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Cardiometabolic Effects of Empagliflozin in Patients Undergoing Elective Percutaneous Coronary Intervention for Type 2 Diabetes Mellitus

Aim	To evaluate cardiometabolic effects of empagliflozin in patients with ischemic heart disease and type 2 diabetes mellitus (DM) following elective percutaneous coronary intervention (PCI).
Materials and Methods	Patients meeting the inclusion/non-inclusion criteria were randomized into two groups of equal number using simple randomization with successively assigned numbers. Group 1 included 37 patients (18 men and 19 women) who gave their consent for the treatment with empagliflozin 10 mg/day in addition to their previous hypoglycemic therapy. The drug administration started one month prior to the elective PCI and continued for the next 11 months (treatment duration, 12 months). Group 2 (comparison group) consisted of age- and DM duration-matched patients (37 patients; 18 men and 19 women) who continued on their hypoglycemic therapy previously prescribed by endocrinologists during the entire study period. Before the study, 36.11% patients of the empagliflozin group and 27.03% of the comparison group had unsatisfactory glycemic control as shown by the level of glycated hemoglobin (HbA1c).
Results	At 6 and 12 months of the study, fasting glycemia and HbA1c were significantly lower in the empagliflozin treatment group. The groups were comparable by the incidence of adverse outcomes: 8 (22.24%) patients in the empagliflozin group and 10 (27.04%) patients in the comparison group ($p=0.787$). The 12-month empagliflozin treatment reduced total cholesterol (C) by 5.56% ($p<0.05$), low density lipoprotein (LDL) C by 3.67% ($p<0.05$), visceral adipose tissue area (VATA) by 5.83% ($p<0.05$), and subcutaneous adipose tissue area (SATA) by 3.54% ($p<0.05$).
Conclusion	The empagliflozin treatment for 30 days prior to and after elective PCI can enhance the effectiveness of myocardial revascularization due to the demonstrated beneficial cardiometabolic effects.
Keywords	Percutaneous coronary intervention; diabetes mellitus; hypoglycemic drugs; empagliflozin
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Glucose-lowering agents are currently under active discussion. Their efficacy for the prevention of cardiovascular complications and reduction of mortality in patients with diabetes mellitus (DM) type 2, such as glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter 2 (SGLT2) inhibitors, was proven in randomized clinical studies [1–5].

The implementation of their positive effects are associated not only with the control of glycemia, but also with a wider range of effects on various metabolic processes, including fat metabolism [6]. In this regard, is highly prospective to study the effects of antidiabetic drugs with pleiotropic effects, such as SGLT2 inhibitors, aimed at minimizing the risk of cardiovascular complications in DM type 2 patients with a history of PCI, being a full-fledged alternative to CABG for patients in need of myocardial revascularization following the current clinical guidelines [7].

Objective

Evaluate cardiometabolic effects of empagliflozin in patients with CAD and DM type 2 after elective PCI.

Material and methods

A prospective randomized comparative study was conducted in the Kemerovo State Medical University (Russia). Patients were recruited in the Research Institute of Complex Problems of Cardiovascular Diseases from November 2016 to May 2019. The study protocol was developed following the

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Good Clinical Practice and the Declaration of Helsinki. The study was approved by the local ethics committee.

Based on the criteria provided below, a total of 74 patients with DM type 2 previously diagnosed according to the criteria of the World Health Organization (WHO) [8], to whom elective primary PCI for stable CAD was indicated, were included in the study.

Inclusion criteria: indications for elective PCI, DM type 2 diagnosed in accordance with the WHO criteria, signed informed consent to participate in the study. Exclusion criteria: age less than 18 years and older than 85 years; body weight more than 130 kg; a history of PCI failure; previous myocardial revascularization (CABG or PCI); ACS during index hospitalization; myocardial infarction within 3 months before the study; decompensated CHF; exacerbation of a concomitant disease; a history of valve replacement; heart valve disease requiring surgery; glomerular filtration rate (GFR; CKD-EPI–Chronic Kidney Disease Epidemiology Collaboration, 2009, modification 2011) less than 45 mL/min/1.73m^2; pregnancy, breastfeeding.

Clinical and demographic characteristics of subjects are provided in Table 1.

