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Protocol Title

The Hemodynamic Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Acute Decompensated Heart Failure

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Objective:

The main purpose of this study is to observe hemodynamic effects of initiating sodium-glucose co-transporter 2 inhibitors (SGLT2i) in patients admitted to the intensive care unit with acute decompensated heart failure.

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 assessed 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 benefit in regards to 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). Also, in the EMPEROR-REDUCED trial, empagliflozin reduced the composite end point of heart failure hospitalization or cardiovascular death (7). Lastly, in the SOLOIST-WHF trial, sotagliflozin was shown to reduce the total number of deaths from cardiovascular causes and hospitalization and urgent visits for heart failure compared to placebo when initiated during a heart failure hospitalization, or within three days of discharge (21). Currently, dapagliflozin is 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 Expert Consensus Decision Pathway 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).

Multiple trials, including DAPA-HF and EMPEROR-Reduced, have shown that SGLT2i have been beneficial in reducing risk of cardiovascular death or hospitalization for patients with HFrEF, but these studies were not conducted in hospitalized acutely decompensated patients requiring ICU admission and continuous hemodynamic monitoring. Similarly, SOLOIST-WHF demonstrated a reduction in the same end points, where an SGLT2i was initiated within three days after a hospitalization for a heart failure exacerbation. Therefore, SGLT2i initiation was not conducted in an acutely decompensated clinical setting. While SGLT2i are FDA approved for use in HFrEF population, there are limited data specifically addressing the role of SGLT2i in the acute setting in patients with acute decompensated heart failure, and even less data related to its use in the patients requiring ICU-level care. Given the limited data, the decision whether or not to use SGLT2i in this population 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 acute decompensated heart failure will similarly benefit from the SGLT2i-associated natriuresis and diuresis. This mechanism should improve invasive hemodynamics during an inpatient ICU stay.

Study Design, Study Procedures, and Statistical Procedures

This study is designed as a single center, prospective, randomized controlled study to assess cardiac benefit of SGLT2i in 40 consecutive patients (20 treatment, 20 control) admitted to University of Chicago Cardiac Intensive Care Unit (CCU) Advanced Heart Failure Service. Patients will be randomized to one of two routine care arms: treatment with an SGLT2i (dapagliflozin 10 mg daily) or no SGLT2i. Assuming a power of 80% and alpha of 0.05, 16 patients are needed in each arm of the study to detect a 5 mmHg change in pulmonary capillary wedge pressure (PCWP), and 18 patients are needed in each arm of the study to detect a 0.75 $L/min/m^2$ change in Fick cardiac index (CI).

Patients ≥ 18 years old, with heart failure with reduced ejection fraction (HFrEF), defined as left ventricular ejection fraction (LVEF) ≤ 40%, who are admitted to the CCU for acute decompensated heart failure and determined to need pulmonary artery catheter in place for continuous hemodynamic monitoring following right heart catherization, will be included in this study. Patients listed for cardiac transplantation or on mechanical support will be excluded. Due to the inability to consent patients following sedation given during the right heart catheterization,

patients determined to have a high likelihood of needing CCU admission, based on individual clinical presentation, will be approached for recruitment and asked for informed, written consent. However, patients will only be enrolled if it is determined independently to admit the patient to the CCU with the pulmonary artery catheter in place. If determined to need CCU care with continuous pulmonary artery catheter monitoring, patients will then be randomized, in a 1:1 fashion using the random number generation function in Microsoft Excel, to either treatment with an SGLT2i (dapagliflozin 10mg once daily) or no SGLT2i. Therefore, we anticipate recruiting and consenting more than 40 patients, but we will only randomize and treat patients that fulfill all inclusion criteria. Patients consented but not meeting randomization criteria will not have any data collected or change to their management.

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.

Data points to be collected: Leveled invasive hemodynamics measured via pulmonary artery catheter at end expiration, standing weights, intake and outputs, blood glucose from basic metabolic panels (BMP) taken at those time points, HbA1C (if not within 3 months), blood pressure (cuff pressure), vasoactive doses, and renal function (measured by serum creatinine and estimated GFR) will be captured at multiple time points during CCU admission, as described below. All data points collected for use in this study are being measured as part of the patient's routine care.

