Efficacy and Safety of Dapagliflozin in Acute Heart Failure

DICTATE-AHF

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Protocol

A Randomized, Open-label Study of Dapagliflozin in Patients with or without Type 2 Diabetes Admitted with Acute Heart Failure

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PROTOCOL VERSION AND AMENDMENT TRACKING

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Abbreviations

ADHF	Acute Decompensated Heart Failure
BNP	B-type natriuretic peptide
BP	Blood pressure
CCC	Clinical Coordinating Center
CEC	Clinical Events Committee
DCC	Data coordinating center
DSMB	Data and Safety Monitoring Board
ED	Emergency department
FENa	Fractional excretion of sodium
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICU	Intensive care unit
IV	Intravenous
LVEF	Left ventricular ejection fraction
PI	Principal Investigator
VUMC	Vanderbilt University Medical Center
WHF	Worsening Heart Failure

CLINICAL TRIAL SUMMARY

Title	**A Randomized, Pilot Study of Dapagliflozin in Patients with or without Type 2 Diabetes Admitted with Acute Heart Failure**
Study Objectives	The primary endpoint is to determine the cumulative change in weight (kilograms) per 40mg of IV furosemide equivalents from enrollment to day 5 or discharge (if earlier) between: 1) protocolized diuretic therapy and 2) dapagliflozin plus protocolized diuretic therapy guided by urine output. <u>Secondary endpoints</u> include comparing differences among the two arms in the following: • Incidence of worsening heart failure during hospitalization requiring IV inotropic therapy, new admission to an intensive care unit, new non-invasive positive pressure ventilation with bi-level positive airway pressure, or increase in the IV diuretic protocol intensity by 2 rows after Study Day 1 as adjudicated by the Clinical Event Committee • Hospital readmission within 30 days of discharge for heart failure or diabetic reasons as adjudicated by the Clinical Event Committee Exploratory endpoints include comparing difference among the two arms in the following: • NT-proBNP at baseline to discharge adjusted for baseline • Urine-output based Diuretic efficiency: 24-h total urine output (ml) per 40mg of IV furosemide equivalents on day 2 of IV diuretic therapy from 24-h urine collection (collected day 2-day 3) • Fractional excretion of sodium (FENa)-based diuretic efficiency on day 2 of IV therapy: FENa per 40mg of IV furosemide equivalents of bolus loop dose using spot urine collected 2 hours after bolus loop dose • Urinary Na/K ratio at day 2 of IV therapy adjusted for baseline • Calculated 6-hour sodium output on day 2 of IV therapy using spot urine sodium collected 2 hours after bolus loop dose • Length of hospital stay, measured as days from admission to discharge • Presence of symptoms of congestion and dyspnea at discharge, measured via blinded-physician exam and patient reported congestion scores

	• Hospital readmission within 30 days of discharge for any cause • Number of days at home without hospitalization or emergency room visit during 30-day follow up period • Mean serum glucose during therapy • Amount of total daily insulin doses (units) utilized per day during therapy among patients with diabetes, compared between treatment arms and to a prior to enrollment outpatient insulin regimen • serum potassium covariate adjusted for baseline with attention to both elevation and depression <u>Safety endpoints from study medication administration to hospital discharge:</u> • estimated Glomerular Filtration Rate by the MDRD equation at discharge adjusted for baseline • Incidence of ketoacidosis • Serum glucose covariate adjusted for baseline with attention to both elevation (> 400mg/dl) and depression (< 70mg/dl) • Incidence of hypovolemic hypotension, defined as symptomatic hypotension with a sustained systolic blood pressure less than 90 mmHg over 30 minutes requiring fluid administration • Inpatient mortality
Study Design	This is a randomized trial of the addition of dapagliflozin to patients with or without diabetes hospitalized with AHF. Participants will be recruited following an initial standard evaluation in the ED and randomized within 24 hours of presentation for AHF in a 1:1 fashion to protocolized diuretic therapy or dapagliflozin + protocolized diuretic therapy.
Number of Participants	240 participants will be randomized
Trial Location	Up to six sites including but not limited to: • Vanderbilt University Medical Center • St Thomas Hospital System • Centennial Hospital • University of Mississippi • Integris Baptist Medical Center

	• University of North Carolina
Inclusion Criteria	1) Age of 18 years or older 2) Randomized within 24 of presentation during a hospital admission for hypervolemic decompensated heart failure defined as either: • pulmonary artery catheterization with a pulmonary capillary wedge pressure greater than 19mmHg plus a systemic physical exam finding of hypervolemia (peripheral edema, ascites, or pulmonary edema on auscultation) • in the absence of pulmonary artery catheterization data 2 of the following signs or symptoms: peripheral edema, ascites, jugular venous pressure > 10mmHg, orthopnea, paroxysmal nocturnal dyspnea, 5-pound weight gain, or signs of congestion on chest x-ray or lung ultrasound 3) Planned or current use of IV loop diuretic therapy during current hospitalizaiton 4) eGFR $\geq$ 25 ml/min/1.73m^2 by the MDRD equation
Exclusion Criteria	Type 1 diabetes Serum glucose < 80mg/dl at enrollment Systolic blood pressure < 90mmHg at enrollment Requirement of intravenous inotropic therapy at enrollment or anticipated need of therapy during the study period History of hypersensitivity to any SGLT2 inhibitors Women who are pregnant or breastfeeding Severe anemia (Hemoglobin < 7.5g/dl) Severe uncorrected aortic or mitral stenosis Inability to perform standing weights or measure urine output accurately History of diabetic ketoacidosis Chronic combination nephron blockade with loop and thiazide therapy as an outpatient scheduled daily for more than 7 days prior to admission (Does not include HCTZ < 50mg for blood pressure) Diffuse anasarca with 4+ edema and projected hypervolemia exceeding 40-pounds Severe hepatic impairment (Child-Pugh class C if severity of hepatic failure is in question) Clinical picture consistent with acute myocardial infarction including troponin elevation or ischemic changes on electrocardiogram Site investigator determines the subject is not a good candidate to participate in study at this time

Primary Endpoint	cumulative change in weight (kilograms) per 40mg of IV furosemide equivalents from enrollment to day 5 or discharge (if earlier) between protocolized diuretic therapy and dapagliflozin plus protocolized diuretic therapy guided by urine output
Assessment Schedule (Appendix A)	Baseline: standing weight, NT-proBNP, BMP, hemoglobin A1c, spot urine values of sodium, potassium, and creatinine (calculate urine sodium/potassium ratio, FENa), vital signs, study loop diuretic and diabetic medication orders, congestion score, document baseline HF and diabetic medications, start urine output quantification, urine biobanking for future investigations including urinary exosomes. Daily: standing weight, BMP, vital signs, urine output quantification, titration of study loop diuretic and diabetic medication orders, document HF and diabetic medications, adverse event assessment Day 2: daily assessments as above plus 2-hour post loop diuretic spot urine sodium, potassium, and creatinine. Calculate FENa, 6-hr sodium output, urine sodium/potassium ratio, 24-hour urine collection for quantification and diuretic efficiency calculation, urine biobanking for future investigations including urinary exosomes. Day 5 or Discharge: standing weight, NT-proBNP, BMP, vital signs, urine output quantification, document HF and diabetic medications, congestion score, outcomes assessment, remind primary team to schedule standard-of-care 3-7-day follow-up visit with endocrinology (if patient has diabetes) and HF 30-day phone follow-up: document HF and diabetic medications, outcomes assessment
Study Duration	Enrollment is anticipated to occur over 14 months with the end of study occurring at hospital discharge and a 30-day phone-call follow-up
Clinical Event Committee	The following events will be adjudicated by a Clinical Event Committee blinded to patient assignment: • Worsening heart failure defined as inpatient administration of an IV inotrope with dobutamine, milrinone, or dopamine, new admission to an intensive care unit, new non-invasive positive pressure ventilation with bilevel positive airway pressure, or increase in the IV diuretic protocol intensity by 2 rows after Study Day 1 • 30-day hospital readmissions due to heart failure or diabetes-related events

	• Prolonged hospitalization as a result of hypoglycemia requiring medical intervention • Prolonged hospitalization as a result of hypotension requiring medical intervention • In-hospital incidence of ketoacidosis • Inpatient mortality
Data and Safety Monitoring Board	An independent Data and Safety Monitoring Board will advise the principal investigator on safety aspects and overall progress of the study.

