International Heart and Vascular Disease Journal • Volume 8, № 27, September 2020

Journal of the Cardioprogress Foundation

The new direction in medical management of chronic heart failure with reduced ejection fraction

Kovalenko E. V., Lozhkina M. V., Markova L. I., Arabidze G. G.

Educational Institution of Higher Education "A.I. Evdokimov Moscow State University of Medicine and Dentistry" of the Ministry of Healthcare of the Russian Federation, Moscow, Russia.

Authors

Elena V. Kovalenko, M.D., Ph.D., associate professor of the Department of Internal Medicine № 2 of the Educational Institution of Higher Education "A.I. Evdokimov Moscow State University of Medicine and Dentistry" of the Ministry of Healthcare of the Russian Federation, Moscow, Russia.

Marina V. Lozhkina, M.D., Ph.D., associate professor of the Department of Internal Medicine № 2 of the Educational Institution of Higher Education "A.I. Evdokimov Moscow State University of Medicine and Dentistry" of the Ministry of Healthcare of the Russian Federation, Moscow, Russia.

Ludmila I. Markova, M.D., Ph.D., professor of the Department of Internal Medicine № 2 of the Educational Institution of Higher Education "A.I. Evdokimov Moscow State University of Medicine and Dentistry" of the Ministry of Healthcare of the Russian Federation, Moscow, Russia.

Grigory G. Arabidze*, M.D., doctor of sciences, professor of the Department of Internal Medicine № 2 of the Educational Institution of Higher Education "A.I. Evdokimov Moscow State University of Medicine and Dentistry" of the Ministry of Healthcare of the Russian Federation, Moscow, Russia.

Summary

The review article presents the results of randomized clinical trials on the use of hypoglycemic agents in patients with cardiovascular diseases. The article reveals the mechanism of action of sodium glucose cotransporter-2 inhibitors (SGLT2), the pathogenetic validity and evidence base of their use in patients with chronic heart failure, both with and without type 2 diabetes mellitus.

Key words: *chronic heart failure, diabetes mellitus, sodium glucose cotransporter-2 inhibitor.*

Conflict of interests: None declared.

Received: *27.12.2019* **Accepted:** *03.04.2020*

* Corresponding author. Tel. +79104035964. E-mail: arabidze@mail.ru

Introduction

Despite the achievements in the managements of chronic heart failure (CHF) over the last years, the prognosis of such patients remains unfavorable. The prevalence of clinically expressed CHF is 4.5% in Russian Federation (RF), and the mortality rate reaches 12% [1, 2]. An increasing number of patients with CHF in RF directly correlates with increased incidence of cardiovascular pathology and cardiovascular disease (CVD) risk factors. Thus, the global number of patients with diabetes mellitus (DM) is growing steadily, and has doubled over the past decade. Our country is no exception. In 2018, over 4.5 million people (3.1% of the population) were diagnosed with DM, and over 4.2 million — with type 2 DM [3]. The results of the NATION study showed that the actual number of patients is twice as large as the official statistics [4]. It has been established that DM is as significant as heart attack in CHF development and progression. In addition, the presence of insulin resistance and related metabolic disorders, including diabetes, aggravates the course of existing cardiovascular pathology and increases the risk of heart failure (HF) decompensation, as well as the frequency of hospitalizations for heart failure [5,6]. An integrated approach for the management of such patients should have a protective effect on the course of concomitant pathology and improve the prognosis. Modern treatment of CHF is based on the inhibition of the renin-angiotensin-aldosterone system (RAAS), and the main groups of medications include: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNi), beta-adrenergic blockers (BAB) and mineralocorticoid receptor antagonists (MRAs). In 2019, foreign and domestic recommendations on CHF included another drugs group that until recently have been used only for the treatment of patients with type 2 DM [2.7]. Initiation of the researchesin this field is associated not only with high prevalence of DM among patients with CHF, but also with similar pathogenesisof these pathologies.

8 classes of sugar-lowering medications are used for the management of patients with DM [3]. However, many of them have limitations in comorbid patients, including patients with CHF. The negative experience of rosiglitazone treatment forced pharmacological companies to provide evidence of cardiovascular safety of newly registered hypoglycemic agents (US Food and Drug Administration Safety (FDA) in 2008 and European Medicines Agency (EMA) in 2012) [8–10]. Subsequently, this lead not only to improvement of the treatment of patients with DM, but also positively affected the prognosis of patients with CHF without DM. The following studies have shown cardiovascular safety of the number of medications. The dipeptidyl peptidase-4 inhibitor saxagliptin did not increase the risk of cardiovascular complications (CC). The combined endpoint included cardiac death (CD), myocardial infarction (MI) and stroke. Obtained results were comparable to placebo (relative risk (RR) 1.0; 95% confidence interval (CI) from 0.89 to 1.12; p= 0.99). At the same time, the saxagliptin increased the risk of hospitalization for HF (RR 1.2; 95% CI from 1.07 to 1.51; p= 0.007) [11]. Other drugs from the same group, such as alogliptin and sitagliptin, did not increase the risk of CD as well as the number of hospitalizations for HF-(RR 1.19; 95% CI from 0.90 to 1.58; p= 0.22) and (RR 1.0; 95% CI from 0.83 to 1.20; p= 0.88), respectively [12,13]. Glucagon-like peptide type 1 agonists showed high efficacy. Liraglutide significantly reduced the risk of combined primary endpoint (CD, nonfatal MI and stroke) compared with placebo (RR 0.87; 95% CI from 0.78 to 0.97; p= 0.01); significantly reduced the risk of CD by 22% (RR 0.78; 95% CI from 0.66 to 0.93; p= 0.007) and all-cause mortality (RR 0.85; 95% CI from 0.74 to 0.97; p= 0.02). The effect on the frequency of hospitalizations for HF (RR 0.87; 95% CI from 0.73 to 1.05; p= 0.14) and unstable angina (RR 0.98; 95% CI from 0.76 to 1, 26; p= 0.87) was comparable with the control group [14]. Semaglutide also significantly reduced the risk of CD (RR 0.74; 95% CI from 0.58 to 0.95; p= 0.02), stroke incidence by 39% (RR 0.61; 95% CI from 0.38 to 0.99; p= 0.04) that most significantly contributed to positive dynamics of combined endpoint. The rates of CD (RR 0.98; 95% CI from 0.65 to 1.48; p= 0.92), nonfatal MI (RR 0.74; 95% CI from 0.51 to 1.08; p= 0, 12) and hospitalizations for HF (RR 1.11; 95% CI from 0.77 to 1.61; p= 0.57) did not differ between studied groups [15]. Lixisenatide and exenatide showed placebo-comparable effect on the risk of CVC and hospitalizations for HF [16, 17].

