**Population-Level Estimation:**

***Trials Replication through Observational study by Yonsei (TROY)***

**Version:** 0.3

Kyung Won Kim, MD, PhD, Yonsei University, Korea

Seng Chan You, MD PhD, Yonsei University, Korea

Jaehyeong Cho, PhD, Yonsei University, Korea

Kyuri Jeon, BPH, Yonsei University, Korea

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# List of abbreviations

ATC Anatomic Therapeutic Chemical

CYCLOPS Cyclic coordinate descent for logistic, Poisson and survival analysis

SNOMED Systematized Nomenclature of Medicine

OHDSI Observational Health Data Sciences and Informatics

OMOP Observational Medical Outcomes Partnership

T Target cohort

C Comparator cohort

O Outcome cohort

PS Propensity Scores

LASSO Least absolute shrinkage and selection operator

CI Confidence Interval

T2DM Type 2 diabetes mellitus

MACE Major Adverse Cardiovascular Events

3P MACE Classical 3-point MACE

HHF Hospitalization for Heart Failure

ACS Acute Coronary Syndrome

MI Myocardial Infarction

GLP-1 Glucose like peptide-1

DPP-4 Dipeptidyl peptidase-4

SGLT-2 Sodium-glucose linked transporter-2

SU Sulfonylurea  
TNF Tumor necrosis factor

RCT Randomized clinical trial

MedDRA Medical Dictionary for Regulatory Activities

# Abstract

In this study we will generate population-level estimates at scale for four diseases: T2DM, atrial fibrillation, acute coronary syndrome, and rheumatoid arthritis. We compare the outcomes among drugs corresponding to each RCT being emulated.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | 1 Mar 2022 | KW. Kim, SC. You, J. Cho, K. Jeon | Initial draft |
| 0.2 | 10 Oct 2022 | KW. Kim, SC. You, J. Cho, K. Jeon | Update document |
| 0.3 | 22 Jun 2023 | KW. Kim, SC. You, J. Cho, K. Jeon | Update document: rationale and background, study population |

# Milestones

|  |  |
| --- | --- |
| Milestone | Planned / Estimated Date |
| Start of analysis | 1 March 2022 |
| End of analysis |  |
| Presentation of results |  |

# Rationale and Background

Randomized controlled trials (RCTs) are considered the gold standard for evaluating medical products, but their ability to fully demonstrate effectiveness in clinical practice is questionable. In the true population, there may be patients with different characteristics from the RCT criteria, suggesting that the effects of the interventions obtained from RCTs may not be completely applicable to the clinical practice. Real-world evidence (RWE) generated from rigorously designed studies is gaining attention as a complementary approach to address this issue. Previous research has attempted to validate the external validity of RCTs by conducting replication studies using real-world data (RWD). The findings of the DUPLICATE study highlight the potential of selected database studies to supplement RCT evidence to understand drug effects in clinical practice.1,2 In addition, Averitt et al compared data from four RCTs with actual data and found significant differences in the clinical characteristics of patients, questioning the generalizability of the RCT results.3 Therefore, we initiated ‘Trials Replication through Observational study by Yonsei (TROY)’ project to generate large population-level evidence for 15 pivotal RCTs in the real world: Type 2 diabetes mellitus, atrial arrhythmia, acute coronary syndrome, and rheumatoid arthritis. We compare outcomes between drugs for each pivotal RCT emulated using the packages included in HADES (formally known as the OHDSI Methods Library).

## Research Questions

In this study, we are interested in comparing selected treatments (target drug [class] Vs comparator drug [class]) in table 1.