Table of Contents:

1.0 Background and Rationale:

Patients with acute decompensated HF (ADHF) are generally admitted due to symptoms of congestion and 90% are treated with a loop diuretic.[1] However at least one-third of these patients are inadequately decongested due primarily to “diuretic resistance” and/ or “cardiorenal syndrome”.[2,3] The inability to achieve decongestion is associated with a worse prognosis and a higher rate of re-hospitalization for ADHF.[2] More than 40% of all patients admitted with ADHF have diabetes and that percentage is growing both in Heart Failure with Reduced Ejection Fraction (HFrEF) and Preserved Ejection Fraction (HFpEF).[4]

The admission blood glucose is elevated in approximately one-half of ADHF hospitalizations. [5,6] We recently demonstrated the admission blood glucose was within 50mg/dl of the chronic average blood glucose in 66% of patients with diabetes admitted with ADHF.[7] The median (IQR) admission blood glucose change from the chronic blood glucose was only -7 (-29, 26) mg/dl.[7] Thus, the acute glucose in patients with T2DM presenting with acute heart failure is most often related to poor chronic glucose control suggesting that these patients would benefit from attempts to initiate therapies to improve chronic glucose control while in the hospital.

No new therapies have been introduced in the United States for ADHF in several decades. Natriuretic peptides such as nesiritide and ularitide have failed to improve outcomes in either the chronic or acute heart failure patients.[8,9] Diuretic resistance and hyperglycemia are common problems in ADHF admissions and represent a therapeutic opportunity for new therapies.[5,10]

The sodium-glucose cotransporter-2(SGLT2) inhibitors, now approved for the anti-hyperglycemic therapies also have an osmotic diuretic and natriuretic effect.[11] In the chronic setting SGLT2 inhibitors reduce weight with modest decrements in systolic and diastolic blood pressure with a marked drop in albuminuria and a small drop in estimated GFR (-5 mL min^{-1}.1.73 m^{-2}) which returns to baseline over time.[11] In patients with diabetes the SGLT2 transporter likely accounts for as much as 14% of total sodium chloride absorption. In the acute setting following a single dose, SGLT2 inhibitors did not increase urine volume.[12] However, the acute diuretic effects have not been studied in a population with heart failure with or without concomitant hyperglycemia who are undergoing diuresis. To our knowledge, no current trials are investigating the effects of SGLT2 inhibition in ADHF. The current studies planned in HF are investigating the acute effects of SGLT2 on stable HF (NCT03027960), the chronic effects of SGLT2 inhibition in compensated, chronic HF (NCT03619213, NCT02653482, NCT03030235, NCT03057977), changes in pulmonary pressure hemodynamics in patients monitored by CardioMEMs devices (NCT03030222), and effects on cardiopulmonary exercise fitness in chronic HF (NCT02862067).

Congestion remains the major cause of hospital readmission for heart failure and an inpatient plan of care that allowed more effective decongestion would be rapidly and widely adopted by the medical community. Therefore, we propose to test the

decongesting effects of the SGLT2 inhibitor dapagliflozin in patients with or without Type II diabetes admitted with an acute decompensation of chronic heart failure.

2.0 Study Outcomes:

2.1 Primary Outcome

- The change in weight in kilograms per 40mg of IV furosemide equivalents from enrollment baseline to day 5 or discharge (if earlier)
    - Standing weights will be performed by study personnel using the same scale throughout the study period with the same clothing (hospital gown without shoes). The patient will be requested to empty their bladder and bowels if needed prior to each weight assessment.
    - The cumulative loop diuretic dose includes all IV and oral doses administered in the study period, converted to IV furosemide equivalents. Diuretic conversion: 80mg oral furosemide = 40mg IV furosemide = 20mg oral torsemide = 1mg oral/IV bumetanide

This primary outcome investigates the decongestive potential of dapagliflozin by its impact on diuretic efficiency. Higher diuretic efficiency has been associated with better outcomes in multiple AHF populations.[13,14] The primary outcome does not quantify the importance of initiating a mortality reducing therapy during hospitalization, which increases chronic adherence. Therefore, even if dapagliflozin does not meet the primary endpoint, this study would still be beneficial to establish the safety and best practices of initiating dapagliflozin during an AHF hospitalization, setting the stage for continuing it into the outpatient setting. The established benefits of such a strategy would emerge over the coming months to years. In addition to mechanistic and diuretic endpoints, additional secondary outcomes are designed to establish the safety across hemodynamic, renal, and glycemic outcomes.

2.2 Secondary Outcomes: Compared between treatment arms

- Incidence of worsening heart failure during hospitalization requiring IV inotropic therapy, new admission to an intensive care unit, new non-invasive positive pressure ventilation with bilevel positive airway pressure, or increase in the IV diuretic protocol intensity by 2 rows after Study Day 1 as adjudicated by the Clinical Event Committee
- Hospital readmission within 30 days of discharge for heart failure or diabetic reasons as adjudicated by the Clinical Event Committee

2.3 Exploratory Outcomes: Compared between treatment arms

- NT-proBNP at discharge adjusted for baseline
- Urine-output based Diuretic efficiency: 24-h total urine output (ml) per 40mg of IV furosemide equivalents on day 2 of IV diuretic therapy from 24-h urine collection (collected day 2-day 3)

- Fractional excretion of sodium (FENa)-based diuretic efficiency on day 2 of IV therapy: FENa per 40mg of IV furosemide equivalents of bolus loop dose using spot urine collected 2 hours after bolus loop dose
- Urinary Na/K ratio at day 2 of IV therapy adjusted for baseline
- Calculated 6-hour sodium output on day 2 of IV therapy using spot urine sodium collected 2 hours after bolus loop dose
- Increase in IV loop diuretic titration grid for urine output below the goal range
- Length of hospital stay, measured as days from admission to discharge
- Hospital admission within 30 days of discharge for any cause
- Number of days at home without hospitalization or emergency room visit during 30-day follow up period
- Presence of symptoms of congestion and dyspnea at discharge, measured via physical exam congestion scores[15]
    - Edema will be categorized as trace/mild (0 points), moderate (1 point), or severe (2 points).
    - Orthopnea will be characterized as present if the patient needed at least 2 pillows to breathe comfortably (2 points) or absent (0 points).
    - The Orthodema Score will be generated by the sum of the individual orthopnea and edema scores as in the table below:

Orthodema Score[15]		
Mild edema No orthopnea	0	No congestion
Moderate edema No orthopnea	1	Low-grade orthodema
Severe edema or orthopnea	2	
Moderate edema and orthopnea	3	High-grade orthodema
Severe edema and orthopnea	4	

Mild edema = below the knee with minimal denting
Moderate edema = below the knee with significant pitting
Severe edema = above the knee

- Mean Serum glucose during therapy
- Amount of total daily insulin doses (units) utilized per day during therapy among patients with type 2 diabetes, compared between treatment arms and to a prior to enrollment outpatient insulin regimen
- serum potassium covariate adjusted for baseline with attention to both elevation and depression

<u>Single-Center Exploratory Outcomes at Vanderbilt University Medical Center</u>

The following exploratory outcomes will only be performed in patients at Vanderbilt University Medical Center who elect to participate in a sub-study. Patients can decline to participate in this sub-study and still participate in parent clinical trial. To explore

changes in the plasma proteome during IV diuresis, we will collect one 15mL blood sample (10mL in purple top EDTA tube and 5mL in red top tube) at baseline and on the final study day (Day 5 or discharge).

