

Novikova M. S.^{1,2}, Minushkina L. O.¹, Allazova S. S.³, Zateyshchikov D. A.^{1,4},
Boeva O. I.^{1,5}, Kotenko O. N.^{5,6}, Vinogradov V. E.⁶, Shilov E. M.³,
Antsiferov M. B.², Koteschkova O. M.², Molina L. P.²

¹ Central State Medical Academy of the Administrative Directorate of the President of the Russian Federation, Moscow, Russia

² Endocrinology Dispensary of the Moscow Department of Health, Moscow, Russia

³ Sechenov First Moscow State Medical University, Moscow, Russia

⁴ Bauman Municipal Clinical Hospital #29 of the Moscow Department of Health, Moscow, Russia

⁵ Pirogov Russian National Research Medical University, Moscow, Russia

⁶ Municipal Clinical Hospital #52 of the Moscow Department of Health, Moscow, Russia

EFFICACY AND SAFETY OF SGLT-2 INHIBITORS IN RENAL ALLOGRAFT RECIPIENTS: AN OPEN-LABEL, SINGLE-CENTER PROSPECTIVE STUDY

<i>Aim</i>	To evaluate the safety and efficacy of sodium-glucose cotransporter-2 inhibitor (SGLT-2i) inhibitor therapy in kidney transplant recipients (KTRs) with and without post-transplant diabetes mellitus (PTDM).
<i>Material and methods</i>	KTRs (n=2 146, with PTDM n=303, or 14%) who had undergone transplantation more than one year ago, with stable graft function (estimated glomerular filtration rate (eGFR) >30 ml/min/1.73 m ²), after excluding patients with combined kidney and pancreas transplantation (n=57), type 1 diabetes mellitus (DM) (n=124), and type 2 DM diagnosed before kidney allotransplantation (KAT) (n=74), were prescribed SGLT-2i (empagliflozin 25 mg/day or dapagliflozin 10 mg/day; n=107), the rest of the KTRs (n=1784) did not receive SGLT-2i. After pseudo-randomization, two groups were formed and included in an open, single-center prospective study: an experimental group with SGLT-2i (n=78; with PTDM n=45) and a control group, without SGLT-2i (n=78; n=45 with PTDM). The groups were comparable in the PTDM duration and the period from KAT to inclusion in the study, as well as in clinical characteristics, including gender, age, history of acute myocardial infarction (AMI) before KAT, levels of glycated hemoglobin (HbA1c), systolic blood pressure (SBP) and diastolic blood pressure (DBP), GFR, microalbuminuria (MAU), blood uric acid concentration, blood lipid profile (total cholesterol (TC), low-density lipoproteins (LDL)), basal blood concentration (C0) of calcineurin inhibitors (CNI), and therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), statins, and metformin (p>0.05).
<i>Results</i>	The relative risk (RR) of all-cause death in the experimental group was reduced by 60% compared with the control group (RR 0.40; 95% confidence interval (CI) 0.17–0.98 vs. RR 2.44; 95% CI 1.01–5.86; p=0.04). The RR of adverse coronary outcomes in the experimental group was reduced by 75% compared with the control group (RR 0.25; 95% CI 0.06–0.89 vs. 4.0; 95% CI 1.11–14.42; p=0.03). The RR of adverse renal outcomes in the experimental group was reduced by 72% compared with the control group (RR 0.28; 95% CI 0.09–0.85 vs. 3.50; 95% CI 1.16–10.49; p=0.02). In addition, in the experimental group, compared to the control group, the GFR decline was slower (–1.29±0.763 ml/min/1.73 m ² /year vs. –3.33±0.767 ml/min/1.73 m ² /year; p=0.047). Also, a pronounced advantage in the dynamic decline in GFR was observed throughout the entire study period (–3.10±1.73 ml/min/1.73 m ² vs. –7.87±1.87 ml/min/1.73 m ² ; p=0.040).
<i>Conclusion</i>	SGLT2i effectively reduce cardiovascular and renal mortality, the risk of adverse renal and coronary outcomes, and slow the progression of chronic kidney disease in KTRs, regardless of the presence of PTDM. A large-scale study evaluating the efficacy of SGLT2i in KTRs is warranted to formulate appropriate clinical recommendations.
<i>Keywords</i>	SGLT2 inhibitors; kidney transplant recipients; post-transplantation diabetes mellitus; cardiovascular mortality; kidney-related mortality
<i>For citations</i>	Novikova M. S., Minushkina L. O., Allazova S. S., Zateyshchikov D. A., Boeva O. I., Kotenko O. N. et al. Efficacy and Safety of Sgl-2 Inhibitors In Renal Allograft Recipients: an Open-Label, Single-Center Prospective Study. <i>Kardiologiia</i> . 2025;65(9):10–18. [Russian: Новикова М. С., Минушкина Л. О., Аллазова С. С., Затеишчиков Д. А., Боева О. И., Котенко О. Н. и др. Эффективность и безопасность ингибиторов натрий-глюкозного котранспортера 2-го типа у реципиентов почечного трансплантата: открытое одноцентровое проспективное исследование. <i>Кардиология</i> . 2025;65(9):10–18].
<i>Corresponding author</i>	Novikova Mariya Sergeevna. E-mail: citrus7474@mail.ru

Introduction

Results of the EMPA-REG (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), CANVAS (CANagliflozin cardioVascular Assessment Study), CREDENCE (Computed Tomographic Evaluation of Atherosclerotic DEterminants of Myocardial IsChEmia), DECLARE-TIMI58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events), DAPA-CKD (Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease), EMPA-KIDNEY (Study of Heart and Kidney Protection With Empagliflozin), DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure), DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure), and EMPERIOR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic hearT Failure With Reduced Ejection Fraction) studies justified prescribing sodium-glucose cotransporter type 2 inhibitors (SGLT2i) as the first-line therapy, regardless of the level of glycated hemoglobin (HbA1c) and treatment with other glucose-lowering drugs in patients with type 2 diabetes mellitus (DM), chronic kidney disease (CKD) and atherosclerotic cardiovascular diseases (CVD) or high risk of their development, as well as with chronic heart failure (CHF) [1–4].

