Efficacy and Safety of Dapagliflozin in Acute Heart Failure

DICTATE-AHF

NCT 04298229

Statistical Analysis Plan

Version Number/Amendment	Approval Date	Summary of Changes
1.0/ Original protocol	10.2021	Not applicable
2.0/Amendment One	3.2023	1. Modified text to include patients without diabetes 2. Sensitivity endpoint analysis - changed diuretic dose analyses to be centered on 40mg IV furosemide from 20mg 3. Defined serum potassium values to define severity categories of hypokalemia 4. Defined serum glucose values to define severity categories of hypoglycemia and subsequent analyses changes for these new categories 5. Added eGFR calculation to also be done with the CKD-EPI calculation 6. Primary Analysis: changed the covariates to only be baseline weight (removing other covariates) 7. Exploratory Outcome: Altered analysis of 30-day readmission to include death as a competing risk 8. Exploratory Outcome: clarified total daily insulin doses will be compared between treatment arms and prior to enrollment 9. Exploratory Outcome: Added 24-hour and spot urine sodium measures 10. Added Heterogenicity of Treatment Effect analyses 11. Added changes in serum chemistries by treatment arm

Introduction

This document describes the statistical analysis plan (SAP) for a randomized, open-label, multi-center trial studying the sodium-glucose cotransporter-2 inhibitor (SGLT2), Dapagliflozin, in patients with or without Type II diabetes (T2DM) admitted with acute decompensated heart failure (ADHF).

Patients with ADHF are typically admitted to the hospital due to symptoms of congestion with loop diuretics being the primary mode of treatment; however, loop diuretics are not always sufficient in helping patients achieve adequate decongestion.[1,2,3] In fact, congestion remains the major cause of hospital readmission for heart failure. In addition, an increasing percentage of patients admitted with ADHF also have T2DM. It has been shown that SGLT2-inhibitors, approved for anti-hyperglycemic therapies, also have diuretic and natriuretic effects.[4] The acute diuretic effects in a population with ADHF, with or without concomitant hyperglycemia, undergoing intravenous diuresis are currently unknown. This trial hypothesizes patients randomized to receive dapagliflozin will have improved decongestion when compared to those receiving structured usual care.

Treatment arms

Patients with or without T2DM hospitalized with ADHF will be randomized within 24 hours of evaluation of ADHF in 1:1 ratio to either intervention or structured usual care defined as follows:

a) **Intervention:** Previous diabetic therapies will be discontinued, and patients will receive 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 – the minimum of 5 days or hospital discharge.
b) **Structured usual care:** Previous diabetic therapies will be discontinued, and patients will receive protocolized diuretic therapy.

Endpoints

Primary Endpoint:

The primary endpoint is to determine the cumulative change in weight (kg) per 40mg of IV furosemide equivalents from enrollment to the minimum of Day 5 or discharge between 1) protocolized diuretic therapy (structured usual care) and 2) dapagliflozin plus protocolized diuretic therapy guided by urine output.

Sensitivity Endpoint:

The cumulative change in weight (kg) per doubling of the cumulative loop diuretic (analyzed as log2 of the cumulative loop diuretic dose centered on 40mg of IV furosemide equivalent and winsorized at 40mg) from enrollment to Day 5 or discharge between 1) structured usual care and 2) dapagliflozin plus structured usual care

Secondary Endpoints: Comparing differences among the two arms in the following:

a) Incidence of worsening heart failure during hospitalization requiring i) IV inotropic therapy, ii) new admission to an intensive care unit (ICU), iii) new non-invasive positive pressure ventilation with bi-level positive airway pressure, or iv) increase in the IV diuretic protocol intensity by 2 rows after Study Day 1 as adjudicated by the Clinical Event Committee (CEC).

b) Hospital readmission within 30 days of discharge for ADHF or diabetic reasons as adjudicated by the CEC.