Sodium-glucose Cotransporter-2 (SGLT2) inhibitors or gliflozins is relatively new group of medications with insulin-independent mechanism of action that already occupies a special place among hypoglycemic agents. This is the only class of medications that improved the prognosis of patients with CHF, including patients without DM [18]. The main mechanism of action of gliflozins is the blockage of renal proximal tubules glucose reabsorption. Normally, glucose glo-

merular filtration rate is approximately 180 g per day. Then the glucose is completely reabsorbed in renal proximal tubules and is not determined in urine analysis. In case the level of blood glucose reaches 10–11 mmol / L (180–200 mg / dL) and exceeds the renal reabsorption potential, it is excreted in the urine [19]. Animal models showed increased expression of renal glucose transporters (SGLT) in mice with diabetes. Most (up to 90 %) of filtered glucose is reabsorbed in the Slproximal nephron segment with the sodium-dependent glucose transporter SGLT2. Remained glucose is reabsorbed in the S2 and S3 segments with sodium glucose transporters 1 (SGLT1). Molecules of SGLT1 and SGLT2 differ by many parameters, including localization, glucose affinity, and specificity. SGLT1 has high affinity with low ability to transport glucose trough the cell membrane. SGLT1 is mainly presented in the cells of small intestine, cardiac, skeletal muscle, trachea, lungs, and to a lesser extent in the renal cells. SGLT1 mutations lead to glucose and galactose malabsorption. SGLT2 is located in the epithelial cells lining the nephron proximal tubule and is the main glucose reabsorption transporter. SGLT2 has low affinity and high glucose transport activity [20].

First SGLT2 inhibitor was isolated from the bark of the apple tree in 1930. The hypoglycemic effect of phorizinwas discovered later in diabetes models in mice. The clinical use of phorizin was limited by non-selective SGLT blockage and rapid beta-glucosidase degradation [21]. Researches in recent decades have focused on the development of selective, breakdown resistant medications. This has led to the appearance of the number of agents with selective SGLT2 inhibition. Its usage disruptsglucose reverse reabsorption in the proximal tubules, followed by glycosuria and blood glucose decrease without hypoglycemia risk. Daily loss of 70–80 g of glucose leads to body weight decrease by 2–4 kg. The drugs also act as osmotic diuretic due to sodium reabsorption impairment, followed by a decrease of circulating blood volume (CBV) and total peripheral resistance (TPR). Thus, blood pressure (BP), intrarenal pressure and urine albumin level decreases and, therefore, fluid retention manifestations control improves in patients with CHF [22–26] (Figure 1).

An additional mechanism of natriuresis of SGLT2 inhibitors is associated with the blockage of 1st (NHE1) and 3rd (NHE3) isoforms of Na+/H+ exchanger. NHE is a membrane glycoprotein involved the maintenance