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Target drug (class) | Comparator drug (or class) | Note |
| LEADER ​ | Liraglutide ​(GLP-1) | DPP-4 | Placebo-controlled RCT  Initial US approval: 01/26/2010  Initial KR approval: 10/06/2010 |
| DECLARE-TIMI 58 ​ | Dapagliflozin ​(SGLT-2) | DPP-4 | Placebo-controlled RCT  Initial US approval: 01/08/2014  Initial KR approval: 11/26/2013 |
| EMPA-REG OUTCOME ​ | Empagliflozin ​(SGLT-2) | DPP-4 | Placebo-controlled RCT  Initial US approval: 03/31/2014  Initial KR approval: 08/12/2014 |
| CANVAS ​ | Canagliflozin ​(SGLT-2) | DPP-4 | Placebo-controlled RCT  Initial US approval: 03/29/2013  Initial KR approval: 04/14/2014 |
| CARMELINA ​ | Linagliptin (DPP-4) | SU | Placebo-controlled RCT  Initial US approval: 05/02/2011  Initial KR approval: 09/14/2011 |
| TECOS ​ | Sitagliptin (DPP-4) | SU | Placebo-controlled RCT  Initial US approval: 10/16/2006  Initial KR approval: 09/21/2007 |
| SAVOR-TIMI 53 ​ | Saxagliptin (DPP-4) | SU | Placebo-controlled RCT  01/24/2011 |
| CAROLINA ​ | Linagliptin (DPP-4) | Glimepiride | In the CAROLINA trial, comparator drug was glimepiride  Initial US approval: 07/31/2009  Initial KR approval: 09/14/2011 |
| TRITON-TIMI 38 ​ | Prasugrel | Clopidogrel | Initial US approval: 07/10/2009  Initial KR approval: 07/29/2010 |
| PLATO ​ | Ticagrelor | Clopidogrel | Initial US approval: 07/20/2011  Initial KR approval: 07/22/2011 |
| ROCKET AF ​ | Rivaroxaban ​ | Warfarin ​ | Initial US approval: 07/01/2011  Initial KR approval: 02/29/2012 |
| ARISTOTLE ​ | Apixaban ​ | Warfarin ​ | Initial US approval: 12/28/2012  Initial KR approval: 02/27/2013 |
| ENGAGE AF-TIMI 48 ​ | Edoxaban ​ | Warfarin ​ | Initial US approval: 07/01/2015  Initial KR approval: 08/25/2015 |
| ORAL​ | Tofacitinib ​ | TNF inhibitor​ | Initial KR approval: 04/02/2014 |
| STAR-RA​ | Tofacitinib​ | TNF inhibitor​ | Initial KR approval: 04/02/2014 |

**Table 1**. List of treatments considered in this study

To compare the drugs (or classes) of the target and comparator, we are interested in the comparative effect on the outcome listed by study in Table 2.

|  |  |  |
| --- | --- | --- |
| Outcome | Description | Study |
| 3P MACE | 3P MACE, a composite outcome of cardiovascular events, was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. | LEADER, EMPA-REG OUTCOME, CANVAS, CARMELINA, SAVOR-TIMI 53, CAROLINA, TRITON-TIMI 38, PLATO, ORAL |
| HHF + Cardiovascular death | A composite outcome of the first occurrence of hospitalization for heart failure or death from cardiovascular causes. | DECLARE-TIMI 58 |
| Stroke + systemic embolism | A composite outcome of the first occurrence of stroke or systemic embolism. | ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48 |
| 3P MACE + Angina | 3P MACE or angina. | TECOS |
| Cancer | Any cancers (excluding nonmelanoma skin cancer). | ORAL |
| MI + stroke | Myocardial infarction or stroke. | STAR-RAL |

**Table 2.** The outcome in this study

Research question

* What is the hazard ratio for the occurrence of 3P MACE between treatment liraglutide and DPP-4?
* What are the differences in the clinical characteristics of patients included in the LEADER trial and those treated according to the liraglutide or DPP-4 indication?
* What is the hazard ratio for the occurrence of HHF + cardiovascular death between treatment dapagliflozin and DPP-4?
* What are the differences in the clinical characteristics of patients included in the DECLARE-TIMI 58 trial and those treated according to the dapagliflozin or DPP-4 indication?
* What is the hazard ratio for the occurrence of 3P MACE between treatment empagliflozin and DPP-4?
* What are the differences in the clinical characteristics of patients included in the EMPA-REG OUTCOME trial and those treated according to the empagliflozin or DPP-4 indication?
* What is the hazard ratio for the occurrence of 3P MACE between treatment canagliflozin and DPP-4?
* What are the differences in the clinical characteristics of patients included in the CANVAS trial and those treated according to the canagliflozin or DPP-4 indication?
* What is the hazard ratio for the occurrence of 3P MACE between treatment linagliptin and SU?
* What are the differences in the clinical characteristics of patients included in the CARMELINA trial and those treated according to the linagliptin or SU indication?
* What is the hazard ratio for the occurrence of 3P MACE between treatment sitagliptin and SU?
* What are the differences in the clinical characteristics of patients included in the TECOS trial and those treated according to the sitagliptin or SU indication?
* What is the hazard ratio for the occurrence of 3P MACE between treatment saxagliptin and SU?
* What are the differences in the clinical characteristics of patients included in the SAVOR-TIMI 53 trial and those treated according to the saxagliptin or SU indication?
* What is the hazard ratio for the occurrence of 3P MACE between treatment linagliptin and SU?
* What are the differences in the clinical characteristics of patients included in the CAROLINA trial and those treated according to the linagliptin or glimepiride indication?
* What is the hazard ratio for the occurrence of 3P MACE between treatment prasugrel and clopidogrel?
* What are the differences in the clinical characteristics of patients included in the TRITON-TIMI 38 trial and those treated according to the prasugrel or clopidogrel indication?
* What is the hazard ratio for the occurrence of 3P MACE between treatment ticagrelor and clopidogrel?
* What are the differences in the clinical characteristics of patients included in the PLATO trial and those treated according to the ticagrelor or clopidogrel indication?
* What is the hazard ratio for the occurrence of stroke + systemic embolism between treatment rivaroxaban and warfarin?
* What are the differences in the clinical characteristics of patients included in the ROCKET AF trial and those treated according to the rivaroxaban or warfarin indication?
* What is the hazard ratio for the occurrence of stroke + systemic embolism between treatment apixaban and warfarin?
* What are the differences in the clinical characteristics of patients included in the ARISTOTLE trial and those treated according to the apixaban or warfarin indication?
* What is the hazard ratio for the occurrence of stroke + systemic embolism between treatment edoxaban and warfarin?
* What are the differences in the clinical characteristics of patients included in the ENGAGE AF-TIMI 48 trial and those treated according to the edoxaban or warfarin indication?
* What is the hazard ratio for the occurrence of cancer between treatment tofacitinib and TNF inhibitor?
* What are the differences in the clinical characteristics of patients included in the ORAL trial and those treated according to the tofacitinib or TNF inhibitor indication?
* What is the hazard ratio for the occurrence of MI + stroke between treatment tofacitinib and TNF inhibitor?
* What are the differences in the clinical characteristics of patients included in the STAR-RA trial and those treated according to the tofacitinib or TNF inhibitor indication?

