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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?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2025/02/Conflict-of-Interest-Form.pdf
https://yoda.yale.edu/wp-content/uploads/2025/02/COI-FORM-KM.pdf
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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. NCT01106651 - 28431754DIA3010 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus Inadequately Controlled on Glucose Lowering Therapy
2. NCT01106677 - 28431754DIA3006 - A Randomized, Double-Blind, Placebo and Active-Controlled, 4-Arm, Parallel Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Monotherapy
3. NCT01081834 - 28431754DIA3005 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin as Monotherapy in the Treatment of Subjects With Type 2 Diabetes Mellitus Inadequately Controlled With Diet and Exercise
4. NCT01106690 - 28431754DIA3012 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sulphonylurea Therapy
5. NCT01106625 - 28431754DIA3002 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Pioglitazone Therapy
6. 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
7. 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
8. 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
9. NCT01137812 - 28431754DIA3015 - A Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Versus Sitagliptin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sulphonylurea Therapy
10. NCT00968812 - 28431754DIA3009 - A Randomized, Double-Blind, 3-Arm Parallel-Group, 2-Year (104-Week), Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 Compared With Glimepiride in the Treatment of Subjects With Type 2 Diabetes Mellitus Not Optimally Controlled on Metformin Monotherapy
11. NCT02025907 - 28431754DIA4004 - A Randomized, Double-blind, Placebo Controlled, 2-arm, Parallel-group, 26-week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sitagliptin Therapy
12. NCT01809327 - 28431754DIA3011 - A Randomized, Double-Blind, 5-Arm, Parallel-Group, 26-Week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in Combination With Metformin as Initial Combination Therapy in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control With Diet and Exercise
13. NCT01064414 - 28431754DIA3004 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week, Multicenter Study With a 26-Week Extension, to Evaluate the Efficacy, Safety and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus Who Have Moderate Renal Impairment

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Impact of SGLT2-inhibitors on frailty and physical function in older adults with type 2 diabetes mellitus: a systematic review and meta-analysis

Narrative Summary:

Frailty is an important problem in older adults that increases the risk of adverse health outcomes. However, effective interventions can improve their mortality and quality of life. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have recently been used because of their beneficial effects on cardiovascular outcomes. However, there is a concern that the weight loss effect and side effects of SGLT2 inhibitors may contribute frailty in older adults.
The purpose of this study is to assess the frailty risk associated with the use of SGLT2 inhibitors in older adults and identify who should use SGLT2 inhibitors carefully through conducting a systematic review.

Scientific Abstract:

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors have recently been used because of their beneficial effects on cardiovascular outcomes. However, for older individuals, there is a concern that weight loss and adverse events can induce physical activity decline, falls, and eventually frailty. Objective: This study aims to assess the frailty risk associated with the use of SGLT2 inhibitors in older adults and identify who should use SGLT2 inhibitors carefully. Study Design: A systematic review and meta-analysis Participants: We will include randomized controlled trials which evaluate SGLT2 inhibitors versus placebo, other glucose-lowering agents in patients with type 2 diabetes aged >=65 years. We will search the MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials. Primary and Secondary Outcome Measure(s): Primary outcomes are change in frailty, all-cause mortality and hospitalization. Secondary outcomes include changes in body weight, HbA1c, body composition, muscle strength, walking speed, cognitive function, quality of life, and adverse events. Statistical Analysis: We will conduct a meta-analysis using a random-effects model. We will calculate the standardized mean difference, hazard ratio, and odds ratios or risk ratios with a 95% confidence interval (CI). Heterogeneity will be assessed using the chi-square test and I^2 statistic. We will undertake subgroup analysis based on comorbidity and medication. We will assess the quality of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation approach.

