Effect of Dapagliflozin at Discharge on Hospital Re-Admissions in Patients with Acutely Decompensated Heart Failure: A Randomized Controlled Study

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Short Title: Dapagliflozin Heart Failure Readmission

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RESEARCH OBJECTIVES AND SPECIFIC AIMS

More than 40% of patients with established heart failure (HF) have diabetes [1]. Several studies have reported that HF patients with diabetes have higher rates of recurrent HF hospitalizations, longer durations of hospital stay [2,3], and significantly higher mortality compared to HF patients without diabetes [4,5]. In a recent 42-month longitudinal study of 902 patients with type 2 diabetes (T2D) and HF, 30% of patients with T2D and HF died and 60% experienced a composite endpoint of death and HF readmission [5]. Despite these statistics, remarkably little is known about optimal strategies for the management of patients with T2D and HF after hospital discharge.

There is strong epidemiologic evidence linking poor glycemic control in patients with T2D with the risk of hospitalization for HF and higher mortality, regardless of ejection fraction [1,5]. A linear relationship between glycemic control and HF events has been reported across several observational studies in T2D, such that, on average, the risk of HF was increased by 15% for each percentage point higher glycosylated hemoglobin (HbA1c) [6,7]. Several clinical trials using traditional glucose lowering drugs have failed to demonstrate either reduction of new-onset HF or hospitalization rates in patients with established heart disease [8-11]. More recently, observational and randomized clinical trials in patients with T2D have shown that treatment with sodium glucose co-transporter 2 inhibitors (SGLT2-i) results in a substantial reduction in hospitalization for HF and reduced mortality in patients with established heart disease [12-15]. The osmotic diuretic effect of SGLT2-i may provide a unique benefit to patients with coexisting T2D and HF, by lowering blood glucose levels and at the same time promoting reduction in plasma volume, weight loss, and lower blood pressure [16]. Additional actions on cardiac metabolism and neurogenic signaling may also contribute to the observed benefits[16-19]. The beneficial effects with SGLT2-i were present within a few months of commencing therapy and continued with ongoing therapy, suggesting that this therapy may be effective in preventing HF admissions in patients with T2D.

Recent cardiovascular outcome trials using SGLT2-i reported a significant reduction in hospitalization for HF [15,20-22]. In the DECLARE trial, dapagliflozin resulted in lower rate of hospitalization for heart failure compared to placebo (HR, 0.73; 95% CI, 0.61 to 0.88)[23]. More recently, among patients with heart failure and a reduced ejection fraction (HFrEF), the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes [22]. Similarly, in the EMPA-REG OUTCOME study with empagliflozin, the HR was 0.65 (95% CI 0.50-0.85) and in the CANVAS program with canagliflozin, the HR was 0.67 (95%CI 0.52-0.87). In the Canvas Program, the rate of hospitalization was dramatically lower in patients with history of HF (28.1% vs 14.1%) compared to those without a history of HF (5.7% vs 4.3%) [11]. The consistency across trials, as well as the results of observation studies [24] indicate that SGLT2-i will be considered in the management of T2D patients with a history of HF [25]. It will be noted, however, that the time of initiation of SGLT2-i therapy has yet to be formally evaluated in patients with T2D and HF.

We propose to perform a randomized clinical trial to evaluate the effects of dapagliflozin on hospital readmission rates in patients with and without T2D after an admission for acutely decompensated heart failure (ADHF). We hypothesize that treatment with dapagliflozin for 26 weeks will reduce the rate of readmissions for HF (primary endpoint), and will improve glycemic control, HF symptoms, NT proBNP levels, quality of life, resource utilization and hospital charges/costs as compared with placebo.

Specific Aims:

<u>Aim 1:</u> To determine whether the composite rate of hospital readmissions, emergency department, urgent clinic visits for HF and death are lower in patients with ADHF treated with dapagliflozin compared to those treated with placebo. Patients with and without diabetes ADHF will be randomized to receive either dapagliflozin (10 mg once daily) or placebo at hospital discharge for 26 weeks.

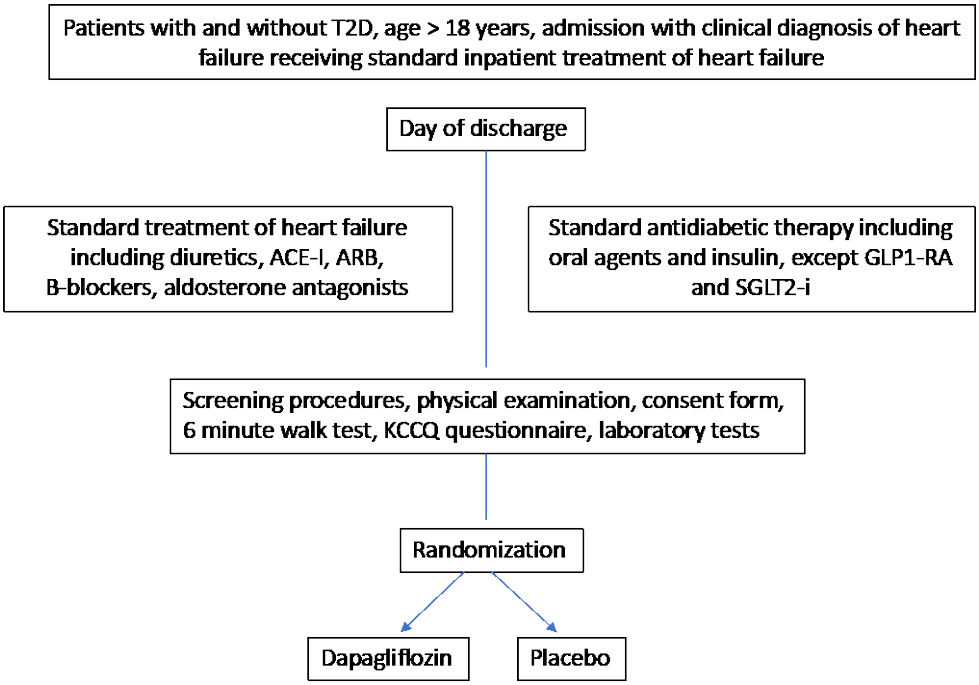
Hypothesis: Treatment with dapagliflozin will significantly reduce the composite rate of hospital admissions, emergency department visits and urgent clinic visits for HF compared to placebo in patients discharged after an ADHF admission.

<u>Aim 2:</u> To determine whether treatment with dapagliflozin compared to placebo will result in lower HF disease-specific biomarker (NT proBNP), improvement in glycemic control (HbA1c) in T2D patients, and improvement in symptoms and quality of life after hospital discharge in patients with ADHF. We will measure changes in HbA1c, NT proBNP levels and HF-specific quality of life assessment using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and improvement in symptoms using the Chronic Heart Failure Questionnaire (CHQ-SAS).
Hypothesis: Treatment with dapagliflozin will result in a greater improvement in HbA1c levels (in T2D patients), HF disease-specific marker (NT proBNP), quality of life (KCCQ scores), improvement of symptoms (CHQ-SAS scores) compared to placebo after hospital discharge at 12 and 26 weeks.

<u>Aim 3.</u> Evaluate the within-trial cost-effectiveness of dapagliflozin compared to placebo in overall healthcare costs in patients with ADHF. We will prospectively collect information on overall health care costs including emergency room visits, urgent clinic visits for HF, and hospitalizations between groups during the 6 months of intervention.

Hypothesis: Treatment with dapagliflozin will be associated lower resource utilization and health care costs compared to placebo after hospital discharge.

Innovation. The proposed study will be the first prospective RCT to determine the safety and efficacy of dapagliflozin treatment in preventing readmissions/ER visits/urgent clinic visits and death in patients with and without T2D after admission for ADHF. Treatment with SGLT2-i has been shown to reduce both HF hospitalization and mortality in patients with established heart disease and a history of HF [12-14,23]. More recently, among patients with HFrEF, dapagliflozin was shown to reduce the risk of worsening heart failure or death from cardiovascular causes compared to placebo, regardless of the presence or absence of diabetes [22]. However, the time of initiation of SGLT2-i therapy has yet to be formally evaluated in patients with ADHF and is the purpose of this study. In addition, we will evaluate the impact of treatment on HF symptoms quality of life, resource utilization and cost-effectiveness of dapagliflozin versus placebo. The results of this study have great potential to influence and facilitate care and to change current clinical guidelines in the management of patients with ADHF.



Rationale on Dapagliflozin treatment. Dapagliflozin (Farxiga®) is a highly selective SGLT2-i, given in once-daily doses[26,27]. It is rapidly absorbed with a time to maximum plasma concentration of two hours and a half-life of 17 hours, with an absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose of 78%. Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment. The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin and related metabolites are mainly eliminated via the renal pathway. The mean plasma terminal half-life for dapagliflozin is approximately 12.9 hours following an oral dose of Farxiga 10 mg.