(1) **Cardiac catherization lab prior to CCU arrival:** Initial baseline hemodynamics obtained in the cardiac catherization lab prior to CCU arrival will be collected.

a) Cardiac index (L/min/m^2) by Indirect Fick Method
b) Right atrial pressure (RAP) (mmHg)
c) Pulmonary artery systolic pressure (PASP) (mmHg)
d) Mean pulmonary artery pressure (mPA) (mmHg)
e) Pulmonary artery diastolic pressure (PADP) (mmHg)
f) Pulmonary capillary wedge pressure (PCWP) (mmHg)
g) Pulmonary artery pulsatility index (PAPI)
h) Right ventricular stroke work index (RVSWI) (mmHg L^{-1} m^{-2})
i) Systemic vascular resistance (SVR) (dynes/sec/cm^5)
j) Pulmonary vascular resistance (PVR) (dynes/sec/cm^5)
k) Systolic, diastolic, and mean blood pressure (SBP/DBP/MAP) (mmHg)
l) Aortic pulsatility index (API)

(2) **Hour 0 –** Leveled hemodynamics, repeated within two hours of arrival to CCU bed from cardiac catherization lab prior to SGLT2i administration/equivalent if randomized to no SGLT2i arm, will be collected. All baseline data points to be collected at this time.

a. Cardiac index (L/min/m^2)
b. RAP (mmHg)
c. PASP (mmHg)

d. mPA (mmHg)
e. PADP (mmHg)
f. PCWP (mmHg)
g. PAPi
h. RVSWI (mmHg L^{-1} m^{-2})
i. SVR (dynes/sec/cm^5)
j. PVR (dynes/sec/cm^5)
k. SBP/DBP/MAP
l. API
m. Standing weight
n. Urine output
o. Blood glucose taken from BMP
p. HbA1c
q. Current Vasoactive doses
r. Renal function (serum Creatinine, serum eGFR)
s. Total diuretic dose

(3) **Hour 1 –** Following repeat hemodynamics in CCU bed, patients will be given SGLT2i if randomized to SGLT2i arm, or not given SGLT2i if randomized to no SGLT2i arm.

(4) **Hour 3**

a. Cardiac index (L/min/m^2)
b. RAP (mmHg)
c. PASP (mmHg)
d. mPA (mmHg)
e. PADP (mmHg)
f. PCWP (mmHg)
g. PAPi
h. RVSWI (mmHg L^{-1} m^{-2})
i. SVR (dynes/sec/cm^5)
j. PVR (dynes/sec/cm^5)
k. SBP/DBP/MAP
l. API
m. Standing weight
n. Urine output
o. Blood glucose taken from BMP
p. HbA1c
q. Current Vasoactive doses
r. Renal function (serum Creatinine, serum eGFR)
s. Total diuretic dose

(5) **Hour 27 -** 2 hours after 2nd dose of SGLT2i, which will be administered 24 hours after first dose, or equivalent time period after which the dose would have been given for the No-SGLT2i arm.

a. Cardiac index (L/min/m^2)
b. RAP (mmHg)
c. PASP (mmHg)
d. mPA (mmHg)
e. PADP (mmHg)
f. PCWP (mmHg)
g. PAPi
h. RVSWI (mmHg L^{-1} m^{-2})
i. SVR (dynes/sec/cm^5)
j. PVR (dynes/sec/cm^5)
k. SBP/DBP/MAP
l. API
m. Standing weight
n. Urine output
o. Blood glucose taken from BMP
p. HbA1c
q. Current Vasoactive doses
r. Renal function (serum Creatinine, serum eGFR)
s. Total diuretic dose

(6) **Hour 51 & Hour 75 - if vasoactives are still required and pulmonary artery catheter is still being used for routine clinical care**, we will continue SGLT2i for up to 4 doses, and the additional invasive hemodynamics repeated two hours after each dose will be collected.

a. Cardiac index (L/min/m^2)
b. RAP (mmHg)
c. PASP (mmHg)
d. mPA (mmHg)
e. PADP (mmHg)
f. PCWP (mmHg)
g. PAPi
h. RVSWI (mmHg L^{-1} m^{-2})
i. SVR (dynes/sec/cm^5)
j. PVR (dynes/sec/cm^5)
k. SBP/DBP/MAP
l. API
m. Standing weight
n. Urine output
o. Blood glucose taken from BMP
p. HbA1c
q. Current Vasoactive doses
r. Renal function (serum Creatinine, serum eGFR)
s. Total diuretic dose

Leveled invasive hemodynamic measurements, standing weights, intake and outputs, blood glucose, blood pressure, vasoactive doses, and renal function will stop being collected for the

study after the fourth dose of SGLT2i, or equivalent timing for those randomized to the No-SGLT2i arm.

The leveled hemodynamic measurements measured via a pulmonary artery catheter at end expiration will be collected. A picture will be taken and shown to an Advanced HF attending not involved with the patient's current care and blinded to treatment for interpretation.

