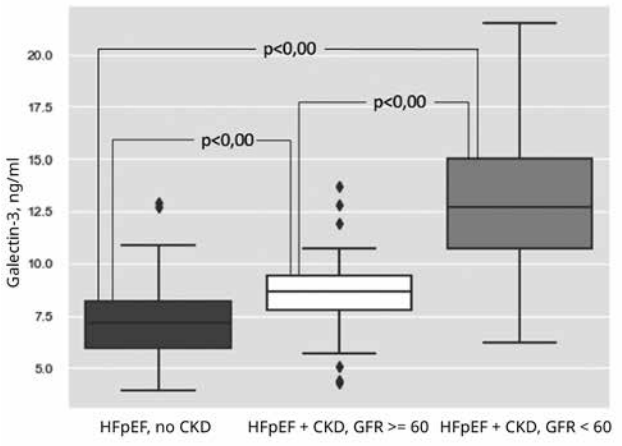

Fig. 3. Galectin-3 values in patients with HFpEF, Type 2 DM without CKD and with CKD in GFR ⩾ 60 ml/min/1.73 м^2 and GFR < 60 ml/min/1,73 м^2 groups

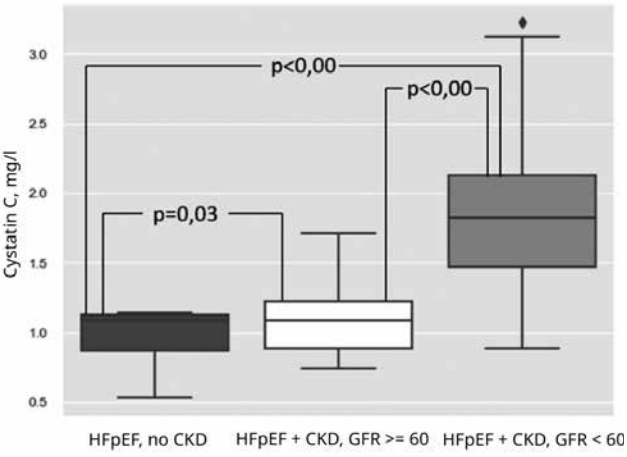

Fig. 4. Cystatin C values in patients with HFpEF, Type 2 DM without CKD and with CKD in GFR ⩾ 60 ml/min/1.73 м^2 and GFR < 60 ml/min/1,73 м^2 groups

galectin-3 and cystatin C increased in proportion to the degree of renal impairment, indicating the interdependence of heart and renal failures (Figures 1–4).

Correlation analysis confirmed close causal relationships between diastolic dysfunction, cardiac remodelling parameters and renal function in patients with HFpEF, type 2 DM combined with CKD. The main criteria of renal dysfunction (cGFR, ACR) showed varying degrees of correlation with parameters of cardiac structural and functional status and cardiac biomarkers. An inverse moderate to high degree of correlation was found between cGFR and LAVI (r=–0.338, p<0.001), E/è (r=–0.481, p<0.001), LVMMI (r=–0. 511, p<0.001), NT-proBNP levels (r=–0.5, p<0.001), sST-2 (r=–0.556, p<0.001), galectin-3 (r=–0.731, p<0.001) and cystatin C (r=–0.931, p<0.001). At the same time, moderate and low direct correlations were observed between ACR levels and the following parameters studied: E/è (r=0.341, p<0.001), LAVI (r=0.254, p=0.001), LVMMI (r=0.250, p=0.001), NT-proBNP levels (r=0.294, p<0.001), sST-2 (r=0.334, p<0.001), galectin-3 (r=0.317, p<0.001), cystatin C (r=0.225, p=0.003). There were also moderate inverse correlations between cGFR levels and the type of diastolic function (r=–0.416, p=0.001), presence of AF (r=–0.327, p<0.001), CHD (r=–0.404, p<0.001) and hospitalization due to CHF in the 12 months prior to enrolment (r=–0.324, p<0.001). The levels of the biomarkers studied had a direct significant association with hospitalization for CHF in the 12 months prior to the study: NT-proBNP (r=0.496, p<0.001), sST2 (r=0.507, p<0.001), cystatin C (r=0.347, p<0.001), galectin-3 (r=0.312, p<0.001).

When analysing the incidence of HF worsening and cardiovascular death (CVD), CEP had been reached in the initially more severely affected patients (Table 3).

Table 3. **Parameters of HFpEF, Type 2 DM and CKD patients according to the development of the combined endpoint of the study**

Parameter	Did not reach CEP, n=111	Reached CEP, n=57	p
Age, years	70 (61; 73)	71 (65; 75)	0.13
Females, n (%)	59 (53.15)	26 (45.61)	0.27
Duration of CH, years	4 (2; 6)	7.0 (5; 11)	<0.001
Duration of DM, years	10.5 (9; 17)	14 (11; 19)	0.003
Duration of CKD, years	2 (1; 3)	3 (2; 4)	<0.001
BMI, kg/m^2	31.62 (29.94; 34.68)	31.64 (29.4; 35.2)	0.82
FC according to NYHA, n (%) I II III	 4 (3.6) 91 (81.98) 16 (14.41)	 0 (0) 27 (47.37) 30 (52.63)	 0.15 <0.001 <0.001
CSS, average score	5.0 (4; 6)	7.0 (5; 8)	<0.001
6MWT, m	385 (336; 410)	290 (270; 365)	<0.001
KCCQ, score	61.3 (53.33; 65.26)	49.53 (45.36; 55.94)	<0.001
MLHFQ, score	37.0 (33; 46)	51.0 (43; 65)	<0.001
HbA1c,%	7.8 (7.1; 8.9)	8.3 (7.1; 9.3)	0.59
Creatinine, μmol/l	95.85 (82.3; 114.8)	109.0 (98.0; 125.0)	<0.001
Cystatin C, mg/l	1.31 (1.09; 1.68)	2.02 (1.6; 2.41)	<0.001
cGFR with creatinine and cystatin, ml/min/1.73 m^2	60.22 (42.15; 69.12)	39.61 (30.99;45.4)	<0.001
NT-proBNP, pg/ml	498 (409; 689)	893 (690; 1112)	<0.001
sST2, ng/ml	32.45 (29.7; 34.1)	38.4 (37.2; 42.39)	<0.001
Galectin-3, ng/ml	9.85 (8.3; 11.9)	14.8 (11.3; 16.9)	<0.001
ACR, mg/g	84 (63; 228)	231 (68; 472)	0.003
Comorbidities, n (%) CHD History of MI PCI CABG History of stroke AF COPD BA	 74 (66.66) 20 (18.02) 31 (27.93) 4 (3.6) 19 (17.12) 25 (22.52) 5 (4.5) 7 (5.65)	 51 (89.47) 26 (45.61) 26 (45.61) 5 (8.77) 10 (17.54) 30 (52.63) 5 (8.77) 0 (0)	 <0.001 <0.001 0.02 0.16 0.94 <0.001 0.27 0.06
CA atherosclerosis, n (%) 1 CA 2 CA 3 or more	 8 (7.2) 16 (14.4) 12 (10.81)	 1 (1.75) 14 (24.56) 15 (26.32)	 0.14 0.1 0.01
Hospitalization due to CHF in the previous 12 months, n (%)	30 (27.03)	43 (75.44)	<0.001
Charlson index	5.5 (5; 7)	7 (6; 8)	<0.001
Kaplan-Feinstein index	13.0 (11; 15)	16.0 (15; 18)	<0.001
Treatment, n (%) ACEi (ARB) Diuretics Beta-blockers MRA AC Antiplateletes Anticoagulants Statins	 111 (100) 107 (94.39) 99 (89.19) 47 (42.34) 67 (60.36) 92 (82.88) 19 (17.12) 110 (99.1)	 57 (100) 57 (100) 54 (94.74) 42 (73.68) 31 (54.39) 27 (47.37) 32 (56.14) 54 (94.74)	 n/a 0.15 0.23 <0.001 0.46 <0.001 <0.001 0.08
DM treatment, n (%) Peroral drugs Peroral drugs+insulins	 111 (100) 48 (43.24)	 57 (100) 36 (63.16)	 n/a 0.01
Distal neuropathy, n (%) Sensory Motor Sensorimotor	 67 (60.36) 0 (0.0) 31 (27.93)	 26 (45.61) 1 (1.75) 27 (47.37)	 0.07 0.16 0.01
Retinopathy, n (%) Non-proliferative Pre-proliferative Proliferative	 74 (66.67) 34 (30.63) 4 (3.6)	 31 (54.39) 19 (33.33) 6 (10.52)	 0.12 0.72 0.07
HR, b/min	74.5 (68;78)	74 (68;81)	0.85
SBP, mmHg	143.5 (137;150)	144 (138;150)	0.90
DBP, mmHg	90 (83;90)	85 (80;90)	0.06
LV EDVI, ml/m^2	58.48 (53.6;64.79)	66.24 (59.3;76.56)	<0.001

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Table continuation 3

Parameter	Did not reach CEP, n=111	Reached CEP, n=57	p
LV EDVI, ml/m^2	20.58 (16.85;24.45)	24.43 (18.91;30.32)	<0.001
LV EF, %	55 (53; 58)	53 (51;55)	0.001
LV EDD, cm	4.9 (4.8;5.2)	5.3 (5.0;5.6)	<0.001
LV ESD, cm	3.2 (2.9;3.4)	3.4 (3.2;3.8)	<0.001
RLWTI	0.52 (0.49;0.55)	0.53 (0.46;0.55)	0.09
LAVI, ml/m^2	34.65 (34.14; 35.44)	36.59 (35.09; 44.86)	<0.001
LVMM, g	255.46 (234.61; 293.82)	297.0 (267.94; 335.47)	<0.001
LVMMI, g/m^2	131.62 (115.03; 148.29)	149.8 (129.9; 164.19)	<0.001
E/A	1.2 (0.74; 1.5)	1.5 (1.3; 1.6)	<0.001
E/è	13.23 (10.21; 15.6)	16.38 (13.26; 17.61)	<0.001

During the follow-up period in the group of patients with HFpEF, type 2 DM and CKD, there were 3 cases of death from cardiovascular causes; 23 cases of hospitalization due to HF decompensation; 31 patients sought outpatient care due to worsening HF symptoms. Logistic regression analysis was used to construct baseline statistical models to predict the likelihood of CVD and HF decompensation in patients with HFpEF, type 2 DM and CKD. Baseline model 1 included CSS, hospitalization due to HF in the previous 12 months, BMI, E/è, distance in the 6MWT and NT-proBNP concentration (Table 4). In the ROC analysis of this model, the AUC was 0.822 (95% confidence interval (CI) 0.677–0.967; p<0.001), indicating good predictive quality of the model (Figure 5). The sensitivity, specificity and accuracy of the model 1 were 61.5%, 80.9% and 77.7%, respectively.To determine the significance of the biomarkers in predicting CEP, we added the concentrations of the studied markers to the baseline model and evaluated their quality. The inclusion of sST2 in the baseline model improved the predictive ability of model 2 (AUC = 0.942; 95% CI: 0.876–1.0; p<0.001), increasing its sensitivity to 92.3%, specificity to 81.8% and accuracy to 87.0% (Table 4, Figure 6). Models 3 and 4, obtained by adding galectin-3 and cystatin C concentrations respectively to the basic components, had almost the same effect on prognostic value with a slight advan-

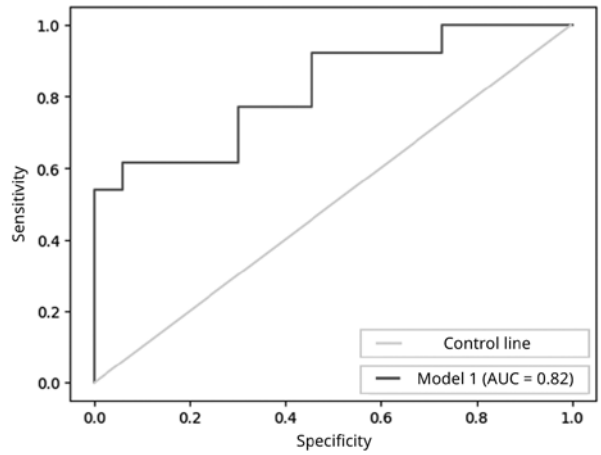

Fig. 5. ROC curve for the baseline model 1 with included NT-proBNP

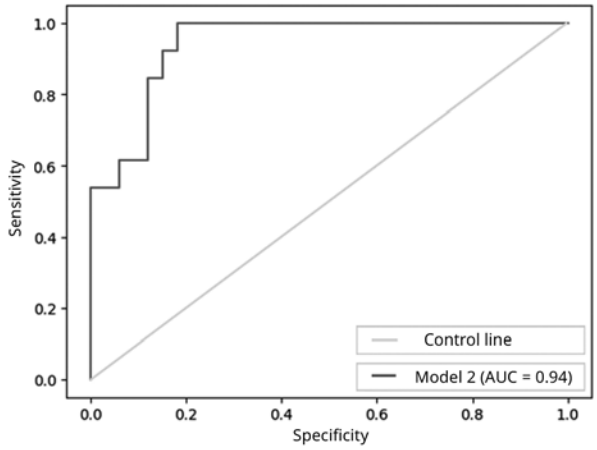

Fig. 6. ROC curve for model 2 with included NT-proBNP and sST2

Table 4. **Risk factors for an unfavourable course of heart failure in multivariate regression analysis (models 1, 2)**

Parameter	Model 1 (AUC 0.822)			Model 2 (AUC 0.942)		
	β	OR (CI 95%)	p	β	OR (CI 95%)	p
NT-proBNP	0.0024	1.01 (1.00–1.02)	0.026	0.0011	1.01 (0.99–1.02)	0.342
BMI	0.1070	1.11 (0.98–1.25)	0.086	0.0112	1.01 (0.89–1.14)	0.86
CSS	0.1958	1.21 (0.59–1.43)	0.238	0.4374	0.64 (0.42–0.97)	0.04
6MWT	–0.0157	0.98 (0.97–0.99)	0.642	–0.0232	0.97 (0.96–0.98)	<0.001
Hospitalization due to CHF in the previous 12 months	1.4077	4.08 (1.38–12.08)	0.011	0.5361	1.71 (0.55–5.23)	0.349
E/è	0.0091	1.01 (1.00–1.02)	0.918	0.0597	1.06 (0.90–1.22)	0.523
sST2	–	–	–	0.2547	1.29 (1.11–1.51)	<0.001

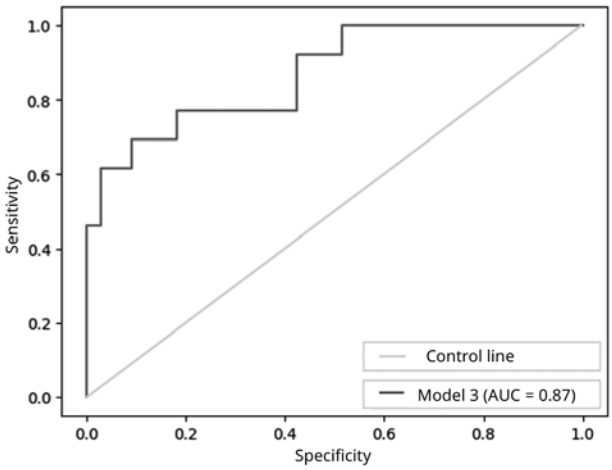

Fig. 7. ROC curve for model 3 with included NT-proBNP and galectin-3

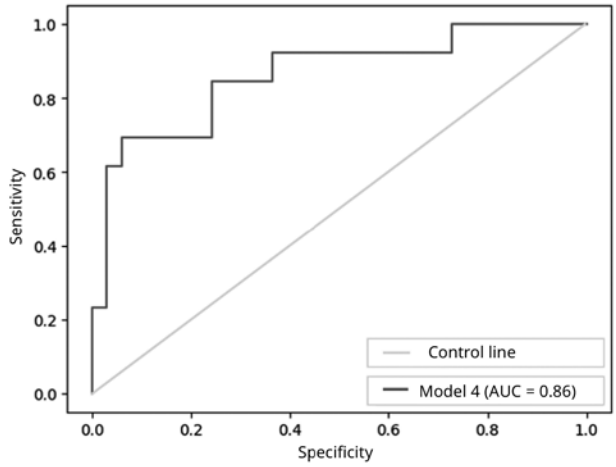

Fig. 8. ROC curve for model 4 with included NT-proBNP and cystatin C

tage of galectin-3 (Table 5). The ROC curves of model 3 (AUC=0.869; 95% CI: 0.738–0.982; p<0.001) and model 4 (AUC=0.862; 95% CI: 0.736–0.992; p<0.001) are shown in Figures 7, 8. The sensitivity, specificity and accuracy of model 3 were 65.0%, 80%, 79% and 63.4%, 79.2%, 78.7% in model 4.

Thus, the best model for predicting CHF and CVD decompensation in HFpEF, Type 2 DM and CKD patients was model 2, including CSS, HF hospitalization in the previous 12 months, BMI, E/è, 6MWT distance, NT-proBNP and sST2 concentrations. Cut-off values for biomarker concentrations and relative risk (RR) of CEP in the next 18 months were determined using single-factor ROC analysis: For NT-proBNP ≥865.88 pg/ml (RR=4.096 with 95% CI: 2.7–6.2; p<0.001), for sST2 ≥37.43 ng/ml (RR=7.1 with 95% CI: 4.4–11.4; p<0.001), for galectin-3 ≥12.83 ng/ml (RR=4.241 with 95% CI: 2.7–6.7; p<0.001), for Cystatin C ≥1.69 mg/l (RR=3.436 with 95% CI: 2.1–5.5; p<0.001).

Discussion

CHF in patients with DM and CKD is a complex pathogenetic model involving multiple links. DM and CKD may be causative and/or aggravating factors in the onset, development and progression of CHD and AH, the main etiological causes of CHF. In our study, all HFpEF and Type 2 DM patients had AH and more than 70% suffered from CHD. However, patients with CKD differed in the longer duration of DM and CHF. Duration of exposure to metabolic and haemodynamic factors is important in the development and progression of cardiovascular diseases, renal dysfunction, complications of DM and increases the risk of cardiovascular events [20,21]. Therefore, patients with a history of myocardial infarction, stroke, and more severe stages of diabetic neuropathy and retinopathy were significantly more common in the cohort of patients with CKD. Patients in the CKD group also had a significantly higher BMI. The polysystemic effects of obesity contribute to the progression of HF, type 2 DM and renal dysfunction [22]. This was also reflected in our study. BMI was included in the baseline prediction model of HF and CVD decompensation in the studied patient population.

