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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?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_coi_anika.pdf
https://yoda.yale.edu/system/files/yoda_coi_pratley.pdf
https://yoda.yale.edu/system/files/yoda_coi_fanchao.pdf
https://yoda.yale.edu/system/files/yoda_coi_thethi.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

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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
3. 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

What type of data are you looking for?: Full CSR

Research Proposal

Project Title

Effects of new antidiabetic agents on cardiovascular outcomes in older adults: systemic review and meta-analysis

Narrative Summary:

This is a meta-analysis of randomized controlled trials of newer anti-hyperglycemic drugs (sodium-glucose cotransporter inhibitors and incretin-based therapies) to assess cardiovascular outcomes in older subgroups (aged ? 65 years; ? 75 years). We will include trials with at least 1000 participants; reporting 3P/ 4P major adverse cardiovascular outcome; with at least 12 months follow-up.
Cardiovascular disease is a major contributor of mortality among diabetes patients. Since we are studying three classes of anti-hyperglycemic drugs by their age subgroups, this study will provide useful insights of cardiovascular safety in geriatric population.

Scientific Abstract:

Background:
With the worldwide increase in the aging population, the population of elderly patients with diabetes are also on the rise. In 2019, the number of people over 65 years of age with diabetes was estimated to be 111 million and it is projected to reach 276 million by 2045. Cardiovascular (CV) disease is a major contributor of mortality and morbidity among diabetes patients. Since older patients with diabetes often have 10 to 20 or more years of productive life, it is imperative to consider appropriate pharmacological agent with safe cardiovascular profile when treating this population.
Objective: To measure the effects of newer anti-hyperglycemic drugs (sodium-glucose cotransporter inhibitors and incretin-based therapies) on the cardiovascular outcomes in older adults.
Study Design: Systemic review and meta-analysis of randomized controlled trials
Participants: We are including randomized controlled trials with at least 1000 participants, aged 18 years and above. Only trials reporting 3P-MACE/ 4P-MACE as an outcome with at least 12 months follow-up are included.
Main Outcome measure: To assess the major adverse cardiovascular events (cardiovascular death, stroke, myocardial infarction) in subgroups by age. The older adults in the analysis will be participants 65 years and above; the aged population will constitute adults 75 years and above.
Additional outcomes include components of major adverse cardiovascular events: cardiovascular death, myocardial infarction, stroke, and all-cause mortality. Outcomes will be assessed according to the sub-groups by age.
Statistical Analysis: All available subgroup data (age< 65 years, ? 65 years, age< 75 years, ? 75 years) of the randomized controlled clinical trials will be included to estimate the effect of treatment compared with that of placebo. The relative risk with 95% confidence interval of each outcome between treatment groups will be calculated for each trial. The summary estimate will be the weighted average, by weighting each trial estimate by the inverse of its variance. Forest plots using fixed- and random-effects models to compare relative treatment effects will be generated. The heterogeneity test and sensitivity analysis will be applied.

Brief Project Background and Statement of Project Significance:

Robust cardiovascular outcome trials (CVOTs) have been ongoing since 2008 when the FDA mandated CV safety trials for newer anti-hyperglycemic drugs. The majority of these trials included type 2 diabetes patients with high cardiovascular risk profile. The number of participants in these CVOTs ranged from 3183 (PIONEER-6) to 17,160 (DECLARE-TIMI 58) and the representation of older adults (? 65 years) varied from 34% in ELIXA to 58% in PIONEER-6 and SAVOR-TIMI-53. All these CVOTs measured 3P/ 4P major adverse cardiovascular outcomes (a composite of cardiovascular death, myocardial infarction, stroke and/or unstable angina). Cardiovascular safety was confirmed in all the trials, consequently, FDA revised its guidelines in 2020. According to new guidelines, the drug companies were no longer mandated to conduct dedicated CVOTs to demonstrate CV safety of newer anti-hyperglycemic agents. However, it was recommended that the safety analysis of newer drugs should include substantial number of patients exposed to the drug for longer periods of time. Also noteworthy is the inclusion of population with underlying CV disease, chronic kidney disease and at least 600 patients older than 65 years of age exposed to the new drug.
Historically, older patients have been excluded from clinical trials because of co-morbidities. Older people with diabetes have long-standing disease, increased complications, more hypoglycemic vulnerability, polypharmacy, and other geriatric syndromes. Therefore, it is imperative to use pharmacological agents with proven safety profile in older adults. We designed this meta-analysis to study the cardiovascular outcomes of newer anti-hyperglycemic drugs in the older adults with high risk of cardiovascular disease. This meta-analysis is registered with PROSPERO (International prospective register of systemic reviews): ID CRD42021260167.