Clinical trial in ambulatory patients with T2D reported a significant reduction in HbA1c of ~ 0.8%-1.5% from baseline in patients with T2D [28-30]. Dapagliflozin as monotherapy and in combination with other antidiabetic drugs is well tolerated and associated with very low rates of hypoglycemia[31-33]. In addition, due to its mechanism of action of increasing urinary glucose excretion, SGLT2-i can reduce systolic blood pressure and body weight compared to placebo in patients with T2D[34,35].

In a recent pooled *post-hoc* analysis of completed clinical trials, treatment with dapagliflozin 10 mg produced clinically meaningful reductions in HbA_{1c} and weight vs placebo in patients with concomitant T2DM and HF. In the recent DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, 4474 patients with and without diabetes with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less assigned to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death. Over a median of 18.2 months, the risk of worsening heart failure or death from cardiovascular causes was significantly lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. In addition, the trend toward a decrease in systolic blood pressure seen with dapagliflozin occurred without an increase in heart rate[36]. Similar results were also reported in the DECLARE Trial[23] in 17,160 patients with T2D who had or were at risk for atherosclerotic cardiovascular disease treated either with dapagliflozin or placebo. Dapagliflozin resulted in a lower rate of cardiovascular death or hospitalization for HF (4.9% vs. 5.8%; hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P=0.005), which reflected a lower rate of hospitalization for heart failure (hazard ratio, 0.73; 95% CI, 0.61 to 0.88). The results of DECLARE and DAPA-HF trials, together with previous SGLT2-i trials indicate that in patients with and without T2D with or at risk for atherosclerotic cardiovascular disease, treatment with SGLT2-I results in lower rate of cardiovascular death or hospitalization for HF.

Study Endpoints:

Primary outcome is to compare the efficacy of dapagliflozin compared with placebo, on the composite rate of hospital admissions, emergency department visits, urgent clinic visits for HF and death after admission with ADHF.

Secondary outcomes are to determine differences between dapagliflozin compared to placebo in:

1. Change in the KCCQ score between baseline score and the scores at 12, and 26 weeks
2. Change in the CHQ-SAS score between baseline score and the scores at 12, and 26 weeks
3. Change in NT proBNP levels between baseline and after 12 and 26 weeks
4. Change in 6-minute walk distance (6MWD) between baseline and after 12 and 26 weeks
5. Change in HbA1c between baseline and after 12 and 26 weeks (in T2D patients).
6. Change in weight between baseline and after 12 and 26 weeks
7. Change in systolic blood pressure between baseline and after 12 and 26 weeks
8. Change from baseline in left atrial volume index and other measures of left ventricular systolic and diastolic function in patients who may undergo repeated echocardiogram during follow up.

9.Change from baseline in serum magnesium at baseline and after 12 and 26 weeks

Safety Variables

1. All-cause mortality
2. Cardiovascular death
3. Non-fatal myocardial infarction (MI)
4. Stroke
5. Acute kidney injury (defined as doubling of serum creatinine based on the RIFLE criteria [37].
6. Adverse events (AEs) and serious adverse events (SAEs). Of special interest are events including diabetic ketoacidosis (DKA), volume depletion (defined as hypotension, syncope, orthostatic hypotension or dehydration), hypoglycemic events and urinary tract infections.

Study Methods:

The trial is a 26-week, randomized, double-blind, placebo-controlled trial investigating the efficacy of dapagliflozin versus placebo in reducing hospital readmission, ER visits, urgent clinic visits for HF and death after discharge, in patients with and without T2D, following an admission with ADHF.

Patients:

Patients admitted with ADHF will be enrolled after signing an informed consent. Patients will be invited to participate during their hospital admission. Those fulfilling the inclusion/exclusion criteria will undergo baseline testing at randomization prior to discharge.

We will recruit 392 patients, hospitalized with ADHF. Patients with T2D can be treated with diet or oral antidiabetic drugs (OAD) except TZDs, or SGLT2-i, or on low-dose insulin therapy (total daily dose [TDD] ≤0.4 unit/kg/day) prior to admission.

Inclusion Criteria

1. Males or females between the ages of 18 and 90 years, with ADHF, and New York Heart Association (NYHA) class II, III, or IV symptoms discharged after hospital admission with a clinical diagnosis ADHF.
2. Elevated NT-pro-BNP ≥300 pg/ml or BNP (≥100 pg/ml) on admission.
3. Interpretable echocardiogram during hospital admission (or within 12 months prior to index hospitalization)
4. Blood glucose level <400 mg/dL without evidence of diabetic ketoacidosis (serum bicarbonate <18 mEq/L or positive serum or urinary ketones)- Applies to patients with T2D.

Exclusion Criteria

1. Age < 18 or > 90 years.
2. Subjects with a history of type 1 diabetes.
3. Treatment with TZDs or SGLT2-i during the past 3 months of admission.
4. Recurrent episodes of severe hypoglycemia or hypoglycemic unawareness.
5. History of recurrent HF admissions considered to be due to non-compliance (evaluated by the research staff for participation)
6. Patients with clinically significant hepatic disease (cirrhosis, jaundice, end-stage liver disease, portal hypertension) and elevated ALT and AST > 3 times upper limit of normal.
7. Patients with impaired renal function (GFR < 25 ml/min).
9. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.
10. Patients on ventricular assist devices (VADs)

11. History of heart transplant or listed for heart transplant
12. History of cardiac surgery* (within 90 days prior to enrollment) or planned cardiac interventions* within the following 6 months
    **Includes: PCI, ablation, CRT-ICD*
13. HF due to restrictive/infiltrative cardiomyopathy, active myocarditis, constrictive pericarditis, severe stenotic valvular diseases, hypertrophic cardiomyopathy, or congenital heart disease.
14. History of SGLT2-i allergy
15. Systolic blood pressure < 100 mmHg
16. Uncontrolled hypertension, defined as a systolic blood pressure > 200 mmHg at randomization
17. Female subjects who are pregnant or breast-feeding at time of enrollment into the study.
18. Females of childbearing potential who are not using adequate contraceptive methods (as required by local law or practice).
19. In hospice or expected life expectancy less than 6 months
20. Patients with diabetic foot infection, osteomyelitis, and history of amputation of lower extremities within 6 months of admission
21. Patients anticipated to undergo major surgical procedures during the following 6 months
22. Patients with active hematuria, urinary tract infection (UTI), or history of frequent UTIs or genital mycotic infections
23. Uncontrolled atrial fibrillation or atrial flutter with a resting heart rate >110bpm documented by ECG at randomization.
24. Any condition that in the opinion of the investigator would contraindicate the assessment of 6MWD
25. Chronic pulmonary disease i.e. with known FEV1 <50% requiring home oxygen, or oral steroid therapy or current hospitalization for severe COPD thought to be a primary contributor to dyspnea, or significant chronic pulmonary disease in the Investigator's opinion, or primary pulmonary arterial hypertension
26. Patients with active history of bladder cancer.
27. Patients with previous history of diabetic ketoacidosis, per ADA criteria [38]

Investigational Drugs:

- Group 1. Dapagliflozin 10 mg once daily (n=196)
- Group 2. Placebo once daily (n=196)

Treatment Protocol:

Patients admitted with exacerbation of chronic heart failure by clinical and radiologic features will be considered as candidates for participation. Patients will be approached and invited to participate during the hospital admission. Patients that fulfill inclusion/exclusion criteria will undergo baseline testing and will be randomize prior to discharge will be randomized 1:1 to receive either dapagliflozin10 mg/day or matching placebo at the time of discharge.

Inpatient Heart failure treatment. Patients will receive standard treatment for ADHF by their primary care team and/or cardiology service including diet and pharmacological treatment with diuretics, ACE-I/ARBs, ARNI, beta receptor antagonists, aldosterone antagonists, hydralazine/nitrate combination following the ACCF/AHA Guidelines for the Management of Heart Failure [39,40].

Inpatient T2D Treatment. Patients with T2D will be treated with a standard insulin regimen during the hospital stay [41,42]. Prior to hospital discharge, patients will be randomized 1:1 to either dapagliflozin or placebo. All patients will receive diabetes education. The day of discharge, dapagliflozin /matching placebo will be added to the subject's pre-admission treatment regimen.