All eligible subjects were divided into two equitable groups by simple randomization using sequential numbers. Group 1 included 37 (18 male and 19 female) patients who agreed to receive empagliflozin 10 mg/day in addition to the administered glucose-lowering therapy. The drug was administered for 1 month before and 11 months after the scheduled PCI (a total duration of treatment was 12 months). Group 2 (control) included 37 (18 male and 19 female) patients, comparable in age and duration of DM, who continued their usual glucose-lowering therapy throughout the study.

Standard therapy for CAD, including dual antiplatelet therapy, was ordered for all patients. The structure of glucose-lowering therapy for the general patient sample is presented in Table 2.

All patients underwent anthropometric assessment of obesity (BMI, WC, HC), laboratory testing of carbohydrate metabolism (glucose, glycated hemoglobin HbA1c), lipid metabolism (TC, LDL, HDL, TG), serum creatinine, high-sensitivity C-reactive protein (hsCRP). Multislice computed tomography (MSCT) scan was performed to assess obesity at baseline and 12 months after randomization. Baseline target level of HbA1c was determined in all patients based on age, life expectancy, the presence of a cardiovascular disease (CVD), and the risk of developing severe hypoglycemia [9].

One month after randomization, fasting venous glucose and HbA1c were measured. Serum creatinine levels were determined and GFR was calculated a day before and 48 hours after PCI.

Empagliflozin and metformin, if administered, were discontinued 48 hours before PCI to prevent acute kidney injury and lactic acidosis. During the withdrawal of glucose-lowering drugs, hyperglycemia was corrected using short-acting insulin.

Enzyme immunoassay was used to determine serum hsCRP (hsCRP Monobind test system), adiponectin

Table 1. Main clinical and anamnestic data of patients of the general sample (n=74)

Parameter	Value
Male, n (%)	36 (48.65)
Age, years (Me [Q1; Q3])	61 [57; 64]
BMI, kg/m2 (M ± SD)	33.28±5.94
WC, cm (M ± SD)	105.27 ± 15.05
HC, cm (M ± SD)	108.91±13.62
WC/HC (M ± SD)	0.97±0.07
Smoking, n (%)	25 (33.78)
Arterial hypertension, n (%)	74 (100)
History of CVA, % (n)	7 (9.46)
Duration of CAD history, years (Me [Q1; Q3])	3.0 [2.0; 5.0]
Duration of DM history, years (Me [Q1; Q3])	5.5 [3.0; 9.0]
History of myocardial infarction, n (%)	37 (50)
Angina pectoris, n (%)	
FC I	5 (6.76)
FC II	44 (59.46)
FC III	12 (16.22)
FC IV	0
CHF, n (%)	
FC I	0
FC II	70 (94.59)
FC III	4 (5.41)
FC IV	0
AF, n (%)	7 (9.46)
Multi-vessel coronary disease, n (%)	37 (50)
Coronary artery lesion, SYNTAX score (Me [Q1; Q3])	12 [7; 17]

WC, waist circumference; HC, hip circumference; CVA, cerebrovascular accident.

Table 2. Treatment of DM in patients of the general sample before inclusion in the study

Parameter	Value, n (%)
Nutrition therapy	11 (14.86)
OGLD	48 (64.86)
Combination therapy (insulin + OGLD)	9 (12.16)
Insulin therapy	6 (8.11)

OGLD, oral glucose-lowering drugs.

(BioVendor Human Adiponectin ELISA test system), and leptin (BioVendor test system).

Urinalysis was performed using UrineRS H10 test strips in a CL-500 automated urine analyzer. The urine sediment was examined using microscopy to assess bacteriuria.

Adipose tissue was quantified by multislice CT scanning on a 64 slice tomograph, at the LIV–LV level in the craniocaudal view. Area and volume of abdominal adipose tissue were evaluated and divided into visceral and subcutaneous components. Visceral obesity was diagnosed if visceral fat area (VFA) was more than 130 cm^2 [10].

During the study period (12 months), data on the development of the following outcomes were collected for all subjects: ACS, repeat revascularization (CABG or PCI), acute cerebrovascular accident (CVA), hospitalization for decompensated CHF, cardiovascular disease death.

