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The use of Dapagliflozin in Acute Decompensated Heart Failure: Results of the Randomized Study

Aim	To determine the effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on kidney function in acute decompensated heart failure (ADHF).
Material and methods	A controlled randomized study on the dapagliflozin treatment in ADHF was performed. Patients were randomized to a main group (standard therapy supplemented with dapagliflozin) or a control group (standard therapy for ADHF). The primary endpoint was the development of acute kidney injury (AKI). 200 patients were included (mean age, 74±12 years; 51% men). 31% of patients had type 2 diabetes mellitus (DM2). Mean left ventricular ejection fraction (LV EF) was 47±14%; in 44.5% of patients, LV EF was less than 45%. Median concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) was 5225 [3120; 9743] pg/ml, glomerular filtration rate (GFR) was 51 [38; 64] ml/min/1.73 m^2.
Results	In-hospital mortality was 6.5%. Analysis of the dynamics of body weight loss showed significant differences (4200 [2925; 6300] g vs. 3000 [1113; 4850] g; p=0.011) in favor of the dapagliflozin group. The requirement for increasing the daily dose of furosemide and adding an another class diuretic (thiazide or acetazolamide) did not differ between the groups. However, median furosemide dose during the stay in the hospital was lower in the dapagliflozin group (80 [67; 120] mg vs. 102 [43; 120] mg; p=0.016). At 48 hours after randomization, GFR significantly decreased in the dapagliflozin group (– 5.5 [– 11; 3] ml/min/1.73 m^2) compared to the control group (– 0.3 [– 4; 5] ml/min/1.73 m^2, p=0.012). Despite this, GFR did not differ between the groups at discharge (51 [41; 66] ml/min/1.73 m^2 and 49 [38; 67] ml/min/1.73 m^2, respectively; p=0.84). In the dapagliflozin group, frequency of AKI episodes was not increased compared to the control group (13 and 9.4%, respectively; p=0.45).
Conclusion	The dapagliflozin treatment in ADHF is associated with more pronounced body weight loss and lower average doses of loop diuretics during the period of stay in the hospital, with no associated clinically significant impairment of renal function.

Keywords	Chronic heart failure; cardiorenal syndrome; acute decompensated heart failure; pharmacology; cardiovascular diseases; dapagliflozin
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Introduction

Acute decompensated heart failure (ADHF) is one of the leading causes of hospitalizations, and it is characterized by an unfavorable prognosis [1]. Treatment of ADHF is based on loop diuretics. However, 30% of patients do not achieve a adequate reduction in congestion due to the development of cardiorenal syndrome (CRS). Acute CRS, or type I CRS, is acute kidney injury (AKI) due to the deterioration of cardiac function manifesting as a decrease in kidney function and the development of diuretic resistance [2]. Oral hypoglycemic agents, such as inhibitors of sodium/glucose cotransporter 2 (SGLT2), reduced cardiovascular mortality and the risk of hospitalization for chronic heart failure (CHF) in patients with type 2 diabetes mellitus (DM) [3]. There are results of two studies of using SGLT2 inhibitors in patients with heart failure with reduced ejection fraction (HFrEF) and without type 2 DM. The Study to Evaluate the Effect Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Chronic Heart Failure (DAPA-HF) [4] evaluated the efficacy of dapagliflozin in combination with the recommended drug therapy for CHF, and the EMPEROR-Reduced

(EMPagliflozin in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction) study [5] investigated the efficacy of empagliflozin. Both studies demonstrated a decrease in the number of hospitalizations for CHF and cardiovascular mortality during the used of SGLT2 inhibitors irrespective of the presence of type 2 DM [6].

Despite the advances in the use of SGLT2 inhibitors for CHF, the issue regarding the use of this group of drugs in ADHF remains. According to Damman et al. [7], empagliflozin had no effect on dyspnea, N-terminal pro-brain natriuretic peptide (NT-proBNP), and response to diuretic therapy in ADHF, but was safe and reduced mortality and rehospitalizations within 60 days after the discharge.

A temporary decrease in glomerular filtration rate (GFR) observed during the administration of SGLT2 inhibitors [7], which may be associated with a worse prognosis, raises concern [8].

Objective

Evaluate the effect of SGLT2 inhibitors on renal function in patients with ADHF.

Material and methods

An open-label controlled randomized study was conducted in the emergency care hospital from 06.12.2020 to 01.11.2021. The study protocol was approved by the local ethics committee of the I. M. Sechenov First Moscow State Medical University.

