Principal Investigator

First Name: Rohan
Last Name: Khera
Degree: MD, MS
Primary Affiliation: Yale School of Medicine
E-mail: rohan.khera@yale.edu
Phone number: 3194006261
Address: 1 Church St Suite 200

City: New Haven
State or Province: Connecticut
Zip or Postal Code: 06510
Country: United States
SCOPUS ID: 55974983700

General Information

Key Personnel (in addition to PI):
First Name: Evangelos
Last name: Oikonomou
Degree: MD, DPhil
Primary Affiliation: Yale-New Haven Hospital
SCOPUS ID: 57217646083

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?: Twitter

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_rkv2.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_eo.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_16.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

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

Research Proposal

Project Title

Exploring heterogeneity in the cardiovascular and renal benefits of canagliflozin in type 2 diabetes mellitus

Narrative Summary:

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of cardiovascular and renal complications (Chatterjee Lancet 2017). Sodium-glucose cotransporter 2 inhibitors, such as canagliflozin, are a relatively novel class of medications that decrease the risk of such complications when compared to placebo. While the benefit and safety profile of these agents has been demonstrated at a population level, understanding these effects at the individual level remains challenging. We hereby propose a posthoc analysis of clinical trial data in order to personalize the expected risk and benefit of prescribing canagliflozin in patients with T2DM.

Scientific Abstract:

Background: Type 2 diabetes mellitus (T2DM) is closely linked to incident cardiovascular and kidney disease. In a series of randomized controlled trials, the sodium-glucose cotransporter 2 inhibitor canagliflozin was shown to decrease the risk of such complications when compared to placebo.
Objective: To individualize the expected cardiovascular and renal benefit of canagliflozin in the management of patients with T2DM.
Study Design: Posthoc observational study involving the original study population of the CANVAS and CANVAS-R trials.
Participants: Patients enrolled in the CANVAS (CANagliflozin cardioVascular Assessment Study, NCT 01032629) and CANVAS-R (CANagliflozin cardioVascular Assessment Study-Renal, NCT01989754) trials.
Main outcome measure(s): Composite of cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke.
Statistical Analysis: Distinct patient phenotypes will be identified using unsupervised clustering approaches based on baseline clinical variables available prior to randomization. Within each cluster and patient neighborhood, personalized risk estimates will be derived using Cox regression models fitted against the time-to-primary outcome and adjusted for age and sex.

Brief Project Background and Statement of Project Significance:

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of cardiovascular and renal complications. In recent clinical trials, sodium-glucose cotransporter 2 inhibitors, such as canagliflozin, have been shown to decrease the rate of such complications when compared to placebo. The landmark CANVAS and CANVAS-R studies (Neal et al. N Engl J Med 2017;377:644-57) enrolled a total of 10,142 participants with type 2 diabetes mellitus and high cardiovascular risk who were randomly assigned to canagliflozin or placebo. Following a mean period of 188 weeks, the incidence of the primary composite endpoint of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke was significantly lower in the canagliflozin compared to the placebo arm, whereas there was also a trend towards improved renal outcomes with canagliflozin treatment. These benefits were partially offset by an increased risk of amputation.
Unfortunately, individualizing the results of a clinical trial for a single patient with a given set of phenotypic characteristics is not a straightforward task. In an effort to explore treatment heterogeneity, several clinical trials report the treatment effect in a priori defined or posthoc analyzed population subgroups, such as different age groups, sex groups and ethnicities. However, these subgroup analyses are often biased either because they are defined as posthoc analyses or because they are selected based on the investigators' assumptions or expectations (Brookes ST et al. J Clin Epidemiol. 2004 Mar;57(3):229-36). In addition, such subgroup analyses do not account for the multitude of a patient's phenotypic traits as well as complex non-linear interaction between such phenotypic parameters.
To better inform patient selection and improving the allocation of an expensive medication, we propose to create a feature space of the CANVAS and CANVAS-R trials that will permit the extraction of treatment effects on individuals with comparable phenotypic features. To this end, our method will use the baseline phenotypic traits collected as part of a randomized controlled trial in order to project the trial population into an n-dimensional

embedding. Using that embedding, we will seek to identify clusters of phenotypically similar patients and therefore link different combinations of phenotypic traits to the cardiovascular/renal benefit and harm seen with the use of canagliflozin in the management of T2DM.