The data obtained were processed using Statistica 10.0. Statistical hypotheses on the distribution were tested using the Kolmogorov-Smirnov/Lilliefors test and the Shapiro-Wilk test. Quantitative variables with normal distribution were described by the means and standard deviations (M ± SD). Quantitative variables with non-normal distribution were presented as the medians and inter-quartile ranges (Me [Q1; Q3]). Categorical data were expressed by absolute values and percentages (n (%)). Differences between two independent groups in quantitative measures were estimated by the Mann-Whitney U-test. The Cohren's Q-test was used to compare percentages in dependent samples. The analysis of repeat measurements was estimated using the Friedman test followed by post-hoc comparisons of variables by the Wilcoxon test. The critical significance level was p=0.05.

Results

Of a total of 74 subjects, 73 patients completed the study: 36 people in the empagliflozin group (1 (2.7%) female patient discontinued therapy in 1 month due to AE of genital infection), and 37 subjects in the control group.

The baseline comparison of patient groups by the main clinical and anamnestic characteristics, and indicators of carbohydrate and lipid metabolism, filtration function of the kidneys, and coronary artery lesions (the SYNTAX score) found no significant differences (Table 3).

Baseline therapy of DM is summarized in Table 4, Figure 1 and Figure 2.

Before the beginning of the study, 36.11% of patients in the empagliflozin group and 27.03% in the control group had poor control of carbohydrate metabolism (HbA1c). Only 16.67% of patients taking empagliflozin failed to achieve their individual target levels of HbA1c in 12 months of empagliflozin therapy. There were no statistically significant changes in the glycemic parameters in the control group. Poor glycemic control was observed in 32.43% of patients after 12 months of the study, which was higher than the corresponding indicator in the empagliflozin group.

A total of 18 (24.66%) cardiovascular events were reported in the general sample within 12 months after PCI (Table 5). There were no deaths. The comparison groups did not differ in the incidence of adverse outcomes.

Empagliflozin therapy resulted in 12 months in a 5.56% decrease in TC ($p<0.05$) and a 3.67% decrease in LDL cholesterol ($p<0.05$). Lipid metabolism did not change in the control group.

Figure 3 shows changes in anthropometric and imaging indicators of obesity in the comparison groups over the study period.

There were statistically significant changes in these indicators in the control group at the end of the study. A decrease in body weight, BMI, WC, WC/HC, SFA, VFA during empagliflozin therapy was statistically significantly higher than that in the control group ($p<0.05$).

During the use of empagliflozin, levels of adiponectin increased by 15.75% versus baseline, levels of leptin and hsCRP decreased by 13.41% and 30.60%, respectively. There were no significant changes in the levels of adiponectin, leptin, and hsCRP in the control group. Patients taking empagliflozin had a greater decrease in leptin and hsCRP levels than those in the control group (Table 6).

Baseline GFR values were comparable in the comparison groups, and there was no significant reduction in GFR in both groups 48 hours after PCI. After 12 months of the study, GFR was statistically significantly lower than at baseline in the treatment group ($p<0.001$) and the control group ($p<0.001$). There were no differences in the rates of GFR reduction between the groups within 12 months (Figure 4).

Contrast X-ray examination revealed1 (2.78%) case of acute kidney damage (KDIGO) in the main group [11]. Since GFR did not reach the target level to cancel the drug, treatment was restarted when serum creatinine stabilized.

It should also be noted that 11 (30.55%) patients from the empagliflozin group were diagnosed with bacteriuria without clinical signs of urinary tract infection in the 1st month of treatment.

Discussion

Prevention of macrovascular complications in patients with DM has been based until recently on antiplatelet and lipid-lowering therapy. However, based on the results of the EMPA-REG OUTCOME, DECLARE-TIMI 58, LEADER, SUSTAIN-6 studies [1–5], the administration of modern glucose-lowering drugs is a priority direction in improving the prognosis of CVDs in patients with DM along with conventional CAD therapy. The 2019 ESC Guidelines on Diabetes, Pre-diabetes, and Cardiovascular Diseases recommend empagliflozin (recommendation class I level B)

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Table 3. Clinical and laboratory characteristics of the study groups