ADHF was diagnosed based on the presence of congestion (pulmonary edema, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, neck vein bulging, hepatomegaly, ascites, hepatojugular reflux) and the need for intravenous administration of loop diuretics. The diagnosis was confirmed by echocardiography (left ventricular ejection fraction (LVEF) <50%) or criteria of LV diastolic dysfunction (ratio of peak mitral inflow velocity to peak early diastolic mitral annular velocity (E/e'>14); left atrial volume index >34 ml/m^2; peak tricuspid regurgitation velocity >2.8 m/s) [9], and the dilation of inferior vena cava which does not collapse with inspiration.

Inclusion criteria:

Clinically diagnosed ADHF, the need for intravenous administration of loop diuretics on day one of hospitalization, age>18 years. Patients were included in the study after signing the informed consent.

Exclusion criteria:

- Cardiogenic shock (systolic blood pressure <90 mm Hg for more than 30 minutes, mean blood pressure less than 65 mm Hg for more than 30 minutes or the need for vasopressors to maintain systolic pressure ≥ 90 mm Hg; signs of critical organ hypoperfusion – abnormal mental status, cold skin, decreased urine output < 30 ml/h, blood lactate >2 mmol/l);
- Active urinary infection;
- History of type 1 DM, episodes of diabetic ketoacidosis or hypoglycemia requiring emergency treatment;
- Pacemaker rate>20% per day;
- Regular use of any SGLT2 inhibitor within 1 month before the hospitalization;
- Potentially reversible causes of heart failure, such as inflammatory myocardial diseases, pericarditis, atrial myxomas, anemia, hyperthyroidism and hypothyroidism, coronary artery disease (CAD), less than 1 month since the onset of acute myocardial infarction (MI); myocardial failure as a component of multiple organ failure, heart defects;
- GFR < 30 ml/min/1.73 m^2 (CKD EPI);
- Individual hypersensitivity to drug components;
- Liver failure (Child-Pugh class C)
- Mental illness (inability to sign the informed consent);
- Pregnancy, lactation.

Protocol of the study

Screening and inclusion were performed within the first 24 hours in hospital. Patients were randomized using sealed envelope method. In the study group, patients received dapagliflozin 10 mg once a day in addition to the standard therapy. Control patients received standard therapy for ADHF based on intravenous loop diuretics [10].

Intravenous administration of furosemide 40 mg was allowed not later than in the first 24 hours from the admission (provided that the patient had not previously received regular loop diuretics). If loop diuretics were used regularly within 1 month before hospitalization, the daily dose was increased more than 2-fold and switched to intravenous administration.

Patients' clinical status and biochemical data (creatinine, urea, uric acid, and electrolytes) were evaluated at randomization, 48 hours after randomization, and at the discharge. Changes in body weight were measured every morning on an empty stomach as an indicator of the efficacy of diuretic therapy during hospital treatment.

Primary endpoint

Development of AKI – blood creatinine level ≥26.4 μmol/L for 48 hours (KDIGO) [11].

Secondary endpoints

Death in hospital. Diuretic resistance (the need for more than 2-fold daily dose of furosemide compared to

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the baseline or the need to add diuretics of another class [12]). Loss of weight during hospital stay. Rehospitalization or all-cause death within 30 days of the discharge.

Follow-up after the discharge

Thirty days after the discharge, patients or their relatives were contacted by phone to find out about cases of rehospitalization and death.

Two hundred patients were included (n=94 in the dapagliflozin group, n=106 in the control group). Mean age was 74±12 years, and 51% of patients were male. Mean LVEF was 47±14%, 44% of patients had preserved LVEF, and 44.5% had LVEF < 45%. CHF was of ischemic origin in 48% of patients. History of type 2 DM was established in 31% of patients. Median NT-proBNP level was 5225 [3120; 9743] pg/ml. GFR was 51 [38; 64] ml/min/1.73m^2.

58% of patients had the history of rehospitalization for CHF. The groups were comparable in the main clinical and functional characteristics (Table 1).

Statistical analysis

All quantitative variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed variables were expressed as the means and the standard deviations. Non-normally distributed variables were described by the median and interquartile range between 25th and 75th percentiles and compared using non-parametric tests. The groups were compared by quantitative variables using the Student's t-test (normal distribution) and the Mann-Whitney test (non-normal distribution). Categorical variables were expressed as the absolute and relative values and were compared the chi-square test or Fisher's exact test. SPSS 22.0 for Windows (SPSS Inc., USA) was used for the statistical analysis. The differences were statistically significant with p value being less than 0.05.