2.4 Safety Outcomes: Compared between treatment arms during the index stay from signing of informed consent to hospital discharge

- Change in the estimated Glomerular Filtration Rate by the MDRD equation at discharge adjusted for baseline
- Incidence of ketoacidosis, identified by the study team as elevated ketones in the urine and an arterial blood pH < 7.35 and adjudicated by the Clincal Events Committee
- Serum glucose covariate adjusted for baseline with attention to both elevation (> 400mg/dl) and depression (< 70mg/dl)
- Potential prolonged hospitalization as a result of hypoglycemia requiring medical intervention as adjudicated by the Clinical Events Committee
- Potential prolongation of hospitalization as a result of incidence of hypovolemic hypotension, defined as a symptomatic hypotension with a sustained systolic blood pressure less than 90 mmHg over 30 minutes and requiring medical intervention as adjudicated by the Clinical Events Committee. All hypotension episodes requiring medical intervention will be evaluated by the Clinical Events Committee.
- Inpatient mortality

3.0 Inclusion/Exclusion criteria

- Inclusion Criteria
    - Age of 18 years or older
    - Randomized within 24 hours of presentation during a hospital admission for hypervolemic decompensated heart failure defined as either:
        - pulmonary artery catheterization with a pulmonary capillary wedge pressure greater than 19mmHg plus a systemic physical exam finding of hypervolemia (peripheral edema, ascites, or rales on auscultation)
        - in the absence of pulmonary artery catheterization data 2 of the following signs or symptoms: peripheral edema, ascites, jugular venous pressure > 10mmHg, orthopnea, paroxysmal nocturnal dyspnea, 5-pound weight gain, or signs of congestion on chest x-ray or lung ultrasound

- Standard-of-care monitoring on an inpatient ward and standard-of-care basic metabolic panel laboratory assessment once daily during the study period
- Planned or current use of IV loop diuretic therapy during current hospitalization
- eGFR $\geq$ 25 ml/min/1.73m^2 by the MDRD equation

- Exclusion Criteria
  - Type 1 diabetes
  - Serum glucose < 80mg/dl at enrollment
  - Systolic blood pressure < 90mmHg at enrollment
  - Requirement of intravenous inotropic therapy at enrollment or anticipated need of therapy during the study period
  - History of hypersensitivity to any SGLT2 inhibitors
  - Women who are pregnant or breastfeeding
  - Severe anemia (Hemoglobin < 7.5g/dl)
  - Severe uncorrected aortic or mitral stenosis
  - Inability to perform standing weights or measure urine output accurately
  - History of diabetic ketoacidosis
  - Chronic combination nephron blockade with loop and thiazide therapy as an outpatient scheduled daily for more than 7 days prior to admission (Does not include HCTZ < 50mg for blood pressure)
  - Diffuse anasarca with 4+ edema and projected hypervolemia exceeding 40-pounds
  - Severe hepatic impairment (Child-Pugh class C if hepatic impairment is in question)
  - Clinical picture consistent with acute myocardial infarction including troponin rise and fall or ischemic changes on electrocardiogram
  - Site investigator determines the subject is not a good candidate to participate in study at this time

4.0 Patient screening, consent, and randomization

We will perform a randomized, open-label, multicenter trial to investigate the safety and clinical effects of initiating dapagliflozin vs standard of care in patients admitted to the hospital with ADHF with protocolized diuretic therapy in both treatment arms.

4.1 Screening

To identify candidates, we will collaborate with our Emergency Department. We are able to screen, consent, and randomized study candidates in the Emergency Department. Additionally, patients with ADHF will be screened on the HF team daily by a member of

the HF team. Finally, we will utilize an electronic HF dashboard embedded within the electronic medical record to identify candidates across the medical center by their International Classification Disease code history, natriuretic peptide concentration adjusted for body-mass index, and use of intravenous loop diuretic therapy.

We will utilize up to 5 additional sites for enrollment including but not limited to:

- Mark Aaron - St Thomas Hospital System in Nashville, TN
- A. Tom McRae – Centennial Hospital in Nashville, TN
- Gabriel Hernandez – University of Mississippi in Jackson, MS
- Luke Cunningham – Integris Baptist Medical Center
- Kirkwood Adams – Univeristy of North Carolina

4.2 Consent

The study will be reviewed with the prospective participant (surrogate) by the investigator or study personnel. The prospective study participant (surrogate) will be given adequate time to read the written consent form. The investigator or study personnel will be available to answer questions about the study including procedures, risks, and alternatives. The informed consent form will be signed and dated by the patient or legally authorized representative as per local regulation.

The consent will allow for protected health information (PHI) to be transferred to REDCap to be analyzed by the Biostatistical team. All privacy regulations will be followed (i.e., Health Insurance Portability and Accountability Act [HIPAA]).

4.3 Randomization

Randomization will occur during the hospitalization within 24 hours of evaluation of AHF. Enrollment and randomization will be accomplished by study personnel logging into REDCap, confirming the inclusion and exclusion criteria have been satisfied, and using the REDCap randomization engine. Participants will then be randomized to either dapagliflozin or standard-of-care and will be registered as *randomized*.