Parameter	Treatment group (n=36)	Control group (n=37)	p
Male, n (%)	18 (50)	18 (48.65)	1.000
Age, years (Me [Q1; Q3])	61 [57; 64.5]	61 [56; 64]	0.943
Body mass index, kg/m2 (M ± SD)	34.40±6.11	32.33±5.70	0.196
WC, cm (M ± SD)	109.03±16.14	101.86±13.34	0.086
HC, cm (M ± SD)	111.89±14.04	105.89±12.87	0.174
WC/HC (M ± SD)	0.97±0.07	0.96±0.07	0.822
Smoking, n (%)	13 (36.11)	12 (32.43)	0.466
Arterial hypertension, n (%)	36 (100)	37 (100)	–
History of CVA, % (n)	3 (8.33)	4 (10.81)	1.000
Duration of CAD history, years (Me [Q1; Q3])	2.0 [1.0; 4.5]	2.0 [2.0; 5.0]	0.216
Duration of DM type 2 history, years (Me [Q1; Q3])	6.5 [3.0; 12.5]	5.0 [3.0; 8.0]	0.269
History of myocardial infarction, n (%)	16 (44.44)	21 (56.76)	0.352
Angina pectoris, n (%)			
FC I	2 (5.56)	3 (8.11)	1.000
FC II	26 (72.22)	17 (45.95)	0.791
FC III	3 (8.33)	9 (24.32)	0.112
CHF, n (%)			
FC I	0	0	
FC II	33 (91.67)	36 (97.30)	0.357
FC III	3 (8.33)	1 (2.7)	
Atrial fibrillation, n (%)	4 (11.11)	3 (8.11)	0.711
Fasting glycemia, mmol/L (Me [Q1; Q3])	8.15 [7.35; 11.35]	7.4 [7.10; 9.40]	0.109
HbA1c, % (Me [Q1; Q3])	7.15 [6.65; 8.15]	7.00 [6.50; 7.50]	0.401
TC, mmol/L, (Me [Q1; Q3])	4.56 [3.77; 5.94]	4.71] 3.64; 6.06]	0.746
LDL cholesterol, mmol/L (Me [Q1; Q3)]	2.47 [2.10; 3.94]	2.86 [2.11; 3.54]	0.865
HDL cholesterol, mmol/L (Me [Q1; Q3)]	1.07 [0.90; 1.63]	1.00 [0.90; 1.22]	0.738
Triglycerides, mmol/L (Me [Q1; Q3])	1.61 [1.02; 2.61]	1.72 [1.30; 2.37]	0.371
GFR (CKD-EPI), mL/min/1.73 m^2 (Me [Q1; Q3])	84.5 [69.5; 97.0]	90.0 [80.0; 96.0]	0.315

WC, waist circumference; HC, hip circumference; CVA, cerebrovascular accident; HbA1c, glycated hemoglobin

Table 4. Treatment of diabetes mellitus in the study groups before the beginning of the study

Parameter	Treatment group (n=36)	Control group (n=37)	p
Nutrition therapy, n (%)	6 (16.67)	5 (13.51)	0.754
OGLD, n (%)	21 (58.33)	26 (70.26)	0.334
Insulin therapy, n (%)	2 (5.56)	4 (10.82)	0.674
Combination therapy (insulin + OGLD), n (%)	7 (19.44)	2 (5.41)	0.085

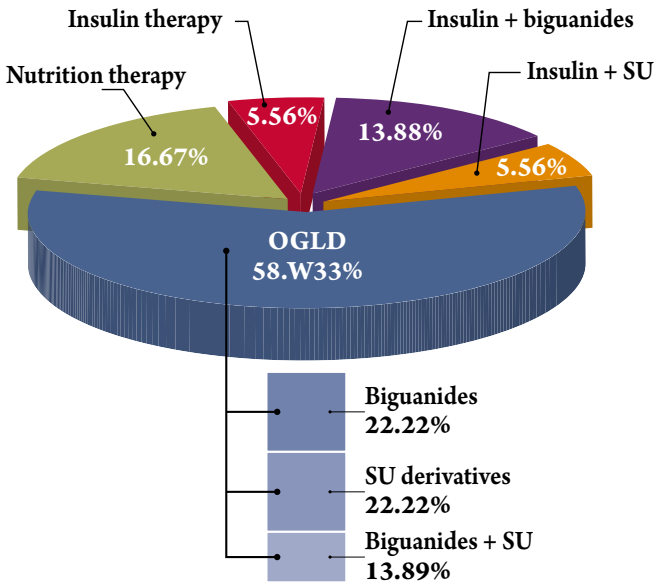
ПССП – пероральные сахароснижающие препараты.