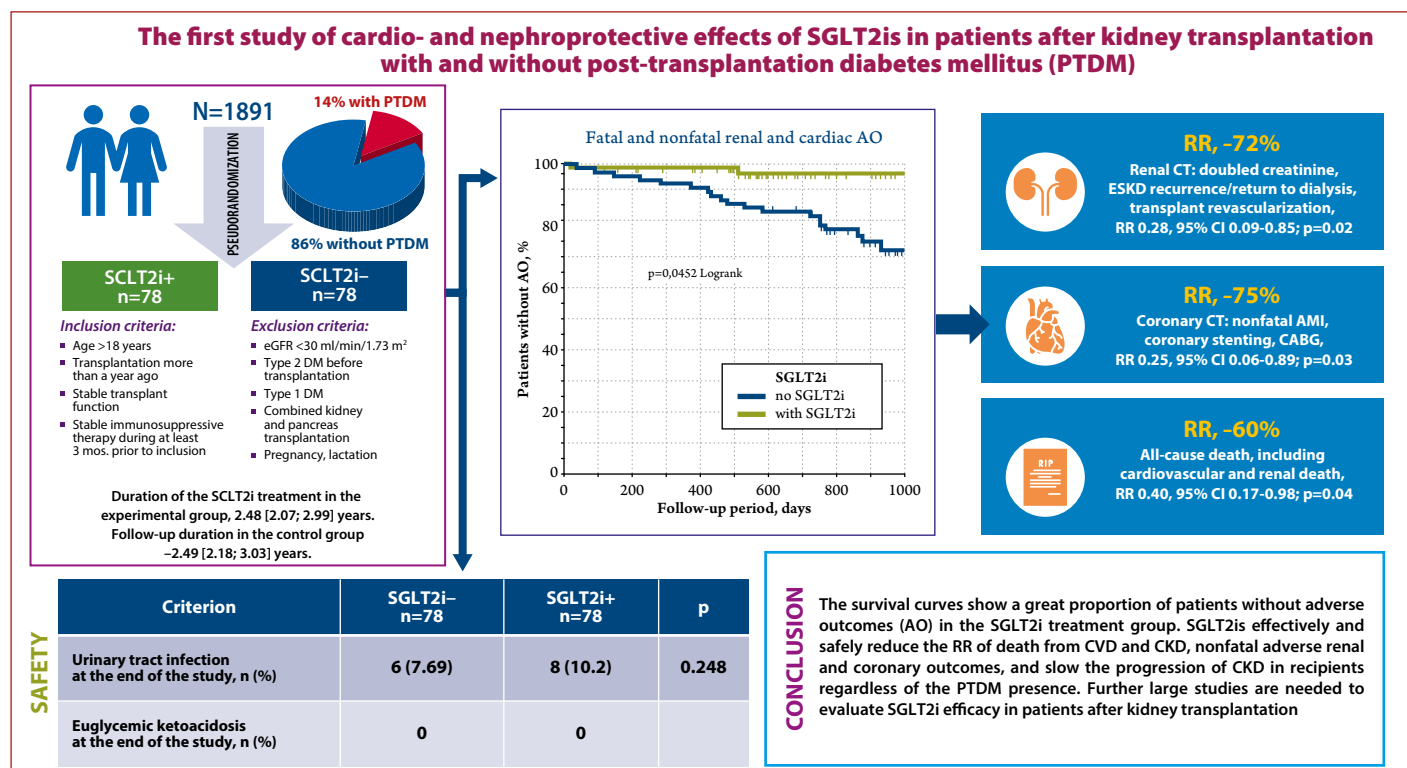
Evidence of the nephroprotective effect of dapagliflozin obtained in the DAPA-CKD study [5] and empagliflozin in the EMPA-KIDNEY study [6] allowed extending the indications for their use to patients with CKD without type 2 DM [1, 2]. This may be of particular importance for kidney transplant recipients (KTR) with a single functioning kidney and a glomerular filtration rate (GFR) of less than 70 ml/min/1.73 m², despite modern immunosuppressive therapy with calcineurin inhibitors (CNIs) (tacrolimus) [7].

Inhibition of SGLT2 reduces intraglomerular pressure, improves tubular oxygenation and metabolism, reduces kidney inflammation and fibrosis, and stabilizes their function [8, 9]. This may potentially have a long-term beneficial effect on kidney graft survival and the overall prognosis in recipients. Preliminary positive reports of using SGLT2i in patients with post-transplantation diabetes mellitus (PTDM) have been previously published [10, 11]. The present study aims to investigate and confirm the efficacy and safety of using SGLT2i in KTRs with and without PTDM.

Material and methods

The study was performed sequentially in three stages (Fig. 1). At the first stage, 2,146 KTRs who had survived for more than one year after kidney allotransplantation (KAT) were recruited from the Interdistrict Nephrology Center, Municipal Clinical Hospital #52 of the Mos-

Central illustration. Efficacy and safety of sodium-glucose cotransporter type 2 inhibitors in kidney transplant recipients: an open single-center prospective study



cow Health Department. The patients were older than 18 years, had stable graft function (serum creatinine concentration change of $\leq 20\%$ during the past 2 months), and had been receiving continuous immunosuppressive therapy for at least 3 months prior to the study.

After excluding KTRs with an estimated GFR (eGFR) of < 30 ml/min/1.73 m²; type 2 DM diagnosed before transplantation; type 1 DM; those who had undergone combined kidney and pancreas transplantation; and pregnant or lactating women, 1,891 patients remained in the cohort. At stage 2, 303 (14%) of these patients were diagnosed with PTDM, based on WHO criteria, at the Endocrinology Dispensary of the Moscow Health Department (fasting plasma glucose concentration > 7.0 mmol/l, or 2-hour plasma glucose concentration > 11.1 mmol/l in a glucose tolerance test (GTT), or HbA1c $> 6.5\%$ (48 mmol/mol)) [12]. Between November 30, 2017, and January 31, 2025, 107 patients (n=66 with PTDM and n=41 without PTDM) who signed informed consent for the SGLT2i therapy were prescribed empagliflozin 25 mg/day or dapagliflozin 10 mg/day. The remaining 1,784 patients (n=237 with PTDM) did not receive SGLT2i. The median duration of the SGLT2i treatment was 20.7 [16.3; 29.1] months or 90 [70.7; 126.3] weeks.

At visits at weeks 4, 8, 16, and every 24 weeks thereafter until the end of observation, clinical and laboratory data were assessed, and adverse effects of the treatment were recorded, including urinary tract infection (UTI), urogenital fungal infection, and euglycemic ketoacidosis. UTI was identified based on the results of a complete urinalysis. Euglycemic ketoacidosis was defined as a state of metabolic acidosis (pH < 7.3), ketonuria, and a blood glucose concentration > 250 mg/dl (13.8 mmol/l) [13]. Patients adhered to their treatments with CNIs, angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), statins and hypoglycemic drugs, including metformin, and maintained a regular diet and physical activity.