## Objectives

Primary objective

* Generate evidence for the comparative effectiveness for each pairwise comparison of treatments for the outcomes of interest.
* Generate evidence for differences in clinical characteristics of each trial-RWD pair in the intervention for the pivotal trial of interest

Secondary objectives

* Asses the bias inherent in each analysis by including negative and positive control outcomes.

# Research methods

## Study Design

This study will be a set of retrospective, observational, new-user cohort studies. By ‘retrospective’ we mean the study will use data already collected at the start of the study. By ‘observational’ we mean no intervention will take place in the course of this study. By ‘new-user’ we mean we will only analyze the first exposure of a subject to the treatment of interest. By ‘cohort study’ we mean two cohorts, a target and comparator cohort, will be followed from index date (start of first exposure) to some end date, and assessed for the occurrence of the outcomes of interest.

## Data Source(s)

The analyses will be performed across a network of observational healthcare databases. All databases have been transformed into the OMOP Common Data Model, version 5. The complete specification for OMOP Common Data Model, version 5 is available at: <https://github.com/OHDSI/CommonDataModel>. The following databases will be included in this analysis:

* Yonsei University Health System database (YUHS)
* Ajou University School of Medicine database (AUSOM)

### Yonsei University Health System (YUHS)

### Ajou University School of Medicine database (AUSOM)

## Study population

All subjects in the database meeting the disease criteria for each replication study are included. (Note: The index date is the start date of first treatment in each replication study)

* Replication study 1: LEADER trial4
* Replication study 2: DECLARE-TIMI 58 trial5
* Replication study 3: EMPA-REG OUTCOME trial6
* Replication study 4: CANVAS trial7
* Replication study 5: CARMELINA trial8
* Replication study 6: TECOS trial9
* Replication study 7: SAVOR-TIMI 53 trial10
* Replication study 8: CAROLINA trial11
* Replication study 9: TRITON-TIMI 38 trial12
* Replication study 10: PLATO trial13
* Replication study 11: ROCKET AF trial14
* Replication study 12: ARISTOTLE trial15
* Replication study 13: ENGAGE AF-TIMI 48 trial16
* Replication study 14: ORAL trial17
* Replication study 15: STRA-RA trial18

### Study population: replication study 1 (LEADER trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for type 2 diabetes)

* A diagnose of T2DM on or preceding the index date
* Exposure to one of the treatments of interest
* The duration of exposure to the therapeutic drug should be 7 days or more
* At least 180 days of observation time prior to the index date

#### Exposures: liraglutide (LEADER trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of liraglutide.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the LEADER trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: DPP-4 (LEADER trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of DPP-4.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the LEADER trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: liraglutide

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of liraglutide.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

#### Exposures: DPP-4

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of DPP-4.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

### Replication study 2 (DECLARE-TIMI 58 trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for T2DM)

* A diagnose of T2DM on or preceding the index date
* Exposure to one of the treatments of interest
* The duration of exposure to the therapeutic drug should be 7 days or more
* At least 180 days of observation time prior to the index date

