Principal Investigator

First Name: Jiaoyang
Last Name: Zheng
Degree: Doctor
Primary Affiliation: ChangZheng Hospital
E-mail: zgykcx@126.com
Phone number: +8613917605264
Address:

City: Shanghai
State or Province: Shanghai
Zip or Postal Code: 200003
Country: China

General Information

Key Personnel (in addition to PI):
First Name: Xi
Last name: Chen
Degree: Master
Primary Affiliation: Shanghai Changzheng Hospital
SCOPUS ID:

First Name: Xingyun
Last name: Hou
Degree: Master
Primary Affiliation: Shanghai Changzheng Hospital
SCOPUS ID:

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: Shanghai "Rising Stars of Medical Talent" Youth Development Program: Youth Medical Talents –Clinical Pharmacist Program."
How did you learn about the YODA Project?: Email/Newsletter/Flier

Conflict of Interest

https://yoda.yale.edu/system/files/scan0038.pdf
https://yoda.yale.edu/system/files/scan0039.pdf
https://yoda.yale.edu/system/files/scan0040.pdf
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https://yoda.yale.edu/system/files/scan0045.pdf
https://yoda.yale.edu/system/files/scan0046.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. NCT00642278 - 28431754DIA2001 - A Randomized, Double-Blind, Placebo-Controlled, Double-Dummy, Parallel Group, Multicenter, Dose-Ranging Study in Subjects With Type 2 Diabetes Mellitus to Evaluate the Efficacy, Safety, and Tolerability of Orally Administered SGLT2 Inhibitor JNJ-28431754 With Sitagliptin as a Reference Arm
2. 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 Sulphonylurea Therapy
3. 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
4. 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
5. 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
6. 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
7. 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
8. 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 Pioglitazone Therapy
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. NCT01340664 - 28431754DIA2003 - 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
11. 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
12. 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

Cardiovascular safety associated with SGLT-2 inhibitors across racial groups in patients with T2DM: a meta analysis and systematic review.

Narrative Summary:

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of antidiabetes agents that reduce hyperglycemia in patients with T2DM by reducing renal glucose reabsorption and thus increasing urinary glucose excretion(UGE).Our study is designed to compare the cardiovascular safety of SGLT2 inhibitors across racial groups in terms of All-cause mortality, CV death, heart failure, myocardial infarction and stroke.Previous studies of SGLT-2 are mostly taiking about the efficiency without seperately analysing each race included.We will integrate the detailed results from databases online and conduct further analysis and comparison.

Scientific Abstract:

Background:Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of antidiabetes agents that reduce hyperglycemia in patients with T2DM by reducing renal glucose reabsorption and thus increasing urinary glucose excretion(UGE),which have showed remarkable cardiovascular protection effects.However,previous studies seldom took racial difference into consideration,and cardiovascular safety data in Asian is rare.Objectives:To assess the effects of SGLT-2 inhibitors for cardiovascular safety across races.Study Design: Analyzing data collected in RCTs,compare cardiovascular outcomes among races.Participants:adults with T2DM.Main Outcome Measure(s):all-cause mortality, cardiovascular mortality and heart failure. Statistical Analysis:Continuous outcomes will be evaluated by computing the weighted mean differences (WMDs) and 95% confidence intervals (CIs). Categorical outcomes will be evaluated by computing the odds ratios (ORs) and accompanying 95% CIs.Due to between-study heterogeneity, Higgins I2 statistics is used to evaluate the percentage of variance.Publication bias will be assessed via a visual inspection of funnel plot.Statistical significance was considered at $P < 0.05$.Statistical analyses were primarily performed using the Review Manager statistical software package (version 5.3).

Brief Project Background and Statement of Project Significance:

Cardiovascular disease?CVD?is the most common cause of death worldwide?and type 2 diabetes mellitus(T2DM) inceases the risk by 2 to 3 fold.Since 2008,the Food and Drug Administration (FDA) have issued guidance to mandate long-term cardiovascular outcomes trials (CVOTs) for all newly developed antidiabetes drugs.Among those,sodium-glucose cotransporter-2 (SGLT-2) inhibitors,which exert antihyperglycemic effects by blocking the sodium-glucose cotransporter 2 to suppress glucose reabsorption and increase glucosuria, have showed remarkable cardiovascular protection effects.
Although CVOTs (EMPAREG-OUTCOME, CANVAS, DECLARE-TIMI 58), and real-world evidence studies (CVD-REAL, EASEL, CVD-REAL 2, OBSERVE-4D) have confirmed cardiovascular benefits in SGLT-2 inhibitors,however only a minority of patients were recruited in Asia.Apart from genetic difference across races,Asians have higher proportion of young onset,metabolic syndrome and ?cell dysfunction and high level of insulin resistance,compared with Caucasian counterparts.For cardiovascular outcomes,hazard ratios were similar in Asian and Caucasian T2DM patients,but were larger in younger people and diverse in leading cause of death(eg.Stroke is the leading cause in Asians,whereas coronary heart disease is the leading cause in Australasia.).
Saad 2017, a meta analysis containing 81 RCTs ,have certificated that SGLT-2 inhibitors reduced all-cause and cardiovascular mortality by decreasing the risk of heart failure,when compared with placebo.And another meta analysis (Monami 2017,71RCTs)comparing cardiovascular outcomes between SGLT-2 inhibitors and placebo,showed the same reduction in death.Additionally, myocardial infarction was significantly reduced,with no increased risk of stroke.However,any of them take racial difference into consideration.Mishriky,et conducted a meta analysis to evaluate SGLT-2 inhibitors cardiovasular safety in Africa Americans in 2019,which did not present significantly cardiovascular benefits.According to increasing prevalence of T2DM in Asia,an analysis targeting Asians is urgently needed.

