Principal Investigator

First Name: benjamin
Last Name: gandesbery
Degree: MD
Primary Affiliation: medical resident, barns-jewish hospital
E-mail: btg27@case.edu
Phone number: 5108131205
Address:

City: st louis
State or Province: missouri
Zip or Postal Code: 63108
Country: United States

General Information

Key Personnel (in addition to PI):
First Name: Benjamin
Last name: Gandesbery
Degree: MD
Primary Affiliation: Barnes-Jewish Hospital
SCOPUS ID: 57196939600

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Internet Search

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT01032629 - 28431754DIA3008 - A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus
2. NCT01989754 - 28431754DIA4003 - A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Correlation between anion gap and urine ketones with hospitalization for heart failure and cardiovascular death in patients receiving canagliflozin

Narrative Summary:

Treatment with SGLT-2 inhibitors has been shown to reduce the composite outcome of Hospitalization for Heart Failure and Cardiovascular Death (HHF/CVD). The mechanism for this is unclear. One proposal is that the ketosis which results from SGLT-2 inhibitor treatment has a protective effect on myocardium. Thus, there may be a negative correlation between ketosis and HHF/CVD. Two potential surrogate markers of ketosis are urine dipstick ketones and increased albumin-adjusted serum anion gap. This study would be a retrospective secondary analysis of the CANVAS and CANVAS-R trials examining the relationship between urine ketones and albumin-adjusted serum anion gap on HHF/CVD.

Scientific Abstract:

Background: SGLT-2 inhibitors have been shown to reduce the risk of Hospitalization for Heart Failure and Cardiovascular Death (HHF/CVD). Two potential surrogate markers of ketosis are urine dipstick ketones and increased albumin-adjusted serum anion gap.

Objective: To determine if an increase in albumin-adjusted serum anion-gap or urinary ketones after initiation of canagliflozin is correlated with a lower frequency of HHF/CVD.

Study Design: Retrospective, secondary analysis of the CANVAS and CANVAS-R trials (integrated CANVAS program).

Participants: Subjects from the integrated CANVAS program who underwent randomization, treatment, and scheduled followup, in both treatment and control arms, excluding patients for which serum chemistry or urinalysis results at both baseline and during the first 60 days of treatment are not available.

Main Outcome Measure: Composite outcome of cardiovascular death and hospitalization for heart failure.

Statistical Analysis: Analysis would be completed in 2 parts: 1) correlation of urinary ketones and HHF/CVD and 2) correlation of increased anion gap and HHF/CVD. For both analyses, the combined pool of subjects from both clinical trials would be split into four groups in a 2x2 factorial design based off of urinary ketones (or anion gap) and on assignment to receive canagliflozin or placebo. Kaplan-meier curves of these 4 groups would be constructed for visualization only. Groups would also be compared with time-dependent cox analysis. "Increase in anion gap" would be defined by increase by 3 or more mEq/L compared to baseline.

Brief Project Background and Statement of Project Significance:

A clear and convincing body of evidence has established that SGLT-2 inhibitors have cardio-protective effects. This has been demonstrated both in subjects with preexisting cardiovascular disease and in subjects without diagnosed disease, and appears to be unrelated to baseline renal function. In particular, SGLT-2 inhibitors appear to be highly effective in preventing heart failure and heart failure exacerbation, as measured by the composite outcome of Hospitalization for Heart Failure and Cardiovascular Death (HHF/CVD). This was first suggested by the Empa-reg trial (2016), and subsequently was verified in the CANVAS trial (2017) and DECLARE trial (2019). Most recently, the DAPA-HF trial recruited 2605 subjects with heart failure with reduced EF, approximately half of whom had type 2 diabetes. This study showed that, regardless of diabetes status, there was a statistically significant decrease in heart failure outcomes and all-cause mortality in the treatment group. Taken together, these trials suggest that SGLT-2 inhibitors are heart failure medications just as much as they are antihyperglycemics, and should considered part of the chronic heart failure treatment toolkit.

However, the mechanism of action of SGLT-2 inhibitors in HF is unclear. One explanation is that SGLT-2 inhibitors act as osmotic diuretics due to increased glucosuria. However, this hypothesis is challenged by the fact that loop- or thiazide-type diuretics, unlike SGLT-2 inhibitors, have not shown a survival benefit in heart failure treatment.

Another hypothesis, based off of animal models, is that these medications lead to inhibition of the cardiomyocyte sodium-proton exchanger, which in turn leads to reduced cytoplasmic sodium and calcium but increased myocardial calcium levels. However, this is challenged by the lack of SGLT-2 receptors on human cardiomyocytes. SGLT2 inhibition may also upregulate M2 macrophages, inhibiting myofibroblast differentiation and reducing cardiac fibrosis.

One theory which is particularly compelling is that the ketosis which results from SGLT-2 inhibitor treatment improves cardiac energy metabolism. Metabolism of non-esterified fatty acids lead to build-up of free fatty intermediates in the heart, which contribute to lipotoxicity. Increased levels of beta-hydroxybuterate may serve as an alternative fuel source, reducing utilization of nonesterified fatty acids. Thus ketones may serve as a cardiac "super-fuel," optimizing energy metabolism.