#### Exposures: dapagliflozin (DECLARE-TIMI 58 trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of dapagliflozin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the DECLARE-TIMI 58 trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: DPP-4 (DECLARE-TIMI 58 trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of DPP-4.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the DECLARE-TIMI 58 trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: dapagliflozin

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of dapagliflozin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

#### Exposures: DPP-4

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of DPP-4.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

### Replication study 3 (EMPA-REG OUTCOME trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for T2DM)

* A diagnose of T2DM on or preceding the index date
* Exposure to one of the treatments of interest
* The duration of exposure to the therapeutic drug should be 7 days or more
* At least 180 days of observation time prior to the index date

#### Exposures: empagliflozin (EMPA-REG OUTCOME trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of empagliflozin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the EMPA-REG OUTCOME trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: DPP-4 (EMPA-REG OUTCOME trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of DPP-4.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the EMPA-REG OUTCOME trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: empagliflozin

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of empaglifozin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

#### Exposures: DPP-4

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of DPP-4.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

### Replication study 4 (CANVAS trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for T2DM)

* A diagnose of T2DM on or preceding the index date
* Exposure to one of the treatments of interest
* The duration of exposure to the therapeutic drug should be 7 days or more
* At least 180 days of observation time prior to the index date

#### Exposures: canagliflozin (CANVAS trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of canagliflozin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the CANVAS trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: DPP-4 (CANVAS trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of DPP-4.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the CANVAS trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: canagliflozin

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of canagliflozin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

#### Exposures: DPP-4

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of DPP-4.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

### Replication study 5 (CARMELINA trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for T2DM)

* A diagnose of T2DM on or preceding the index date
* Exposure to one of the treatments of interest
* The duration of exposure to the therapeutic drug should be 7 days or more
* At least 180 days of observation time prior to the index date

#### Exposures: linagliptin (CARMELINA trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of linagliptin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the CARMELINA trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: DPP-4 (CARMELINA trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of sulfonylureas.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the CRMELINA trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: linagliptin

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of linagliptin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

#### Exposures: sulfonylureas

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of sulfonylureas.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

### Replication study 6 (TECOS trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for T2DM)

* A diagnose of T2DM on or preceding the index date
* Exposure to one of the treatments of interest
* The duration of exposure to the therapeutic drug should be 7 days or more
* At least 180 days of observation time prior to the index date

#### Exposures: sitagliptin (TECOS trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of sitagliptin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the TECOS trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: sulfonylureas (TECOS trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of sulfonylureas.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the TECOS trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: sitagliptin

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of sitagliptin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

#### Exposures: sulfonylureas

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of sulfonylureas.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

### Replication study 7 (SAVOR-TIMI 53 trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for T2DM)

* A diagnose of T2DM on or preceding the index date
* Exposure to one of the treatments of interest
* The duration of exposure to the therapeutic drug should be 7 days or more
* At least 180 days of observation time prior to the index date

#### Exposures: saxagliptin (SAVOR-TIMI 53 trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of saxagliptin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the SAVOR-TIMI 53 trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: DPP-4 (SAVOR-TIMI 53 trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of sulfonylureas.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the SAVOR-TIMI 53 trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: saxagliptin

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of saxagliptin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

#### Exposures: sulfonylureas

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of sulfonylureas.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

### Replication study 8 (CAROLINA trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for T2DM)

* A diagnose of T2DM on or preceding the index date
* Exposure to one of the treatments of interest
* The duration of exposure to the therapeutic drug should be 7 days or more
* At least 180 days of observation time prior to the index date

#### Exposures: linagliptin (CAROLINA trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of linagliptin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the CAROLINA trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: DPP-4 (CAROLINA trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of sulfonylureas.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control
* In addition, the inclusion/exclusion criteria follow the CAROLINA trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: linagliptin

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of linagliptin.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

#### Exposures: sulfonylureas

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of sulfonylureas.

Inclusion rules based on the index date:

* A diagnose of T2DM on or preceding the index date
* Patients without a diagnosis of Type 1 DM
* Patients without a diagnosis of acute decompensation of glycemic control

### Replication study 9 (TRITON-TIMI 38 trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for ACS)

* Exposure to one of the treatments of interest
* The duration of exposure to the therapeutic drug should be 7 days or more
* At least 180 days of observation time prior to the index date
* A diagnosis of ACS within 7 days or on the index date

#### Exposures: prasugrel (TRITON-TIMI 38 trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of prasugrel.

Inclusion rules based on the index date:

* In addition, the inclusion/exclusion criteria follow the TRITON-TIMI 38 trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: clopidogrel (TRITON-TIMI 38 trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of clopidogrel.