At stage 3, two groups (SGLT2i+ and SGLT2i-) of 78 patients each were formed using pseudorandomization, matched for age, gender, clinical characteristics, concomitant therapy, and duration of treatment and follow-up. The median duration of the SGLT2i treatment in the experimental group was 2.48 [2.07; 2.99] years, while the duration of follow-up in the control group was 2.49 [2.18; 3.03] years (p=0.351).

The primary endpoint was all-cause death, including death from CVD or chronic kidney disease (CKD). Secondary endpoints included a combination of adverse coronary outcomes (nonfatal acute myocardial infarction, coronary stenting, coronary artery bypass grafting)

and adverse renal outcomes (doubling of serum creatinine concentration, recurrence of end-stage kidney disease (ESKD) or return to dialysis, and transplant revascularization).

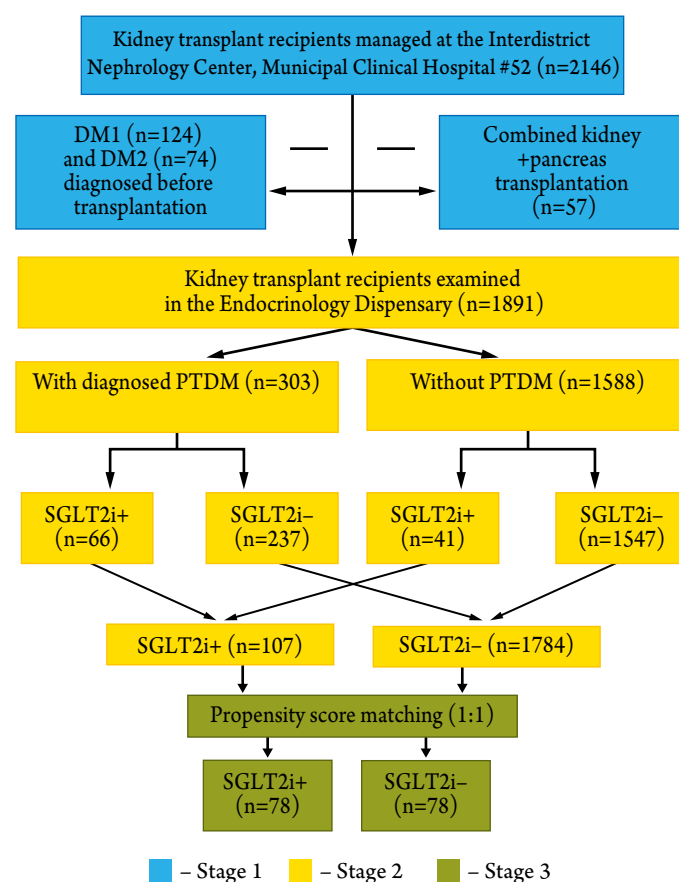
GFR was calculated according to the Modification of Diet in Renal Disease (MDRD) formula:

$$\text{GFR (ml/min/1.73 m}^2\text{)} = 175 \times (\text{Scr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ for women}),$$

where Scr is the serum creatinine concentration, $\mu\text{mol/l}$ [14].

Statistical analysis was performed using the SPSS version 25.0 software. Continuous variables were presented as mean $\pm$ standard deviation or median with interquartile range; categorical variables were presented as percentages. Student's t-test was used to assess differences in continuous variables, and the chi-square test was used for categorical variables. The Shapiro-Wilks test was used to check the distribution normality. If the data did not correspond to the normal distribution law (stage 2), the Mann-Whitney test was used to assess differences in continuous variables. The groups treated and not treated with SGLT2i were balanced by pseudorandomization using the propensity score matching. The propensity scores

Figure 1. Algorithm of patient inclusion in the study



DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; PTDM, post-transplantation diabetes mellitus; SGLT2i, sodium-glucose co-transporter type 2 inhibitors.

were calculated taking into account the intergroup differences in age, duration of treatment, follow-up duration (time between control points for measuring blood creatinine concentration), concomitant hypoglycemic therapy, and the baseline GFR. Pairs of patients receiving SGLT2i were matched using the nearest neighbor matching method. The relative risk (RR) of endpoints was determined as a ratio of the number of events in treated patients (P exposed) to the number of events in patients not receiving SGLT2i (P unexposed):

$$RR = P \text{ exposed} / P \text{ non-exposed}.$$

A RR=1 indicates no difference in risk between the two groups; a RR <1 indicates that the event occurred less frequently in the experimental group than in the control group; an RR >1 indicates that the event occurred more frequently in the experimental group than in the control group. The Kaplan-Meier method with the log-rank test was used for survival analysis. Differences were considered statistically significant at $p < 0.05$.

Ethics Statement. This study was approved by the Central State Medical Academy (Protocol #120 dated February 3, 2017) and was conducted in strict consistency with the World Medical Association's Declaration of Helsinki (1964) and the Ethical Principles for Medical Research Involving Human Subjects [15], according to which all patients signed informed consent.

Results

Patients included in stage 2 of the study and receiving SGLT2i differed from those who were not prescribed this treatment in several characteristics (Table 1).

Patients in the experimental and control groups formed by pseudorandomization (study stage 3) did not significantly differ in demographic and clinical-anamnestic characteristics, and were also comparable in the time elapsed from KAT to inclusion in the study, the time of PTDM onset after KAT, and the duration of PTDM before inclusion in the study (Table 2).

Comparison of treatment outcomes between the study groups showed that the use of SGLT2i reduced the risk of all-cause death by 60% (RR 0.40; 95% CI 0.17–0.98 vs. RR 2.44; 95% CI 1.01–5.86 in the control group; $p = 0.04$), of non-fatal adverse coronary outcomes by 75% (RR 0.25; 95% CI 0.06–0.89 vs. RR 4.0; 95% CI 1.11–14.42 in the control group; $p = 0.03$), and of adverse renal outcomes by 72% (RR 0.28; 95% CI 0.09–0.85 vs. RR 3.50; 95% CI 1.16–10.49 in the control group; $p = 0.02$). As shown on Figure 2, the decrease in eGFR in the experimental group (-1.29 ± 0.76 ml/min/1.73 m²/year) was almost 67% less than in the control group (-3.33 ± 0.76 ml/min/1.73 m²/year; $p = 0.047$).

