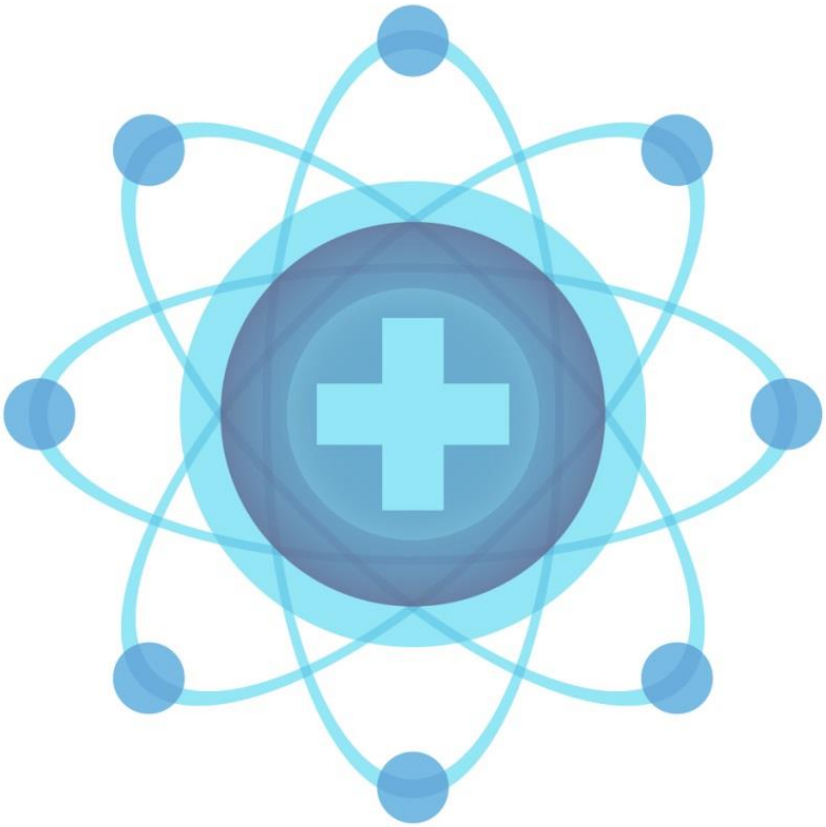

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Efficacy of empagliflozin in older patients with chronic heart failure with preserved left ventricular ejection fraction

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Abstract: Chronic heart failure (CHF) is the leading cause of hospitalization in Europe, the United States and Asia. Mortality in CHF increases with each hospitalization. CHF with preserved ejection fraction (EF) occurs when the heart muscle contracts ineffectively and there is reduced blood flow in the body compared to a normally functioning heart. Numerous studies have shown that symptoms associated with heart failure, such as shortness of breath and fatigue, can negatively affect quality of life.

Keywords: Chronic heart failure,

Introduction. Despite the availability of a wide choice of medications for the treatment of CHF, which can improve the survival rate of patients, the prognosis of the disease remains unfavorable [1, 2], therefore, the search for new treatment options for this pathology is an urgent task of modern cardiology. There are numerous contradictory data regarding the use of empagliflozin in CHF. Empagliflozin, a selective inhibitor of the sodium-dependent glucose transporter type 2 (SGLT2), became the first antihyperglycemic drug to be superior to placebo in cardiovascular safety.

Empagliflozin, a specific inhibitor of SGLT2, is a representative of a promising new class of drugs that lower glucose levels, independent of insulin. In addition to its well-proven glycemic effect, ample evidence suggests cardioprotective potential. Empagliflozin is able to improve myocardial microvascular perfusion, eNOS activity, and endothelium-dependent relaxation. Empagliflozin may have a beneficial effect by

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inhibiting DM-induced mitochondrial division in a 5'AMP-activated protein kinase (AMPK) - dependent manner. On the one hand, the action induced by this drug can slow down the aging of endothelial cells by suppressing oxidative stress, which leads to an improvement in their viability and barrier function. On the other hand, empagliflozin-induced endothelial migration as a result of F-actin homeostasis may promote angiogenesis [4]. With the progression of diabetes, endothelial damage is detected at an early stage. Thanks to these mechanisms, empagliflozin improves the blood supply to the myocardium. Significant data indicate the ability of empagliflozin to reduce systolic blood pressure by facilitating osmotic diuresis, influencing the microvascular diastolic response by stimulating eNOS phosphorylation, vascular remodeling, reducing the level of inflammatory proteins, and decreasing collagen synthesis [4]. The principle of action of type 2 sodium glucose cotransporter inhibitors is based on a decrease in glucose reabsorption in the proximal renal tubules, which leads to an increase in urinary glucose excretion and a subsequent decrease in plasma glucose levels. This mechanism of action is insulin-independent and, therefore, has a low risk of hypoglycemia [3, 4, 5]. It should be noted that earlier, within the framework of the EMPEROR-Reduced study, it was shown that the SGLT2 inhibitor empagliflozin reduces the risk of death and hospitalization due to CHF decompensation in patients with reduced LVEF by a quarter [8]. It is important to note that the EMPEROR-Preserved and EMPEROR-Reduced projects are part of a program to study empagliflozin in patients not only with metabolic disorders, but also with pathologies of the cardiovascular system and kidneys. Thus, the drug is currently being investigated in patients with chronic kidney disease (CKD), as well as in patients with acute myocardial infarction and a high risk of CHF [8].