Inclusion rules based on the index date:

* In addition, the inclusion/exclusion criteria follow the TRITON-TIMI 38 trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: prasugrel

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of prasugrel.

#### Exposures: clopidogrel

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of clopidogrel.

### Replication study 10 (PLATO trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for ACS)

* Exposure to one of the treatments of interest
* The duration of exposure to the therapeutic drug should be 7 days or more
* At least 180 days of observation time prior to the index date
* A diagnosis of ACS within 7 days or on the index date

#### Exposures: prasugrel (PLATO trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of ticagrelor.

Inclusion rules based on the index date:

* In addition, the inclusion/exclusion criteria follow the PLATO trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: clopidogrel (PLATO trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of clopidogrel.

Inclusion rules based on the index date:

* In addition, the inclusion/exclusion criteria follow the PLATO trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: ticagrelor

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of ticagrelor.

#### Exposures: clopidogrel

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of clopidogrel.

### Replication study 11 (ROCKET AF trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for atrial fibrillation)

* Exposure to one of the treatments of interest
* At least 180 days of observation time prior to the index date
* The duration of exposure to the therapeutic drug should be 7 days or more
* A diagnosis of atrial fibrillation within 180 days or on the index date

#### Exposures: rivaroxaban (ROCKET AF trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of rivaroxaban.

Inclusion rules based on the index date:

* Patients without a diagnosis of hemodynamically significant mitral valve stenosis
* Patients not treated with TAVR
* Patients who have not undergone dual antiplatelet therapy within 1 year
* In addition, the inclusion/exclusion criteria follow the ROCKET AF trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: warfarin (ROCKET AF trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of warfarin.

Inclusion rules based on the index date:

* Patients without a diagnosis of hemodynamically significant mitral valve stenosis
* Patients not treated with TAVR
* Patients who have not undergone dual antiplatelet therapy within 1 year
* In addition, the inclusion/exclusion criteria follow the ROCKET AF trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: rivaroxaban

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of rivaroxaban.

Inclusion rules based on the index date:

* Patients without a diagnosis of hemodynamically significant mitral valve stenosis
* Patients not treated with TAVR
* Patients who have not undergone dual antiplatelet therapy within 1 year

#### Exposures: warfarin

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of warfarin.

Inclusion rules based on the index date:

* Patients without a diagnosis of hemodynamically significant mitral valve stenosis
* Patients not treated with TAVR
* Patients who have not undergone dual antiplatelet therapy within 1 year

### Replication study 12 (ARISTOTLE trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the first treatment for atrial fibrillation)

* Exposure to one of the treatments of interest
* At least 180 days of observation time prior to the index date
* No exposure of any atrial fibrillation treatment before the index date
* A diagnose of atrial fibrillation on or preceding the index date
* No diagnose of the outcome of interest preceding the index date
* With age greater or equal to 18

#### Exposures: replication study 13

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) of interest (apixaban and warfarin).

Inclusion rules based on the index date:

* At least 180 days of observation time prior to the index date
* No exposure to the target or comparator ingredient(s) before the index date
* A diagnose of atrial fibrillation on or preceding the index date

### Replication study 13 (ENGAGE AF-TIMI 48 trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for atrial fibrillation)

* Exposure to one of the treatments of interest
* At least 180 days of observation time prior to the index date
* The duration of exposure to the therapeutic drug should be 7 days or more
* A diagnosis of atrial fibrillation within 180 days or on the index date

#### Exposures: edoxaban (ENGAGE AF-TIMI 48 trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of edoxaban.

Inclusion rules based on the index date:

* Patients without a diagnosis of hemodynamically significant mitral valve stenosis
* Patients not treated with TAVR
* Patients who have not undergone dual antiplatelet therapy within 1 year
* In addition, the inclusion/exclusion criteria follow the ENGAGE AF-TIMI 48, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: warfarin (ENGAGE AF-TIMI 48 AF trial)

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of warfarin.

Inclusion rules based on the index date:

* Patients without a diagnosis of hemodynamically significant mitral valve stenosis
* Patients not treated with TAVR
* Patients who have not undergone dual antiplatelet therapy within 1 year
* In addition, the inclusion/exclusion criteria follow the ENGAGE AF-TIMI 48 trial, and detailed rules can be found at the following link: https://a.co.kr.

#### Exposures: edoxaban

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of rivaroxaban.

Inclusion rules based on the index date:

* Patients without a diagnosis of hemodynamically significant mitral valve stenosis
* Patients not treated with TAVR
* Patients who have not undergone dual antiplatelet therapy within 1 year

#### Exposures: warfarin

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient of warfarin.