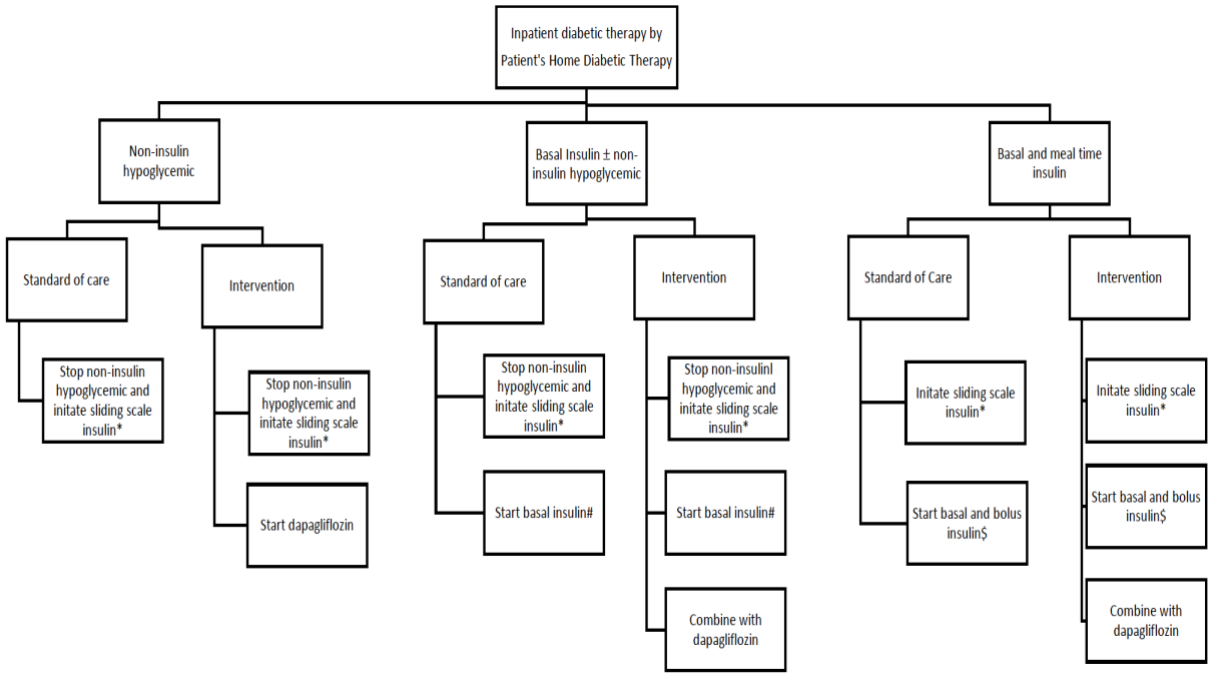
5.0 Study Procedures

All patients will receive a low sodium diet (2g/day) with a 2000ml fluid restriction. Patients will receive standard-of-care laboratory monitoring (including at minimum once daily basic metabolic panel and baseline complete metabolic panel), vital sign monitoring, and strict urine output monitoring/quantification.

5.1 Diabetic Therapies for patients with a diagnosis of Type 2 diabetes

After enrollment, all previous diabetic therapies will be discontinued. Patients will be randomzed in a 1:1 ratio to standard of care with protocolized diuretic therapy or standard of care with protocolized diuretic therapy plus the addition of open label SGLT2 inhibitor therapy with dapagliflozin 10 mg orally once daily for the duration of the study, which will be until 5 days or hospital discharge. The patient will receive standard

of care point of care blood glucose monitoring 4 times daily (before meals and at bedtime) and correctional insulin according to a blood glucose scale. For patients requiring large doses of basal insulin, the patient will be continued on a reduced dose of basal insulin. Insulin initiation and titration algorithms are in Appendix B.



Non-insulin hypoglycemic: chronic, outpatient oral hypoglycemic medications which may include but are not limited to sulfonylureas, DPP-4 inhibitors, and/or metformin.

5.2 Heart Failure Therapies

The titration of non-diuretic heart failure therapies will be left to the direction of the treating physician.

5.3 Diuretic Therapies

5.3.1 Initial loop diuretic regimen

If the patient has received loop diuretic dose(s) prior to randomization, proceed to Section 5.3.2 and titrate the current loop diuretic regimen according to diuretic protocol provided.

If the patient's first IV loop diuretic dose is after enrollment, the initial loop diuretic regimen after enrollment will be as follows:

Loop diuretic naïve: If the patient does not take a scheduled loop diuretic as an outpatient, the initial IV loop diuretic dose will be 40mg of furosemide equivalents every 12 hours. (1mg IV bumetanide = 40mg IV furosemide)

Chronic, oral loop diuretic therapy: If the patient takes a scheduled loop diuretic regimen as an outpatient prior to hospital admission, the initial IV loop diuretic daily dose will be 2 to 2.5 times the total daily home regimen dose. The calculated daily dose will be given as 50% the total daily dose as an IV bolus dose every 12 hours. Individual bolus doses exceeding 200mg IV furosemide equivalents will be capped to 200mg IV furosemide equivalents, so that the highest initial regimen will be 200mg IV every 12 hours.

Diuretic conversion: 80mg oral furosemide = 40mg IV furosemide = 20mg oral torsemide = 1mg oral/IV bumetanide

5.3.2 Loop diuretic titration

Diuretic therapy can be titrated every 12 - 24 hours. Diuretic titration recommendations will be provided per the table below to first maximize IV loop diuretic therapy before addition of combination nephron blockade to limit non-loop diuretic therapy impact.

Goal urine output		Suggested Diuretic Regimen Titration
Over 12 h	Over 24 h	
< 1.5 liters	< 3 liters	Move down diuretic grid 1 row to increase diuretic intensity
1.5 – 2.5 liters	3-5 liters	Continue on same diuretic regimen
> 2.5 liters	> 5 liters	Move up diuretic grid 1 row to decrease diuretic intensity

Current IV Diuretic Regimen (Furosemide IV Equivalent mg/day)	**Suggested New IV Diuretic Regimen** (Furosemide IV Equivalent in mg)
≤ 80 mg /day	160mg daily: 80mg IV Q12H
81-200mg/day	320mg daily: 160mg IV Q12H
201-320mg/day	480mg daily: 240mg IV Q12H or 20mg/h infusion*
321-480mg/day	600mg daily: 300mg IV Q12H or 25mg/h infusion*
481-600mg/day	720mg daily: 30mg/h infusion*
601-720mg/day	960mg daily: 40mg/h infusion*
721-960mg/day	1,440mg daily: 60mg/h infusion* + metolazone 5 mg daily
>960mg/day	1,920mg daily: 80mg/h infusion* + metolazone 10 mg daily

*Continuous IV infusions will be preceded by a 80mg IV furosemide loading dose unless a bolus dose was given in the previous 2 hours.

Non-study diuretic therapies

Use of non-study diuretic therapies including: spironolactone doses ≥100mg/day, eplerenone ≥ 100mg/day, non-study thiazides (metolazone or HCTZ> 12.5mg or other thiazide), non-study loop diuretics, systemic acetazolamide, triamterene, or amiloride therapy is discouraged and considered a protocol deviation.

5.4 Clinical Event Committee

The CEC will consist of 3 independent clinicians, which will consist of at least one endocrinologist and at least one heart failure specialist. The members of this committee

will be independent of the study implementation teams and will be blinded to study arm assignment. This committee will review abstracted clinical data to determine when primary endpoints and major events have occurred. The CEC will review data for the following study outcomes:

- Potential inhospital worsening heart failure events identified by the following criteria:
    - New intravenous inotropic therapy
    - New admission to an intensive care unit
    - New non-invasive positive pressure ventilation with bilevel positive airway pressure
    - 2 or more increases in IV diuretic protocol intensity after Study Day 1
- 30-day readmission events for heart failure or diabetes-related care
- *Prolonged hospitalization as a result of the following safety outcomes:* hypotension requiring medical intervention or hypoglycemia requiring medical intervention
- In-hospital incidence of ketoacidosis
- Inpatient mortality for causality

All criteria and definitions will be pre-specified in detail in the Clinical Events Committee Charter. Only outcomes adjudicated as such by the Clinical Events Committee will be considered. If there are valid reasons for questioning an adjudication, such as an inexplicable outlier during analysis, the Principal Investigator may formally request a review of the case. In such situations, the Clinical Events Committee has final determination.