Exploratory Endpoints: Comparing differences among the two arms in the following:

a) NT-proBNP at baseline to discharge adjusted for baseline.
b) Urine-output based diuretic efficiency defined as the Day 2 24-hour total urine output (ml) per 40/mg of IV furosemide equivalents
    a. Repeated as per doubling of the cumulative loop diuretic dose (log2 cumulative loop diuretic dose centered at 40mg)
c) Urine sodium-based diuretic efficiency defined as the Day 2 24-hour total urine sodium excretion (mmol) per 40mg of IV furosemide equivalents (total loop diuretic dose over Day 2)
    a. Repeated as per doubling of the cumulative Day 2 loop diuretic dose (log2 cumulative loop diuretic dose centered at 40mg)
d) Spot urine sodium-based diuretic efficiency defined as the spot urine sodium concentration (mmol/L) on Day 2 per 40mg of IV furosemide equivalents (preceding loop diuretic dose)
e) Fractional excretion of sodium (FENa)-based diuretic efficiency on Day 2 of IV therapy defined as the FENa from a spot urine test on Day 2 of IV therapy collected ~2 hours after bolus loop dose per 40 mg of IV furosemide equivalents.
    a. Repeat as per doubling of the cumulative loop diuretic dose (log2 cumulative loop diuretic dose centered at 40mg)
f) Urinary Na/K ratio at Day 2 of IV therapy adjusted for baseline.
g) Calculated 6-hour sodium output on Day 2 of IV therapy using spot urine sodium collected 2 hours after bolus loop dose.
h) Length of hospital stay, measured as days from admission to discharge
i) Presence of symptoms of congestion and dyspnea at discharge, measured via blinded-physician exam and patient reported congestion scores.
j) Hospital readmission within 30 days of discharge for any cause.
k) Number of days at home without hospitalization or emergency room visit during 30-day follow up period.
l) Mean serum glucose during therapy
m) Amount of total daily insulin doses (units) utilized per day during therapy, compared between treatment arms and to a "prior to enrollment" outpatient insulin regimen.
n) Analyze the change in basic metabolic panel laboratory values and hemoglobin from baseline to end of study
o) Serum potassium covariate with attention to both elevation and depression.

    Hypokalemia levels are defined as

    a. Not hypokalemic: serum potassium > 3.4 mEq/L
    b. Mild: serum potassium 3.0 – 3.4 mEq/L
    c. Mod-Severe: serum potassium < 3.0 mEq/L

    Hyperkalemia levels are defined as

    a. Not hyperkalemic: serum potassium < 5.1 mEq/L
    b. Mild: serum potassium 5.1 – 5.5 mEq/L
    c. Severe: serum potassium > 5.5 mEq/L

Safety Endpoints: Comparing differences among the two arms in the following:

a) Estimated Glomerular Filtration Rate by the MDRD equation at discharge adjusted for baseline. A sensitivity analysis of eGFR by the CKD-EPI equation will also be done.
b) Incidence of ketoacidosis as adjudicated by the CEC
c) Serum glucose with attention to both elevation and depression.
    a. Hypoglycemia is defined as:
        i. Not hypoglycemic: serum glucose > 70 mg/dl
        ii. Mild: serum glucose 54-69 mg/dl
        iii. Mod-Severe: serum glucose < 54 mg/dl
    b. Hyperglycemia is defined as:
        a. Not hyperglycemic: serum glucose < 200 mg/dl
        b. Mild: serum glucose 200-300 mg/dl
        c. Severe: serum glucose > 300 mg/dl
d) Incidence of hypovolemic hypotension, defined as symptomatic hypotension with a sustained systolic blood pressure less than 90 mmHg lasting at least 30 minutes requiring fluid administration.
e) Inpatient mortality

Design Considerations

Randomization

Patients will be randomized in a 1:1 ratio to receive either intervention or structured usual care. Randomization will use block randomization stratified by site with block sizes of 4.

