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Effect of sodium glucose cotransporter 2 inhibition immediately prior to heart transplantation

Lisa M. Raven, MBBS, FRACP,[a,b,c,*]
Christopher A. Muir, MBBS (Hons), FRACP, PhD,[a,c]
Ricardo C. Deveza, MD, FRACP,[c,d,e]
Cassia Kessler Iglesias, MD (Hons), FRACP,[c,d,e]
Nicole K. Bart, MBBS (Hons), BSc (Med Sci), DPhil (Oxon), FRACP,[c,d,e]
Kavitha Muthiah, MBChB, PhD, FRACP,[c,d,e]
Eugene Kotlyar, MBBS, MD, MPVD, FRACP,[c,d,e]
Christopher S. Hayward, BMedSc, MBBS (Hons), MD, FRACP,[c,d,e]
Peter S. Macdonald, MBBS, MD, PhD, FRACP,[c,d,e]
Andrew Jabbour, BSc (Med), MBBS (Hons), PhD, FRACP,[c,d,e] and
Jerry R. Greenfield, MBBS (Hons 1), PhD, FRACP[a,b,c]

[a]*Department of Diabetes and Endocrinology, St Vincent's Hospital, Sydney, NSW, Australia*
[b]*Clinical Diabetes, Appetite and Metabolism Laboratory, Garvan Institute of Medical Research, Sydney, NSW, Australia*
[c]*School of Clinical Medicine, St Vincent's Campus, Faculty of Medicine and Health, University of New South Wales, Sydney, NSW, Australia*
[d]*Department of Heart and Lung Transplantation, St Vincent's Hospital, Sydney, NSW, Australia*
[e]*Victor Chang Cardiac Research Institute, Sydney, NSW, Australia*

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Sodium glucose cotransporter 2 inhibitors (SGLT2i) are an established treatment for heart failure and type 2 diabetes. Guidelines suggest withholding SGLT2i preoperatively due to the risk of ketoacidosis. Orthotopic heart transplantation (OHT) occurs without sufficient notice to cease SGLT2i treatment before surgery. In a retrospective analysis of 163 OHT recipients (40 exposed to SGLT2i, 123 not exposed), we show no increase in rates of mild, moderate, or severe acidosis postoperatively. No cases of ketoacidosis occurred, likely due to the fact that 97% of patients received insulin infusions post-operatively for transient postoperative hyperglycemia. Patients exposed to SGLT2i had shorter length of stay in the intensive care unit and improved adjusted survival overall. These findings support the safety of SGLT2i use up to the time of OHT with routine use of a postoperative insulin infusion.
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*Corresponding author: Lisa M. Raven, MBBS, FRACP, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, NSW 2010, Australia.
E-mail address: l.raven@garvan.org.au.

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Sodium glucose cotransporter 2 inhibitors (SGLT2i) are an established treatment for type 2 diabetes (T2DM), heart failure, and chronic kidney disease. Orthotopic heart transplantation (OHT) is a life-saving procedure for treatment of end-stage heart failure. As SGLT2i are a pillar of heart failure treatment, it is anticipated that most patients on the OHT waitlist will be prescribed these medications.[1,2] There is limited research on the safety of SGLT2i use before OHT.[3] Euglycaemic ketoacidosis is a rare but serious adverse event associated with SGLT2i use. Prolonged fasting can precipitate ketoacidosis and guidelines recommend that SGLT2i be withheld for at least 3 days before major surgery.[4] OHT occurs at short notice and SGLT2i are only withheld on arrival to hospital, which is usually < 12 hours before surgery.

The aim of the present study was to assess the likelihood of acidosis and other post-transplant outcomes in patients treated with SGLT2i up until the time of OHT.

A retrospective cohort study was conducted of consecutive OHT recipients at a single center between January 2020 and December 2022, with follow-up until December 2023. The primary outcome was incidence of acidosis (defined as pH ≤ 7.30) in patients receiving SGLT2i vs those not receiving SGLT2i within 24 hours of OHT.[5] Secondary outcomes were incidence of ketosis (defined as ketones > 1.6 mmol/liter), incidence of bicarbonate ≤18 mmol/liter, length of stay in hospital, length of stay in the intensive care unit (ICU), and mortality.[5,6] Subgroup analyses were performed to assess the effect of SGLT2i exposure on survival in patients with T2DM. The study was approved by the Hospital Research Ethics Committee (2023/ETH00366).