6.0 Risks

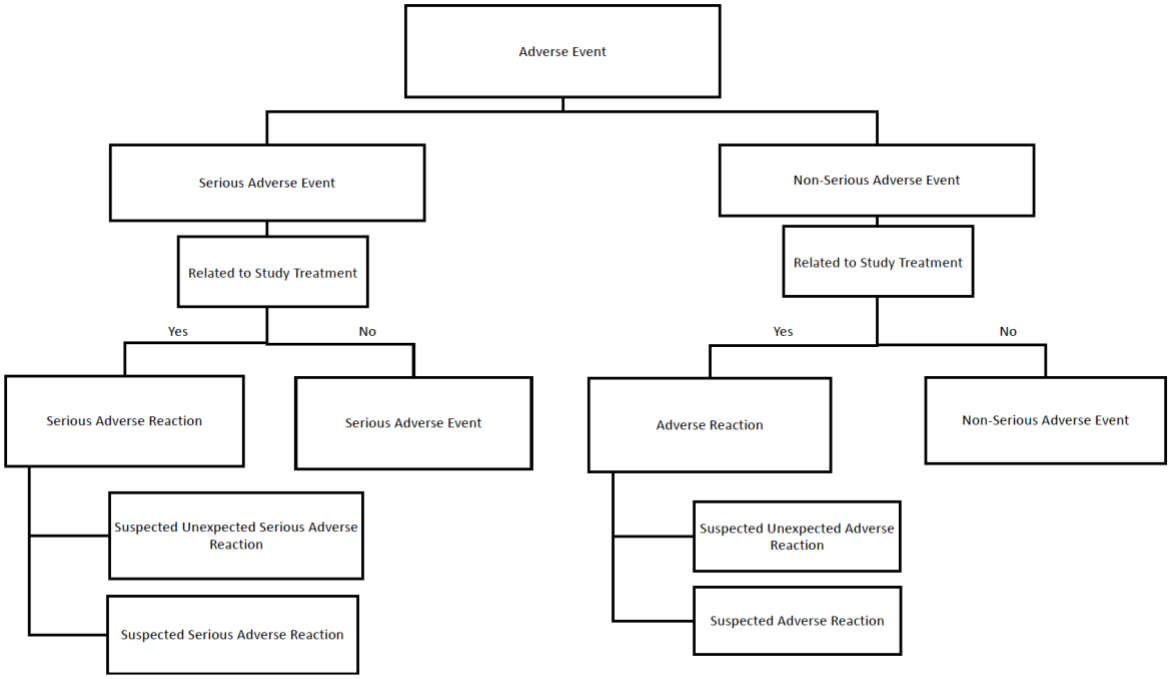
This study will evaluate the addition of oral dapagliflozin to standard-of-care heart failure therapies in patients with hypervolemic heart failure. We do not expect the risk of the dapagliflozin treatment arm will be different than the standard of care treatment arm. Dapagliflozin has a lower hypoglycemia risk than standard of care insulin therapy. Study procedures are designed to manage and minimize risks through careful selection of the patients who participate in the trial. We have developed a standardized protocol for diabetic therapies with endocrinology to minimize hypoglycemia risk in patients with diabetes. Participants will be monitored throughout the treatment phase of the study, throughout hospitalization, and at 30-day follow-up. Further, an independent DSMB will monitor safety of the participants throughout the study.

7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

An Adverse Event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a

pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no

study treatment has been administered. The term AE is used to include both serious and non-serious AEs. The time period of AE evaluation in this study will start after signature of the informed consent and will conclude at the end of the follow up period 30 days after hospital discharge.



7.1 Safety Standards

The determination of adverse event severity rests on medical judgment of a medically qualified investigator. The severity of AEs will be graded using the following definitions:

- *Mild:* awareness of sign, symptom, or event, but easily tolerated;
- *Moderate*: discomfort enough to cause interference with usual activity and may warrant intervention;
- *Severe*: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

A Serious Adverse Event (SAE) is an adverse event that:

- Results in death
- Is life-threatening

- Requires prolongation of hospitalization which is not specifically required by the protocol nor is it elective
- Results in permanent impairment of a body function or permanent damage to a body structure
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

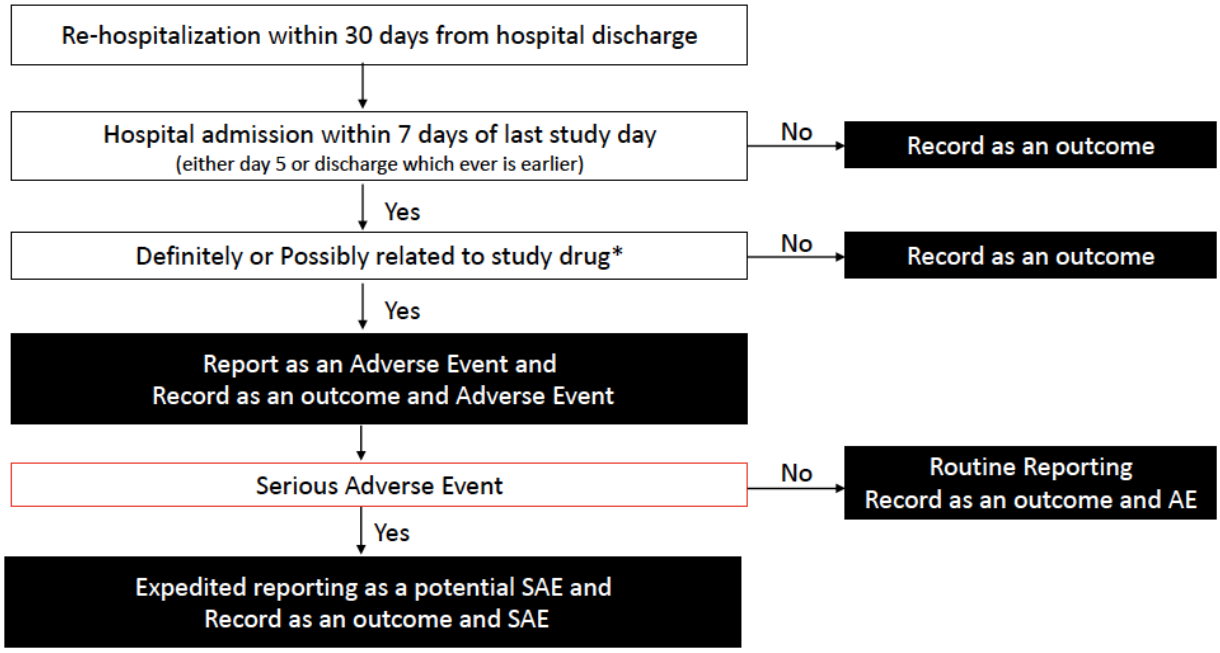
Additionally, important medical events that may not result in death, be life-threatening, or prolong hospitalization may be considered SAEs when they jeopardize the patient or require medical or surgical intervention to prevent one of the serious outcomes listed above. Example of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in prolonged hospitalization, or the development of drug dependency or drug abuse. Medical and scientific judgment must be exercised when classifying events as serious.

Serious Adverse Events (SAE) related to dapagliflozin will be categorized as:

- Suspected Unexpected Serious Adverse Reaction (SUSAR):
    - unintended response to dapagliflozin, which is not listed in the applicable product labeling, and meets the severity definition(s) of a SAE as above
- Suspected Serious Adverse Reaction (SSAR):
    - unintended response to dapagliflozin, which is listed as a potential adverse reaction in the product labeling, and meets the severity definition(s) of a SAE as above

7.2 Adjudication and Reporting of Re-hospitalizations during the 30-day follow-up period

We will evaluate all re-hospitalizations occurring 30-days from the date of discharge from index hospitalization during which the study occurred. Thirty-day rehospitalizations are very common and expected in patients with heart failure. The purpose of this is to clarify if the hospitalization is a study outcome, AE, or both.



