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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?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/03/CoI_Sacre.pdf
https://yoda.yale.edu/wp-content/uploads/2024/03/CoI_Shaw.pdf
https://yoda.yale.edu/wp-content/uploads/2024/03/CoI_Salim.pdf
https://yoda.yale.edu/wp-content/uploads/2024/03/CoI_Gerstein.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

Validation of a novel clinical risk score for cardiovascular outcomes in type 2 diabetes

Narrative Summary:

There are many clinical risk scores available to predict a range of cardiovascular (CV) events (eg stroke, heart failure, CV death). However, it is difficult to compare the risks of each of these events in any one individual, given available risk scores were developed and validated using different methods and different study populations. We have developed a new score that provides directly comparable risks of two key outcomes in type 2 diabetes: "MACE" (major adverse CV events; i.e. heart attack, stroke, or CV death), and "HHF or CV death" (i.e. heart failure hospitalisation or CV death). This tool is aimed at identifying who may be most at risk of one outcome or the other, so as to better individualise treatment. The proposed study will test how well this risk score performs in external cohorts.

Scientific Abstract:

Background: A cardiovascular (CV) risk score with the capacity to provide comparable discrimination of both major adverse CV event (MACE) and heart failure hospitalisation/CV death (HHF) risks in type 2 diabetes may help guide therapy. We have developed a new CV risk score for this purpose, and now seek to undertake external validation using the CANVAS and CREDENCE trials.
Objective: To validate a CV risk score that includes clinical prediction models for both MACE and ‘HHF or CV death’ outcomes. Secondarily, we aim to examine the effects of canagliflozin on CV outcomes across risk groups defined according to this new score.
Study design: Observational study of the CANVAS and CREDENCE trial participants. We will also undertake post-hoc analyses of canagliflozin effects across risk score subgroups.
Participants: People with type 2 diabetes in the CANVAS and CREDENCE trials.
Primary and Secondary Outcome Measures: MACE (composite of myocardial infarction (MI), stroke or CV death) and ‘HHF or CV death’ represent the primary outcomes. CV outcomes will also be analysed individually (MI, stroke, CV death and HHF).
Statistical Analysis: Predicted risks of MACE and ‘HHF or CV death’ according to our risk score will be calculated for individuals in CANVAS and CREDENCE. Harrell’s C-index will be used to assess discrimination of the prediction models for each of MACE and HHF/CV death. Calibration quality will be assessed by comparing observed vs. predicted event rates. Cox regression with an interaction term will be used to assess canaglifozin effects across different risk groups.

Brief Project Background and Statement of Project Significance:

The efficacy of new type 2 diabetes therapies such as SGLT2 inhibitors and GLP-1 receptor agonists for reducing cardiovascular (CV) events has raised questions about how to identify individuals most likely to benefit from these treatments (1). Fundamental to this issue is the need for accurate discrimination of CV risk. Most CV risk scores target prediction of a specific event type (mostly atherosclerotic), even if it is a composite outcome such as MACE (i.e. first of myocardial infarction [MI], stroke, or CV death) (e.g. SCORE2-Diabetes [2]). However, this traditional approach overlooks other major CV events such as hospitalisation for heart failure (HHF), which we have reported is the second-most frequent non-fatal CV event in type 2 diabetes (3).
Using data from other CV outcomes trials in type 2 diabetes (REWIND [4] and ORIGIN [5]), we have developed and partially validated a new tool that offers multi-outcome risk prediction; i.e. risk estimates for MACE and 'HHF or CV death' outcomes that may be directly compared by virtue of the underlying prediction models reflecting the same methods and arising from the same derivation cohort. In line with existing risk scores, the prediction models use readily available clinical parameters (age, sex, CV disease history, traditional CV risk factors [e.g. blood pressure, lipids], and kidney disease markers) to predict risks of each outcome. The potential for outcome differentiation (e.g. higher risk of MACE compared with 'HHF or CV death' [or vice versa]) despite shared risk factors (e.g. age) arises from differences in the strength of associations of each CV outcome with each individual risk factor – a concept that aligns with our previous observations from aggregated CV outcomes trial data (6).
Our tool has shown good discrimination of CV outcomes in the training cohort (C-indices >0.65 for both MACE and HHF/CV death), and importantly, also demonstrated the capacity for divergence of MACE and HHF/CV death risk at an individual level; i.e. estimated risks of these outcomes may be similar, or may vary, depending on the clinical profile. We now need to test the performance of these risk prediction models in external validation datasets.
The CANVAS (7) and CREDENCE (8) trials are ideal for this purpose given they are CV outcomes trials in type 2 diabetes with the same high quality adjudicated MACE and HHF/CV death outcomes. In the CANVAS Program, ~70% of participants had prior CVD and ~15% had prior heart failure, which provides an appropriately broad spectrum of CV risk. Moreover, CREDENCE offers the opportunity to validate the prediction models in the setting of diabetic nephropathy.

Specific Aims of the Project:

The primary purpose of this project is to validate our prediction models in external cohorts of people with type 2 diabetes (including tests of both discrimination and calibration). We will further examine the distributions of predicted risks of the CV outcomes in the validation cohorts, and identify/characterise subgroups of individuals based on their predicted risk profiles. Potential heterogeneity of canagliflozin efficacy across the distributions of predicted CV risks will also be assessed with respect to CV outcomes.