Patients with CKD had significantly higher values of SBP and DBP, which may be due to volume overload

Table 5. **Risk factors for an unfavourable course of heart failure in multivariate regression analysis (models 3, 4)**

Parameter	Model 3 (AUC 0.869)			Model 4 (AUC 0.862)		
	β	OR (CI 95%)	p	β	OR (CI 95%)	p
NT-proBNP	0.003	1.01 (1.00–1.02)	0.026	0.0023	1.01 (1.00–1.02)	0.04
BMI	0.0415	1.04 (0.91–1.19)	0.547	0.0532	1.05 (0.93–1.18)	0.383
CSS	0.1960	1.21 (0.96–1.49)	0.304	0.1598	1.17 (0.93–1.53)	0.362
6MWT	–0.0163	0.98 (0.97–0.99)	0.002	–0.0145	0.98 (0.97–0.99)	0.002
Hospitalization due to CHF in the previous 12 months	0.4025	1.49 (0.47–4.73)	0.494	0.6966	2.0 (0.68–5.91)	0.207
E/è	0.0834	1.08 (0.94–1.26)	0.356	0.0231	1.02 (0.86–1.21)	0.798
Galectin-3	0.2817	1.32 (1.10-1.59)	0.003	–	–	–
Cystatin C	–	–	–	1.0259	2.78 (1.00–7.71)	0.048

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from increased renal sodium reabsorption, systemic proinflammatory state aggravating microvascular dysfunction [6]. Significant structural and functional changes of the heart detected in all study participants are associated with the features of CHF formation in the disorders of carbohydrate metabolism and renal function impairment. Thus, in Type 2 DM myocardial damage occurs in conditions of insulin resistance (IR), hyperinsulinemia with inadequate activation of renin-angiotensin-aldosterone system (RAAS), leading to LV myocardial rigidity, pathological remodelling processes, and LAV increase. In this case, IR alters energy metabolism, impairs mitochondrial function and reduces cardiomyocyte contractility. In the context of inadequate glucose delivery to the cell, metabolism shifts towards fatty acid oxidation. The end products of non-enzymatic glycosylation of lipids, lipoproteins and amino acids affect the processes of collagen formation, lead to increased expression of transforming growth factor ß, impair the degradation of the extracellular matrix by decreasing the expression of matrix metalloproteinase-2, increase fibrosis and diastolic dysfunction of the heart [23]. The product of glucose metabolism β-N-acetylglucosamine has a similar negative effect on myocardium through modification of Ca2þ/calmodulin-dependent protein kinase II, phospholamban and myofilaments. β-N-acetylglucosamine, by binding to mitochondrial proteins, impairs mitochondrial function and increases the production of reactive oxygen species. Multifactorial negative effects lead to the progression of fibrosis and inflammation in the myocardium with subsequent activation of cardiomyocyte apoptosis [24]. In renal dysfunction additional unfavourable pathogenetic mechanisms are involved. More pronounced diastolic dysfunction and higher values of indexed LAV, LVMM, RLWTI in the group of patients with CKD can be associated with both impaired water-electrolyte metabolism and the systemic negative effect of uremia.

In addition to direct damaging effect on cardiomyocytes, uremic toxins lead to an increase in the level of proinflammatory cytokines, which inhibit proliferation and increase apoptosis of endothelial cells, reduce nitric oxide (NO) bioavailability by inhibiting endothelial nitric oxide synthase (eNOS), and increase the expression of adhesion molecules. There is leukocyte activation with differentiation of fibroblasts into myofibroblasts, increased collagen production in the extracellular matrix, migration and proliferation of vascular smooth muscle cells. In addition, the level of circulating and cellular advanced glycation end products (AGEs) increases in patients with DM and CKD due to their increased production and decreased clearance. It was found that prolonged circulation of AGEs worsens the course of CHF and positively correlates with diastolic dysfunction [24, 25].

All these processes contribute to the development and progression of microvascular dysfunction and pathological remodelling of the heart and vessels. Although we have demonstrated a relationship between CKD, remodelling processes and LV diastolic function, the direction of this relationship cannot be precisely established. CKD may be an aggravating factor that leads to impaired cardiac functioning. At the same time, changes in cardiac structure and/or function, reduced cardiac output in HFpEF may increase renal venous congestion and worsen renal function. Thus, in patients with HFpEF, Type 2 DM and CKD a vicious circle of bilateral relationships is formed, the rupture of which may positively influence the rate of progression of cardiorenal insufficiency and reduce the risks of complications.

Our study revealed a strong relationship between cardiac structural changes, myocardial remodelling, LV diastolic function, cGFR, and biomarkers of cardiorenal dysfunction. We observed an increase in biomarker concentrations corresponding to the degree of cGFR decline, indicating the interdependence of cardiac and renal dysfunction. In the study, we also evaluated the impact of NT-proBNP and a number of markers actively studied in cardiorenal pathology on prognosis in patients with HFpEF, type 2 DM and CKD. To date, the assessment of NT-proBNP levels is an integral part and "gold standard" of CHF diagnosis. According to the results of numerous studies, an NT-proBNP concentration <125 pg/ml is highly predictive of HF absence [1, 2]. The dependence of NT-proBNP concentration on CHF phenotype has been established. In one study, despite higher NT-proBNP levels in CHF patients with reduced ejection fraction (HFrEF) than in HFpEF individuals (median 2723 vs. 5644 ng/l, p<0.001), the relationship between elevated levels of this marker and prognosis did not differ between these groups (p=0.956 for death from any cause; p=0.351 for the CEP including all-cause death or hospitalization for HF) [26]. The results of another study in outpatients showed that NT-proBNP levels

above the median of 1428 pg/ml in HFpEF patients were associated with an increased risk of death and hospitalization for HF [27].

In our study, a cut-off value of NT-proBNP ≥865.88 pg/ml significantly predicted the development of CHF decompensation and CVD. This finding may be due to the characteristics of the patient population studied. An inverse correlation was found between NT-proBNP levels, hyperinsulinemia and degree of obesity. Therefore, in CHF patients with type 2 DM, whose median BMI was 31.14 kg/m^2 (28.09; 33.73), additional markers were used to assess the severity of CHF progression. One of these is sST2, whose gene is also expressed in cardiomyocytes and fibroblasts in CHF and reflects the development of pathological remodelling and fibrosis [16]. Two isoforms of ST2 are important in cardiovascular pathology: sST2 and transmembrane ligand (ST2L). Under conditions of cardiomyocytes stress, ST2L becomes susceptible to interleukin-33 (IL-33), the synthesis of which is increased. The interaction of IL-33 with ST2L exerts a cardioprotective antifibrotic effect, whereas sST2 blocks the beneficial effect of IL-33. When the ST2/IL-33 system is disturbed, sST2 hyperproduction with the development of inflammatory and neurohormonal activation leads to the formation and progression of HF. In addition, sST2 is involved in the development of vascular remodelling [28,29].

Numerous studies have shown an association between sST2 and myocardial stretch, fibrosis, pathological cardiac remodelling, inflammation, haemodynamic impairment and vascular disease. The high independent prognostic significance of this marker in CHF patients has been demonstrated in many studies. Several studies in CHF patients with different phenotypes have performed a multimarker analysis to predict adverse events. In a study by Dupuy A.M. et al, 2016, sST2 predicted both all-cause mortality (RR=2.75) and CVD risk (RR=3.78) well compared to other classical markers: NT-proBNP, hsTn alone or in combination. The results of studies show different sST2 thresholds in patients depending on cardiovascular pathology. An sST2 level >24.6 ng/ml was an independent predictor of death in stable CHD, and in the HF-ACTION study in CHF patients, a threshold sST2 level of 35 ng/ml was used to assess prognosis [30]. In another study, the optimal level of sST2 for predicting all-cause death, CVD and hospitalization due to HF was 28 ng/ml [31]. In the study by Grakova E.V. et al, sST2 levels ≥34.18 ng/ml were associated with the development of cardiovascular events within 12 months in patients with stable CHD and CHF after revascularisation [32]. In our study, the addition of sST2 to the baseline model including NT-proBNP increased the prognostic value to a greater extent than the addition of the other markers studied. The threshold of sST2 ≥37.43 ng/ml obtained by ROC analysis (RR=7.1 with 95% CI: 4.4–11.4; p<0.0001) significantly stratified the risk of negative course of CHF. The value of the marker was higher than that reported in several other studies. In our opinion, this is due to the severity of health condition in comorbid CHF patients studied.

To improve the prognostic value in CHF with different phenotypes, many studies have investigated the influence of several markers simultaneously. For example, in CHF patients with moderately reduced EF, the prognostic value of NT-proBNP, hsTn, sST2, galectin-3, high-sensitivity C-reactive protein, cystatin C, neprilysin and soluble transferrin receptor biomarkers was similar to CHF patients with HFrEF, except for lower NT-proBNP levels. In HFpEF, neprilysin and galectin-3 showed greater importance in risk stratification [13]. We also evaluated the significance of galectin-3 in the studied cohort of patients with HFpEF. Interest in this biomarker is related to its pathophysiological features. Galectin-3 is secreted by activated macrophages and is involved in the processes of inflammation and fibrosis. The biomarker may reflect the processes of fibrosis in the heart and ventricular remodelling, impaired renal function, which is very important in patients with CHF and CKD [14, 33]. A recent meta-analysis using data from 27 studies showed that high levels of galectin-3 are associated with the risk of HFpEF developing, with a high risk of death and CEP (all-cause death, CVD, hospitalization for HF), as well with parameters reflecting diastolic function (E/è r=0.425, 95% CI: 0.184-0.617; p<0.001). In addition, galectin-3 levels are stable during rapid haemodynamic changes. Therefore, the determination of galectin-3 levels may help in the diagnosis of HFpEF, the assessment of the risk of unfavourable outcomes and the efficacy of therapy [34]. Galectin-3 levels were significantly elevated in patients with both acute and chronic HF and predicted the risk of new-onset HF and the likelihood of adverse outcomes in patients with CHF [35-37]. The results of experimental and clinical studies have demonstrated the possibility of using galectin-3 as a

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prognostic factor not only in HFpEF but also in CKD. In our study of patients with HFpEF, type 2 DM and CKD, we confirmed the association of elevated galectin-3 levels with parameters of cardiac and renal dysfunction. There were moderate direct correlations between galectin-3 concentration and diastolic function markers, such as LV remodelling: E/è (r=0.452, p<0.001), LAVI (r=0.350, p<0.001); LVMMI (r=0.436, p<0.001); high direct correlation with cystatin C level (r=0.803, p<0.001) and high inverse correlation with cGFR (r=–0.731, p<0.001). ROC curve analysis showed that galectin-3 levels ⩾12.83 ng/ml increased the risk of CVD and HF decompensation in HFpEF, type 2 DM and CKD patients in the next 18 months (RR=4.241 with 95% CI: 2.7–6.7; p<0.0001). The increased concentration of this marker in patients with CKD may be due to a decrease in its clearance, which may reduce its prognostic value in CHF patients with CKD. On the other hand, the decreased excretion of galectin-3 in CHF patients not only explains the association between renal dysfunction and galectin-3, but is also one of the reasons for the unfavourable impact of renal dysfunction on the long-term prognosis of CHF patients. The high concentration of galectin-3 may also be related to its increased production in organs other than the heart and kidneys with ongoing systemic inflammation in conditions of cardiorenal dysfunction [38].

In our study, we evaluated the level of the reference marker for renal dysfunction, cystatin C, and its role in predicting CEP. Significant differences in creatinine, cystatin and cGFR levels were observed between the study groups. In all patients, GFR using serum creatinine concentration was overestimated compared to GFR using cystatin C. In the HFpEF, type 2 DM and CKD group, the median cGFR using creatinine was 58.07 ml/min/1.73 m^2 (42.28; 73.1) and was significantly different from the cGFR using cystatin C of 42.53 ml/min/1.73 m^2 (29.42; 60.37), p<0.001. In view of this, the use of cystatin C will be most useful in the early stages of CKD to take timely action to prevent CKD progression. Correlation analysis confirmed strong cardiorenal correlations. Moderate to high correlations were found between cystatin C and NT-proBNP (r=0.564; p<0.001), sST2 (r=0.602; p<0.001), galectin-3 (r=0. 803; p<0.001), LVEF (r=–0.410; p<0.001), LAVI (r=0.350; p<0.001), LVMMI (r=0.480; p<0.001), E/è (r=0.448; p<0.001). Numerous studies have demonstrated not only the diagnostic value of cystatin C in evaluating GFR, but also its high prognostic value in determining the risk of new cases of HF, CHF decompensation and death [29]. In our study, the addition of cystatin C concentration to the baseline model for estimating the probability of CEP improved the prognostic quality of the model. The obtained cut-off value for cystatin C ⩾1.69 mg/l allows a reliable classification of CHF patients with CKD into high and low risk categories for the development of CEP (RR=3.436 with 95% CI: 2.1–5.5; p<0.001).

Conclusion

Patients with CHFpEF, type 2 DM and CKD have more severe clinical and functional cardiovascular and carbohydrate metabolic disorders than patients with CHFpEF without CKD. In the course of the study, a significant inverse relationship was found between the degree of renal function decline (cGFR) and structural and functional cardiac parameters, LV diastolic function, concentration of markers of myocardial dysfunction. The analysis of the obtained results showed that the use of multimarker models improves the quality of prediction of unfavourable course of HF in patients with CHFpEF, type 2 DM and CKD. At the same time, the determination of myocardial and renal dysfunction markers in clinical practice will allow the selection of patients at high risk for HF decompensation and cardiac death in the population of comorbid patients and the timely implementation of therapeutic measures.

Conflict of interest: none declared.

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Influence of the patient's age on the probability of reoperation after aortic valve neocuspidalisation surgery (Ozaki technique)

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The aim of this study to determine the influence of age on the probability of postoperative regurgitation in patients of different age groups.
Methods. A single-centre retrospective study included 720 patients who underwent aortic valve neocuspidalisation surgery in Penza. Patients were divided into three groups according to age by WHO classification. Among them — 60 patients of young age group, 166 patients of middle age group and 494 elderly patients who underwent this procedure between 2015 and 2022.
Results. According to the data of our center, postoperative regurgitation occurred in 54 patients from different age groups. Univariate regression analysis was performed to identify the significance of patient age as a predictor of postoperative regurgitation. The analysis revealed a statistically significant increase in the probability of regurgitation in younger patients. Increasing the age by 1 year decreases the probability of regurgitation by 3 % (OD=0.970; p=0.03).
Conclusion. Neocupidalisation surgery shows good long-term results. Younger age can be considered as a risk factor for postoperative regurgitation.
Keywords: Ozaki technique, neocuspidalisation, aortic valve stenosis.

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Introduction

Aortic valve (AV) stenosis is the most common indication for surgical intervention in valvular heart disease. In the Russian Federation, aortic stenosis (AS) occurs in 1–2% to 4% of patients over the age of 65. According to D.S. Bach, the prevalence of aortic valve disease is 1.4% in women, 2.7% in men, and 10.7% in people over 65. According to some studies, there is an association between the age of the patient and the prevalence of AS. Thus, in the group under 65 years of age, AS occurs in 0.2% of cases, in 65–74 years of age — 1.3% of cases, and in the group over 75 years of age — 2.8% of cases [1].

The indication for surgical treatment is a severe/critical AS. The issues of surgical tactics in this pathology are still under active discussion. To date, only AV replacement with biological or mechanical prostheses has found a place in clinical recommendations. The operation of neocuspidation of the AV leaflets from the autopericardium, proposed by S. Ozaki in 2011, is gaining popularity. This procedure has shown good results in elderly patients. However, the prospects of this procedure in young (18–44 years according to WHO) and middle-aged (45–59 years according to WHO) patients remain controversial.

The aim of this study was to to determine the influence of age on the probability of postoperative regurgitation in patients of different age groups.

Methods

A single-centre retrospective study included 720 patients who underwent aortic valve neocuspidalisation surgery in Federal Centre of Cardiovascular Surgery of the Ministry of Health of Russia, Penza.

Patients were divided into three groups according to age by WHO classification. Among them — 60 patients of young age group, 166 patients of middle age group and 494 elderly patients.

The maximum follow-up period was 72 months.

Patients with coronary heart disease, multi-valve heart disease and other pathologies requiring surgical intervention were excluded from the study.

Table 1 shows the main clinical, demographic and echocardiographic data of the patients.

Table 1. **Clinical, demographic and echocardiographic data of the patients before the surgery**

Parameter, n	Young age, n=60	Middle age, n=166	Old age, n=494
Clinical and demographic data			
Age, years	35±7	54±4	66±4
Males, n	47 (74%)	104 (59%)	227 (46%)
BMI, kg/m^2	26±5	29±5	30.2±5.02
Body surface area, m^2	1.9±0.2	2±0.2	1.9±0.20
Diabetes, n	3(4%)	14(8%)	93 (19%)
Obesity, n	16(25%)	68(38%)	249 (50%)
EuroSCORE II	3.2±4.3	2.7±2.9	4.08±2.35
Echocardiographic data			
EF, %	53.13±15.16	58.5±12.49	59.81±12.25381
AVA, cm^2	1.8±1.63	1.0 ±0.79	0.986598±0.804756
G mean, mmHg	30.3±20.38	42.7±21.99	47.71±21.59
G max, mmHg	54.0±34.79	73.4±34.73	82.36±35.76
Fibrous ring (FR), mm	24.3±4.11	23.11±3.46	22.39±3.103902

Surgical technique

The procedure was performed through a median sternotomy. The autopericardium was then harvested and treated with glutaric acid solution, followed by exposure of the autopericardium to saline. Antegrade blood cardioplegia was performed in cases of preserved AV; in cases of insufficiency, cardioplegia was performed selectively in the coronary artery orifices. The intercommissural space was measured using classic Ozaki sizers after careful decalcification of the AV fibrous ring (FR). The excised leaflets were implanted in the desired position. The valve stability was assessed immediately after the implantation by hydroassay and by transesophageal echocardiogram control. The leaflets were stable in all patients.

Statistical analysis

Statistical processing of the material was performed using SPSS version 21 software package (IBM Corp., Armonk, USA). The arithmetic mean (M = ∑ / n) and standard deviation from the general population (s) were calculated to compare the results obtained between groups. Data are presented as mean (M) and standard deviation (SD) or as absolute values (n) and percentages (%). Categorical data were compared using Pearson's criterion. The critical significance level was set at 0.05. Univariate regression analysis was performed to identify predictors of reoperation after AV neocuspidalisation.

Results

The echocardiographic data of the patients after the surgery are shown in Table 2.

In the young age group, regurgitation was detected in 7 patients.

In the middle age group, regurgitation occurred in 19 patients.

In the elderly age group, regurgitation occurred in 28 patients.

Univariate regression analysis was performed to identify predictors of regurgitation after Ozaki operation. The results are presented in Table 3.

