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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?: Internet Search

Conflict of Interest

https://yoda.yale.edu/system/files/s38c0034719102316450.pdf
https://yoda.yale.edu/system/files/s38c0034719102316451.pdf
https://yoda.yale.edu/system/files/image_aj.pdf
https://yoda.yale.edu/system/files/image_ck.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 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

Exploration of regional heterogeneity in trials assessing the efficacy of recent non-insulin glucose lowering drugs on cardiovascular outcomes

Narrative Summary:

Recently marketed drugs, such as glucagon-like peptide-1 receptor agonist and sodium glucose linked transporter-2 inhibitor, have further shown efficacy to reduce cardiovascular events in type 2 diabetes (derived from international clinical trials). In a preliminary subgroup meta-analysis of trials assessing the efficacy of glucagon-like peptide (GLP-1) analogs and sodium-glucose cotransporter 2 (SGLT2) inhibitors on cardiovascular outcomes, we have shown that geographic variations might exist (8). We thus aim at confirming these preliminary results with more recent data, and at further exploring these differences.

Scientific Abstract:

Background. Cardiovascular events are considered as the foremost cause of death in patients with type 2 diabetes. Recently marketed drugs, such as glucagon-like peptide-1 receptor agonist and sodium glucose linked transporter-2 inhibitor, have shown efficacy to reduce cardiovascular events in large RCTs. In a preliminary analysis (1), we have shown that geographic variations might exist in these trials, suggesting that benefit from these drugs might differ according to the region of the world.
Objective. The primary objective of this study is to assess whether the efficacy of GLP-1 analogs and SGLT-2 inhibitors on cardiovascular events is homogenous across the different regions of the world, and if not, to find the factors explaining such variability.
Study design. Sub-group meta-analyses of RCTs according to the region of inclusion and development status (defined according to the UN classification) will be conducted.
Participants. Patients with type 2 diabetes included in large RCTs assessing the safety and efficacy of GLP-1 analogs and SGLT-2 inhibitors.
Main outcome measures. Major cardiovascular events, defined as a composite of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, +/- hospitalization for unstable angina.
Statistical analysis. Hazard ratios for subgroups will be computed and interaction tests between subgroups will be conducted<0.05. Individual patient data meta-analysis will be conducted to assess the influence of covariates.

1. Roustit et al, N Engl J Med 2017, 376;12:1196-97.

Brief Project Background and Statement of Project Significance:

Major Adverse Cardiovascular Events (MACE) are considered as the foremost cause of death in patients with type 2 diabetes (1,2). While most oral glucose-lowering drugs have shown efficacy to control chronic hyperglycemia, glucagon-like peptide-1 receptor agonists (GLP-1Ra) and glucose-sodium co-transporter inhibitors (SGLT2i) further present efficacy in reducing cardiovascular events, or even all-cause mortality (3). Yet, there were some discrepancies in the results between the different large randomized, controlled, trials assessing the effect of these agents on MACE. The American Diabetes Association (ADA), has reported that causes of variability in the efficacy of current therapies against diabetes mellitus are multifactorial (4).

Among them, geographic variations in clinical trials are a well-known phenomenon, and they can be attributed to several factors: genetic variations (5), differences in lifestyle, diet, background therapy, or treatment adherence, etc (6). In 2013, Panagiotou et al. conducted a meta-epidemiological review of 139 meta-analyses with mortality as the main outcome, regrouping 1297 clinical trials, and showed that the treatment effects were more favorable in developing countries, vs higher income countries (7), suggesting that development status was a prominent contributor to regional heterogeneity. In order to explore whether geographic variations existed in trials assessing the efficacy of GLP-1Ra and SGLT2i, we conducted a subgroup meta-analysis including 25,725 patients, which revealed a greater benefit on MACE in trials subgroups conducted in Latin America, Africa and Asia, in comparison with those in Europe and North America (8). Yet, interpreting these results should be done with caution, especially because there was a limited number of trials. Furthermore, we could not explain whether these differences were attributed to development status or other causes, since individual patient data of detailed data per region were not available.

1. Hicks KA, et al. J Am Coll Cardiol. 28 juill 2015;66(4):403?69.
2. Røder ME. Ther Adv Chronic Dis. jan 2018;9(1):33?50.
3. Zheng SL, et al JAMA. 17 avr 2018;319(15):1580?91.
4. Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S1?2.
5. Moon MK, et al. Diabetes Metab J. oct 2017;41(5):357?66.
6. Yusuf S, Wittes J. N Engl J Med. 8 déc 2016;375(23):2263?71.
7. Panagiotou OA, et al. BMJ. 12 févr 2013;346:f707.
8. Roustit M, et al. N Engl J Med. 23 2017;376(12):1196?7.

Specific Aims of the Project:

The objective of this work is thus to expand and update our preliminary study with more recent data. The primary aim is to assess whether there is significant heterogeneity in the effect size of recent non-insulin antidiabetics (SGLT2i and GLP-1Ra), on cardiovascular outcomes, according to the region of patient inclusion and to development status. We further aim at explaining these differences using individual-patient data.

