

BRIEF REPORT

Diabetes Therapy With SGLT2i After Heart Transplant

A Multi-Institutional Analysis



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Heart transplantation markedly improves health-related quality of life and survival in patients with advanced heart failure.^{1,2} However, heart transplant (HT) recipients remain at elevated risk for chronic kidney disease (CKD) and cardiovascular morbidity and mortality.³⁻⁵ Diabetes is common after HT procedures and further increases the risk of CKD and cardiovascular disease.⁶ Mitigating the negative effects of these comorbidities is a critical unmet need. Sodium-glucose cotransporter 2 inhibitors (SGLT2is) improve outcomes in patients with diabetes, heart failure, and/or CKD who are not HT recipients.⁷⁻⁹ SGLT2i may offer similar benefits after transplantation, but HT recipients were excluded from the pivotal clinical trials of SGLT2i.

METHODS

We sought to evaluate the possible benefits associated with SGLT2i in HT recipients, as well as SGLT2i safety and tolerability after HT, by performing a retrospective, multicenter cohort study of U.S. veteran HT recipients using the Veterans Affairs Informatics and Computing Infrastructure. We included patients with a diagnosis of type 2 diabetes before 2018, who received an HT before 2021, and who were prescribed long-acting insulin or an SGLT2i after receiving the HT. We assessed patient outcomes beginning at the index date of insulin or SGLT2i prescription through the end of follow-up in June 2023.

Our efficacy outcomes included cardiometabolic and kidney markers, erythropoiesis, and mortality. Our safety outcomes were hypoglycemic events and genitourinary (GU) infections. To balance baseline characteristics across the 2 drug classes, we performed inverse probability treatment weighting (IPTW) by computing generalized propensity scores under a logistic regression model that predicted the probabilities of initiating long-acting insulin or SGLT2i from the baseline covariates.¹⁰ We used the mixed-effects models to show changes in

What is the clinical question being addressed?

What are the potential benefits of SGLT2i use for HT recipients with diabetes? Are these therapies safe?

What is the main finding?

Use of SGLT2i agents in HT recipients is associated with several cardiometabolic benefits, with a favorable safety and tolerability profile.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Manuscript received January 31, 2025; revised manuscript received April 11, 2025, accepted May 21, 2025.

**ABBREVIATIONS
AND ACRONYMS****CKD** = chronic kidney disease**EPPY** = events per 100 person-years**GU** = genitourinary**Hb** = hemoglobin**HT** = heart transplant**IPTW** = inverse probability treatment weighting**SGLT2i** = sodium-glucose cotransporter 2 inhibitor

cardiometabolic and erythropoietic parameters over time and performed separate Cox regression models with IPTW to relate drug classes to subsequent mortality, hypoglycemia, or GU infections.

This study was approved by the Institutional Review Board of the Salt Lake City Veterans Affairs Medical Center and the University of Utah (both in Salt Lake City, Utah, USA).

RESULTS

Of the 1,058 HT recipients with diabetes who met the inclusion criteria, 845 received long-acting insulin and 213 received an SGLT2i. Patients had a mean age of 67.9 ± 8.8 years and were predominantly male (97.5%), with 73.2% self-identifying as White and 23.4% as Black. The mean time since transplantation was 5.8 ± 5.4 years. Additional baseline characteristics are shown in **Figure 1A**.

Over 24 months after drug initiation, patients in the SGLT2i group experienced more favorable changes in the majority of the parameters of interest compared with patients treated with insulin, including a reduction in mean systolic blood pressure (-3.2 mm Hg vs $+1.4$ mm Hg; $P = 0.01$), a greater decrease in mean body mass index (-1.2 kg/m 2 vs -0.4 kg/m 2 ; $P < 0.01$), and an increase in serum hemoglobin (Hb) ($+0.4$ g/dL vs -0.2 g/dL; $P < 0.01$) (**Figure 1B**).

These findings, in general, persisted after applying IPTW, with changes favoring the SGLT2i group, including a decrease in systolic blood pressure (-3.7 mm Hg vs $+1.6$ mm Hg; $P = 0.04$), a greater decrease in body mass index (-1.3 kg/m 2 vs -0.5 kg/m 2 ; $P = 0.04$), and a nonsignificant increase in Hb ($+0.3$ g/dL vs -0.2 g/dL; $P = 0.14$) (**Figure 1B**). The change in estimated glomerular filtration rate over 24 months was similar in both the SGLT2i and insulin groups: -2.2 mL/min/1.73 m 2 vs -2.3 mL/min/1.73 m 2 ($P = 0.88$) (unweighted) and -2.6 mL/min/1.73 m 2 vs -2.2 mL/min/1.73 m 2 ($P = 0.77$) with IPTW (**Figure 1B**). The change in HbA $_{1c}$ over 24 months in the SGLT2i and insulin groups was -0.07% vs -0.40% ($P = 0.01$) (unweighted) and -0.22% vs -0.39% ($P = 0.27$) with IPTW.