Based on the results of univariate regression analysis, age is a predictor of regurgitation. Increasing the age by 1 year reduces the probability of regurgitation in the remote postoperative period by 3% (OD=0.970; p=0.01).

Discussion

Surgical treatment of AV defects (AVD) is becoming increasingly important as the population ages and the incidence of various AVD increases. It is particularly important to determine the surgical tactics in patients younger than 60 years of age. AV prosthesis with mechanical valve is the most commonly performed procedure for AVD.

However, this procedure has a significant impact on the patient's quality of life. The first is the need to take anticoagulants for the rest of the patient's life. This therapy is associated with a high risk of complications such as gastrointestinal bleeding, liver damage, etc. A special observation group is women of childbearing age, for whom pregnancy is contraindicated after AV prosthesis with mechanical valve, as well as patients with small AV FR, who often develop complications such as patient-prosthesis mismatch [4].

Table 2. **The echocardiographic data of the patients after the surgery**

Parameter, n	Young age, n=63	Middle age, n=175	Old age, n=494
LVEDV, ml	144±53,29	132,05±48,92	115,87±37,47
LVESV s, ml	61,05±43,10	56,66±36,68	47,52±26,42
Stroke volume (SV), ml	82,95±18,97	75,75±21,11	68,18±16,60
EF, %	60,27±8,97	59,63± 10,38	60,89±9,54
AVA, cm^2	2,89±1,01	2,88±1,12	2,71±1,11
G mean, mmHg	6,79±3,87	6,75±4,37	6,44±4,45
G max, mmHg	13,82±8,15	14,20±9,10	13,57±8,24
FR, mm	23,15±3,03	22,05±2,88	20,98±2,69

Table 3. **Results of the univariate regression analysis of reoperation**

Predictors	OD	95% CI	p
Age	0,970	0,951–0,99	0,03

In 2011, S. Ozaki proposed an operation for AV leaflet neocuspidalisation (AVNeo) using autopericardium, pretreated with glutaric acid. This procedure showed good results in the older age group, with low mortality and reoperation rates [5].

According to the latest 2017 American Heart Association guidelines, patients with AVD between the ages of 50 and 70 can choose between a bioprosthesis and a mechanical prosthesis [6]. Implantation of a biological prosthesis frees the patient from taking anticoagulants, however, its durability is inferior to that of a mechanical one.

For patients with small FR of AV, guidelines favour transcatheter aortic valve implantation (TAVI), which has shown good results only in patients over 75 years old, and is still under the research in patients under 75 years [7].

The AVNeo procedure does not require anticoagulants, which makes future pregnancies possible, improves the quality of life, and increases the effective AV orifice due to the absence of a cuff to attach to the FR. Thus, this procedure may be an optimal solution for patients at high risk of bleeding, patients planning pregnancy, and patients with narrow FR [4, 8].

Amabile et al. point out in their study that the occurrence of aortic regurgitation is one of the most common causes of reoperation in patients (4.2 %) [10].

Iida Y. et al. in their study of this technique in patients younger than 65 years old report a high survival rate (88.9 % at 72 months of follow-up) and high reoperation-free rate (87.3 % at 72 months of follow-up) of patients undergoing the Ozaki procedure [11].

According to some data, the occurrence of regurgitation in the postoperative period may be as high as 7 % [12].

The Ozaki technique uses the patient's own pericardium, which, unlike other types of prostheses, is an inert tissue for the body. However, the pericardium undergoes various biodegradation processes. After implantation of neo-leaflet prostheses, hyperproliferation and hyperplasia of connective tissue are activated through various mechanisms. Also, immune-mediated factors leading to migration of immune cells (macrophages, neutrophils, T-lymphocytes, etc.) should be considered. All the above processes lead over time to irreversible changes of the neo-valve and its dysfunction. In the young age group, the biodegradation mechanisms are more prominent than in the older age group and lead to valve dysfunction faster [13, 14].

Our study included patients of different ages who underwent AVNeo surgery. It was found that younger patients had a higher risk of regurgitation than older patients. This will be the subject of further research.

Conclusion

Neocupidisation surgery shows good long-term results. It is now comparable to procedures such as TAVI and biological prosthesis implantation. This procedure is recommended for older patients because of the better long-term results in this group. Younger age can be considered a risk factor for regurgitation in the distant postoperative period.

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Evaluation of the GRACE scale in patients with acute myocardial infarction

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The aim was to study the clinical characteristics, echocardiographic data, N-terminal brain natriuretic peptide (NT-proBNP) levels at the hospital stage in patients with acute ST-segment elevation myocardial infarction (STEMI) in relation to the risk of in-hospital mortality (GRACE scale) and glomerular filtration rate (GFR).

Methods. Patients with STEMI who were followed in hospital were included on the first day of the cardiovascular event (n=150). The objective, laboratory data, including NTproBNP level, EchoCG in the dynamics of hospital treatment of patients depending on the risk level of the GRACE scale, GFR <60 ml/min/1.73 m2 and ≥60 ml/min/1.73 m2 were evaluated. Statistical processing of the material was performed with "Statistica 10.0 for Windows".

Results. On the first day of STEMI, NT-proBNP concentration increased independently of the risk of in-hospital mortality (GRACE scale) and remained high at the in-hospital stage. Positive correlations: NTproBNP levels at hospital admission and discharge; NTproBNP levels at hospital admission with functional class of chronic heart failure and GRACE scale ($p<0.05$) indicated an unfavourable prognosis. High-risk STEMI patients on the GRACE scale were characterised by more severe diastolic and systolic myocardial function of the left ventricle. Patients with reduced GFR had a higher risk of in-hospital mortality with signs of left ventricular dilatation.

Conclusion. Patients at high risk according to the GRACE scale have older age, reduced left ventricular ejection fraction and the most severe changes in diastolic function. Evaluation of heart failure markers, GFR during the hospital stage of STEMI allows to choose the correct tactics of patient management.

Keywords: acute myocardial infarction, heart failure, glomerular filtration rate.

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Introduction

Modern cardiology expands the treatment options for acute myocardial infarction (AMI): correction of cardiovascular risk factors (RF), drug therapy and surgical tactics with an emphasis on the fact that the early initiation of treatment can improve prognosis. [1]. Risk stratification of AMI patients includes following criteria: Risk stratification of AMI patients includes demographic, clinical, laboratory and instrumental test results. In clinical practice it is possible to use risk scales in a calculator format. The GRACE scale — Global registry of acute coronary events assesses the risk of hospital mortality within six months. The parameters in the GRACE scale are: age, class of acute heart failure according to the T. Killip classification, the fact of cardiac arrest, systolic blood pressure (SBP), heart rate (HR), assessment of ST segment change according to electrocardiograms, blood creatinine level, markers of myocardial necrosis. The sum of all the indicators is used to calculate a score and the risk of in-hospital mortality is determined accordingly: low, intermediate or high risk in patients with acute coronary syndrome (ACS).

Laboratory markers contribute to the assessment of AMI prognosis. N-terminal brain natriuretic peptide (NTproBNP) levels are known to be elevated in patients with AMI, predicting the risk of heart failure [2, 3]. Currently, NTproBNP is widely used in modern practice. A number of studies have confirmed that NTproBNP is a prognostic marker for survival and the development of heart failure in patients with ACS [4]. The high levels of NTproBNP during a year in ACS patients predict an increase in mortality, risk of recurrent ACS, clinically significant heart failure. NTproBNP is one of the factors for sudden death, together with the following parameters: age, sex, arterial hypertension, diabetes mellitus, left ventricular (LV) ejection fraction (EF), troponin I [5].

Assessment of haemorrhagic complications RF in a patient with AMI allows timely selection of management tactics at the hospital treatment stage. According to clinical guidelines, in AMI with ST-segment elevation electrocardiogram 2020 it is necessary to assess the prognostic risks of patients with AMI for haemorrhagic complications (haemoglobin level, erythrocytes, platelets), the risk of thromboembolic complications, control carbohydrate metabolism, lipid metabolism data, calculate GFR [6]. Renal dysfunction in the general population occurs in 12-17 % of people, in patients with Non ST-elevation ACS- 42.9 %, in patients with ST-elevation ACS- 30.5 % [7].

The importance of studying and searching for new prognostic markers in patients with AMI in the hospital stage should be noted. Patients with AMI with ST-segment elevation (STEMI) have the most unfavourable prognosis on the first day and during the hospital stage. In our opinion, it is important to study the NT-proBNP prognostic marker in STEMI patients depending on the GRACE risk scale.

The aim was to study the clinical characteristics, echocardiographic data, N-terminal brain natriuretic peptide (NT-proBNP) levels at the hospital stage in patients with acute ST-segment elevation myocardial infarction (STEMI) in relation to the risk of in-hospital mortality (GRACE scale) and glomerular filtration rate (GFR).

Methods

The study included 150 patients with STEMI on day one. The trial was conducted in accordance with good clinical practice and the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolment. The diagnosis of STEMI was confirmed according to clinical guidelines (2020), taking into account data on symptoms, physical examination, markers of myocardial necrosis (CPK-MB and troponin I), and electrocardiogram dynamics [6].

Inclusion criteria: first-day STEMI, history of arterial hypertension. Exclusion criteria: known history of autoimmune diseases, connective tissue diseases, oncological diseases, diabetes mellitus type 1 and 2, acute kidney injury, liver failure, bronchial asthma, women of reproductive age, complicated percutaneous coronary intervention, infectious diseases at the time of enrolment.

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Clinical, laboratory and instrumental data of patients with STEMI on admission to the cardiology department and at discharge were evaluated. Those included:

- Clinical data: age, body mass index (BMI), SBP, diastolic blood pressure (DBP), HR.
- Laboratory data: clinical blood analysis, biochemical blood analysis, myocardial necrosis markers (CPK-MB, troponin I), lipidogram data (total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides (TG)).

Plasma NTproBNT levels were determined by immunometric method using reagents from the VITROS immunodiagnostic products. Electrocardiograms and echocardiography were performed in all patients. We calculated the risk of in-hospital mortality of patients during hospitalization according to the GRACE scale: < 126 points — low risk (<2 %) of in-hospital mortality; 126-154 points — intermediate risk (2–5 %); >154 points — high risk (>5 %). Taking into account the GRACE risk score, the study population of STEMI patients was divided into low, intermediate and high risk groups [6].

Statistical processing of the obtained material was performed using the statistical software package "Statistica 10.0 for Windows". Statistical differences were evaluated using non-parametric Mann-Whitney, Wilcoxon criteria. The Spearman correlation coefficient method and its significance level were used to assess the dependencies between variables. The values studied are presented as mean values and mean errors (M±m). Differences in values were considered statistically significant at $p<0.05$.

Results

Characteristics of the general group of patients with STEMI on admission:

- Age: 61.70±2.96 years;
- Clinical data: BMI — 29.43±3.62 kg/m^2; SBP level — 135.00±27.60 mmHg, DBP level — 81.91±14.92 mmHg, HR — 81.62±18.50 beats/min.
- Laboratory data: Troponin I level — 13.22± 1.40 ng/ml, creatinine phosphokinase (CPK) — 320.21±35.64 U/L, CPK-MB — 61.60±14.93 U/L, alanine aminotransferase (ALT) — 45.01±2. 62 U/L, aspartate aminotransferase (AST) — 86.3±8.7 U/L, urea 6.6±2.3 mmol/L, creatinine 84.74±33.03 μmol/L, GFR — 81.17±1.98 ml/min/1.73 m^2; lipidogram data: TC level — 5.70±1.30 mmol/l, LDL — 2.87±0.06 mmol/l, HDL — 1.33±0.03 mmol/l, TG — 1.74±0.07 mmol/l.

According to the GRACE hospital mortality scale, the mean value in STEMI patients at the time of hospitalization was 162.21±2.53 points.

In our study in the general group of STEMI patients, the mean NTproBNP level at hospital admission — 2683.95±299.05 pg/ml, at discharge — 2489.46±275.06 pg/ml ($p>0.05$) did not differ statistically significantly in the dynamics of hospital treatment. The level of NTproBNP increased on the first day of STEMI and remained high throughout the hospital course. Positive correlations were found: between NTproBNP levels at admission and discharge $r=0.67$ ($p<0.01$); between NTproBNP levels at admission with functional class of chronic heart failure (CHF) $r=0.20$ ($p<0.04$) and GRACE scale $r=0.38$ ($p<0.01$), indicating an unfavourable prognosis. NT-proBNP levels have no significant dynamics in the hospital phase of treatment, which determines the further development of heart failure.

EchoCG parameters were calculated in the studied STEMI patients: Left atrium (LA) — 41.38±0.34 mm, left ventricular end-systolic dimension (LV ESD) — 40.84±3.59 mm, left ventricular end-diastolic dimension (LV EDD) — 53.43±3.48 mm, end-systolic volume (ESV) — 75.02±16.94 cm^3, end-diastolic volume (EDV) — 140.70±21.45 cm^3, stroke volume (SV) — 64.51±8.27 ml, peak transmittal blood flow velocity in the phase of early filling E — (50.19±0.99 cm/s), late filling (A) — 60.40±1.12 cm/s, right atrium (RA) — 32.84±0.21 mm, right ventricle (RV) — 29.95±0.19 mm, tricuspid valve (TV) V max –248.47±2.43 cm/s.

In AMI, there are changes in myocardial relaxation and impaired diastolic filling. There is a decrease in early ventricular diastolic filling (E), increase in peak late systolic filling (A), E/A ratio becomes less than 1. With the background of myocardial diastolic function progression, E/A ratio=1-1.5 with moderate increase in LA pressure reflects moderate degree of diastolic dysfunction. When the E/A ratio is >2, severe diastolic dysfunction (with restrictive filling) is observed with increased LA pressure and decreased LV compliance [8, 9].

Low-risk STEMI patients had a GRACE score of 117.00±1.66 points, intermediate-risk patients 144.36±2.23 points ($p<0.05$) and high-risk patients 182.53±2.72 points ($p<0.05$). A statistically significant

increase in GRACE score was found in STEMI patients as the risk rose. Table 1 shows the clinical and laboratory characteristics of STEMI patients according to GRACE scale risk (low, intermediate and high risk). High-risk GRACE patients were older, had higher creatinine levels and lower SBP, DBP, GFR (p<0.05). At the same time, low-risk patients had maximum troponin I levels. Other clinical and laboratory data did not show statistically significant differences (p>0.05).

According to EchoCG data, changes are observed depending on the risk level of in-hospital mortality. With increasing risk level according to the GRACE scale in patients with STEMI, there is a statistically significant decrease in E parameters, E/A ratio (p<0.05); increase in A (p<0.05), which confirms the presence of diastolic dysfunction. At the same time, there is a decrease in EF (p<0.05) with the lowest values in high-risk patients according to the GRACE scale (Table 1). Other EchoCG parameters were not statistically significantly different according to risk level (p>0.05).

Thus, diastolic dysfunction and reduced EF LV in the hospital setting in patients with STEMI have been shown to be associated with an increased risk of mortality according to the GRACE scale.

The study of the laboratory marker NTproBNP provided data to characterise the increased risk of developing heart failure in STEMI patients. Figure 1 shows the tendency for NTproBNP levels to increase (p<0.05) in STEMI patients with increasing risk according to the GRACE scale. Furthermore, NTproBNP concentration is three times higher in intermediate risk patients (p<0.05) and 8.3 times higher in high risk patients compared to low risk GRACE STEMI patients (p<0.05). The risk-related increase in NTproBNP levels may be related to the age of the patients. At the same time, NTproBNP levels did not change with treatment.

Thus, regardless of risk according to the GRACE scale, NTproBNP levels increase on the first day of STEMI. The highest NTproBNP levels are found in high-risk patients on admission to hospital and persist throughout the hospital course of STEMI patients, which is associated with the highest risk of heart failure.

Taking into account the statistically significant reduction in GFR in relation to the risk of death according to the GRACE scale, we analysed the data of patients with GFR <60 ml/min/1.73 m^2 and ⩾ 60 ml/min/1.73 m^2. According to the literature, an average of 30 % of patients with AMI experience a reduction in GFR. At the same time, GFR reduction is an exclusion criterion in most AMI randomized clinical trials.

Of the patients studied, 22 % (n=33) had reduced GFR and 78 % (n=117) had preserved GFR. STEMI patients with GFR <60 ml/min/1.73 m^2 were older than 69.48±2.01 years (p<0.05), haemodynamic data were not different: SBP — 132.18±5.54 mmHg, DBP — 80.21±3.50 mmHg, HR — 81.84±3.45 b/min compared

Table 1. **Parameters of STEMI patients according to the GRACE scale hospital mortality risk score (M±m)**

Parameter	Low risk	Intermediate risk	High risk	p low — intermediate risk	p low — high risk
Clinical data					
Age, years	44,15±2,13	54,47±1,17	67,65±0,96	<0,05	<0,05
SBP, mmHg	149,61±4,40	145,86±4,23	128,12±2,69	>0,05	<0,05
DBP, mmHg	88,46±2,73	86,63±1,89	78,51±1,62	>0,05	<0,05
HR, b/min	82,46±4,50	79,89±1,90	82,36±2,22	>0,05	>0,05
Laboratory data					
HGB, g/l	153,23±3,81	143,42±3,39	140,78±2,17	>0,05	0,03
HCT, %	48,69±4,65	41,90±1,33	41,07±0,96	>0,05	>0,05
CPK, U/l	182,58±60,87	354,73±64,14	323,63±44,77	>0,05	>0,05
CPK-MB, U/l	36,75±8,02	50,01±10,70	71,42±22,96	>0,05	>0,05
Troponin I, ng/ml	19,71±6,15	10,40±1,56	13,66±1,97	0,03	>0,05
Creatinine, mmol/l	65,69±6,46	83,80±3,52	87,49±3,87	0,02	0,04
GFR, ml/min/1,73 m^2	108,45±4,17	88,24±2,96	73,86±2,38	0,01	0,01
TC, mmol/l	5,82±0,28	5,81±0,20	5,68±0,14	>0,05	>0,05
EchoCG data					
EF, %	49,23±3,18	47,70±0,77	44,87±0,52	>0,05	<0,05
E, m/s	49,23±3,18	55,60±1,82	46,52±1,09	>0,05	<0,05
A, m/s	54,84±3,94	55,24±1,99	63,74±1,35	>0,05	<0,05
E/A	1,14±0,13	1,10±0,07	0,78±0,04	>0,05	<0,05

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to the group of patients with GFR ≥60 ml/min/1.73 m^2: 60.26±1.11 years, SBP 135.77±2.43 mmHg, DBP 82.69±1.21 mmHg, HR 81.89±1.67 b/min (p>0.05). Notably, STEMI patients with reduced GFR had a higher risk of in-hospital mortality GRACE 181.15±5.84 than the group of patients with preserved GFR 159.83±2.79 points (p<0.05).