Table 1. Clinical characteristics of patients included in the study stage 2 with and without SGLT2i therapy

Characteristics	SGLT2i – (n=1,784)	SGLT2i + (n=107)	p
Male patients, n (%)	997 (55.9)	61 (57)	0.821
Age, years	53.8 [43.4; 63.1]	58.5 [49.7; 66.4]	0.002
BMI, kg/m ²	25.1 [22.2; 28.1]	27.3 [24.4; 30.7]	0.001
AMI before KAT, n (%)	35 (2.3)	5 (4.7)	0.121
SBP, mm Hg	130 [120; 135]	130 [120; 130]	0.671
DBP, mm Hg	80 [70; 80]	80 [70; 80]	0.092
TC, mmol/l	5.11 [4.39; 5.94]	5.16 [4.46; 6.04]	0.681
LDL, mmol/l	2.95 [2.34; 3.66]	2.96 [2.15; 3.46]	0.611
GFR, ml/min/1.73 m ²	46.2 [32.3; 59.2]	46.0 [33.8; 58.0]	0.619
Uric acid, μmol/l	406 [344; 474]	381 [322; 456]	0.031
MAU, mg/l	110 [50; 300]	100 [43; 410]	0.891
HbA1c, %	5.6 [5.3; 6.1]	6.6 [5.6; 7.5]	0.001
Metformin, n (%)	21 (1.8)	22 (20.6)	0.001
ACEi /BAR, n (%)	935 (52.4)	89 (83.2)	0.001
Statins, n (%)	812 (45.5)	73 (68.2)	0.001
Sirolimus dose, ng/ml	2.0 [1.5; 2.9]	2.0 [1.3; 3.5]	0.576
Cyclosporin dose, ng/ml	150 [125; 200]	150 [125; 200]	0.582
Tacrolimus C0, ng/ml	6.7 [5.7; 7.9]	6.8 [6.1; 7.7]	0.531
Everolimus C0, ng/ml	3.82±1.66	4.33±1.67	0.412
Cyclosporin C0, ng/ml	112.8 [87.0; 133.9]	97.2 [61.2; 110.8]	0.015
PTDM, n (%)	237 (13.3)	66 (61.7)	0.001
Time from KAT to PTSD onset, years	2.1 [0.1; 8.1]	5.2 [0.7; 8.1]	0.271
PTDM duration, years	9.1 [6.2; 13.7]	6.9 [3.9; 11.1]	0.003

BMI, body mass index; AMI, acute myocardial infarction; KAT, kidney allotransplantation; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL, low-density lipoproteins; GFR, glomerular filtration rate; MAU, microalbuminuria; HbA1c, glycated hemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; C0, basal blood concentration of the drug, measured in the morning before taking the next dose; PTDM, post-transplantation diabetes mellitus, SGLT2i, sodium-glucose cotransporter type 2 inhibitor.

The slower decline in kidney graft filtration in the experimental group compared to the control group remained throughout the study (Fig. 3) and showed a statistically significant advantage starting from week 24 (Fig. 4).

Figure 5 (A-B) shows survival curves that reflect a higher proportion of patients without adverse events (AEs) in the KTR group receiving SGLT2i.

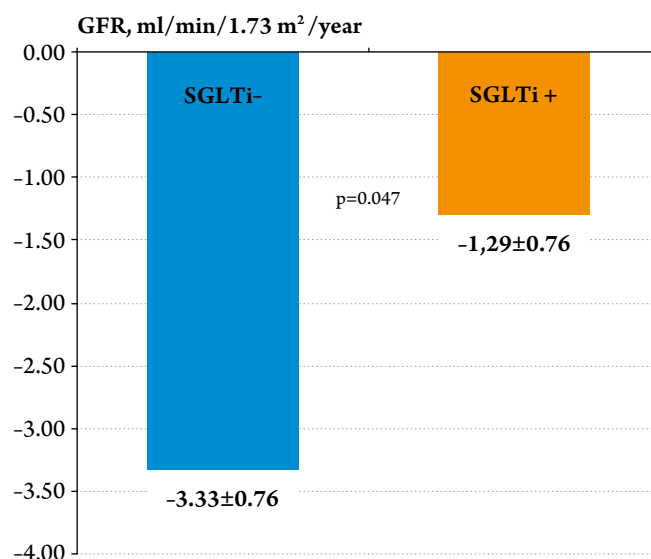
Our study did not reveal any adverse effects of the SGLT2i treatment. The incidence of UTI in the experimental group was similar to that in the control group; there were no cases of euglycemic ketoacidosis (see Table 2).

Table 2. Clinical characteristics of patients in the control (GLTC2i –) and experimental (GLTC2i +) groups formed by pseudorandomization at the time of inclusion in the study

Characteristics	SGLT2i – (n=78)	SGLT2i + (n=78)	p
Male patients, n (%)	34 (43.6)	34 (43.6)	1.000
Female patients, n (%)	43 (56.4)	43 (56.4)	
Age, years	50.9±11.5	51.6±11.1	0.719
No DM, n (%)	33 (42.3)	33 (42.3)	1.000
PTDM, n (%)	45 (57.7)	45 (57.7)	1.000
Time from KAT to inclusion in the study, years	13.5±6.1	13.4±6.7	0.768
Time from KAT to PTDM onset, years	6.1±6.1	6.8±7.0	0.273
Time from PTDM to inclusion in the study, years	7.0±5.5	6.6±3.5	0.367
SBP, mm Hg	126.7±11.3	127.8±9.6	0.847
DBP, mm Hg	75.8±6.5	77.0±7.4	0.661
GFR, ml/min/1.73 m ²	50.2±15.2	50.0±14.9	0.776
TC, mmol/l	5.38±1.22	5.49±1.15	0.836
LDL, mmol/l	2.98±0.87	2.86±1.19	0.417
Uric acid, μmol/l	429.7±18.9	428.9±13.7	0.726
MAU, mg/l	389.9±63.9	307.2±68.9	0.282
HbA1c, %	6.79±1.19	6.93±1.26	0.326
Metformin, n (%)	11 (14.3)	11 (14.3)	1.000
ACEi /BAR, n (%)	55 (70.5)	62 (79.5)	0.196
Statins, n (%)	56 (71.8)	53 (67.9)	0.601
AMI before KAT, n (%)	9 (11.5)	4 (5.1)	0.148
Tacrolimus dose, ng/ml	7.02±2.48	12.10±39.98	0.104
Cyclosporin dose, ng/ml	86.13±41.17	106.53±30.47	0.201
Everolimus dose, ng/ml	3.95±1.76	4.15±1.79	0.668
BMI, kg/m ²	26.6±4.9	27.0±5.4	0.138
Tacrolimus C0, ng/ml	4.98±3.31	5.16±2.55	0.820
Cyclosporin C0, ng/ml	146.43±45.61	153.85±59.45	0.502
Everolimus C0, ng/ml	2.75±1.99	2.04±0.78	0.128
Follow-up/treatment duration, years	2.77±0.92	2.65±1.16	0.190
UTI by the end of the study, n (%)	6 (7.69)	8 (10.2)	0.248
Euglycemic ketoacidosis by the end of the study, n (%)	0	0	