Binary outcomes were compared by Fisher's exact test and nonparametric comparisons by Mann-Whitney test. Associations between SGLT2i use and acidosis were assessed using binary logistic regression that included all baseline factors with $p < 0.05$. Results of binary logistic regression are presented as odds ratio (OR) and associated 95% confidence interval (CI). Associations between SGLT2i use and survival were assessed by Cox proportional hazards, including all baseline factors with $p < 0.05$. Results of Cox proportional regression are presented as hazard ratio (HR) and associated 95% CI. Analyses were conducted using Statistical Package for Social Sciences (SPSS) version 28 (SPSS Inc, Chicago, IL, USA) and figures were created using GraphPad Prism version 10 (GraphPad Software, Boston, MA, USA).

One hundred and sixty-three heart transplant recipients, including 9 heart-lung transplants and 2 heart-kidney transplants, were included. Forty were exposed to SGLT2i before surgery (14 empagliflozin; 26 dapagliflozin) and 123 were not. None of the 11 combined transplant recipients were exposed to SGLT2i pretransplant. As per local protocol, insulin infusions were routinely commenced for the management of hyperglycemia, with 97% of patients receiving intravenous insulin in the first 24 hours post-transplant. Baseline characteristics are shown in Table 1.

Table 1 Baseline Characteristics at Time of Heart Transplantation

Characteristic	SGLT2i (*n* = 40)	No SGLT2i (*n* = 123)	*p*-value
Age (years); median (IQR)	59 (53-64)	54 (42-63)	**0.02**
Male; *n* (%)	35 (88)	88 (72)	0.06
Weight (kg); mean (SD)	86 ± 17	77 ± 17	**< 0.01**
Body mass index (kg/m^2); mean (SD)	29 ± 5	26 ± 5	**< 0.01**
Underlying cardiomyopathy; *n* (%)			0.18
Ischemic	16 (40)	25 (20)	
Dilated	15 (38)	49 (40)	
Familial	3 (8)	8 (7)	
Infiltrative	2 (5)	10 (8)	
Toxic	0	7 (6)	
Congenital	1 (3)	12 (10)	
Other	3 (8)	12 (10)	
Time on transplant waitlist (days); median (IQR)	73 (23-162)	71 (16-238)	0.99
Admitted to hospital > 24 hours prior; *n* (%)	5 (13)	18 (15)	0.99
Inotrope use prior; *n* (%)	3 (8)	10 (8)	0.99
Donor ischemic time (minutes); median (IQR)	237 (198-359)	262 (212-356)	0.57
Organ care system use; *n* (%)	14 (35)	44 (35)	0.99
Type of organ care system; *n* (%)			
XVIVO	8 (20)	8 (7)	**0.03**
TransMedics	6 (15)	36 (29)	0.09
Diabetes; *n* (%)	19 (48)	20 (16)	**< 0.01**
LVAD; *n* (%)	14 (35)	45 (37)	0.99
pH; median (IQR)	7.37 (7.35-7.41)	7.38 (7.35-7.41)	0.42
Bicarbonate (mmol/liter); median (IQR)	25 (24-28)	25 (23-27)	0.89
Creatinine (μmol/liter); median (IQR)	109 (88-137)	110 (88-138)	0.99

Abbreviations: ICU, intensive care unit; IQR, interquartile range; LVAD, left ventricular assist device; SD, standard deviation; SGLT2i, sodium glucose cotransporter 2 inhibitor.

Bold values indicates *p*-value < 0.05.