Biochemical data of STEMI patients were analysed according to GFR <60 ml/min/1.73 m^2 and GFR ≥ 60 ml/min/1.73 m^2. The laboratory values of the group of patients with reduced GFR: AST 83.46±24.18 U/L, ALT 41.17±5.50 U/L, urea 10.38±2.94 mmol/L, CPK 319.78±90.19 U/L, CPK-MB 101.08±61.57 U/L and preserved GFR: AST 87.04±8.99 U/L, ALT 46.09±2.91 U/L, urea 9.5±1.64 mmol/L were comparable (p>0.05). In the group of STEMI patients with reduced GFR: creatinine values 118.67±7.57 mmol/l, calculated GFR 46.09±1.87 ml/min/1.73 m^2 and preserved GFR: creatinine 75.01±1.97 mmol/l, GFR 90.87±1.54 ml/min/1.73 m^2 were statistically significantly different (p<0.05). In patients with reduced GFR TC 5.89±0.23 mmol/l, LDL 3.11±0.14 mmol/l, HDL 1.40±0.05 mmol/l, TG 1.51±0.12 mmol/l and in patients with preserved GFR TC 5.70±0.12 mmol/l, LDL 2.80±0.07 mmol/l, HDL 1.31±0.03 mmol/l, TG mmol/l 3.67±1.32 mmol/l (p>0.05). In the analysis of myocardial necrosis markers, troponin I levels (13.81±3.51 and 13.05±1.51 ng/ml), CPK levels (319.78±90.19 and 320.36±37.89 U/L), CPK-MB (101.08±61.57 and 49.94±6.65 U/L) showed no statistically significant differences (p>0.05). However, potassium levels were higher in the group of patients with reduced GFR (5.60±1.15 mmol/L) compared to those with GFR≥60 ml/min/1.73 m^2 (potassium 4.24±0.05 mmol/L (p<0.05)).

As a result, STEMI patients with reduced GFR were older and had a higher risk of hospital mortality according to the GRACE scale. There were no statistically significant differences in biochemical parameters and lipid metabolism depending on GFR.

Assessing the prognosis of patients in hospital is an urgent task. We performed a correlation analysis between GFR and the risk of acute heart failure, HCF, and the hospital mortality scale GRACE. We obtained negative correlations of GFR with the degree of acute heart failure in STEMI patients (r=–0.48, p=0.001), the degree of CHF progression (r=–0.23, p=0.038), hospital mortality according to the GRACE scale (r=–0.48, p=0.0001) and unfavourable prognosis at the hospital stage (r=–0.40, p=0.043).

Figure 2 shows the dynamics of NTproBNP levels during hospital treatment of STEMI patients with GFR < 60 ml/min/1.73 m^2 and GFR ≥ 60 ml/min/1.73 m^2. There were no statistically significant differences in NT-proBNP levels according to GFR. At the same time, it should be noted that in the dynamics of hospital treatment of STEMI patients, there was a tendency for NTproBNP levels to decrease in the group with GFR ≥60 ml/min/1.73 m^2 and for the studied marker to increase in patients with reduced GFR.

When examining the EchoCG data in STEMI patients depending on GFR, a statistically significant in-

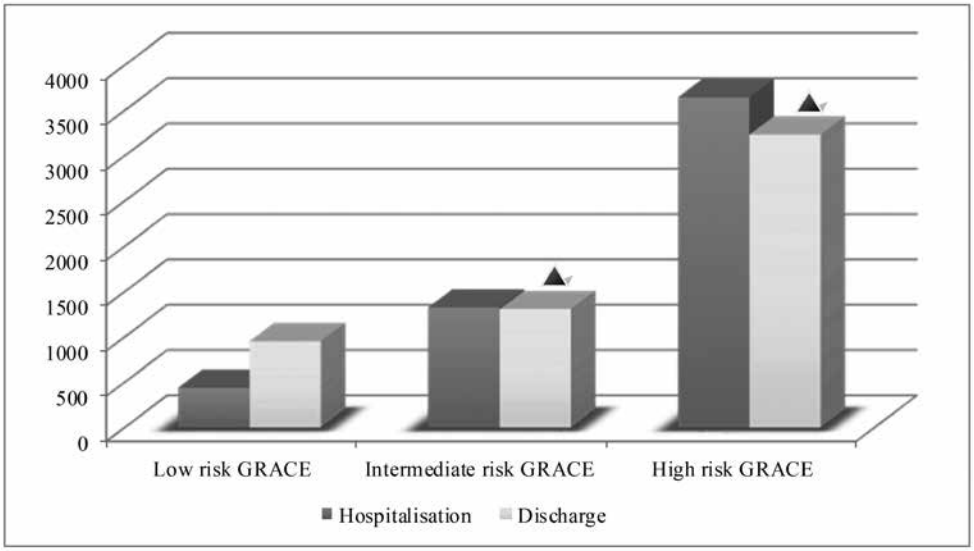

Fig. 1. Dynamics of NTproBNP level in STEMI patients depending on the risk of hospital mortality according to the GRACE scale
***Note**. p<0.05 in the studied groups with the increasing degree of the risk.

crease in LA 45.03±2.20 mm, LV ESD 44.41±2.12 mm, LV EDD 56.41±1.74 mm was observed in patients with reduced GFR compared to the group with preserved GFR: LA 41.48±0.65 mm, LV ESD 40.98±0.64 mm, LV EDD 53.48±0.52 mm ($p<0.05$). In the GFR < 60 ml/min/1.73 m^2 and GFR ⩾ 60 ml/min/1.73 m^2 groups, E (48.80±2.72 and 51.52±1.19 cm/s), A (62.09±2.91 and 60.68±1.28 cm/s), E/A (4.15±3.29 and 1.84±0.91) values were comparable ($p>0.05$).

Thus, changes in echocardiographic data with a tendency of increased left heart chambers size during the hospital follow-up period of STEMI patients are one of the important predictors of heart failure development in the future. Laboratory control of the increased NTproBNP level reflects the risk of heart failure progression.

Discussion

There are currently a large number of scales for assessing the prognosis of patients with AMI. In clinical trials and real-world clinical practice, the Killlip T. AMI patients' acute heart failure scale and the GRACE scale for assessing the risk of in-hospital mortality are widely used. The use of available criteria, objective and laboratory data in the GRACE scale allows timely assessment of the prognosis of ACS patients, and the use of the NT-proBNP increases the accuracy of heart failure prognosis. The obtained EchoCG data in high-risk patients according to the GRACE scale: decrease of E parameters, E/A ratio ($p<0.05$), increase of A ($p<0.05$) confirm the presence of diastolic dysfunction and progression of heart failure in STEMI patients at the hospital stage of treatment.

Clinical studies in ACS patients confirm the presence of varying degrees of renal failure in 35–40 % of patients [7]. Severe renal dysfunction is known to be associated with an unfavourable prognosis and is an independent predictor of cardiovascular complications in ACS patients [10]. GFR assessment is not only a prognostic marker of renal dysfunction, but also an important criterion for the selection of management tactics in patients with ACS. According to the literature, renal failure is common in patients after AMI, and the presence of chronic kidney disease is associated with high in-hospital and long-term mortality in patients with AMI [10, 11].

Among the STEMI patients we studied, 22 % had reduced GFR. Patients with STEMI GFR <60 ml/min/1.73 m^2 were older and had a high risk of in-hospital mortality according to the GRACE scale. Objective and laboratory data were comparable in patients with reduced and preserved GFR. According to the EchoCG data, patients with reduced GFR had increased LA and LV dimensions, a marker of heart failure progression. The calculated negative correlations of GFR with the degree of acute heart failure in patients with STEMI, the degree of CHF progression and hospital mortality according to the GRACE scale confirm the importance of GFR in assessing prognosis at the hospital treatment stage [11, 12].

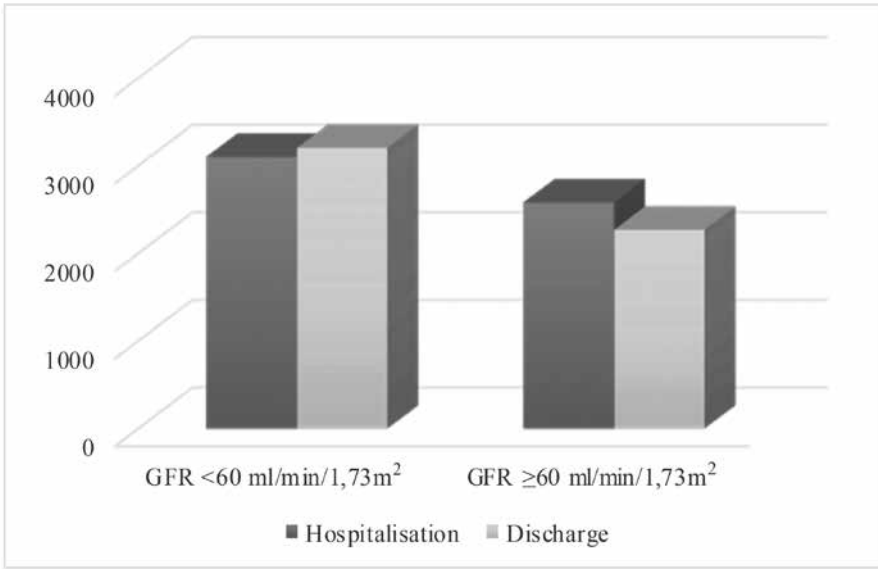

Fig. 2. NTproBNP levels during the hospitalization of STEMI patients depending on the GFR

Conclusion

The GRACE scale for in-hospital mortality is easy to use and can be applied in real-world clinical practice in patients with ACS. Patients at high GRACE risk tend to be older, with reduced LV EF and the severe diastolic dysfunction. NT-proBNP concentration increases with increasing GRACE risk and does not change at the end of the hospital phase of STEMI treatment. The detection of heart failure markers in the conditions of hospital treatment of STEMI allows the selection of the right tactics of patient management in the hospital and outpatient phases of treatment. Comprehensive assessment of patients with STEMI during the inpatient follow-up is an important guide to the future prognosis of patients.

Conflict of interest: none declared.

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The role of SGLT-2 inhibitors in the treatment of acute decompensation of chronic heart failure: a meta-analysis of large clinical trials

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We present a systematic review and meta-analysis of the literature data from the studies conducted to determine the effect of early (up to 24 hours) administration of SGLT-2 inhibitors in patients with acute decompensated chronic heart failure on immediate outcomes and the effect of the therapy on reducing levels of inpatient heart failure markers.

Keywords: sodium-glucose transport protein 2 inhibitors, acute decompensation of chronic heart failure.

Conflict of interest: none declared.

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Introduction

Chronic heart failure (CHF) associated with an unfavourable prognosis of patients regardless of its origin. Until recently, three groups of drugs known as "triple neurohumoral blockade" were used to improve prognosis in terms of reduced mortality. This included therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEi/ARBs), beta-blockers (BBs) and mineralocorticoid receptor antagonists (MRAs). It was first adjusted following positive results from studies in which therapy with angiotensin/neprilysin receptor antagonists (ARNIs) demonstrated high efficacy in reducing mortality and risk of rehospitalization. Importantly, the identified benefits were realised in a selective group of patients with CHF with reduced ejection fraction (HFrEF).

A breakthrough in the medical management of CHF was the addition of sodium-glucose cotransporter type 2 inhibitors (SGLT2i) to the standard therapy — dapagliflozin and empagliflozin. They were found to reduce the rehospitalization rate in patients with CHF regardless of EF and the presence of diabetes mellitus, and to improve prognosis in patients with HFrEF [1]. Following the results of the EMPEROR trial, empagliflozin was the first drug to demonstrate efficacy in the treatment of CHF with preserved EF (HFpEF) [2]. The updated optimal medical therapy (OMT) has been termed "quadrotherapy". An analysis of comparative trials of early versus updated OMT at a median of 18–27 months (depending on the trial) showed a 50 % reduction in cardiovascular mortality and a 68 % reduction in the risk of rehospitalization for CHF decompensation in the HFrEF group [3].

The episode of acute decompensation of chronic heart failure (ADHF) is one of the main criteria for the effectiveness of CHF treatment, reflecting its crucial role in the prognosis of these patients. In patients hospitalized with ADHF, the risk of death within one year is 18.5 % if compensation is achieved at the hospital stage. If CHF cannot be fully compensated (subcompensation) and congestion persists at the time of discharge, the mortality rate within one year reaches 28 % [4]. In their study, Chioncel O. et al. identified independent predictors of CHF subcompensation. These include: diabetes mellitus, anemia and tricuspid regurgitation. Predictors suggestive of compensation included CHF de novo, beta-blocker use at the time of hospitalization and any cardiovascular intervention during hospitalization [4].

The successful use of SGLT2i in CHF was the trigger for evaluating the effect of this class of drugs on the prognosis of patients with ADHF. The additional possibility of achieving compensation at the hospital stage when adding SGLT2i to therapy is explained by the the pharmacological action of the drug. Boorsma E.V. et al. showed that the increase in diuresis with the use of SGLT2i in ADHF is achieved through an increase in glucose excretion, but not sodium excretion. The authors also noted a significant decrease in glomerular filtration rate (GFR) during the first 24–72 hours of therapy, with subsequent recovery of renal function at 96 hours and up to 30 days [5]. The beneficial effects of SGLT2i in ADHF have been confirmed in two large clinical trials. The SOLOIST-WHF study was the first to demonstrate the high efficacy and safety of SGLT2i administration in patients with ADHF and type 2 DM immediately after the stabilisation of the condition [6]. Sotagliflozin therapy reduced the incidence of the combined endpoint (mortality and hospitalizations due to ADHF) by 33 % at a median follow-up of 9 months. Another large study (EMPULSE) investigated the role of empagliflozin under similar conditions — administration of the drug after the stabilisation in patients with ADHF, regardless of the type 2 DM presence, was associated with a reduction in mortality and rehospitalization within 90 days [7]. In the EMPULSE study, empagliflozin therapy was administered 1–5 days after hospitalization. Earlier administration of SGLT2i may reduce the time required to achieve HF compensation and may also be associated with an improved prognosis in these patients as soon as possible after an episode of ADHF. However, current studies investigating the role of early (up to 24 hours) initiation of SGLT2i are characterised by small sample sizes and a lack of conclusive results on the efficacy and safety of ADHF treatment.

The aim of this meta-analysis is therefore to review the results of the trials and determine the impact of early (up to 24 hours) administration of SGLT2i in patients with ADHF on immediate prognosis, as well as the effect of therapy on reducing levels of HF markers at the hospital stage.

The information retrieval algorithm was developed according to the PRISMA guidelines for systematic reviews and meta-analyzes [8]. Publications were searched in the English language Pubmed and Google Scholar databases using search queries, keywords (including MeSH) and logical operators. The follow-

ing query was used in the Pubmed database: (acute decompensated heart failure) AND (reduced ejection fraction) AND (Sodium-glucose co-transporter 2) OR (Empagliflozin) OR (Dapagliflozin) OR (Sotagliflozin) NOT (Preserved). Additionally, a query in MeSH — "Sodium-Glucose Transporter 2 Inhibitors/therapeutic use" was performed [MAJR]. In both cases, the filter "randomized clinical trials" was used. To search the Google Scholar database, an advanced search was used with the following queries: "sodium glucose co-transporter 2 inhibition in heart failure" in the string "with all of the words", "acute decompensated heart failure" in the string "with the exact phrase". In order to search for additional sources of information, the reference list of the found publications was used, as well as recommendations from the Pubmed database in the section "similar articles". The search was carried out in the period from 01.01.2020 to 31.10.2022.

The systematic review included randomized clinical trials that investigated the effect of early (up to 24 hours) administration of SGLT2i on the prognosis in patients hospitalized for ADHF with at least 30 days of follow-up. In addition, studies that researched the effect of SGLT2i therapy on NT-proBNP levels in patients hospitalized for ADHF with at least 7 days of follow-up were included. Non-randomized trials, clinical cases or case series, abstracts and reviews were excluded. We assessed the dynamics of NT-proBNP levels on therapy and/or 30-day mortality after discharge as endpoints.

The initial screening using the above search algorithms yielded 322 and 200 publications in the Pubmed keyword and MeSH databases, respectively, and 1140 publications in the Google Scholar database. After removing duplicates and analysing titles and their abstracts, 1655 publications were removed. From the remaining 7 publications, 5 articles (0.03 %) were selected based on the full-text version analysis. The obtained publications were processed using statistical analysis. The results of the selection are shown in Figure 1.

The risk of systematic bias. Systematic error (SB) was assessed using an adapted scale developed by Cochrane University experts [9], which takes into account 6 sources of SB (domains). (1) Randomization method; (2) concealment of the randomization sequence; (3) blinding of patients and nursing staff during treatment; (4) blinding of physicians when assessing the effect of the intervention, (5) patient drop-

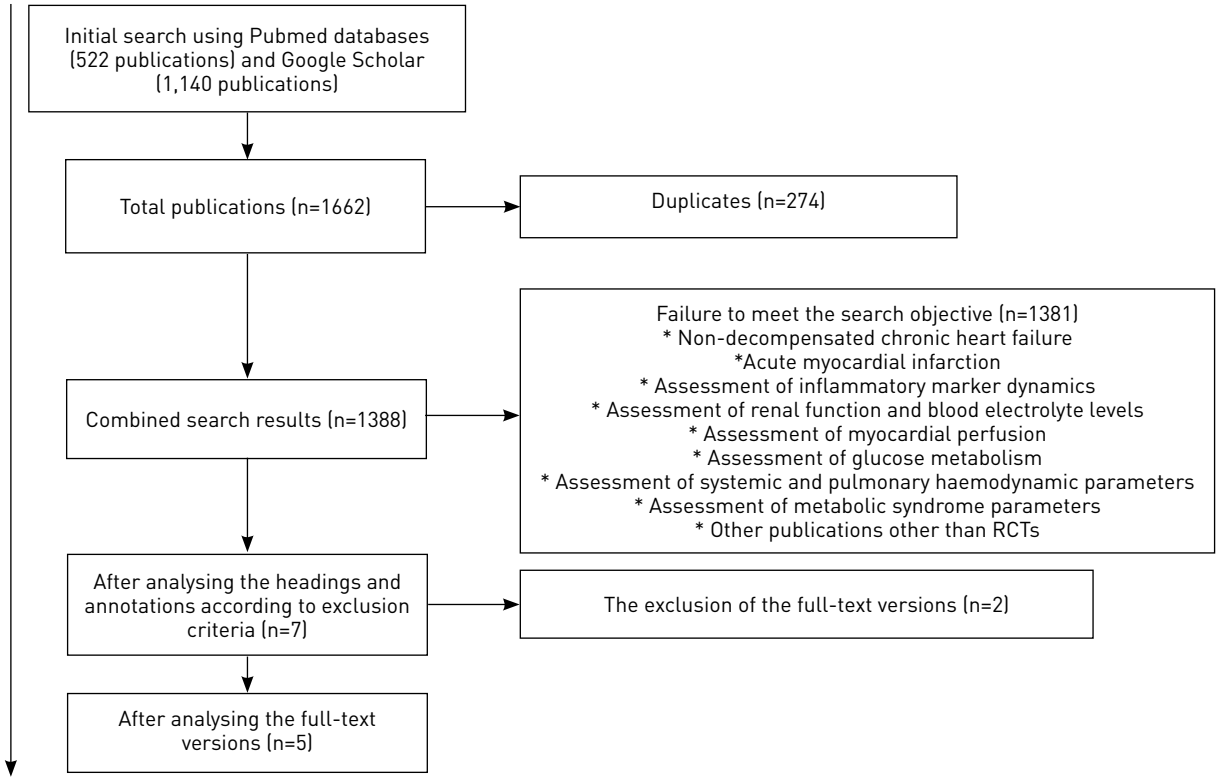

Fig. 1. Publication selection algorithm

out from the study; and (6) presentation of results in a publication. In addition, SB was assessed for the following domains: conflict of interest, complex study design, deviations from the study protocol, insufficient duration of the follow-up and small sample size. For each domain, the risk of SB was classified into three categories: low (0), uncertain (1) and high (2). If there were two or more domains of uncertain probability and one or more of high probability, the overall risk of SB was considered low. If two or more domains of uncertain probability were present, the overall risk of SB was considered uncertain. When one or more high probability domains were present, the overall risk of SB was regarded as uncertain. Thus, three publications out of five were categorised as high risk for the conflict of interest part, one of them with a notable small sample size. Publications were not excluded from the meta-analysis.

