Principal Investigator

First Name: Florian
Last Name: Naudet
Degree: MD, PhD
Primary Affiliation: Université de Rennes 1
E-mail: gouraudh@gmail.com
Phone number:
Address:
2 Avenue du Professeur Léon Bernard
City: Rennes
State or Province: Bretagne
Zip or Postal Code: 35000
Country: France

General Information

Key Personnel (in addition to PI):
First Name: Henri
Last name: Gouraud
Degree: Master 2 degree student
Primary Affiliation: Rennes 1 University

First Name: Florian
Last name: Naudet
Degree: MD, PhD
Primary Affiliation: Rennes 1 University
SCOPUS ID: 393620700500

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: French ANR (ANR-17-CE36-0010)
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_4_0.pdf
https://yoda.yale.edu/system/files/microsoft_word_-_yoda_project_coi_fn_form_for_data_requestors_2019_5.docx_-_copie.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. 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
7. 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
8. 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
9. NCT01381900 - 28431754DIA3014 - A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, 18-Week 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 Alone or in Combination With a Sulphonylurea
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. 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. 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
13. 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

Vibration of effects in pooled analyses of Canagliflozin vs placebo, randomized, double blind trials

Narrative Summary:

In this case study, we will explore VoE in pooled analyses of clinical trials focusing on clinical trials evaluating the efficacy and safety of Canagliflozin in the treatment of type 2 diabetes mellitus. We will use IPD from trials data that

are available for other researchers within the YODA (Yale University Open Data Access) project (https://yoda.yale.edu/).
We will perform all possible pooled analyses comparing Canaglifozin versus Placebo to explore how much three different outcomes can change across the universe of all possible combinations of trials. Our evaluation will focus on efficacy (HbA1c and MACE, i.e. Major Cardiovascular Events) and one safety (SAE i.e. Serious Adverse Event)

Scientific Abstract:

background: Vibration of effect (VoE) describes the extent to which an effect may change under multiple distinct analyses, such as different model specifications in epidemiological research (1): any analysis involves a universe of possible analytical choices that might influence the effects observed.
objective: In this case study, we will explore VoE in pooled analyses of clinical trials focusing on clinical trials evaluating the efficacy and safety of Canagliflozin in the treatment of type 2 diabetes mellitus.
study design: case study
participants: Studies were identified and selected from the YODA project platform. Preliminary searches identified 13 study datasets fulfilling our inclusion criteria.
Main outcome measure: Effect sizes will be expressed in terms of: Mean difference for HbA1c; Hazard ratio for Major Cardio-vascular Events (this will be analyzed as survival data / the first event will be considered); Hazard ratio for Serious Adverse Events (this will be analyzed as survival data / the first event will be considered);
Statistical analysis: HbA1c measures, MACE and serious adverse events, will be analyzed in 3 different analyses. All these analyses will be performed for different timepoints. In each pooled analysis, data will be pooled using a one?stage IPD meta?analysis approach. We will compute the distribution of point estimates of these effect sizes and their corresponding p values under various analytical scenarios defined by the combination of studies.

Brief Project Background and Statement of Project Significance:

Vibration of effect (VoE) describes the extent to which an effect may change under multiple distinct analyses, such as different model specifications in epidemiological research (1): any analysis involves a universe of possible analytical choices that might influence the effects observed. More recently, such a phenomenon has been identified in the field of evidence synthesis, with the case study of indirect comparisons of naltrexone versus nalmefene (2) two similar drugs used in the treatment of alcohol use disorders. This is of concern because evidence synthesis is generally considered as a very reliable domain resulting in high grade evidence. There is therefore a need to explore VoE for various methods of evidence synthesis, such as for instance pooled analyses.

Indeed, performing pooled analyses of randomized controlled trials (i.e. non-exhaustive quantitative syntheses that pool individual patient data (IPD) from several independent trials exploring similar research questions) is a common practice in therapeutic research. For instance, for the antidepressant duloxetine, 43 pooled-trials publications were found for 30 papers which explored the efficacy of duloxetine in a clinical trial for the treatment of major depression (3). Pooled analyses often explore secondary analyses (e.g. subgroup effects) or examine new questions (3)(4). In other situations, the increased sample size resulting from pooling different studies may help to solve power issues of the initial studies. However, in contrast with individual patient data meta-analysis, pooled analyses are not exhaustive of all the available studies retrieved in a systematic review and may be prone to p-hacking by selecting a posteriori combination of studies based on their results (3). And indeed, the use of pooled analyses has been described as a strategy used by pharmaceutical firms to “hide” negative studies results by publishing these studies with the positive ones (5). In addition, a posteriori selection of clinical trials to be pooled may result in differences in observed results and the multiplicity of possibilities it involves implies a certain degree of VoE.

We decided to explore this question in the field of Type 2 diabetes mellitus. There is still a tension in this field about the clinical value of the drugs that reduce chronic hyperglycemia. While there is no doubt about efficacy of these drugs on the surrogate marker of HBA1C levels, there is still a heated debate about their impact on clinical outcomes including cardiovascular ones (6). The case study of rosiglitazone even suggests that this drug was associated with an increase in Serious adverse events and more specifically a cardiovascular risk, especially for heart failure events (7). Canaglifozin is such a drug used for glycemic control and data of its clinical development program are shared on YODA platform making any analysis of VoE possible. We therefore designed this study to explore VoE in pooled analyses of clinical trials evaluating the efficacy and safety of Canagliflozin in the treatment of type 2 diabetes mellitus.

