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RESEARCH CORRESPONDENCE

Empagliflozin in the management of diabetes mellitus after cardiac transplantation

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Post-transplant diabetes mellitus (PTDM) is a well-recognized complication of solid-organ transplantation.[1] PTDM has been associated with increased rates of serious infection, graft rejection, and graft dysfunction and reduced long-term survival compared with non-diabetic transplant recipients.[1] Empagliflozin, a selective sodium-glucose cotransporter-2 (SGLT-2) inhibitor, is a novel oral therapy for management of type 2 diabetes mellitus. When added to standard diabetes care in patients at high cardiovascular risk, empagliflozin is associated with significant reductions in major adverse cardiovascular events, all-cause mortality, and hospitalizations for heart failure.[2] It has also been shown to delay the progression of diabetic nephropathy in patients with established chronic kidney disease.[3] Despite proven efficacy in the non-transplant setting, the safety and efficacy of empagliflozin in heart transplant recipients, a patient population at high cardiovascular risk, have not been specifically examined.

We retrospectively studied clinical outcomes in consecutive heart transplant recipients with diabetes attending a heart transplant follow-up clinic between January 1, 2016, and August 31, 2016. The primary study aim was to document rates of empagliflozin use in the heart transplant population, including changes in body weight, blood pressure, glycated hemoglobin (HbA_{1c}), diuretic (furosemide) dose, and renal function. Only patients with follow-up data after a minimum treatment period of 3 months were included for analysis. Adverse events potentially attributable to empagliflozin were documented, with specific focus on genital and urinary tract infections given that transplant recipients are actively immunosuppressed. Data are expressed as mean ± SD if normally distributed or median (interquartile range) if non-normally distributed. Non-paired *t*-tests were used to compare the groups. Paired *t*-tests were used to analyze pre-treatment and post-treatment data in empagliflozin-treated patients.

Over the 8-month study period, 316 heart transplant recipients presented to the clinic. The study population was predominately male (71%) with a mean age of 55.8 years ± 14.4. Average time from cardiac transplantation was 9.6 years ± 8.3. Diabetes was prevalent in 106 (33%) of patients, with an average diabetes duration of 7.9 years ± 7.4. Baseline demographic characteristics by treatment group are shown in Table 1.

There were 19 diabetic patients treated with empagliflozin in addition to standard diabetes therapy. Dose was not standardized and was decided by the prescribing physician. In our cohort, 10 patients received 10 mg daily, and 9 patients received 25 mg daily. All but 2 patients started empagliflozin after transplantation, with a median time to start of empagliflozin after transplant of 5.5 years (interquartile range 0–11 years). Median treatment duration was 9 months (interquartile range 6.5–11 months). Pre-treatment and post-treatment data with >3 months of follow-up were available for 16 heart transplant recipients. Two patients were excluded because of insufficient empagliflozin exposure time (<3 months), and 1 patient was excluded because follow-up had not been recorded since starting empagliflozin, and thus post-treatment results were not available.

Empagliflozin use resulted in a significant reduction in body weight of 2.7 kg ± 5.1 ($p = 0.05$), with a mean reduction in body mass index of 0.9 kg/m^2 ± 1.7 ($p = 0.04$). Weight reduction occurred despite a significant decrease in mean furosemide dose ($p = 0.05$), potentially mediated through the diuretic effect of SGLT-2 inhibition with subsequent glycosuria. Following empagliflozin use, systolic blood pressure was reduced by 12 mm Hg ± 19 ($p = 0.03$), and diastolic blood pressure was reduced by 7 mm Hg ± 11 ($p = 0.03$). There was a non-significant reduction in HbA_{1c} of 0.6% ($p = 0.11$) (Table 2).

Of 87 heart transplant recipients treated with standard care (no empagliflozin exposure), 74 had pre-treatment and post-treatment data with >3 months of follow-up available. Standard care using non–empagliflozin-based diabetes therapies was not associated with reductions in body weight, body mass index, blood pressure, furosemide dose, or HbA_{1c}. There was a trend toward increased serum creatinine ($p = 0.07$) (Table 2).

