MODERN APPROACHES TO THE TREATMENT OF TYPE 2 DIABETES MELLITUS WITH CHRONIC HEART FAILURE

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Abstract. *Type 2 diabetes mellitus (DM2) and chronic heart failure (CHF) often occur together, exacerbating each other's course and worsening the patient's prognosis. The relationship between these diseases is determined by pathophysiological mechanisms, including insulin resistance, inflammation, and endothelial dysfunction.*

Diabetes mellitus, a widespread socially significant disease with numerous micro- and macrovascular complications, acts both as a risk factor for heart failure and as a condition that significantly exacerbates its course.

The relationship between diabetes and CHF is complex and is caused by several mechanisms. Diabetes contributes to the development of cardiomyopathy, impaired diastolic function of the heart and the progression of coronary artery atherosclerosis, which eventually leads to the development or worsening of CHF [9].

Keywords: *SGLT-2 inhibitors, chronic heart failure, type 2 diabetes mellitus, ejection fraction, NT-proBNP.*

Introduction. Studies confirm the high prevalence of CHF among patients with T2DM. According to a multicenter study, CHF is detected in 39.2% of patients with T2DM [13]. In a Russian study, concomitant DM2 was recorded in 20.2% of patients with CHF, which significantly increased the risk of heart attacks, strokes, and chronic renal failure [2].

According to scientific research, the cost of treating T2DM is about 569 billion rubles per year, of which 34.7% is due to complications from the cardiovascular system [1].

Patients with a combination of type 2 diabetes mellitus (DM2) and chronic heart failure (CHF), especially those with reduced ejection fraction (EEF), are at high risk of adverse clinical outcomes. The presence of T2DM worsens the course of CHF, enhances myocardial remodeling, promotes the progression of renal dysfunction, and significantly increases mortality from cardiovascular causes.

According to large cohort studies and meta-analyses, 5-year mortality in combination with DM2 and CHF exceeds 50% [5,8]. The prognosis is particularly unfavorable in patients with an uncontrolled glycemic profile, decreased renal function (GFR <60 ml/min/1.73 m2) and elevated levels of NT-proBNP.

DM2 increases the risk of hospitalization for CHF decompensation by about 1.5–2 times compared with patients without diabetes [10]. This is due both to the direct negative effect of hyperglycemia and insulin resistance on the myocardium, and to a more pronounced activation of neurohumoral mechanisms (RAAS, sympathetic system).

As is known, patients with type 2 diabetes have insulin resistance, in which tissues, including the myocardium, lose sensitivity to insulin. This reduces glucose utilization and increases the dependence of the heart muscle on free fatty acids (FFA), the metabolism of which is less efficient and leads to excess oxygen consumption [7].

Chronic hyperglycemia and protein glycation. Chronic hyperglycemia and protein glycation. Constantly elevated glucose levels lead to protein glycation and the formation of glycation end products (AGEs), which cause oxidative stress, inflammation, and myocardial fibrosis, contributing to the progression of CHF [3].

Activation of the renin-angiotensin-aldosterone system (RAAS). In patients with CHF and T2DM, hyperactivation of the RAAS is observed, which leads to vasoconstriction, sodium and water retention, myocardial hypertrophy, and deterioration of the pumping function of the heart [12].

Inflammation and oxidative stress. DM2 is accompanied by chronic low-level inflammation. Cytokines (for example, TNF-α, IL-6) damage the endothelium, increase fibrosis, impair diastolic function, and promote cardiac remodeling [15].

Diabetic cardiomyopathy. Even without severe atherosclerosis, patients with DM2 may develop diabetic cardiomyopathy characterized by diastolic dysfunction, left ventricular hypertrophy, and increased myocardial stiffness [4].

Microangiopathy and deterioration of myocardial perfusion. DM2 causes microvascular lesions, including capillary reduction and thickening of the basement membranes, which impairs myocardial perfusion and promotes the development of ischemia even in the absence of stenosing atherosclerosis [16].

In recent years, SGLT-2 inhibitors have attracted special attention, which demonstrate a pronounced cardioprotective effect, regardless of the presence of diabetes. Large RCTs, including DAPA-HF [11] and EMPEROR-Reduced [14], have shown a reduced risk of cardiovascular death and hospitalization for CHF in patients with SFV, including patients with T2DM.

The main risk factors for worsening the prognosis in patients with DM2 and CHF are: High levels of NT-proBNP (> 2000 pg/ml); Decreased LVEF <30%

- Chronic kidney disease (GFR <45 ml/min/1.73 m2)
- Elderly (>70 years old)
- A history of frequent hospitalizations
- Glycosylated hemoglobin (HbA1c) >8.5%
- Concomitant diseases: anemia, atrial fibrillation, obesity

Adequate management of such patients requires a multidisciplinary approach with an emphasis on optimizing drug therapy (SGLT-2 inhibitors, beta blockers, ace inhibitors/ACE inhibitors, mineralocorticoid antagonists), correction of glycemia, control of blood pressure and kidney function.

