Protocol Title
Heart Failure Patients with Left Ventricular Assist Devices Being Treated with Sodium-Glucose Co-Transporter 2 Inhibitors

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Objective:

The main purpose of this study is to observe outcomes of sodium-glucose co-transporter 2 inhibitors (SGLT2i) in heart failure patients with left ventricular assist devices (LVAD).

Study Purpose and Rationale:

In 2008, the U.S. Food and Drug Administration (FDA) mandated new diabetes medications be tested for cardiovascular safety following the increase in heart failure hospitalizations seen with rosiglitazone in the RECORD trial (1). SGLT2i recently came onto the market, and accordingly multiple trials have been done to assess the cardiovascular safety of SGLT2i. These medications inhibit the sodium-glucose co-transporter 2 in the proximal tubule of the glomerulus, leading to reduced absorption, and increased excretion, of sodium and glucose (2). Not only were these medications found to be safe, but they have shown improved cardiovascular outcomes.

First, the EMPA-REG OUTCOME trial reported a significant reduction in the primary composite outcome of myocardial infarction, stroke, and cardiovascular death, as well as a 35% reduction in heart failure (HF) hospitalization in patients randomized to empagliflozin, versus placebo, with established atherosclerotic cardiovascular disease (ASCVD) (3). The CANVAS trial then showed similar results with canagliflozin in a mixed cohort of patients with established, or risk factors for, ASCVD (4). The DECLARE-TIMI-58 trial showed reduced cardiovascular death or HF hospitalization in patients randomized to dapagliflozin versus placebo. Interestingly, this trial had a majority of enrolled patients with only risk factors for ASCVD, without established disease. Additionally, the reduction in HF hospitalization was seen in both patients with and without HF at baseline, of which only 10% of enrolled patients carried the diagnosis (5). The DAPA-HF trial demonstrated significantly less major adverse cardiac events in heart failure with reduced ejection fraction patients, regardless of underlying diabetes status (6). Lastly, in the EMPEROR-REDUCED trial, empagliflozin reduced the composite end point of heart failure hospitalization or cardiovascular death (7). Currently, both dapagliflozin and empagliflozin are FDA approved for use in patients with heart failure with reduced ejection fraction (HFrEF), regardless of diabetes status.

The proposed mechanism of reduction in heart failure hospitalization with SGLT2i is multi-factorial, with the most significant reason thought to be due be reduced plasma volume and neurohormonal activation via its natriuretic and osmotic diuretic effects (8). Additionally, animal models have suggested favorable effects on the sympathetic nervous system and sodium-hydrogen exchanger leading to reduced cardiac injury, hypertrophy, fibrosis, remodeling, and systolic dysfunction (9,10). Furthermore, increased ATP production, improved systolic function, and reduced cardiac work in non-diabetic mice with heart failure treated with empagliflozin, versus placebo, has been reported (11).

In the updated 2021 guidelines for management of HFrEF, SGLT2i are recommended in patients on beta blockade and ARNI/ACE/ARB with EF ≤40%, NYHA Class II-IV HF, regardless of a diagnosis of diabetes (12). While guideline-directed medical therapy (GDMT) is FDA approved for use in this population, there is limited data specifically addressing the role of GDMT after LVAD implantation. There are some data to support the use of ACE/ARB and beta blockade in the LVAD population, thus suggesting medical management in addition to mechanical support can be of benefit to HFrEF patients after LVAD implantation. However, there is limited guidance on dosing and timing of initiation (13-16). SGLT2i are increasingly being utilized in the LVAD population, but the decision whether or not to initiate therapy is currently based on the individual physician's discretion. The exact mechanism of cardiovascular benefit continues to be the source of further research. We hypothesize that heart failure patients with LVADs will similarly benefit from the SGLT2i-associated natriuresis and diuresis, which in turn reduces preload. This is further associated with reduced heart failure readmissions and right ventricular failure (17-19). Additionally, the animal models indicating reduced cardiac work and remodeling in this population may benefit these patients as one of the goals of LVAD implantation is to reduce cardiac energy expenditure and promote remodeling and recovery in these patients (9-11,20,21).

Study Design, Study Procedures, and Statistical Procedures:

This study is designed as a prospective, randomized controlled study to assess cardiac benefit of SGLT2i in 44 consecutive patients with heart failure undergoing LVAD implantation. Assuming a power of 80% and alpha of 0.05, 22 patients are needed in each arm to detect a change in ramp stage of at least one stage to achieve hemodynamic optimization. Patients will be randomized to one of two routine care arms: management with an SGLT2i (empagliflozin 10 mg daily or dapagliflozin 10 mg daily) or no SGLT2i.