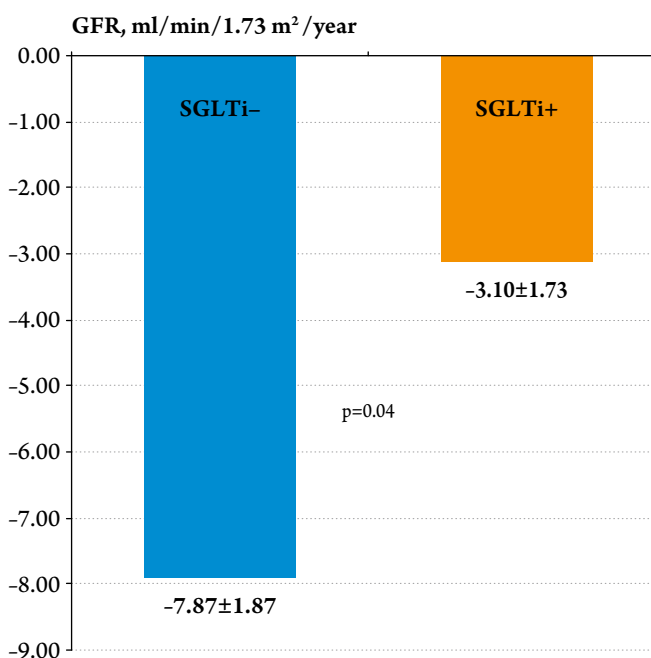
SGLT2i, sodium-glucose cotransporter-2 inhibitor; DM, diabetes mellitus; PTDM, post-transplantation diabetes mellitus; KAT, kidney allotransplantation; SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; TC, total cholesterol; LDL, low-density lipoproteins; MAU, microalbuminuria; HbA1c, glycated hemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AMI, acute myocardial infarction; BMI, body mass index; C0, basal blood concentration of the drug measured in the morning before taking the next dose; UTI, urinary tract infection.

Figure 2. Mean decrease in eGFR, ml/min/1.73 m²/year in the control and experimental groups



SGLT2i, sodium-glucose cotransporter type 2 inhibitor; eGFR, estimated glomerular filtration rate.

Figure 3. Total decrease in eGFR, ml/min/1.73 m² during the observation period in the study groups

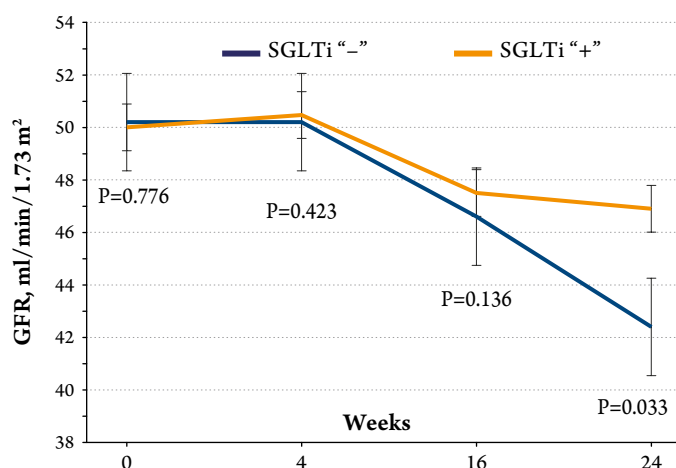


SGLT2i, sodium-glucose cotransporter type 2 inhibitor; eGFR, estimated glomerular filtration rate

Discussion

In our study, the SGLT2i therapy significantly improved survival of patients with and without PTDM. This suggests that dapagliflozin and empagliflozin may be considered for reducing the risk of death and nonfatal adverse coronary and renal outcomes in KTRs, regardless of the presence of PTDM.

Figure 4. Dynamics of eGFR during the treatment by week (visit points)



SGLT2i, sodium-glucose cotransporter type 2 inhibitor;
eGFR, estimated glomerular filtration rate.