**Definitely or possibly related to study drug* = the rehospitalization was related to known or potential adverse events from dapagliflozin as defined in the U.S. marketed dapagliflozin package insert or according to investigator judgement in accordance with Section 7.3 below.

Rehospitalizations that are within 7 days of the last study day and are definitely/possibly related to the study drug will be reported as Adverse Events according the procedures detailed in protocol Section 7.4. All other rehospitalizations will be documented as study outcomes and adjudicated by the CEC according to protocol Section 5.4.

7.3 Assessment of Causality and Expectedness

A medically-qualified investigator must assess the relationship of any AE to the use of study drug, based on available information, using the following guidelines:

Causality

Possibly Related - There is a reasonable possibility that the adverse event may have been caused by the study drug. The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the observed event.

Not Possibly Related- It is unlikely that the event was caused by the study drug. The temporal relationship of the adverse event to the study drug administration makes causal relationship unlikely and other drugs, therapeutic interventions or underlying conditions provide a more likely explanation for the event.

Expectedness

The expectedness of an adverse event or suspected adverse reaction shall be determined according to the package insert for U.S. marketed furosemide and dapagliflozin. Any AE that is not identified in nature, severity, or specificity in the current U.S. package insert is considered unexpected. Events described in the U.S. package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not specifically mentioned as occurring with the particular drug under investigation are considered unexpected.

7.4 Reporting of Adverse Events and SAEs

All adverse events occurring from signing of the Informed Consent through the 30-day follow-up period will be collected and reported. The Site Investigator is responsible for monitoring the safety of patients enrolled into the study. The following adverse events are anticipated, disease related-events in patients with decompensated heart failure; however, they should still be reported on the Adverse Event form in the REDCAP Database (some may require reporting as study endpoints):

- *New Ventricular Arrhythmia*: Ventricular tachycardia lasting longer than 30 seconds, or frequent non-sustained VT causing hemodynamic instability with MAP < 60 mmHg requiring intervention or > 1 intra-cardiac defibrillation or external cardiac defibrillation shock or ventricular fibrillation requiring defibrillation or requiring transfer to the intensive care unit
- *Hypotension*: SBP < 90 for 2 repeated measurements within 30 minutes or lasting at least 30 minutes or symptomatic hypotension necessitating clinical intervention (defined as vasopressor support, intravenous fluid boluses, or initiation of inotropes)
    - *Hypovolemic hypotension*: subset of “hypotension” requiring fluid administration for hypovolemia
- *Cardiac arrest*: any ventricular arrhythmic or pulseless electrical event that requires immediate life-sustaining medical therapies
- *Acute kidney injury requiring renal replacement therapy*: an acute renal failure event that began during the study period and necessitates new renal replacement therapy during the hospitalization
- *Prolonged hospitalization as a result of the following safety outcomes:* hypotension requiring medical intervention or hypoglycemia requiring medical intervention
- *Diabetic ketoacidosis as adjudicated by the CEC*
- *Death*

All serious adverse events must be recorded in the Adverse Event Record of the patient’s REDCAP database. All serious adverse events should be monitored until stabilization or resolution.

The process of reporting of SAEs will be as follows:

1. The investigator team informs the site investigator of an SAE
2. The site investigator reports the SAE to the local IRB and to the coordinating center and PI within 24 hours of being aware of the event. The site investigator will electronically submit the necessary supporting documentation to the coordinating site.
3. The coordinating center and PI will report the SAE to AstraZeneca.
4. If the coordinating set determines the SAE is a SUSAR, the coordinating site will report the SUSAR to the FDA.

Reporting to the Coordinating Site

All serious adverse events will be reported to the coordinating center (Vanderbilt) by the investigational site within 24 business hours of being aware of the event.

Reporting to Local IRB. Investigators are also responsible for promptly reporting unexpected adverse events (serious and non-serious) to their reviewing IRB in accordance with local requirements. The Vanderbilt investigational site will report DSMB reports to the Vanderbilt IRB annually at the time of continuing review at a minimum. SAEs will be reported to the local IRB within 24 business hours of being aware of the event.

Reporting to the Data Safety Monitoring Board

Adverse event reports will be generated and presented to the DSMB at each meeting for review. The DSMB will also be alerted to SAEs prior to scheduled meetings if the number of individual SAEs in the data safety and monitoring plan are met.

Reporting to AstraZeneca

The coordinating center will notify AstraZeneca of each SAE. The SAE will be submitted as an individual case report. The causality of SAEs (their relationship to all study treatments/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca. The Investigator is responsible for informing the local authorities (FDA) and ethical committees, of any SAEs as per local requirements, and concurrently AstraZeneca. When reporting to AstraZeneca, a cover page will accompany the SAE form indicating the following:
• External Sponsored Research (ESR)
• The site investigator's and coordinating center's name and address
• The trial name/title and AstraZeneca ESR reference number
SAEs will be reported by way of fax to AstraZeneca's designated fax line: +1 302 886 4114 or email if a secure is set up: AEMailboxClinicalTrialTCS@astrazeneca.com

7.5 Study Termination

The study may be terminated based on the DSMB review of serious adverse events and unexpected events.

7.6 Non-serious Adverse Events

Non-serious AEs will be reported to the IRB and AstraZeneca in annual scheduled reports. Additionally, the investigator will notify AstraZeneca of all non-serious AEs as a line item list at the end of the study. Non-serious AEs will be presented to the DSMB at each interim analysis.

The following events are examples of potential non-serious suspected adverse reactions unless the seriousness meets criteria for a SAE as defined above.

- Incidence of mycotic genital infection, defined as a new symptomatic infection requiring treatment
- Incidence of symptomatic cystitis, defined as new symptoms of dysuria, frequency, and/or urgency, plus a urine culture with at least 10^2 colony forming units of a uropathogen requiring treatment with antibiotic therapy
- Incidence of symptomatic pyelonephritis, defined as new symptoms of dysuria, frequency, and/or urgency plus acute flank pain, plus a urine culture with at least 10^2 colony forming units of a uropathogen requiring treatment with antibiotic therapy

7.7 Pregnancy

Pregnancy is an exclusion criteria for this trial. It is unlikely that a patient would become pregnant during this study, as it takes place during hospitalization for acute heart failure. If a patient becomes pregnant during the course of the study, dapagliflozin will be discontinued immediately and an Astra Zeneca representative notified. Pregnancy itself is not regarded as an AE unless there is a suspicion that dapagliflozin may have interfered with the effectiveness of a contraceptive medication. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) will be followed up and documented even if the patient was discontinued from the study. All pregnancies and outcomes of pregnancy will be reported to AstraZeneca's designated fax line: +1 302 886 4114 or email: AEMailboxClinicalTrialTCS@astrazeneca.com

8.0 Data Handling and Record Keeping

The primary data collection system for our study will be the REDCap system, which uses a web-based electronic data capture. All data collected at any point in the trial are entered into this EDC system. At regular intervals, all data will be transferred from the EDC database for statistical summarization, data description, and data analysis. Further crosschecking of the data will be performed, and discrepant observations flagged and appropriately resolved through a data query system. The biostatistical team will perform internal database quality-control checks, and data audits throughout the course of the trial.