Patients ≥ 18 years-old with implanted LVAD will be recruited for the trial. After informed, written consent is obtained, patients will be enrolled into the study. At the time of discharge from the LVAD implant hospitalization, patients will be randomized, in a 1:1 fashion using the random number generation function in Microsoft Excel, to either management with an SGLT2i or no SGLT2i. The patient's treating physician will be able to override randomization

assignment if the physician determines that the assignment is not in the patient's best interest. These patients would be kept on study and their data would be used for observational research within this study. In the SGLT2i arm, the medication prescribed, either empagliflozin or dapagliflozin, will be based on available formulary coverage, as there is equipoise within these medications of the same class.

Patients' initial weight, vitals, medications, trans-thoracic echocardiogram, 24-hour urine output, and serum laboratory measurements, including markers of end-organ perfusion, will be recorded. These same data points will be repeated three to six months after enrollment. The median values of the above measurements will be compared between each arms. All tests, procedures, and treatments in this study are currently the standard of care for follow-up of patients post-LVAD implantation.

Patients' additional heart failure and anti-hypertensive therapy will follow the University of Chicago's standard of care protocol, which is guideline-directed medical therapy recommended for heart failure patients in the ACC 2021 Update to the 2017 Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment (12). This medical therapy is normal protocol at the university, but it is not mandated for this study.

The patient's participation in the study will end after 6-months of follow-up. At that time point, the physician will discuss the ongoing treatment plan with the patient, particularly as it relates to continuation or discontinuation of the SGLT2i.

Outcomes:

Primary outcome: Change in number of ramp stages needed to achieve hemodynamic optimization.

Secondary outcomes: Change in left ventricular end-diastolic dimension (LVEDD), Changes in weight, 24-hour urine output, diuretic dose, transthoracic echocardiographic measures, renal function, and liver function.

The below measures are all part of the routine standard of care for patients at the University of Chicago.

1. Baseline
    a. HbA1C
    b. Weight
    c. 24-hour urine output
    d. Diuretic dose
    e. Renal function as measured by serum laboratory data
    f. Liver function as measured by serum laboratory data

g. Trans-thoracic echocardiogram

2. Three-Six month follow-up
    a. HbA1C
    b. Weight
    c. 24-hour urine output
    d. Diuretic dose
    e. Renal function as measured by serum laboratory data
    f. Liver function as measured by serum laboratory data
    g. Trans-thoracic echocardiogram
    h. Right heart catheterization

Study Drugs:

There are no experimental drugs being used in this study. Per the FDA "SGLT2 inhibitors are a class of prescription medicines that are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. Medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, and empagliflozin" (22). In May 2020, the FDA approved dapagliflozin for use in HFrEF, regardless of diabetes status (23). In August 2021, empagliflozin was also approved for use if HFrEF patients.

Study Subjects:

The study will include patients at UCMC being followed by the advanced heart failure group for their LVAD care.

Inclusion criteria:

1. LVAD implantation
2. Have not already been prescribed management with an SGLT2i
3. Estimated glomerular filtration rate (eGFR) $\geq$ 30 ml/min/1.73 m^2
4. Age $\geq$ 18 years-old
5. Able to provide informed consent

Exclusion criteria:

1. Diagnosis of Type 1 DM
2. eGFR < 30 ml/min/1.73 m^2
3. Age < 18 years-old

Recruitment:

Patients admitted to the hospital who are undergoing LVAD implantation, fitting the inclusion criteria, will be recruited by the members of Advanced Heart Failure team. Patients will be approached once they are stable and nearing discharge.

Informed Consent Process:

The consent process will take place in the inpatient hospital room. Patients will be given an informed consent and allowed as much time as needed to read all components and be provided time to formulate questions. If questions arise, the PI or a member of the research team will provide answers to the patient regarding participation in the research study. Family members or caretakers will also be encouraged to participate in the informed consent process if applicable.

Ample time will be given for the informed consent process. After a complete explanation of the study, the informed consent document will be reviewed. Subjects will be asked to verbalize their understanding of the study and encouraged to ask questions. Family members or caretakers will also be encouraged to participate in the informed consent process if applicable.

Confidentiality of Study Data and Privacy Protections:

Data will be abstracted into an electronic database. The database will be within the Department of Medicine, Section of Cardiology. The data will be password protected and covered by all of the firewalls and security features of the Department of Medicine. The data will also be housed on a password protected encrypted laptop using University of Chicago standards per CBIS.

Once collected, an individual's data will not be available to anyone other than the investigators and study personnel involved in this project. The data will be abstracted and entered into an electronic database by a member of the research team. The database will be within the Department of Medicine, Section of Cardiology. The data will be password protected and covered by all of the firewalls and security features of the Department of Medicine. Name, address, email address, phone number and medical record number will be stored separately from the database. In the database, a code will be recorded with the data instead. Only the study staff will be able to link the code to the subject's name and other identifying information. The link to identifiers will be destroyed at the end of 6 years per HIPAA regulations.

