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Requires Data Access? Yes

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: NIH P30 AR072571
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2026/01/COI-Felson.pdf
https://yoda.yale.edu/wp-content/uploads/2026/01/COI-FORM-AL.pdf
https://yoda.yale.edu/wp-content/uploads/2026/01/COI-FORM-NU.pdf
https://yoda.yale.edu/wp-content/uploads/2026/01/COI-FORM-MK.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. 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
3. 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

Do SGLT2 inhibitors reduce the risk of knee and hip replacements for osteoarthritis compared to placebo: a secondary analysis of SGLT2 Trials

Narrative Summary:

A major driver of osteoarthritis (OA) pain is inflammation. While some anti-inflammatory drugs have been tested for osteoarthritis, these drugs have mostly targeted a single path within a complex inflammatory cascade. Some drugs that are currently used for other diseases have broader anti-inflammatory effects. Among these is SGLT2 drugs. This class of drugs developed for diabetes has been found to be effective in preventing progressive kidney disease, in lessening the risk of heart disease, and in preventing a related arthritis disorder, gout. The goal of the proposed study is to see if SGLT2 drugs reduce the risk of end stage osteoarthritis by seeing if patients on these drugs in a randomized trial get fewer knee and hip replacement for OA than those randomized to placebo.

Scientific Abstract:

Background: Osteoarthritis is a common inflammatory disorder with no disease-modifying therapies. Whether SGLT2 inhibition can reduce the consequences of large joint osteoarthritis is unclear
Objective: To determine whether SGLT2 inhibition reduces incident total hip or knee replacement (THR/TKR) for osteoarthritis
Design: Secondary analysis of SGLT2 vs placebo trials with at least 2 year median follow-up
Participants: Deidentified participants in SGLT2 trials (active treatment and placebo) who had THR/TKR noted in trial database
Outcome Measures: The primary outcome measure will be TKR. THR will be a secondary outcome
Statistical analysis: Our first step is to assess whether this project is feasible by determining whether the trials have data on THR/TKR and its date. If the data show this effort is feasible, we will carry out a Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs for the primary analysis of time to first incident THR/TKR for all SGLT2 doses combined vs. placebo. All analyses will be performed on an intention-to-treat basis. Individual participant follow-up time will be censored at the time of death, loss to follow-up, or withdrawal of consent; participants who had THR/TKR due to acute fracture or in a joint with previous arthroplasty will not be censored because other joints are still at risk. In addition to the primary analysis including the full trial cohort, sensitivity analyses will be performed that exclude participants with a history of gout, gouty arthritis, psoriatic arthritis or rheumatoid arthritis at baseline if identified

Brief Project Background and Statement of Project Significance:

Osteoarthritis (OA) is the most common form of arthritis with joint pain from OA affecting roughly 600 million persons worldwide. It affects mostly older persons and is a leading cause of disability. Non-surgical treatment for OA of the knees/hips, the most commonly symptomatic joints, has been disappointing, and there are no approved treatments that reduced disease progression and also diminish pain. Affected patients seek knee/hip replacements when pain is severe and non-surgical treatments have failed. Rates of knee/hip replacements are rising rapidly in both US and European countries because of the aging populations, increasing rates of obesity, and because of the paucity of effective nonsurgical treatments. New treatments are urgently needed.
The goal of the proposed study is to see if SGLT2i drugs reduce the risk of end stage osteoarthritis by seeing if patients on these drugs in a randomized trial get fewer knee and hip replacement for osteoarthritis than those randomized to placebo.
It's very challenging to identify drugs that may be effective in treating OA. Animal models of disease have identified promising treatments but testing these treatments in humans has required large studies with long follow-ups (cartilage loss occurs slowly), and these studies have been frustratingly negative. The greatest promise has emerged recently from a large trial of GLP1 agonists which causes major weight loss reducing the obesity that is a major risk factor for disease. GLP1 agonists not only cause weight loss that also serve as pleiotropic anti-inflammatory medications which may account for some of their efficacy.
SGLT2 inhibitors have promise as a treatment for osteoarthritis. While they cause modest weight loss, they have pleiotropic effects on inflammation and also promote the conversion of monocytes to the M2 antiinflammatory macrophage phenotype. There is evidence that they are effective in gout, a related disorder. In recent work, it's reported that persons starting SGLT2 inhibitors have a modestly lower risk of new total knee/hip replacements than persons starting GLP1 agonists. The subset of GLP1 users starting semaglutide had a roughly equivalent risk of THR and TKR compared with SGLT2 inhibitors. Those on earlier GLP1 agonists which caused much less weight loss had a higher risk of THR and TKR than those starting SGLT2 inhibitors. These findings suggest that SGLT2 inhibitors may have therapeutic efficacy for OA.
The outcomes we propose for this study are THR and TKR, not reports of osteoarthritis. In our experience 1st Claims for OA do not usually represent incident disease. Since OA is a slowly evolving disorder, the date of incidence is very hard to estimate or define. By using THR and TKR outcomes, we can use outcomes that are not only clinically relevant but can be dated precisely. Given the high burden of OA in the community and the paucity of effective treatments, the identification of a treatment already approved and widely used that may have an additional indication would be of substantial significance. For frustrated patients who have been unable to find effective treatments for their pain, SGLT2i could provide a valuable option.