8.1 Data Confidentiality and Retention

Computerized data will be accessible only by password, and a centralized monitoring system will record and report all access to data. Electronic CRFs (eCRFs) will be identified by study number only, to ensure participant anonymity. No participant identifiers will be used in the presentation of data. Study records that might identify participants will be kept confidential as required by law. Except when required by law, participants will not be identified by name, personal identification number (e.g. social security number, social insurance number), address, telephone number, or any other direct personal identifier in study records. Participants will be informed that the study physician and his/her study team will report the results of study-related tests to the investigators and to the NIH. Participants will be informed that their records may be reviewed in order to meet federal, state or regional/local regulations. Reviewers may include the study team monitors, IRBs/ECs, the NIH, other government regulators as dictated by local law, or their delegates. Study records will be maintained by the investigators for a period of six (6) years following the expiration of the grant or length of time as required by local regulations, whichever is longer.

9.0 Study Withdrawal/Discontinuation

A patient may withdraw at the study at any time. The patient will inform the site investigator of their desire to withdraw. All study-based therapy will stop at this point, and the attending cardiologist will perform any further care. All study data collected to that time point will be included in the analysis. The withdrawal reason will be documented. All patients will be followed per the study protocol through Day 30.

10.0 Statistical Methods

The full statistical methods are detailed separately in the *Statistical Analysis Plan*.

The primary analysis model will be the semiparametric proportional odds (PO) ordinal logistic regression model[16] for continuous outcome variables[17]. The PO model does not make any distributional assumption for the response variable, is robust to extreme values, and is invariant to transformations of the response variable. It is also extremely efficient when compared to linear regression if normality holds. The Wilcoxon nonparametric two-sample test is a special case of the PO model, but the PO model allows for baseline covariate adjustment. Note that we use covariate adjustment instead of change from baseline so as to not assume that (1) the baseline variable is linearly related to the response variable and (2) the slope of the baseline variable is 1.0.

For binary outcomes we will use the special case of the PO model that is the binary logistic regression model.

For safety analysis of clinical lab variables we use the most powerful and least arbitrary continuous variable analyses and include the empirical cumulative distribution function of post-randomization values of these variables. These continuous analyses will also provide estimates of incidence of such outcomes as hyper- and hypo-kalemia, but will be more sensitive than using only binary responses.

Changes in body weight from admission to discharge in previous literature

Trial	Experimental agent	Mean decrease in weight (kg) Experimental, (%)	Mean decrease in weight Control, (%)	Within group SD in Experimental Group (kg)
TRUE-AHF[8]	Ularitide	---	---	---
RELAX-AHF[18]	Serelaxin	3.6	3.0	4.4
ASCEND-HF[9]	Nesirtide	---	---	---
EVEREST[19]	Tolvaptan	3.3	2.7	3.3
TACTICS[20]	Tolvaptan	3.7	2.5	4.4
Secrets of HF[21]	Tolvaptan	3.5	2.4	2.0
ROSE-HF[22]	Nesiritide	3.25	3.5	0.9
ROSE-HF[22]	Dopamine	3.4	3.5	0.9
MEAN		3.5	2.9	2.7

Changes in weight by IV 40mg Furosemide Equivalents (FE)

Trial	Experimental agent	Duration (days)	Daily IV loop diuretic dose in FE, mean or median (IQR)*	Median (IQR) decrease in weight (kg)/40mg IV FE	Difference associated with adverse HF outcomes
RELAX-AHF[23]	Serelaxin	5	80	0.42 (1.00, 0.14)	Below median value
DIUR-HF[14]	None	3-5	137 (100, 200)	0.20 (0.281, 0.082)	Below median value
ASCEND-HF[24]	Nesiritide	2	----	0.42 (1.0, 0.05)	Below median value
PROTECT[25]	Rolofylline	4	80 (47, 133)	0.38 (0.8, 0.13)	Below median value
EVEREST[19,26]	Tolvaptan	4	80	0.30 (0.79, 0.03)	Below median value
Average across clinical trials				0.34 (0.78, 0.09)	

FE= Furosemide Equivalents (FE)

Multiple clinical trials have examined and validated the diuretic efficiency metric of mean weight loss (kg)/40mg IV furosemide in contemporary AHF study populations. [14 14 14 14] The average cumulative median weight loss/40mg furosemide across these trials was 0.34 (IQR 0.78, 0.09) kg/40mg. Patients with this diuretic efficiency metric in the lower two quartiles had higher incidence of adverse outcomes including hospitalization and mortality across time frames of 30 to 180 days after multivariate analyses. These findings have been confirmed by diuretic efficiency metrics using urine output/40mg IV furosemide in several other populations. In an AHF population at our medical center, we also found a the weight based diuretic efficiency to be similar, with a mean 0.25 kg/40mg but a higher standard deviation (0.47 kg/40mg).

We anticipate dapagliflozin to increase the weight loss while decreasing the cumulative furosemide dose required to achieve euvolemia. On the basis of the historical literature, we project an increase in diuretic efficiency by 0.1kg/40mg IV furosemide in the dapagliflozin arm to be a clinically meaningful difference. We project that our diuretic protocol will decrease variations in loop diuretic dosing, which drive large standard deviations. We project a normally distributed standard deviation within each arm to be 0.25kg/40mg. A sample size of 120 experimental subjects and 120 control subjects will have 87% power to detect a probability of 0.611 that an observation in the dapagliflozin arm is less than an observation in the standard of care arm using a Wilcoxon (Mann-Whitney) rank-sum test with a 0.05 two-sided significance level.

For descriptive statistical analyses of baseline characteristics we will compute proportions for categorical data. Continuous variables will be described by sample quantiles, mean, and Gini's mean differencewill be descrbied using sample quantiles.

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Appendix A: Schedule of study assessments

Assessment	Screening	Baseline (may be Day 1)	Day 1	Day 2	Days 3-4 (if not discharged)	Day 5 or discharge	30-days post discharge
Inclusion /exclusion		X					
Consent		X					
Randomization			X				
Study drug dose			#1	#2	#3, #4	#5	
Laboratory Assessments							
HgbA1c		X					
NT-proBNP		X				X	
Serum chemistries	X			X	X	X	
Pregnancy test	X						
VUMC proteomic sub-study†		X				X	
Urine Assessments							
Urine measurement			X	X	X	X	
24-h urine collection***				X			
Spot urine electrolytes and creatinine*		X		X			
VUMC urine biobanking†		X		X			
Medication Assessments							
Loop diuretic titration per protocol			X	X	X	X	
Insulin titration per protocol among diabetics only			X	X	X	X	
CV medication reconciliation		X	X	X	X	X	X
Diabetic medication reconciliation		X	X	X	X	X	X
Other Assessments							
Vital signs**	X	X	X	X	X	X	
Standing weight**		X	X	X	X	X	
Congestion score		X				X	
Adverse Event assessment			X	X	X	X	X
Study outcomes			X	X	X	X	X

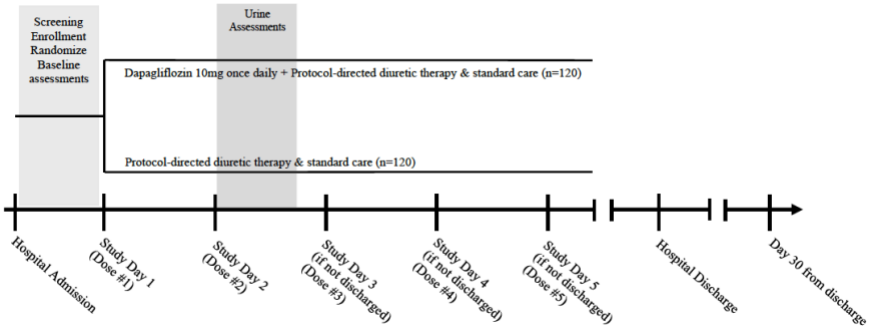
HgbA1c= hemoglobin A1c; BNP= b-type natriuretic peptide; CV = cardiovascular

* Urine sodium, urine potassium, and urine creatinine collected approximately 2 hours after an IV loop diuretic dose. For baseline, this can be 2 hours after the first open-label IV loop diuretic dose prior to randomization.