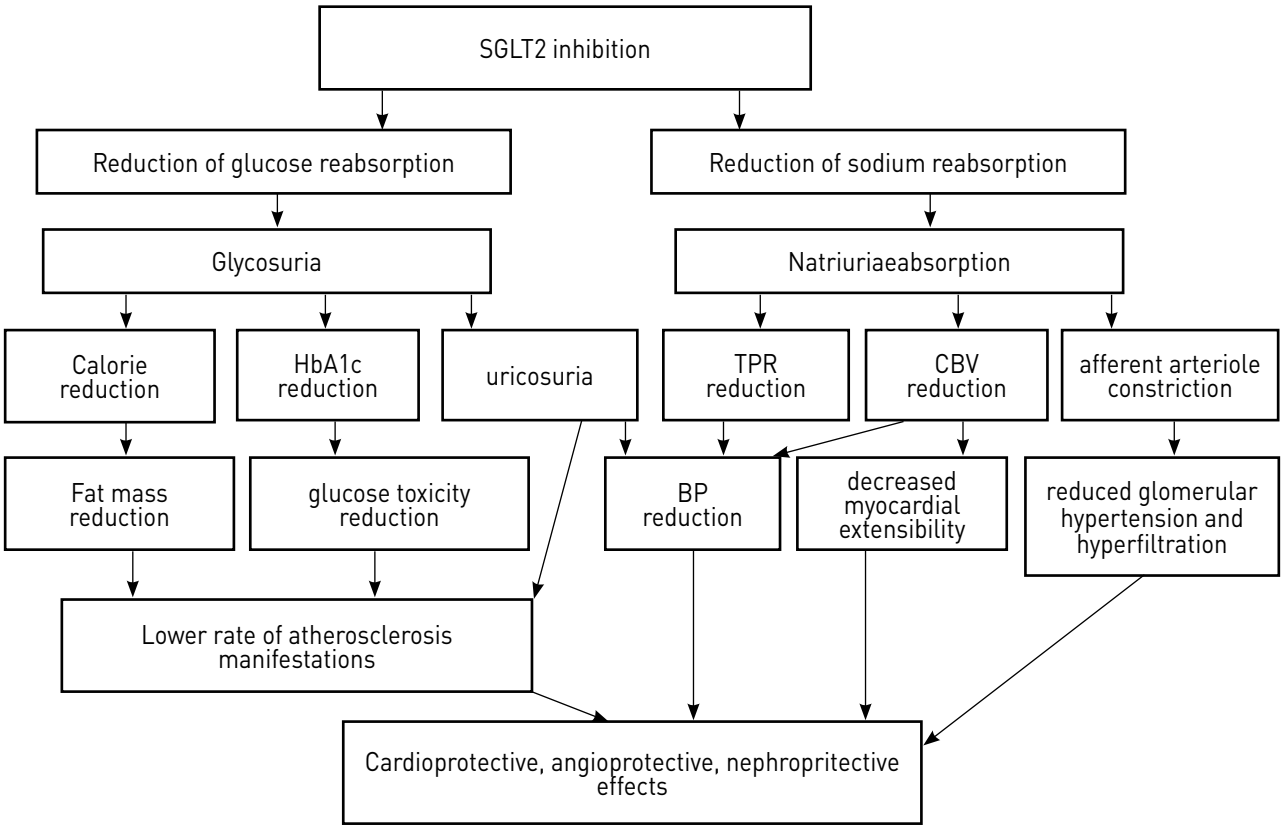

Figure 1. The main sodium-glucose co-transporter 2 inhibition manifestations

of intracellular pH and Na+ concentration. NHE activation due to Na+ / Ca2+ exchange leads to calcium metabolism impartment and, therefore, contributes to the pathogenesis of many CVDs, including HF. It was found that patients with HF have increased NHE3 expression in the proximal tubular epithelial cells and increased sodium reabsorption. Therefore, SGLT2 inhibitors enhance natriuresis in patients with HF through NHE3. Its cardioprotective effect is also associated with NHE1 inhibition and decreasedconcentration of sodium and calcium in the cytoplasm and increased amount of calcium in myocardial mitochondria. Gliflozins also reduces the activity of the sympathoadrenal system that plays one of the main roles in HF pathogenesis [27,28].

In our country, 3 medications from this group are available: dapagliflozin, empagliflozin and canagliflozin. The cardiovascular safety of these drugs has been proven in clinical studies.

The Phase III trial of EMPA-REG Outcome study was randomized, double-blind, placebo-controlled study that involved 590 clinical centers from 42 countries [29]. The inclusion criteria were: type 2 diabetes, age≥ 18 years old, body mass index (BMI)≤ 45 kg/m^2, glycated hemoglobin (HbA1c) 7–10% (average HbA1c 8.1%), with estimated glomerular filtration rate (eGFR)≥30 ml / min / 1.73 m^2 calculated using the MDRD (Modification of Diet in Renal Disease) formula and confirmed CVD (coronary heart disease, arterial hypertension, myocardial infarction or stroke history, peripheral artery disease). The study was performed from September 2010 to April 2013 and included 7028 patients. The average follow-up was 3.1 years. The analysis involved data from 7020 patients. All patients were randomized into three observation groups: the placebo group (n= 2333), the empagliflozin 10 mg per day group (n= 2345), and the empagliflozin 25 mg per day group (n=2342). Participants received basic CVD therapy that included ACE inhibitors or ARBs in 81% of patients, BAB in 65% of patients, diuretics in 43%, and MRAs in 6%. The primary endpoint included: CD, nonfatal MI or stroke. The secondary endpoint included primary endpoints and hospitalizations for unstable angina. In addition, the following were evaluated: hospitalizations for HF, the total hospitalization rate for CHF or CVD, with the exception of fatal strokes. Compared with placebo group, empagliflozin significantly decreased CD by 38%, all-cause mortality by 32%, and hospitalizations for HF by 35%. Decreased CD and all-cause mortality was observed at early stage of the study and persisted throughout all observation period. Groups did not differ significantly by the secondary endpoint. The main results of the EMPA-REG Outcome study are presented in Table 1 [29].

Patients from empagliflozin group less frequently needed additional prescription of loop diuretics. Empagliflozin significantly reduced the frequency of combined events: hospitalizations for HF or loop diuretics prescription (RR 0.63; 95% CI from 0.54 to 0.73; p<0.001); hospitalizations for HF, CD or loop diuretics prescription (RR 0.64; 95% CI from 0.56 to 0.73; p<0.001). Subanalysis of the study results showed that empagliflozin was superior to placebo in patients without initial HF by the following parameters: "hospitalization for HF or CD", "hospitalization for HF", "CD", "all-cause mortality." However, patients with initial HF showed changes comparable

Table 1. **Main results of the EMPA-REG OUTCOME trial: primary and secondary endpoints**