Results

Outcomes of hospital treatment

Hospital mortality was 6.5% – 7 (7.4%) and 6 (5.6%) patients died in the control group and the dapagliflozin group respectively (p=0.26).

The analysis of weight loss revealed statistically significant intergroup differences (4200 [2925; 6300;] g vs 3000 [1113; 4850] g; p=0.011) favoring the dapagliflozin group.

The need to increase the daily dose of furosemide and the addition of diuretics of another class (thiazides or acetazolamide) did not differ between the groups (p=0.3 and p=0.6 respectively). There were also no differences

Table 1. Baseline characteristics of the patients examined

Parameter	Dapagliflozin group	Control group	p
Age, years	73±12	75±12	0.13
Male, n (%)	53 (56)	49 (48)	0.15
History of CHF, n (%)	60 (64)	56 (53)	0.12
Myocardial infarction, n (%)	44 (47)	49 (48)	0.93
PCI, n (%)	21 (22)	15 (15)	0.13
CABG, n (%)	4 (4)	5 (5)	0.88
DM type 2, n (%)	27 (29)	35 (34)	0.61
Glucose, mmol/L	7.4±3	7.5±3	0.78
Arterial hypertension, n (%)	90 (96)	101 (99)	0.88
Atrial fibrillation, n (%)	61 (65)	72 (71)	0.65
Permanent pacemaker, n (%)	3 (3.2)	5 (4.7)	0.58
GFR, ml/min/1.73m^2	52 [39; 77]	48 [37; 60]	0.07
GFR < 60 ml/min/1.73 m^2, n (%)	30 (32)	40 (38)	0.39
Anemia, n (%)	47 (50)	61 (58)	0.29
Pleural effusion, n (%)	56 (60)	70 (72)	0.34
Edema syndrome, n (%)	56 (60)	70 (69)	0.34
SBP, mm Hg	131±16.5	130±18	0.28
DBP, mm Hg	79±8.5	79±9.6	0.98
HR, bpm	94±19	98±22	0.14
Outpatient treatment			
ACE inhibitors/ ARBs, n (%)	71 (76)	72 (71)	0.23
Beta-blockers, n (%)	61 (65)	65 (64)	0.6
Spironolactone, n (%)	44 (47)	37 (36)	0.087
Loop diuretics, n (%)	59 (63)	55 (54)	0.12
Echocardiography			
LVEF ≥ 50 %, n (%)	40 (42.5)	47 (44)	0.065
LVEF 41–49%, n (%)	14 (15)	25 (24)	0.12
LVEF <40%, n (%)	40 (42.5)	34 (32)	0.13
Mean LVEF, %	45±15	48±14	0.15

CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; SBP, systolic blood pressure; DM, diabetes mellitus; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; CHF, chronic heart failure; PCI, percutaneous coronary intervention; HR, heart rate.

Table 2. Changes in GFR in treated patients

Parameter	Dapagliflozin group	Control group	p
Changes in GFR (randomization; 48 hours after randomization), ml/min/1.73 m²	–5.5 (–11; 3)	–0.3 (–4; 5)	0.012
Changes in GFR (48 hours after randomization, day of discharge), ml/min/1.73 m²	–1 (–5.6; 7.6)	2 (–3.75; 7)	0.3
Changes in GFR (admission, discharge), ml/min/1.73 m²	–5 (–15; 4)	4.25 (1.25; 8.5)	0.02
GFR, ml/min/1.73m²			
• At randomization	52 [39; 77]	48 [37; 60]	0.07
• 48 hours after randomization	50 [42; 67]	48 [38; 68]	0.24
GFR at discharge	51 [41; 66]	49 [38; 67]	0.84

GFR, glomerular filtration rate.

in the incidence of diuretic resistance – 24 (26%) and 32 (30%) in the dapagliflozin group and in the control group respectively (p=0.46). However, dapagliflozin was associated with lower doses of furosemide during hospital treatment (80 [67; 120] mg versus 102 [43; 120] mg; p=0.016).