Power and Sample Size

We anticipate dapagliflozin will 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 structured usual care arm using a Wilcoxon (Mann-Whitney) rank-sum test with a 0.05 two-sided significance level.

Statistical Approach

Descriptive Analysis

Initially, we will describe the study cohort pooled across all sites, both overall and grouped by treatment assignment. To characterize the study sample, demographic, clinical, and lab data will be described overall and by treatment arm. Categorical variables will be described using frequencies and proportions; continuous variables will be described using means and standard deviations as well as medians and interquartile ranges (IQR). Missingness will be recorded for each variable. To further assess the distribution of variables, graphical summaries will be displayed using graphs such as box-plots, dot-plots,

violin-plots, and/or histograms. No statistical testing will be done to compare characteristics across groups. At a minimum, the following baseline variables will be described:

- Age (years)
- Sex
- Race (American Indian or Alaskan Native; Asian; Black or African American, Haitian; Native Hawaiian or Pacific Islander; White Origins in Europe, Middle East, North Africa; Other; Declined to disclose)
- Medical history (Yes/No)
    - Heart failure
    - Myocardial infarction
    - Chronic kidney disease (CKD)
    - Chronic obstructive pulmonary disease (COPD)
    - Hypertension
    - Atrial fibrillation or flutter
- Description of Heart failure
    - Ejection Fraction (%)
    - Ischemic cardiomyopathy
    - Implantable cardiac defibrillator therapy
    - Cardiac resynchronization therapy
- Enrollment vitals
    - Weight (kg)
    - BMI (kg/m^2)
    - Systolic blood pressure (SBP)
    - Diastolic blood pressure (DBP)
    - Heart rate
    - Respiratory rate
    - Temperature (ºC)
- Enrollment labs
    - Sodium
    - Potassium
    - Chloride
    - Serum Bicarbonate
    - Glucose
    - BUN
    - Calcium
    - Creatinine
    - eGFR
    - BNP
    - NT-proBNP
    - Troponin
    - Hemoglobin A1c
- Home Medications
    - Home diabetes medications

        - Metformin n (%)
        - Sulfonylurea n (%)
        - DPP-4 inhibitor n (%)
        - SGLT2-inhibitor n (%)
        - GLP-1 receptor agonist n (%)
        - Insulin n (%)
            - Total daily insulin dose (units)
    - Home heart failure medications n (%)
        - ACEI/ARB/ARNI
        - Beta blocker
        - Aldosterone Antagonist (mra's)
        - Oral loop diuretic total daily dose in furosemide equivalents (mg)
- In-hospital Medications at Baseline n (%)
    - IV furosemide as total daily dose (mg)
    - Beta Blocker
    - ACEI
    - ARB
    - ARNI
    - Aldosterone Antagonist
    - Long acting (Basal) insulin
    - Rapid acting (meal time) insulin
    - Total daily insulin dose (units) as sum of all insulin products in a day

Description of Endpoints

Inpatient and 30-day endpoints of interest will be summarized overall and by treatment assignment. Categorical variables will be described using frequencies and proportions; continuous variables will be described using means and standard deviations as well as medians and interquartile ranges (IQR). Missingness will be recorded for each variable. For those endpoints that are a composite of multiple endpoints, such as incidence of worsening heart failure (requiring IV inotropic therapy, new admission to an ICU, new non-invasive positive pressure ventilation with bi-level positive airway pressure, or increase in the IV diuretic protocol intensity by 2 rows after Day 1 as adjudicated by the CEC) and hospital readmission within 30 days of index hospitalization discharge (for heart failure-related reasons or diabetic reasons), frequencies will be summarized overall and for each level.

No statistical testing will be done to compare characteristics across groups.

Main Analysis

All model results (unadjusted and adjusted) will be summarized with point estimates, 95% confidence intervals (CIs), and p-values displayed in tabular form or graphically, along with appropriate model fit statistics. Missingness in adjusting covariates will be addressed using multiple imputation based on predictive mean matching.