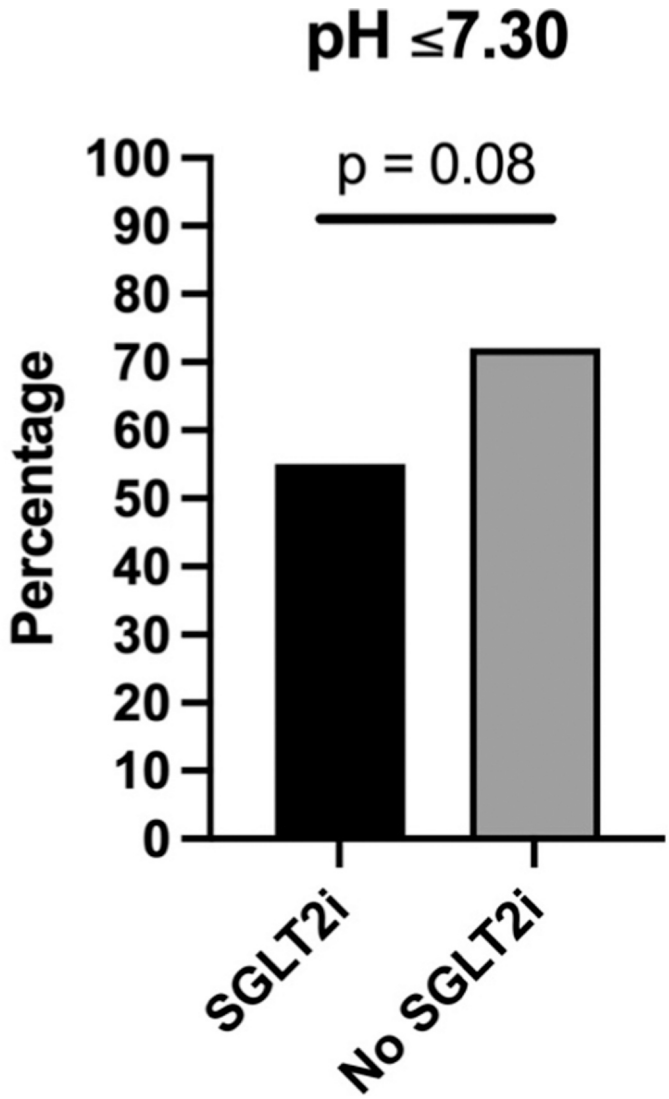

Figure 1 Percentage of patients with acidosis defined as pH ≤ 7.30 by SGLT2i exposure. SGLT2i, sodium glucose co-transporter 2 inhibitor.

Patients treated with SGLT2i were older, had higher weights, and were more likely to have T2DM.

During the first 4 days post-transplant, the incidence of acidosis was not different between SGLT2i exposed and nonexposed patients (22/40 vs 88/123, respectively, $p = 0.08$) (Figure 1). The likelihood of acidosis between groups remained similar when assessed by regression analysis adjusted for age, body mass index (BMI), diabetes status, and XVIVO use (OR 2.1; 95% CI 0.9-4.7; $p = 0.09$). Sensitivity analyses using pH thresholds of 7.25 and 7.00 were also not different between groups. Incidence of bicarbonate level ≤18 mmol/liter was lower in SGLT2i exposed patients compared to nonexposed patients (2/40 vs 40/123, respectively, $p < 0.001$). Between group differences were still present when assessed by regression adjusted for age, BMI, diabetes status, and XVIVO use (OR 0.07; 95% CI 0.02-0.36, $p = 0.001$).

No clinically significant ketosis was measured in SGLT2i exposed patients; the peak ketone level recorded in any patient was 1.6 mmol/liter. There was no difference in peak ketone level between those with and without diabetes (median 0.4 mmol/liter [IQR 0.2-0.7] vs 0.4 mmol/liter [0.3-0.5], respectively, $p = 0.89$). No cases of ketoacidosis were recorded.

SGLT2i exposure pre-OHT was associated with shorter length of stay in the ICU (median 97 hours [IQR 71-158] vs 128 [77-247], respectively, $p = 0.04$). There was no difference between hospital length of stay (median 33 days [IQR 20-64] vs 28 [17-49], respectively, $p = 0.44$).

Over a median follow-up of 29 months (IQR 18-39), there were 32 (20%) deaths, 4 in the SGLT2i group (median follow-up 22 months, IQR 15-29), and 28 in the group not exposed to SGLT2i (median follow-up 32 months, IQR 20-41). SGLT2i use was associated with improved survival adjusted for age, BMI, diabetes status, and XVIVO use (HR 0.24, CI 0.08-0.77, $p = 0.02$) (Figure 2). There was no interaction between SGLT2i use and diabetes status (HR 0.51, CI 0.05-5.63, $p = 0.58$), despite the subgroup of patients with T2DM having improved adjusted survival associated with SGLT2i use (HR 0.19, CI 0.04-0.80, $p = 0.02$).

Our study of 163 patients with advanced heart failure undergoing OHT suggests that SGLT2i exposure up to and immediately preceding OHT is not associated with an increased risk of acidosis or ketosis during the first 4 days postsurgery. The routine use of postoperative intravenous insulin in the first 24 hours was likely protective, due to the potent effect of insulin in suppressing fatty acid metabolism and associated ketogenesis, as reported in other studies of SGLT2i use in urgent major surgery.[7]

This cohort was selected as it encompassed the change in clinical practice of SGLT2i use in heart failure.[8] SGLT2i use naturally increased in Australia after national subsidization added heart failure as an indication in early 2022 and hence the follow-up time in the SGLT2i group was shorter. However, adjusted survival curves separate early, and as such is unlikely to impact the significant difference in survival we found between SGLT2i exposed and unexposed patients. Additionally, during this time, the use of the XVIVO Heart Preservation System was also introduced, resulting in higher rates of XVIVO use in the SGLT2i exposed group.[9]

We acknowledge the limitations of this retrospective audit and possible selection bias. A causal link cannot be made between SGLT2i use before OHT and the observed mortality benefit in our cohort. Benefit may be a direct effect of SGLT2 inhibition or due to another factor, such as improved preoperative heart failure and/or diabetes optimization. However, our results warrant further dedicated prospective investigation.