At randomization, GFR was 52 [39; 77] ml/min/1.73 m² and 48 [37; 60] ml/min/1.73 m² in the dapagliflozin group and the control group respectively (p=0.07). In 48 hour, GFR decreased in the dapagliflozin group (– 5.5 [– 11; 3] ml/min/1.73 m²) compared to the control group (– 0.3 [– 4; 5] ml/min/1.73 m²; p=0.012), which was not accompanied by statistically significant intergroup differences in GFR (50 [42; 67] ml/min/1.73 m² in the dapagliflozin group and 48 [38; 68] ml/min/1.73 m² in the control group; p=0.24). At the discharge, GFR did not differ in the dapagliflozin group and the control group (51 [41; 66] ml/min/1.73 m² and 49 [38; 67] ml/min/1.73 m²; p=0.84). During hospital treatment, GFR decreased statistically significant in the dapagliflozin group (– 5 [– 15; 4] ml/min/1.73 m² versus 4.25 [1.25; 8.5] ml/min/1.73 m²; p=0.02; Table 2).

There were no episodes of deterioration in renal function (blood creatinine increased by ≥26.4 μmol/l within 48 hours) in the study group versus the control group (13% and 9.4%, respectively; p=0.45). Discontinuation of dapagliflozin due to GFR < 30 ml/min/1.73 m² was necessary in 23 (11.5%) patients; treatment was resumed after the normalization of creatinine levels in 14 (60%) patients.

During follow-up, none of the patients had severe hypoglycemia, diabetic ketoacidosis and genitourinary infections.

We collected information over telephone from 187 (94%) patients (96% in the dapagliflozin group and 92% in the control group). The 30-day mortality was 13 (14%) and 18 (17%) patients in the dapagliflozin group and in the control group respectively (p=0.54); the number of rehospitalizations was 24 (24.5%) and 30 (28%) respectively (p=0.66). Information on hospitalization outcomes and 30 day prognosis is presented in Table 3.

Discussion

Decreased response to diuretics and deterioration of renal function as manifestations of CRS significantly limit the treatment options for patients with ADHF [13]. Diuretic resistance can be overcome by using of high-dose furosemide, which is associated in such patients with a worse prognosis. The symptoms of fluid overload can be alleviated with diuretics of other classes (thiazide, thiazide-like diuretics, and carbonic anhydrase inhibitors), but the results of their combined use with loop diuretics is limited to better diuresis without improving the prognosis [14].

Table 3. Outcomes of hospital treatment

Parameter	Dapagliflozin group	Control group	p
Number of deaths, n (%)	7 (7.4)	6 (5.6)	0.26
Death within 30 days, n (%)	13 (14)	18 (17)	0.54
Rehospitalization within 30 days, n (%)	24 (24.5)	30 (28)	0.66
Diuretic resistance, n (%)	24 (26)	32 (30)	0.46
Furosemide dose increase, n (%)	15 (16)	23 (22.5)	0.3
Addition of diuretics of another class, n (%)	13 (14)	12 (11.8)	0.6
Doses of furosemide during hospital stay, mg	80 [67; 120]	102 [43; 120]	0.016
Deterioration of renal function, n (%)	12 (13)	10 (9.4)	0.45
Changes in body weight, g	4200 [2925; 6300;]	3000 [1113; 4850]	0.011

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Our findings suggest a better response to diuretic therapy in the dapagliflozin group. Firstly, smaller doses of furosemide were used in the dapagliflozin group. Secondly, dapagliflozin was associated with greater weight loss in patients. At the same time, greater changes in body weight over during hospital stay was shown in the recent study EMPULSE (Effects of Empagliflozin on Symptoms, Physical Limitations and Quality of Life in Patients Hospitalized for Acute Heart Failure), which evaluated the efficacy of empagliflozin in ADHF [15].

A decrease in GFR 48 hours after starting dapagliflozin was expected, although it was the main reason for discontinuing the drug. The findings confirm the literature data available on the reduction of GFR after the initiation of SGLT2 inhibitors [7]. In the study by Boorsma et al. [16], the addition of SGLT2 inhibitors to the recommended therapy of ADHF was also associated with a decrease in GFR in the empagliflozin group compared to placebo on Day 4 of hospital stay. The decrease in GFR is likely to be associated with several factors: firstly, due to the inhibition of sodium reabsorption in the proximal convoluted tubule, its delivery to macula densa increases, which increases the release of adenosine, which in tern causes afferent glomerular arteriole narrowing. Secondly, glomerular hypertension is reduced due to a block of the reabsorption of glucose with sodium. The resulting decrease in GFR and filtration fraction manifests as a decrease in GFR followed by its stabilization [17]. In our study, GFR did not differ in the dapagliflozin group and the control group by the time of the discharge from hospital. In the study be Damman et al. [7] and the EMPULSE study [15], the use of SGLT2 inhibitors was not associated with an increase in the incidence of AKI, which is consistent with our data.