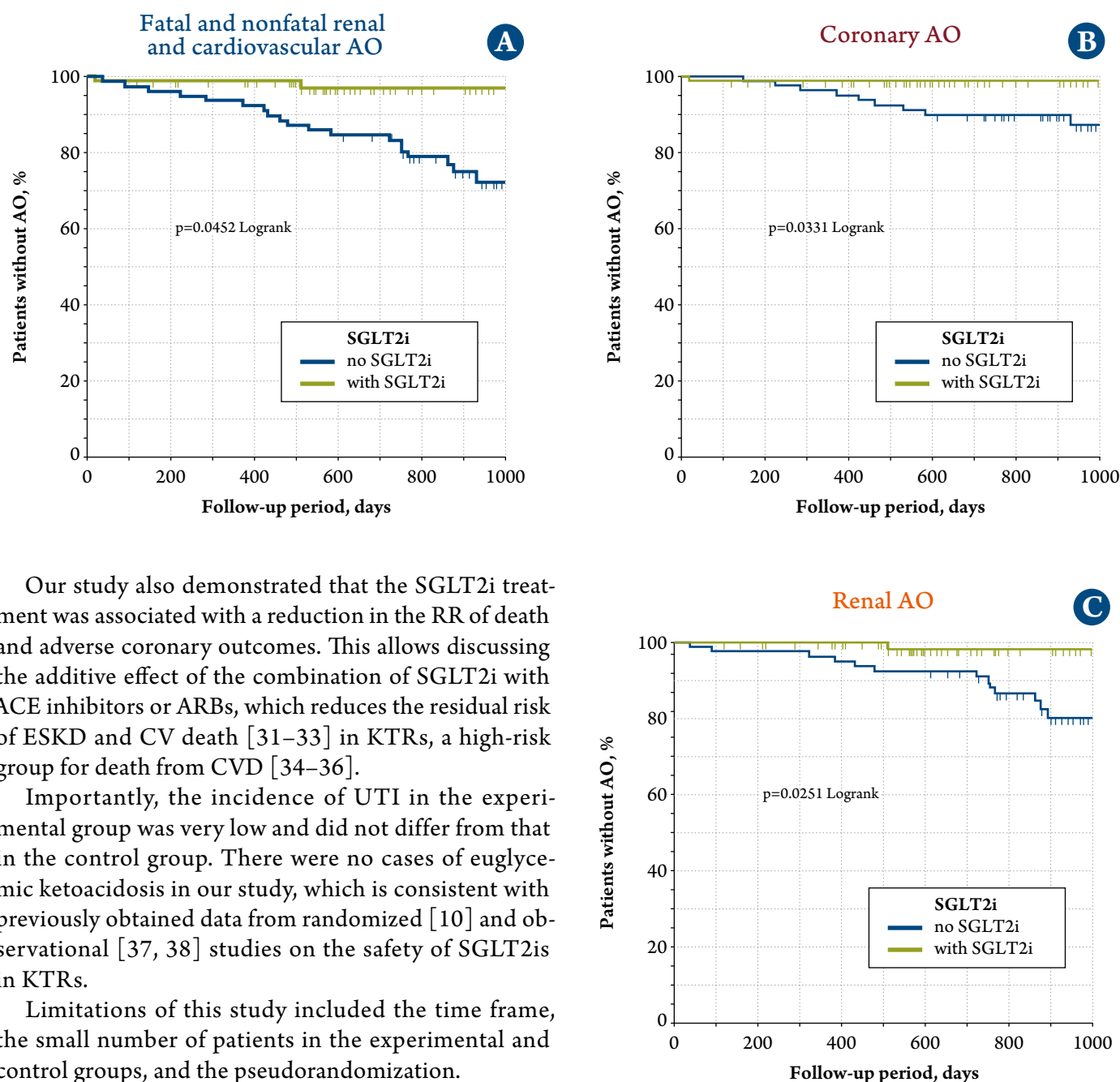
The nephroprotective effect of SGLT2is that has been demonstrated in large international randomized clinical trials [5, 6], is of a particular importance for renal transplantation due to the presence of a single functioning kidney and immunosuppressant (CNIs and steroids)-induced insulin resistance (IR) [16, 17]. The transplant, which performs a dual functional load and is constantly exposed to CNIs, is unprotected against hyperfiltration, the main non-immune mechanism of nephroangiosclerosis [18] and tubular disorders associated with increased sodium reabsorption [19]. The nephroprotective effect of SGLT2is is explained by an increase in sodium delivery to the macula densa and an ensuing decrease in glomerular hyperfiltration due to enhanced tubuloglomerular feedback [20]. In addition, SGLT2is have anti-inflammatory and antifibrotic effects in diabetic kidney disease [21] and reduce tacrolimus-induced hypoxic damage to renal tubular cells [22]. In our study, SGLT2is also prevented the progression of CKD after transplantation. The decrease in graft filtration function in the experimental group was almost 67% less than in the control group and did not exceed -1.3 ml/min/1.73 m²/year. This is apparently associated with the absence of rapid progression of renal failure characteristic of a decrease in GFR >5 ml/min/1.73 m²/year [23] and an increased risk of death observed with a decrease in GFR >3 ml/min/1.73 m²/year [24]. A significant advantage in preserving the filtration function of the renal graft in the experimental group was achieved at week 24 of the study without an initial sharp decrease in eGFR. However, its gradual decrease was observed up to week 16. A possible explanation for this fact may be the data presented in the post factum analysis in the EMPA-REG

study [25] and a large Korean multicenter observational study of the SGLT2i treatment in KTRs with DM [26]. In the EMPA-REG study, among 6,668 patients taking empagliflozin, only 1,887 (28.3%) had an acute decline in eGFR at week 4. In multivariate logistic regression, a diuretic treatment and more advanced CKD (stage 3B) at baseline were independent predictors of the initial decline in GFR [25]. J. Lim et al. [26], in turn, showed that among 2,083 KTRs with DM, an acute sharp decline in eGFR $>10\%$ during the first month was observed in only 35 (15.6%) patients of 226 treated with SGLT2is. In 191 (84.4%) patients, the total eGFR remained stable without an initial sharp decline after using SGLT2i. Risk factors for a sharp decline in eGFR were the time between transplantation and the initiation of SGLT2i treatment and the mean trough tacrolimus concentration. The cutoff value for predicting an acute decline in GFR was an interval of <397 days between kidney transplantation and the initiation of SGLT2i treatment, and the mean tacrolimus trough concentration exceeding 7.5 ng/ml [26]. In our study, the period from KAT to the enrollment in the study was significantly longer (13.4 ± 6.7 years) and the tacrolimus C0 level was much lower (5.16 ± 2.55 ng/ml). We excluded patients with an eGFR <30 ml/min/1.73 m² from the study, and the majority of them ($n=49$; 63%) had an eGFR greater than 45 ml/min/1.73 m² (CKD 3A); also we tried to avoid using diuretics in combination with SGLT2i. It is possible that all these factors together helped avoid the initial sharp decrease in eGFR and ensured its gradual reversible decline, which reflected a decrease in the hemodynamic load on individual glomeruli of the single functioning kidney/graft.

It should be noted that we did not use clearance methods for measuring renal filtration, since eGFR can be considered as a prognostic marker for long-term survival of the recipient and the kidney transplant, similarly to the generally accepted concept of CKD [23, 27, 28].

The beneficial effect of SGLT2is on renal transplant revascularization, which we included in the composite endpoint by analogy to myocardial revascularization, may be mediated by the metabolic effect of the SGLT2i therapy due to a decrease in insulin secretion and increased synthesis of glucagon, non-esterified fatty acids, ketone utilization, lipolysis, and gluconeogenesis. These effects mediate a decrease in plasma LDL and an increase in plasma HDL, as well as the inhibitory effect of increased natriuresis on the sympathetic nervous activity followed by vasodilation and improvement of the endothelial function [29]. In addition, the inhibition of SGLT2 simultaneously initiates natriuresis and glucosuria to reduce IR and the associated risk of the development and/or progression of PTDM and CVD [29, 30].