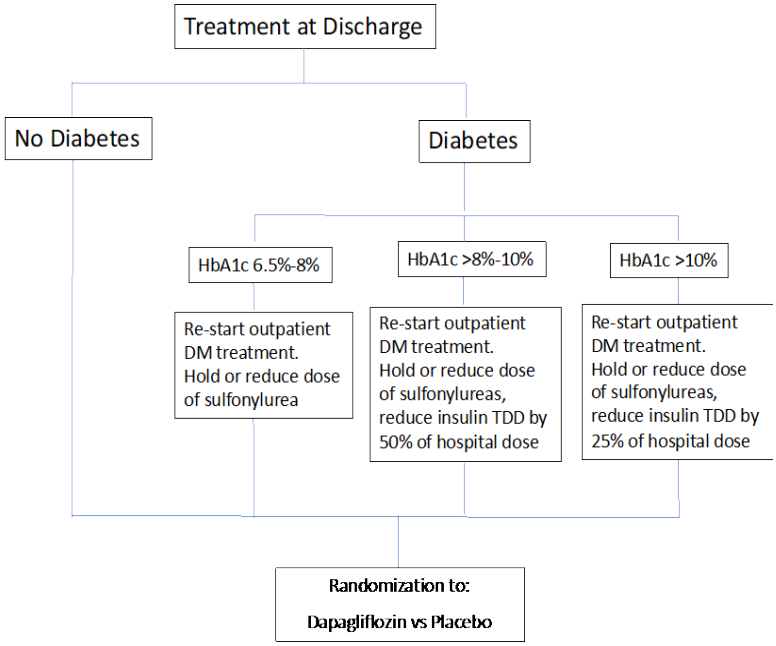
Hospital Heart Failure Education. Hospital discharge HF education will be conducted by the Advanced Practice Providers. They will provide comprehensive education on HF, diet, symptoms, and medications.

Hospital T2D Education. Prior to discharge, all patients with T2D will receive information on:

1. Diabetes education, if not received within 1 year of admission.
2. Blood glucose target between 80 and 180 mg/d before meals.
3. Use of glucose meters for home glucose self-monitoring.
4. Measurement of urinary ketones.
5. Keeping BG records. Participants will receive a logbook to record glucose tests results.
6. Hypoglycemia recognition and management.
7. Insulin administration (if needed).
8. Education about signs and symptoms of diabetic ketoacidosis, use of glucose monitoring and urinary ketone testing.

Treatment recommendations at discharge in patients with diabetes

Study Medications: Study subjects will be randomized 1:1 to receive either dapagliflozin 10 mg or matching placebo at the time of discharge.



Admission HbA1c between 6.5% and 8%:

- Start study medication (dapagliflozin or placebo) once daily
- If no contraindications, re-start OADs (metformin, DPP4-i) at the same dose prior to admission
- Hold sulfonylureas or insulin secretagogues if HbA1c < 7.0%. If HbA1c >7%, reduce dose of sulfonylurea and insulin secretagogues by 50% or stopped according to physician discretion.
- In patients receiving insulin prior to admission, reduce TDD of hospital dose by 50% [42,43].

Admission HbA1c between 8% and 10%:

- **Patients receiving OAD treatment prior to admission:**
  - Start study medication (dapagliflozin or placebo) once daily
  - If no contraindications, re-start OADs prior to admission (metformin, DPP-4 inhibitors)
  - Hold sulfonylureas or insulin secretagogues if HbA1c < 8.0%. If HbA1c >8%, reduce dose of sulfonylurea and insulin secretagogues by 50% or stopped according to physician discretion.
- **Patients receiving OAD and insulin combination prior to admission:**
  - Start study medication (dapagliflozin or placebo) once daily
  - If no contraindications, re-start OADs prior to admission, except for sulfonylureas, insulin secretagogues or thiazolidinedione (as described above).
  - Discharge patient on basal insulin at 50% of daily hospital dose.
- **Patients receiving basal bolus insulin treatment prior to admission:**

- Start study medication (dapagliflozin or placebo) once daily
- Discharge on basal insulin at 50% of hospital dose or 75% of pre-admission daily insulin dose.

Admission HbA1c > 10%:

- **Patients receiving OAD treatment prior to admission:**
  - Start study medication (dapagliflozin or placebo) once daily
  - If no contraindications, re-start OADs prior to admission (metformin, DPP-4 inhibitors)
  - If HbA1c >10%, reduce dose of sulfonylurea and insulin secretagogues by 50%.
  - Insulin naïve patients prior to admission, reduce TDD of hospital insulin dose by 25%.
- **Patients receiving OAD and insulin combination prior to admission:**
  - Start study medication (dapagliflozin or placebo) once daily
  - If no contraindications, re-start OADs prior to admission, except for sulfonylureas, insulin secretagogues or thiazolidinedione.
  - In patients receiving insulin prior to admission, reduce TDD of hospital dose by 25%.
- **Patients receiving basal bolus insulin treatment prior to admission:**
  - Start study medication (dapagliflozin or placebo) once daily
  - Discharge on basal insulin at 50% of hospital dose or 75% of pre-admission daily insulin dose.

Algorithm for basal insulin dose adjustment after hospital discharge:

Basal Insulin	
If mean **FBG > 180 mg/dL** for the last 2 consecutive days and no episodes of hypoglycemia (BG <70 mg/dL)	Increase TDD by 4 IU
If mean **FBG > 140 mg/dL** for the last 2 consecutive days and no episodes of hypoglycemia (BG <70 mg/dL)	Increase TDD by 2 IU
If mean **FBG between 100 to 140 mg/dL** for the last 2 days and no hypoglycemia	No Change
If any FBG between 70 – 99 mg/dl	Decrease by 4 IU or 10% of TDD
If any FBG or RBG < 70 mg/dl	Decrease by 8 IU or 20% of TDD
If any FBG or RBG < 40 mg/dl	Decrease TDD by 30%

Schedule of Clinic and Phone Visits:

The study will include 10 study contacts: 1 screening visit and 1 randomization visit while subjects are still in the hospital. After discharge, patients will have a total of 5 in-person clinic visits and 3 phone contacts over a 26-week period.

At the Screening Visit, patients will be evaluated for participation using inclusion and exclusion criteria. At Visit 1 - Randomization, subjects will be randomized to receive the study drug that will commence after discharge and will be added to the ongoing therapy. The study treatment period will end at Visit 9 (week 26). The following table provides information as to the study procedures to be completed at each visit.

Schedule of Assessments:

Visit	Screening	Randomization (Discharge)[e]	2	3	4	5	6	7	8	9
Week	0	0	2	6	8	12	16	20	24	26
Clinic / CTSA Visit		X	X	X		X		X		X
Phone Visit					X		X		X	
Sign Informed Consent	X									
Medical History	X									
Weight, BMI	X	X		X		X		X		X
Physical Exam	X	X		X		X		X		X
Vital Signs	X	X		X		X		X		X
Blood & Urine Sampling [a]	X	X		X^		X		X^		X
Urine Pregnancy Test [b]	X			X		X		X		X
6-minute Walk Distance			X			X				X
KCCQ Questionnaire		X				X				X
CHQ-SAS Questionnaire		X				X				X
AEs and SAEs		X	X	X	X	X	X	X	X	X
Electrocardiogram		X[d]								
Echocardiogram [c]		X				X				
Review Home BG Testing Results in T2D			X	X	X	X		X	X	X
Home Urine Ketone Testing, if Indicated			X	X	X	X		X	X	X
Study Drug Dispensing		X				X				
Study Drug Returned						X				X
T2D Education	X									
Heart Failure Education	X									

[a]Admission tests: For screening purposes we will use available laboratory results during current admission (chemistry including eGFR, HbA1c, urine studies), additional testing will be necessary to meet all the baseline lab requirements such as serum magnesium, NT-proBNP, ketones (patients with T2D at investigator's discretion), albumin/creatinine ratio, random urine sodium , at baseline (prior to discharge). Follow up testing at 12 and 26 weeks; other ^blood tests at 6 and 20 weeks and urine culture will be performed at investigator's discretion. [b] Urine pregnancy test for women with childbearing potential at investigator's discretion [c] Echocardiogram during hospital admission (or within 6 months prior to index hospitalization) and at 12 weeks follow up visit. All visits have a +/-7-day visit window. [d] the most current ECG during admission. [e] *Randomization can be performed prior to discharge or up to 7 days after discharge (if discharge planning over the weekend. **COVID-19: For modified study visit options applicable during the time period of the COVID-19 emergency, please see appendix B.*

Drug Dispensing Scheme
Three bottles of dapagliflozin 10 mg or matching placebo will be dispensed by investigational pharmacy at randomization and at the 12-week clinic visit. Each bottle containing 35 tablets.