At the time of the study, dapagliflozin was recommended in the absence of type 2 DM only for LVEF <40%. However, patients were included in our study irrespective of the levels of LVEF. This decision was made first of all in line with the leading role of inflammation in the pathogenesis of HFpEF, where SGLT2 inhibitors can be beneficial due to a block of NH1 receptors [18]. Secondly, SGLT2 inhibitors were shown to improve LV diastolic function [19]. In the EMPA-REG OUTCOME study, empagliflozin also reduced the number of rehospitalization and mortality in patients with type 2 DM regardless of LVEF [20]. Thirdly, ADHF treatment is on diuretic therapy irrespective of LVEF [2], and the natriuretic properties of SGLT2 inhibitors can be useful [3].

Despite the fact that the design of study is generally similar to that of the EMPULSE study [15], there are some differences that could affect the results: firstly, we included patients within the first 24 hours in hospital, while randomization and inclusion took place in the EMPULSE study on Days 2–5 of hospital stay. Secondly, the use of stable doses of loop diuretics for 6 hours before randomization was an inclusion criteria in the EMPULSE study. We have no such criterion regarding dose stability.

Mean LVEF was 47% in our study, and 44% of patients had preserved LVEF. Thus, our population differs from that in the study by Damman et al. [7] and EMPULSE [15], where mean LVEF was 36% and 31% respectively. This may explain the difference in the results obtained. Indirect evidence that LVEF could affect our findings may be the results of SGLT2 inhibitor use in patients with stable CHF. In a recent study including patients with LVEF ≥ 40%, a decrease in the composite endpoint of all-cause mortality and the rate of hospitalizations for ADHF was the empagliflozin group [21]. However, the results obtained were mainly determined by a reduction in the number of hospitalizations rather than deaths. It should be emphasized that 12.5% of our patients had LVEF>65%. According to the pooled analysis [22], the effect of empagliflozin on outcomes in patients with CHF was significant and comparable in LVEF < 65% and decreased in higher LVEF.

In our study, there were no differences in the hospital prognosis between the groups. The 30 day post-discharge prognosis was also evaluated. There were less deaths and hospitalizations in the dapagliflozin group, but the difference was not significant in the obtained sample (p=0.54 and p=0.66 respectively). Thus, we did not establish that dapagliflozin improved prognosis in ADHF. Given that almost 44% of the patients included had LVEF>50%, and taking into consideration the recent study on HFpEF [21], we can assume that our results were largely determined by the patient population. At the same time, our findings are consistent with the available data on the effect of SGLT2 inhibitors on the prognosis for ADHF patients after the discharge: the difference in the number of rehospitalizations and deaths was achieved by Day 60 after the discharge from hospital in the study Damman et al. [7] and Day 90 in the EMPULSE study [15].

Limitations

Small sample of patients limits the power of the study. Since the study did not include patients with GFR < 30 ml/min/1.73 m^2 and patients needing intravenous inotropic drugs and vasodilators, the results cannot be

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applied to the general population of ADHF patients. The study was not placebo-controlled.

Despite the fact that 26% of patients had LVEF < 35%, there were no patients who took angiotensin receptor-neprilysin inhibitors during outpatient treatment and patients with implantable cardioverter-defibrillator and cardiac resynchronization therapy.

Due to the lack of a common treatment protocol, it was up to attending physicians to make decisions on diuretic doses. The duration of hospital stay was reduced due to the COVID-19 pandemic. Since the study protocol did not include clinical examination of patients after the discharge, we do not have data on changes in laboratory data and the clinical condition of patients after the discharge.

Conclusion

Adding dapagliflozin to standard therapy for acute decompensation of cardiac failure is associated with a more pronounced decrease in body weight and lower doses of loop diuretics during hospital stay. The incidence of acute kidney injury did not increase in the dapagliflozin group. Further study of using SGLT2 inhibitors in acute decompensated heart failure is necessary in a larger sample of patients to confirm the results obtained.

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