Principal Investigator

First Name: Ruth
Last Name: Sim
Degree: Pharmacy
Primary Affiliation: Monash University Malaysia
E-mail: Ruth.Sim@monash.edu
Phone number: 0184054420
Address:
Jalan Lagoon Selatan, Bandar Sunway, 47500
City: Subang Jaya
State or Province: Selangor
Zip or Postal Code: 47500
Country: Malaysia

General Information

Key Personnel (in addition to PI):
First Name: Ruth
Last name: Sim
Degree: Bachelor of Pharmacy
Primary Affiliation: Monash University Malaysia
SCOPUS ID: 0000-0002-5667-9521

First Name: Shaun
Last name: Lee Wen Huey
Degree: Phd in pharmacy
Primary Affiliation: Monash University Malaysia
SCOPUS ID: 0000-0001-7361-6576

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?: Internet Search

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_ruth.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_1.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

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

Mellitus

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

Research Proposal

Project Title

Cardiorenal outcomes of second-line antidiabetic drugs in patients with Type 2 diabetes: a systematic review and network meta-analysis

Narrative Summary:

The rise in new antidiabetic drugs have provided clinicians with more choices to tailor Type 2 diabetes mellitus pharmacotherapy according to patient characteristics. In comparison to older second-line antidiabetic drugs like sulphonylurea, these drugs have comparable glycaemic control and better side effect profile. Additionally, some of these these drugs confer cardiorenal benefits in cardiovascular outcome trials. This study aims to compare efficacy and cardiorenal effectiveness of second-line antidiabetic drugs after metformin using systematic review and network meta-analysis.

Scientific Abstract:

Background
The rise in new antidiabetic drugs have provided clinicians with more choices to tailor Type 2 diabetes mellitus pharmacotherapy according to patient characteristics. In comparison to older second-line antidiabetic drugs like sulphonylurea, these drugs have comparable glycaemic control and better side effect profile. Additionally, some of these drugs confer cardiorenal benefits in cardiovascular outcome trials. The comparative effectiveness these drugs remain unclear.
Objective
To compare the cardiovascular and renal effectiveness of second-line antidiabetic drugs in patients with Type 2 diabetes mellitus.
Study Design
EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials will be searched for RTCs reporting cardiovascular and renal outcomes.
Participants
Patients with Type 2 diabetes mellitus
Main Outcome Measure(s)
Cardiovascular outcomes including MACE, myocardial infarction, stroke, cardiovascular death, cardiovascular mortality, all-cause mortality, unstable angina, heart failure, transient ischemic attack,
Renal outcomes including renal composite outcome, development of end-stage renal disease, decline in eGFR, dialysis, kidney transplantation, renal death, loss of kidney function, acute kidney injury.

Statistical Analysis
Network meta-analysis and pairwise meta-analysis will be conducted. Statistical heterogeneity in effects between studies calculating by the I^2 index. Publication bias will be assessed using funnel plot. Statistical analysis will be carried in R statistical software.

Brief Project Background and Statement of Project Significance:

Diabetes mellitus is a metabolic disorder currently affecting 463 million adults worldwide. Among them, 90% are Type 2 Diabetes Mellitus (T2DM) patients(1). In comparison to healthy populations, T2DM patients are at higher risk for cardiovascular and renal problems which might lead to disabilities and deaths. Lifestyle changes and metformin are the first line treatments to achieve glycaemic control. However, most T2DM patients require a combination of drugs to keep their blood glucose within the recommended limit. While traditional oral antidiabetic drugs are useful in keeping blood glucose in control, they are often characterized by their limited beneficial effects on long term outcomes including cardiovascular and renal effects. In the last two decades, the rise in approval of

oral antidiabetic drugs by United States Food and Drug Administration (FDA) has provided us with more choices to tailor therapies according to patient characteristics(2). These include drugs like dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium-glucose co-transporter-2 (SGLT2) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, bile acid sequestrants and dopamine-2 agonists. Previous reviews focused on the cardiovascular outcomes of respective drug class and there is limited number of reviews that look at both the cardiovascular and renal outcomes of these drugs as a whole. Additionally previous systematic reviews have not included some of the more recent cardiovascular and renal outcome trials(3,4).

Specific Aims of the Project:

To compare the cardiovascular and renal effectiveness of second-line antidiabetic drugs in patients with Type 2 diabetes mellitus using systematic review and network meta-analysis.

