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General Information

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/wp-content/uploads/2023/08/COI-FORM-YD.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 - 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. NCT02065791 - A Randomized, Double-blind, Event-driven, Placebo-controlled, Multicenter Study of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus and Diabetic Nephropathy
3. NCT01989754 - 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

Efficacy and safety of canagliflozin in diabetic patients with erythrocytosis: A pooled analysis of the CANVAS Program and CREDENCE trial

Narrative Summary:

SGLT2 inhibitors (SGLT2i) is the cornerstone of treatment for patients with heart failure and chronic kidney disease. Several mediation analyses revealed that increases in hemoglobin and hematocrit levels explain a large part of the cardiorenal benefit of SGLT2i. Conversely, symptomatic erythrocytosis requiring phlebotomy has been demonstrated as a potential adverse effect of SGLT2i. Concerns are raised about whether SGLT2i-induced erythropoiesis increases cardiovascular events in patients with erythrocytosis, considering the link between erythrocytosis and poor cardiovascular outcomes. This study aimed to evaluate the efficacy and safety of SGLT2i in patients with erythrocytosis.

Scientific Abstract:

Background: Mediation analyses revealed that hemoglobin (Hb) and hematocrit (Hct) level increases substantially explain the beneficial effects of SGLT2i. However, the effects of SGLT2i in patients with erythrocytosis remained unknown.

Objective: This study aimed to evaluate the efficacy and safety of SGLT2i on cardiovascular (CV) outcomes in patients with erythrocytosis.

Study Design: Individual participant data meta-analysis of the CANVAS Program and CREDENCE trial

Participants: We will enroll participants with type 2 diabetes mellitus (T2DM) and high risk of CV disease (i.e., CANVAS Program) and chronic kidney disease (i.e., CREDENCE trial) randomly assigned to canagliflozin or placebo groups. Erythrocytosis is defined as a Hb of >16.5 g/dL or Hct of >49% in males and Hb of >16.0 g/dL or Hct of >48% in females.

Primary and Secondary Outcome Measures: Primary outcome includes a composite of myocardial infarction (MI), stroke, and any thromboembolism. Key secondary outcomes include each primary outcome component, CV death, hospitalization for heart failure, and a composite of kidney outcomes (end-stage kidney disease, doubling of serum creatinine level, or renal death)

Statistical Analysis:
The Cox models stratified by trials with an intention-to-treat approach will be used to analyze the effects of canagliflozin compared to placebo on primary and secondary outcomes. The treatment heterogeneity across the two groups with or without erythrocytosis at baseline will be tested by adding the term for erythrocytosis-by-treatment interaction to the Cox model.

Brief Project Background and Statement of Project Significance:

Robust evidence supports the use of SGLT2i in individuals with T2DM at high risk of atherosclerotic cardiovascular (CV) disease, heart failure, or chronic kidney disease, leading to their endorsement in international guidelines1-3. Mediation analyses consistently emphasize the crucial role of increased red blood cell parameters (Hb and Hct) in cardiorenal protection provided by SGLT2i4-9. Importantly, Hb and Hct increases with SGLT2i are not merely indicative of hemoconcentration due to diuretic effects; rather, they reflect erythropoiesis promotion, as SGLT2i modulates iron-related proteins similarly to hypoxia-inducible factor prolyl hydroxylase enzyme inhibitors10,11.
Large observational studies have revealed associations between elevated Hb and Hct levels and adverse CV outcomes12-15. Individuals with erythrocytosis often show multiple CV risk factors, including diabetes, obesity, hypertension, metabolic syndrome, dyslipidemia, and smoking15, thus they may be considered suitable candidates for SGLT2i treatment if clinically indicated. However, various warning reports have raised concerns about SGLT2i-induced erythrocytosis, with some cases

requiring phlebotomy and others diagnosed with unstable angina possibly linked to erythrocytosis. Consequently, SGLT2i is now recognized as one of the causes of erythrocytosis in the hematology community16.
Recent meta-analyses have revealed that SGLT2i reduce 3P-major adverse CV events (MACE), due to their positive effect on heart failure, while neutrally affecting the incidence of ischemic events, such as MI, stroke, and thromboembolism17-19. Theoretically, erythrocytosis, which increases blood viscosity, may hinder adequate blood flow to vital organs and increase the risk of clot formation. Hence, SGLT2i can provide potentially harmful effects in patients with erythrocytosis, particularly on ischemic events and thromboembolism. Currently, data on evaluating the effectiveness and safety of SGLT2i in patients with erythrocytosis are lacking. Our study aims to investigate whether SGLT2i has different effects on patients with or without erythrocytosis. The results of this research provide valuable insights into the risks and benefits of SGLT2i treatment in patients with erythrocytosis, thereby guiding clinical decisions and optimizing patient care in this specific population.

Specific Aims of the Project:

Study objectives
To explore the possible harmful effect of the SGLT2i on CV events and thromboembolism in patients with erythrocytosis.