On the other hand, SGLT-2 inhibitors have also shown a significant reduction in the risk of hospitalization not only for CHF, but also for end-stage CKD. As a consequence of this growing body of evidence, the focus of T2DM treatment has shifted from glucose control to organ preservation. SGLT-2 inhibitors have become a

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key tool in the treatment of CVD and in reducing the progression of CKD. The results of large randomized controlled trials, which included patients with and without type 2 diabetes, have shown that glyflozin therapy is associated with a decrease in hospital admissions for CHF and the progression of CKD. In T2DM, the positive effects of SGLT-2 inhibitors appear early and do not depend on the effect on lowering the level of glycemia [6, 7, 8]. The above aspects made it possible to determine the purpose of the study.

Target. To assess the effect of the inhibitor empagliflozin on exercise tolerance, quality of life, on the endpoints of CHF in older persons with preserved left ventricular ejection fraction.

Material and research methods. This study evaluated the efficacy and safety of empagliflozin in patients with chronic CHF with preserved LVEF. The present study included 115 patients aged from 62 to 78 years (average age 71.2 ± 3.6 years) with CHF with verified data of clinical and instrumental analyzes diagnosed with CHF functional class (FC) II and III. The New York Heart Association (NYHA) Classification by Functional Class was used to enroll patients in the study groups.

Patients, depending on the therapy performed by the method of "random" sampling, were divided into 2 groups: group 1 (n = 75, main group) of patients on the background of standard CHF therapy took empagliflozin (Emgalif, Orville services) 10 mg / day and group 2 (control group, n = 40) who took only standard therapy. The observation period was 12 weeks. The study was carried out at the clinical base of the Department of Cardiology and Gerontology of the Center for the Development of Professional Qualifications of Medical Workers at the Ministry of Health of the Republic of Uzbekistan.

All patients underwent a 6-minute walk test at baseline and at the end of the study, and underwent quality of life, blood lipid composition, and resting echocardiography.

The criteria for exclusion from the main study group were:

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hypertrophic, restrictive, obstructive or dilated cardiomyopathy, constructive pericarditis, primary pulmonary hypertension or cor pulmonale, myocarditis; acute myocardial infarction (or less than 30 days after its development), coronary artery bypass surgery (within 6 months), unstable angina pectoris, valvular heart disease, acute cerebrovascular accident (within 6 months), renal or hepatic failure, autoimmune or endocrine diseases.

The data obtained during the study were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel-2012 software package, including the use of built-in statistical processing functions. Methods of variational parametric and nonparametric statistics were used with the calculation of the arithmetic mean of the studied indicator (M), standard deviation ($\chi 2$), standard error of the mean (m), relative values (frequency,%), the statistical significance of the measurements obtained when comparing the mean values was determined by the criterion Student's t (t) with the calculation of the error probability (P) when checking the normal distribution (according to the kurtosis criterion) and the equality of general variances (F - Fisher's test).

Research results. The results of the assessment of the severity of the clinical condition according to the scale of the assessment of the clinical condition (SACC) showed that the patients in the general sample (n = 115) had an average of 4.4 ± 2.0 points. The average score of the 6-minute walk test (TSW) for the entire group was 329.8 ± 80 m, while the average survey result on the scale of quality of life assessment (MLHFQ) was 42.3 ± 7.8 points.

