Principal Investigator

First Name: Yohei
Last Name: Doi
Degree: MD
Primary Affiliation: Osaka University Graduate School of Medicine
E-mail: cdprocyon7@gmail.com
Phone number: +81-6-6879-3857
Address:

City: Suita
State or Province: Osaka
Zip or Postal Code: 565-0871
Country: Japan

General Information

Key Personnel (in addition to PI):
First Name: Yohei
Last name: Doi
Degree: MD
Primary Affiliation: Osaka University Graduate School of Medicine
SCOPUS ID:

First Name: Satoshi
Last name: Yamaguchi
Degree: MD, PhD
Primary Affiliation: Japan Community Health Care Organization, Osaka Hospital
SCOPUS ID:

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/2021nian_01yue_29ri_14shi_34fen_31miao_.pdf
https://yoda.yale.edu/system/files/yoda_coi_sy_20210712.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. NCT02065791 - 28431754DNE3001 - 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

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

supporting documentation

Research Proposal

Project Title

Mediators between Canagliflozin and End-stage kidney disease: Post-hoc mediation analyses of the CREDENCE trial

Narrative Summary:

SGLT2 inhibitors (SGLT2Is) confer renal benefits for type 2 diabetic patients through a variety of mechanisms. Prior mediation analyses reported that the increase in erythropoiesis was most responsible for boosting kidney health; however, the mechanisms underlying the renoprotective effects of SGLT2Is have been largely unexplored especially among more advanced chronic kidney disease with type 2 diabetes at high risk for end-stage kidney disease (ESKD). Using clinical trial data, we aim to identify significant mediators between SGLT2Is and ESKD. The current mediation analysis will provide valuable insight into the mechanisms underlying the renoprotective effect of SGLT2Is.

Scientific Abstract:

Background: SGLT2Is reduce renal events in patients with type 2 diabetes. To date, the renoprotective mechanisms of SGLT2Is have not been fully investigated especially among patients with overt albuminuria.
Objective: To identify mediators that underly the efficacy of SGLT2Is on ESKD.
Study Design: Post-hoc mediation analyses of the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial
Participants: Individuals were ?30 y, had type 2 diabetes, an HbA1c between 6.5% and 12.0%, an estimated glomerular filtration rate (eGFR) of 30 to <90 mL/min/1.73 m2, a urinary albumin-to-creatinine ratio (UACR) 300–5000 mg/g and received renin-angiotensin system blockade drugs.
Main Outcome Measure(s): ESKD, defined as dialysis, kidney transplantation, or a sustained eGFR of <15 mL/min/1.73 m2.
Statistical Analysis: We will examine two associations between: 1) Canagliflozin use and serial changes in candidate mediators following canagliflozin use by using mixed-effects models or ANCOVA (analysis of covariance); and 2) potential mediators and time to ESKD using Cox models. For each mediator, the percentage of their effect will be calculated by comparing the hazard ratios of unadjusted and adjusted Cox models. Also, we will examine combined effects by building a model that includes mediators with large percentage values.

Brief Project Background and Statement of Project Significance:

Type 2 Diabetes mellitus (T2DM), the leading cause of kidney failure worldwide, is one of the most challenging health problems to manage. Emerging data have revealed that SGLT2Is are successful at treating cardiovascular and renal comorbidities in patients with T2DM (1-3). Explanations for this include their ability to improve glycemic levels, blood pressure, body weight, and excretion of albuminuria (4). Previous mediation analyses among diabetic patients with normal or mildly impaired renal function found that SGLT2I increased erythropoiesis, which likely explains the renoprotection that has been observed (5); however, most of the patients who reached the renal composite endpoint in this study did not reach ESKD since a 40% decline in eGFR was the most common outcome. It remains unknown whether this is also the case with diabetic patients at high risk for ESKD since erythropoiesis is impaired with advancing CKD stage (6). Besides, several potential mediators (e.g., acute eGFR decline following SGLT2Is, serum calcium, phosphate, and magnesium) have not been investigated. Our proposed mediation analyses are expected to provide meaningful insight into the mechanisms responsible for the renoprotection by SGLT2Is among diabetic patients at high risk for ESKD.

Specific Aims of the Project:

This study aims to identify significant mediators between SGLT2Is and ESKD. SGLT2Is decrease risk factors involved in the progression of ESKD, including hypertension, obesity, and UACR. Among them, we surmise that

increased serum magnesium levels after SGLT2Is mediate their renoprotection because hypomagnesemia was common and reported to be a predictor of ESKD in patients with T2DM (7). Hypomagnesemia is also well-known to associate with hypertension, insulin resistance, and endothelial dysfunction; common risk factors for the progression of CKD (8). Assuming that serum magnesium elevation following SGLT2Is has an impact on renal prognosis, a large increase in magnesium levels might predict better renal outcomes.

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

Research Methods

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

We will perform the current analyses using individual participant-level data from the CREDENCE trial (2). Briefly, patients were included if they were ?30 y, had type 2 diabetes, an HbA1c level between 6.5% and 12.0%, an eGFR of 30 to <90 mL/min/1.73 m2, a UACR 300–5000 mg/g and received renin-angiotensin system blockade drugs. We will exclude participants without baseline or follow-up data of mediators, as well as those who developed ESKD before follow-up data was obtained.

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

The main outcome will be defined as ESKD (dialysis, transplantation, or a sustained estimated glomerular filtration rate of <15 mL/min/1.73 m2). Ancillary outcomes will include:
1. Renal composite endpoint of ESKD, doubling of serum creatinine and renal death
2. Renal composite endpoint of dialysis, transplantation, and renal death

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

As candidate mediators, we will consider the following biomarkers based upon our knowledge and present perspectives (4): HbA1c, systolic blood pressure (BP), diastolic BP, heart rate, LDL-cholesterol (C), HDL-C, triglycerides, eGFR, UACR, body weight, body mass index, hematocrit, hemoglobin, serum albumin, urate, calcium, phosphate, magnesium. We note that the examination of these biomarkers will be dependent on the availability of data. We will treat all biomarkers as continuous and, if necessary, categorical variables (e.g. hemoglobin, based on the presence of anemia).

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

As mentioned above, we will treat potential mediators as continuous and categorical variables.

Statistical Analysis Plan:

We plan to perform mediation analyses to explore the mechanisms underlying the efficacy of canagliflozin on reducing the incidence of ESKD. First, we will select potential mediators based upon our knowledge and present perspectives (see the details in the Main Predictor section). For mediators to be eligible, we will assess whether canagliflozin affects post-randomization values, and whether these levels associate with ESKD using a mixed-effects model and a Cox model, respectively. We will calculate the percentages of mediation effects using the traditional method proposed by Baron and Kenny (9), which consists of comparing hazard ratios from unadjusted and adjusted Cox models. The 95% confidence intervals for these percentages will be estimated using a bootstrap sampling method. Next, we will select mediators with large percentage values to build a multivariable model for examining how the mediators collectively contribute to renoprotection. Mediators will be added into the model until the mediation effect reaches 100% (or nearly). For a sensitivity analysis, we will employ an inverse odds ratio-weighted approach because it can handle complex interactions between the treatment and mediator(s) (10).
Software Used:
STATA
Project Timeline:

We are ready to carry out the proposed research. The analyses will be completed within 6 months. We will spend another 3 months writing (and subsequently submitting) the manuscript.

Dissemination Plan:

We expect to have impressive and meaningful results to share with healthcare providers. We plan to submit to a top diabetes or nephrology journal, such as Lancet Diabetes & Endocrinology, Diabetes Care, or Journal of the American Society of Nephrology.

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