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
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:

We will search all eligible randomized controlled trials (RCTs) assessing the efficacy of SGLT-2 inhibitors and GLP-1 agonists versus placebo in patient with type 2 diabetes mellitus. We will restrict our research to these two drug classes only, since they are the only classes which demonstrated a significant effect on cardiovascular outcomes in latest meta-analyses (see for example Zheng et al.) (3). Language restrictions include studies published in English or French; there is no restrictions regarding the publication period. The search will be conducted in MEDLINE® and the Cochrane database. Additional search of non-published trials through registries (i.e. clinicaltrials.gov) will be conducted.
1.Eligibility criteria
RCTs will be deemed eligible if one of the primary or secondary endpoint is major cardiovascular events (MACE) validated by an adjudication committee. Moreover, only international multicenter trials will be selected.
2.Participants/ population
Patients with Type 2 Diabetes mellitus, males and female, aged >=18 years.

We recently obtained agreement to access data from other trials (semaglutide & liraglutide, Novo Nordisk).

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

The main outcome is major cardiovascular event (MACE), defined as a composite of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, +/- hospitalization for unstable angina.

Additional outcomes are death from any cause, death from cardiovascular causes, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, transient ischemic attack, coronary revascularization procedure, hospitalization for cardiovascular causes.

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

Data per region are usually available only for the primary outcome. We therefore address a request to the sponsors of these trials to obtain individual patient data or aggregated data per region for all the variables of interest. The following data are requested, from most to least preferred:
1. Individual patient data
2. Data by country. In order to avoid any breach of confidentiality regarding personal data, countries for which 15 patients or less were included in a single trial will be excluded. Data by country will allow addressing whether variability is related to geographic variations or development status.
3. Alternatively, aggregated data by region, and by development status will be sought. There will be 14 regions, following the UN definition: Northern America, Latin America and the Caribbean, Northern Africa, Sub-Saharan Africa, Northern Europe, Southern Europe, Eastern Europe, Western Europe, Central Asia, Eastern Asia, South-eastern Asia, Southern Asia, Western Asia and Oceania; and there will be 2 development status: developed and developing .

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

o Characteristics of the study (authors, year of publication, regions, number of participants by country, follow-up duration, study design);
o Characteristics of participants at baseline (age, sex, ethnicity, BMI, heart rate, systolic and diastolic pressure, HbA1c, fasting glucose, eGFR, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, current smoking, family history of cardiovascular disease, hypertension, coronary artery disease, peripheral artery disease, cerebrovascular disease, heart failure, stroke, myocardial infarction, atrial fibrillation, duration of diabetes, retinopathy, neuropathy, nephropathy);
o Concomitant medication at baseline (insulin, metformin, sulfonylurea, DPP4 inhibitor, SGLT-2 inhibitor, GLP-1 analog, thiazolidinediones, antiplatelet agents, angiotensin converting enzyme inhibitor or angiotensin II receptor blockers, beta-blocker, statin, ezetimibe, diuretics);
o Cardiovascular outcomes (main outcomes and additional outcomes listed above).

Statistical Analysis Plan:

This systematic review complies with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement guideline(9)(10).
The protocol and systematic search strategy are available online (PROSPERO registry, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=120221). Data extraction will be conducted independently by two reviewers. Any discrepancy will be solved by a third reviewer.
A. Data collection and protection
An electronic database will be created for the study and validated by a data manager from Grenoble Alpes University Hospital. Data entry will be performed by the investigation team, under the responsibility of the principal investigator. Any person allowed to complete the database will be clearly identified in the document describing task distribution. Electronic data will be kept on a specific, secured research shared drive hosted by Grenoble Alpes University Hospital, with restricted access. No data will be stored on personal computers or USB drives.
B. Data analysis
Subgroup meta-analyses of extracted hazard ratio according to the region of inclusion and development status will be conducted. A test of subgroup difference <0.05 will be considered as significant, as previously done in our preliminary assessment (Roustit et al, N Engl J Med 2017, 376;12:1196-97) (8). Regions and development status will be defined according to the UN classification (11). If available, individual patient data will be used to explore covariates potentially associated with these geographic differences. Otherwise, meta-regression analyses will be performed to assess the potential influence of predetermined variables of interest (type of gluycose-lowering, baseline characteristics of patients, study characteristics). All statistical analyses will be performed using R statistical software (version 3.2.4), with the metafor and meta packages for direct meta-analyses.

We indeed identified additional trials, and obtained access to the full data for a few of them. However, data access

through portals do not permit to merge all the data into a single database. In addition, others have published summary results by region. Therefore, the purpose is to use the data from these 2 trials, to conduct the analyses, and then merge the summary data with already calculated estimates from others trials.
Software Used:
RStudio
Project Timeline:

Anticipated project start date : Janvier 2020
Analysis completion date : December 2020
Date manuscrit drafted and first submitted for publication : March 2021
Date results reported back to the YODA project : January 2021

Dissemination Plan:

The results are going to be presented as article:
Tentative title : “Exploration of regional heterogeneity in trials assessing the efficacy of recent non-insulin glucose lowering drugs on cardiovascular outcomes”
Estimated Submission Date : March 2021
Examples of target journal: Diabetes Care, Diabetes Obesity & Metabolism, JCEM

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