Inclusion rules based on the index date:

* Patients without a diagnosis of hemodynamically significant mitral valve stenosis
* Patients not treated with TAVR
* Patients who have not undergone dual antiplatelet therapy within 1 year

### Replication study 14 (ORAL trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for rheumatoid arthritis)

* Exposure to one of the treatments of interest
* At least 180 days of observation time prior to the index date
* No exposure of any rheumatoid arthritis treatment before the index date
* A diagnose of rheumatoid arthritis on or preceding the index date

#### Exposures: replication study 14

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) of interest (tofacitinib and TNF inhibitor).

Inclusion rules based on the index date:

* At least 180 days of observation time prior to the index date
* No exposure to the target or comparator ingredient(s) before the index date
* A diagnose of rheumatoid arthritis on or preceding the index date

### Replication study 15 (STRA-RA trial)

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for rheumatoid arthritis)

* Exposure to one of the treatments of interest
* At least 180 days of observation time prior to the index date
* A diagnose of rheumatoid arthritis on or preceding the index date

#### Exposures: replication study 15

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) of interest (tofacitinib and TNF inhibitor).

Inclusion rules based on the index date:

* At least 180 days of observation time prior to the index date
* No exposure to the target or comparator ingredient(s) before the index date
* A diagnose of rheumatoid arthritis on or preceding the index date

## Outcomes

### 3P MACE

**Cohort Entry Events**People may enter the cohort when observing any of the following:

1. condition occurrences of 'Acute myocardial Infarction'.
2. condition occurrences of 'Sudden cardiac death'.
3. condition occurrences of 'Ischemic stroke'.
4. condition occurrences of ' Intracranial bleed Hemorrhagic stroke'.

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit', starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

**Cohort Exit**  
The cohort end date will be offset from index event's start date plus 7 days.

**Cohort Eras**  
Entry events will be combined into cohort eras if they are within 180 days of each other.

### 3P MACE + angina

**Cohort Entry Events**People may enter the cohort when observing any of the following:

1. condition occurrences of 'Acute myocardial Infarction'.
2. condition occurrences of 'Sudden cardiac death'.
3. condition occurrences of 'Ischemic stroke'.
4. condition occurrences of ' Intracranial bleed Hemorrhagic stroke'.
5. condition occurrences of ' Unstable angina'.

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit', starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

**Cohort Exit**  
The cohort end date will be offset from index event's start date plus 7 days.

**Cohort Eras**  
Entry events will be combined into cohort eras if they are within 180 days of each other.

### HHF + cardiovascular death

**Cohort Entry Events**People enter the cohort when observing any of the following:

1. visit occurrences of 'Inpatient or ER visit'; with any of the following criteria:
   1. having at least 1 condition occurrence of '[LEGEND-T2DM] Heart Failure ', starting between 0 days before and all days after 'Inpatient or ER visit' start date and starting anytime on or before 'Inpatient or ER visit' end date.
   2. having at least 1 condition occurrence of '[LEGEND HTN] Sudden cardiac death', starting between 0 days before and all days after 'Inpatient or ER visit' start date and starting anytime on or before 'Inpatient or ER visit' start date.

**Cohort Exit**  
The cohort end date will be offset from index event's end date plus 0 days.

**Cohort Eras**  
Entry events will be combined into cohort eras if they are within 7 days of each other.

### Stroke + systemic embolism

**Cohort Entry Events**People may enter the cohort when observing any of the following:

1. condition occurrences of 'Stroke (ischemic or hemorrhagic)', a condition type that is: "primary condition".
2. condition occurrences of 'systemic embolism', a condition type that is: "primary condition".

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit', starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

**Cohort Exit**  
The cohort end date will be offset from index event's start date plus 7 days.

**Cohort Eras**  
Entry events will be combined into cohort eras if they are within 180 days of each other.

### Cancer

**Cohort Entry Events**People may enter the cohort when observing any of the following:

1. condition occurrence of 'Malignant neoplasm except non-melanoma skin cancer' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

**Cohort Entry Events**

1. Hospitalization with primary diagnosis of cancer
   1. Entry events having at least 1 condition occurrence of 'Malignant neoplasm except non-melanoma skin cancer', starting between 0 days after and all days after cohort entry start date; a condition type that is: "primary condition", "inpatient detail - primary", "inpatient detail - primary position", "inpatient header - primary", "inpatient header - primary position" or "first position condition"; a visit occurrence that is: "emergency room visit", "inpatient visit" or "emergency room and inpatient visit".