Table 5. Main adverse outcomes within 12 months after elective percutaneous coronary intervention in the study groups

Parameter	Treatment group (n=36), n (%)	Control group (n=37), n (%)	p
All adverse outcomes	8 (22.22)	10 (27.03)	0.787
ACS	1 (2.78)	—	—
ACS + PCI for restenosis	2 (5.56)	4 (10.82)	0.674
ACS + PCI de novo	2 (5.56)	2 (5.41)	1.000
Elective CABG	1 (2.78)	1 (2.70)	1.000
CVA	1 (2.78)	1 (2.70)	1.000
Hospitalization for CHF	1 (2.78)	2 (5.41)	1.000

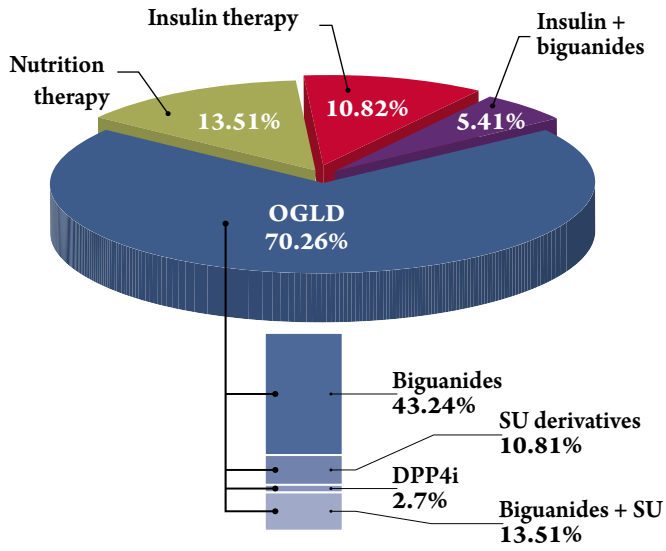
CVA, cerebrovascular accident.

Figure 1. Groups of oral glucose-lowering drugs used before the beginning of the study in the empagliflozin group, n (%)



OGLD, oral glucose-lowering drugs; SU, sulfonylurea derivatives.

Figure 2. Groups of oral glucose-lowering drugs used before the beginning of the study in the control group, n (%)

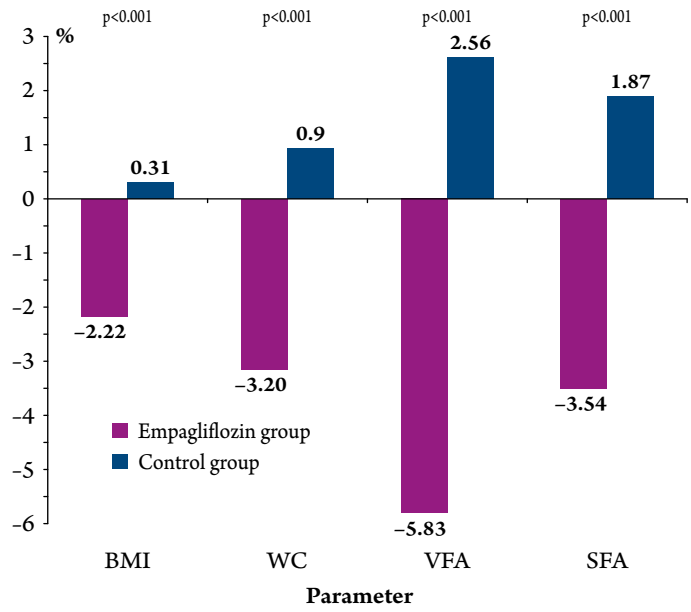


OGLD, oral glucose-lowering drugs; SU, sulfonylurea derivatives; DPP4i, dipeptidyl peptidase 4 inhibitors.

Table 6. Changes in the levels of adipocytokines and pro-inflammatory markers in the study groups

