Principal Investigator

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General Information

Key Personnel (in addition to PI):

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/system/files/conflict_of_interest_form_for_yoda.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?: Full CSR

Research Proposal

Project Title

GLP-1RAs and SGLT-2is reduce cardiovascular events in women with type 2 diabetes. A systematic review and meta-analysis

Narrative Summary:

Men with no diabetes are at higher risk for developing heart disease compared to women; however, differences diminish in individuals with diabetes. GLP-1RAs and SGLT-2is improve diabetes control, lead to weight loss, and decrease the risk for developing heart disease. While diabetes guidelines recommend GLP-1RA or SGLT-2i once metformin fails, sulfonylureas remain the most common secondary agent prescribed.
We plan to perform a meta-analysis to explore if GLP-1RAs and SGLT-2i reduce the incidence of heart disease in women with type 2 diabetes. If the trial show that those medications are beneficial, this would help reduce health disparities.

Scientific Abstract:

Background: Women may develop cardiovascular disease later in age compared to men. This has led to the misperception that women are protected against cardiovascular disease. Thus, controlling risk factors in women may be delayed.
Objective: To explore if glucagon-like peptide-1 receptor agonist (GLP-1RA) and sodium glucose co-transporter-2 inhibitor (SGLT-2i) reduce cardiovascular events in women with type 2 diabetes.
Study Design: A meta-analysis of the cardiovascular outcome trials (CVOT). Since the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) updated their recommendations for individuals with type 2 diabetes and cardiovascular disease based on the CVOT showing cardiovascular benefit, our analysis will include trials that had a statistically significant either primary or secondary outcome. We will then extract the incidence of Major Adverse Cardiovascular Events (MACE) in women from those trials. If the results are not reported as absolute numbers of women, the data will be requested.
Participants: Women with type 2 diabetes and increased cardiovascular risk.
Main Outcome Measures: The incidence of MACE in women with type 2 diabetes.
Statistical Analysis: Analyses will be performed using the Review Manager Software. A random effects model will be used. Dichotomous data will be summarized as relative risk with 95% confidence interval. The number needed to treat will be calculated for statistically significant outcomes. A sensitivity and subgroup analysis will be performed based in the class of diabetes medications.

Brief Project Background and Statement of Project Significance:

While the absolute rates of cardiovascular disease are higher in men compared to women in the absence of diabetes, these differences between both genders would diminish in individuals with diagnosed type 2 diabetes.5,7,8 Although cardiovascular death continues to be the leading cause of death in both men and women, health disparities exist.9 Women are usually underdiagnosed and would have a delay in diagnosis of cardiovascular disease.4 While the ADA and EASD algorithm for the management of type 2 diabetes and established cardiovascular disease recommend adding either GLP-1RA or SGLT-2i when metformin fails, sulfonylureas remain the most common secondary agent prescribed.10 GLP-1RAs and SGLT-2is are potent diabetes medications that reduce hemoglobin A1c, lead to weight loss, and show cardiovascular benefit.11 We aim to explore if the ADA and EASD recommendation can be applied to women like the general population. If those medications are associated with cardiovascular benefit in women, this would help reduce health disparities relates to preventable differences in the burden of disease between population groups.

Specific Aims of the Project:

Aim: To explore if GLP-1RAs and SGLT-2i reduce cardiovascular events in women with type 2 diabetes.
Hypothesis: GLP-1RAs and SGLT-2is will show a statistically significant lower incidence of MACE in women with type 2 diabetes and established cardiovascular disease.

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
Summary-level data meta-analysis
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

Data required:
• Data from CANVAS12 and CANVAS-R12 will be requested since it is not reported as absolute numbers. Will need the absolute number of women who developed MACE in the canagliflozin group and in the placebo group. This data is presented in Figure 4 in the published article NEJM 2017; 377: 652. No participant-level data is needed.
• Data from other CVOT will be extracted as the absolute number of women who developed MACE in the diabetes medications group versus placebo.
• After obtaining the data from the CANVAS Program, all data from the CVOT will be pooled together.
Inclusion criteria:
• Randomized controlled trial that explore a diabetes medication (GLP-1RA or SGLT-2i) to placebo in individuals with type 2 diabetes.
• The primary outcome of the trial investigating the incidence of MACE (defined as cardiovascular death, myocardial infarction, or stroke).
• CVOT with a statistically significant either primary or secondary outcome.
Exclusion criteria:
• Trials investigating type 1 diabetes.

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

Incidence of MACE in women in the diabetes medication group (GLP-1RA or SGLT-2i) compared to placebo.

This will be dichotomous data. Results from the CANVAS Program will be added to other cardiovascular outcome trials.

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

NA

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

NA

Statistical Analysis Plan:

Analyses will be performed using the Review Manager Software. A random effects model will be used.
Dichotomous data will be summarized as relative risk with 95% confidence interval. The number needed to treat will be calculated for statistically significant outcomes. A sensitivity and subgroup analysis will be performed based in the class of diabetes medications.
Data will be collected from the trials. No participant-level data will be analyzed.
Software Used:
I am not analyzing participant-level data / I will not be using these software for analyses in the secure platform
Project Timeline:

January 2019: Submit an abstract for consideration at the American Diabetes Association Scientific Meeting.
December 2019 – January 2020: Drafting the manuscript for consideration for publications.
January 2020 – February 2020: Submit the manuscript for consideration for publication.

Dissemination Plan:

• If accepted at the American Diabetes Association Scientific Meeting, it will be potentially presented to a diversity group of general practitioners, endocrinologist, and cardiologist.
• Publications plan: Diabetes Obesity and Metabolism.

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