The meta-analysis of the differences between the mean values of the parameters in the study and control groups was performed on the mean SB standard deviation data, taking into account the number of subjects in the compared groups. Quantitative parameters in the meta-analysis are presented as mean and standard deviation. Quantitative data given as median in the original publications were converted to mean SB standard deviation using the formula of Luo et al. 2018 and Wan et al. 2014 [8, 9]. The effect was considered statistically significant at $p<0.05$.

Five trials (318 patients) that met the inclusion and exclusion criteria were included in the systematic review and meta-analysis (Table 1). The majority of patients were men (47 % to 62 %), with a mean age of 72 to 82 years. In general, the proportion of patients with the de novo development of CHF was about half (47 % to 80 %) of the total number of patients studied in all publications. The median follow-up varied from 7 to 90 days.

Four out of five studies analyzed the dynamics of the HF marker — brain natriuretic peptide precursor (NT-proBNP) — in the background of SGLT2i treatment compared to placebo. The first analysis for blood NT-proBNP was performed at the stage of randomization (on admission), the second analysis was performed on days 4 to 7 after the start of therapy. All patients received standard treatment plus a drug from the SGLT2i group or placebo. The mean baseline NT-proBNP levels differed between the studies, ranging from 3060 to 4775 pg/mL in the SGLT2i group and from 3996 to 6641 pg/mL in the placebo group. Positive dynamics in terms of a decrease in NT-proBNP levels were observed in all studies (Table 2).

Based on the results of the data obtained, we calculated the difference in mean NT-proBNP levels using statistical analysis methods to assess the benefit of SGLT2i therapy in reducing levels of cardiac markers. To do this, we performed a meta-analysis of the difference in mean NT-proBNP levels between the two groups (Fig. 2).

Figure 2 shows the mean dynamics of NT-proBNP levels in two groups. The values of the HF marker with SGLT2i treatment compared to placebo did not differ in any of the studies. According to the results of the meta-analysis, statistically significant differences were not achieved ($p=0.920$). The heterogeneity of the trials was considered to be low. SGLT2i therapy

Table 1. **Synopsis of the studies that were included in the systematic review**

Author	Sample size, n	Chosen drug and the treatment start	Follow-up period	Endpoints	
				NT-proBNP dynamics	Posthospital mortality
Dammam K., 2020 [10]	79	Emp and 24 h	60 days	Yes	Yes (60 days)
Tamaki S., 2021 [11]	59	Emp and 96 h	7 days	Yes	No
Thiele K., 2022 [12]	19	Emp and 72 h	7 days	Yes	No
Schulze C., 2022 [13]	59	Emp and 12 h	30 days	Yes	Yes
Charaya K., 2022 [14]	102	Dap and 24 h	30 days	No	Yes

Table 2. **NT-proBNP levels in different groups before and after treatment**

Author	NTproBNP (pg/ml) with SGLT2i		NTproBNP (pg/ml) with placebo	
	Before treatment	After treatment	Before treatment	After treatment
Dammam K., 2020 [10]	4775±3157	2196±2147	6641±5625	3852±3881
Tamaki S., 2021 [11]	3060±2374	1618±506	5081±5020	2200±624
Thiele K., 2022 [12]	3562±2527	2050±3243	3996±6293	2202±5807
Schulze C., 2022 [13]	4276±4516	2415±4516	4823±4995	4096±4995

Study or subgroup	SGLTi			Placebo				Std. Mean Difference	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight (%)	95 % CI	95 % CI
Dammam K.	2.579	7.634	40	2.789	13.665	39	36.5	−0.02 [−0.46.0.42]	
Thiele K.	1.512	8.221	10	1.794	17.124	9	8.8	−0.02 [−0.92.0.88]	
Schulze C.	1.861	4.516	30	727	4.995	30	27.5	0.24[−0.27.0.74]	
Tamaki S.	1.442	7.634	30	2.881	10.476	29	27.2	−0.16 [−0.67.0.36]	
Total (95 % CI)			110			107	100	0.01[-0.25.0.28]	
Heterogenity: Tau²=0.00; Chi²=1.18, df=3(P=0.76), I²=0 %									
Test for overall effect Z=0.10 (P=0.92)									Better in the SGLT2i group / Better in the placebo group

Fig. 2. Blobogram. Results of the meta-analysis of the mean values of NT-proBNP level difference in SGLT2i and placebo groups
Note. ▢ — weighted effect size for each individual study (size of green squares corresponds to study weight), ◆ — 95 % CI, reflects weighted average of mean NT-proBNP values

in patients with ADHF did not have an advantage over placebo in reducing NT-proBNP levels.

Three of the five trials studied post-hospital mortality. These studies included 240 people, 120 in each group. Post-hospital mortality was 9.2 % in the SGLT2i group and 14.2 % in the placebo group. The results of the three trials were combined in a meta-analysis (Fig. 3).

All trials showed a reduction in post-hospital mortality in the SGLT2i group. The results of the meta-analysis demonstrated a 38 % reduction in the probability of death in the immediate post-discharge period. However, there were no statistically significant differences (p=0.772). It is important to note that the first study [10], which showed the best results (69 % reduction in mortality), used 60-day mortality as the endpoint, whereas the other two studies used 30-day mortality. The heterogeneity of the trials was considered to be low. The results suggest that there is an association between early initiation of SGLT2i therapy and the risk of post-hospital mortality. Further large studies are needed to clarify the effect of SGLT2i therapy on the immediate prognosis of patients hospitalized with ADHF.

Studies	Std. Mean Difference (95 % CI)	Death/Total in SGLT2i group	Death/Tota in placebo group	Relative risk of death
Dammam K.,2020	0,308 (0,031; 3,094)	1/40	1/39	
Charaya K.,2022	0,732 (0,278; 1,926)	9/50	12/52	
Schulze C,2022	0,466 (0,040; 5,433)	1/30	2/29	
Overall I^2=0 %(P=0,772)	0,619 (0,268; 1,432)	11/120	17/120	
				Odds ratio (log scale)

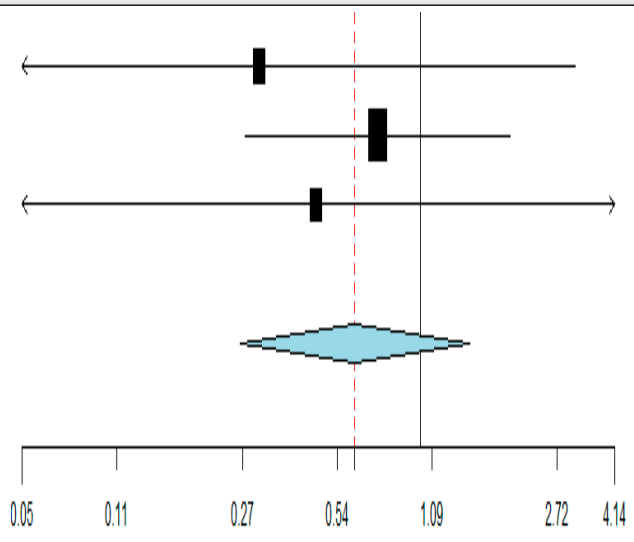

Fig. 3. Blobogram. Results from the meta-analysis of the relative risk of post-hospitalization death in the SGLT2i and placebo groups
Note. ▮— weighted effect size for each case study (the size of the black squares corresponds to the weight of the study), ◇ — 95 % CI, reflects the weighted mean of the mean NT-proBNP values.

Discussion

The results of SGLT2i treatment in ADHF were first analyzed in the EMPA-RESPONSE-AHF pilot study (79 patients). The study did not show an improvement in hospital outcomes. However, the finding of a high safety profile of SGLT2i in ADHF, demonstrated for the first time by the authors, should be considered important. An improvement in clinical outcomes was observed when assessing the combined endpoint (HF worsening at pre-hospital stage, rehospitalization for CHF and all-cause mortality at 60 days) [10]. The EMPULSE study was a logical continuation of this work with a larger number of patients (n=530). For the first time, a statistically significant improvement in clinical status was seen with empagliflozin in patients hospitalized for ADHF (53.9 % vs. 39.7 %, p=0.005). All-cause mortality within 90 days of hospitalization was 2-fold lower in the SGLT2i group compared with the placebo group (4.2 % vs 8.3 %) [7]. We did not include this trial in our meta-analysis because SGLT2i therapy was started within 1–5 days (median 3 days). Another large study, SOLOIST-WHF [6], was excluded from the meta-analysis for the same reasons. In our opinion, the long randomization window may have inadvertently excluded the most severe cohort of ADHF patients; the use of SGLT2i in this group of patients is likely to be of greatest clinical interest.

The main result of our meta-analysis was the demonstration of a 1.7-fold reduction in post-hospital mortality in the immediate postoperative period. At the same time, mortality at 30 to 60 days was higher than in the EMPULSE trials (90 days). In the SGLT2i group, the mortality rate was 9.2 % vs. 4.2 %, while in the placebo group it was 14.2 % vs. 8.3 %. We believe that this difference may be explained by the more comorbid cohort of patients included in the trials analyzed on the first day of hospitalization. Overall, we believe that the results of the meta-analysis show encouraging prospects for improving the prognosis of patients hospitalized with ADHF.

Another finding of the meta-analysis was the lack of change in NT-proBNP levels with SGLT2i therapy. NT-proBNP is one of the most important prognosis predictors in patients with CHF. According to our hypothesis, the benefits of SGLT2i in terms of improvement in clinical status should have been reflected in the reduction of NT-proBNP levels. However, the results obtained show almost similar dynamics of the HF marker.

According to the studies, SGLT2i therapy in ADHF is associated with rapid volume reduction and improvement in LV end-diastolic pressure and diastolic function [12, 15]. However, it remains unclear whether this is a consequence of the diuretic effect of SGLT2i. Packer M. et al. analyzed the EMPEROR study and showed that the efficacy of empagliflozin therapy was comparable in CHF groups with and without congestion [16]. In addition, the authors showed that there was no correlation between NT-proBNP levels and weight loss, regardless of the therapy. The obtained results allowed to conclude that the diuretic effect is not the dominant one in SGLT2i therapy in patients with CHF. It is likely that a similar mechanism of action can be used in the group of patients with ADHF. The search for other, more important properties of the SGLT2i group of drugs may be the subject of future studies.

SGLT2i therapy in ADHF is of great scientific and clinical interest, as reflected in the domestic and international literature [15, 17]. The results from large trials (DICTATE AHF, DAPA-MI, EMPACT-MI, DAPA ACT HF-TIMI 68) are expected in the next few years [18-21]. The EMPACT-MI trial will evaluate whether empagliflozin can reduce the risk of HF and death compared to placebo in patients with acute MI and first-ever LV systolic dysfunction or signs and symptoms of pulmonary congestion [20]. The DAPA-MI study (NCT04564742) will provide information on the efficacy of dapagliflozin compared to placebo in preventing hospitalization for HF or cardiovascular death in patients with acute MI and the evidence of reduced LV systolic function. An important aspect of these two trials is that the DAPA-MI trial will only randomize patients without a known diagnosis or evidence of type 2 DM, whereas the EMPACT-MI trial will include both diabetic and non-diabetic patients. Taking into account the results of the meta-analysis, as well as the results of other studies on the efficacy and safety of SGLT2i in ADHF, we expect that emergency cardiologists will have an additional option to improve the clinical status and prognosis of patients.

This meta-analysis has several limitations. The first one is the small number of studies, the high risk of the systematic bias in most of the included studies, and the small sample size in the study by Thiele K [12]. However, it is important to note that the number of trials investigating SGLT2i in ADHF is limited to date. Other limitations include the differences in the

endpoint of post-hospital mortality described above, as well as the calculated formulas for quantifying NT-proBNP parameters. However, it is important to note that the heterogeneity in both analyzes was low, which should be considered an advantage of the study.

Conclusion

According to a meta-analysis, SGLT2i therapy given early (up to 24 hours) to patients hospitalized for ADHF may reduce the risk of all-cause mortality in the immediate post-discharge period (30–60 days). Larger studies are needed to investigate the effect of SGLT2i on prognosis in this group of patients.

Study limitations. The presented meta-analysis has a number of limitations. These include the small number of studies, the high risk of systematic error in most of the included studies, and the small sample size in the article of Thiele K. It is important to note, that the number of studies investigating SGLT2i in ADHF is limited. Other limitations include the differences in the endpoint of posthospital mortality described above, as well as the calculation formulae for quantifying NT-proBNP levels.

Conflict of interest: none declared.

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Percutaneous coronary interventions in oncological patients

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Cancer patients are both older and have many comorbidities, including CHD, which is often severe. Several cancer treatments, such as radiotherapy, chemotherapy and immunotherapy, increase the risk of cardiovascular events and mortality. Percutaneous coronary intervention (PCI) is often required, but the presence of procoagulant states, haematological disorders such as anemia and thrombocytopenia pose challenges in the management of these patients with anticoagulants, antiaplatelet drugs and PCI. PCI in cancer patients is associated with an increased risk of bleeding, in-hospital and long-term mortality, and the need for repeat revascularisation. Correct management

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of oncological patients with concomitant CHD will reduce the risk of periprocedural complications during PCI, at least partially by using the best surgical techniques.
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Introduction

The comorbidity of oncological and cardiovascular diseases (CVD) associated with atherosclerosis is a pressing problem in modern medicine. It is caused by a decline in the quality and duration of life in patients with combined pathology.

In recent years, an increase in new cases of malignant neoplasms has been observed in the Russian Federation. At the end of 2021, the number of patients under dispensary observation was 3,940,529 (2.7 % of the population of the Russian Federation) [1, 2]. The development and progression of coronary heart disease (CHD) can have a significant impact on patient survival. The prevalence of CHD in cancer patients is higher than in the general population [3]. Patients with current or previous cancer undergoing percutaneous coronary intervention (PCI) are at increased risk of CVD and mortality [4, 5]. Numerous studies have shown that the type of cancer and its stage are important determinants of outcomes, including in-hospital mortality and bleeding [4, 6–8].

Link between coronary heart disease and cancer

The inflammatory process is known to underlie pathological changes in cardiovascular and oncological diseases. The atherosclerotic process is characterised by low inflammatory activity [9], but at the same time, optical coherence tomography (OCT) studies of coronary arteries have shown that most atherosclerotic plaques that rupture and lead to acute coronary syndrome have significant macrophage infiltration and higher levels of serum C-reactive protein (CRP) [10]. Similarly, the role of inflammation in the pathogenesis of malignant cell transformation, carcinogenesis, invasion and metastasis [11] is well established in several forms of oncology, including breast cancer [12], cervical cancer (mediated by human papillomavirus), gastric cancer (mediated by Helicobacter pylori) and lymphoma (mediated by Epstein-Barr virus) [13]. Libby and Ebert proposed the modern concept of CHIP (clonal haematopoiesis of indeterminate potential) as an independent risk factor for CVD development in cancer patients [14]. CHIP refers to mutated stem cells in the peripheral circulation that are known to increase the risk of haematological malignancies. Interestingly, while most people with these cells in their peripheral blood never develop a full-blown malignancy, the presence of CHIP doubles the risk of CHD [15]. Even from an epidemiological point of view, smoking, diabetes and obesity are considered risk factors for both CVD and cancer (Fig. 1) [3].

Various cancer treatments such as radiotherapy, chemotherapy and immunotherapy also increase the risk of CVD and mortality [16]. Thoracic irradiation for lymphoma and breast cancer is associated with a higher incidence of obstructive CHD: an estimated 30 % of patients receiving radiotherapy have a severe multivessel lesion involving the left coronary artery and/or the right coronary artery. Ionising radiation causes the release of multiple inflammatory and profibrotic cytokines, resulting in endothelial damage both in the coronary arteries and in the microcirculatory bed [17]. The role of several chemotherapeutic agents in increasing the risk of developing CVD has been demonstrated: anthracyclines and trastuzumab are known to cause cardiomyopathy, whereas several other drugs such as cisplatin, fluorouracil, methotrexate, cytarabine, fludarabine, vinca alkaloids, interferons and interleukin-2 have been associated with an increased incidence of ACS [18]. The use of immunotherapy, such as rituximab [19] and bevacizumab [20], is associated with an increased risk of myocardial infarction and arterial thrombosis. Hormonal drugs used in the treatment of breast and prostate cancer are also associated with worsening

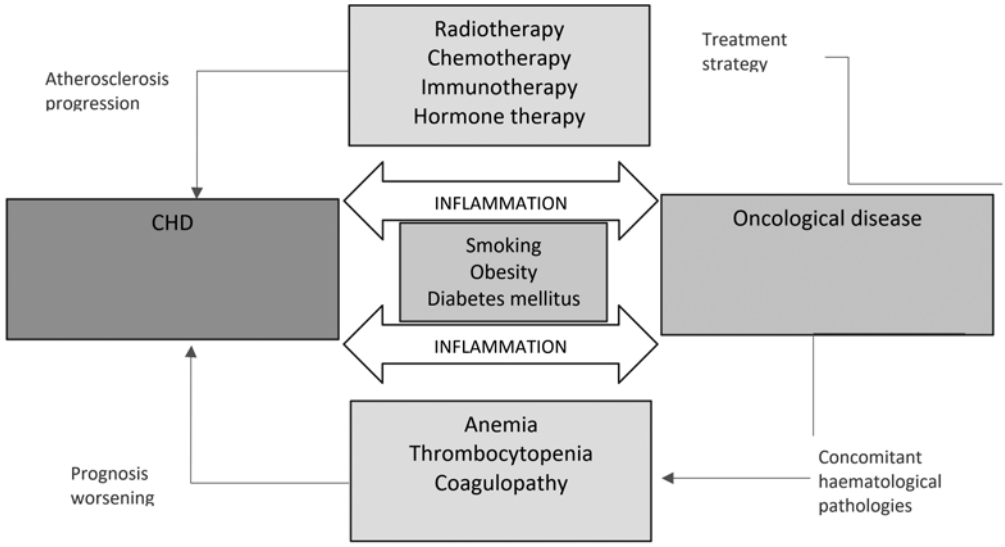

Fig. 1. Associations between CHD and cancer

of angina pectoris due to CHD progression and the development of ACS [21]. Therefore, clinicians need to be aware of the cardiovascular toxicity of anticancer drugs and screen patients prophylactically for CHD prior to initiation of these therapies and during long-term follow-up [22].

