

Principal Investigator

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General Information

Key Personnel (other than PI):

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SCOPUS ID:

Requires Data Access? Yes

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?: Other

Conflict of Interest

<https://yoda.yale.edu/wp-content/uploads/2025/01/COI-JPF-1.pdf>

<https://yoda.yale.edu/wp-content/uploads/2025/01/COI-PM-1.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](#)
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

Sodium-glucose co-transporter 2 inhibitors induced polycythemia and risk of cardiovascular events

Narrative Summary:

Sodium glucose co-transporter 2 inhibitors (SGLT2i) increase urinary sodium ("salt") and glucose ("sugar") excretion and have proven beneficial effects in heart failure, type 2 diabetes and chronic kidney disease. SGLT2i stimulate the production of red blood cells. While this is salutary in conditions like anemia, among patients with a predisposition for elevated red blood cell counts e.g., smokers or patients with lung diseases, SGLT2i may cause abnormal red blood cells elevation, named "polycythemia". We aim to study those who develop polycythemia under SGLT2i treatment, the associated risk factors and whether the presence of polycythemia increases the risk of cardiovascular events.

Scientific Abstract:

Background: Sodium-glucose co-transporter 2 inhibitors (SGLT2i) use is associated with increased hemoglobin and hematocrit levels, with some patients developing polycythemia. The clinical implications of SGLT2i-associated polycythemia remain unclear, notably its impact on the risk of thromboembolic events.

Objective: To study the proportion of patients who develop polycythemia under SGLT2i treatment, identify risk factors for SGLT2i-induced polycythemia and whether the presence of polycythemia increases the risk of cardiovascular events.

Study Design/Participants: Individual participant data (IPD) meta-analysis using data from the EMPA REG OUTCOME, EMPEROR Program, CREDENCE and CANVAS trials.

Primary and Secondary Outcome Measure(s): The primary outcome will focus on the effect of polycythemia on composite outcome of cardiovascular death or heart failure hospitalization. Secondary outcomes will include the individual components of the primary outcome and the association between polycythemia and the incidence of myocardial infarction, ischemic stroke and venous thromboembolic diseases including pulmonary embolism.

Statistical Analysis: Stepwise Cox regression models will be used to study the associations between patient's characteristics and new-onset polycythemia throughout the follow-up and time-varying Cox regression models will be used to study the associations between polycythemia and outcomes.

Brief Project Background and Statement of Project Significance:

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) primarily act by blocking the reabsorption of glucose and sodium mediated by the SGLT2 transporter in the epithelial cells of the proximal renal tubule (1). Beyond their natriuretic and glycosuric properties, SGLT2i use (versus non-use) is associated with significant increases in hemoglobin and hematocrit, effects that have emerged as key statistical mediators of the cardiorenal benefits observed with SGLT2i therapy (2). The underlying mechanisms of SGLT2i-induced erythrocytosis include enhanced iron mobilization and utilization, driven by upregulation of the erythropoietin-erythroferrone-transferrin receptor protein 1 (TfR1) axis. Interestingly, data from randomized clinical trials (RCTs) indicate that these hematologic effects occur independently of baseline hemoglobin or hematocrit levels and are observed regardless of the presence or absence of anemia. As a result, polycythemia, defined as a hematocrit $\geq 49\%$ in men and $\geq 48\%$ in women, was reported in up to 6% of empagliflozin-treated patients in the EMPEROR-Reduced trial (3).

The clinical implications of SGLT2i-associated polycythemia remain unclear. Unlike the increased thromboembolic risk associated with erythropoiesis-stimulating agents (ESAs) or hypoxia-inducible factor prolyl-hydroxylase inhibitors (HIF-PHIs), trials involving SGLT2i across diverse cardiorenal populations have not shown a signal of increased thromboembolic events. However, individual trials may have been underpowered to detect a significant association between SGLT2i-induced polycythemia and cardiovascular risk, warranting further investigation.

With this in mind, we sought to use data from SGLT2i outcome driven cardiorenal RCTs that collected

data on baseline and follow-up hemoglobin and hematocrit events. We hypothesize that polycythemia following SGLT2i use is consistent across different cardiorenal populations and not associated with an increased risk of thromboembolic events, comparing to those not developing polycythemia. The results of this analysis are clinically relevant as we hypothesize that our analysis will corroborate the safety of SGLT2i in patients with SGLT2i-induced polycythemia will encourage clinicians to continue this agents.

While performing the analysis for the above-referenced project, two additional ideas/hypothesis came to mind. These are:

#1. To study the effects of SGLT2 inhibitors when eGFR drops<25 ml/min during follow-up
Background: Patients with eGFR<25ml/min were excluded from SGLT2 inhibitor trials; however, these patients can experience eGFR drops below 25 ml/min during follow-up.

and #2. To study the effects of SGLT2 inhibitors across the full spectrum of albuminuria
Background: The kidney benefits of SGLT2 inhibitors among patients with low albuminuria are not well-studied.