Specific Aims of the Project:

Data from randomized controlled trials with newer anti-hyperglycemic drugs (sodium-glucose cotransporter inhibitors and incretin-based therapies) will be analysed to :
Aim 1: compare the primary outcome of 3P-MACE/ 4P-MACE between the drug and placebo/active comparator among the subgroups (age< 65 years, ? 65 years, age< 75 years, ? 75 years)
Aim 2: compare the individual outcomes including cardiovascular death, myocardial infarction, stroke and all-cause mortality between the drug and placebo/active comparator among the subgroups (age< 65 years, ? 65 years, age< 75 years, ? 75 years)
Hypothesis 1: There will be no difference in primary outcome of 3P-MACE/ 4P-MACE between the groups when subdivided by age category.
Hypothesis 2: There will be no difference in the individual outcomes including cardiovascular death, myocardial infarction, stroke and all-cause mortality between groups when subdivided by age category.
***Please see the supplementary material for the data we are requesting for our meta-analysis.

What is the purpose of the analysis being proposed? Please select all that apply.
Summary-level data meta-analysis

Research Methods

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

Inclusion criteria:
1. Randomised, controlled, event-driven, cardiovascular or kidney outcome trials versus active or placebo control.
2. Participants aged > 18 years.
3. Trials with at least 1000 participants.
4. Published trials with newer anti-hyperglycemic drugs: like incretin-based therapies (Dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists) and sodium/glucose cotransporter inhibitors.
5. Studies with at least 12 months follow up.
6. Studies reporting 3P-MACE/ 4P-MACE as an outcome.
Exclusion criteria:
1. Studies which are not randomized controlled trials.
2. Studies with less than 1000 patients
3. Studies in pediatric population
4. Studies with less than 12 months of follow-up.
5. Studies which do not have sub-group analysis by age
6. Studies completed before the Food and Drug Administration (FDA) guidance in 2008.

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

The main purpose of the meta-analysis is to compare the composite of major adverse cardiovascular events (cardiovascular death, stroke, myocardial infarction) in the newer anti-hyperglycemic agents vs. placebo/active comparator.
Additional outcomes include individual components of major adverse cardiovascular events including cardiovascular death, myocardial infarction, stroke and all-cause mortality.

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

Cardiovascular outcomes will be compared between the newer anti-hyperglycemic drugs and placebo for the following subgroups:
1. Adults less than 65 years
2. Adults of 65 years and above
3. Adults less than 75 years
4. Adults of 75 years and above

Statistical Analysis Plan:

We will analyze three classes of anti-hyperglycemic drugs in this meta-analysis: Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium/glucose cotransporter inhibitors. Cardiovascular outcomes will be analyzed in each class of drug from the pooled trials data in its category. All available subgroup data (age< 65 years, ? 65 years, age< 75 years, ? 75 years) of the randomized controlled clinical trials will be included to estimate the effect of treatment compared with that of placebo. The primary outcome includes 3P-MACE, defined as the composite of cardiovascular mortality, myocardial infarction (MI), and stroke. Secondary outcomes include cardiovascular mortality, all-cause mortality, myocardial infarction, and stroke. The relative risk with 95% confidence interval of each outcome between treatment groups will be calculated for each trial. The summary estimate will be the weighted average, by weighting each trial estimate by the inverse of its variance. Forest plots using fixed- and random-effects models to compare relative treatment effects will be generated. The heterogeneity test will be applied. To test the robustness of the meta-analysis results, the sensitivity analysis will be conducted by assessing the effect of removing individual trials. All analyses will be applied using SAS (9.4) and R (4.10). The p-value < 0.05 was considered statistically significant.
Software Used:
I am not analyzing participant-level data / plan to use another secure data sharing platform
Project Timeline:

The project has already started and this meta-analysis is registered with PROSPERO (International prospective register of systemic reviews): ID CRD42021260167. The published data has been extracted. We are requesting the unpublished data from scientific committee members of different trials. The analysis completion date will depend on the data availability from different trials but is expected to be in first quarter of 2022. The manuscript will be drafted and submitted for publication in second quarter of 2022.

Dissemination Plan:

Data dissemination will occur through presentation at major scientific conferences and/or publication in peer-reviewed journals targeting endocrinology, geriatrics, and cardiology like
1. JAMA cardiology
2. Diabetes, Obesity and Metabolism

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/yoda_canagliflozin_data_request.docx