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Short communication

Safety and effects of SGLT-2 inhibitor use among LVAD patients with type 2 diabetes mellitus

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ABSTRACT

SGLT-2 inhibitors have been shown to confer reduced risk of adverse cardiovascular events in patients with heart failure, and have also been studied preliminarily among heart transplant patients, with overall positive findings. Use of SGLT-2 inhibitors among patients with durable mechanical circulatory support has not been studied. Here we present our results from a combined retrospective cohort of LVAD patients on SGLT-2 inhibitors at two major academic centers, which showed a good safety profile but prompted questions for further investigation. We advocate for further research into the safety and impact of SGLT-2 inhibitors among LVAD patients.

1. Introduction

Several major trials have recently shown SGLT-2 inhibitors (SGLT2i) confer a reduced risk of adverse cardiovascular (CV) events in patients with heart failure. Initially, the CANVAS trial showed a reduction in CV death in patients on canagliflozin versus placebo [1]. Subsequently, dapagliflozin, empagliflozin and sotagliflozin have shown benefit in improving death and/or heart failure outcomes among ambulatory heart failure with reduced ejection fraction as well as worsening heart failure in the DAPA-HF, EMPEROR-Reduced and SOLOIST-WHF trials, respectively [2–4]. Whether this is applicable to patients living with advanced heart failure, particularly those with durable mechanical support, however, is unknown. The aim of this study was to assess the safety and potential benefit of SGLT2 inhibitors among patients with diabetes mellitus on left ventricular assist device (LVAD) support.

2. Methods

We retrospectively studied safety and clinical outcomes in patients implanted and placed on LVAD support with diabetes mellitus at our two institutions between January 1, 2010 and October 31, 2021 with Institutional Review Board approval. The primary study goal was to document rates of SGLT2i use among patients on LVAD support, and subsequent impact including changes in BMI, A1c, diuretic dose (furosemide equivalent), and renal function over time. Adverse events potentially attributed to SGLT2i were specifically documented, including acute kidney injury, genitourinary infection, diabetic ketoacidosis, volume depletion, fracture, limb amputation, and hypersensitivity reactions. Given concern for genitourinary infections with SGLT2i, we also tabulated driveline infection (DLI) incidence in our LVAD population. All patients had at least 30-day follow-up. Data are reported as mean (standard deviation (SD)) if normally distributed, or median (interquartile range (IQR)) if non-normally distributed. Paired *t*-tests were used to compare post-treatment to pre-treatment variables if normally distributed. Paired t-tests were used to compare post-treatment to pre-treatment variables if normally distributed.

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Table 1
Baseline characteristics.

Demographics	
Age (years)	56.1 ± 10.6
Sex	
Male	27 (79.4 %)
Ethnicity	
White	19 (57.6 %)
Black	9 (27.3 %)
Hispanic	4 (12.1 %)
Asian	1 (3 %)
Other	0 (0 %)
Medical history	
BMI	33.6 ± 7.2
Comorbid conditions	
CABG	4 (11.8 %)
DM	34 (100 %)
CKD	16 (47.1 %)
Pulmonary disease	5 (14.7 %)
Myocardial infarction	10 (29.4 %)
Malignancy	8 (23.5 %)
Ventricular arrhythmias	14 (41.2 %)
PAD	4 (11.8 %)
Smoking history	
Never	9 (26.5 %)
Former	21 (61.8 %)
Active	4 (11.8 %)
Medications	
Antiplatelets	25 (75.8 %)
Statin/ezetimibe	21 (63.6 %)
Beta blocker	13 (39.4 %)
ACEi/ARB	9 (27.3 %)
ARNI	5 (15.2 %)
MRA	21 (63.6 %)
Loop diuretics	29 (87.9 %)
Thiazide diuretics	3 (9.1 %)
Insulin	18 (54.5 %)
Metformin	9 (27.3 %)
Sulfonylurea	2 (6.1 %)
DPP-4 inhibitor	7 (21.2 %)
GLP1-receptor agonist	11 (33.3 %)
Heart failure characteristics	
ICM	17 (50 %)
LVEF (n = 31)	18.6 ± 10.4
NYHA class (mean) (n = 27)	2.5 ± 0.9
NYHA class (median) (n = 27)	2 ± 0.9
Daily furosemide dose (n = 33)	53.1 ± 62.2
INTERMACS profile	
1	5 (15.6 %)
2	5 (15.6 %)
3	19 (59.4 %)
4	3 (9.4 %)
>4	0 (0 %)
VAD type	
HVAD	9 (26.5 %)
HM2	7 (20.6 %)
HM3	18 (52.9 %)
Device strategy	
BTT	11 (35.5 %)
DT	20 (64.5 %)

Prior complications	
Heart failure admission	4 (12.1 %)
DLI	0 (0 %)
Pump thrombosis	0 (0 %)
GIB	4 (12.1 %)
Ischemic CVA	0 (0 %)
Hemorrhagic CVA	0 (0 %)
Right heart failure	8 (24.2 %)

BMI, body mass index; CABG, coronary artery bypass graft; DM, diabetes mellitus; CKD, chronic kidney disease; PAD, peripheral arterial disease; ACEi, angiotensin-converted enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; DPP-4, dipeptidyl peptidase-4; GLP-1Ra, Glucagon-like peptide-1 receptor agonist; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; DLI, driveline infection; GIB, gastrointestinal bleed; CVA, cerebrovascular accident.

Table 2
SGLT2-inhibitor use.