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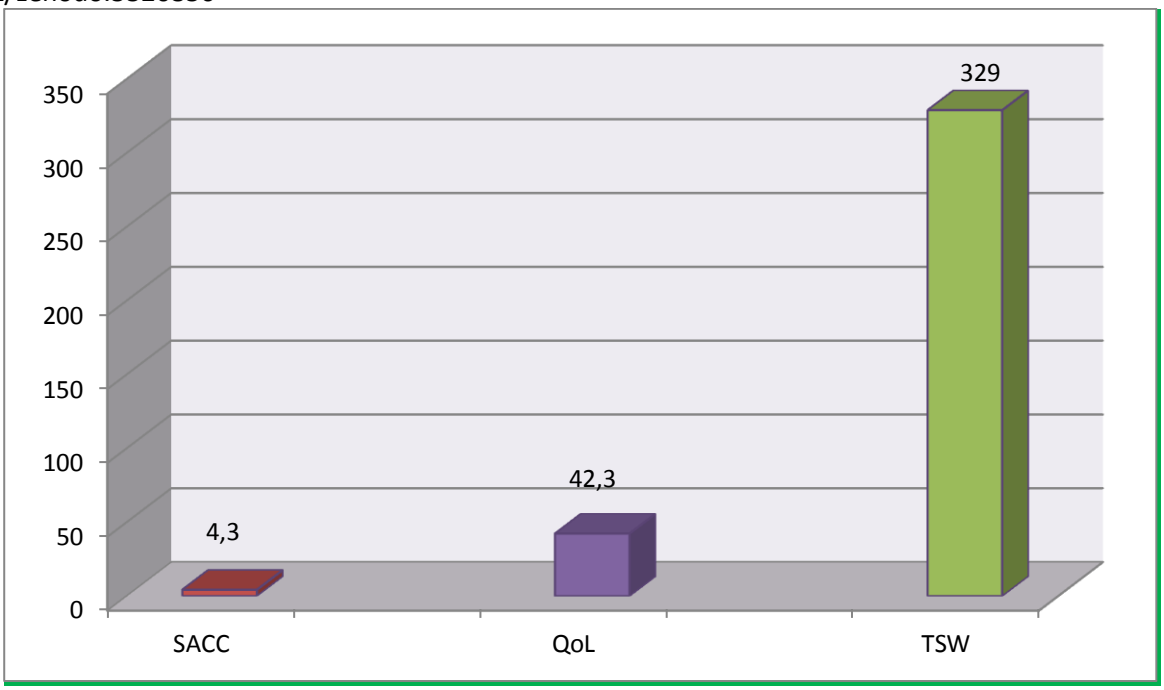


Fig. 1. The results of assessing the main indicators of the severity of CHF (score, meter)

Among the patients of the main group, after the therapy (after 12 weeks), 1 (1.3%) lethal outcomes and 1 (1.3%) cases of FC 2 change to FC 3 were observed. Among the untrained, there were 2 (5%) deaths and 2 (5%) cases of changes in FC CHF.

The assessment of the number of visits of patients with CHF according to the family polyclinic showed a generally satisfactory level of clinical examination in the main group - on average, the indicator of planned visits was 2.3 times (3.1%) in the control group.

The dynamics of the main hemodynamic parameters (the number of heartbeats (NHB), systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients in the study groups also had a positive trend. In the main group, the average heart rate decreased significantly ($p > 0.05$) and SBP ($p > 0.05$) in comparison with the indices at the beginning of the study It is noteworthy that in the patients of the control group there was an increase in the mean indices of heart rate, SBP and DBP after 12 weeks of observation.

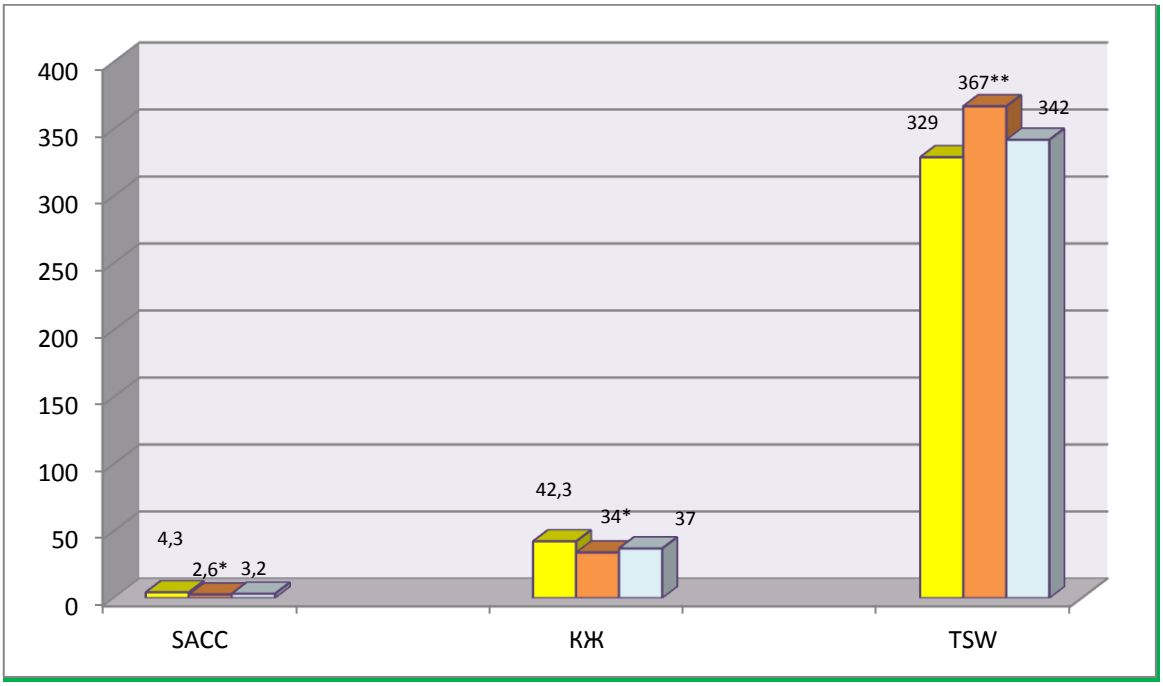
Table 1.