**Cohort Exit**  
The person exits the cohort at the end of continuous observation.

**Cohort Eras**  
Entry events will be combined into cohort eras if they are within 0 days of each other.

### Negative control outcomes

Negative controls are concepts known to not be associated with the target or comparator cohorts, such that we can assume the true relative risk between the two cohorts is 1. Negative controls are selected using a similar process to that outlined by Voss et al. Person counts of all potential drug-condition pairs are reviewed in observational data; this person count data helps determine which pairs are even probable for use in calibration. Given the list of potential drug-condition pairs, the concepts in the pairs must meet the following requirements to be considered as negative controls: (1) that there is no Medline abstract where the MeSH terms suggest an association between the drug and the condition, (2) that there is no mention of the drug-condition pair on a US Product Label in the “Adverse Drug Reactions” or “Postmarketing” section, (3) there are no US spontaneous reports suggesting that the pair is in an adverse event relationship, (4) that the OMOP Vocabulary does not suggest that the drug is indicated for the condition, (5) that the concepts are usable (i.e. not too broad, not suggestive of an adverse event relationship, not pregnancy related), and (6) the exact concept itself is utilized in patient level data (i.e. concepts that are not usually used within the data are usually indicative a broad concept that has a child that is more specific). The remaining concepts are “optimized”, meaning parent concepts remove children as defined by the OMOP Vocabulary (e.g. if both “Non-Hodgkin’s Lymphoma” and “B-Cell Lymphoma” we selected, child concept “B-Cell Lymphoma would be removed for its parent “Non-Hodgkin’s Lymphoma”). Once potential negative control candidates were selected, manual clinical review to exclude any pairs that may still be in a causal relationship or similar to the study outcome was be performed to select the top concepts by patient exposure. The final list can be found in Table 3.

|  |  |
| --- | --- |
| Abnormal cervical smear | Homocystinuria |
| Abnormal pupil | Human papilloma virus infection |
| Abrasion and/or friction burn of trunk without infection | Ileostomy present |
| Absence of breast | Impacted cerumen |
| Absent kidney | Impingement syndrome of shoulder region |
| Acid reflux | Ingrowing nail |
| Acquired hallux valgus | Injury of knee |
| Acquired keratoderma | Irregular periods |
| Acquired trigger finger | Kwashiorkor |
| Acute conjunctivitis | Late effect of contusion |
| Amputated foot | Late effect of motor vehicle accident |
| Anal and rectal polyp | Leukorrhea |
| Burn of forearm | Macular drusen |
| Calcaneal spur | Melena |
| Cannabis abuse | Nicotine dependence |
| Cervical somatic dysfunction | Noise effects on inner ear |
| Changes in skin texture | Nonspecific tuberculin test reaction |
| Chondromalacia of patella | Non-toxic multinodular goiter |
| Cocaine abuse | Onychomycosis due to dermatophyte |
| Colostomy present | Opioid abuse |
| Complication due to Crohn's disease | Passing flatus |
| Contact dermatitis | Postviral fatigue syndrome |
| Contusion of knee | Presbyopia |
| Crohn's disease | Problem related to lifestyle |
| Derangement of knee | Psychalgia |
| Difficulty sleeping | Ptotic breast |
| Disproportion of reconstructed breast | Regular astigmatism |
| Effects of hunger | Senile hyperkeratosis |
| Endometriosis | Somatic dysfunction of lumbar region |
| Epidermoid cyst | Splinter of face, without major open wound |
| Feces contents abnormal | Sprain of ankle |
| Foreign body in orifice | Strain of rotator cuff capsule |
| Ganglion cyst | Tear film insufficiency |
| Genetic predisposition | Tobacco dependence syndrome |
| Hammer toe | Vaginitis and vulvovaginitis |
| Hereditary thrombophilia | Verruca vulgaris |
| Herpes zoster without complication | Wrist joint pain |
| High risk sexual behavior | Wristdrop |

**Table 3**. Negative control outcomes

For each negative control outcome, a patient enters the negative control outcome cohort at the occurrence of a diagnose code identified by the concepts listed above, or any one of its descendant codes.

## Covariates

### Propensity score covariates

Propensity scores (PS) will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates.

The types of baseline covariates used to fit the propensity score model will be:

* Demographics
  + Gender
  + Age
  + Age group (5-year bands)
  + Index year
  + Index month
* Conditions
  + In prior 30d
  + In prior 365d
* Condition aggregation
  + SNOMED
* Drugs
  + In prior 30d
  + In prior 365d
  + Overlapping index date
* Drug aggregation
  + Ingredient
  + ATC Class
* Procedure
  + In prior 30d
  + In prior 365d
* Risk scores
  + Charlson comorbidity index

All covariates that occur in fewer than 0.1% of the persons between the target and comparator cohorts combined will be excluded prior to model fitting for computational efficiency.