Challenges of PCI in cancer patients

Performing both planned and emergency percutaneous coronary intervention (PCI) in patients with cancer presents a number of challenges (Fig. 2).

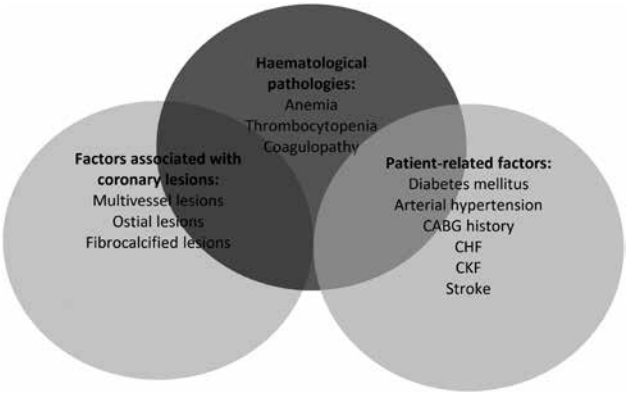

Fig. 2. Challenges of PCI in cancer patients разместить после рисунка

Firstly, these patients tend to be older and more likely to have severe comorbidities and a more severe course of CHD [4, 23, 24]. A study by Plotts J.E. et al on PCI outcomes in over 6 million patients showed that patients with oncology were generally older and had more comorbidities and often depended on the type of cancer process. For example, patients with lung cancer (compared to patients without cancer) had the highest prevalence of chronic lung disease (50.8% vs. 15.2%) and congestive heart failure (5.2% vs. 0.9%), patients with a history of lung cancer had: the highest prevalence of peripheral vascular disease (18% vs. 10.2%), smoking (52.4% vs. 35.5%), and prior PCI (23.8% vs. 18.7%). Patients with current colorectal cancer had the highest prevalence of anemia (34.1% vs. 8.3%) [4]. Subgroup analysis of the BleeMACS multicentre observational registry (n=14631) showed differences between patients with and without cancer among ACS patients and PCI survivors. Patients with cancer were older (70.8±10.3 vs. 62.8±12.6 years, p<0.001), more often female (28.7% vs. 22.8%, p<0.001) and had a higher prevalence of DM (28.7% vs. 23.5%, p=0.001), arterial hypertension (65% vs. 57.8%, p<0.001), stroke (8.3% vs. 5.4%, p=0. 001), congestive heart failure (5.4% vs. 2.9%, p=0.001), chronic kidney disease (CKD; 6.4% vs. 2.9%, p=0.001), history of ACS (15.4% vs. 11.5%, p=0.001), coronary artery bypass graft (CABG) (4.7% vs. 3.1%, p=0.01) and history of bleeding (11% vs. 4.9%, p<0.001) [24].

In addition, the presence of procoagulant states [25], haematological abnormalities such as anemia and thrombocytopenia pose challenges in the management of these patients with anticoagulants, antiaggregants and, if necessary, PCI. The Academic Research Consortium Consensus Document on High Bleeding Risk identified active malignancy, anemia (baseline haemoglobin level <11 g/dl) and thrombocytopenia (platelet count <100×109/l) as three independent predictors of high bleeding risk during PCI [26]. Bleeding risk is considered high if the occurrence

of future bleeding is Bleeding Academic Research Consortium (BARC) type 3 or 5 and its probability within one year is ≥4 % or the probability of intracranial haemorrhage ≥1 % [27]. Most patients with acute leukaemia, lymphoma and multiple myeloma have thrombocytopenia [28]. Its prevalence in patients with solid tumours receiving chemotherapy ranges from 10 % to 25 % [29].

A subgroup analysis of the HORIZONS-AMI trial showed that thrombocytopenia was associated with early and late adverse events, both bleeding and ischemia [30]. The presence of chronic thrombocytopenia in patients undergoing PCI was associated with a higher risk of haemorrhagic complications requiring blood or platelet transfusion, vascular complications, ischemic stroke and higher in-hospital mortality [31]. Anemia diagnosed in cancer patients is either a consequence of the disease or a complication of treatment. In a large meta-analysis of patients undergoing PCI, anemia was associated with a significant increase in postoperative mortality, major adverse cardiac events (MACE), reinfarction and bleeding [32]. An analysis of 6528 patients after PCI showed that severe anemia (mean haemoglobin level 98±11 g/L) was associated not only with an increased risk of death, cardiac death and myocardial infarction, but also with stent thrombosis [33]. In addition, patients with oncological processes often require invasive diagnostic and therapeutic procedures such as biopsy or resection, which raises concerns about their ability to receive continuous dual antiplatelet therapy.

Outcomes after PCI in cancer patients

Numerous studies (Table 1) have demonstrated that cancer patients undergoing PCI are at increased risk of bleeding [7, 24], hospital [5, 7] and long-term mortality [24, 35, 36].

Data from the BleeMACS registry showed that after one year of follow-up, patients with ACS and cancer who underwent PCI were more likely to have a combined endpoint of death or reinfarction (15.2 % vs. 5.3 %, p<0.001) and bleeding (6.5 % vs. 3 %, p<0.001) than those without cancer [24]. Results from large population-based registries suggest that cancer type may also play an important prognostic role. In a study by Plotts J.E. et al, lung cancer was associated with the highest risk of in-hospital mortality (odds ratio (OR) 2.81, 95 % confidence interval (95 % CI) 2.37–3.34), whereas colorectal cancer was associated with the highest risk of bleeding compared with those without cancer (OR 3.65, 95 % CI 3.07–4.35). In the same study, the presence of metastases, regardless of cancer type, was associated with an increased risk of in-hospital mortality and complications of PCI, including major bleeding [4]. A separate analysis focusing on patients with leukaemia undergoing PCI showed that these patients had an increased risk of in-hospital mortality and bleeding compared with the general population. In addition, the type of leukaemia also determined the prognosis: patients with acute myeloid leukaemia had a fivefold higher risk of in-hospital mortality after PCI than patients without leukaemia [7]. Another analysis of the NIS database, focusing only on cancer patients with ST-elevation myocardial infarction (STEMI), reported that patients with lung cancer had the highest in-hospital mortality (57.1 %). This study also showed that the use of primary PCI was 30.8 %, 20.2 % and 17.3 % in patients with breast, lung and colorectal cancer, respectively [8]. Valders et al, in their analysis of data from a multicentre registry in the Netherlands, reported that cancer patients with STEMI had higher all-cause mortality (17.4 % vs. 6.5 % in other patients) and cardiovascular mortality at 1 year (10.7 % vs. 5.4 % in other patients). A recent cancer diagnosis within the previous 6 months was strongly associated with early cardiac mortality [36]. In addition, PCI was performed according to a meta-analysis that included 5 studies that evaluating 1-year all-cause, cardiovascular, and non-cardiovascular mortality in patients with an active cancer or with the history of one. Patients in the cancer group had higher annual all-cause mortality [RR 2.22 (1.51–3.26; p<0.001)], including higher cardiovascular [RR 1.34 (1.1–1.65; p=0.005)] and non-cardiovascular mortality [RR 3.42] (1.74–6.74; p≤0.001). Notably, meta-regression analysis showed that the difference in annual all-cause and cardiovascular mortality between the cancer and non-cancer groups was not associated with baseline characteristics, PCI characteristics, or medications at discharge [37]. A retrospective observational study by Tabata et al. also showed that malignancy was an independent predictor of cardiovascular events in patients undergoing PCI, with an increased risk in patients with low ankle-brachial index/high brachial-ankle pulse wave velocity [38].

Studies have also shown that cancer patients who have undergone PCI are at increased risk of bleed-

Table 1. **The largest studies analysing PCI outcomes in cancer patients**

Authors	Studied population	Conclusions
Potts et al. [4]	National sample of inpatients, 2004–2014 yrs., N > 6 mln patients with PCI	— Active and past lung cancer increased the risk of in-hospital mortality; — Active colorectal cancer was associated with an increased risk of bleeding; — Current breast cancer was not associated with increased mortality or bleeding; — The presence of metastases was associated with an increased risk of bleeding and mortality, regardless of cancer type.
Potts et al. [7]	National sample of inpatients, 2004–2014 yrs., N > 6 mln patients with PCI	— The presence of leukaemia was associated with an increased risk of death and bleeding; — Acute myeloid leukaemia increased the risk of in-hospital mortality fivefold.
Pothineni et al. [8]	National sample of inpatients, N=3,7 mln patients with STEMI	— The performance of primary PCI was 30.8%, 20.2% and 17.3% in patients with breast, lung and colorectal cancer, respectively; — Patients with lung cancer had the highest in-hospital mortality.
BleeMACS registry [24]	BleeMACS registry of patients with ACS, N=15401	— The presence of cancer was the strongest independent predictor of the primary combined endpoint (death and reinfarction) and bleeding.
Valders et al. [36]	Multicentre registry of STEMI patients, N=3423	— Cancer patients with STEMI had increased all-cause and cardiovascular mortality at 1 year; — A recent cancer diagnosis within the previous 6 months was strongly associated with early cardiac mortality.
Shivaraju et al. [39]	National sample of inpatients, 1998–2006 yrs., N=1.2 mln	— The main independent predictor of gastrointestinal bleeding after PCI was malignancy (based on the odds ratio of rectal > gastric > oesophageal > colorectal cancer)
van Werkum et al. [40]	Dutch Stent Thrombosis Registry, 437 cases of definite stent thrombosis	— Active malignancy was an independent risk factor for stent thrombosis, OR 13.08 (CI 1.99–85.93, p=0.0074).
Tabata et al. [35]	Kumamoto University Registry for Malignant Tumours and Atherosclerosis (KUMA)	— Active malignancy or the history of malignancy was an independent predictor of TLR at 1 year; — The risk of TLR was highest in patients with ongoing cancer or recent cancer treatment.
Landes et al. [5]	Retrospective analysis in a single centre from Israel, N=12,785 consecutive patients who underwent PCI between April 2004 and October 2014.	— Cancer survivors (mean interval between cancer diagnosis and PCI 3.6±3.4 years) had a 40% increased risk of the combined endpoint of death, non-fatal myocardial infarction, target vessel revascularisation and coronary artery bypass graft surgery (mean follow-up 6.4±5.9 years).
Hess et al. [23]	Retrospective single-centre analysis (Duke Information Systems for Cardiovascular Care and the Duke Tumor Registry) N=15008	— The 3 study groups were «cancer before PCI» (any cancer treatment before PCI), «cancer after PCI» (received cancer treatment after the PCI), and «recent cancer» (cancer treatment within 1 year before PCI); — The adjusted risk of long-term cardiovascular mortality was not significantly different in patients with cancer before PCI compared with patients without cancer; — Patients with cancer after PCI (latent malignancy during PCI) had a significantly higher adjusted risk of cardiovascular mortality.
Wang et al. [41]	Retrospective analysis of a single centre from the Mayo Clinic PCI database, N=2346 STEMI patients from November 2000 to October 2010.	— Cancer patients had higher in-hospital non-cardiac mortality but the same cardiac mortality as the control group; — Recent cancer diagnosis (within 6 months of STEMI onset) had the highest risk of acute in-hospital mortality; — Even after a median follow-up of 6.2 years, the higher mortality observed in the cancer group was due to non-cardiac causes.
Quintana et al. [37]	Meta-analysis of trials evaluating all-cause, cardiovascular, and non-cardiovascular mortality at 1 year in PCI patients with active cancer or history of cancer, N=33175	— Cancer patients who underwent PCI had higher annual all-cause mortality, cardiovascular, and non-cardiovascular mortality; — Cancer patients had higher one-month all-cause and non-cardiovascular mortality, but no difference in cardiovascular mortality compared with non-cancer patients undergoing PCI.

ing, thrombosis, and repeat revascularisation. An analysis of the NIS database, which examined time trends in gastrointestinal bleeding after PCI, showed that the top four independent predictors of gastrointestinal bleeding were: rectal cancer (OR 4.64; 95% CI 3.20–6.73; p<0.0001), gastric cancer (OR 2.74; 95% CI 1.62–4.66; p=0.0002), oesophageal cancer (OR 1.99; 95% CI 1.08–3.69; p=0.0288) and colorectal cancer (OR 1.69; 95% CI 1.43–2.02; p<0.0001) [42]. The Dutch Stent Thrombosis Registry showed that current malignancy was an independent risk factor for stent thrombosis with an OR of 13.08 (CI 1.99–85.93, p=0.0074) [40]. Tabata et al. who studied the incidence of target lesion revascularisation (TLR) in cancer patients undergoing PCI, showed that current or recent history of malignancy was an independent predictor of TLR after 1 year. Time since completion of anticancer therapy also played a role, with the risk of TLR being higher in patients with a current or recent cancer history [35]. In a retrospective analysis in Israel, cancer survivors (mean interval between cancer diagnosis and the PCI was 3.6±3.4 years) had a 40%

increased risk of a combined endpoint consisting of death, non-fatal myocardial infarction, target vessel revascularisation and coronary bypass surgery (mean follow-up 6.4±5.9 years) [5].

However, researchers analysing PCI data in cancer patients from the Duke [23] and Mayo [41] registries showed opposite results. In this analysis, patients were divided into three groups: "pre-PCI cancer" (any cancer treatment prior to PCI), "post-PCI cancer" (patients receiving cancer treatment after the PCI), and "recent cancer" (cancer treatment within 1 year prior to PCI). The adjusted risk of long-term CVD mortality was not significantly different in patients with cancer before PCI compared with patients without one. However, patients with cancer after PCI (some of whom may have had underlying malignancy at the time of PCI) had a significantly higher adjusted risk of CVD mortality [23]. An analysis of data from STEMI patients undergoing primary PCI at the Mayo Clinic showed that cancer patients had higher in-hospital cardiac and non-cardiac mortality, similar to controls. A recent cancer diagnosis (within 6 months of STEMI) had the highest risk of acute in-hospital mortality. Even with a median follow-up of 6.2 years, the higher mortality observed in the cancer group was due to non-cardiac causes [41].

Special considerations for cancer patients undergoing PCI Indications for PCI

Revascularisation in patients with a history of oncology should be approached with a careful risk-benefit assessment, especially in planned clinical situations. Because of the high risk of bleeding, PCI should be reserved for absolute indications, even in patients with an acceptable oncological prognosis [42]. Patients with a life expectancy of less than 1 year and acute coronary syndromes (STEMI, high-risk non-STEMI, and unstable angina) should be offered revascularisation in the same way as patients without cancer. However, in stable angina, every effort should be made to optimise the patient's condition with conservative medical therapy, which may include treatment of concomitant oncological conditions such as anemia and hypoxia in addition to anti-anginal drugs [43].

Procedural specifics

According to the Society for Coronary Angiography and Interventions (SCAI) expert consensus document, careful caution should be exercised to minimise the risk of bleeding and optimise stenting outcomes when performing PCI in cancer patients [43]. Radial access should be one of the preferred routes for PCI given the significantly lower risk of vascular complications, bleeding and MACE compared to femoral access [44]. Notably, in patients with a history of breast cancer, the use of ipsilateral radial access does not increase the likelihood of developing lymphedema [45]. When radial access is not possible, the ulnar artery or attempted contralateral radial artery may be considered. In cases when radial/lateral access is not possible, to minimise periprocedural complications of the access site, the common femoral artery should be punctured under ultrasound and fluoroscopic control, and a suturing device should be used if possible. Case series and retrospective analysis of cancer patients with thrombocytopenia (including those with severely reduced platelet counts <30,000/mm^3) have demonstrated the safety of cardiac catheterisation and PCI as long as careful arterial access and post-procedural haemostasis are ensured [46, 47]. Intravascular ultrasound or optical coherence tomography should be used to assess the lesion and optimise stent implantation (location, apposition, dilatation and absence of marginal dissection) to improve short- and long-term outcomes in the event of early discontinuation or interruption of dual antiplatelet therapy. Data suggest that optical coherence tomography can also be used to identify low-risk patients (defined as those with adequate stent cell coverage, apposition and absence of stent restenosis or intraluminal masses) in whom dual antiplatelet therapy can be safely discontinued for cancer-related surgery [48]. During PCI, the use of bivalirudin may have an advantage over heparin because of the reliability of anticoagulation and the shorter half-life of the drug [43]. The SCAI consensus document also recommends that only coronary balloon angioplasty should be considered when a patient has a very low platelet count (<30,000/dL), when a platelet count is expected to decline, or when high-risk emergency surgery is warranted. When considering revascularisation in patients with platelet counts >30,000/dL who require an invasive procedure or chemotherapy that can be delayed >4 weeks, advanced drug-eluting stents should be considered over bare-metal stents. The polymer- and carrier-free BioFreedom stent (Biosensors Europe) [49] and the Endeavour Sprint stent with rapid release of zotarolimus (Medtronic Vascular,

Minneapolis, Minnesota) [50] have been shown to be superior to metallic stents, reducing the duration of dual antiplatelet therapy to 4 weeks. Similarly, a new generation drug-eluting stent should be considered in patients with platelet counts >30,000/ml who do not require immediate invasive procedures or chemotherapy. In addition, the X-ray endovascular surgeon should avoid complex bifurcation stenting, try to minimise the number of stents, the length of the stented area, and stent layering as this increases the likelihood of stent thrombosis and restenosis [43].