Events	Placebo, n=2333, (%)	Empagliflozin, n=4687, (%)	RR (95% CI)	p
CD, nonfatal MI and stroke	282 (12.1)	490 (10.5)	0.86 (0.74–0.99)	0.04
CD, nonfatal MI and stroke or hospitalization for unstable angina	333 (14.3)	599 (12.8)	0.89 (0.78–1.01)	0.08
All-cause mortality	194 (8.3)	269 (5.7)	0.68 (0.57–0.82)	<0.001
Cardiovascular mortality	137 (5.9)	172 (3.7)	0.62 (0.49–0.77)	<0.001
Fatal or nonfatal MI excluding painless myocardial infarction	126 (5.4)	223 (4.8)	0.87 (0.70–1.09)	0.23
Nonfatal MI excluding painless myocardial infarction	121 (5.2)	213 (4.5)	0.87 (0.70–1.09)	0.22
Myocardial revascularization	186 (8.0)	329 (7.0)	0.86 (0.72–1.04)	0.11
Fatal and nonfatal stroke	69 (3.0)	164 (3.5)	1.18 (0.89–1.56)	0.26
Hospitalization for HF	95 (4.1)	126 (2.7)	0.65 (0.50–0.85)	0.002
Hospitalization for HF or cardiovascular death excluding fatal stroke	198 (8.5)	265 (5.7)	0.66 (0.55–0.79)	<0.001

to placebo by the same parameters. Patients with initial HF were older and more frequently had history of MI or atrial fibrillation, higher BMI, and decreased GFR<60 ml / min / 1.73 m^2 [30]. Empagliflozin also reduced body weight by 2.5 kg on average, waist circumference, blood uric acid levels, both systolic (SBP) and diastolic blood pressure (DBP) and did not increase heart rate at the same time. Medication insignificantly increased low- and high-density lipoproteins. Many patients did not reach glycemic control targets (average HbA1c values in the empagliflozin and placebo groups were 7.81% and 8.16%, respectively). Obtained data confirmed that empagliflozin reduced the risk of CVC not only due to hypoglycemic effect, but also due to cardio-, nephro-, angioprotective effects. The effectiveness of different empagliflozin doses (10 mg and 25 mg) was comparable, despite moderate dose-dependent effect on metabolic parameters. Epmagliflozin showed favorable tolerance profile. The incidence of hypoglycemia, diabetic ketoacidosis, thromboembolic complications, bone fractures, and events associated with decreased blood volume did not differ significantly between groups. Empagliflozin significantly increased the risk of genital infections (p<0.001) and urinary tract infections in women (p<0.05) compared with placebo. In general, the incidence of total adverse effects, severe adverse effects and adverse effects that required medication discontinuation was comparable between empagliflozin and placebo groups. All patients with initial HF (from both placebo and empagliflozin group) had higher incidence of adverse events (AE), including requiring medication discontinuation, compared with patients without initial HF. At the same time, patients from empagliflozin group showed lower frequency of total AEs, severe AEs and AEs requiring medication discontinuation compared with placebo group. Empagliflozin was safe for the function of kidneys. The number of patients with acute renal failure was lower in the empagliflozin group compared with placebo (p<0.01). Empagliflozin also showed significant nephroprotective effect. Medication significantly decreased the risk of doubling of serum creatinine level by 44% (p<0.001) and also decreased the frequency of renal replacement therapy (RRT) by 55% (p= 0.04). The combined "renal point" that included both mentioned above parameters decreased by 46% (p<0.001). By the end of 20th week of observation, the empagliflozin group showed decreased GFR (according to the CKD-EPI equation) [31]. Other studies confirmed nephroprotective effect of empagliflozin. Its administration for 52 weeks decreased the rate albuminuria in patients with type 2 DM and chronic kidney disease (CKD). 25 mg/day of empagliflozin in patients with stage 3 CKD decreased the amount of patients with albuminuria progression from normalbuminuria to microalbuminuria (12.2% of patients in the empagliflozin group; 22.2% of patients in the placebo group) and from microalbuminuria to proteinuria (2% of patients in the empagliflozin group; 11.4% of patients in the placebo group) and increased the amount of patients with reverse changes (macroalbuminuria → microalbuminuria: 32.6% in the empagliflozin group; 8.6% in the placebo group; microalbuminuria → normoalbuminuria: 27.5% in the empagliflozin group; 21.4% in the placebo group) [32]. The study of 851 patients with type 2 DM showed that empagliflozin compared with placebo significantly decreased the urine albumin to creatinine ratio (ACR) in patients with initial microalbuminuria by 32% (p<0.001), in patients with initial proteinuria by 41% (p<0.001). The degree of ACR reduction did not depend on HbA1c, SBP, and body weight [33]. These results confirm that cardio- and nephroprotective metabolic effects of empagliflozin is not directly associated with its hypoglycemic effect.

In June 2017, the results of the CANVAS and CANVAS-Renal studies (CANVAS-R) were published. These studies assessed the effectiveness of another medication from SGLT2 inhibitors — canagliflozin. Canagliflozin has been studied in one of the largest cardiovascular outcome programs among all SGLT2 inhibitors. The CANVAS cardiovascular risk assessment study included 4,330 patients, and CANVAS-R trial with the study of renal outcomes included 5,812 patients. All patients had type 2 DM with HbA1c level of 7–10.5%, CVD or high risk of CVC development. All CANVAS study participants were randomized into 3 groups: two groups received 100 and 300 mg per day of canagliflozin, the third group received placebo. The average duration of drug administration was 4.3 years with following observation of about 5.7 years. Patients from CANVAS-R study were randomly assigned to once-daily placebo or canagliflozin 100 mg (with optional up titration to 300 mg) and placebo. Planned average of drug administration was approximately 1.8 years with the following observation for 2.5 years. The analysis of CANVAS and CANVAS-R studies showed that canagliflozin was superior to placebo and reduced combined primary endpoint by 14% (RR 0.86; 95% CI from 0.75 to 0.97; p= 0.02). At the same time, CVD risk decreased by 13% (RR: 0.87;