Figure 5. Probability of the primary composite endpoint (cardiovascular and renal adverse fatal and nonfatal outcomes (A)), secondary composite coronary endpoint (B), and renal adverse outcomes (C) in the compared groups (Kaplan-Meier analysis)



Our study also demonstrated that the SGLT2i treatment was associated with a reduction in the RR of death and adverse coronary outcomes. This allows discussing the additive effect of the combination of SGLT2i with ACE inhibitors or ARBs, which reduces the residual risk of ESKD and CV death [31–33] in KTRs, a high-risk group for death from CVD [34–36].

Importantly, the incidence of UTI in the experimental group was very low and did not differ from that in the control group. There were no cases of euglycemic ketoacidosis in our study, which is consistent with previously obtained data from randomized [10] and observational [37, 38] studies on the safety of SGLT2is in KTRs.

Limitations of this study included the time frame, the small number of patients in the experimental and control groups, and the pseudorandomization.

Conclusion

This study demonstrated increased survival of KTRs associated with the use of SGLT2is, regardless of the presence of PTDM, due to a reduction in all-cause mortality. This study also demonstrated the nephroprotective and cardioprotective effects of SGLT2is and their safety. Long-term prospective randomized studies of the ef-

fects of SGLT2is on long-term outcomes of kidney transplantation are needed.

No conflict of interest declared.

The article was received on 11/05/2025

REFERENCES

1. National Association of Nephrologists. Clinical guidelines. Chronic kidney disease (CKD). 2024. Av. at: <https://rusnephrology.org/wp-content/uploads/2024/06/>

KP_ХБП_от_10.06.2024.pdf. [Russian: Национальная Ассоциация нефрологов. Клинические рекомендации. Хроническая болезнь почек (ХБП). 2024. Доступно на:

- https://rusnephrology.org/wp-content/uploads/2024/06/КР_ХБП_от_10.06.2024.pdf]
2. Stevens PE, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney International*. 2024;105(4S): S117–314. DOI: 10.1016/j.kint.2023.10.018
3. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D et al. Improving Care and Promoting Health in Populations: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023;46(Suppl 1): S10–8. DOI: 10.2337/dc23-S001
4. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *European Heart Journal*. 2023;44(39):4043–140. DOI: 10.1093/eurheartj/ehad192
5. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F et al. Dapagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine*. 2020;383(15):1436–46. DOI: 10.1056/NEJMoa2024816
6. The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ et al. Empagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine*. 2023;388(2):117–27. DOI: 10.1056/NEJMoa2204233
7. Ekberg H, Tedesco-Silva H, Demirbas A, Vitko Š, Nashan B, Gürkan A et al. Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation. *New England Journal of Medicine*. 2007;357(25):2562–75. DOI: 10.1056/NEJMoa067411
8. Bailey CJ, Day C, Bellary S. Renal Protection with SGLT2 Inhibitors: Effects in Acute and Chronic Kidney Disease. *Current Diabetes Reports*. 2022;22(1):39–52. DOI: 10.1007/s11892-021-01442-z
9. Vallon V, Verma S. Effects of SGLT2 Inhibitors on Kidney and Cardiovascular Function. *Annual Review of Physiology*. 2021;83(1):503–28. DOI: 10.1146/annurev-physiol-031620-095920
10. Halden TAS, Kvitne KE, Midtvedt K, Rajakumar L, Robertsen I, Brox J et al. Efficacy and Safety of Empagliflozin in Renal Transplant Recipients With Posttransplant Diabetes Mellitus. *Diabetes Care*. 2019;42(6):1067–74. DOI: 10.2337/dc19-0093
11. Novikova M. S., Allazova S. S., Molina L. P., Koteschkova O. M., Antsiferov M. B., Kotenko O. N. et al. Effectiveness and safety of SGLT-2 inhibitors for renal allograft recipients with post-transplant diabetes mellitus: an open single-center prospective study. *Clinical Nephrology*. 2022;14(2):33–41. [Russian: Новикова М. С., Аллазова С. С., Молина Л. П., Котешкова О. М., Анциферов М. Б., Котенко О. Н. и др. Эффективность и безопасность иНГЛТ-2 для реципиентов почечного аллотрансплантата с посттрансплантационным сахарным диабетом: открытое одноцентровое проспективное исследование. *Клиническая нефрология*. 2022;14(2):33–41]. DOI: 10.18565/nephrology.2022.2.33-41
12. American Diabetes Association. Executive Summary: Standards of Medical Care in Diabetes-2012. *Diabetes Care*. 2012;35(Suppl 1): S4–10. DOI: 10.2337/dc12-s004
13. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic Crises in Adult Patients With Diabetes. *Diabetes Care*. 2009;32(7):1335–43. DOI: 10.2337/dc09-9032
14. Levey AS, Coresh J, Greene T, Stevens LA, Zhang Y (Lucy), Hendriksen S et al. Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate. *Annals of Internal Medicine*. 2006;145(4):247–54. DOI: 10.7326/0003-4819-145-4-200608150-00004
15. The Helsinki Declaration of the World Medical Association. Ethical principles of medical research involving humans as subjects of research. Av. at: <https://lec.kpfu.ru/wp-content/uploads/2024/02/helsinskaya-deklaraciya-vsemirnoj-mediczinskoj-assocziaczii.pdf>. [Russian: Хельсинкская Декларация Всемирной Медицинской Ассоциации. Этические принципы медицинских исследований с участием человека в качестве объекта исследования. Доступно на: <https://lec.kpfu.ru/wp-content/uploads/2024/02/helsinskaya-deklaraciya-vsemirnoj-mediczinskoj-assocziaczii.pdf>]
16. Hjelmæsæth J, Midtvedt K, Jenssen T, Hartmann A. Insulin Resistance After Renal Transplantation: impact of immunosuppressive and antihypertensive therapy. *Diabetes Care*. 2001;24(12):2121–6. DOI: 10.2337/diacare.24.12.2121
17. Oliveras L, Coloma A, Lloberas N, Lino L, Favà A, Manonelles A et al. Immunosuppressive drug combinations after kidney transplantation and post-transplant diabetes: A systematic review and meta-analysis. *Transplantation Reviews*. 2024;38(3):100856. DOI: 10.1016/j.trre.2024.100856
18. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: A paradigm shift in nephrology. *Kidney International*. 1996;49(6):1774–7. DOI: 10.1038/ki.1996.265
19. Esteve-Font C, Ars E, Guillen-Gomez E, Campistol JM, Sanz L, Jimenez W et al. Ciclosporin-induced hypertension is associated with increased sodium transporter of the loop of Henle (NKCC2). *Nephrology Dialysis Transplantation*. 2007;22(10):2810–6. DOI: 10.1093/ndt/gfm390
20. Upadhyay A. SGLT2 Inhibitors and Kidney Protection: Mechanisms Beyond Tubuloglomerular Feedback. *Kidney360*. 2024;5(5):771–82. DOI: 10.34067/KID.0000000000000425
21. Klen J, Dolžan V. SGLT2 Inhibitors in the Treatment of Diabetic Kidney Disease: More than Just Glucose Regulation. *Pharmaceutics*. 2023;15(7):1995. DOI: 10.3390/pharmaceutics15071995
22. Jin J, Jin L, Luo K, Lim SW, Chung BH, Yang CW. Effect of Empagliflozin on Tacrolimus-Induced Pancreas Islet Dysfunction and Renal Injury. *American Journal of Transplantation*. 2017;17(10):2601–16. DOI: 10.1111/ajt.14316
23. Vestergaard AHS, Jensen SK, Heide-Jørgensen U, Frederiksen LE, Birn H, Jarbøl DE et al. Risk factor analysis for a rapid progression of chronic kidney disease. *Nephrology Dialysis Transplantation*. 2024;39(7):1150–8. DOI: 10.1093/ndt/gfad271
24. Masrouri S, Tamehri Zadeh SS, Pishgahi M, Azizi F, Shapiro MD, Hadaegh F. Kidney function decline is associated with mortality events: over a decade of follow-up from Tehran Lipid and Glucose Study. *Journal of Nephrology*. 2023;37(1):107–18. DOI: 10.1007/s40620-023-01756-z
25. Kraus BJ, Weir MR, Bakris GL, Mattheus M, Cherney DZI, Sattar N et al. Characterization and implications of the initial estimated glomerular filtration rate ‘dip’ upon sodium-glucose cotransporter-2 inhibition with empagliflozin in the EMPA-REG OUTCOME trial. *Kidney International*. 2021;99(3):750–62. DOI: 10.1016/j.kint.2020.10.031
26. Lim J-H, Kwon S, Jeon Y, Kim YH, Kwon H, Kim YS et al. The Efficacy and Safety of SGLT2 Inhibitor in Diabetic Kidney Transplant Recipients. *Transplantation*. 2022;106(9):e404–12. DOI: 10.1097/TP.0000000000004228
27. Novikova M. S., Minushkina L. O., Kotenko O. N., Zateyshchikov D. A., Boeva O. I., Allazova S. S. et al. Systematic review and meta-analysis of the effect of calcineurin inhibitors on long-term prognosis in kidney transplant recipients. *Clinical Nephrology*. 2023;15(4):34–43. [Russian: Новикова М. С., Минушкина Л. О., Котенко О. Н., Затеишчиков Д. А., Боева О. И., Аллазова С. С. и др. Систематический обзор и мета-анализ влияния