The role of the multidisciplinary team

The treatment of cancer with stable angina or ACS is often a complex scenario. Several factors must be considered, including the patient's life expectancy, the risk of bleeding, the anticipated need for invasive procedures (such as biopsy or surgical resection) in the near future, and the consequent interruption or complete withdrawal of antiplatelet therapy. These urgent decisions should be made in a multidisciplinary team discussion including surgical and/or medical oncology, X-ray endovascular surgery, radiation, palliative oncological basis of medicine and cardiology. In recent years, cardio-oncology has been considered an important field that specialises in CVD prevention and screening in patients with cancer pathology [51]. Finally, the risks, benefits and alternatives to any treatment should be thoroughly discussed with patients and their families, and their wishes should be taken into account.

Conclusion

PCI in cancer patients is associated with an increased risk of bleeding, in-hospital and long-term mortality, and the need for repeat revascularisation. The type of cancer and the presence of metastases also play a key role in determining outcomes. In addition, studies have also shown that recent cancer diagnosis and recent treatment predict worse outcomes after PCI. Older age, increased comorbidities and the presence of haematological and coagulation disorders pose challenges for PCI in this group of high surgical risk patients. These risks can be at least partially mitigated by using the best surgical operative techniques for performing interventions, and informed treatment decisions should be made with a multidisciplinary approach.

Conflict of interest: none declared.

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Notable clinical trials and meta-analyzes presented in the HOT LINE of ESC Congress 2022

Results from 22 international multicentre clinical trials were presented in HOT LINE sessions at the recent European Congress of Cardiology. The studies focused on different areas of cardiology, including arterial hypertension, coronary heart disease, atrial fibrillation, lipid-lowering therapy, pharmacotherapy of heart failure, intensive care in cardiology and healthcare organisation in cardiology.
Keywords: clinical trials, meta-analyzes, cardiovascular diseases.

The **TIME** study included 21,104 patients with arterial hypertension (AH) (median age 65.1 years) who were randomized to receive all of their prescribed antihypertensive therapy in the morning (06:00–10:00) or evening (20:00–00:00). At a median follow-up of 5.2 years, the combined primary endpoint of vascular death or hospitalization for non-fatal myocardial infarction (MI) or non-fatal stroke was reported at a comparable incidence of 0.69 and 0.72 per 100 patient-years in the evening and morning dosing groups, respectively (RR 0.95 with 95% CI 0.83 to 1.10; p=0.53). No treatment safety issues were identified. Evening versus morning administration of regular antihypertensive medication did not differ in terms of major cardiovascular outcomes. Patients can be advised to take their regular antihypertensive medication at a time that is convenient for them. According to the authors, this conclusion is definitive, at least for drugs with a guaranteed duration of action of 24 hours. However, the study did not identify and take into account specific groups of patients with AH, such as those with daily blood pressure (BP) profiles of non-dippers, night-peakers, over-dippers, for whom the timing of antihypertensive medication intake may be of significant importance.

In the **SECURE** trial, 2499 patients (median age 76 years) who had had an MI within the previous 6 months were randomized to polypill therapy (aspirin 100 mg + ramipril 2.5, 5.0 or 10 mg + atorvastatin 20 or 40 mg) or conventional therapy. At a median follow-up of 36 months, the combined primary endpoint event rate (cardiovascular death, non-fatal type 1 MI, non-fatal ischemic stroke or urgent revascularisation) was 9.5% vs. 12.7% (RR 0.76 with 95% CI 0. 60 to 0.96; p=0.02), and death from cardiovascular events, non-fatal type 1 MI or ischemic stroke was 8.2% versus 11.7% (RR 0.70 with 95% CI 0.54 to 0.90; p=0.005) in the polypill and conventional treatment groups, respectively. The better results in the polypill group were attributed to better adherence to treatment and the incidence of adverse events was similar between groups. The results of SECURE may have important implications for secondary prevention in patients with recent MI, as prescribing the polypill (aspirin + ACEi + statin) at hospital discharge simplifies treatment, increases adherence to drug therapy and improves cardiovascular prognosis.

In the Danish population-based **DANCAVAS** study, men aged 65–74 years were invited (n=16 736) or not

invited (n=29 790) in a 1:2 ratio to undergo screening for subclinical cardiovascular disease. Randomization was based on computer-generated random numbers and stratified by municipality. Screening included computed tomography to determine coronary artery calcium index and detect aortic aneurysms, electrocardiography to diagnose atrial fibrillation (AF), upper arm and ankle BP measurement to detect peripheral arterial disease and AH, and blood tests to detect DM and hypercholesterolemia. In an intention-to-treat analysis after a median follow-up of 5.6 years, the incidence of death from any cause (primary endpoint) was 12.6% versus 13.1% in the invited and control groups, respectively (RR 0.95 with 95% CI 0.90 to 1.00; p=0.06). The risk ratios for stroke were 0.93 (95% CI 0.86 to 0.99), MI 0.91 (95% CI 0.81 to 1.03), aortic dissection 0.95 (95% CI 0.61 to 1.49) and aortic rupture 0.81 (95% CI, 0.49 to 1.35) in the invited group compared with the controls. After more than 5 years, an invitation to comprehensive cardiovascular screening was not associated with a significant reduction in mortality from any cause in men aged 65 to 74 years. The effect of invitation to screening may have been underestimated because only 63% of those invited attended.

Acetazolamide, a carboanhydrase inhibitor that reduces sodium reabsorption in the proximal tubule, was evaluated for its potential to improve the efficacy of loop diuretics in the **ADVOR** trial in 519 patients with acute decompensated heart failure and signs of volume overload (oedema, pleural effusion or ascites), N-terminal brain natriuretic peptide levels greater than 1000 pg/ml or brain natriuretic peptide levels greater than 250 pg/ml. After randomization, acetazolamide (500 mg once daily) or placebo was added to the intravenous loop diuretic therapy at twice the oral maintenance dose. The primary endpoint of successful resolution of congestion, defined as no evidence of volume overload and no indication for increased diuretic therapy 3 days after randomization, was achieved in 42.2% of patients in the acetazolamide group and 30.5% in the placebo group (RR 1.46 with 95% CI 1.17 to 1.82; p<0.001). Death from any cause or rehospitalization for heart failure within 3 months of follow-up occurred in 29.7% of patients in the acetazolamide group and 27.8% in the placebo group (RR 1.07 with 95% CI 0.78 to 1.48). Treatment with acetazolamide was associated with greater cumulative diuresis and natriuresis. The incidence of renal dysfunction, hypokalemia and hypotension was similar between groups. More active diuretic therapy resulted in a shorter hospital stay (8.8 vs. 9.9 days; p=0.016). The addition of acetazolamide to loop diuretic therapy in patients with acute decompensated heart failure increases the rate of successful relief of congestion, indicating the importance of early aggressive therapy to ensure natriuresis.

The **BOX** study included 789 patients in coma after successful resuscitation for out-of-hospital cardiac arrest who were randomized according to a 2×2 factorial design to oxygen therapy to achieve an arterial blood partial pressure of oxygen of 9–10 kPa (68–75 mm Hg) or 13–14 kPa (98–105 mm Hg) and vasopressor/inotropic therapy to achieve a mean BP of 63 mm Hg or 77 mm Hg). The primary endpoint of death from any cause or hospital discharge with severe disability/coma was observed in 32.0% vs. 33.9% of patients in the lower vs. higher target arterial partial pressure of oxygen groups (RR 0.95 with 95% CI 0.75 to 1.21; p=0.69) and in 34% vs. 32% of patients in the lower vs. higher target mean arterial partial pressure of oxygen groups (RR 1.08 with 95% CI 0.84 to 1.37; p=0.56). Comparable variants of oxygen therapy intensity and use of vasopressor/inotropic therapy did not show significant differences in outcomes (death from any cause or discharge from hospital with severe disability/coma) within 90 days of successful resuscitation for out-of-hospital cardiac arrest.

In the **REVIVED-BCIS2** trial, 700 patients with LV dysfunction (ejection fraction of 35% or less) caused by coronary artery stenoses treatable by PCI and with the evidence of myocardial viability received PCI in addition to optimal medical therapy (PCI group) or optimal medical therapy alone (optimal medical therapy group) randomly. At a mean follow-up of 41 months, the combined primary endpoint (death from any cause or hospitalization for heart failure) occurred in 37.2% of patients in the PCI group and 38.0% in the optimal medical therapy group (RR 0.99 with 95% CI 0.78 to 1.27; p=0.96). At 6 and 12 months, there were no differences in mean LVEF between the two groups. Quality of life was better in the PCI group at 6 and 12 months, but this difference was lost at 24 months. In patients with severe ischemic LV systolic dysfunction who were receiving optimal medical therapy, myocardial revascularisation with PCI did not reduce the risk of death from any cause or hospi-

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talization for heart failure, nor did it improve LVEF or quality of life.

Allopurinol is a drug that lowers uric acid levels in the blood and is used to treat gout. The **ALL-HEART** trial enrolled patients with CHD aged over 60 years (mean age 72 years) with no history of gout. Patients were randomized to receive conventional therapy with the addition of allopurinol up to 600 mg/day (n=2853) or to continue therapy without allopurinol (n=2868). With a mean follow-up of 4.8 years, the event rate of the combined endpoint (non-fatal MI, non-fatal stroke or cardiovascular death) was similar in the conventional treatment group (11.3 %) and the addition of allopurinol (11.0 %; p=0.65), and all-cause mortality was not different between the two groups (p=0.77). ALL-HEART is the first large, prospective, randomized trial of the effect of allopurinol on major cardiovascular outcomes in patients with CHD without a history of gout and shows that allopurinol should not be recommended for secondary prevention of adverse events in this group of patients.

The **DELIVER** trial included 6263 patients with CHF and LVEF greater than 40 % who were receiving standard therapy to which dapagliflozin 10 mg/day or placebo was added after randomization. During a median follow-up of 2.3 years, the primary endpoint event of worsening heart failure (unplanned hospitalization for heart failure or urgent care visit for heart failure) or cardiovascular death occurred in 16.4 % of patients in the dapagliflozin group and 19. 5 % in the placebo group (RR 0.82 with 95 % CI 0.73 to 0.92; p<0.001), including worsening heart failure in 11.8 % vs. 14.5 % (RR 0.79 with 95 % CI 0.69 to 0.91) and cardiovascular death in 7.4 % vs. 8.3 % (RR 0.88 with 95 % CI 0.74 to 1.05) of patients, respectively. Symptom severity was significantly lower in the dapagliflozin group than in the placebo group. The results were similar in patients with LVEF of 60 % or more and less than 60 % with and without DM. The incidence of adverse events did not differ between groups. Dapagliflozin reduces the combined risk of worsening heart failure or CVD mortality in patients with heart failure and moderately reduced or preserved LVEF.

A pooled meta-analysis of two trials of dapagliflozin, **DAPA HF** and **DELIVER**, in participants with heart failure and different ranges of LVEF (⩽40 % and >40 %) was prespecified to examine the effect of treatment on endpoints and to test the consistency of the drug effect over a wide range of ejection fractions. The prespecified endpoints were death from cardiovascular causes; death from any cause; total number of hospitalizations for heart failure; and the sum of the major CVEs — death from cardiovascular causes, MI or stroke. A total of 11,007 participants with an average LVEF of 44 % were included. Dapagliflozin reduced the risk of death from cardiovascular causes (RR 0.86 with 95 % CI 0.76 to 0.97; p=0.01), death from any cause (RR 0.90 with 95 % CI 0.82 to 0.99; p=0.03), total hospitalizations for heart failure (RR 0.71 with 95 % CI 0.65 to 0.78; p<0.001) and major CCO (RR 0.90 with 95 % CI 0.81 to 1.00; p=0.045). There was no evidence that the effect of dapagliflozin differed by LVEF. In a pooled meta-analysis of patients with heart failure across the entire range of LV ejection fractions, dapagliflozin reduced the risk of death from cardiovascular causes and hospitalization for heart failure, severe CVEs.

After preliminary meta-analyzes of the **DELIVER** and **EMPEROR-Preserved** trials in chronic heart failure (CHF) with preserved or moderately reduced LV EF patients, outcomes in CHF with reduced LV EF patients (DAPA-HF and EMPEROR-Reduced) and those hospitalized with worsening heart failure regardless of LV EF (SOLOIST-WHF) were included in further statistical analysis. Among 12,251 participants in the DELIVER and EMPEROR-Preserved studies, sodium-glucose cotransporter type 2 inhibitors reduced the pooled risk of cardiovascular death or first hospitalization for heart failure (RR 0.80 with 95 % CI 0.73 to 0.87) with a concomitant reduction in the risk of both components of this primary endpoint (cardiovascular death — RR 0.88 with 95 % CI 0.77 to 1.00; first hospitalization for heart failure — RR 0.74 with 95 % CI 0.67 to 0.83). When the results of 5 studies involving 21,947 patients were summarised, sodium-glucose cotransporter type 2 inhibitors reduced the risk of cardiovascular death or hospitalization for heart failure (RR 0.77 with 95 % CI 0.72 to 0.82), cardiovascular death (RR 0.87 with 95 % CI 0.79 to 0.95), first hospitalization for heart failure (RR 0.72 with 95 % CI 0.67 to 0.78) and all-cause mortality (RR 0.92 with 95 % CI 0.86 to 0.99).

For each of the endpoints evaluated, the effects of treatment with type 2 sodium-glucose cotransporter inhibitors were consistently observed in heart failure trials with moderately reduced or preserved LV EF and in all 5 trials selected for meta-analysis. The effect of treatment on primary endpoint events was generally

similar in all 14 subgroups studied. Sodium-glucose cotransporter 2 inhibitors reduce the risk of cardiovascular death and hospitalization for heart failure in a wide range of patients with heart failure, supporting the role of these drugs as first-line therapy for heart failure regardless of LV EF or treatment setting.

The **INVICTUS** trial enrolled 4531 patients with AF and echocardiographically confirmed rheumatic heart disease, CHA_2DS_2-VASc thromboembolic risk of at least 2, mitral valve area of 2 cm^2 or less, spontaneous left atrial echocontrast or left atrial thrombus. Patients were randomized to receive standard doses of rivaroxaban or a dose-adjusted vitamin K antagonist. With a mean follow-up period of 3.1 years, the risk of the primary endpoint: a combination of stroke, systemic embolism, MI, or death from vascular (cardiac or noncardiac) or unknown causes, was higher in the rivaroxaban group than in the vitamin K antagonist group (OR 1, 25 with 95 % CI 1.10 to 1.41). That included a higher risk of death (RR 1.23 with 95 % CI 1.09 to 1.40) and ischemic stroke (RR 1.53 with 95 % CI 1.06 to 2.20) in the rivaroxaban group, and the incidence of bleeding was similar between the two anticoagulant therapy options. Vitamin K antagonists should remain the standard of care for AF associated with rheumatic heart disease because of their advantage in preventing mortality.

Oral Factor XIa inhibitors may modulate coagulation and prevent thromboembolic complications without significantly increasing the risk of bleeding. In the phase 2 **PACIFIC AMI** trial in 1601 patients (median age 68 years), the oral factor XIa inhibitor asundexian at doses of 10, 20 or 50 mg or placebo once daily for 6–12 months was added to treatment with aspirin and ticagrelor or prasugrel, PCI, within 5 days of the diagnosis of MI after randomization. Asundexian produced a dose-dependent inhibition of XIa activity that was greater than 90 % at the 50 mg dose. At a median follow-up of 368 days, Bleeding Academic Research Consortium type 2, 3 or 5 bleeding events occurred in 7.6 %, 8.1 %, 10.5 % and 9.0 % of patients receiving asundexian 10, 20 or 50 mg and placebo, respectively. Cumulative ischemic complications (cardiovascular death, MI, stroke or stent thrombosis) occurred in 6.8 %, 6.0 %, 5.5 % and 5.5 % of patients in the asundexian 10, 20 or 50 mg and placebo groups, respectively. In patients with recent MI, three doses of asundexian, when added to aspirin and a P2Y12 receptor inhibitor, dose-dependently and almost completely inhibited factor XIa activity without significantly increasing the incidence of bleeding or reducing the incidence of ischemic events. These data support the evaluation of asundexian at a dose of 50 mg/day in patients with MI in a phase 3 clinical trial with adequate statistical power.

The Phase 2b PACIFIC-Stroke dose-finding study of the oral Factor XIa inhibitor asundexian enrolled patients with acute (48 hours after symptom onset) non-cardioembolic ischemic stroke aged 45 years or older who were on antiplatelet monotherapy or dual antiplatelet therapy and were able to undergo brain MRI. After randomization, 1808 participants received asundexian 10 mg (n=455), 20 mg (n=450) or 50 mg (n=447) or placebo (n=456) once daily. At 26 weeks, the primary efficacy outcome (dose-response relationship on the combined incidence of occult MRI brain infarcts and recurrent symptomatic ischemic stroke) was met in 19 % of patients in the placebo group, compared to 19 % in the 10 mg asundexian group, 22 % in the 20 mg asundexian group and 20 % in the 50 mg asundexian group (p=0.80), while the primary safety outcome (major or clinically significant minor bleeding as defined by the International Society on Thrombosis and Haemostasis) was observed in 2 %, 4 %, 3 % and 4 % of patients, respectively. Factor XIa inhibition with asundexian in patients with acute non-cardioembolic ischemic stroke did not reduce the cumulative incidence of occult brain infarction or ischemic stroke or increase the major or clinically significant minor bleeding compared with placebo.

Digital smart devices are capable of detecting AF, but the effectiveness of this type of digital screening has not been directly compared with conventional care in detecting treatment-significant AF. The **eBRAVE-AF** trial randomized 5551 insured individuals (mean age 65 years, 31 % women) without AF at baseline to digital screening (n=2860) or usual care (n=2691). In the digital screening group, participants used a certified app on their smartphone to detect pulse wave abnormalities. Abnormal results were assessed with an external ECG recorded with a loop recorder over 14 days. The primary endpoint was AF first diagnosed within 6 months and treated with oral anticoagulants by an independent physician not involved in the study. After 6 months, participants were invited to enter the second phase of the study with reverse allocation for secondary analyzes. The primary endpoint of the study was met as digital screen-

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ing more than doubled the detection rate of treatment-significant AF in both phases of the study, with an odds ratio of 2.12 (95% CI 1.19 to 3.76; p=0.010) and 2.75 (95% CI 1.42 to 5.34; p=0.003) in phases one and two, respectively. The digital screening technology used offers significant advantages in AF detection over conventional management and has potential for widespread application due to its accessibility on common smartphones. Further studies are needed to test whether digital AF screening leads to better AF management outcomes.