95% CI from 0.72 to 1.06), nonfatal MI risk by 15% (RR: 0.85; 95% CI from 0.69 up to 1.05) and the risk of nonfatal stroke by 10% (RR: 0.90; 95% CI from 0.71 to 1.15). Unfortunately, the assessment of the secondary endpoint, including all-cause mortality (RR 0.87; 95% CI from 0.74 to 1.01; p= 0.24), was not performed due to the lack canagliflozin benefits. The medication affected carbohydrate metabolism by reducing HbA1c by 0.58% (95% CI from –0.61 to –0.56; p<0.001) compared with placebo. Therefore, the need for additional hypoglycemic medications decreased by 9.3% (95% CI from –11.0 to –7.6). Canagliflozin also led to body weight decrease by 1.60 kg on average (95% CI from –1.70 to –1.51; p<0.001) and SBP regression by 3.93 mm Hg on average (95% CI, from –4.30 to –3.56; p<0.001), and DBP by 1.39 mm Hg (95% CI –1.61 to –1.17; p<0.001) compared with placebo. It is also remarkable that canagliflozin reduced the risk of hospitalization for heart failure by 33% (RR: 0.67; 95% CI from 0.52 to 0.87). The medication also showed significant nephroprotective effect. Patient taking canagliflozin, showed not only the slowdown in albuminuria progression (RR 0.73; 95% CI from 0.67 to 0.79), but also the regression of albuminuria severity compared with placebo group (293.4 versus 187.5 patients with albuminuria regression per 1000 patient-years; RR 1.70; 95% CI from 1.51 to 1.91). The combined endpoint for renal outcomes, consisting of 40% eGFR reduction, the need for RRT, or death from renal causes, was less common in the study group compared with placebo (5.5 versus 9.0 participants per 1000 patient-years, RR 0.60; 95% CI 0.47 to 0.77) [34]. Serious AEs occurred less frequent in patients from canagliflozin group compared with placebo group (104.3 versus 120.0 patients per 1000 patient-years; RR 0.93; 95% CI from 0.87 to 1.00; p= 0.04). There were no significant differences between the groups on AE leading to medication discontinuation (35.5 versus 32.8 per 1000 patient-years; RR 1.13; 95% CI from 0.99 to 1.28; p= 0.07). However, unanticipated increase in the risk of lower-limb amputation, predominantly at the level of the toe or metatarsal, was observed with canagliflozin (6.3 versus 3.4 per 1000 patient-years RR 1.97; 95% CI 1.41–2.75; p<0.001). Patients who already had amputation or had peripheral vascular disease had higher risk of amputation. Patients taking canagliflozin significantly more often reported male genital infection (34.9 versus 10.8 per 1000 patient-years, p<0.001), osmotic diuresis-related adverse events (34.5 versus 13.3; p<0.001), female genital mycotic infections (68.8 vs 17.5; p<0.001). Patients from canagliflozin group showed higher incidence of all fractures compared with placebo group (15.4 versus 11.9 per 1000 patient-years; RR 1.26; 95% CI from 1.04 to 1.52) [34, 35].

The DECLARE-TIMI 58 study investigated the efficacy of 10 mg per day dapagliflozin in 17160 patients with diabetes and CVD (40% of participants) or cardiovascular risk factors (CVR) (60% of participants). The median follow-up was 4.2 years. Medication did not decrease primary outcome rate defined as cardiovascular death, myocardial infarction, or ischemic stroke (8.8% versus 9.4%; RR 0.93; CI from 0.84 to 1.03; p= 0.17). In patients with history of MI (3584 patients), dapagliflozin significantly reduced the safety outcome by 16% (RR 0.84; 95% CI from 0.72 to 0.99; p=0.039). Dapagliflozin showed significant superiority over placebo by the primary efficacy outcomes defined as composite of cardiovascular death or hospitalization for heart failure (4.9% versus 5.8%; RR 0.83; 95% CI from 0.73 to 0 95; p= 0.005). These results can be explained by major reduction of hospitalization for heart failure decompensation by 27% (RR 0.73; 95% CI from 0.61 to 0.88). Serious adverse events were more often observed in the placebo group (2925 cases versus 3100 in the placebo group; 95% CI 0.91 from 0.87 to 0.96; p<0.001). However, adverse events leading to discontinuation of the drug prevailed in the dapagliflozin group (693 cases versus 592; 95% CI 1.15 from 1.03 to 1.28; p= 0.01). Episodes of hypoglycemia and acute renal damage were less common in the dapagliflozin group (58 versus 83 cases in the placebo group; 95% CI 0.68 from 0.49 to 0.95; p= 0.02) and (125 against 175 cases; 95% CI 0.69 from 0.55 to 0.87; p= 0.002). Dapagliflozin compared with placebo increased the risk of genital infection (76 versus 9 cases; 95% CI 8.36 from 4.19 to 16.68; p<0.001) and diabetic ketoacidosis (27 versus 12 cases; 95% CI 2, 18 from 1.10 to 4.30; p=0.02). It is remarkable that lower rate of bladder cancer with dapagliflozin than with placebo was observed (26 vs. 45 cases; 95% CI 0.57 from 0.35 to 0.93; p= 0.02). The rates of amputation, fracture, volume depletion, and hypersensitivity were balanced between the groups [36].

The CVD-REAL study, published in March 2017, evaluated the risk of hospitalization for heart failure and death from any cause in patients with type 2 DM treated with SGLT-2 inhibitors. The study included over 300,000 patients from 6 countries, who predominantly (87%) had no history of CVD. The results of the study showed that patients with type 2 DM taking SGLT-2 inhibitors such as dapagliflozin,