SGTL2-inhibitor initiation	
Time from LVAD implantation to SGLT2-inhibitor initiation ($n = 34$)	659.3 ± 703
SGTL2-inhibitor	
Canagliflozin	2 (5.9 %)
Empagliflozin	22 (64.7 %)
Dapagliflozin	10 (29.4 %)
Ertugliflozin	0 (0 %)
Timing of SGLT2-I initiation	
Prior to VAD implant	2 (5.9 %)
During VAD implant admission	0 (0 %)
Post VAD implant admission	32 (94.1 %)

3. Results

3.1. Baseline characteristics

A total of 509 patients on LVAD support with diabetes were identified, of whom 34 (6.7 %) were treated with SGLT2i. Baseline demographic and clinical characteristics for these patients on SGLT2i are shown in Table 1. Over half were implanted with the HeartMate 3 LVAD ($n = 18$, 52.9 %). The majority of patients were male (79.4 %), with a large proportion of Black and Hispanic patients. Half of patients had ischemic cardiomyopathy (50 %) and CKD (47.1 %), and approximately 70 % had a BMI over 30. Most patients were placed on empagliflozin (64.7 %), with a minority on dapagliflozin (29.4 %) and canagliflozin (5.9 %); no patients sampled were on ertugliflozin (Table 2). Almost all patients were started on SGLT2i after LVAD placement (94.2 %, mean 659.3 days post-LVAD, SD 703).

3.2. Outcomes

At 30-, 60-, and 180-days follow-up, there was no significant change in BMI, A1c, or diuretic dose, but there was a difference noted in BUN at 180 days (Table 3). Potential SGLT2i-related adverse events included 3 genitourinary infections, 2 episodes of AKI, and 2 limb amputations. During the monitored timeframe, 4 DLI occurred. There were no episodes of diabetic ketoacidosis, volume depletion, fracture, or hypersensitivity reactions.

4. Discussion

Since SGLT2i have been shown to provide clinical benefit in patients with heart failure, we present a retrospective analysis of patients with DM on LVAD support who were placed on an SGLT2i. We did not find significant changes in renal function, weight, and diuretic dosing over this timeframe. During the monitored timeframe, there were some potential SGLT2i-related adverse events, specifically genitourinary infections, AKI, and limb amputations as well as four DLI. However, these are nonspecific events, and it is difficult to know with this analysis whether they were truly due to SGLT2i initiation or chance statistical findings without clinical significance given lack of a comparator group or propensity score matching. When considering the DLI events per patient year of this cohort, it is similar to expected published rates of infection in MOMENTUM 3 [5]. Nonetheless, this warrants further investigation in prospective studies. For further analysis, it would be important to examine these safety parameters in a prospective manner with a comparator group. In particular, it will be important to examine rates of infectious complications such as GU infections and DLI in these patients. This study serves as a stepping stone for potential future avenues of research and clinical care among LVAD patients.

Given the overwhelming data suggesting benefit in ambulatory heart failure, SGLT2i therapy is included in the 2021 update to the 2017 Expert Consensus Pathway for optimization of Heart Failure treatment, as well as the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure [6,7]. SGLT2i use is also being investigated in heart transplant recipients, among whom empagliflozin has been noted to assist with weight loss, blood pressure reduction, and diuretic dosing without significant changes in renal function with possibly iterative benefits with GLP-1 receptor agonists [8–10]. Stabilizing renal function and optimizing BMI is paramount for overall cardiometabolic health in

Table 3
Outcomes.

Laboratory data	SGLT2-inhibitor initiation	30 days	P	60 days	P	180 days	P
Cr	1.4 ± 0.4	1.3 ± 0.5	0.179	1.3 ± 0.5	0.963	1.4 ± 0.5	0.941
BUN	27 ± 10	25.4 ± 10.6	0.152	26.2 ± 10.5	0.634	25 ± 10	0.049
GFR	59 ± 19	61.0 ± 20.5	0.202	61.6 ± 23.6	0.571	60.2 ± 20.3	0.882
Potassium	4.3 ± 0.5	4.3 ± 0.4	0.584	4.3 ± 0.4	0.878	4.2 ± 0.4	0.833
Sodium	137 ± 4	136.4 ± 3.4	0.923	136.5 ± 3.2	0.411	137.3 ± 2.7	0.583
Bicarbonate	26.4 ± 3.5	26.1 ± 3	0.485	26.2 ± 3	0.946	26.2 ± 3	0.680
BNP (n = 5)	360 ± 298	202.9 ± 5	0.525	331.6 ± 342.6	0.331	373.3	NA
A1c (n = 33)	8 ± 2.1	8.2 ± 1.7	0.820	8 ± 1.4	0.397	7.3 ± 1.6	0.305
SBP (n = 12)	90.5 ± 9.5	99.3 ± 9.6	0.149	91.4 ± 7.1	0.054	83.4 ± 16.1	0.318
BMI	33.6 ± 7.2	33.4 ± 6.6	0.641	33.7 ± 6.7	0.312	35.6 ± 5.7	0.585
Diuretic dose	53.1 ± 62.2	59.6 ± 64.8	0.176	45.6 ± 52.1	0.077	60.2 ± 51.5	0.410
NYHA class	2.3 ± 1	1.9 ± 0.8	0.720	2 ± 0.7	1	2.1 ± 0.6	0.585

Cr, creatinine; BUN, blood urea nitrogen; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; A1c, glycated hemoglobin; SBP, systolic blood pressure; BMI, body mass index.

patients on LVAD support to avoid progression to needing renal replacement therapy, combating obesity or even obviating the need for dual organ heart kidney transplantation in patients listed for heart transplantation. We advocate for further investigation of SGLT2i, and possibly in combination with GLP-1 receptor antagonists, as a means to achieve overall cardiometabolic and cardiorenal benefits for LVAD supported patients especially as they may await cardiac transplantation.

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Author contributions

All authors were involved in the conception and design of the data, drafting of the manuscript, revising it critically for content and its final approval.

Declaration of competing interest

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