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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?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2026/06/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. 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

Research Proposal

Project Title

Glomerular Hyperfiltration, Cardiorenal Risk, and Response to SGLT2 Inhibition in Type 2 Diabetes

Narrative Summary:

People with type 2 diabetes may have abnormally high kidney filtration early in the course of kidney disease, a condition named glomerular hyperfiltration. This study will use participant-level data from the CANVAS Program trials to test whether high estimated glomerular filtration rate (eGFR), used as

a practical marker of glomerular hyperfiltration, identifies participants at increased risk of cardiorenal disease. We will also assess whether the SGLT2 inhibitor canagliflozin reduces cardiovascular, heart failure, kidney, albuminuria, and mortality outcomes in this subgroup. The results may clarify whether high eGFR is an early, clinically useful marker of cardiorenal vulnerability and may inform earlier risk stratification and treatment with SGLT2 inhibitors.

Scientific Abstract:

Background: Glomerular hyperfiltration is an early renal hemodynamic phenotype in diabetes, but its prognostic and therapeutic implications remain uncertain.

Objective: To determine whether high age- and sex-specific eGFR identifies CANVAS Program participants with type 2 diabetes at increased cardiorenal risk and whether canagliflozin modifies this risk.

Study Design: Post-hoc participant-level integrated analysis of the randomized, double-blind, placebo-controlled CANVAS and CANVAS-R trials.

Participants: Participants with type 2 diabetes, elevated cardiovascular risk, baseline eGFR >=30 mL/min/1.73 m2, and available baseline kidney-function and outcome data from the CANVAS Program.

Primary and Secondary Outcome Measures: Primary cardiovascular outcome: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Primary heart failure outcome: hospitalization for heart failure. Primary kidney outcome: sustained 40% eGFR reduction, renal-replacement therapy, or renal death. Secondary outcomes include cardiovascular death or heart-failure hospitalization, albuminuria progression, broader kidney composites, and all-cause death.

Statistical Analysis: Participants will be classified as high, normal, or low eGFR using prespecified age- and sex-specific criteria. Cox models will estimate prognostic associations among placebo-treated participants and canagliflozin effects within and across eGFR strata, with prespecified covariate adjustment and interaction testing.

Brief Project Background and Statement of Project Significance:

Cardiovascular and kidney complications remain major causes of morbidity and mortality in type 2 diabetes [1,2]. Glomerular hyperfiltration is increasingly recognized as an early diabetic kidney phenotype reflecting increased single-nephron filtration, increased intraglomerular pressure, enhanced proximal tubular sodium and glucose reabsorption, altered tubuloglomerular feedback, and metabolic stress [3,4]. Despite biological plausibility, its clinical interpretation remains uncertain because definitions vary, measured GFR is rarely available, and high creatinine-based eGFR may be overlooked as apparently preserved kidney function [5,6].

Prior work from the proponent's group supports the clinical relevance of hyperfiltration. In a 21-year longitudinal cohort with measured GFR, glomerular hyperfiltration predicted kidney function decline and mortality in type 1 and type 2 diabetes [7]. In a population-based study of adults with type 2 diabetes, this group also showed that hyperfiltration is a measurable contemporary phenotype with identifiable clinical correlates [8]. These observations justify evaluation of hyperfiltration in large randomized trial datasets with adjudicated cardiovascular and renal outcomes.

SGLT2 inhibitors are mechanistically relevant because they reduce proximal tubular glucose and sodium reabsorption, increase sodium delivery to the macula densa, restore tubuloglomerular feedback, and reduce intraglomerular pressure [9,10]. In the CANVAS Program, canagliflozin reduced major cardiovascular events and improved kidney outcomes in participants with type 2 diabetes at high cardiovascular risk [11,12]. However, it is not established whether participants with high baseline eGFR are at increased cardiovascular, heart-failure or kidney risk, nor whether this early

hemodynamic phenotype identifies a subgroup with meaningful benefit from SGLT2 inhibition.

This project will materially enhance generalizable scientific and medical knowledge by clarifying whether high eGFR is a useful early cardiorenal risk marker in a large randomized trial population and by assessing the effect of canagliflozin in that subgroup. Findings will support hypothesis generation for earlier identification of high-risk patients, improve interpretation of high eGFR in diabetes care, and provide a rationale for prospective studies of hyperfiltration-guided SGLT2 inhibitor therapy.

Specific Aims of the Project:

Aim 1: To determine whether baseline high eGFR, defined using age- and sex-specific criteria and used as a pragmatic marker of glomerular hyperfiltration, is associated with subsequent cardiovascular, heart-failure, kidney, albuminuria, and mortality outcomes among placebo-treated CANVAS Program participants.
Hypothesis 1: Compared with normal eGFR, high eGFR will be associated with higher risks of cardiovascular disease, hospitalization for heart failure, kidney disease progression, and mortality, independent of baseline clinical risk factors.