Specific Aims of the Project:

The main objectives of this study are to:

- # study the proportion of patients who develop polycythemia under SGLT2i treatment
- # identify the risk factors for polycythemia development
- # study whether the presence of polycythemia increases the risk of cardiovascular events including venous thrombotic events
- # assess whether the presence of polycythemia influences the effects of SGLT2 inhibitors

Main hypothesis: We hypothesize that polycythemia following SGLT2i use is consistent across different cardiorenal populations and not associated with an increased risk of thromboembolic events, comparing to those not developing polycythemia.

Additional analysis:

#1 - To study the effects of SGLT2 inhibitors when eGFR drops<25 ml/min during follow-up
Aims: To assess the efficacy of SGLT2 inhibitors when patients experience eGFR drops below 25 ml/min throughout the follow-up.

and #2. To study the effects of SGLT2 inhibitors across the full spectrum of albuminuria
Aims: To assess the efficacy of SGLT2 inhibitors across the full spectrum of albuminuria.

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

New research question to examine treatment safety

Confirm or validate previously conducted research on treatment effectiveness

Confirm or validate previously conducted research on treatment safety

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research Methods

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

Inclusion criteria: All patients with available baseline hemoglobin/hematocrit laboratory results will be included in the requested trials. No other inclusion criteria will be used.

Exclusion criteria: None.

Other studies being used: EMPEROR-Preserved (NCT03057951), EMPEROR-Reduced (NCT03057977), EMPA REG-OUTCOME(NCT01131676)

Data Source: Vivli.

Platform for IPD analysis: STATA

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

Outcomes will include (per study objectives):

1. study the proportion of patients who develop polycythemia under SGLT2i treatment
2. identify the risk factors for polycythemia development
3. study whether the presence of polycythemia increases the risk of cardiovascular events including venous thrombotic events

Primary outcome:

Cardiovascular death or Heart Failure Hospitalizations (no =0; yes =1)

Secondary outcomes:

Cardiovascular death (no =0; yes =1)

Heart failure hospitalization (no =0; yes =1)

Myocardial infarction (no =0; yes =1)

Ischemic stroke (no =0; yes =1)

Deep venous thrombosis including pulmonary embolism (no =0; yes =1)

4. assess whether the presence of polycythemia influences the effects of SGLT2 inhibitors

Primary outcome:

Cardiovascular death or Heart Failure Hospitalizations (no =0; yes =1)

Secondary outcomes:

Cardiovascular death (no =0; yes =1)

Heart failure hospitalization (no =0; yes =1)

Myocardial infarction (no =0; yes =1)

Ischemic stroke (no =0; yes =1)

Deep venous thrombosis including pulmonary embolism (no =0; yes =1)

Additional analysis:

#1 - To study the effects of SGLT2 inhibitors when eGFR drops<25 ml/min during follow-up

Primary outcome: Cardiovascular death or Heart Failure Hospitalizations (no =0; yes =1)

Secondary outcomes: Cardiovascular death (no =0; yes =1); Heart failure hospitalization (no =0; yes =1); MACE (no =0; yes =1)

and #2. To study the effects of SGLT2 inhibitors across the full spectrum of albuminuria (ie., 300 mg/g) and with albuminuria as continuous covariate

Primary outcome: Cardiovascular death or Heart Failure Hospitalizations (no =0; yes =1)

Secondary outcomes: Cardiovascular death (no =0; yes =1); Heart failure hospitalization (no =0; yes =1); MACE (no =0; yes =1)

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

Main predictor/Independent variables will include (per study objectives):

1. study the proportion of patients who develop polycythemia under SGLT2i treatment &
2. identify the risk factors for polycythemia development

Outcome variables

- Polycythemia (no = 0; yes = 1)

Predictor variables

- Smoking (no =0; yes =1)

- Chronic obstructive pulmonary disease (no =0; yes =1)

- Treatment (canagliflozin =1; placebo =0)

3. Study whether the presence of polycythemia increases the risk of cardiovascular events including venous thrombotic events & 4. assess whether the presence of polycythemia influences the effects of SGLT2 inhibitors

Predictor variables

- Polycythemia (no=0; yes=1)

Outcome variables

- Primary and secondary outcomes listed above

Interaction term (study objective 4)

- Treatment (canagliflozin =1; placebo =0)

Additional analysis

Main predictor/Independent variables will include:

#1 - To study the effects of SGLT2 inhibitors when eGFR drops<25 ml/min during follow-up