canagliflozin, empagliflozin for 4 years hadreduced hospitalization rate for heart failure by 39 % (p<0.001) and all-cause mortality by 51 % (p<0.001) compared with other sugar-lowering drugs. The frequency of events of the combined endpoint including hospitalizations for heart failure and death from any cause decreased by 46 % (p<0.001). Similar unidirectional results of the EMPA-REG OUTCOME and CVD-REAL studies indicate the reproduction of the positive effects of taking drugs from the SGLT-2 group in real clinical practice and their high efficiency not only in patients with type 2 DM and a high risk of CVC, but also in patients with lower CVR. Given the absence of significant differences between the efficacy of different SGLT-2representatives, researchers suggested the presence of class-specific cardioprotective effect of SGLT-2 inhibitors [37]. Similar results were obtained in 2019 in meta-analysis that included participants from the EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 studies. The effect of this group of medications was more pronounced in patients with atherosclerosis, that led to 11 % decrease of CVD risk (RR 0.89; 95 % CI from 0.83 to 0.96; p=0.001). The nephroprotective effect of medications was reflected in the decrease of combined "renal" endpoint events, including episodes of decreased renal function, terminal renal failure, and "renal" death by 45 % (RR 0.55; 95 % CI from 0.48 to 0.64; p<0.0001). Significant reduction in the risk of HF decompensation and related hospitalizations by 31 % (RR 0.69; 95 % CI from 0.61 to 0.79; p<0.0001) makes SGLT-2 inhibitors the only group of hypoglycemic medications with positive influence on the course of heart failure [38].

The results of presented studies show not only cardiovascular safety, but also the effectiveness of SGLT-2 inhibitors in patients with heart failure, including patients without DM. In 2019 the results of a randomized, placebo-controlled parallel DAPA-HF study were announced and influenced clinical guidelines for the management of patients with heart failure with reduced ejection fraction (HFrEF), regardless of the presence of DM. The study included 4744 patients with HF of II functional class (FC) and higher, left ventricular ejection fraction (LVEF)⩽40 % and a moderate increase of N-terminal pro–B-type natriuretic peptide ((NT-proBNP)⩾600 pg / ml (⩾400 pg / ml for patients with hospitalization for heart failure over the past 12 months;⩾900 pg / ml for patients with atrial fibrillation / flutter). The study did not include patients with SBP less than 95 mm Hg, type 1 DM, eGFR less than 30 ml / min / 1.73 m^2. The analysis of the results was carried out between four age subgroups: 636 patients (13.4 %) — under 55 years of age; 1242 patients (26.2 %) — aged 55 to 64 years; 1717 patients (36.2 %) — aged 64 to 74 years and 1149 (24.2 %) patients — 75 years and older. Great number of patients had HF of FC II according to NYHA; 1983 patients (41.8 %) had type 2 DM. In addition to optimal medication therapy for heart failure, including ACE inhibitors in 2661 patients (56.1 %); ARB — in 1307 patients (27.6 %); ARNI — in 508 patients (10.7 %); BAB — in 4558 patients (96 %); MRAs — in 3370 patients (71 %); diuretics — 4433 patients (93.4 %), patients received 10 mg per day of dapagliflozin or placebo. The primary outcome was composite of hospitalization for heart failure or CD. The additional secondary outcomes analyzed re-hospitalizations due to HF or CD, the change from baseline to 8 months in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), a composite of worsening renal function, which was defined as a sustained decline in the eGFR of 50 % or greater, end-stage renal disease (defined as a sustained [⩾28 days] eGFR of<15 ml per minute per 1.73 m^2, sustained dialysis, or renal transplantation), or renal death; and death from any cause. The effect of dapagliflozin compared with placebo did not dependon age. The dynamics of the analyzed outcomes was comparable between all subgroups. The primary outcome occurred in 16.3 % of cases in dapagliflozin group compared with 21.2 % in the placebo group (p<0.001). The primary outcome did not depend on the presence of DM (RR 0.75; 95 % CI from 0.63 to 0.90; absence of DM: RR 0.73; 95 % CI from 0.60 to 0.88; p= 0.80). The main results of the study are presented in table 2 [18].

A more significant decrease in the primary outcome compared with placebo was observed in patients aged 75 years and older (RR 0.68; 95 % CI from 0.53 to 0.88; p= 0.003) mainly due to decreased risk of hospitalization for HF: the dynamics of this parameter was more significant in the subgroups of 55–64 and 75 years and older (RR 0.56; 95 % CI from 0.40 to 0.78; p= 0.001 and RR 0.64; 95 % CI from 0, 47 to 0.88; p= 0.006). The same subgroups also showed significant regression of the secondary outcome (CD / re-hospitalizations for HF) by 32 % (RR of 0.68; 95 % CI from 0.51 to 0.91; p=0, 01)) and by 30 % (PP 0.70; 95 % CI from 0.53 to 0.94; p=0.016), respectively. The effect of dapagliflozin in the subgroup of patients 55 years and younger was comparable to placebo. In general, CD was recorded in 9.6 % of cases in the dapagliflozin group and in 11.5 % in the placebo group; hospital-

Table 2. **The main results of DAPA-HF study**

Results	Prespecifiedsubgroups							
	Age< 55 years (n=636)		Age 55–64 years (n=1242)		Age 65–74 years (n=1717)		Age≥ 75 years (n=1149)	
	Placebo n=296	Dapagliflozin n=340	Placebo n=630	Dapagliflozin n=612	Placebo n=887	Dapagliflozin n=830	Placebo n=558	Dapagliflozin n=592
CD or hospitalization for HF/ urgent visit for HF								
n (%)	53 (17.9)	52 (15.3)	131 (20.8)	96 (15.7)	184 (20.7)	135 (16.3)	134 (24.0)	103 (17.4)
RR (95% CI), p	0.87 (0.60–1.28), 0.49		0.71 (0.55–0.93), 0.012		0.76 (0.61–0.95), 0.015		0.68 (0.53–0.88), 0.003	
CD								
n (%)	29 (9.8)	28 (8.2)	70 (11.1)	60 (9.8)	107 (12.1)	79 (9.5)	67 (12.0)	60 (10.2)
RR (95% CI), p	0.85 (0.51–1.43), 0.54		0.87 (0.62–1.23), 0.45		0.78 (0.58–1.04), 0.089		0.83 (0.58–1.17), 0.29	
Hospitalization for HF/ urgent visit for HF								
n (%)	29 (9.8)	34 (10.0)	90 (14.3)	52 (8.5)	117 (13.2)	86 (10.4)	90 (16.1)	65 (11.0)
RR (95% CI), p	1.05 (0.64–1.72), 0.85		0.56 (0.40–0.78), 0.001		0.76 (0.58–1.01), 0.056		0.64 (0.47–0.88), 0.006	