Treatment and modern approaches: the combination of DM2 and CHF requires an integrated approach combining glycemic control and correction of cardiovascular risk. In recent years, the treatment paradigm has undergone significant changes, especially due to the introduction of drugs with both hypoglycemic and cardioprotective effects.

The current ESC (2021) and AHA (2022) guidelines identify four key classes of drugs that are proven to improve prognosis.:

- RAAS inhibitors: ACE inhibitors (enalapril, ramipril) or angiotensin II / neprilysin receptor antagonists (ARNI – sacubitril/valsartan).

Beta blockers: bisoprolol, carvedilol, nebivolol or metoprolol succinate.

- Mineralocorticoid antagonists (MPas): spironolactone, eplerenone.
- SGLT-2 inhibitors: dapagliflozin, empagliflozin — regardless of the presence of diabetes.

Prescribing all four classes of drugs significantly reduces mortality and the frequency of hospitalizations [1].

SGLT-2 inhibitors are a new therapeutic strategy. Sodium-glucose cotransporter type 2 (SGLT-2) inhibitors were initially used as hypoglycemic agents, but numerous RCTs have proven their powerful cardioprotective and nephroprotective effects.

Basic drugs:

- Dapagliflozin — DAPA-HF study: reducing the risk of death or hospitalization due to CHF by 26% [2].
- Empagliflozin — EMPEROR-Reduced study: similar results, especially in the population with T2DM [6].

SGLT-2 inhibitors also reduce the progression of CKD, reduce edema, improve quality of life, and have a diuretic effect without significantly lowering blood pressure.

Glycemic control. The target HbA1c level in patients with CHF should be individualized (usually in the range of 6.5–7.5%), avoiding both hypoglycemia and severe hyperglycemia. Metformin remains the drug of choice with preserved renal function, however, in CHF, a combination with SGLT-2 inhibitors is preferred.

Thiazolidinediones (pioglitazone), which can cause fluid retention and worsen CHF, should be avoided [4].

Other important aspects: Diuretics — for signs of fluid retention, in the lowest effective doses. Statins are used in the presence of atherosclerotic CC disease. Blood pressure control — target level <130/80 mmHg (if tolerated). Assessment of kidney function is mandatory monitoring of GFR and potassium levels. Lifestyle modification — weight control, salt restriction, physical activity within tolerance limits.

Modern approaches to the treatment of DM2 in patients with CHF are based on the principles of individualization, organoprotection and evidence-based medicine. The use of drugs with proven effects on cardiovascular outcomes (primarily SGLT-2 inhibitors) has become a major achievement in recent years. An integrated and personalized approach significantly improves the prognosis and quality of life of such patients.

The aim of the study. Based on the above, we set ourselves the goal of conducting a comparative analysis of the effectiveness of dapagliflozin and empagliflozin therapy in patients with chronic heart failure with reduced ejection fraction and concomitant type 2 diabetes mellitus. We focused on assessing changes in the level of NT-proBNP, left ventricular ejection fraction, quality of life (KCCQ), and the frequency of hospitalizations for CHF decompensation during the six-month follow-up period.

Materials and methods. The study included 34 patients with a diagnosis of chronic heart failure (CHF) with reduced ejection fraction (LVEF < 40%) and concomitant type 2 diabetes mellitus (DM2). The inclusion criteria were stable CHF (NYHA class II–III), NT-proBNP level > 1000 pg/ml, age from 45 to 75 years, as well as stable glycemic therapy for ≥3 months prior to the start of the study. The patients were randomized into two therapeutic groups (17 people each): 1. The dapagliflozin group received the drug at a dose of 10 mg/day orally; 2. The empagliflozin group received the drug at a dose of 10 mg / day orally. Gender composition: 14 women and 20 men, distributed proportionally between the groups. The patients were followed up for 6 months. All participants continued to receive standard CHF therapy (beta blockers, ace inhibitors/ARNI, MRA, and diuretics, if necessary), which remained unchanged throughout the follow-up period.

Assessment of clinical outcomes:

• Functional status was assessed using the KCCQ scale (Kansas City Cardiomyopathy Questionnaire), with the change in score recorded by the 6th month.

• Hemodynamic parameters — NT-proBNP and left ventricular ejection fraction (LVEF) — were determined upon activation and after 6 months.

• The frequency of hospitalizations for CHF decompensation was recorded during follow-up.

• Side effects were monitored on each visit.

For statistical analysis, descriptive statistics methods, Student's t-test for comparing averages, and the $\chi 2$-test for categorical variables were used. The p value < 0.05 was considered statistically significant.

Results. During the six-month follow-up, we noted positive dynamics of clinical parameters in patients of both study groups. However, statistically significant differences in a number of key parameters were recorded between the groups receiving dapagliflozin and empagliflozin.