Primary Analysis: Our main analysis will be a covariate-adjusted proportional odds (PO) regression model with our outcome being cumulative change in weight per 40mg of IV furosemide equivalents from

enrollment to the minimum of Day 5 or discharge and the main predictor being treatment assignment. Adjusting covariates will be pre-specified and include baseline weight. Baseline weight will be fit with restricted cubic splines with 3 knots to relax the linearity assumptions.

Secondary Analyses:

Appropriate model diagnostics will be run to assess model fit. If model diagnostics suggest the planned approach violates necessary assumptions, alternative methods will be pursued.

a) Binary logistic regression will be used to assess the association of the incidence of worsening heart failure as adjudicated by the CEC with treatment assignment.
b) A time to event analysis is proposed to assess the association of 30-day hospital readmission for ADHF or diabetes-related reasons. Cumulative incidence of hospital readmission for heart failure or diabetes-related reasons will be graphed by treatment arm death as a competing risk. Multivariable Cox proportional hazards models stratified by enrollment site will be fit to assess the association of time to hospital readmission for reasons of interest with treatment assignment.

Exploratory Analyses:

Appropriate model diagnostics will be run to assess model fit. If model diagnostics suggest the planned approach violates necessary assumptions, alternative methods will be pursued.

a) The association of NT-proBNP at discharge with treatment arm will be modeled using covariate-adjusted PO regression, adjusting for NT-proBNP at baseline (Day 1).
b) The association of Day 2 24-hour total urine output per the following methods in which diuretic dose is centered at 40mg and values less than 40mg are winsorized to 40mg:
    a. 40 mg of IV furosemide equivalents will be analyzed using the Wilcoxon Rank Sum test
    b. Doubling of the loop diuretic dose to account for the logarithmic dose-response curve will be analyzed using the Wilcoxon Rank Sum test.
c) Urine sodium-based diuretic efficiency defined as the Day 2 24-hour total urine sodium excretion (mmol) per 40mg of IV furosemide equivalents (total loop diuretic dose over Day 2) will be analyzed using the Wilcoxon Rank Sum test.
    a. Repeated as per doubling of the cumulative Day 2 loop diuretic dose (log2 cumulative loop diuretic dose centered at 40mg) will be analyzed using the Wilcoxon Rank Sum test.
d) Spot urine sodium-based diuretic efficiency defined as the spot urine sodium concentration (mmol/L) on Day 2 per 40mg of IV furosemide equivalents (preceding loop diuretic dose) will be analyzed using the Wilcoxon Rank Sum test.
e) The association of Day 2 fractional excretion of sodium (FENa)-based diuretic efficiency determined from spot urine collected 2 hours after bolus loop dose with treatment arm will be analyzed using the Wilcoxon Rank Sum test.
f) The association of Day 2 urinary Na/K ratio with treatment arm will be analyzed using covariate-adjusted PO regression, adjusting for baseline (Day 1) urinary Na/K ratio.
g) The association of calculated Day 2 6-hour sodium output with treatment assignment will be analyzed using the Wilcoxon Rank Sum test
h) The association of length of hospital stay with treatment assignment will be analyzed using the Wilcoxon Rank Sum test