Specific Aims of the Project:

To assess the effects of SGLT-2 inhibitors for preventing macrovascular complications?reducing the risk of all-cause and cardiovascular death, heart failure,Myocardial infarction and stroke in different racial T2DM patients.Assuming that racial difference in gene and diabetic characteristics leads to diverse cardiovascular outcomes,we would compare the risk ratios of all outcomes across races.
The RCTs included are listed below:
NCT00528879,NCT01340664,NCT01106625,NCT01081834,NCT01106677,NCT00968812,NCT01106690,NCT01

137812,NCT00642278,NCT01381900,NCT01081834,
NCT01064414,NCT01989754,NCT01032629,NCT01106651,NCT01059825,NCT01031680,NCT01042977,NCT00859898,NCT02096705,NCT00528372,NCT02229396,
NCT00673231,NCT00357370,NCT00680745,NCT00683878,NCT00643851,NCT00976495,NCT01195662,NCT01137474,NCT01217892,NCT00643851,NCT01606007,
NCT00736879,NCT00984867,NCT01095653,NCT01095666,NCT01392677,NCT00663260,NCT00660907,NCT02182830,NCT01131676,NCT01289990,NCT00881530,
NCT00789035,NCT01370005,NCT01649297,NCT01177813,NCT01164501,NCT01306214,NCT01422876,NCT01011868,NCT00855166,NCT02220920,NCT00972244,
NCT01022112,NCT01413204,NCT01294423,NCT01193218,NCT01368081,NCT01095653
Other data resources :Astrazeneca,boehringeringelheim
We only proposed to do participant-level data meta-analysis .

What is the purpose of the analysis being proposed? Please select all that apply.
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources
Participant-level data meta-analysis
Participant-level data meta-analysis using only data from YODA Project
Participant-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 source:We searched the following sources from inception of each database to the specified date and placed no restrictions on the language of publication.
• Cochrane Central Register of Controlled Trials (CENTRAL) (15 January 2019).
• PubMed (subsets not available on Ovid) (15 January 2019).
• EMBASE <1974 to 2016 January 20> (15 January 2019).
• ClinicalTrials.gov (15 January 2019).

Inclusion criteria:
?Types of studies
RCT,reported cardiovascular outcomes were included
?Types of participants
Adults with T2DM
?Diagnostic criteria for people at risk of T2DM development
The diagnosis should have been established using the standard criteria valid at the trial start
(e.g. ADA 1997; ADA 2010; NDDG 1979; WHO 1999)
?Types of interventions
Intervention:SGLT 2 inhibitors
Comparator:Placebo
?Minimum duration of intervention
irrespective of the duration

Exclusion criteria:
?metabolic syndrome
?Pregnancy
?participants with intermediate hyperglycaemia in combination with another condition, e.g. cystic fibrosis, acute myocardial infarction and stroke, if such trials were identified.

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

Main outcomes:All-cause mortality, cardiovascular mortality and heart failure
Additional outcomes:Myocardial infarction,stroke.

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

• Age.

• Gender
• BMI
• HbA1c
• Duration of T2DM
• Duration of intervention
• Comorbidities and complications

Statistical Analysis Plan:

The primary endpoint of this study is comparisons of the all-cause mortality, cardiovascular mortality and heart failure odds ratios between SGLT-2 inhibitors and placebo in T2DM patients.
The secondary endpoints are designed to compare myocardial infarction and stroke between the two treatments,i.e. SGLT-2 inhibitors and placebo.
Then the data will be further stratified into two groups according to the racial groups(Asian, Caucasian,Africa American,etc.)
Continuous outcomes will be evaluated by computing the weighted mean differences (WMDs) and 95% confidence intervals (CIs). Categorical outcomes will be evaluated by computing the odds ratios (ORs) and accompanying 95% CIs.Due to between-study heterogeneity, Higgins I2 statistics is used to evaluate the percentage of variance. A high level of heterogeneity is defined as I2 > 50%; a low level of heterogeneity is defined as I2?50%. Publication bias will be assessed via a visual inspection of funnel plot.Statistical significance was considered at P < 0.05.Statistical analyses were primarily performed using the Review Manager statistical software package (version 5.3;Nordic Cochrane Centre, Copenhagen, Denmark). Analyses were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.
Software Used:
Open Office
Project Timeline:

15/07/2019 Preliminary searches
15/07/2019-21/07/2019 Piloting of the study selection process
22/07/2019-25/08/2019 Formal screening of search results against eligibility criteria
26/08/2019-31/12/2019 Data request
01/01/2020-29/02/2020 Data extraction
01/03/2020-31/03/2020 Risk of bias (quality) assessment
01/04/2020-30/04/2020 Data analysis
01/05/2020-31/05/2020 Drafting manuscript
01/06/2020 First submitted for publication
01/08/2020 Results reported back to the YODA Project

Dissemination Plan:

This research results are plan to published on the Journal of Diabetes Obes Metab.

Bibliography:

1.Basem M. Mishriky,James R. Powell,Jennifer A. Wittwer,et al.Do GLP-1RAs and SGLT-2is reduce cardiovascular events in black patients with type 2 diabetes? A systematic review and meta-analysis[J].Diabetes Obes Metab. 2019:1-10.
2.Saad M , Mahmoud A N , Elgendy I Y , et al. Cardiovascular outcomes with sodium–glucose cotransporter-2 inhibitors in patients with type II diabetes mellitus: A meta-analysis of placebo-controlled randomized trials[J]. International Journal of Cardiology, 2016:S0167527316336580.
3.Woodward M. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region.[J]. Diabetes Care, 2003, 26(2):360-366.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/sglt-2xin_xie_guan_feng_xian_zai_bu_tong_chong_zu_de_yan_jiu_-zhu_ce_2.pdf