In the **FOURIER** study, the PCSK9 inhibitor evolocumab, when added to statins, significantly reduced LDL cholesterol levels and the risk of CVE in patients with atherosclerotic CVD and was safe and well tolerated over a mean follow-up of 2.2 years. The **FOURIER-OLE** study was designed to address the lack of large-scale long-term follow-up of this therapy by continuing the use of evolocumab (n=3355) in an open-label setting compared to placebo (n=3280). With a median follow-up of 5.0 years and a maximum exposure to evolocumab from randomization in FOURIER of 8.4 years, the incidence of serious adverse events, muscle symptoms, new-onset DM, haemorrhagic stroke and neurocognitive decline did not exceed that of the corresponding parameters in the placebo group, with a sustained LDL reduction of <40 mg/dL in 63.2% of patients. At the follow-up period of the FOURIER-OLE, patients initially randomized to the evolocumab group had a reduced cumulative risk of CVD death, MI, stroke, hospitalization for unstable angina or coronary revascularisation (RR 0.85 with 95%, CI 0.75 to 0.96; p=0.008), the risk of CVD death, MI or stroke by 20% (RR 0.80 with 95%, CI 0.68 to 0.93; p=0.003) and CVD death by 23% (RR 0.77 with 95%, CI 0.60 to 0.99; p=0.04) compared to placebo. Long-term LDL lowering with everolocumab is associated with a consistently low incidence of adverse events and a reduced incidence of CCO for more than 8 years, similar to placebo.

Statin therapy is widely used and effective in preventing atherosclerotic CVD, but concerns remain that it may cause muscle pain or weakness. **The Cholesterol Treatment Trialists' Collaboration meta-analysis** included 19 large, randomized, double-blind trials of statins versus placebo (n=123,940) and 4 double-blind trials of more and less intensive statin therapy (n=30,724). During a median follow-up of 4.3 years, 27.1% of those receiving statins compared with 26.6% of those receiving placebo reported muscle pain or weakness (OR 1.03 with 95% CI 1.01 to 1.06). During the first year of statin therapy, there was a relative increase in the incidence of muscle pain or weakness (RR 1.07 with 95% CI 1.04 to 1.10), which corresponds to an absolute excess incidence of 11 events per 1000 person-years, meaning that only one in 15 ([1.07–1.00]/1.07) of these reports of statin therapy were actually related to statins. After 1 year of follow-up, there was no excess incidence of first-time muscle symptoms in the statin group compared with placebo (RR 0.99 with 95% CI 0.96 to 1.02). High-intensity statin regimens (atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/day) were associated with a higher risk of muscle symptoms than low-intensity and moderate-intensity statin regimens at 1 year follow-up compared with placebo (RR 1.05 with 95% CI 0.99 to 1.12). There was no clear evidence that the risk differed for individual statin molecules or in different clinical situations. Statin therapy causes a small, clinically insignificant increase in mean blood creatine kinase levels. Statin treatment causes a small increase in patient complaints of muscle pain, most of which are mild. The majority (>90%) of all reports of muscle symptoms in patients treated with statins are not statin-related. The risk of muscular symptoms is much lower than the known cardiovascular benefits of statins.

ARB and BB are widely used in the treatment of Marfan syndrome in attempt to reduce the rate of progression of aortic root dilatation accompanying this pathology. **The Marfan Treatment Trialists' Collaboration** meta-analysis included 10 randomized comparisons of ARB versus control or ARB versus BB in patients with Marfan syndrome who had not previously undergone aortic surgery (n=1442). The primary endpoint was the annual rate of change in aortic root Z-score (sinuses of Valsalva) adjusted for body surface area. At a median follow-up of 3 years, ARB administration approximately halved the annual rate of change in aortic root Z-score (mean annual increase of 0.07 in the ARB group versus 0.13 in controls; p=0.012). Prespecified subgroup analyzes showed that the effects of ARB were particularly significant in patients with pathogenic fibrillin-1 variants compared with those without it, and there was no evidence to suggest that the effect of ARB varied with BB use (p=0.54 for heterogeneity). Three trials (n=766) compared ARB with BB in eligible participants. At a

median follow-up of 3 years, the annual change in aortic root Z-score was similar in the matched groups (0.08 in the ARB group versus 0.11 in the BB group; p=0.48), whereas the difference in the annual change in aortic root Z-score between the ARB and control groups was 0.09 (p=0.042). In people with Marfan syndrome and without previous aortic surgery, ARB reduced the rate of increase in aortic root Z-score by about half, including those taking BB. The beneficial effects of BB and ARB are comparable, and their combination from the time of diagnosis will provide a greater reduction in the rate of aortic dilation than monotherapy, which over several years of therapy may delay the need for aortic surgery.

The **PANTHER** meta-analysis included 7 studies — ASCET, CADET, CAPRIE, DACAB, GLASSY, HOST-EXAM and TiCAB — conducted in 492 centres in Europe, Asia and North America. After exclusion, the final study population included 24,325 patients (mean age 64.3 years, 21.7% women) with confirmed CHD, of whom 12,178 received monotherapy with P2Y12 inhibitors (clopidogrel in 62% or ticagrelor in 28% of cases) and 12,147 received aspirin monotherapy. The mean duration of treatment was 557 days. The primary endpoint of the study (death from CVD, MI or stroke) occurred in 5.5% of patients in the P2Y12 inhibitor group versus 6.3% of patients in the aspirin group (RR 0.88 with 95% CI 0.79 to 0.97; p=0.014). The incidence of major bleeding type 3 or 5 according to the Bleeding Academic Research Consortium was similar when comparing P2Y12 inhibitor or aspirin antiplatelet therapy regimens (1.2% vs. 1.4%; p=0.23). When ischemic and haemorrhagic outcomes were combined, there was a lower cumulative risk of these adverse events in the P2Y12 inhibitor group, 6.4% versus 7.2% of cases in the aspirin group (RR 0.89 with 95% CI 0.81 to 0.98; p=0.020). Antiplatelet therapy is indicated after MI, PCI, stroke and coronary artery bypass graft surgery to prevent recurrent events. Based on these findings, long-term P2Y12 inhibitor monotherapy is preferable to long-term aspirin monotherapy in the secondary prevention of CHD.

Several randomized controlled trials have compared transradial and transfemoral access for the invasive treatment of CHD, with the former showing a lower mortality rate. **The Radial Trialists' Collaboration** meta-analysis included data from 7 randomized trials using transradial (n=10,775) or transfemoral (n=10,825) access. The mean age of patients was 63.9 years, 31.9% were female, 95% had ACS and 75.2% had undergone PCI. The primary endpoint (all-cause mortality at 30 days) was less frequent with transradial (1.6%) versus transfemoral (2.1%) access (RR 0.77 with 95% CI 0.63 to 0.95; p=0.012), and major bleeding at 30 days was also less frequent (1.5% versus 2.7%; RR 0.55 with 95% CI 0.45 to 0.67; p<0.001). Subgroup analysis of mortality showed consistent results except for baseline haemoglobin level (p=0.033), indicating superiority of transradial access in patients with significant anaemia, but not in those with mild or no anaemia. After adjustment, transradial access remained associated with a 24% RR reduction in all-cause mortality and a 51% reduction in major bleeding. In the invasive treatment of CHD, transradial access was associated with lower rates of all-cause mortality and major bleeding at 30 days compared with transfemoral access. The positive effect of transradial access on mortality is seen in patients with anaemia. The reduced risk of major bleeding only partially explains the reduction in mortality.

The efficacy and safety of prophylactic use of full-dose anticoagulant and antiplatelet therapy in patients with critically severe COVID-19 remained uncertain. In the open-label, controlled **COVID-PACT** trial with a 2×2 factorial design and blinded endpoint adjudication, 390 patients with COVID-19 in the ICU were randomized to treatment with full or standard prophylactic doses of anticoagulants. If antiplatelet therapy was not indicated, patients were also randomized to receive clopidogrel or no antiplatelet therapy. The primary efficacy endpoint (death related to venous or arterial thrombosis, pulmonary embolism, clinically evident deep vein thrombosis (DVT), type 1 MI, ischemic stroke, systemic embolism or acute limb ischemia and clinically silent DVT before hospital discharge or within 28 days) was achieved less frequently in the full-dose anticoagulant group compared to the standard-dose group (9.9% versus 15.2% of cases, RR 0.56 with 95% CI 0.32 to 0.99; p=0.046). The primary safety endpoint of fatal or life-threatening bleeding occurred in 2.1% of patients on the full dose and 0.5% of patients on the standard dose of anticoagulants (p=0.19); the secondary safety endpoint of moderate/severe bleeding occurred in 7.9% and 0.5% of patients, respectively (p=0.002). There were no differences in all-cause mortality between the full-dose and standard-dose anticoagulant

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groups (RR 0.91 with 95% CI 0.56 to 1.48; p=0.70). There were no differences in the incidence of the primary efficacy or safety endpoints with clopidogrel compared to no antiplatelet therapy. In patients with severe COVID-19, full-dose anticoagulation, but not clopidogrel, reduced the risk of thrombotic complications with an increased incidence of bleeding and no apparent effect on mortality. Enrolment was stopped in early March 2022 (≈50% of planned enrolment) due to declining admissions to intensive care units with a diagnosis of COVID-19.

COVID-19 is associated with dysregulation of the immune response and hypercoagulability. The open-label, controlled **ACT** trial with a 2×2 factorial design enrolled 2749 patients from 62 centres in 11 countries who were hospitalized with symptoms of laboratory-confirmed COVID-19 and randomized (1:1) to receive anti-inflammatory therapy with colchicine at a dose of 1.2 mg followed by 0.6 mg 2 hours later and then 0.6 mg twice daily for 28 days (n=1304) or conventional treatment (n=1307). For the second time, patients were randomized (1:1) to receive antithrombotic therapy with a combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily for 28 days (n=1063) or usual care (n=1056). After 45 days of follow-up, 28.2% of patients in the colchicine group and 27.2% of patients in the control group had a primary endpoint event (need for high-flow oxygen therapy, ventilation or death) (OR 1.04 with 9 5% CI 0.90 to 1.21; p=0.58), and the other primary endpoint event (MI, stroke, acute limb ischemia or pulmonary embolism) was reported in 26.4% of patients in the rivaroxaban + aspirin group versus 28.4% in the control group (RR 0.92 with 95% CI 0.78 to 1.09; p=0.32). The results were confirmed by the subgroup analysis and were independent of vaccination status, baseline disease severity and time from symptom onset to randomization. Adverse reactions, mainly gastrointestinal, leading to discontinuation were observed in 0.61% of patients in the colchicine group. Bleeding was observed in 1.6% of patients in the rivaroxaban plus aspirin group versus 0.66% in the control group (p=0.042), but the incidence of major bleeding was not significantly different — 0.19% versus 0.57% (p=0.18). In addition, there were no serious adverse events in the rivaroxaban plus aspirin group that led to discontinuation of study treatment. In patients hospitalized for COVID-19, neither colchicine nor rivaroxaban plus aspirin prevented disease progression or death.

The open-label, controlled, 2×2 factorial **ACT** trial enrolled 3917 outpatients from 48 centres in 11 countries with symptomatic, laboratory-confirmed COVID-19 with a high risk of disease progression. The participants were randomized (1:1) to receive anti-inflammatory therapy with colchicine 0.6 mg twice daily for 3 days followed by 0.6 mg once daily for 25 days (n=1939) or usual treatment (n=1942). Secondly, patients were randomized (1:1) to receive antithrombotic therapy with aspirin 100 mg once daily for 28 days (n=1945) or usual care (n=1936). After 45 days of follow-up, the primary endpoint (hospitalization or death) occurred in 3.4% of patients in the colchicine group and 3.3% in the control group (OR 1.02 with 95% CI 0.72 to 1.43; p=0.93). The other primary endpoint (major thrombosis, hospitalization or death) occurred in 3.0% of patients in the aspirin group and 3.8% in the control group (RR 0.80 with 95% CI 0.57 to 1.13; p=0.21). The results were consistent across all predefined subgroups and were independent of vaccination status, timing of randomization from symptom onset and timing of enrolment in relation to pandemic phase. Serious adverse reactions occurred in 1.8% of patients in the colchicine group and 1.4% in the control group; 1.6% of patients in the aspirin group versus 1.6% in the control group, but none of these events led to discontinuation of the study medication. The results do not support the use of colchicine or aspirin to prevent COVID-19 progression or death in outpatients.

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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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1) *Original papers* present the results of clinical studies. The word limit is 3.000 (including references, tables, and figure legends). The maximal number of references is 15. The structured abstract should contain 5 sections (**Aim, Material and Methods, Results, Conclusion**, and **Key words**), and be no longer than 300 words.

2) *Lectures*, or clinically oriented reviews, are written by experts in broader areas of medicine. Lectures could be focused on epidemiology, pathophysiology, diagnostics, treatment, and prevention. The word limit is 5.000 (including references, tables, and figure legends). The maximal reference number is 80. The unstructured abstract is no longer than 150 words.

3) *Literature reviews* are focused on more specific topics, compared to lectures. The word limit is 4.500 (including references, tables, and figure legends). The maximal reference number is 50. The unstructured abstract is up to 150 words.

4) *Clinical case* is a brief report on a complex diagnostic problem and its solution, or a description of

a rare clinical observation. The word limit is 600 (including references, tables, and figure legends). The maximal number of references is 5. No abstract is required.

5) *Clinical opinion* informs the readers on the topics of cardiovascular medicine and related disciplines. The word limit is 2.500 (including references, tables, and figure legends). The maximal number of references is 15.

The journal accepts for publication original phase 2, 3 and 4 clinical studies. Literature reviews should be based on sources not older than 5 years.

II. Information about the article, which includes the following sections, is combined into a single file "letter (cover)":

1) the manuscript is not under consideration in another edition; 2) has not been previously published; 3) contains a full disclosure of the conflict of interest; 4) all authors meet the criteria of authorship, it was read and approved; 5) the author (s) are responsible for the power of attorney submitted in the manuscript materials. 6) all contact information of the author responsible for correspondence; 7) information about previous publications of the authors on the same topic or pre-publication.

If the manuscript is a part of the thesis, it is necessary **to specify** the estimated terms of thesis defense.

The "letter of direction (accompanying)" should be made out on one or two sheets. Using the form of the official institution-at the choice of the author's team. In the address: "to The chief editor of the Russian cardiology journal, academician of RAS, Professor Oganov R. G.". The signatures of **all authors** should be placed at the bottom.

"Directional (cover) letter" is scanned. File format. jpeg attached as an additional file of the manuscript.

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III. Registration on the Website and information about the authors.

Any of the authors can submit an article to the journal. Usually it is the one who then conducts correspondence with the editorial office and to whose mail notification letters come (when submitting a manuscript through the site, you can choose to send notifications to all authors).

The author registers on the site, entering his full name. In the form to be filled in when submitting an article, all authors and all additional information (places of work, positions, academic titles, institutions, ORCID — all authors) are indicated.

If the author has several places of work, it is written: 1. "The name of the institution..." 2. "Name of institution."... The name of the institution is written in abbreviated form, for example, Moscow state University, Moscow. Brackets are not put.

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Positions and titles (using traditional abbreviations: PhD, senior researcher, leading researcher, PhD, C.b.N., MD), head reduces to the head., then write the full name of the laboratory/Department / Department; Director, head, Professor — is not reduced.

The order of the authors. Authors ' priority should be entered into the system in accordance with the order of the article. The movements are made by small arrows "top" / "bottom", which are located under the data of each of the authors. The data of the author responsible for the correspondence, put a dot in a circle denoting this information. Other authors point do not put.

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Keyword. They are written with a small letter, separated by a semicolon. At the end put a point. In the text of the article the keywords are written separated by commas.

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Title page of the manuscript. The title of the manuscript is written in capital letters, without hyphenation, in bold. Initials and surnames of authors-Ivanov I. I., Petrov P. p. the full name of organization (s) from which (s) there was a manuscript, the city, the country is Given. Footnotes are in Arabic numerals after the authors ' names and before the names of institutions.

Example of design:

THE PREVALENCE OF RISK FACTORS OF NONCOMMUNICABLE DISEASES IN THE RUSSIAN POPULATION IN 2012–2013. THE RESEARCH RESULTS OF THE ESSE-RF

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

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

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

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

Information about the authors, where indicated: full name, place of work of all authors, their positions, ORCID; full contact information is required for one (or more) of the author and includes e-mail, available phone number.

All members of the group of authors should meet all four criteria of authorship set forth in the ICMJE recommendations: 1) concept and design development or data analysis and interpretation, and 2) manuscript justification or verification of critical intellectual content, and 3) final approval for publication of the manuscript, and 4) consent to be responsible for all aspects of the work, and assume that issues relating to the thoroughness and diligent execution of any part of the study submitted are duly investigated and resolved. This information should also be contained in the document.

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Information about grants. Should be mentioned at the end of the article in the section Acknowledgements and at the end of the section Material and methods — with a full description of the role of the source of funding in the performance of work (design, information collection, analysis, data interpretation, etc.).

Information and ethics in the study.

Example of design:

The study was carried out in accordance with the standards of good clinical Practice (Good Clinical Practice) and the principles of the Helsinki Declaration. The study Protocol was approved by the Ethical committees of all participating clinical centers. Prior to being included in the study, written informed consent was obtained from all participants.

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All additional information (permits, questionnaires, etc.) can be requested from the authors in addition to the preparation of the work for printing.

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Information about the obtained consent in patients for the study.

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

For all clinical trials: information about the registration and placement of data on the study in any public register of clinical trials. The term "clinical study" refers to any research project that affects people (or groups of subjects) with/or without a comparative control group, studies the interaction between inter-

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

The number of words in the article (excluding summaries, sources of literature, figure captions and tables), the number of tables and figures.

The absence of an information file or incomplete text (not containing the above items) is the basis for refusal to accept the manuscript for consideration.

IV. Manusctipt submision check-list

Since the main file of the manuscript is automatically sent to the reviewer for» blind review», it should not contain the names of the authors and institutions. The file contains only the following sections:

Article title
Summary with key words
List of abbreviations
Text
Acknowledgements (if any)
List of references
Tables, figures (if they can be embedded in the text of Word format).

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

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

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

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

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

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

Acknowledgements — all participants who do not meet the authorship criteria should be listed in the Acknowledgements section, which is located at the end of the article before the Literature section.

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

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

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

Abbreviations should be listed in a footnote below the table in alphabetical order (for tables its list of abbreviations!).

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References to works that are not in the list of references and Vice versa, references to unpublished works, as well as to works of many years ago (>10 years) are not allowed. The only exceptions are rare highly informative works. Especially close attention to this item, please pay to those authors who submit "literature Review".

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Book:

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

Chapter:

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

Russian chapter:

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

Webpage:

Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004)

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— checking the completeness of the manuscript: if you do not comply with the requirements of the Rules for the authors to complete the manuscript or its design, the Editors have the right to refuse to publish or in writing to require to send the missing materials or to correct the version already downloaded to the site.

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

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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.

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

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XIII. Journal subscription

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

XIV. Journal subscription

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

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

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