i) The association of presence of symptoms of congestion and dyspnea at discharge measured via blinded physician exam and patient reported congestion scores with treatment assignment will be analyzed using the Pearson chi-square test. A proportional odds model will be used to assess the association of discharge congestion score with treatment assignment, adjusting for baseline congestion.
j) Cumulative incidence of all cause hospital readmission within 30 days of index hospitalization discharge will be graphed by treatment arm treating death as a competing risk. The association of all cause hospital readmission within 30 days of index hospitalization discharge with treatment assignment will be analyzed using the Pearson chi-square test.
k) The association of number of days at home without hospitalization or emergency room visit during the 30-day follow-up period with treatment assignment will be analyzed using the Wilcoxon Rank Sum test. For purposes of analysis, subjects who died within 30 days of the index hospital discharge will be assigned a value of 0 days at home
l) The association of mean serum glucose during therapy with treatment assignment will be analyzed using the Wilcoxon Rank Sum test
m) Total daily insulin doses (units) utilized per day during therapy will be compared between treatment arms in all comers and in those with diabetes at baseline using a Wilcoxon Rank Sum Test. Total daily insulin doses utilized per day during therapy will be compared to a 'prior to enrollment' utilization using the Wilcoxon Signed Rank Test.
n) The change in basic metabolic panel laboratory values and hemoglobin from baseline to the end of study will be compared across treatment groups using the Wilcoxon Rank Sum test.
o) Serum potassium trends over time by treatment assignment will be graphed. Descriptive statistics of the daily raw potassium values and kalemic status during hospitalization by treatment group will be reported and compared across treatment assignments by Wilcoxon Rank Sum tests and Pearson's chi-square tests, respectively.

Safety Analyses:

All multivariable models will adjust for the same key covariates as specified for the primary outcome, as sample size permits. Appropriate model diagnostics will be run to assess model fit. If model diagnostics suggest the planned approach violates necessary assumptions, alternative methods will be pursued.

a) The association of estimated Glomerular Filtration Rate (eGFR) at discharge, calculated using the MDRD equation, with treatment assignment will be modeled using covariate-adjusted PO regression, adjusting for baseline eGFR. The analysis will be repeated calculating eGFR using the CKD-EPI equation as well.
b) The association of the incidence of ketoacidosis as adjudicated by the CEC with treatment assignment will be analyzed using the Pearson chi-square test.
c) Serum glucose trends over time by treatment assignment will be graphed. Descriptive statistics of the daily raw glucose values and the glycemic status during hospitalization by treatment group will be reported and compared across treatment assignment by Wilcoxon Rank Sum tests and Pearson's chi-square tests, respectively.
d) The association of incidence of hypovolemic hypotension, defined previously, with treatment assignment will be analyzed using the Pearson chi-square test.

e) The association of inpatient mortality with treatment assignment will be analyzed using the Pearson chi-square test and univariate logistic regression.

Sensitivity Analyses:

Our sensitivity analysis will be a covariate-adjusted proportional odds (PO) regression model with our outcome being log-transformed weight at the minimum of Day 5 or discharge and the main predictor being treatment assignment. Adjusting covariates will be as defined in the primary analysis. Appropriate model diagnostics will be run to assess model fit. If model diagnostics suggest the planned approach violates necessary assumptions, alternative methods will be pursued.

Heterogenicity of Treatment Effect:

Heterogenicity of Treatment Effect (HTE) will be assessed refitting the primary model with the covariate of interest interacted with treatment assignment. The HTE analysis will include the following variables:

- Sex (male or female)
- Baseline edema score (No-Mild/Moderate/Severe)
- Baseline NTproBNP
    - Continuous
    - Dichotomize by median NTproBNP [above/below]
- Baseline BMI-adjusted BNP: defined as a 4% increase in NT-proBNP for every 1 unit increase in baseline BMI above a BMI of 20kg/m^2
    - Continuous
    - Dichotomize by median BMI-adjusted NTproBNP [above/below]
- Baseline BMI
    - Continuous
    - Dichotomize by median BMI [above/below]
- Baseline eGFR (calculated using MDRD)
    - Continuous
    - Dichotomize by median eGFR [above/below]
- Baseline weight
    - Continuous
    - Dichotomize by median baseline weight [above/below]
- Diabetes comorbidity at baseline (Yes or No)
- Left ventricular ejection fraction
    - <= 40 vs > 40
    - < 50 vs >= 50
- Day 1 Fractional excretion of sodium (FENa)-based diuretic efficiency (per 40mg IV furosemide)
    - Continuous
    - Dichotomize by median FENa [above/below]

References

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