izations for HF in dapagliflozin group — 9.7% versus 13.4% compared with placebo. The number of patients from dapagliflozin group with more than 5 points according to KCCQ questionnaire increased that significantly increased the total KCCQ score by 2.3 between baseline and month 8 compared with placebo (p<0.0001). The number of AEs after medication discontinuation increased with age in the placebo group. Renal function impairment was observed in 1.2% of patients from dapagliflozin group versus 1.6% of patients from placebo group (p= 0.17). Renal AEs were more frequent in the first two age subgroups (<55 and from 55 to 64 years old) with dapagliflozin, however, a greater increase in the number of serious renal adverse effects was recorded in placebo. Since the majority of patients received concomitant diuretic therapy, the comparable frequency of volume depletion is of particular importance [18]. The researchers concluded that dapagliflozin is highly effective in patients with HFrEF. The medication reduced the risk of CD and HF decompensation, improved quality of life with comparable tolerance with placebo in wide age range of patients including 75 years and older. Therefore, nowadays, dapagliflozin is recommended for patients with HFrEF with symptoms of HF despite treatment with ACE inhibitors, BAB and MRAs in order to reduce the risk of CD hospitalization for HF [2].

In the near future, we expect the results of the studies that assess the effect of empagliflozin on the HF progression — EMPERIAL and EMPEROR. The EMPERIAL study included patients with confirmed HF with preserved or reduced EF with and without type 2 DM [39–42].

The studies on the new medications with different mechanisms of action contribute the improvement of the prognosis in patients with HF. Only about 10% of patients took ARNI in the DAPA-HF study. Therefore, the effectiveness of the combination of ARNI and SGLT-2 inhibitors require further investigation.

Conclusion

The review of the studies presented in this article clearly demonstrates the clinical efficacy of SGLT-2 inhibitors in the treatment of patients with cardiovascular diseases. The results concluded that dapagliflozin may be recommended in patients with heart failure with reduced ejection fraction and symptoms of HFwho already take angiotensin-converting enzyme inhibitors, BAB and mineralocorticoid-receptor antagonists to reduce the risk of cardiovascular death and hospitalization for heart failure.

Conflict of interests: None declared.

References

1. Mareev V.Yu., Ageev F. T., Arutyunov G. P. et al. Clinical recommendations OSSN — RKO — RNMOT. Heart failure: chronic (CHF) and acute decompensated (ODSN). Diagnosis, prevention and treatment Cardiology. 2018; 58 (S6): 1–157 (8–164). DOI: 10.18087 / cardio. 2475. Russian.
2. V.S. Nesterov, I.A. Urvantseva, A. S. Vorobev. Chronic heart failure: modern problems and their solutions. LechaschiVrach Journal. 2018;7:11–14. Russian.
3. Algorithms for specialized medical care for patients with diabetes mellitus; Ed. by I.I. Dedova, M.V. Shestakova, A.Yu.

Mayorova. 9th edition. M.: UP PRINT; 2019. Diabetes mellitus. 2019; 22 (S1): 1–212. Russian.