Specific Hypotheses:
1. Canagliflozin increases the risk of a composite of MI, stroke, and any thromboembolism in patients with erythrocytosis.
2. Canagliflozin increases the risk of MI in patients with erythrocytosis.
3. Canagliflozin increases the risk of stroke in patients with erythrocytosis.
4. Canagliflozin increases the risk of venous, arterial, or any thromboembolism in patients with erythrocytosis.
5. Canagliflozin increases the risk of MACE in patients with erythrocytosis.
6. Canagliflozin increases the risk of CV death in patients with erythrocytosis.
7. Canagliflozin increases the risk of death from any cause in patients with erythrocytosis.
8. Canagliflozin decreases the risk of hospitalization for heart failure in patients with erythrocytosis.
9. Canagliflozin decreases the risk of composite kidney events in patients with erythrocytosis.
10. Canagliflozin increases the Hb and Hct in patients with erythrocytosis.
11. Canagliflozin does not decrease blood pressure in patients with erythrocytosis.

Study Design:

Methodological research

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

New research question to examine treatment safety

Participant-level data meta-analysis

Research Methods

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

We will perform pooled data analysis using individual participant data from the CANVAS Program19 and CREDENCE trial20. Briefly, CANVAS Program included patients with T2DM and an HbA1c of 7.0%–10.5% who were aged ≥30 years and had a history of atherosclerotic vascular disease, or who were aged ≥50 years with ≥2 risk factors for CV disease19. CREDENCE trial included patients with

T2DM and HbA1c of 6.5%–12.0% who were aged ≥30 years and had an eGFR of 30 to <90 mL/min/1.73 m2, a UACR of 300–5000 mg/g, and received renin-angiotensin system blockade20. We will exclude participants without baseline Hb or Hct data.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

The primary outcome will be a composite of MI (fatal and nonfatal), stroke (fatal and nonfatal), and any thromboembolism.
Secondary outcomes will include:
1. MI (fatal and nonfatal)
2. Stroke (fatal and nonfatal)
3. Any thromboembolism
4. Arterial thromboembolism
5. Venous thromboembolism
6. MACE (CV death, nonfatal MI, or nonfatal stroke)
7. CV death
8. Death from any cause
9. Hospitalization for heart failure
10. End-stage kidney disease, doubling of serum creatinine level, or renal death
All outcomes, except for arterial, venous, or any thromboembolism, were adjudicated by independent adjudication committee members in each trial. Arterial, venous, and any thromboembolism will be identified using the prespecified Standard MedDRA (Medical Dictionary for Regulatory Activities) Query (SMQ) search strategies (sub-SMQ 20000082, sub-SMQ 20000083, and sub-SMQ 20000084).

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

Erythrocytosis is defined following the 2016 World Health Organization (WHO) classification as a Hb concentration of >16.5 g/dL or Hct of >49% in males and Hb concentration of >16.0 g/dL or Hct of >48% in females15,21. Ancillary analyses will be performed based on the 2008 WHO classification as Hb concentration of >18.5 g/dL or Hct of >52% in males and Hb concentration of >16.5 g/dL or Hct of >48% in females15 or top decile of sex-specific baseline Hb or Hct values.

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

None

Statistical Analysis Plan:

We plan to use individual participant data from the CANVAS Program19 and CREDENCE trial20. We will use the chi-square test for categorical variables and Mann–Whitney test for continuous variables to compare baseline characteristics of patients with and without erythrocytosis. Mixed effects models of repeated measures (MMRM) will be employed to examine the effects of all canagliflozin groups combined versus the placebo on serial change in Hb, Hct, and blood pressure. MMRM includes the fixed effects of treatment, trial, trial visit, treatment-by-visit interaction, and baseline value-by-visit interaction. The dose-effect will be investigated in the CANVAS trial, which randomly assigned participants at 1:1:1 to canagliflozin 100 mg, 300 mg, or placebo. Effect modification by erythrocytosis at baseline will be tested by adding the two-way and three-way interaction terms between treatment, visit, and baseline erythrocytosis. Hazard ratios and 95% confidence intervals will be estimated using stratified Cox regression models with a stratification variable of trial, for all canagliflozin groups combined versus placebo in the intention-to-treat population. The heterogeneity will be assessed by adding the interaction term between baseline erythrocytosis and treatment to the Cox model. Sensitivity analyses will be performed based on the 2008 WHO classification as Hb or Hct concentrations of >18.5 g/dL or >52% in males, respectively, and that in females are >16.5 g/dL or >48%, respectively,15 or highest decile of sex-specific baseline Hb or Hct values. All statistical

tests will be two-tailed, and p-values <0.05 will be considered statistically significant, whereas P < 0.1 will indicate statistical significance for interactions. No adjustment will be made for multiplicity.

Software Used:

STATA

Project Timeline:

We are ready to conduct the proposed research. The analyses will be completed within 6 months. We will spend another 6 months writing (and subsequently submitting) the manuscript.

Dissemination Plan:

Impressive and meaningful results were expected to share with healthcare providers. We plan to submit to top diabetes or cardiology journal, such as Lancet Diabetes & Endocrinology, Diabetes Care, or Circulation.

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