Study Design:

Other

Study Design Explanation:

Observational analysis and individual trial analyses

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 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:

The trials requested (CANVAS Program [7]; CREDENCE [8]) were selected in part due to their eligibility criteria aligning with the required patient sample (i.e. people with type 2 diabetes). Beyond the inclusion/exclusion criteria of the trials, we will primarily seek to validate the prediction models among participants randomised to placebo (due to the known efficacy of the active treatment for reduction of CV outcomes, particularly HHF). We will also restrict the primary validation cohort to those participants who were not concurrently treated with either SGLT2 inhibitor or GLP-1 receptor agonist medications (at baseline, or in-trial drop-in).

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

The primary outcomes measures are:
- MACE (i.e. composite of nonfatal myocardial infarction, nonfatal stroke, or CV death)
- Hospitalisation for heart failure (HHF) or CV death

Secondary outcomes include:
- HHF
- MI
- Stroke
- CV death

Definitions of each of these will be in line with the protocols of the requested trials, and reported in the existing trial publications. Dates of CV events will be required in addition to binary (yes/no) indicators of events.

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

Our models were developed by selecting predictors substantively contributing to risk discrimination from a broad range of readily available demographic/clinical variables, including: baseline age, sex, race, CV disease history (prior myocardial infarction, prior stroke, prior heart failure, prior peripheral artery disease, prior atrial fibrillation, prior coronary revascularisation, prior peripheral revascularisation), traditional CV risk factors (smoking, BMI, blood pressure, hypertension history, lipid panel), diabetes-specific factors (HbA1c, diabetes duration, insulin use, history of microvascular complications [including retinopathy, nephropathy]), and markers of chronic kidney disease (eGFR, urine albumin-creatinine ratio). Definitions of predictors will align with existing trial publications (Table 1 of primary CANVAS and CREDENCE publications), though unit conversions and transformations will be performed as required (e.g. mg/g to mg/mmol).

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

We will also consider concurrent medications (diabetes, antihypertensive, lipid-lowering, and others), and other available medical history variables. In terms of outcomes, we will also explore a global composite CV outcome (MACE or HHF), death due to non-cardiovascular causes; all-cause death; hospitalisation for unstable angina; and hospitalisation for any cause.

Statistical Analysis Plan:

To validate our prediction models, we will first apply any necessary data transformations and centering, to ensure the definition of predictor variables in the validation dataset align with those used in the training cohort. We will then calculate the predicted risks of the relevant CV outcomes for each individual in the CANVAS/CREDENCE validation cohorts, using the coefficients from our existing prediction models. Absolute predicted risks (i.e. probability of event) will be calculated according to the standard Cox proportional hazards formula, based on baseline survival rates from the derivation cohort. Discrimination of the prediction models in the validation datasets will be based on Harrell's C-

index (Cox regression post-estimation test). Calibration will be assessed by comparing predicted vs. observed event rates (visually via calibration plots, and via formal tests such as Greenwood–Nam–D'Agostino). Scaling factors will be derived if recalibration appears necessary (e.g. we might expect the need for recalibration in people with diabetes and nephropathy based on the CREDENCE validation).
Discrimination and calibration will also be assessed within relevant subgroups (e.g. prior CV disease vs. no prior CV disease, prior heart failure vs. no prior heart failure). To verify the specificity of individual prediction models for their intended outcome, validation tests will be performed across all CV outcomes for each outcome-specific prediction model.
The distributions of predicted CV outcome risks will be examined with histograms and other relevant plots, and will inform the creation of risk score strata; i.e. participants will be grouped into “low” and “high” MACE and HHF/CV death risk groupings. It can be expected that some participants will be classified at similarly low or high risk of each outcome, while others will demonstrate a mismatch in predicted risk; i.e. a combination of higher MACE / lower HHF risk, or vice versa. The effects of canagliflozin on CV outcomes across risk groups will be compared by including an interaction term (i.e. interaction of risk group and treatment assignment) in a Cox model, and deriving subgroup-level hazard ratios and their corresponding 95% CIs. Absolute risk reduction within subgroups will also be calculated. Incidence rates of CV outcomes (n, N, and rate per 1000 person-years) across risk strata will also be reported.
With respect to descriptive statistics, continuous variables will be reported as mean +/- standard deviation or median (interquartile range), as appropriate for the distribution. Categorical variables will be reported as n (%).

Software Used:

RStudio

Project Timeline:

Assuming a project start date in May 2024, we would allow up to 6 months for all analyses (Nov 2024). As more than one manuscript may be expected from this project, we would aim for Aug 2024 for an initial manuscript submission, and Jan 2025 for a final manuscript (and reporting of results back to YODA).

Dissemination Plan:

We will target leading diabetes and/or cardiovascular journals for manuscript publication (two manuscripts expected). We will also disseminate the findings via conference abstract submissions (e.g. American Diabetes Association [ADA] or European Association for the Study of Diabetes [EASD] meetings).

Bibliography:

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