Rescue therapy
Patients with T2D will be discharge on pre-admission oral agents and or insulin therapy except for sulfonylureas or TZDs. Dose of OADs and/or insulin will be adjusted as an outpatient to achieve and maintain a fasting BG between 80-140 mg/dl and a random BG < 180 mg/dl.

Duration of treatment
26 weeks.

Measurements During follow-up:

1. Clinical Outcomes:
    a. Hospital readmissions, emergency department / urgent clinic visits for HF management and death (See appendix A: Heart Failure Hospitalization, ER visit and urgent outpatient clinic visit)
2. Glycemic control:
    a. Mean daily fasting and pre-meal blood glucose levels.
    b. HbA1c concentration at 12 and 26 weeks (T2D patients)
    c. Number of hypoglycemic events
        i. Clinically significant hypoglycemia defined as a BG < 54 mg/dl
        ii. Symptomatic hypoglycemia defined as an event with typical symptoms (i.e., sweating, palpitation, and feeling of hunger) with or without confirmation by plasma glucose <70 mg/dl (3.9 mmol/L).
        iii. Severe hypoglycemia defined as episodes necessitating assistance and associated with measured plasma glucose < 40 mg/dl (2.2 mmol/L) or with prompt recovery after administration of carbohydrates, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by low plasma glucose.
3. T2D treatment:
    a. Number of patients receiving insulin therapy, dosage, and compliance.
    b. Use of other oral agents, dosage, and compliance.
4. Blood pressure and heart rate
    a. The most recent documented blood pressure (BP) of the day of screen can be used to determine enrollment eligibility. At randomization, the seated BP will be recorded in both the left and the right arms. Blood pressure (BP) and heart rate (HR) will be measured after the patient has been sitting and resting for at least 5 minutes. The arm with the highest seated systolic BP readings will be the one used for all subsequent readings (preferred arm).
5. Orthostatic blood pressure
    a. Supine BP and pulse- The supine BP and pulse must be measured prior to the standing BP and pulse. After the patient rests in the supine position for at least 5 minutes, supine BP and pulse will be determined in the preferred arm

b. Standing BP and pulse - After the supine BP and pulse measurements are obtained, the patient will stand for 2 to 3 minutes. Standing BP and pulse will be determined from the preferred arm.

All readings must be recorded. For study analyses, the average of the BP and pulse readings will be used.

6. Anthropomorphic measurements
   a. Weight, height, waist, and hip circumference.
   b. Weight: Body weight will be measured without shoes and wearing light clothing.
   c. Height: Height (without shoes) will be measured in centimeters.
   d. Body Mass Index (BMI): BMI will be calculated by the formula: body weight (Kg)/m^2.

7. Six-minute walk distance (6MWD)
   a. The six-minute walk test requires a 100-ft hallway. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. The six-minute walk test serves as a standardized test for functional capacity quantification of HF patients and is predictive of adverse cardiovascular outcomes [44]. Most patients do not achieve maximal exercise capacity during the 6-minute walk test [45]; instead, they choose their own intensity of exercise and can stop and rest during the test.

9. Kansas City Cardiomyopathy Questionnaire (KCCQ)[46] is a disease-specific health status instrument composed of 23 items that quantify the domains of physical limitation, symptoms, self-efficacy, social limitation, and quality of life limitation due to HF. Scores range from 0 to 100. For the KCCQ overall summary score, a small but clinically meaningful change is ≥ 5 points.

10. The Chronic Heart Failure Questionnaire (CHQ-SAS) is a validated questionnaire that assesses patients' perception of their HF and measures the impact of HF symptoms [47,48]. The CHQ-SAS contains16 standardized questions that assess dyspnea during daily activities, fatigue and emotional function. Items are rated on a 7-point Likert scale ranging from 1 to 7.

11. Echocardiogram
    Echocardiograms will be performed at baseline (standard of care) and during follow-up. Echocardiographic measurements will include measurements of LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), left atrial dimension (LAD), interventricular septal (IVS) and LV posterior wall (LVPW) thickness by 2D echocardiography or M-mode. LVEF assessment based on 2D echocardiography using the quantitative 2D biplane volumetric Simpson method from 4- and 2-chamber views. Patients with repeated echocardiography during the hospitalization or during follow-up, we will use the data from the examination performed closest to discharge.

12. Cost-effectiveness evaluation of resource utilization overall healthcare costs after hospital discharge in patients with ADHF. We propose to conduct an accompanying within-trial cost-effectiveness analysis using observed trial data. We will adopt a healthcare payer perspective for this analysis. The primary outcomes include total costs of trial participants. Per the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine[49] and of the Consolidated Health Economic Reporting Standards (CHEERS)[50], we will provide an impact inventory table and reporting checklist in our reports.
    Data for cost outcomes will be derived from observed trial data based on abstraction of electronic medical record systems.

Costs: All costs will be expressed in uniform currency such as 2020 U.S. dollars. Total costs will include all direct costs associated with clinical care provided, and external health care service utilization (ER visits and hospitalizations). External healthcare service utilization will include routine office visits, after-hour clinic visits, after-hour clinic visits (urgent care), ambulance use, emergency room visits, and hospitalizations. To calculate the total costs of utilization at 6 months, the median prices of each healthcare service[51] will be multiplied by the number of each service use during the trial.

13. Laboratory assessments. Blood and urine samples for determination of clinical chemistry, and NT proBNP levels will be obtained as per Study Plan. Serum magnesium and random urine sodium will be measured at baseline and repeated at 12 and 26 weeks.
14. Treatment Compliance/Adherence
    e. The administration of study medication will be recorded. All stops of study medication prescribed by the investigator will be recorded. Study personnel will collect/record any decrease in oral agents and insulin dosage, and if the investigator determined to stop any previously used OADs or insulin during the study.
    f. Missed doses of dapagliflozin or placebo blinded study medication will not be taken. If a dose is missed, the next regularly scheduled dose will be taken and will not be doubled.
15. Drug Accountability
    g. The study personnel will account for all study medication dispensed to and returned from the patient.
    h. Patients will be asked to bring all unused study medication and empty packages to the site at each office visit. Any discrepancy between dispensed and returned study medication will be explained.
    i. Any patient found to be noncompliant would be counseled on the importance of taking their study medication as prescribed.

Randomization and Blinding

This is a double blinded, randomized, placebo-controlled trial in patients with heart failure. Computer-generated randomization tables will be provided by Dr. Limin Peng at the Emory School of Public Health. Block randomization based on diabetes (with or without) status. The randomization tables will be mailed to each institution where a member of the research team will oversee the randomization process and group assignment.

Procedures for unblinding the study:

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment. The Emory University of Atlanta physician (Guillermo Umpierrez or delegate) should be consulted whenever possible prior to the investigator breaking the blind.

Recruitment and Retention: Potential study subjects will be identified and pre-screened among patients admitted with ADHF. For each center, a research coordinator will screen all admission daily to identify patients with a diagnosis of ADHF. Once a potential participant is identified, the research coordinator will first contact the primary care team/provider to discuss protocol (if needed) and request permission to approach patient and relatives. Then the research coordinator will approach the potential participant/and or family members to explain the purpose, intervention, and potential benefits/risks of participating in this study. A study coordinator will conduct informed consent in eligible subjects prior to any study procedures. Screening and recruitment reports will be generated weekly that include actual

and expected recruitment statistics. Strategies to address potential problems with recruitment will include weekly communications with Drs. Umpierrez and research team.

Subject retention and study adherence are the two most important barriers in research trials in hospital and post-discharge trials. Our team has applied problem-solving approach to promote continued adherence in previous intervention studies, with adherence to previous inpatient/discharge trials exceeding 85%. During screening, participants and family members will be informed about which clinically intervention, treatment and relevant test and when these tests will be performed during the study. Only subjects who fully understand these commitments and appear likely to follow the study protocol will be enrolled. We will have dedicated study coordinators who will conduct screening and obtain consent for participation.

Withdrawal Criteria

1. The subject may withdraw at will at any time.
2. The subject may be withdrawn from the trial at the discretion of the investigator due to a safety concern or if judged non-compliant with trial procedures or included in contravention to the inclusion and/or exclusion criteria.
3. Adverse events (AE), i.e., any clinical, laboratory abnormality or concurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the patient.
4. Doubling of serum creatinine above the baseline value confirmed by a repeated measurement within one week (study medication can be discontinued and continue study visits as described in the premature treatment discontinuation).
5. Pregnancy or intention to become pregnant.

Subject Replacement

There will be no replacement of subjects in this trial.

Unscheduled Visits

Additional unscheduled phone and/or clinic visits may also be performed at any time during the study at investigator's discretion (abnormal results, etc.).