Aim 2: To estimate the effect of canagliflozin versus placebo on cardiovascular, heart-failure, kidney, albuminuria, and mortality outcomes among participants with high baseline eGFR.
Hypothesis 2: Canagliflozin will reduce cardiorenal outcomes among participants with high baseline eGFR.

Aim 3: To assess whether relative treatment effects of canagliflozin differ across high, normal, and low eGFR strata, and to explore clinically relevant subgroups within the high-eGFR stratum.
Hypothesis 3: Treatment effects may be numerically greater in the high-eGFR stratum, but interaction analyses will be interpreted as exploratory.

Study Design:

Meta-analysis (analysis of multiple trials together)

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

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

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:

Data source: Participant-level data and supporting documentation for the CANVAS Program trials requested through the YODA Project: CANVAS and CANVAS-R. No external participant-level datasets will be pooled with YODA data.

Parent trial population: The CANVAS Program enrolled participants with type 2 diabetes, inadequate glycemic control, and established cardiovascular disease or elevated cardiovascular risk. Eligible participants had HbA1c 7.0-10.5% and were either aged >=30 years with established atherosclerotic cardiovascular disease or aged >=50 years with at least two cardiovascular risk factors. Participants

were required to have baseline eGFR >=30 mL/min/1.73 m2.

Study sample for this analysis: Randomized CANVAS or CANVAS-R participants with available baseline serum creatinine/eGFR, age, sex, treatment assignment, follow-up time, and outcome data required for the planned analyses.

Exclusion criteria for this analysis: missing baseline kidney-function data needed to define eGFR strata; missing age or sex required for age- and sex-specific eGFR classification; missing treatment assignment; no follow-up time or no ascertainable outcome status for the endpoint under analysis. For albuminuria-progression analyses, participants with baseline macroalbuminuria will be excluded, consistent with analyses restricted to participants eligible to progress from normoalbuminuria or microalbuminuria.

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

Primary outcome measures:
- Primary cardiovascular composite: time from randomization to first cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.
- Primary heart failure outcome: time from randomization to first hospitalization for heart failure.
- Primary kidney composite: time from randomization to first sustained 40% reduction in eGFR, renal-replacement therapy, or death from renal causes.

Secondary outcome measures:
- Individual cardiovascular components: cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.
- Composite of cardiovascular death or hospitalization for heart failure.
- Individual kidney endpoints: sustained 40% reduction in eGFR; renal-replacement therapy or renal death; doubling of serum creatinine.
- Progression of albuminuria, assessed among participants with normoalbuminuria or microalbuminuria at baseline and defined as worsening albuminuria category accompanied by an increase in urinary albumin-to-creatinine ratio, consistent with CANVAS Program renal analyses.
- Broader kidney composite including sustained 40% eGFR reduction, renal-replacement therapy, albuminuria progression, or renal death.
- Death from any cause.

All outcomes will be time-to-first-event outcomes unless specified otherwise. Endpoint definitions will be aligned with CANVAS Program adjudication and data documentation.

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

The main prognostic independent variable is baseline eGFR group. Baseline eGFR will be defined using the CANVAS Program creatinine-based method, expected to be the MDRD equation, expressed in mL/min/1.73 m2.

Primary eGFR categories:
- High eGFR: eGFR above the 90th age- and sex-specific percentile, used as a pragmatic marker of glomerular hyperfiltration.
- Low eGFR: eGFR below the 10th age- and sex-specific percentile or below 60 mL/min/1.73 m2.
- Normal eGFR: all participants not meeting high- or low-eGFR criteria.

The main randomized treatment independent variable is treatment assignment to canagliflozin versus placebo. In CANVAS, canagliflozin 100 mg and 300 mg groups will be combined; in CANVAS-R, canagliflozin 100 mg with optional uptitration will be analyzed as canagliflozin.

For treatment-effect heterogeneity, the key independent variable will be the treatment-by-eGFR-group interaction. Within high eGFR, exploratory treatment-by-subgroup interactions will be

evaluated for prespecified clinical characteristics.

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

Variables used to describe the cohort and for prespecified multivariable adjustment will include: age; sex; race/ethnicity as available in the trial dataset; body mass index; systolic and diastolic blood pressure; smoking status; duration of diabetes; HbA1c; baseline eGFR; urinary albumin-to-creatinine ratio; albuminuria category; history of cardiovascular disease; history of heart failure; and baseline medication use.

Albuminuria categories will be defined using urinary albumin-to-creatinine ratio: normoalbuminuria 300 mg/g. Baseline medication variables will include metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, thiazolidinediones, insulin, renin-angiotensin-aldosterone system inhibitors, diuretics, beta blockers, calcium-channel blockers, statins, fibrates, and antithrombotic agents, as available.