Brief Project Background and Statement of Project Significance:

Frailty is widely known as a state of vulnerability that increases the risk of death, hospitalization, falls, institutionalization, and surgical complications [1][2]. Decreased physical activity, chronic disease, and poor nutritional status are important factors for the loss of physiological reserves, leading to frailty [1] [3]. Weight loss, decline in physical activity, and falls can lead to frailty. However, frailty can be improved through resistance training, adequate nutrition, and vitamin D and improving polypharmacy [2]. Therefore, early intervention is important to improve health outcomes and quality of life while reducing care costs in older adults at risk for frailty.
Sodium-glucose cotransporter 2 (SGLT2) inhibitors have recently been used because of their beneficial effects on cardiovascular and renal outcomes [4-6]. However, the adverse events may be frequent in older adults, such as volume depletion, fractures, and urinary tract infection [7-8]. Thats effect in weight loss and these adverse events can induce physical activity decline, falls, and eventually frailty; therefore, some guidelines recommend the careful use of SGLT2 inhibitors in older adults [9-10].

There is a systematic review that is focus on the relationship between SGLT2 inhibitors and sarcopenia [11]. It suggested that SGLT2 inhibitors improve fat mass and body weight but also decrease muscle mass, indicating a need to pay attention to the risk of sarcopenia. However, the risk of sarcopenia in older adults remains unclear, as the participants in this study are relatively younger. In addition, the impact on muscle strength due to reduced muscle mass and risk of frailty, other than physical frailty, also remain unclear. Major RCTs reporting CVD benefits of SGLT2 inhibitors also target relatively younger patients [12-16], it is unclear which has the greater impact either CVD benefits or frailty risks in patient aged >65 years.
The purpose of this study is to assess the frailty risk associated with the use of SGLT2 inhibitors in older adults and identify who should use SGLT2 inhibitors carefully.

Specific Aims of the Project:

This study aims to investigate whether SGLT2 inhibitors can be safely used in patients aged 65 and older.
There is a concern that the weight loss effect of SGLT2 inhibitors may contribute to sarcopenia. However, it is primarily attributed to fat reduction, which occurs to a greater extent than muscle mass loss. These side effects such as dehydration may be more frequent in older patients, but individual factors such as underlying diseases, concomitant medications, and nutritional status have not been adequately considered.
Our hypothesis is that, with careful consideration of underlying diseases and concomitant medications, SGLT2 inhibitors can be used safely in older adults without increasing the risk of frailty, including decline in muscle strength, gait speed, and quality of life (QOL).
To achieve this, we aim to identify specific patient characteristics that may require special attention by conducting a comprehensive analysis of patient backgrounds.

Study Design:

Meta-analysis (analysis of multiple trials together)

What is the purpose of the analysis being proposed? Please select all that apply.

Summary-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:

We will include randomized controlled trials which evaluate SGLT2 inhibitors versus placebo, other glucose-lowering agents in patients with type 2 diabetes aged >=65 years. We will include studies that analyze subgroups of patients aged >=65 years, but we will not analyze IPD data. We will assess the effect of assignment to intervention. We will exclude studies with a follow-up duration <24 weeks and involving surgery, including PCI or ablation.
We will search the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials. We will also search the following trial registers: ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). We will search for references using guidelines published since 2014.

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

The time point will be divided into short-term (1 year).

Primary Outcomes
1. Change in Frailty (mean difference (95% CI), measured by Fried Frailty Tool or others)

2. All-cause Mortality and Hospitalization (hazard ratio, odds ratios, or risk ratios (95% CI))

Secondary Outcomes
changes in the following parameters (mean difference (95% CI)):
2. Frailty (e.g., Fried Frailty Tool)
3. Body weight, body mass index, HbA1c, grip strength, walking speed.
4. Body composition (e.g., Dual-energy X-ray Absorptiometry)
5. Balance (e.g., measured by Berg balance scale)
6. Activities of daily living (e.g., Barthel Index)
7. Instrumental Activities of Daily Living (e.g., Lawton Instrumental Activities of Daily Living Scale)
8. Cognitive function (e.g., Mini-Mental State Examination)
9. Depression and anxiety (e.g., Patient Health Questionnaire-9, Generalized Anxiety Disorder-7)
10. Caregiver burden (e.g., Zarit Burden Interview 4-item screening questionnaire)
11. Quality of life (e.g., SF-36)
12. Emergency department visits (hazard ratio, odds ratios, or risk ratios (95% CI))
13. Adverse events