Specific Aims of the Project:

The overall objective of this project is to determine if, based on trial data, those randomized to SGLT2 drugs have a lower rate of THR/TKR for osteoarthritis than those randomized to placebo.
Aim 1. To determine if data available from trial datasets will identify participants undergoing THR or TKR surgeries with the date and will provide information about indication for the surgery. H1: The trial data sets will provide information on THR/TKR in the adverse events files.
Aim 2. To determine if rates of THR/TKR were lower on SGLT2 trial participants than those randomized to placebo.

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

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

Research Methods

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

All trials will be from the YODA project. All patients randomized in these trials will be included with no exclusions.
The 3 trials of interest for this project are:
NCT01032629
NCT02065791
NCT01989754

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

The primary outcome will be total knee replacement (TKR) surgery and its date
The secondary outcome will be total hip replacement (THR) surgery and its date.

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

The main predictor for these analysis will be treatment, whether the patient was randomized to SGLT2 inhibitor or placebo.

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

In addition to the primary analysis including the full trial cohort, sensitivity analyses will be performed that exclude participants with a history of gout, gouty arthritis, psoriatic arthritis or rheumatoid arthritis at baseline if identified.

No covariates will be added to the model.

Statistical Analysis Plan:

Our first step is to assess whether this project is feasible by determining whether the trials have data on THR/TKR and its date.

If the data show this effort is feasible, for each trial, we will carry out a Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs for the primary analysis of time to first TKR for all SGLT2 doses combined vs. placebo. All analyses will be performed on an intention-to-treat basis. Individual participant follow-up time will be censored at the time of death, loss to follow-up, or withdrawal of consent. After the analysis of the primary outcome, TKR, we will carry out a similar analysis of THR, the secondary outcome. If the indication for the surgery is available from the datasets, we will restrict all analyses above to surgery for osteoarthritis. The central outcome measure will be the hazard ratio of risk of TKR in those randomized to SGLT2 vs. placebo. If addition, we will construct Kaplan-Meier curves to display the results over time.

Participants who had THR/TKR due to acute fracture or in a joint with previous arthroplasty will not be censored because other joints are still at risk. In addition to the primary analysis including the full trial cohort, sensitivity analyses will be performed that exclude participants with a history of gout, gouty arthritis, psoriatic arthritis or rheumatoid arthritis at baseline if identified.

Software Used:

Python, R, RStudio

Project Timeline:

January 31, 2026 -- January 30, 2027

Dissemination Plan:

The deliverable will be abstracts presented at scientific meetings, especially the American College of Rheumatology (ACR) and the Osteoarthritis Research Society International (OARSI). We will target presentations at these meetings in 2027 at the latest.
The manuscript reporting main findings will be submitted to a general medical journal such as the Annals of Internal Medicine and secondarily to Arthritis and Rheumatology, the leading Rheumatology journal in the US.

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