**Vital Signs and weights are done as close to randomization time as possible for each day

***24 h urine collection started on day 2 plus or minus 6 hours from randomization

† At Vanderbilt University Medical Center study site only



Appendix B: Insulin algorithms for patients with Type 2 diabetes

Insulin lispro is listed as the rapid acting insulin but may be substituted with a equivalent rapid acting insulin for formulary differences across investigation sites

Insulin glargine is listed as the long acting insulin but may be substituted with a equivalent long acting insulin for formulary differences across investigation sites

*Correctional Insulin regimens based upon blood glucose measured 4 times daily (before meals and at bedtime or every 6 hours if NPO):

Blood Glucose	**Moderate dose correctional scale**
< 70 mg/dl	Hypoglycemia protocol per hospital protocol
70 -139mg/dl	No action
140 - 159mg/dl	1 unit insulin lispro
160 - 189 mg/dl	2 units insulin lispro
190- 219 mg/dl	3 units insulin lispro
220 - 249 mg/dl	4 units insulin lispro
250 - 279mg/dl	5 units insulin lispro
280 - 309mg/dl	6 units insulin lispro
310 - 339mg/dl	7 units insulin lispro
340 - 369mg/dl	8 units insulin lispro
370 - 379mg/dl	9 units insulin lispro
>380mg/dl	10 units insulin lispro and notify medical team

Blood Glucose	**High dose correctional scale**
< 70 mg/dl	Hypoglycemia protocol per hospital protocol
70 -139mg/dl	No action
140 - 159mg/dl	2 units insulin lispro
160 - 179 mg/dl	3 units insulin lispro
180 - 199 mg/dl	4 units insulin lispro
200 - 219 mg/dl	5 units insulin lispro
220 - 239mg/dl	6 units insulin lispro
240 - 259mg/dl	7 units insulin lispro

260 - 279mg/dl	8 units insulin lispro
280 - 299mg/dl	9 units insulin lispro
300 - 319mg/dl	10 units insulin lispro
300 - 319mg/dl	10 units insulin lispro
320 - 339mg/dl	11 units insulin lispro
340 - 359mg/dl	12 units insulin lispro
360 - 379mg/dl	13 units insulin lispro
380 - 399mg/dl	14 units insulin lispro
>400mg/dl	15 units insulin lispro and notify medical team
Blood Glucose	**Very high dose correctional scale**
< 70 mg/dl	Hypoglycemia protocol per hospital protocol
70 -139mg/dl	No action
140 - 174mg/dl	3 units insulin lispro
175 - 204 mg/dl	5 units insulin lispro
205 - 234 mg/dl	7 units insulin lispro
235 - 264mg/dl	9 units insulin lispro
265 - 294mg/dl	11 units insulin lispro
295 - 324mg/dl	13 units insulin lispro
325 - 354mg/dl	15 units insulin lispro
355 - 384mg/dl	17 units insulin lispro
385 - 399mg/dl	19 units insulin lispro
>400mg/dl	20 units insulin lispro and notify medical team

#Basal insulin regimen

Glargine once daily - starting daily dose:
• Patients with BG between 140-200 mg/dL= 0.2 units per kg weight per day.
• Patients with BG between 201-400 mg/dL= 0.25 units per kg weight per day.
• Glargine insulin will be given once daily, at the same time of the day.
• Patients will receive the full-dose of glargine insulin (even if NPO) except for those that have GFR <50 ml/min. • Patients with GFR <50ml/min will receive only one-half of the calculated insulin dose
Supplemental (correction) insulin:
• Give supplemental insulin lispro following the “correctional scale” protocol* for elevated blood glucose
• If a patient is able and expected to eat all, give supplemental lispro insulin after each meal and at bedtime following the high dose correctional scale
• If a patient is not able to eat, give supplemental lispro insulin every 6 hours (6-12-6-12) following the moderate dose correctional scale
Daily insulin adjustment:
• Fasting and pre-meal BG between 100-140 mg/dl without hypoglycemia the previous day: no change

• Fasting and pre-meal BG between 141-180 mg/dl: increase glargine dose by 10% every day
• Fasting and pre-meal BG >180 mg/dl: increase glargine dose by 20% every day
• Fasting and pre-meal BG between 70-99 mg/dl: decrease glargine dose by 10% every day
• If a patient develops hypoglycemia (BG <70 mg/dL), decrease glargine dose by 20%.
• If a patient develops hypoglycemia (BG <40 mg/dL), decrease glargine dose by 30-40%.
Blood glucose monitoring:
• Measure BG before each meal and at bedtime (or every 6 hours if a patient is not eating) using a glucometer.

[$]Basal and Bolus Meal Coverage Insulin

Glargine once daily - starting daily dose:
• Patients with BG between 140-200 mg/dL= 0.4 units per kg weight per day.
• Patients with BG between 201-400 mg/dL= 0.5 units per kg weight per day.
• Half the total insulin daily dose will be given as glargine and the other half as lispro.
• Glargine insulin will be given once daily, at the same time of the day.
• Patients will receive the full-dose of glargine insulin (even if NPO) except for those that have GFR <50 ml/min. • Patients with GFR <50ml/min will receive only one-half of the calculated insulin dose
• Insulin lispro will be given in three equally divided doses after each meal. To prevent hypoglycemia, if a subject is not able to eat, the dose of lispro will be held. Patients with GFR <50ml/min receive one-half of the calculated insulin dose.
Supplemental (correction) insulin:
• Give supplemental insulin lispro following the “correctional scale” protocol* for elevated blood glucose
• If a patient is able and expected to eat all, give supplemental lispro insulin after each meal and at bedtime following the high dose correctional scale
• If a patient is not able to eat, give supplemental lispro insulin every 6 hours (6-12-6-12) following the moderate dose correctional scale
Daily insulin adjustment:
• Fasting and pre-meal BG between 100-140 mg/dl without hypoglycemia the previous day: no change
• Fasting and pre-meal BG between 141-180 mg/dl: increase glargine dose by 10% every day
• Fasting and pre-meal BG >180 mg/dl: increase glargine dose by 20% every day

• Fasting and pre-meal BG between 70-99 mg/dl: decrease glargine dose by 10% every day
• If a patient develops hypoglycemia (BG <70 mg/dL), decrease glargine dose by 20%.
• If a patient develops hypoglycemia (BG <40 mg/dL), decrease glargine dose by 30-40%.
Blood glucose monitoring:
• Measure BG before each meal and at bedtime (or every 6 hours if a patient is not eating) using a glucometer.