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

Potential confounding factors that may increase the risk of frailty include comorbid diseases such as heart failure and renal failure, and patient factors such as poor glycemic control. To assess the influence of these confounding factors, we will conduct a subgroup analysis based on comorbidities (CVD, osteoarthritis, chronic kidney disease, and Neuromuscular disorders), hypoglycemia or hyperglycemia (HbA1c 8.2), BMI (<24 or ≧30), exercise intervention, medication (GLP-1 receptor agonists, angiotensin converting enzyme inhibitors, angiotensin Ⅱreceptor blockers, diuretics, and sedative medications). Furthermore, a sensitivity analysis will be performed to evaluate the robustness of the results by excluding these factors.

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

We will analyze age, sex, ethnic groups, body weight, HbA1c, comorbidities, previous medications as baseline characteristics.

Statistical Analysis Plan:

Strategy for data synthesis
1. Meta-analysis
We will conduct a meta-analysis where possible, using a random-effects model. If the clinical and methodological diversity is too large, we will not conduct a meta-analysis and the findings will be presented in text or tabular form as a narrative summary.
We will calculate the standardized mean difference with a 95% confidence interval (CI) for the following continuous outcomes: frailty, body weight, BMI, HbA1c, lean body mass, muscle mass, fat mass, walking speed, grip strength, balance, ADL, IADL, cognitive function, depression and anxiety, caregiver burden, and QOL. We will calculate the hazard ratio with a 95% CI for the following time-to-event outcomes: mortality, hospitalization, and ED visits. We will calculate the odds ratios or risk ratios for dichotomous outcomes.
We will synthesize the data using Stata version 17 (StataCorp LLC. 4905 Lakeway Drive, College Station, TX 77845, USA.).

2. Assessment of heterogeneity
Heterogeneity will be assessed using the chi-square test and I^2 statistic. Thresholds for the interpretation of the I^2 statistic were as follows: 0--40%, might not be important; 30--60%, may represent moderate heterogeneity; 50--90%, may represent substantial heterogeneity; and 75--100%, considerable heterogeneity. When heterogeneity is identified, we will not perform meta-analysis and investigate the cause of the heterogeneity by conducting a subgroup analysis or meta-regression.

3. Missing data
We will contact the original authors to ask them about the missing data. We will investigate whether this is randomly missing. Sensitivity analyses will be performed when data are not missing at random.

4. Publication bias
We will search trial registers, such as ClinicalTrials.gov and ICTRP, to identify completed but unpublished trials. If more >10 studies are included, we will generate a funnel plot and test for funnel plot asymmetry using Egger's test.

5. Sensitivity analysis
Following sensitivity analyses will be undertaken to assess the robustness of results.
1. Repeat meta-analysis in the study with low risk of bias.
2. Repeat meta-analysis removing the study with data not missing at random.

6. Subgroup analysis
If sufficient data and adequate numbers of studies are obtained, we will undertake subgroup analysis based on comorbidity (CVD, osteoarthritis, CKD, and Neuromuscular disorders), hypoglycemia or hyperglycemia (HbA1c 8.2), BMI (<24 or ≧30), exercise intervention, medication (GLP-1 receptor agonists, angiotensin converting enzyme inhibitors, angiotensin Ⅱreceptor blockers, diuretics, and sedative medications).

Software Used:

STATA

Project Timeline:

project start date: 09/14/2023
analysis completion date: 06/17/2025
date manuscript drafted: 05/21/2025
first submitted for publication: 07/02/2025
date results reported back to the YODA Project: 07/02/2025

Dissemination Plan:

We will submit this study for publication to a peer-reviewed English language journal, including: Journal of General Internal Medicine, Annals of Family Medicine, British Journal of General Practice, BMC Primary Care, Family Practice, Family Medicine, Journal of the American Geriatrics Society, Journal of Diabetes Investigation, Diabetes Therapy, Cardiovascular diabetology, Journal of General and Family Medicine, Internal Medicine

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Supplementary Material:

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