Premature Treatment Discontinuation:

Patient agrees to undergo the Premature Treatment Discontinuation Visit and then continue in-person study visits

The patient agrees to undergo the Premature Treatment Discontinuation Visit (PTDV) as visit 9 and then continue in-person study visits according to plan. This is the preferred option and patients who discontinue study medication will always be asked if they agree to this approach. If agreed, as above, the patient will undergo their PTDV at the next scheduled office visit after the study medication is stopped. The patient will continue attending subsequent study visits according to schedule,

Patient refuses to continue in-person study visits but agrees to undergo modified follow-up

If the patient refuses to continue in-person study visits, but agrees to undergo modified follow up, the in-person PTDV visit (as visit 9) should be performed as soon as possible after the study medication is stopped. All subsequent visits until the end of study date will be done as modified follow-ups (e.g., regular telephone contacts, a contact at study closure, or other means) in order to ascertain whether any endpoints or safety events had occurred. Such a patient has not withdrawn his/her consent or withdrawn from the study.

Patient refuses any form of follow-up
If the patient refuses any form of follow-up, he/she officially withdraws from the study and withdraws consent. This decision must be documented. At the end of the study, vital status on all such patients will be collected from publicly available sources, in accordance with local regulations.

Lost to follow up patients
To prevent patients being lost to follow-up, patient's contact details, including next of kin contacts will be collected initially and updated regularly by the research team. The research coordinators will educate the patient on the importance of contact with the research team throughout the study. Repeated attempts will be made to locate and obtain pertinent medical information for patients who are initially lost to follow-up. A patient will be classified as lost to follow up only if he/she has failed to return for the required study visits and his/her vital status remains unknown despite multiple attempts to contact him/her via telephone, fax, e-mail, certified letter or through patient locator agencies (if allowed by national regulation). The informed consent forms will include language to grant the option to employ outside companies to assist in obtaining updated contact information or ascertainment of vital status of lost patients using publicly available source.

Study Sites: This study will be performed at 4 academic institutions:
Grady M. Hospital: Endocrinology section: Guillermo Umpierrez, MD, CDE (Principal investigator), Francisco Pasquel, MD, MPH, Georgia Davis, MD, Maya Fayfman, MD, Saumeth Cardona, MD, MPH
-Cardiology section: Modele O. Ogunniyi, MD, MPH, Nanette K. Wenger, MD
Emory University Hospital:
- Endocrinology section: Alexandra Migdal, MD (Co-PI), Rodolfo Galindo, MD
- Cardiology section: Alanna Morris, MD, Arshed A. Quyyumi, MD
Emory Saint Joseph's Hospital:
-Cardiology Section: David Markham, MD, Ryan Martin, MD
Non-Emory/Grady Centers for consideration: Two centers will be selected among Tulane University, Temple University and University of Michigan, which have collaborated with Emory in conducting clinical research studies in hospitalized patients and hospital discharge studies.

Tulane University: Dragana Lovre, MD (Site PI)
Temple University: Daniel Rubin, MD (Site PI)

Statistical Methods
This study is randomized placebo-controlled trial. The overall hypothesis is that dapagliflozin will reduce the rates of the combined outcomes of hospital readmissions, ER visits, clinic visits for HF and death (primary endpoint) and improve symptoms, quality of life and results in a reduction in NT proBNP and resource utilization/costs as compared with placebo in patients with ADHF.

Sample Size and Power Calculations: The sample size calculation is based on the primary endpoint measured as the proportion of patients who have hospital readmission, emergency department (ER) visits, and urgent unplanned clinic visit for HF and death during the 26-weeks follow-up period.

Approximately 5.7 million people have been diagnosed with HF ion the US [52]. Patients hospitalized for HF are at high risk for readmission, with a 1 and 3-month readmission rate between 20-30% [53-56] and a 6-month readmission rate as high as 50% to 60% [57,5859]. An analysis of Medicare data from the Centers for Medicare and Medicaid Services among 28,919 patients with HF hospitalizations, the 6—9 month following the initial HF admission, 60% of patients had 1 or more readmissions for any cause [58]. Similarly, the national registry of heart failure in Spain with 45.3% of patients with diabetes, a known diagnosis of diabetes was associated with increased all-cause mortality (HR 1.54; 95%CI 1.20–1.97, p = 0.001) and readmissions (HR 1.46; 95%CI 1.18–1.80, p < 0.001). In that study, 40.9% of patients with

diabetes were readmitted within 6-12 months after discharge [60]. An additional study of 462 hospitalized patients with T2D, 44% of the HF events were readmitted to the hospital within 6-month of the primary admission [61]. Thus, our review of the literature indicates that about ~ 40-60% of patients with diabetes with heart failure will be readmitted within 6-month of follow-up.

SGLT2-is have been shown to markedly reduced HF hospital admissions in patients with and without diabetes. In the CVD-Real Study, which included 961 HF cases, SGLT2-i reduced the rates of HF hospitalizations hazard ratio, 0.61; 95% confidence interval, 0.51-0.73; P<0.001. [62] The CVD-Real 2 multinational study of 235,064 patients with T2D, initiation of an SGLT-2i was also associated with a lower risk of all-cause death and hospitalization for heart failure, as compared to other glucose lowering drugs [24]. The use of SGLT-2i vs. other glucose lowering drugs was associated with lower risk of death and heart failure [24]. Recent RCT examining cardiovascular outcome using SGLT2-i reported a significant reduction in hospitalization for HF [20,21]. In the DECLARE trial, dapagliflozin resulted in lower rate of hospitalization for heart failure compared to placebo (HR, 0.73; 95% CI, 0.61 to 0.88)[23]. The EMPA-REG OUTCOME study showed a 35% reduction in HF hospitalizations [20]. In addition, in the CANVAS Program the benefits were greater in patients with a previous history of HF compared with those without HF at baseline (HR, 0.87; 95% CI, 0.72–1.06; *P* interaction = 0.021) [11]. In the Canvas Program, the rate of HF was reduced in patients with history of HF from 28.1% to 14.1% between patients treated with canagliflozin and placebo.

Based on data summarized above, we assume the composite event rate in the placebo group is between 40-60%, which would be reduced by 30% in the dapagliflozin group. Based on two-sided Chi-square test, with preserved alpha=0.05, with 176 subjects, we would achieve over 80% power to detect a 30% reduction in proportion of patients with readmission, ER visits, urgent unplanned clinic visit for HF or death if the composite event rate in the placebo group is 50%. Accounting for 10% attrition, we propose to recruit 392 patients (196 per group).

In the table below, we provide estimated power based on the same method, corresponding to different placebo composite event rates that are between 40-60%:

Composite event rate in the placebo group	40%	45%	50%	55%	60%
Estimated Power	62%	72%	82%	88%	93%

The results in the above table suggest promising power for the proposed study.

We will implement an adaptive design[63-65] with conditional power calculation and potential for re-estimation of the sample size, if necessary, after the interim analysis scheduled to be performed after 50% of the patients were enrolled and completed the 26 weeks of study period (196 patients) and undergone adjudication of the primary composite endpoint. Sample size re-estimation will be performed based on the observed composite event rate per group at the time of the interim analysis. See below "interim efficacy analysis".

Analysis of Primary Endpoint:
We will first compare the proportion of patients with at least 1 readmission, ER visit or unplanned urgent clinic visit for HF or death between the two study groups, using Chi-squares test or Fisher's Exact tests. Logistic regression will be conducted to adjust for the effects of other potential confounders (e.g. age, gender). Stepwise, backward, or forward model selection strategy will be adopted to determine the variables to be included in the final model. Standard diagnostic and model checking procedures,

such as deviance residual plot and Hosmer- Lemeshow test, will be applied to examine the fit of the developed models.

Analysis of Secondary Endpoints: The secondary endpoints include continuous longitudinal outcomes (e.g. change in KCCQ score from baseline at 6, 12, and 26 weeks), and discrete outcomes (e.g. whether patients with a ≥ 5pts increase in KCCQ score). To analyze continuous longitudinal outcomes, we will first conduct cross-sectional analyses based on nonparametric Wilcoxon tests (or t-tests), followed by multivariate linear regression, where responses may be transformed to better meet the normality assumption. Then we will apply repeated measures ANOVA or repeated measures linear regression model to assess the outcome differences between the two study groups, simultaneously evaluating the outcomes measured at different time points while appropriately accommodating the within-subject correlations. For discrete outcomes, we will conduct univariate analyses based on Chi-square tests (or Fisher's Exact tests). For binary discrete outcomes, we will use logistic regression models to account for the effects of other potential confounders. For other types of discrete outcome (e.g. counts), we will apply Poisson regression models or Negative Binomial regression models to address the confounding effects of other variables. Standard model selection and checking procedures will be applied to ensure the adequacy of the adopted models.