SGLT2i are a cornerstone of treatment for heart failure.[1,2,8] Given the observed safety, reduced ICU length of stay, and potential mortality benefit observed in our study, we propose that patients waitlisted for OHT should continue treatment with SGLT2i until the time of transplant providing there is routine institution of a postoperative insulin infusion.

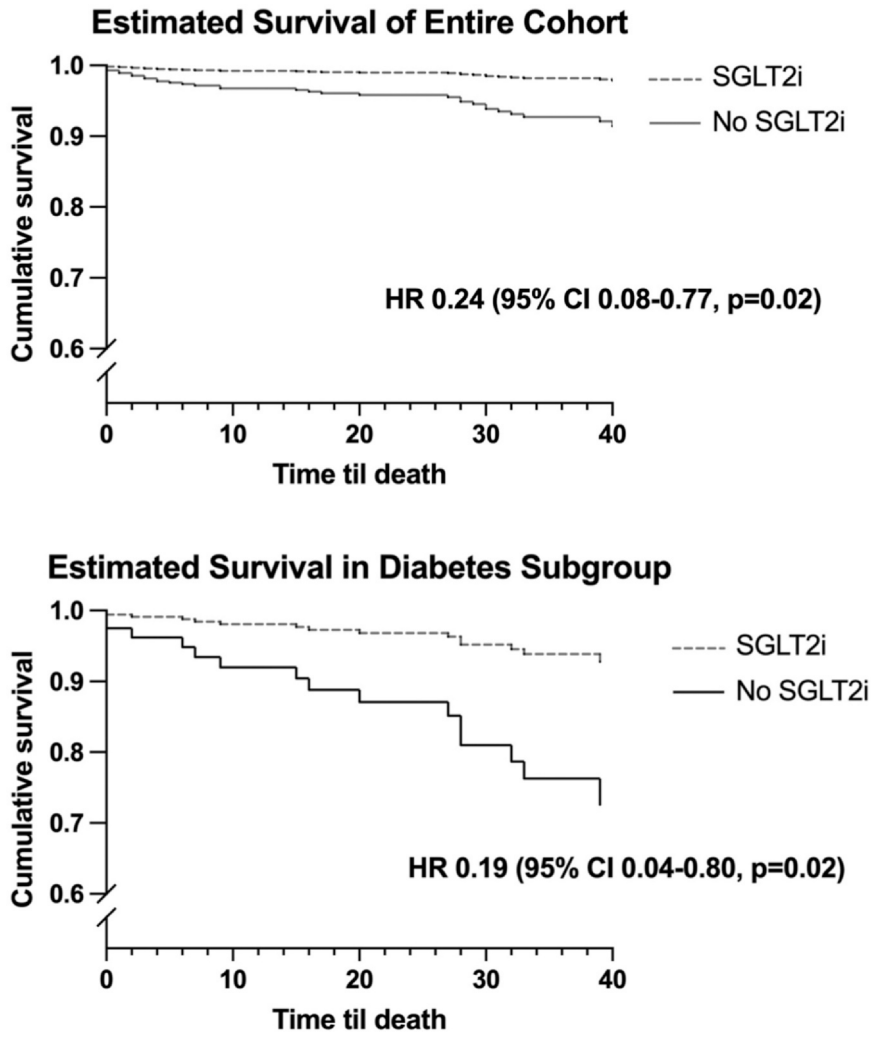

Figure 2 Adjusted survival (months) in heart transplant recipients. (A) Overall survival in heart transplant recipients exposed to SGLT2i before transplant vs those not exposed, adjusted for age, diabetes status, body mass index, and XVIVO use. (B) Survival in subgroup of patients with type 2 diabetes exposed to SGLT2i before transplant vs those not exposed, adjusted for age, body mass index, and XVIVO use.

CRediT authorship contribution statement

Lisa M. Raven: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Visualization. **Christopher A. Muir:** Conceptualization, Methodology, Visualization, Supervision, Writing – review and editing. **Ricardo C. Deveza:** Writing – review and editing. **Cassia Kessler Iglesias:** Writing – review and editing. **Nicole K. Bart:** Writing – review and editing. **Kavitha Muthiah:** Writing – review and editing. **Eugene Kotlyar:** Writing – review and editing. **Christopher S. Hayward:** Writing – review and editing. **Peter S. Macdonald:** Writing – review and editing. **Andrew Jabbour:** Writing – review and editing. **Jerry R. Greenfield:** Conceptualization, Methodology, Visualization, Supervision, Writing – review and editing.

Disclosure statement

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travel reimbursement. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. There was no involvement from funding bodies in the study design, conduct, and reporting of this work.

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