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Table 1 Characteristics of Patients at Baseline

Characteristic	With empagliflozin ($n = 16$)	Without empagliflozin ($n = 74$)	p-value
Age, years, mean ± SD	55.0 ± 13.2	58.2 ± 10.2	0.29
Male sex (%)	13 (81.3)	53 (71.6)	0.43
Comorbidities (%)			
Chronic kidney disease	14 (87.5)	65 (87.8)	0.97
Hypertension	15 (93.8)	67 (90.5)	0.60
Diabetes duration, years, mean ± SD	7.1 ± 6.2	8.7 ± 7.7	0.42
Time since transplant, years, mean ± SD	8.2 ± 8.1	9.6 ± 7.7	0.52
HbA_{1c}, %, mean ± SD	7.3 ± 1.0	6.8 ± 1.2	0.21
Diabetes treatment (%)			
Insulin	5 (31.3)	37 (50.0)	0.17
Metformin	11 (68.8)	27 (36.5)	0.02[a]
Sulfonylurea	5 (31.3)	9 (12.2)	0.06
DPP-4 inhibitor	2 (12.5)	5 (6.8)	0.44
GLP-1 agonist	0 (0.0)	1 (1.4)	0.64
Diet controlled	2 (12.5)	11 (14.9)	0.81
Number of diabetes medications			
0	2	11	
1	6	41	
2	4	16	
≥3	3	6	
Prednisone use (%)	11 (68.8)	39 (52.7)	0.24
Diuretic use (%)	6 (37.5)	28 (37.8)	0.98

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin.
[a]$p < 0.05$

Empagliflozin was well tolerated. After 147 months of cumulative empagliflozin exposure in 19 patients, only 2 experienced side effects. One patient reported dizziness, and the other reported polyuria and exacerbation of pre-existing lower urinary tract symptoms.

We present a retrospective analysis of empagliflozin use after cardiac transplantation. In our cohort of 16 patients, empagliflozin use was associated with significant reductions in body weight, blood pressure, and furosemide dose that were not observed in diabetic patients treated with standard care using non–empagliflozin-based therapies. Post-transplant care is complex, with most patients requiring multiple long-term immunosuppressive and anti-infective therapies with significant potential for treatment-related morbidity. In our cohort of patients treated with empagliflozin, there were no apparent drug-drug interactions of empagliflozin apart from the reduction in diuretic use observed in patients requiring furosemide after cardiac transplantation. Chronic kidney disease is common in the post-transplant setting, and, importantly, empagliflozin use did not adversely affect renal function in our cohort—consistent with the renoprotective effect observed in the non-transplant setting.[3] SGLT-2 inhibitor use has also been associated with development of euglycemic ketoacidosis, especially when continued during surgery or acute illness. Heart transplant recipients would seemingly be at higher risk for the development of this side effect. However, we did not observe ketonemia or significant acid-base disorders in our cohort of patients treated with empagliflozin.

In initial studies, empagliflozin was associated with significantly increased rates of genital infection and

Table 2 Metabolic and Hemodynamic Measures in Diabetic Heart Transplant Recipients Before and After ≥3 Months of Treatment With Standard Diabetes Care With or Without Empagliflozin

	With empagliflozin			Without empagliflozin		
Clinical parameter	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value
Weight, kg	89.2 ± 15.4	86.5 ± 16.1	0.05[a]	80.0 ± 16.0	80.1 ± 16.3	0.90
Body mass index, kg/m^2	29.8 ± 4.2	28.9 ± 4.5	0.04[a]	27.8 ± 5.3	27.8 ± 5.5	0.88
Systolic blood pressure, mm Hg	134 ± 16	122 ± 16	0.03[a]	138 ± 20	138 ± 21	0.91
Diastolic blood pressure, mm Hg	82 ± 11	75 ± 11	0.03[a]	84 ± 9	82 ± 11	0.41
Furosemide dose, mg	45 ± 76	16 ± 43	0.05[a]	36 ± 73	31 ± 105	0.56
HbA_{1c}, %	7.3 ± 1.0	6.7 ± 1.0	0.11	6.8 ± 1.2	7.2 ± 1.2	0.12
eGFR, ml/min	57 ± 18	58 ± 20	0.95	54 ± 20	53 ± 20	0.59
Serum creatinine, μmol/liter	122 ± 29	125 ± 39	0.71	130 ± 60	138 ± 70	0.07

eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin.
[a]$p < 0.05$

uncomplicated urinary tract infection in female patients.[3] Given the immunosuppressed status of heart transplant recipients, theoretical risk of serious genitourinary infection needs to be considered when prescribing empagliflozin. Our data did not substantiate this risk, and no genitourinary infections were documented with >147 months of cumulative use. That considered, we would still use caution in prescribing these agents to patients with history of urinary tract infection or pre-existing urinary symptoms.

Limitations of our study include the retrospective, non-randomized study design. The decision to introduce empagliflozin was made at the discretion of the treating endocrinologist or cardiologist, and it is possible that improvements we documented after introduction of empagliflozin may have been achieved by other approaches to diabetes management. However, the lack of improvement observed in the patients who received conventional diabetes management suggests that this is not the case. Metformin use was higher in empagliflozin-treated patients. This may have contributed to the weight loss observed but is unlikely to explain the improvements in blood pressure control and lower diuretic use. Ideally, our findings should be replicated in a prospective randomized trial of empagliflozin in patients with PTDM.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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