Subgroup variables will be prespecified and categorized as follows where data allow: age >=65 years; sex; race categories as reported; BMI >=30 kg/m2; blood pressure controlled versus uncontrolled using SBP >=140 and DBP >=90 mmHg; diabetes duration >=10 years; HbA1c >=8%; albuminuria present versus absent; history of cardiovascular disease; history of heart failure; baseline RAAS inhibitor use; diuretic use; statin use; beta-blocker use; antithrombotic use; and insulin use. Categories may be harmonized with the CANVAS data dictionary if variable coding differs.

Statistical Analysis Plan:

Baseline eGFR will be calculated or extracted according to the CANVAS Program method using serum creatinine and the MDRD equation. Participants will be classified into high, normal, and low eGFR groups using prespecified age- and sex-specific percentiles. HighGFR will be defined as eGFR above the 90th age- and sex-specific percentile. LowGFR will be defined as eGFR below the 10th age- and sex-specific percentile or below 60 mL/min/1.73 m2. NormGFR will include all remaining participants.

Baseline characteristics will be summarized by eGFR group in the overall population and by treatment allocation within each eGFR group. Continuous variables will be reported as mean with SD or median with IQR, as appropriate, and categorical variables will be reported as counts and percentages. Between-group differences will be assessed using ANOVA, Kruskal-Wallis tests, or χ^2 tests, as appropriate. Pairwise comparisons will be adjusted using Bonferroni correction.

We will first evaluate the prognostic significance of HighGFR by restricting analyses to placebo-treated participants. Event rates will be calculated per 1000 patient-years. Hazard ratios and 95% CIs will be estimated using Cox proportional-hazards models, with NormGFR as the primary reference group. We will also compare HighGFR with LowGFR to contextualize the risk associated with high eGFR relative to established reduced kidney function. Multivariable Cox models will be adjusted for clinically relevant baseline covariates selected a priori: age, sex, race, body-mass index (BMI), systolic blood pressure, smoking, diabetes duration, glycated hemoglobin, albuminuria, history of cardiovascular disease, history of heart failure, use of renin-angiotensin-aldosterone system (RAAS) inhibitors, statin use, or antithrombotic treatment.

We will then assess the effect of canagliflozin versus placebo within the HighGFR group. Cox proportional-hazards models will be used to estimate hazard ratios and 95% CIs for cardiovascular, heart failure, kidney, albuminuria, and mortality outcomes. Adjusted treatment-effect models will use the same baseline covariates as the prognostic models. To evaluate whether the effect of canagliflozin differs across baseline eGFR groups, we will fit models including treatment assignment, eGFR group, and a treatment-by-eGFR group interaction term.

We will perform exploratory subgroup analyses within the HighGFR group for clinically relevant baseline characteristics, including age, sex, race, BMI, blood pressure control, diabetes duration,

glycated hemoglobin, albuminuria, history of cardiovascular disease, history of heart failure, RAAS inhibitor use, diuretic use, statin use, beta-blocker use, antithrombotic treatment, and insulin use. Treatment heterogeneity across subgroups will be assessed by inclusion of treatment-by-subgroup interaction terms. These subgroup and interaction analyses will be considered exploratory.

Sensitivity analyses: If data allow, sensitivity analyses will test alternative high-eGFR definitions, including eGFR above the 95th age- and sex-specific percentile and/or absolute eGFR thresholds, and will assess whether findings are consistent after excluding participants with very short follow-up. Additional sensitivity analyses may evaluate trial indicator adjustment for CANVAS versus CANVAS-R or stratification by trial if required by the integrated dataset structure.

Software Used:

R, STATA

Project Timeline:

Month 0-2: YODA approval, Data Use Agreement execution, and secure-platform access.

Months 2-3: Review clinical study reports, data dictionaries, and dataset structure; finalize executable analysis code and outcome-variable mapping. Construct analytic cohorts, define eGFR strata, validate baseline tables, and complete Aim 1 prognostic analyses.

Months 3-5: Complete Aim 2 treatment-effect analyses and Aim 3 interaction/subgroup analyses; run diagnostics and sensitivity analyses.

Months 5-6: Internal review of outputs, table and figure preparation, and interpretation. Draft manuscript and circulate among coauthors. Submit manuscript to a peer-reviewed journal.

Months 8-12: Report results back to the YODA Project and prepare any requested public summary materials

Dissemination Plan:

The principal product will be a full-length peer-reviewed manuscript reporting the prognostic significance of high eGFR and the effect of canagliflozin in this phenotype using CANVAS Program participant-level data. Target audiences include diabetologists, nephrologists, cardiologists, clinical trialists, and guideline developers interested in early cardiorenal risk stratification and SGLT2 inhibitor therapy.

Results may also be presented at scientific meetings in diabetes, nephrology, and cardiometabolic medicine, subject to YODA and data-holder publication requirements.

All dissemination will acknowledge the YODA Project and comply with the Data Use Agreement.

Results will be reported back to the YODA Project within the approved access period.

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