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
Confirm or validate previously conducted research on treatment effectiveness
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:

Trials included: NCT02128932, NCT01720446, NCT02692716, NCT01394952, NCT01179048, NCT01147250, NCT02465515, NCT01144338, NCT00968708, NCT00790205, NCT01107886, NCT01243424, NCT01897532, NCT02065791, NCT01131676, NCT01730534, NCT00968812, NCT00377676, NCT01959529, NCT00700856, NCT00174993, NCT00379769, NCT00069784, NCT00145925, NCT00954447, NCT01167881, NCT00856284, NCT00622284, NCT01106677

Search on Medline, Embase, and Cochrane Central Register of Controlled Trials up to February 2020
Inclusion criteria: 1) RCT 2) Patients with Type 2 diabetes 3) Study population more than 1000 patients 4) Standard of care background including mmetformin 5) reported at least one of cardiovascular outcomes including MACE, myocardial infarction, stroke, cardiovascular death or renal outcomes including renal composite outcome, development of end-stage renal disease, changes in eGFR and urine creatine ratio, dialysis, kidney transplantation, renal death, loss of kidney function and acute kidney injury 7) Second-line antidiabetic drugs including drugs of drugs
Exclusion criteria: conference report, letter or abstract

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

Cardiovascular outcomes including MACE, myocardial infarction, stroke, cardiovascular death, cardiovascular mortality, all-cause mortality, unstable angina, heart failure
Renal outcomes including renal composite outcome, development of end-stage renal disease, decline in eGFR, dialysis, kidney transplantation, renal death, loss of kidney function, acute kidney injury.
Adverse events: Hypoglycaemia, Gastrointestinal disorder, acute pancreatitis, Serious adverse event, Adverse event, Fracture, Neoplasm, Urinary tract infection, Genital infection, Amputation, Volume depletion, Sensitivity reaction

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

History of cardiovascular disease, study follow-up period

Statistical Analysis Plan:

Number of events and participants will be collected for summary level meta-analysis. Results of dichotomous outcomes will be reported as risk ratio and continuous data will be reported as mean difference, together with corresponding 95% confidence intervals.

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

Pairwise meta-analysis will be carried out with trials pooled using random-effect inverse variance method. Heterogeneity between studies will be assessed by using I2 statistics, with I2 of <25% as low, 25-75% moderate and >75% high.
Network meta-analysis will be conducted. Drug of different doses will be combined into single dose. SUCRA will be used to assess intervention effectiveness. Local and global inconsistency will be assessed. Additionally, comparison-adjusted funnel plot is used to identify bias of small-study effects.Statistical analysis will be carried in R statistical software.
Sensitivity analysis will be conducted by excluding trials with high risk of bias, trials which only makes up less than 2 trials per arm.
Systematic review will be reported in line with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.
Software Used:
R

Project Timeline:

8/02/2020-1/03/2020 Formal screening of search results against eligibility criteria
1/03/2020-31/04/2020 Data request
01/04/2020-01/06/2020 Data extraction
01/06/2020-1/07/2020 Data analysis
01/07/2020-1/09/2020 Drafting manuscript
01/10/2020 First submitted for publication
01/10/2020 Results reported back to the YODA Project

Dissemination Plan:

Potentially suitable journals: Journal of Diabetes Obes Metab

Bibliography:

1. IDF Diabetes Atlas 9th edition 2019. Diabetesatlas.org. 2019.
2. What are the direct medical costs of managing Type 2 Diabetes Mellitus in Malaysia?. Med J Malaysia. 2019;72(5):271-277.
3. Grenet G, Ribault S, Nguyen G, Glais F, Metge A, Linet T et al. GLUcose COntrol Safety & Efficacy in type 2 DIabetes, a systematic review and NETwork meta-analysis. PLOS ONE. 2019;14(6):e0217701.
4. Fei Y, Tsoi M, Cheung B. Cardiovascular outcomes in trials of new antidiabetic drug classes: a network meta-analysis. Cardiovascular Diabetology. 2019;18(1).

Supplementary Material:

https://yoda.yale.edu/sites/default/files/prospero_ruth_100220_sr_nma_cardiorenal_antidiabetic.pdf
https://yoda.yale.edu/sites/default/files/yoda_changes_271221.pdf