Specific Aims of the Project:

- To identify distinct phenogroups of T2DM patients that seem to benefit most from the use of canagliflozin as compared to placebo with regards to
o The risk of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke
o The risk of albuminuria progression or reduction in estimated glomerular filtration rate
o Improvement in glycemic control and beta-cell function
o Risk of adverse events, including non-traumatic amputations
- To create treatment effect phenomaps for canagliflozin in the management of type 2 diabetes mellitus

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:

YODA repository of individual patient data for the CANVAS (CANagliflozin cardioVascular Assessment Study, NCT 01032629) and CANVAS-R (CANagliflozin cardioVascular Assessment Study-Renal, NCT01989754) trials.

Inclusion/exclusion criteria
Participant inclusion criteria: all patients included in the original studies
Participant exclusion criteria: No systematic exclusions. In certain analyses patients who did not undergo treatment as per the study-specific protocol will be excluded.

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

Hazard ratio (HR) for a composite endpoint (major adverse cardiovascular events [MACE] including CV death, nonfatal myocardial infarction (MI), or nonfatal stroke). The definition of the composite endpoint, as well as the individual endpoints, will be consistent with the one used in the original trials (Neal et al. N Engl J Med 2017;377:644-57).

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

The predictors will represent the set of baseline patient characteristics defining the study population and will be used to define phenogroups of patients.
These include characteristics presented in Table 1 of the CANVAS trial publication (N Engl J Med 2017;377:644-57) and include age, sex, race (white/black/Asian), current smoker status, hypertension, heart failure, duration of diabetes, history of retinopathy, nephropathy or neuropathy, history of atherosclerotic cardiovascular disease, history of amputation, blood pressure (systolic and diastolic), glycated hemoglobin at baseline, lipid panel, baseline glomerular filtration rate, albumin-to-creatinine ratio.

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

- Additional outcome variables: hospitalization for any cause, hospitalization for heart failure, death from any cause, the progression of albuminuria, 40% reduction in eGFR (estimated glomerular filtration rate), renal-replacement therapy, renal death, amputation
- ALL variables will be defined according to the respective definition used in the original trials (Neal et al. N Engl J Med 2017;377:644-57).

Statistical Analysis Plan:

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

Missing variables will be imputed using chained random forests and other multiple imputation strategies, as appropriate. Following imputation, continuous variables will be transformed into standardized scores (z-scores) by subtracting the mean and dividing by the standard deviation. Next, a dissimilarity index will be computed that classifies individuals based on their detailed clinical characteristics. For each patient included in the analysis we will identify a topological neighborhood consisting of the most phenotypically similar participants. Within each patient-centered neighborhood, we will explore the treatment effect of canagliflozin using age- and sex-adjusted Cox regression analysis for the primary outcome measure of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. The level of significance will be set at 0.05.

Additional analyses are being requested in this project - we need to report validation in CANVAS-R using an at-randomization approach - i.e. applying the phenomap-derived tool from CANVAS at the time of enrollment to evaluate whether the validation holds in identifying not only high-responders (as had been proposed above), but also high-responders truly had a measurable shortened time in the trial. This is a critical validation to ensure that we replicate the real-world implementation of our algorithm where the entirety of the patient's treatment course will not be known at enrollment.
Software Used:
RStudio
Project Timeline:

Anticipated project start date: February 2021
Anticipated analysis completion date: August 2021
Anticipated date for manuscript drafting: October 2021
Anticipated date for reporting results back to the YODA project: January 2022

Dissemination Plan:

We would aim to submit the results of our work to national meetings, such as the American Heart Association Scientific Sessions. The final manuscript will also be submitted for publication to a peer-review journal, such as Circulation, Journal of American College of Cardiology or a JAMA family journal.

Bibliography:

Brookes ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol. 2004 Mar;57(3):229–36.

Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet. 2017 Jun 3;389(10085):2239–51.

Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017 Aug 17;377(7):644–57.