Cost-Effectiveness Analyses: The endpoints include healthcare charges, and numbers and incidences of emergency room visits, urgent clinic visits for HF, and hospitalizations. For continuous outcomes (e.g. charges), we will use Wilcoxon rank-sum test to compare them between the two groups. Linear regression or quantile regression will be performed to assess the group difference adjusting for other potential confounders such as baseline utility scores. The Chi-square test will be used to compare categorical outcomes (e.g. categorized frequency of emergence room visits), followed by generalized linear models (e.g. logistic regression model) which adjusts for other potential confounders. . To model repeatedly measured cost-related outcomes (e.g. utility scores) over time, repeated measures analyses via linear mixed models or generalized linear mixed model will also be performed to estimate the effect of dapagliflozin, time, and their interaction. Potential covariates such as age, gender, race, insurance, and duration of T2D, along with baseline utility score, will be adjusted. Standard model selection and checking procedures will be applied to ensure the adequacy of the adopted models.

DATA AND SAFETY MONITORING BOARD

An independent Data and Safety Monitoring Board (DSMB) is established and responsible for monitoring the trial according to the protocol to ensure the safety of patients in the trial. During the course of the study, the DSMB will review the cumulative data collected, evaluate the risk/benefit profile. The DSMB plans to meet after every 6 months or after 150 patients are enrolled.
The DSMB would recommend one of the following actions:

1. Continue the study without modification
2. Modify protocol - based on the safety findings may include frequency of safety monitoring, alterations in study procedures. A recommendation on sample size increase/decrease will be considered after the 50% interim efficacy analysis review.
3. Stop the study - because there is overwhelming efficacy or safety concern, i.e., the risks to patients exceed the benefits to be obtained.

Interim Efficacy Analysis

For this study, one interim efficacy analysis is planned for the purpose of sample size re-estimation after 50% of the enrolled patients (n=196) have completed the 26 weeks of study period and undergone adjudication of the primary composite endpoint. The process of performing this interim efficacy analysis would, by definition, lead to unblinding of patient treatment to the DSMB. The efficacy analysis and sample size re-estimation will be performed by DSMB members and Dr. Limin Peng from the School of Public Health.

Stopping Due to Overwhelming Evidence of Efficacy
Group sequential tests would be performed when 70% of randomized patients have a completed follow-up assessment and have their events adjudicated, using the Gamma family alpha spending function (with gamma = -5)[63-65].

Safety

Potential risks associated with dapagliflozin use:
Hypoglycemia. It is possible that following the proposed protocol, T2D patients receiving basal insulin or dapagliflozin alone or in combination with antidiabetic treatment may develop hypoglycemia (< 54 mg/dl). The frequency of hypoglycemia in patients with T2D treated with dapagliflozin is expected to be < 10%. The number of reports of hypoglycemia will be analyzed statistically. For this analysis, hypoglycemia is defined as a capillary and/or laboratory BG <70 mg/dl, and clinically significant hypoglycemia a BG < 54 mg/dl. Severe hypoglycemia is defined as an event with symptoms consistent with hypoglycemia in which the subject required the assistance of another person and blood glucose less than 40 mg/dl.

Volume depletion. SGLT2-is, including dapagliflozin may cause intravascular volume contraction. Treatment with SGLT2-i leads to increased diuresis, which may result in a modest reduction in blood pressure [66,67]. The risk of volume depletion is enhanced when two diuretics are used in combination, especially with the use of loop diuretics. Therefore, the drug should be given with caution in patients with volume depletion and hypotension. In this trial, we will exclude patients with hemodynamic shock with systolic blood pressure <100 mm Hg after initial fluid resuscitation.

Hypotension. SGLT2-is, including dapagliflozin may cause natriuresis and intravascular volume contraction that may lead a modest reduction in blood pressure [66,67]. The risk of hypotension may be higher in elderly patients with renal impairment receiving two diuretics and the use of loop diuretics. In this trial, we will exclude patients with systolic blood pressure <100 mm Hg and during therapy, diuretic and/or antihypertensive drugs may need to be adjusted in patients with blood pressure < 100 mmHg.

Urinary tract infection. Dapagliflozin as all of the SGLT2-i are associated with more frequent urinary tract infections compared with placebo. The percentage of diagnosed urinary tract infections in a recent safety analysis was 3.6% for dapagliflozin and 3.7% for placebo. Urinary tract infections were observed in a greater proportion in patients with a history of recurrent urinary tract infection compared with those without a history of recurrent infection. In this trial, patients with a diagnosis of pyelonephritis or recurrent urinary tract infections will be excluded, and symptoms/signs of UTI will be closely monitored during the clinical trial.

Mycotic genital infection. The use of SGLT2-i has been associated with increased susceptibility to genital mycotic infections [68,69]. In the recent DECLARE study (REF), the rate of genital infections that led to discontinuation of the regimen or that were considered to be serious adverse events (0.9% vs. 0.1%, P<0.001). This AE is usually mild in intensity, respond to local/systemic treatment, and rarely result in drug discontinuation. In this trial, patients with recurrent genital mycotic infections will be excluded, and symptoms/signs of mycotic genital infection will be closely monitored during the trial.

Diabetic ketoacidosis is a rare complication in patients with T2D reported with the use of SGLT2-i. In the recent DECLARE study, diabetic ketoacidosis was more common with dapagliflozin than with placebo (0.3% vs. 0.1%, P=0.02), as was the rate of genital infections that led to discontinuation of the regimen or that were considered to be serious adverse events (0.9% vs. 0.1%, P<0.001). Patients treated with dapagliflozin who present with signs and symptoms consistent with severe metabolic acidosis will be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated

with dapagliflozin may be present even if blood glucose levels are less than 250 mg/dL [70-72]. If ketoacidosis is suspected, the drug should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of DKA may require insulin, fluid replacement [73,74].

Acute kidney injury and impairment in renal function. There have been reports of acute kidney injury in patients receiving SGLT2-I [74-76]. Dapagliflozin should be avoided during prolonged fasting or fluid losses (such as gastrointestinal illness). SGLT2-i may increase serum creatinine and decreases eGFR. Patients with moderate renal impairment (eGFR less than 25 mL/min/1.73 m2) should not be started on dapagliflozin.

Lower limb amputation. An increased risk for lower limb amputation (primarily of the toe) has been observed in clinical studies with SGLT2-I therapy [77,78]. In the recent DECLARE study, the rate of non-traumatic lower limb amputations was not increased compared to placebo treatment. Patients at increased risk of amputations including such as a history of prior amputation and diabetic foot ulcers will not be enrolled in this trial.

Changes in serum magnesium. Recent reports and a meta-analysis of 18 RCTs involving 15,309 patients provided evidence that SGLT2 inhibitors significantly increase serum magnesium levels in patients with T2D [79]. On average, serum magnesium levels were raised by 0.04-0.06 mmol/l for all SGLT2-I agents indicating a drug class effect. The mechanisms are not completely understood, but likely relates to SGLT2 i- induced glucosuria and osmotic diuresis. The significant elevations in serum magnesium levels are not known, with some studies reporting an association between high magnesium levels and total mortality in individuals with heart failure [80] and those receiving hemodialysis [81]. However, in the general population and in people with type 2 diabetes, high end of the normal range of serum magnesium has been associated with a lower risk of cardiovascular events [79], lower systolic BP by 2.00 mmHg and diastolic BP by 1.78 mmHg compared with placebo [79]. It has been hypothesized that a modest increase in serum magnesium could have contributed to a reduction in cardiovascular mortality observed among participants with type 2 diabetes in the EMPA-REG OUTCOME trial [20,79].

Definition of Adverse Events

An **Adverse Event (AE)** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Serious Adverse Events. A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect?
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g. medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury is also considered an important medical event.
- Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug is an SAE.

NOTE: The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

Serious Adverse Event Collection and Reporting

- The collection of AEs will start after the signing of the informed consent. All SAEs, whether related or not related to study drug, will be collected, including those thought to be associated with protocol-specified procedures. An SAE report will be completed for any event where doubt exists regarding its seriousness.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship will be specified in the narrative section of the SAE Report Form.
- SAEs, whether related or not related to study drug, and pregnancies must be reported to the IRB and sponsor within 24 hours. SAEs will be recorded on an SAE Report Form; If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report will be sent within 24 hours to the Emory IRB and sponsor using the same procedure used for transmitting the initial SAE report.
- All SAEs will be followed to resolution or stabilization.

Non-serious Adverse Events

- A **non-serious adverse event** is an AE not classified as serious.

