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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?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_15.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_ms.pdf
https://yoda.yale.edu/system/files/yoda_tcopeland.pdf
https://yoda.yale.edu/system/files/2020.12.28_-_couture_yoda_coi.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. NCT01106625 - 28431754DIA3002 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sulphonylurea Therapy
2. NCT01106677 - 28431754DIA3006 - A Randomized, Double-Blind, Placebo and Active-Controlled, 4-Arm, Parallel Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Monotherapy
3. NCT00968812 - 28431754DIA3009 - A Randomized, Double-Blind, 3-Arm Parallel-Group, 2-Year (104-Week), Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 Compared With Glimepiride in the Treatment of Subjects With Type 2 Diabetes Mellitus Not Optimally Controlled on Metformin Monotherapy
4. NCT01106651 - 28431754DIA3010 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus Inadequately Controlled on Glucose Lowering Therapy
5. NCT01809327 - 28431754DIA3011 - A Randomized, Double-Blind, 5-Arm, Parallel-Group, 26-Week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in Combination With Metformin as Initial Combination Therapy in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control With Diet and Exercise
6. 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
7. 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

Examination of implications of acute declines in kidney function with SGLTII inhibitors

Narrative Summary:

The goal of this proposal is to examine whether acute changes in kidney function during the initiation of SGLTII inhibitors impacts the response to therapy and long-term kidney and cardiovascular outcomes.

Scientific Abstract:

Background: Acute declines in kidney function occur with many interventions that may improve outcomes.
Objective: The goal of this study is to compare the declines in kidney function observed with SGLT II inhibition to that observed with renin-angiotensin system (RAS) inhibitors, and to understand whether the magnitude of the decline is associated with cardiovascular or kidney outcomes.
Study design: Retrospective cohort study.

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Participants: Prior Invokana trial enrollees.
Main outcomes: End-Stage Kidney disease, 50% decline in kidney function, or cardiovascular (CV) events.
Statistical analysis: We will use cox models to associate acute declines in kidney function with end-stage kidney disease (ESKD) and cardiovascular (CV) events by randomization arm assignment (SGLT II inhibitors versus placebo), thus examining the presence of interaction between acute declines in kidney function and randomization arm. We will compare this to observed changes with RAS inhibitors.

Brief Project Background and Statement of Project Significance:

Chronic kidney disease (CKD) is associated with significant morbidity and mortality: Medicare spent 98 billion dollars for CKD care in 2017. To date, the two interventions that have been shown to improve cardiovascular disease (CVD) risk or slow the progression of CKD are use of SGLT II inhibitors or use of renin-angiotensin system (RAS) blockers. However, during both interventions, acute declines in estimated glomerular filtration rate (eGFR) occur in the majority of patients, especially if baseline CKD is present. Traditionally, these acute declines in kidney function (e.g. serum creatinine increases of up to 30% during RAS blockade) have been thought to be benign, reversible, and not associated with long-term sequelae, but more recent studies have questioned whether even smaller changes in kidney function during these interventions could be associated with long-term kidney or CV risk. Few studies have systematically quantified the magnitude of acute decline in eGFR during SGLT II inhibition and determined if there is a threshold that may be associated with higher risk of adverse renal or CVD outcomes in patients with underlying chronic kidney disease (stage II or above). Our objective is to determine the long-term kidney and CV implications of the acute changes in eGFR during SGLTII inhibitor therapy. We will compare these changes to the changes observed with RAAS inhibition (we are conducting a large meta-analysis of > 10 trials with this issue).

Specific Aims of the Project:

Aim 1: To examine whether acute declines in kidney function with SGLT II inhibition are associated with higher risk of ESKD.
Hypothesis: The acute declines in kidney function observed with SGLT II inhibition will not modify the effect of SGLT II inhibitors on kidney outcomes.
Aim 2: To examine whether acute declines in kidney function with SGLT II inhibition are associated with higher risk of CVD.
Hypothesis: The acute declines in kidney function observed with SGLT II inhibition will not modify the effect of SGLT II inhibitors on cardiovascular disease outcomes.

What is the purpose of the analysis being proposed? Please select all that apply.
Confirm or validate previously conducted research on treatment effectiveness
Confirm or validate previously conducted research on treatment safety
Participant-level data meta-analysis
Participant-level data meta-analysis using only data from YODA Project

Research Methods

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

Inclusion criteria. All participants of INVOKANA trials who have repeated measures of kidney function during the first year of study and long-term follow-up for outcomes.
Exclusion criteria. Participants who dropped out prior to a second visit where a second measurement of kidney function was obtained.

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

The main outcomes will be
End-Stage kidney disease (defined as onset of dialysis or kidney transplant needs)
50% Decline in kidney function (Starting from after the acute decline in kidney function occurred)
Cardiovascular events (heart failure, myocardial infarction, stroke, peripheral arterial disease or death)

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

The main predictor will be change in kidney function between randomization and whichever visit is closest to three months following randomization. We will compute the eGFR and the percent change in kidney function during this period.

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

Covariates will include age, sex, race/ethnicity, baseline kidney function, baseline levels of albuminuria, hemoglobin A1C

Statistical Analysis Plan:

We will use adjusted Cox models and include interaction terms between treatment arm assignment (e.g. SGLT II inhibitor versus comparator arms) and acute changes in eGFR (either as a continuous predictor or by categor(ies) of change to predict ESKD risk, accounting for the covariates described in Section B1.3 and adding a stratification variable for trial data source. Death from any cause will be treated as a censoring event, although in sensitivity analysis we will also use Fine-Gray models and treat death as a competing event for the outcome of ESKD and account for factors that may lead to informative censoring using inverse probability weighting. We will use the same approach for the risk of CV for each intervention. A p-value <0.05 will be considered statistically significant interaction.
Software Used:
STATA
Project Timeline:

Project start date: January 1, 2021
Analysis completion date: December 1, 2021
Manuscript drafting June 30, 2022
Data report back: June 30, 22

Dissemination Plan:

We plan to submit our publication to JASN or similar journal

Bibliography:

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7. Ku E, Bakris G, Johansen KL, Lin F, Sarnak MJ, Campese VM, Jamerson K, Gassman JJ, Smogorzewski M, Hsu CY. Acute Declines in Renal Function during Intensive BP Lowering: Implications for Future ESRD Risk. Journal of the American Society of Nephrology : JASN. 2017;28(9):2794-801. doi: 10.1681/ASN.2017010040. PubMed PMID: 28473636.
8. Ku E, Ix JH, Jamerson K, Tangri N, Lin F, Gassman J, Smogorzewski M, Sarnak MJ. Acute Declines in Renal Function during Intensive BP Lowering and Long-Term Risk of Death. Journal of the American Society of Nephrology : JASN. 2018. Epub 2018/07/15. doi: 10.1681/asn.2018040365. PubMed PMID: 30006417.
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