Parameter	Treatment group (n=36)	Control group (n=37)	p
Adiponectin, mg/mL (Me [Q1; Q3])			
Baseline	6.21 [5.46; 7.75]	7.45 [6.32; 8.74]	0.052
In 6 months	7.14 [6.45; 8.96]	7.21 [6.40; 8.82]	0.839
In 12 months	7.24 [6.85; 8.78]	7.16 [6.34; 9.58]	0.479
Δ	0.94 [0.36; 1.88]	0.11 [–0.59; 0.40]	<0.001
p Δ	<0.001	0.368	
Leptin, ng/mL (Me [Q1; Q3])			
Baseline	24.98 [15.55;26.65]	19.23 [12.33; 27.08]	0.499
In 6 months	17.74 [14.01; 24.14]	18.95 [12.33; 26.95]	0.788
In 12 months	18.92 [13.65; 27.08]	19.84 [12.29; 27.09]	0.882
Δ	–1.34 [–5.37; –0.26]	0.26 [–1.21; 1.30]	<0.001
p Δ	<0.001	0.297	
HsCRP, mg/L (Me [Q1–Q3])			
Baseline	4.00 [3.08; 4.76]	3.00 [2.70; 4.00]	0.006
In 6 months	3.15 [2.63; 3.59]	3.10 [2.86; 3.75]	0.657
In 12 months	2.83 [2.38; 3.00]	3.05 [2.69; 3.65]	0.002
Δ	–1.2 [–1.64; –0.70]	–0.15 [–0.31; 0.05]	<0.001
p Δ	<0.001	0.086	—

Figure 3. Changes in obesity markers in the comparison groups 12 after the beginning of the study



VFA, visceral fat area; SFA, subcutaneous fat area.

as first-line therapy in patients with documented CVDs of atherosclerotic origin. And metformin is a first-line drug only in patients with DM type 2 without CVDs [7].

The study did not establish the benefits of empagliflozin for the incidence of cardiovascular complications within 12 months after elective primary PCI with stent implantation (22.24% of patients in the treatment group and 27.04% in the control group had cardiovascular complications; p=0.787), which is probably due to the limited number of observations. At the same time, a recent Japanese study confirmed the positive effect of empagliflozin in patients with DM type 2 subjected to coronary revascularization: suppression of neointima hyperplasia was shown by optical coherence tomography 12 months after coronary stenting [12].

Nevertheless, the administration of empagliflozin provided cardiometabolic control in most patients: an improvement

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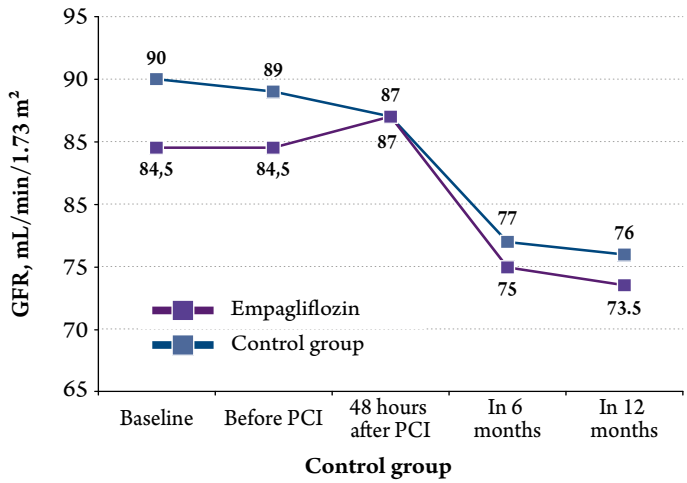
in glycemia was noted in 1 month of the therapy, and 83.33% of patients achieved individual target levels of HbA1c by the end of the study. There was also a lipid-lowering effect of empagliflozin such as a decrease in TC mainly due to a decrease in LDL cholesterol by 3.67% compared to the baseline, but changes were not statistically significantly different from the control group. The data on the effects of SGLT2 inhibitors on lipid metabolism are contradictory. Several studies report an increase in HDL cholesterol and no changes in TC, LDL cholesterol, and TG [13]. At the same time, the levels of LDL and HDL cholesterol increased in the EMPA-REG OUTCOME study. A potential effect of empagliflozin on lipid metabolism may be mediated by a positive effect on insulin resistance with increased glucose excretion in the urine, irrespective of insulin levels, which promotes slowing down lipogenesis and activation of lipolysis and depends on the duration of therapy [14].

The positive effects of empagliflozin on markers of abdominal obesity compared to baseline were also established: body weight decreased by a mean of 2.15 kg, BMI by 2.22%, and WC decreased by 3.0 cm. Moreover, a significant decrease in VFA by 5.83% and SFA by 3.54% was noted. Our findings are consistent with the results of previous studies [15, 17].