The patient's participation in the study will end after completion of 4 doses of the SGLT2i or sooner if patient is transferred out of the CCU and continuous hemodynamic monitoring is discontinued, or if patient develops any of the safety end points as listed below. The physician will discuss the ongoing treatment plan with the patient at this point.

Outcomes

Primary outcome: Change in Indirect Fick cardiac index and change in PCWP

Secondary outcomes: changes in pulmonary artery pulsatility index (PAPi), Right atrial pressure (RAP), pulmonary artery systolic pressure (PASP), mean pulmonary artery pressure (mPA), pulmonary artery diastolic pressure (PADP), right ventricular stroke work index (RVSWI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), mean arterial pressure (MAP), renal function, 24 hour urine output, changes in weight, changes in vasoactive dose, and blood glucose levels

Safety End Points

1. Need for initiation of second vasoactive medication and/or MAP < 60
2. Development of acute kidney injury, based on eGFR value < 30ml/min/1.73m^2
3. Adverse events reflecting urinary tract infection, genital infection, bone fracture, and diabetic ketoacidosis

Study Drugs

There are no new study 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 levels in adults with type 2 diabetes. Medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, and empagliflozin" (18). In May 2020, the FDA approved dapagliflozin for use in HFrEF, regardless of diabetes status (19).

Study Subjects

The study will include patients at UCMC who are admitted to the CCU by the advanced heart failure service after right heart catherization for acute decompensated heart failure requiring vasoactive support.

Inclusion Criteria

1. Age ≥ 18 years old
2. Reduced ejection fraction (HFrEF) of 40 or less
3. Estimated glomerular filtration rate (eGFR) > 30ml/min/1.73m^2
4. Admitted to CCU by advanced heart failure service for decompensated heart failure requiring continuous hemodynamic monitoring with a pulmonary artery catheter

Exclusion Criteria

1. Diagnosis of type 1 DM
2. eGFR < 30ml/min/1.73m^2
3. age < 18 years old
4. Jehovah's witnesses
5. Diagnosis of group 1 pulmonary arterial hypertension
6. Insulin requirement above standard low dose sliding scale
7. Patients with a history of DKA
8. Allergies to SGLT2i medications
9. History of intolerance to SGLT2i medications
10. Patients listed for cardiac transplantation or on mechanical support
11. Pregnant or breastfeeding

Recruitment

Patients undergoing a right heart catheterization, either as outpatient or inpatient, who are determined to have a high likelihood of needing CCU admission for acute decompensated heart failure requiring continuous invasive hemodynamic monitoring with a pulmonary artery catheter, will be recruited by members of the Advanced Heart Failure team. Patients will be approached before sedation is given for the right heart catheterization procedure.

Informed Consent Process

The consent process will take place during a routine visit or inpatient hospital stay. 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 UCMC 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 (5,20). However, due to its direct effect on the kidneys, SGLT2i are labeled for patients with eGFR $\geq$ 20ml/min/1.73m^2 or GFR $\geq$ 30ml/min/1.73m^2 depending on the medication. Due to this, we will exclude patients with eGFR < 30ml/min/1.73m^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). We will not be using canagliflozin in this study.

The adverse reactions of dapagliflozin 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 its use in the ICU-setting in patients with acute decompensated heart failure. If benefit is shown in the SGLT2i population, the arm without SGLT2i would lose the hypothesized benefit of renal and cardiovascular benefits during the CCU stay.

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. All patients in this study are closely monitored throughout the duration of activity in this study as, by nature, they are in the CCU. Any study-related adverse events will be reported to the IRB according to the IRB's reporting requirements. Adverse events related to the SGLT2i will be reported to the manufacturer or directly to the FDA as would normally occur for safety reporting of routine medications.

40 subjects in this initial pilot study are followed for less than 4 days. We believe that this is the minimum required to clarify potential benefit of SGLT2 inhibitor therapy in the acute setting in patients with acute decompensated heart failure. We do not anticipate adequate data prior to study completion evidencing benefit that would justify study stoppage or redesign.

Potential Benefits

SGLT2i data 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 patients with acute decompensated heart failure (9-11,13-17). 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 recommendations to include SGLT2i as standard of care. Therefore, it is hypothesized that the benefit of SGLT2i seen in HFrEF patients will also be effective in the acute setting in patients with acute decompensated heart failure.

Alternatives

Participation is voluntary, and the alternative is not to participate in this study. Outside of the study, the decision whether or not the patient receives 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 (UCMC). This is not a multicenter study; thus, University of Chicago will be the only institution involved with the research.

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