# Data Analysis Plan

## Calculation of time-at risk

Two time-at-risk periods will be used:

* On-treatment. Starting on the day of treatment initiation, and stopping at treatment end, allowing for a maximum gap of 30 days between prescriptions.
* Intent-to-treat: Starting on the day of treatment initiation and stopping at the end of observation.

## Model Specification

In this study, we compare the target cohort with the comparator cohort for the hazards of outcome during the time-at-risk by applying a Cox proportional hazards model.

The time-to-event of outcome among patients in the target and comparator cohorts is determined by calculating the number of days from the start of the time-at-risk window (the cohort start date), until the earliest event among 1) the first occurrence of the outcome, 2) the end of the time-at-risk window as defined in section 9.1 (i.e. ‘on-treatment’ or ‘intent-to-treat’), and 3) the end of the observation period that spans the time-at-risk start.

Patients with the outcome observed prior to target or comparator cohort entry are excluded from consideration.

Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates. In this study, the propensity score is estimated for each patient, using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross, a starting variance of 0.01 and a tolerance of 2e-7. Covariates to be used in the propensity score model are listed in section 8.6.

In one analysis the target cohort and comparator cohorts will be stratified into ten quantiles of the propensity score distribution. A second analysis will use variable ratio matching based on the propensity score, using a caliper of 0.2 on the standardized logit scale. The final outcome model will apply a conditional Cox proportional hazard model, conditioned on the propensity score strata or matched sets.

Incidence rates will be computed for each outcome in each exposure group, in both the on-treatment and intent-to-treat windows.

### Pooling effect estimates across databases

Effects will be pooled across databases using a random-effects meta-analysis. Estimates for negative and positive controls will be pooled before performing empirical calibration on the pooled estimates.

## Analyses to perform

### Comparative analyses

The following comparative analyses will be performed if sufficient data is present

* 15 comparison between two target and comparator treatments
  + Target drug\*Outcome of interest\*Analysis settings (15\*1\*4) =60
* One outcome of interest corresponding to each replicate study
* 2 time-at-risk definitions: on-treatment and intent-to-treat
* 4 models: Cox regression using propensity score stratification and Cox regression using 1:1 and variable ratio propensity score matching

### Descriptive analyses

The following incidence rate computations will be performed:

* 60 cohorts of interest:
  + 15 target and comparator
    - RCT criteria cohort
    - Indication cohort
* One outcome of interest corresponding to each replicate study
* 2 time-at-risk definitions: on-treatment and intent-to-treat
* databases: YUHS CDM and AUSOM CDM

## Output

The output will be stored, which is described elsewhere.

## Evidence Evaluation

We have executed diagnostics to determine if the analysis can be appropriately conducted. The diagnostics include:

* Propensity score distribution
* Covariate balance before and after propensity score matching
* Estimation for negative controls, to assess residual error
* Negative control exposures and outcomes will be used to evaluate the potential impact of residual systematic error in the study design, and to facilitate empirical calibration of the p-value and confidence interval for the exposures and outcome of interest.

Negative control outcomes in the context of this study are outcomes that are not believed to be caused by neither exposure in any comparison and where therefore the true hazard ratio is equal to 1. We will execute the same analysis used for the primary hypotheses to produce hazard ratio estimates for the negative controls. The distribution of effect estimates across all negative controls will be used to fit an empirical null distribution which models the observed residual systematic error. The empirical null distribution will then be applied to the target exposures and outcome of interest to calibrate the p-value.

Empirical calibration serves as an important diagnostic tool to evaluate if the residual systematic error is sufficient to cast doubt on the accuracy of the unknown effect estimate. The calibration effect plot and calibration probability plots will be generated for review. We will report the traditional and empirically calibrated p-value and confidence interval for each negative control, as well as the hypothesis of interest.

# Study Diagnostics

## Sample Size and Study Power

This will be reported in the output.

## Cohort Comparability

This will be reported in the output.

## Systematic Error Assessment

This will be reported in the output.

# Strengths and Limitations of the Research Methods

Strength

* Cohort studies allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date.
* PS matching allow balancing on a large number of baseline potential confounders.
* Use of negative and positive control outcomes allow for evaluating the study design as a whole in terms of residual bias.

Limitations

* Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or misspecified confounders.

# Protection of Human Subjects

The study is using only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

# Management and Reporting of Adverse Events and Adverse Reactions

This study uses coded data that already exist in an electronic database. In this type of database, it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse events reports. The study results will be assessed for medically important results.

# Plans for Disseminating and Communicating Study Results

The study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

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