An additional benefit of empagliflozin therapy was established during the study, which was an improve adipokine profile, such as a 15.75% increase in adiponectin levels and a 13.41% decrease in leptin. There was also a 30.06% decrease in hsCRP. A similar effect of empagliflozin on the levels of adipocytokines was noted in some other studies. Wu et al. [18] conducted a meta-analysis, which confirmed that the use of SGLT2 inhibitors reduced the levels of circulating leptin and increased the concentrations of circulating adiponectin. In another study, empagliflozin reduced insulin resistance due to a decrease in the activity of chronic systemic inflammation [19]. Several studies showed that abnormal adipocytokine and inflammation marker profile is associated with a worse prognosis of CVDs and worse angiographic outcomes of PCI. Moreover, the leptin/adiponectin ratio correlated with the degree of coronary artery lesion irrespective of the course of CAD [20]. There is evidence that patients with stent restenosis have higher levels of leptin than those without [21]. Another study confirmed the role of adiponectin as a predictor of long-term cardiovascular complications after PCI, including death, myocardial infarction, or stroke, but no association was found between adiponectin levels and the frequency of revascularization of the target vessel [22]. In another study, serum levels of adiponectin>6 mg/mL were associated with a lower risk of restenosis irrespective of the presence of carbohydrate metabolism [23].

In our study conducted, a statistically significant decrease in GFR by 8.30% was noted in patients taking empagliflozin and by 14.28% in the control group over 12 months. One of

Figure 4. Changes in glomerular filtration rate in both groups over 12 months of the study



the features of SGLT2 inhibitor pharmacodynamics is an increase in sodium delivery to macula densa, which leads to the restoration of the tubuloglomerular feedback mechanism, resulting in a narrowing of the afferent arteriole, a decrease in intraglomerular pressure, and a reduction in hyperfiltration. This is manifested clinically by a decrease in GFR by about 4–6 mL/min/1.73 m² during the initiation of treatment with subsequent stabilization [24]. The results of studies show that there GFR fully recovers 1 week after discontinuation of the drug, even after several years of treatment. By contrast, GFR continues to decrease steadily in patients with diabetes from the placebo group, which is a manifestation of progressive diabetic nephropathy. Thus, experts believe that the initial decrease in GFR during pharmacological inhibition of SGLT2 is not associated with a decrease in the number of functioning nephrons and serves in most cases as an indicator of efficacy rather than adverse effect of the drug [25]. In general, SGLT2 inhibitors have rather favorable safety profile.

Therapeutic glucosuria caused by empagliflozin is a favorable environment for the propagation of conditional pathogenic microflora, including yeasts. According to the EMPA-REG OUTCOME study, empagliflozin increases about 3-fold the risk of developing genital fungal infections, along with autonomic neuropathy and bladder atony and vesicoureteral reflux characteristic of patients with DM. At the same time, the incidence of bacterial urinary tract infections does not differ from that in the placebo group [3].

Conclusion

Satisfactory glycemic control was observed in 83.33% of patients with significant decreasing dynamics (p=0.008) who took empagliflozin 10 mg/day for 1 month before and 11 months after elective percutaneous coronary intervention. The target levels of glycated hemoglobin before percutaneous coronary intervention were achieved by 72.97% of patients

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who received other glucose-lowering therapy without significant changes in the levels of glycated hemoglobin during the study period (p=0.414). Positive changes in the glycemic characteristics during empagliflozin therapy were accompanied by a significant decrease by 30.06% in the serum levels of high-sensitivity C-reactive protein. Moreover, significant changes in the anthropometric and biochemical indicators of fat metabolism were noted: a decrease in body mass index by 2.22%, a decrease in waist circumference by 3.20%, visceral fat area by 5.83%, subcutaneous fat area by 3.20%, and a decrease in the levels of total cholesterol by 5.56%, low-density lipoprotein cholesterol by 3.67%, and leptin by 13.41% compared to the baseline levels. By contrast, values of these indicators increased in patients who did not receive empagliflozin over 12 months of the study. Levels of adiponectin increased in patients taking empagliflozin by 15.75% and decreased during other glucose-lowering therapy. The best possible safety profile of empagliflozin is worth noting given its effect on the kidney filtration function, its decline was statistically insignificant and turned out to be lower than in other glucose-lowering therapy over 12 months of the study.

Thus, despite the absence of a direct effect of empagliflozin on the incidence of cardiovascular complications within 12 months after elective percutaneous coronary intervention, the administration of the drug 1 month before the intervention can become a way to increase the efficacy of elective myocardial revascularization given the documented positive cardiometabolic effects.

Limitations

Small number of observations.

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