There were 39 deaths, 6 hypoglycemic events, and 26 GU infections among the 213 patients in the SGLT2i group and 355 deaths, 100 hypoglycemic events, and 162 GU infections among the 845 patients in the insulin group. On the basis of the Cox regression model with IPTW, the rate of mortality events per 100 person-years (EPPY) in the SGLT2i-treated patients was numerically lower compared with the insulin

group, 6.8 EPPY (95% CI: 3.6-14.1 EPPY) vs 11.6 EPPY (95% CI: 10.3-12.9 EPPY), (HR for mortality: 0.58; 95% CI: 0.31-1.07). The rate of hypoglycemia in the SGLT2i vs insulin group was 1.5 EPPY (95% CI: 0.5-6.3 EPPY) vs 3.4 EPPY (95% CI: 2.8-4.3 EPPY), (HR for hypoglycemia: 0.39; 95% CI: 0.14-1.10), and the rate of GU infection was 5.8 EPPY (95% CI: 2.8-12.6 EPPY) vs 6.0 EPPY (95% CI: 5.1-7.1 EPPY), (HR for GU infection: 0.92; 95% CI: 0.45-1.91).

DISCUSSION

These findings provide observational evidence that SGLT2i may offer unique cardiometabolic benefits to HT recipients with diabetes and a survival advantage compared with therapy with insulin. Because SGLT2i benefits are similar in non-HT patients with and without diabetes, it is likely that SGLT2i would also have positive effects in HT recipients without diabetes.^{8,9}

Out of concern for interactions with immunosuppressive drugs and the potential for side effects in immunosuppressed patients, there is general hesitance to test novel pharmacotherapies in transplant recipients. However, transplant recipients carry a disproportionately high risk for CKD and CV disease and thus may experience enhanced benefits from recently approved medications. Our results provide reassurance that SGLT2i agents are safe after transplantation and support a need for prospective randomized studies in transplant recipients.

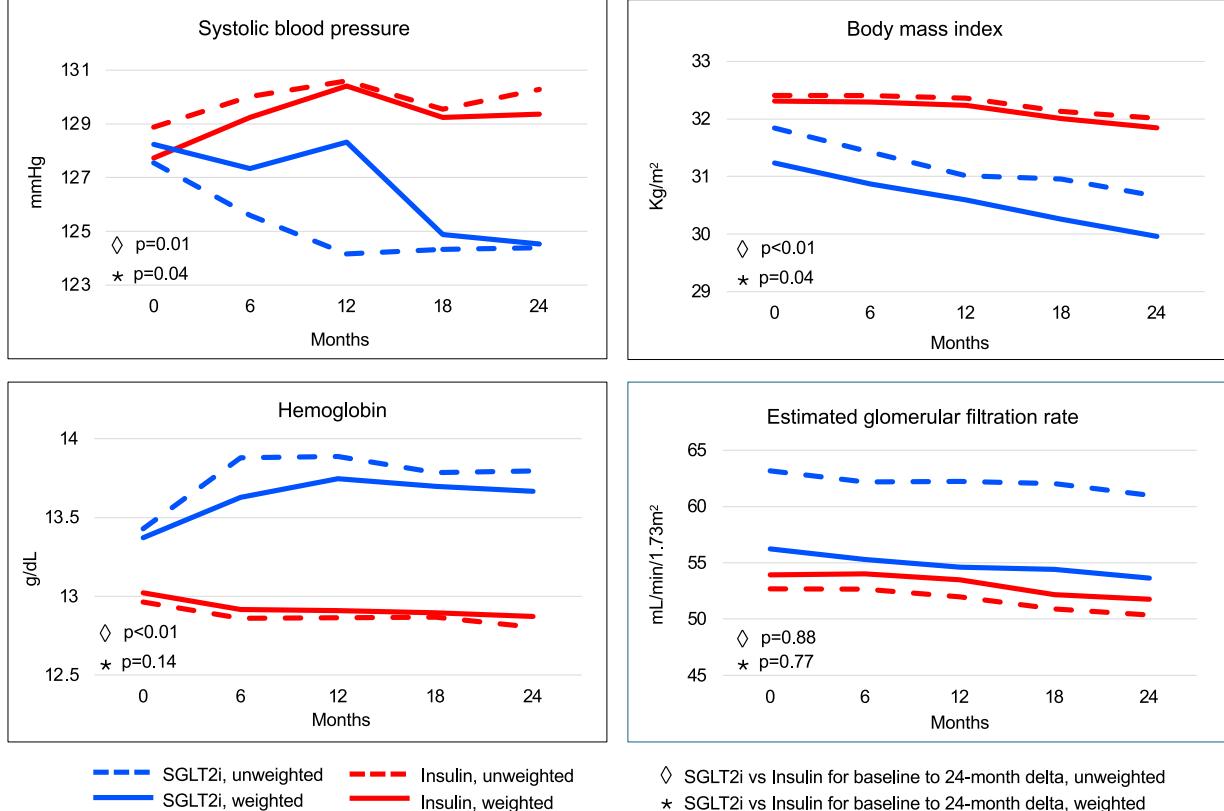
STUDY LIMITATIONS. Our study has limitations that relate to its retrospective design. There were baseline differences between the patients treated with an SGLT2i and those treated with insulin. Even after IPTW, some imbalances persisted, and unmeasured confounding variables may have been present. Specifically, we did not have detailed data on immunosuppression use, rejection history, and use of antihypertensive agents. Within 2 years of the index date, 33 of 213 patients in the SGLT2i group were started on long-acting insulin, and 84 of the 845 patients in the insulin group were started on an SGLT2i. Although this “crossover” is a limitation, its effect would likely decrease the differences we report in outcomes between the 2 groups. Our results show the average impact of insulin and SGLT2i treatment on cardiometabolic outcomes, rate of GU infection, and mortality. Whether the balance of these effects changes as a function of time since transplantation, given the differences in immunosuppression intensity and cardiometabolic risk, is not addressed by this study. Finally, women were underrepresented in this study (2.5%). Although we are not aware of sex-based