- The collection of non-serious AE information should begin at initiation of study drug. Non-serious AE information will also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.
- Non-serious AEs will be followed to resolution or stabilization or reported as SAEs if they become serious. Follow-up will be performed for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified non-serious AEs will be recorded and described on the non-serious AE page of the CRF.
- Completion of supplemental CRFs will be performed for AEs and/or laboratory abnormalities that are reported/identified during the study.

Overdose

- An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose will be reported as an SAE.

Laboratory Test Result Abnormalities

The following laboratory test result abnormalities will be captured on the non-serious AE CRF page or SAE Report Form as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary, for subject safety).

Protocol-required procedures for study discontinuation and follow-up will be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures will be considered if indicated.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study 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) should be followed up and documented even if the patient was discontinued from the study.

The investigator will immediately notify the sponsor and IRB within 24 hours and in accordance with SAE reporting procedures. All pregnancies and outcomes of pregnancy should be reported to AstraZeneca's

designated fax line: +1 302 886 4114 or email: AEMailboxClinicalTrialTCS@astrazeneca.com if a secure line is set up.

Recording of adverse events

Adverse Events will be collected throughout the study until and including the last visit/contact.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Whether this event is potentially a clinical endpoint /event of special interest
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.
- It is important to distinguish between serious and severe AEs. An AE of severe intensity need not necessarily be considered serious. If the intensity of an AE changes, only the maximum intensity of the event will be recorded; however, the AE intensity will be recorded at the time of reporting.

Maximum intensity will be graded according to the following rating scale:

- Mild (awareness of event but easily tolerated)
- Moderate (discomfort enough to cause some interference with usual activity)
- Severe (inability to carry out usual activity)

Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters will be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

Hepatic disorders

All patients with a confirmed result of AST and/or ALT >3x ULN, will have additional central laboratory tests performed throughout the study. For patients who are discontinued from the study as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of end of Treatment Visit.

Pre-defined liver enzyme elevations will undergo adjudication. The definitions of events to be adjudicated are provided in the Event Reporting Manual. For all events identified for adjudication, the Investigator will complete the appropriate eCRF pages and provide source documentation as detailed in the Event Reporting Manual.

Hematuria

All events of hematuria (confirmed by microscopy at the central laboratory) during the study will be worked up for a possible cause. If no immediate or benign cause is identified as judged by the Investigator (e.g., menstruation, kidney stone, urinary tract infection [UTI] where hematuria is subsequently resolved after successful treatment), patients will undergo further evaluation by the investigator or another qualified professional. The choice of tests will be per local standard of care. The patient will continue to receive IP treatment during these investigations (unless otherwise contraindicated). All confirmed events of bladder cancer will lead to the discontinuation of investigational product.

Possible malignancies

All possible malignancies (except for non-melanoma skin cancer) will be identified based on a pre-specified list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The identified events will be independently adjudicated. For all events identified for adjudication, the Investigator will complete the appropriate eCRF pages and provide source documentation as detailed in the Event Reporting Manual. The Investigator will clearly describe the event as benign or malignant if known. All confirmed events of bladder cancer will lead to the discontinuation of investigational product.

Renal disorders

For patients with signs of deteriorating renal function additional monitoring needs to be conducted. Any patient with an increase ≥ 50% above baseline will be scheduled for a re-test within 1 week whenever possible.

If the re-tested serum creatinine is < 50% above baseline the patient can resume normal visit schedule.

If the re-tested increase in increase in serum creatinine ≥ 50% above baseline, the patient's renal function will continue to be monitored according to the judgment of the Investigator. In this circumstance, the Investigator will consider evaluating the patient for potentially reversible causes of

renal dysfunction including: concurrent use of NSAIDS, antibiotics, or other medications known to affect measures of serum creatinine; volume depletion; urinary tract infection and obstructive uropathy. If the eGFR falls below 25 ml/min, continue current dose of 10mg to reduce the risk of further eGFR decline.

Hypoglycemic events

At each visit the Investigator will inquire about occurrence of major hypoglycemic events according to the below definition.

Major hypoglycemic event defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behavior, and prompt recovery after glucose or glucagon administration. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low blood glucose concentration.

Hypoglycemic episodes or symptoms of hypoglycemia will only be reported if the event fulfills the definition of a major hypoglycemic event, the protocol criteria for an SAE or leads to discontinuation of IP.

Volume depletion

Dapagliflozin has a modest diuretic effect. The risk of volume depletion is enhanced when two diuretics are used in combination and in patients that otherwise are at risk for volume depletion. Therefore, caution will be exercised when administering to patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics. These patients will be carefully monitored for volume status, electrolytes, and renal function.

UTI

If the Investigator believes that a UTI may be present, a properly collected set of urine cultures will be obtained and sent to a local laboratory prior to initiation of antibiotic therapy to confirm a presumptive diagnosis of cystitis, urinary tract infection, pyelonephritis. Clinical judgment and local standards of care should apply to decisions concerning therapy.

In patients with clinical evidence of upper UTI (e.g., pyelonephritis) or presumed urosepsis, the Investigator may consider temporarily stopping IP until the course of treatment of the infection has been completed and clinical recovery has occurred. It is recommended that a follow-up urine culture is obtained within 7 days of clinical recovery from a documented UTI.

Asymptomatic bacteriuria

During enrollment, randomized treatment and follow up of patients in this trial, the Investigator may discover a patient with asymptomatic bacteriuria. Asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection. Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases.

Adjudication of suspected CV endpoints

The primary outcome of the study is to compare the efficacy of dapagliflozin compared with placebo, on the composite rate of hospital admissions, emergency department visits, urgent clinic visits for HF and death after admission with ADHF.

Definition of heart failure hospitalization, emergency department visit and urgent ambulatory heart

failure is included in Appendix A.

Suspected CV outcome events in the study will be identified either by the Investigator and reported AEs. For all events identified for adjudication the Investigator will enter information in the eCRF and provide source documentation.

Reporting of serious adverse events

Investigators and other study site personnel will inform the Emory IRB, FDA and sponsor (AZ) of any SAE via a MedWatch/AdEERs form that occurs in the course of the study immediately or within 24 hours of when he or she becomes aware of it. Follow-up information on SAEs will also be reported by the Investigator with the same time frame. It is the responsibility of the investigator to compile all necessary information and ensure that the Emory IRB, sponsor and FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded. All SAEs collected in the study are to be reported to AstraZeneca.

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 and ethical committees, of any SAEs as per local requirements, and concurrently AstraZeneca.

SAEs that do not require expedited reporting need to be reported to AstraZeneca at least quarterly, preferably as they occur, either as individual case reports or as line listings.

When reporting to AstraZeneca, a cover page should accompany the SAE form indicating the following:
• External Sponsored Research (ESR)
• The investigator's name and address
• The trial name/title and AstraZeneca ESR reference number

Investigative site must indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications.

Send SAE report and accompanying cover page 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

Hypoglycemia risk protection:

We will follow safeguards to minimize the risk to our subjects: a) we will carefully monitor response to medical treatment every 2 weeks by telephone contact and during clinic visits, b) women of reproductive age who are sexually active will undergo a urine pregnancy tests prior to participation in the study, c) patients with significant comorbidities such as chronic kidney disease greater than stage II, cirrhosis, gastroparesis, and pancreatic disease will be excluded from the study.

Hypoglycemia: We expect that less than 10% of dapagliflozin treated patients will experience hypoglycemia during follow-up; however, approximately 20% to 30% of subjects treated with basal insulin and study drug will experience one or more episodes of hypoglycemia. Patients will receive diabetes education prior to discharge and will be instructed on hypoglycemia sign/symptoms and

treatment. Patients will be asked to call the T2D center and/or PCP in the event of hypoglycemia. If a patient develops hypoglycemia, the daily dose of insulin will be reduced by 10% to 30%.

Treatment of Hypoglycemia (BG <70 mg/dL)
For BG < 70 mg/dL, follow hypoglycemic orders below:

- If patient is alert and can tolerate oral intake, give 20 grams of fast-acting carbohydrate (6 oz. fruit juice or regular soda, crackers).
- If patient is not alert and cannot tolerate oral intake, call 911, give 1 mg glucagon IM or SQ
- Check finger stick BG q 15 minutes and repeat above treatment until BG > 100 mg/dL.
- Once BG > 100 mg/dL, repeat finger stick BG 1 hour later and provide a meal or carbohydrate

Potential Benefits to the Subject: We believe that all subjects will benefit greatly from this study. Improved glycemic control after hospital discharge may significantly reduce complications and reduce readmissions as well as the risk of hyperglycemia and hypoglycemia.

Potential Benefits to Society: This study will provide important information on the benefits of dapagliflozin after discharge for the management of patients with T2D. We will determine whether glycemic control is different among insulin and dapagliflozin after hospital discharge.