- ингибиторов кальциневрина на долгосрочный прогноз у реципиентов почечного трансплантата. Клиническая нефрология. 2023;15(4):34–43]. DOI: 10.18565/nephrology.2023.4.34-43
28. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. American Journal of Kidney Diseases. 2002;39(2 Suppl 1): S1–266. PMID: 11904577
29. Salvadori M, Rosati A, Rosso G. Update on Sodium Glucose Cotransporter Type 2 Inhibitors Use in Kidney Transplant Patients. Transplantation. 2024;5(3):224–33. DOI: 10.3390/transplantation5030022
30. Tuttle KR, Brosius FC, Cavender MA, Fioretto P, Fowler KJ, Heerspink HJL et al. SGLT2 Inhibition for CKD and Cardiovascular Disease in Type 2 Diabetes: Report of a Scientific Workshop Sponsored by the National Kidney Foundation. Diabetes. 2021;70(1):1–16. DOI: 10.2337/dbi20-0040
31. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving H-H et al. Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy. New England Journal of Medicine. 2001;345(12):861–9. DOI: 10.1056/NEJMoa011161
32. Wang W, Chen LY, Walker RF, Chow LS, Norby FL, Alonso A et al. SGLT2 Inhibitors Are Associated With Reduced Cardiovascular Disease in Patients With Type 2 Diabetes. Mayo Clinic Proceedings. 2023;98(7):985–96. DOI: 10.1016/j.mayocp.2023.01.023
33. Blazek O, Bakris GL. The evolution of “pillars of therapy” to reduce heart failure risk and slow diabetic kidney disease progression. American Heart Journal Plus. 2022;19:100187. DOI: 10.1016/j.ahjo.2022.100187
34. Tsai T-H, Huang K-H, Chen H, Gau S-Y, Su K-Y, Tsai M-L et al. Risks of cardiovascular disease and cerebrovascular disease following kidney transplantation: A nationwide, population-based cohort study. International Journal of Medical Sciences. 2025;22(9):2237–46. DOI: 10.7150/ijms.108744
35. Birdwell KA, Park M. Post-Transplant Cardiovascular Disease. Clinical Journal of the American Society of Nephrology. 2021;16(12):1878–89. DOI: 10.2215/CJN.00520121
36. Novikova M. S., Minushkina L. O., Kotenko O. N., Zateyshchikov D. A., Boeva O. I., Allazova S. S. et al. Mortality in kidney transplant recipients: a systematic review and meta-analysis of cohorts and clinical registries. Clinical Nephrology. 2023;15(1):5–12. [Russian: Новикова М. С., Минушкина Л. О., Котенко О. Н., Затеищиков Д. А., Боева О. И., Аллазова С. С. и др. Смертность у реципиентов почечного трансплантата: систематический обзор и мета-анализ когорт и клинических регистров. Клиническая нефрология. 2023;15(1):5–12]. DOI: 10.18565/nephrology.2023.1.5-12
37. AlKindi F, Al-Omary HL, Hussain Q, Al Hakim M, Chaaban A, Boobes Y. Outcomes of SGLT2 Inhibitors Use in Diabetic Renal Transplant Patients. Transplantation Proceedings. 2020;52(1):175–8. DOI: 10.1016/j.transproceed.2019.11.007
38. Schwaiger E, Burghart L, Signorini L, Ristl R, Kopecky C, Tura A et al. Empagliflozin in posttransplantation diabetes mellitus: A prospective, interventional pilot study on glucose metabolism, fluid volume, and patient safety. American Journal of Transplantation. 2019;19(3):907–19. DOI: 10.1111/ajt.15223