FIGURE 1 Baseline Characteristics of HT Recipients and Longitudinal Changes in Biomarkers

A

Baseline variables	Unweighted			Inverse probability weighted	
	Total N=1058	Insulin n=845	SGLT2i n=213	Insulin	SGLT2i
Age, years, mean (SD)	67.9 (8.8)	68.0 (8.8)	67.6 (8.8)	67.9 (8.8)	68.0 (8.3)
Time since HT, years, mean (SD)	5.8 (5.4)	5.8 (5.2)	5.5 (5.2)	5.7 (5.4)	6.0 (5.3)
Female, n (%)	26 (2.5)	21 (2.5)	5 (2.3)	2.3%	0.8%
Race, n (%)					
White	773 (73.1)	638 (75.5)	135 (63.4)	73.6%	70.3%
Black	248 (23.4)	181 (21.4)	67 (31.5)	23.4%	27.9%
SBP, mmHg, mean (SD)	128.6 (16.1)	129.1 (16.1)	126.4 (16.1)	128.5 (16.3)	125.9 (19.3)
BMI, kg/m ² , mean (SD)	31.8 (6.2)	31.9 (6.3)	31.7 (5.8)	31.8 (6.2)	31.8 (5.5)
HbA _{1c} %, mean (SD)	8.0 (1.7)	8.2 (1.8)	7.5 (1.3)	8.1 (1.8)	8.0 (1.3)
eGFR, mL/min/1.73m ² , mean (SD)	55.1 (21.7)	53.1 (21.6)	62.8 (20.2)	54.9 (22.1)	55.3 (19.1)
Medications, n (%)					
Metformin	323 (30.5)	217 (25.7)	106 (49.8)	28.5%	39.7%
Sulfonylurea	206 (19.5)	139 (16.4)	67 (31.5)	19.4%	18.4%
Diuretic	612 (57.8)	473 (56.0)	139 (65.3)	57.3%	52.9%

B



(A) Unweighted and inverse probability-weighted baseline characteristics at the time of initiation of a sodium-glucose cotransporter 2 inhibitor (SGLT2i) or long-acting insulin. (B) Longitudinal outcomes after initiation of an sodium-glucose cotransporter 2 inhibitor (blue) or long-acting insulin (red). Unweighted results are represented by dashed lines, weighted results by solid lines. For each outcome, the change (delta) over 24 months in the sodium-glucose cotransporter 2 inhibitor group is compared with the change (delta) over 24 months in the insulin group. The diamond and asterisk denote the P value for the comparison of the 2 deltas in the unweighted and weighted analyses, respectively. BMI = body mass index; eGFR = estimated glomerular filtration; HbA_{1c} = hemoglobin A_{1c}; HT = heart transplant; SBP = systolic blood pressure.

mechanistic differences in the effects of SGLT2i use, some clinical outcomes after heart transplantation differ by sex. Therefore, the predominantly male population in our cohort may limit the generalizability of the results to women.

CONCLUSIONS

In this large cohort of contemporary HT recipients with diabetes, SGLT2i use was associated with modest improvements in important cardiometabolic parameters. SGLT2i also appeared to be safe in this group of transplant recipients who were receiving immunosuppression. If benefits of SGLT2i use after heart transplantation can be confirmed in prospective studies, this could represent a rare opportunity to add evidence-based therapy and improve outcomes in the extended post-transplantation period.

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FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Kyriakopoulos has received funding from the National Heart, Lung, and Blood Institute (2T32HL007576-36). Dr Melenovsky has received funding from the National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, ID Project No. LX22NPO5104 - Next Generation EU). Dr Stehlik has served as a consultant to Natera, NovoNordisk, Sanofi, Medtronic, and TransMedics; has received research support from Natera, Merck, and the National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, ID Project No. LX22NPO5104 - Next Generation EU); and has received funding as principal investigator from the Veterans Health Administration CSR & D Merit Review (I01CX002816-01A1). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS cardiometabolic, chronic kidney disease, diabetes, erythropoiesis, heart transplant, sodium-glucose cotransporter 2 inhibitors