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General Information

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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: Texas Health Resources Clinical Scholarship
How did you learn about the YODA Project?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_9.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_pandey_0.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

Creatinine kinase levels among concomitant statin and SGLT2 use

Narrative Summary:

Many patients on SGLT2 inhibitors for diabetes control are also on statin medications to lower cholesterol. SGLT2 medications have lower drug-drug interactions compared to other classes of diabetes medications. However, the association of SGLT2 medication and concurrent statin medication use is unknown. We intend to evaluate the levels of creatinine kinase, a protein found in muscle, among individuals on SGLT2 and statin medications. We will compare the protein levels to individuals on SGLT2 or statin medications alone and on neither.

We hypothesize that concurrent SGLT2 and statin medication use will not raise creatinine kinase levels.

Scientific Abstract:

Background:
Many individuals on SGLT2 inhibitors are on concomitant statin medications. The risk of concurrent medication use and risk of myotoxicity is unknown.

Objective:
We aim to evaluate the association of concurrent SGLT2 inhibitor and statin medication use and risk of myotoxicity and elevated creatinine kinase levels.

Study design:
For this analysis, we will use the CANVAS trial dataset to evaluate creatinine kinase levels among individuals on both SGLT2 inhibitors and statin medications, on one of the two, and on neither.

Participants:
All patients. We will exclude participants with missing medication data.

Main Outcome Measures:
Our main outcome of interest is creatinine kinase level over time.

Statistical Analysis:
Linear mixed effect models will be devised to evaluate creatine kinase levels over time. We will calculate the least squared means to evaluate creatinine kinase levels over time between different medication groups.

Brief Project Background and Statement of Project Significance:

The sodium-glucose cotransporter 2 inhibitors (SGLT2i), a class of glucose-lowering therapies, have been shown to reduce risk of HF in at-risk patients with T2DM (type 2 diabetes mellitus), and are now supported as second-line therapies (after metformin) in patients with T2DM and cardiovascular risk factors or with prevalent ASCVD (atherosclerotic cardiovascular disease)[1-3]. However, limited guidance is available regarding concurrent SGLT2i use and statin medications[4]. Since many individuals at risk for cardiovascular disease are also on statin medications, it is unclear if there is an increased risk of myotoxicity with concurrent use.

As such, we aimed to evaluate the association of concurrent SGLT2i and statin use and risk of elevated creatinine kinase levels among individuals from the CANVAS trial.

Specific Aims of the Project:

For this project, we aim to evaluate the association of concurrent SGLT2i and statin use and risk of elevated creatinine kinase levels among individuals from the CANVAS trial.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment safety

Research Methods

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

We will exclude participants with missing concurrent medication data

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

Our primary outcome of interest is creatinine kinase level over time. Our secondary outcome of interest is AST level over time.

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

Our main predictor variable is a 4 category variable: 1) concurrent SGLT2i and statin use, 2) only SGLT2i use, 3) only statin use, 4) neither SGLT2i or statin use.

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

We will further adjust models for age, sex, race, creatinine level, body mass index, and trial site.

Statistical Analysis Plan:

Individuals will be categorized into one of 4 categories: 1) concurrent SGLT2i and statin use, 2) only SGLT2i use, 3) only statin use, 4) neither SGLT2i or statin use. We will then evaluate the trend in creatinine kinase levels over time using linear mixed effect models. The least square means will be calculated for each of the 4 groups and differences between groups will be determined. Differences will be reported as estimate and 95% confidence interval. Analyses all be performed using R with a $P < 0.05$ indicating significance.
Software Used:
R
Project Timeline:

Since we have a prior DUA for CANVAS data, we hope for an expedited timeline.
1 month: project evaluation/review
1 month: reform analysis
1 month: write manuscript
1 month: submit manuscript proposal to YODA
3 months: submit manuscript and revise based on reviewer comments
1 month: report results back to YODA

Dissemination Plan:

We plan to publish this project in a general medicine journal such as Annals of Internal Medicine or American Journal of Medicine.

Bibliography:

[1]Degorter, Marianne K., et al. “Clinical and Pharmacogenetic Predictors of Circulating Atorvastatin and Rosuvastatin Concentrations in Routine Clinical Care.” Circulation: Cardiovascular Genetics, vol. 6, no. 4, 2013, pp. 400–408., doi:10.1161/circgenetics.113.000099.
[2]Mamidi, Rao N. V. S., et al. “In Vitro and Physiologically?Based Pharmacokinetic Based Assessment of Drug–Drug Interaction Potential of Canagliflozin.” British Journal of Clinical Pharmacology, vol. 83, no. 5, 2016, pp. 1082–1096., doi:10.1111/bcp.13186.
[3]Perkovic, Vlado, et al. “Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy.” New England Journal of Medicine, vol. 380, no. 24, 2019, pp. 2295–2306., doi:10.1056/nejmoa1811744.
[4]Brailovski, Eugene, et al. “Rosuvastatin Myotoxicity After Starting Canagliflozin Treatment: A Case Report.” Annals of Internal Medicine, 2020, doi:10.7326/l20-0549.

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