Potential Risks:

SGLT2i have been shown to have beneficial effects on renal function (5,24). However, due to its direct effects on the kidneys, SGLT2i are labeled for patients with eGFR $\geq$ 20 ml/min/1.73 m^2 or GFR $\geq$ 30 ml/min/1.73 $m^{2,}$ depending on the medication. Due to this, we will exclude patients with eGFR < 30 ml/min/1.73 m^2. Increased risk of genital mycotic infections (i.e. vaginitis and balanitis), urinary tract infections, pyelonephritis, urosepsis, and perineal necrotizing fasciitis have been reported, but only genital infections have been shown to be a significant risk in large randomized trials (3-5). Additionally, there has been a small increased risk of diabetic ketoacidosis associated with the use of SGLT2i, though this was predominantly in patients on

insulin, who will not be included in this study (5). Lastly, canagliflozin was associated with an elevated risk of lower limb amputation and bone fractures compared to placebo in the CANVAS trial, but this was not seen with the CREEDANCE trial of canagliflozin, or in other SGLT2i randomized controlled trials, including the EMPA-REG OUTCOME, DECLARE-TIMI-58, DAPA-HF, EMPEROR-Reduced trials completed for empagliflozin and dapagliflozin (4,7). We will not be using canagliflozin in this study.

The overall risk levels associated with being prescribed empagliflozin versus dapagliflozin are considered relatively equal, given the similar class effect. The adverse reactions of empagliflozin in order of incidence include urinary tract infections, genital yeast infections, upper respiratory infections, increased urination, dyslipidemia, arthralgia, nausea, increased in serum creatinine, increase in hematocrit, necrotizing fasciitis of the perineum, ketoacidosis, sepsis. The adverse reactions of dapagiflozin in order of incidence include female genital mycotic infections, nasopharyngitis, urinary tract infection, back pain, increased urination, male genital mycotic infections, nausea, influenza, dyslipidemia, constipation, dysuria, pain in extremity, increase in creatinine, increase in hematocrit, dyslipidemia, hypersensitivity reactions, urosepsis, necrotizing fasciitis of the perineum.

Since patients are randomized to two routine care arms, we do not believe there is additional risk incurred by participating in this study. The treating physician will be notified of the randomization assignment and can override the assignment if they believe it to be in the best interest of the patient. While SGLT2 inhibitor therapy is approved for use in patients with HFrEF, there is not sufficient data guiding their use in the LVAD population. If benefit is shown in the SGLT2i group, the arm without SGLT2i would lose the hypothesized benefit of renal and cardiovascular benefits.

Data and Safety Monitoring:

Data safety measures will be maintained as above. Appropriate CBIS and risk management personnel will be contacted immediately if any data loss is suspected. LVAD patients are all closely followed by the multi-disciplinary Heart Failure team and will be monitored for any adverse events, and specifically side effects of SGLT2 inhibitors. Any adverse events will be reported to the IRB according to the IRB's reporting requirements.

Subjects in this study are followed for 6 months. We believe that this is the shortest duration required to clarify potential benefit of SGLT2 inhibitor therapy in LVAD patients. We do not anticipate adequate data prior to this point evidencing benefit that would justify study stoppage or redesign.

Potential Benefits:

Data in studies of empagliflozin, dapagliflozin, and canagliflozin indicates improvement in cardiovascular outcomes, including cardiovascular death and heart failure hospitalization in patients with and without known heart failure (3-7). The proposed mechanisms of action of SGLT2i leading to these improved cardiovascular outcomes, specifically increased natriuresis and diuresis and reduced cardiac work and remodeling, should have beneficial effects on LVAD patients (9-11,17-21). Recently, it has been shown that SGLT2i decreased heart failure exacerbations and cardiovascular mortality regardless of a diagnosis of diabetes (6,7). To this end, the 2021 Heart Failure Treatment guidelines have updated its recommendation to include SGLT2i as standard-of-care for HFrEF patients. There is noThe overall benefit levels associated with being prescribed empagliflozin versus dapagliflozin are considered relatively equal, given the similar class effect, as the above benefits were seen in both medications

Data for SGLT2i use in patients with an LVAD in place is limited. It is hypothesized that the benefit seen in HFrEF patients will be applicable to HFrEF patients with an LVAD in place.

Alternatives:

All tests, procedures, and treatments in this study are currently within the standard of care for follow-up of patients post-LVAD implantation. Participation is voluntary, and the alternative is not to participate in this study. Outside of the study, the decision whether or not the patient received management with an SGLT2i would be based on the treating physician's discretion.

Research at External Sites:

All research will be conducted at University of Chicago Medical Center. This is not a multicenter study; thus, University of Chicago will be the only institution involved with the research.

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