Outcome variables

- Primary and secondary outcomes listed above

Predictor variables

- Age (continuous); Baseline GFR (continuous); albuminuria (continuous); diabetes status (no = 0; yes = 1); atherosclerotic cardiovascular disease (no = 0; yes = 1); background RAS blocker use (no = 0; yes = 1); SGLT2i group (no = 0; yes = 1)

Interaction terms

- Treatment (canagliflozin =1; placebo =0); Diabetes status (no = 0; yes = 1)

#2. To study the effects of SGLT2 inhibitors across the full spectrum of albuminuria (ie., 300 mg/g) and with albuminuria as continuous covariate

Outcome variables

- Primary and secondary outcomes listed above

Predictor variables

- Age (continuous); Baseline GFR (continuous); HF status (no = 0; yes = 1); atherosclerotic cardiovascular disease (no = 0; yes = 1); background RAS blocker use (no = 0; yes = 1); SGLT2i group (no = 0; yes = 1)

Interaction terms

- Treatment (canagliflozin =1; placebo =0); Diabetes status (no = 0; yes = 1)

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

Age (continuous)

Sex (1 =men; 2 =women)

Estimated glomerular filtration rate (continuous)

Diabetes (no =0; yes =1)

Hemoglobin, hematocrit (continuous)

Statistical Analysis Plan:

Polycythemia will be defined as serum hematocrit (Hct) >49% in men and >48% in women or hemoglobin (Hgb) >16.5 g/dL in men or >16.0 g/dL in women (4).

Patient characteristics will be compared between those with and without polycythemia at baseline using parametric and non-parametric tests, as appropriate.

Associations between patient's characteristics and new-onset polycythemia throughout the follow-up will be studied using stepwise Cox regression models, including all available variables plus the randomized treatment (SGT2i or placebo).

Associations between polycythemia and outcomes will be tested using time-varying Cox regression models with polycythemia as independent variable.

The treatment effect modification will be tested with a treatment (SGT2i or placebo) by polycythemia

interaction term within the time-varying Cox model.

We will use an individual participant data (IPD) meta-analysis whereby studies will be independently identified (eg EMPEROR-Preserved =1, EMPEROR-Reduced =2, EMPA-REG-OUTCOME =3, CREDENCE =4, CANVAS =5) and data homogenized across trials.

Data will be presented as "overall effects" with heterogeneity tests to assess whether the findings diverge significantly between studies. No data imputation will be performed.

Two-sided P-values of less than 0.05 will be considered statistically significant.

No multiple testing correction will be applied. Complete case analysis will be performed i.e., no data imputation will be done.

Additional analysis

#1 - To study the effects of SGLT2 inhibitors when eGFR drops<25 ml/min during follow-up

Methods: Time-varying Cox proportional hazards models with eGFR drops treated as a time-varying covariate using the EMPEROR-Preserved, EMPEROR-Reduced, EMPA-REG OUTCOMES, CANVAS-Renal, and CREDENCE studies.

and #2. To study the effects of SGLT2 inhibitors across the full spectrum of albuminuria

Methods: Cox proportional hazard models by categories of albuminuria at baseline (ie., 300 mg/g) and across the full range of albuminuria as a continuous covariate, using the EMPEROR-Preserved, EMPEROR-Reduced, EMPA-REG OUTCOMES, CANVAS-Renal, and CREDENCE studies.

Software Used:

STATA

Project Timeline:

Target Analysis Start Date: 1/30/25

Estimated Analysis Completion Date: 4/30/25

Date manuscript drafted: 05/30/25

First submitted for publication: 06/15/25

Results reported back to the YODA Project: within a week of paper publication.

Additional analysis:

Target Analysis Start Date: 09/01/25

Estimated Analysis Completion Date: 11/30/25

Date manuscript drafted: 01/01/26

First submitted for publication: 03/01/26

Results reported back to the YODA Project: within a week of paper publication.

Dissemination Plan:

Submit to a major cardiovascular journal (e.g., Circulation) once the paper is ready. This will depend on data availability promptness.

We do not aim to present this work at medical conferences.

Bibliography:

1. Braunwald E. Gliflozins in the Management of Cardiovascular Disease. New England Journal of Medicine 2022;386:2024-2034. 2. Inzucchi SE, et al. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. Diabetes care. 2018 1;41(2):356-633. 3. Ferreira JP, Anker SD, Butler J et al. Impact of anaemia and the effect of empagliflozin in heart failure with reduced ejection fraction: findings from EMPEROR-Reduced. Eur J Heart Fail 2022;24:708-715. 4. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. (May 2016). "The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia". Blood. 127 (20): 2391--2405. doi:10.1182/blood-2016-03-643544.