Dynamics of hemodynamic parameters in the analyzed groups of patients

Studied indicators	On the first visit	After the therapy (after 12 weeks)	
		Control group (n=40)	Main group (n=75)
NHB	75,7±10,3	76,7±10,4	70,1±8,7*
SBP	142,0±15	141,0±13,9	139,1±15,7*
DBP	85±11,1	86±11,0	82,2±7,9

*Note: * p> 0.05 - reliability of differences in relation to the initial data. NHB - heart rate, SBP - systolic blood pressure, DBP - diastolic blood pressure.*

Indicators of the dynamics of the clinical and functional state of patients in the form of SACC and TSW within 12 weeks. from the beginning of observation in the compared groups are shown in Figure 2. In the main group, significant differences were noted as TSW (p <0.01), SACC (p <0.01) and quality of life (QoL) (p <0.01), whereas in the control group, no significant and reliable positive dynamics was observed.



*Note: * p <0.05: ** p <0.01 - reliability of differences in relation to the initial data*

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Figure 2. Data of QoL, SACC and TSW in patients of the compared groups against the background of the therapy (score, meter).

Table 3.

Lipid composition of blood in the analyzed groups (M±m)

Indicators	Main Group (n=75)	Control Group (n=40)	Initial Data (n=115)
Total CS, mg / dl	196±5,1	202±5,0	219±3,0
TG, mg / dl	185,0±4,6*	196,0±9.7	208±6,2
CS LDL, mg / dl	138±2,5*	140± 3,7	148±3,4
CS HDL, mg / dl	34,2± 1.1	33,2±1,0	33,4± 1.0
CA, rel.	4.1±0,11	4,3±0,1	4,8±0,3

*Note: * P <0.001-reliability of differences in relation to healthy groups, CS-cholesterol, TG-triglycerides, LDL-low-density lipoproteins, HDL-high-density lipoproteins, CA-coefficient of atherogenicity.*

After 12 weeks. During the course of treatment in patients in the main group, there was a significant decrease in triglycerides (p <0.01) and low-density lipoproteins (LDL) (p <0.01) in the control group, similar dynamics were not revealed.

Table 4.

Indicators of LV systolic function in middle-aged patients.

	Initial data	Main group	Control group
EDS, sm	5,0±0,32	4,6±0,3	4,9±0,2
ESS, sm	4,9±0,2	4,3±0,21	4,7±0,22
EDV, ml	124,5±52	119,5±42*	121,3±50
ESV, ml	52±18,0	43±14,0*	49±17,0
EF, %	56,5±5,0	58,3±4,3	57,2±5,5
IVS, mm	12,6±1,1	11,0±1,02	12,0±1,1

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*Note: * p <0.05 - reliability of differences in relation to the initial data, EDS-end diastolic size, ESS-end systolic size, EDV-end diastolic volume, ESV-end systolic volume, EF-ejection fraction, IVS-interventricular septum..*

The analysis of echocardiographic parameters in patients in 2 study groups in patients with CHF was carried out on the basis of a study of the main indicators of systolic and diastolic LV dysfunction. In the main group of patients with CHF, after the therapy, a significant decrease in ESV and a relative decrease in EDV in relation to the initial values was revealed by 21% ($p < 0.05$). Along with this, IVS in the main group also tends to decrease. Whereas in the control group, significant dynamics in terms of Echocardiography indicators is not observed.

Thus, for patients with chronic heart failure with preserved left ventricular ejection fraction, the use of the SGLT2 inhibition drug, empagliflozin for 12 weeks against the background of the main therapy, demonstrated a positive effect in relation to an increase in exercise tolerance according to the data of the 6-minute walk test with an improvement in quality parameters. life on the SHOKS scale.

A positive trend of restoration of the contractility of the left ventricular myocardium was shown according to the end-systolic and end-diastolic volumes with a positive cardiac effect.

Therapy with the inclusion of empagliflozin is aimed at preventing manifestations such as chronic heart failure, which is aimed at reducing the progression of morbidity and mortality in older patients with preserved left ventricular ejection fraction.

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