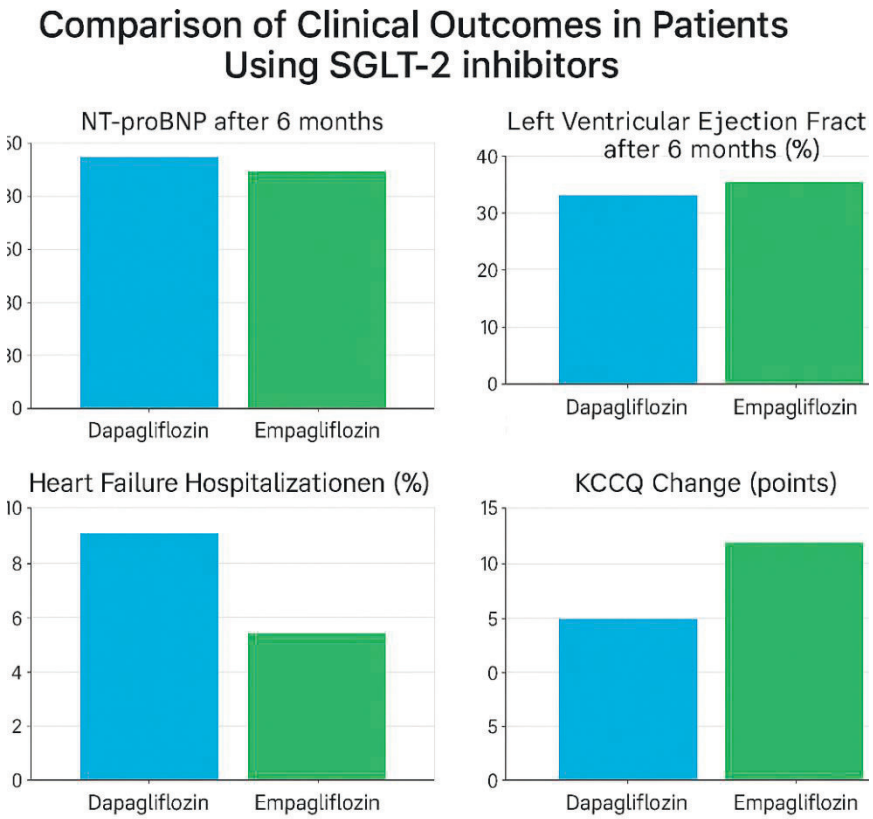
Table.

Comparison of clinical outcomes in patients treated with dapagliflozin and empagliflozin (n=34)

Indicator	Dapagliflozin (n=17)	Empagliflozin (n=17)	p-value
Average age, years	64 ± 7	63 ± 6	0.71
Men / Women	10 / 7	10 / 7	1.00
NT-proBNP, baseline (pg/ml)	2300 ± 480	2250 ± 450	0.66
NT-proBNP, after 6 months (pg/ml)	1800 ± 400	**1500 ± 350**	**0.02**
LV ejection fraction, % (initial)	31 ± 4	32 ± 5	0.53
LV ejection fraction, % (after 6 months)	35 ± 5	**39 ± 4**	**0.01**
CHF hospitalizations, n (%)	5 (29%)	**2 (12%)**	**0.04**
Δ KCCQ score (quality of life)	+8 ± 2	**+12 ± 3**	**0.01**
Side effects, n (%)	2 (11.8%)	1 (5.9%)	0.55

Note:

- The p-values were calculated using ANOVA and χ2-test.
- The best results among the groups are highlighted in bold.
- Δ KCCQ — change from baseline



We found that the level of NT-proBNP decreased in both groups, but the decrease was more pronounced in the empagliflozin group, from an average of 2,250 ± 450 to 1,500 ± 350 pg/ml, compared with 2,300 ± 480 to 1,800 ± 400 pg/ml in the dapagliflozin group (p = 0.02).

Ejection fraction The left ventricle in patients treated with empagliflozin increased from 32 ± 5% to 39 ± 4%, whereas in the dapagliflozin group the increase was from 31 ± 4% to 35 ± 5% (p = 0.01). We regard this as a more pronounced restoration of systolic function during empagliflozin therapy.

The frequency of hospitalizations for CHF decompensation during the observed period was 5 cases (29%) in the dapagliflozin group and 2 cases (12%) in the empagliflozin group (p = 0.04), which, in our opinion, indicates a more stable clinical course with the use of empagliflozin.

We also recorded an improvement in quality of life on the KCCQ scale: in the empagliflozin group, the increase was 12 ± 3 points, while in the dapagliflozin group it was 8 ± 2 points (p = 0.01).

Side effects were rare and had no serious clinical consequences. We registered adverse reactions in 2 (11.8%) patients in the dapagliflozin group and in 1 (5.9%) patient in the empagliflozin group (p = 0.55), the differences were statistically insignificant.

Thus, according to the results of our analysis, empagliflozin demonstrated a more pronounced positive effect on functional and biomarker parameters in patients with CHF and T2DM, with a similar safety profile with dapagliflozin.

Conclusion. Thus, the presence of diabetes in patients with CHF requires special attention and an integrated approach to treatment aimed at both glycemic control and optimizing therapy for heart failure.

SGLT-2 inhibitors are an effective component of CHF therapy with reduced ejection fraction. Empagliflozin may have a more pronounced beneficial effect on cardiovascular outcomes in this population.

Thus, our data allow us to recommend empagliflozin as the preferred drug in the combination therapy of CHF in patients with concomitant DM2, subject to individual tolerability and compliance with treatment standards.

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