4. Dedov I.I., Shestakova M.V., Galstyan G.R. The prevalence of type 2 diabetes in the adult population of Russia (NATION study). Diabetes. 2016; 19 (2): 104–112. doi: 10.14341/DM2004116–17. Russian.
5. MacDonald M.R., Petrie M.C., Hawkins N.M. et al. Diabetes, left ventricular systolic dysfunction, and chronic heart failure / Eur Heart J. 2008. № 29. P. 1224–1240.
6. Kovalenko E.V., Lozhkina M.V. Optimization of therapy for patients with chronic heart failure and metabolic disorders. Therapist. 2019; 10: 4–9. Russian.
7. Petar M. Seferovic, Piotr Ponikowski, Stefan D. Anker, Johann Bauersachs, Ovidiu Chioncel, John G.F. Cleland, Rudolf A. de Boer, Heinz Drexel, Tuvia Ben Gal, Loreena Hill, Tiny Jaarsma, Ewa A. Jankowska, Markus S. Anker, MitjaLainscak, Basil S. Lewis, Theresa McDonagh, Marco Metra, Davor Milicic, Wilfried Mullens, Massimo F Piepoli, Giuseppe Rosano, Frank Ruschitzka, Maurizio Volterrani, Adriaan A. Voors, GerasimosFilippatos, Andrew J.S. Coats. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019; 21 (10): 1169–1186.
8. Singh S., Loke Y.K., Furburg C.D. Long term risk of cardiovascular events with rosiglitazone: a meta–analysis. JAMA. 2007; 298 (10): 1189–95.
9. Lago R.M., Singh P.P., Nesto R.W. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomized clinical trials. Lancet. 2007; 370:1129–36.
10. Center for Drug Evaluation and Research. (n.d.). Non-Inferiority Clinical Trials., 2010. from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials
11. Scirica B.M., Bhatt D.L., Braunwald E. et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013; Vol. 369 (14): 1317–26.
12. White W.B., Cannon C.P., Heller S.R. et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013; Vol. 369 (14): 1327–35.
13. Green J.B., Bethel M.A., Paul S.K. et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. Am Heart J. 2013; Vol. 166 (6): 983–9.
14. Marso S.P., Daniels G.H., Brown-Frandsen K. et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375 (4): 311–22.
15. Marso S.P., Bain S.C., Consoli A. et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375 (19): 1834–44.
16. Pfeffer M.A., Claggett B., Diaz R. et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med. 2015;373 (23): 2247–57.
17. Holman R.R., Bethel M.A., Mentz R.J. et al. EXSCEL Study Group. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2017 Sep 28;377 (13): 1228–39.
18. McMurray J.V., Solomon S.D., Inzucchi S.E. et al Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction.N Engl J Med 2019; 381:1995–2008
19. Mogensen C.E. Maximum tubular reabsorption capacity for glucose and renal hemodynamcis during rapid hypertonic glucose infusion in normal and diabetic subjects. Scand J Clin Lab Invest. 1971;28 (1): 101–109.
20. Wright E.M., Hirayama B.A., Loo D.F. Active sugar transport in health and disease. J Intern Med. 2007; 261: 32–43.
21. Hummel C.S., Lu C., Loo D.D. et al. Glucose transport by human renal Na+/ D-glucose cotransporters SGLT1 and SGLT2. Am J Physiol Cell Physiol. 2011;300 (1): C14–21.
22. Hardman T.C. et al. Sodium-Glucose Co-Transporter 2 Inhibitors: From Apple Tree to 'Sweet Pee'. Curr Pharm Des. 2010; 16: 3830–3838.
23. Schwartz V.Ya. A new principle for the treatment of type 2 diabetes mellitus by stimulating glucosuria Problems of endocrinology. 2012; 58 (4): 54–57. doi: 10.14341/ probl201258454–57. Russian.
24. RahmanA., KittikulsuthW., FujisawaY., SufiunA., RafiqK., HitomiH. Et al. Effects of diuretics on sodium-dependent glucose cotransporter 2 inhibitor-induced changes in blood pressure in obese rats suffering from the metabolic syndrome. Journal of Hypertension. 2016;34 (5): 893–906.
25. Ferrannini E., DeFronzo R.A. Impact of Glucose-lowering Drugs on Cardiovascular Disease in Type 2 Diabetes Eur Heart J. 2015; 36 (34): 2288–2296.
26. Abdul-Ghani M.A., DeFronzo R.A. Inhibition of Renal Glucose Reabsorption: A Novel Strategy for Achieving Glucose Control in Type 2 // Diabetes Mellitus EndocrPract. 2008; 14: 782–790.
27. Verma S., McMurray J.J.V. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia.2018;61 (10): 2108–17.
28. Sano M. A new class of drugs for heart failure: SGLT2 inhibitors reduce sympathetic overactivity. Journal of Cardiology. 2018;71 (5): 471–6.
29. Zinman B., Wanner C., Lachin J.M., Fitchett D., Bluhmki E., Hantel S. et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. New England Journal of Medicine. 2015;373 (22): 2117–28.
30. Fitchett D., Zinman B., Wanner Ch. et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur. Heart J. 2016.

31. Wanner C., Inzucchi S. E., Lachin J. M. et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016;375 (4): 323–334.
32. Barnett A. H., Mithal A., Manassie J. et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. The Lancet Diabetes & Endocrinology. 2014;2 (5): 369–384.
33. Cherney D., Lund S. S., Perkins B. A. et al. The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. Diabetologia. 2016;59 (9): 1860–1870.
34. Neal B., Perkovic V., Mahaffey K. W., de Zeeuw D., Fulcher G., Erondu N. et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017;377 (7): 644–57.
35. Neal B., Perkovic V., Mahaffey K. W., et al. Optimizing the analysis strategy for the CANVAS Program: a prespecified plan for the integrated analyses of the CANVAS and CANVAS-R trials. Diabetes Obes Metab. 2017;19:926–935.
36. Rajasekeran H., Lytvyn Y., Cherney D. Z. Sodium-glucose cotransporter 2 inhibition and cardiovascular risk reduction in patients with type 2 diabetes: the emerging role of natriuresis. Kidney Int. 2016;89 (3): 524–526.
37. Kosiborod M. et al. Lower risk of heart failure and death in patients initiated on SGLT-2 inhibitors versus other glucose-lowering drugs: The CVD-REAL Study. Circulation. 2017.
38. Zelniker T. A., Wiviott S. D., Raz I., Im K., Goodrich E. L., Bonaca M. P. et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. The Lancet. 2019;393 (10166): 31–9.
39. EMPagliflozinoutcomEtRial in Patients With chrOnicheaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved)//clinicaltrials.gov/ct2/show/NCT03057951?term=emperor&rank=2. Last accessed January 2018.
40. EMPagliflozinoutcomEtRial in Patients With chrOnicheaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) // clinicaltrials.gov/ct2/show/NCT03057977?term=emperor&rank=1. Last accessed January 2018.
41. A phase III randomised, double-blind trial to evaluate the effect of 12 weeks treatment of once daily EMPagliflozin 10 mg compared with placebo on ExeRcise ability and heart failure symptoms, In patients with chronic HeArtFaiLure with preserved Ejection Fraction (HFpEF) (EMPERIAL-Preserved) // clinicaltrials.gov/ct2/show/NCT03448406?term=EMPERIAL&rank=1. Last accessed March 2018.
42. A phase III randomised, double-blind trial to evaluate the effect of 12 weeks treatment of once daily EMPagliflozin 10 mg compared with placebo on ExeRcise ability and heart failure symptoms, In patients with chronic HeArtFaiLure with reduced Ejection Fraction (HFrEF) (EMPERIAL-Reduced) // clinicaltrials.gov/ct2/show/NCT03448419?term=EMPERIAL&rank=2. Last accessed March 2018.