This theory would suggest that there is a negative correlation between ketosis and HHF/CVD. While serum ketones have not been serially monitored in any trials of SGLT-2 inhibitors to date, two potential, though admittedly imprecise, surrogate markers of ketosis are urine dipstick ketones and increased albumin-adjusted serum anion gap.

While a study using these markers would be hypothesis-forming, at best, a positive result would support further areas of research, namely correlation of serum ketone levels with clinical outcomes in patients receiving SGLT-2 inhibitors. Such an avenue of study could shed light on the cardiac mechanism of a powerful, albeit poorly understood, group of drugs.

Specific Aims of the Project:

Primary aims:

1. To determine if there is a relationship between positive urine ketones on dipstick testing and hospitalization for heart failure and cardiovascular death in patients receiving Canagliflozin.

(Hypothesis) There will be a negative relationship between positive urine ketones on dipstick testing and hospitalization for heart failure and cardiovascular death in patients receiving Canagliflozin.

2. To determine if there is a relationship between increase in albumin-adjusted serum anion gap and hospitalization for heart failure and cardiovascular death in patients receiving Canagliflozin.

(Hypothesis) There will be a negative relationship between increase in albumin-adjusted serum anion gap and hospitalization for heart failure and cardiovascular death in patients receiving Canagliflozin.

Additional aims:

3. To determine if there is a relationship between positive urine ketones and hospitalization for heart failure and cardiovascular death in patients not receiving Canagliflozin.

(Hypothesis) There will not be a relationship

4. To determine if there is a relationship between increased anion gap and hospitalization for heart failure and cardiovascular death in patients not receiving Canagliflozin.

(Hypothesis) There will not be a relationship

What is the purpose of the analysis being proposed? Please select all that apply.
Research on clinical prediction or risk prediction

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Inclusion criteria:

Subjects from the integrated CANVAS program (CANVAS and CANVAS-R trials) who underwent randomization, treatment, and scheduled followup, in both treatment and control arms.

Exclusion criteria:
- serum chemistry not available at baseline (prior to treatment initiation)
- urinalysis not available at baseline
- serum chemistry not available within first 60 days after initiation of treatment
- urinalysis not available within first 60 days after initiation of treatment
- outcome data (cardiovascular death, hospitalization) not available

Main Outcome Measure and how it will be categorized/defined for your study:

Composite of CV death or hospitalization for heart failure - this was included as a secondary endpoint during the original CANVAS and CANVAS-R trials. These were adjudicated by an adjudication committee, using definitions included in the committee's charter. For the purposes of this study we would use these variables as adjudicated by the CANVAS and CANVAS-R adjudication committee.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

"Increase in anion gap" would be defined by an increase by 3 or more mEq/L in the albumin-adjusted serum anion gap within the first 60 days after treatment initiation, compared to baseline value prior to treatment initiation.

"Urinary ketones" would be defined as positive urinary dipstick testing within the first 60 days after treatment initiation in a patient who had negative ketone dipstick testing at baseline testing (before initiation of treatment).

"Treatment group" would be defined as whether the subject received canagliflozin or placebo.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

not applicable

Statistical Analysis Plan:

Analysis would be completed in 2 parts: 1) correlation between urinary ketones and HHF/CVD and 2) effect of increased anion gap on HHF/CVD.

For the first portion of analysis, the combined pool of subjects from both clinical trials would be split into four groups in a 2x2 factorial design based off of urinary ketones and on assignment to receive canagliflozin or placebo. Kaplan-meier curves of these 4 groups would be constructed for visualization only. Groups would also be compared with time-dependent cox analysis. A separate multivariate model would be constructed which controls for age, estimated GFR, preexisting heart failure, preexisting ASCVD, and preexisting diabetes.

For the second portion of analysis, the combined pool of subjects from both clinical trials would be split into four groups in a 2x2 factorial design based off of change in anion gap and on assignment to receive canagliflozin or placebo. Kaplan-meier curves of these 4 groups would be constructed for visualization only. Groups would also be compared with time-dependent cox analysis. A separate multivariate model would be constructed which controls for age, estimated GFR, preexisting heart failure, preexisting ASCVD, and preexisting diabetes.

All data analysis will be conducted using the secure platform and with R/R studio.
Software Used:
RStudio
Project Timeline:

Project start date: 1 month after approval
Analysis completion date: 4 months after approval
Manuscript drafted: 6 months after approval
Submission of results to YODA project: 6 months after approval

Submission of 1st draft: 8 months after approval

Dissemination Plan:

Anticipated product would be a brief manuscript
Target audience - clinicians, including physicians specializing in cardiac disease and endocrinology, as well as general practitioners
Journal for submission - PLOS ONE, or similar

Bibliography:

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6. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018;61(10):2108-2117. doi:10.1007/s00125-018-4670-7

Supplementary Material:

https://yoda.yale.edu/sites/default/files/yoda_project_coi_form_for_data_requestors_2019.pdf