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Specific Aims of the Project:

In this case study, we will explore VoE in pooled analyses of clinical trials focusing on clinical trials evaluating the efficacy and safety of Canagliflozin in the treatment of type 2 diabetes mellitus. We will use IPD from trials data that are available for other researchers within the YODA (Yale University Open Data Access) project (https://yoda.yale.edu/).
We will perform all possible pooled analyses comparing Canaglifozin versus Placebo to explore how much three different outcomes can change across the universe of all possible combinations of trials. Our evaluation will focus on efficacy (HbA1c and MACE, i.e. Major Cardiovascular Events) and one safety (SAE, i.e. Serious Adverse Events) outcome.

Our hypotheses are that VoE will not be observed for HbA1c while it will be observed for both MACE and SAE. There will be no specific statistical test for this as the existence of VoE is defined by very simple descriptive parameters described in the analysis section.

What is the purpose of the analysis being proposed? Please select all that apply.
Research on clinical trial methods

Research Methods

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

Studies will be selected if they meet the following criteria:
? Patient population:
o At least 18 years old;
o Diagnosis of type 2 diabetes mellitus;
o All sexes are accepted;
o All BMI are accepted;
o All screening HbA1c concentration are accepted;
? Intervention:
o Canagliflozin at a dose between 100 and 300mg;
o This could be used in association with another treatment or not;
? Comparator:
o Placebo only;
? Outcomes:
o HbA1c (primary or secondary outcomes);
o Major cardiovascular events (MACE) during all the study period (that can be retrieved within the serious adverse events);
o Serious Adverse Events during all the study period;
? Study design:
o Randomized, controlled, double blind trials.

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

Effect sizes will be expressed in terms of:
? Mean difference for HbA1c;
? Hazard ratio for Major Cardio-vascular Events (this will be analyzed as survival data / the first event will be considered);
? Hazard ratio for Serious Adverse Events (this will be analyzed as survival data / the first event will be considered);

We will compute the distribution of point estimates of these effect sizes (ESs) and their corresponding p values under various analytical scenarios defined by the combination of individual studies. Pooled analyses will be considered to be “statistically significant” if the ES is associated with a p value < 0.05. The presence of a “Janus effect” will be investigated by calculating the 1st and 99th percentiles of the distribution of the ES (8). A Janus effect will be defined as an ES which is in the opposite direction between the 1st and 99th percentiles of pooled analyses. It demonstrates the presence of substantial VoE (8). Our hypotheses are that VoE will not be observed for HbA1c while it will be observed for both MACE and SAE.

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

Effect sizes will be expressed in terms of:
? Mean difference for HbA1c;
? Hazard ratio for Major Cardio-vascular Events (this will be analyzed as survival data / the first event will be considered);
? Hazard ratio for Serious Adverse Events (this will be analyzed as survival data / the first event will be considered);

Statistical Analysis Plan:

HbA1c measures, MACE and serious adverse events, will be analyzed in 3 different analyses. All these analyses will be performed for different timepoints: (12 [or closest date], 18 [or closest date], 26 [or closest date] and 52 weeks [or closest date]).

In each pooled analysis defined above, data will be pooled using a one?stage IPD meta?analysis approach that will analyze all the patient?level data from all the trials in a single step, using a hierarchical (random effects) model that accounts for the clustering of patients within studies.

Effect sizes will be expressed in terms of:
? Mean difference for HbA1c;
? Hazard ratio for Major Cardio-vascular Events (this will be analyzed as survival data / the first event will be considered);
? Hazard ratio for Serious Adverse Events (this will be analyzed as survival data / the first event will be considered);

We will compute the distribution of point estimates of these effect sizes (ESs) and their corresponding p values under various analytical scenarios defined by the combination of individual studies. Pooled analyses will be considered to be “statistically significant” if the ES is associated with a p value < 0.05. The presence of a “Janus effect” will be investigated by calculating the 1st and 99th percentiles of the distribution of the ES (8). A Janus effect will be defined as an ES which is in the opposite direction between the 1st and 99th percentiles of pooled analyses. It demonstrates the presence of substantial VoE (8). Our hypotheses are that VoE will not be observed for HbA1c while it will be observed for both MACE and SAE.

All analyses will be performed using R (https://www.r-project.org/). The results will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) format (http://www.prisma-statement.org/). The data and code will be shared on the Open Science Framework (https://osf.io/). The protocol will be registered on the Open Science Framework (https://osf.io/) before starting the study.
Software Used:
R
Project Timeline:

Project start : May 2020
Data request : September 2020
Analyses start : March 2021
Project finish : September 2021

Dissemination Plan:

We will try to publish this case study as a case study article in a medical journal as BMJ.

Bibliography:

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8. Patel CJ, Burford B, Ioannidis JPA. Assessment of vibration of effects due to model specification can demonstrate the instability of observational associations. Journal of Clinical Epidemiology. 2015 Sep 1;68(9):1046–58.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/protocol.pdf