Risk/Benefit Assessment: There are no prospective, randomized studies to assess the efficacy and safety of dapagliflozin for the management of T2D after hospital discharge in patients with a recent HF admission. This study will test the efficacy of dapagliflozin in preventing hospital readmissions during the following 6-months after hospital discharge in patients with and without diabetes.

Therapeutic Alternatives: Patients can be treated with insulin regimen and oral agents (glyburide, glipizide, DPP4 inhibitors and GLP1 analogs) currently available for the treatment of T2D. In addition, there are several well-established medications that have been proven effective in improving cardiac function in patients with a history of heart failure.

Inclusion of women. We anticipate that ~50% of the study subjects will be female. No patients under the age of 18 and no pregnant women will be included in the study. Absence of pregnancy will be demonstrated by blood or urine testing prior to randomization (in female of childbearing potential only).

Inclusion of minorities. Patients will not be excluded based on race or ethnic origin. We anticipate that half of patients will be African Americans, 10% Hispanics, and the rest Caucasians.

Inclusion of children. No patients under the age of 18 will be recruited in this study.

Confidentiality. Informed consent will follow the procedure of Emory University Institutional Review Board. Every potential participant will be informed in writing and verbally with the important and key points of the study. The research team will obtain a witnessed informed consent prior to inclusion of a patient into the study. Data collection records with personal identifiers will be stored in locked file cabinets. Presentation of the study results at scientific meetings or in publications will not identify subjects. Access to research and confidential records will be limited to clinical investigators, coordinators and the IRB at Emory University.

Payment for Participation. Participation in this study is voluntary. Patients will receive twenty-five dollars ($25.00) during the hospital stay and visit 2, and fifty dollars ($50.00) after each clinic visit after discharge. Total compensation up to three hundred dollars ($300).

Financial Obligation. No additional cost to patients or to the institution will be incurred for research purposes. Research studies will be performed at no cost to study subjects. Dapagliflozin and matching placebo will be provided by the sponsor at no cost to participants.

Research Injuries. If a patient is injured because of taking part in this study, Dr. Umpierrez and investigators, along with the medical facility will make medical care available to the patient at the patient's own cost. Financial compensation for such things as lost wages, disability or discomfort due to an injury related to the study is not available.

Financial Conflict of Interests. None of the investigators in this study have any outside activities that may represent a conflict of interest. None of the investigators have an economic interest in an outside entity, or act as officers, directors, employees or consultants with such an entity, whose financial interest may be affected by this research study.

Informed Consent. After identification of eligible patients these individuals will be provided basic information regarding the study and, if interested, they will then be screened by research staff using the inclusion/exclusion criteria delineated elsewhere in this protocol. The consent form, potential risks and benefits, and the rights of research participants will be explained to the participant by the investigators or research coordinator. Individuals will be asked if they have any questions, and research staff will answer these questions. The principal investigator will also be available to answer questions that participants may have during the consent procedure or during the time a participant is enrolled in the study. The consent form will be completed in accordance with the IRB guidelines of Emory University. A signed copy of the consent form will be provided to the participant and a copy will be placed in the file that is maintained for each participant in the study office.

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Appendix A: Heart Failure Hospitalization, Emergency Room visit for heart failure and urgent outpatient clinic visit

Heart Failure (HF) Hospitalization is defined as an event that meets ALL of the following criteria:

1. The patient is admitted to the hospital with a primary diagnosis of heart failure
2. The patient exhibits new or worsening HF symptoms, including at least ONE of the following:

    a) Dyspnea (dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
    b) Decreased exercise tolerance
    c) Fatigue
    d) Other symptoms of worsened end-organ perfusion or volume overload

3. The patient has objective evidence worsening heart failure, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including:
    1. Physical examination findings:
        a) Peripheral edema
        b) Increasing abdominal distention or ascites
        c) Pulmonary rales/crackles/crepitations
        d) Increased jugular venous pressure and/or hepatojugular reflux
        e) S3 gallop
        f) Clinically significant weight gain thought to be related to fluid retention

    2. Laboratory evidence of heart failure, including:
        a) Increased N-terminal pro-BNP (NT- proBNP) or B-type natriuretic peptide (BNP) concentrations consistent with decompensation of heart failure.
        b) Radiological evidence of pulmonary congestion
        c) Non-invasive or invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output by echocardiogram report.
        d) The patient receives initiation or intensification of treatment specifically for heart failure, including at least ONE of the following:
            a. Augmentation in oral diuretic therapy
            b. Intravenous diuretic, inotrope, or vasodilator therapy
            c. Mechanical or surgical intervention, including: Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device) or Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

Emergency Room Visit for Heart Failure: defined as an event that meets all of the following:

1. Unscheduled visit to the Emergency Department (ED) with worsening symptoms and with a primary diagnosis of heart failure, with intensified HF treatment but not requiring HF hospitalization.

2. The patient exhibits new or worsening symptoms due to heart failure as described above, including at least ONE of the following:
    a) dyspnea (dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea),
    b) decreased exercise tolerance, increasing fatigue,

c) symptoms of worsened end-organ perfusion or volume overload

3. The patient has objective evidence worsening heart failure, with at least TWO physical examination findings OR one physical examination finding and ONE laboratory criterion):

A) Physical examination findings:
   2. Peripheral edema
   3. Increasing abdominal distention or ascites
   4. Pulmonary rales/crackles/crepitations
   5. Increased jugular venous pressure and/or hepatojugular reflux
   6. S3 gallop
   7. Clinically significant weight gain thought to be related to fluid retention

B) Laboratory evidence of heart failure, including:
   1. Increased N-terminal pro-BNP (NT- proBNP) or B-type natriuretic peptide (BNP) concentrations consistent with decompensation of heart failure.
   2. Radiological evidence of pulmonary congestion
   3. Non-invasive or invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output by echocardiogram report.
   4. The patient receives initiation or intensification of treatment specifically for heart failure, including at least ONE of the following:
   1. Augmentation in oral diuretic therapy
   2. Intravenous diuretic, inotrope, or vasodilator therapy
   3. Mechanical or surgical intervention, including: Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device) or Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

Urgent Heart Failure Visit: defined as an event that meets all of the following:

1. The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of heart failure, but not meeting the criteria for a heart failure hospitalization.

2. All signs and symptoms for heart failure hospitalization (i.e., a) symptoms; b) physical examination findings/laboratory evidence of new or worsening heart failure, as indicated above)

3. The patient receives initiation or intensification of treatment specifically for heart failure, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

Appendix B: COVID-19

On March 11, 2020, the World Health Organization declared the 2019 novel coronavirus – and COVID-19, disease caused by the virus – a global pandemic. In response, efforts to contain the spread of COVID-19 have been implemented across the United States and have impacted the conduct of clinical research trials. In an effort to maintain, as much as possible, the integrity of the DAPA HF on Hospital Readmission trial so that the data can be used to answer the questions that the trial intended, certain adjustments in visit procedures may be considered on a case-by-case basis, as outlined below. Emory University should be notified before making these adjustments.

- **Screening/randomization Visit (Visit S/R) – hospital admission:**
  o Screening/randomization activities may be suspended at sites until such time that it is considered appropriate by the site to resume activities

- **Visit 2 (Week 2) - office visit**:
  o This visit can be conducted at 2 weeks or less. This visit is usually conducted at the same time participant has been scheduled for follow up with heart failure services after hospital discharge.

- **Visit 3 (Week 6), 7 (Week 20) - office visit:**
  - an office visit is preferred
  - The visit could be delayed and the visit window extended to accommodate an office visit
  - Conducting the visit by phone could be considered
  - If conducted by phone, complete the phone visit procedures outlined in the **Schedule of Assessments** on page 9
  - If laboratory collection is needed at investigator's discretion, please mail/email study laboratory requisition for participant to choose a convenient LabCorp location

- **Visit 4 (Week 8), 6 (Week 16), and 8 (Week 24) - phone visits:**
- Conduct visits, as scheduled, by phone

- **Visit 5 (Week 12) - office visit:**
  - An office visit is needed to collect study endpoints (echocardiogram, laboratories, questionnaires, 6-minute walk test, and dispensing IP)
  - The visit could be delayed and the visit window extended to accommodate an office visit
  - If needed, study drug could potentially be mailed by sites to a patient to keep them on study drug (depending upon local regulations) until such time that the Week 12 visit can be conducted in the office

- **Visit 9 (Week 26) - office visit:**
  - An office visit is needed to collect study endpoints (laboratories, questionnaires, and 6-minute walk test).

  The visit could be delayed and the visit window extended to accommodate an office visit