**Population-Level Estimation:**

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

**Version:** 0.1

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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 (and class) corresponding to each RCT being emulated.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | 1 Mar 2022 | KW. Kim, SC. You, J. Cho, K. Jeon | Initial draft |

# Milestones

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

# Rationale and Background

The TROY (Trials Replication through Observational studY) project aims to generate real-world evidence of the effectiveness of medical interventions by conducting studies that replicate previously performed RCTs using observational healthcare data.

This study employs pivotal RCTs that are plausible to emulate from real world data, makes estimates at the population-level designed to be as similar as possible, compares results, and evaluates external validity.

## 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 KR approval: 10/06/2010 |
| DECLARE-TIMI 58 ​ | Dapagliflozin ​(SGLT-2) | DPP-4 | Placebo-controlled RCT  Initial KR approval: 11/26/2013 |
| EMPA-REG OUTCOME ​ | Empagliflozin ​(SGLT-2) | DPP-4 | Placebo-controlled RCT  Initial KR approval: 08/12/2014 |
| CANVAS ​ | Canagliflozin ​(SGLT-2) | DPP-4 | Placebo-controlled RCT  Initial KR approval: 04/14/2014 |
| ~~NCT01505426 ​~~ | ~~Ipragliflozin ​(SGLT-2)~~ | ~~DPP-4~~ | ~~Placebo-controlled RCT~~ |
| CARMELINA ​ | Linagliptin (DPP-4) | SU | Placebo-controlled RCT  Initial KR approval: 09/14/2011 |
| TECOS ​ | Sitagliptin (DPP-4) | SU | Placebo-controlled RCT  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 KR approval: 09/14/2011 |
| TRITON-TIMI 38 ​ | Prasugrel | Clopidogrel | Initial KR approval: 07/29/2010 |
| PLATO ​ | Ticagrelor | Clopidogrel | Initial KR approval: 07/22/2011 |
| ROCKET AF ​ | Rivaroxaban ​ | Warfarin ​ | Initial KR approval: 02/29/2012 |
| ARISTOTLE ​ | Apixaban ​ | Warfarin ​ | Initial KR approval: 02/27/2013 |
| ENGAGE AF-TIMI 48 ​ | Edoxaban ​ | Warfarin ​ | 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 |
| ~~T2DM remission~~ | ~~HbA1c<=6.5?, Fasting glucose.~~ | ~~NCT01505426~~ |
| 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 (GLP-1) and DPP-4?
* What is the hazard ratio for the occurrence of HHF + cardiovascular death between treatment dapagliflozin (SGLT-2) and DPP-4?
* What is the hazard ratio for the occurrence of 3P MACE between treatment empagliflozin (SGLT-2) and DPP-4?
* What is the hazard ratio for the occurrence of 3P MACE between treatment canagliflozin (SGLT-2) and DPP-4?
* What is the hazard ratio for the occurrence of T2DM remission ipragliflozin (SGLT-2) and DPP-4?
* What is the hazard ratio for the occurrence of 3P MACE between treatment linagliptin (DPP-4) and SU?
* What is the hazard ratio for the occurrence of 3P MACE between treatment sitagliptin (DPP-4) and SU?
* What is the hazard ratio for the occurrence of 3P MACE between treatment saxagliptin (DPP-4) and SU?
* What is the hazard ratio for the occurrence of 3P MACE between treatment linagliptin (DPP-4) and SU?
* What is the hazard ratio for the occurrence of 3P MACE between treatment prasugrel and clopidogrel?
* What is the hazard ratio for the occurrence of 3P MACE between treatment ticagrelor and clopidogrel?
* What is the hazard ratio for the occurrence of stroke + systemic embolism between treatment rivaroxaban and warfarin?
* What is the hazard ratio for the occurrence of stroke + systemic embolism between treatment apixaban and warfarin?
* What is the hazard ratio for the occurrence of stroke + systemic embolism between treatment edoxaban and warfarin?
* What is the hazard ratio for the occurrence of cancer between treatment tofacitinib and TNF inhibitor?
* What is the hazard ratio for the occurrence of MI + stroke between treatment tofacitinib and TNF inhibitor?

## Objectives

Primary objective

* Generate evidence for the comparative effectiveness for each pairwise comparison of treatments for the outcomes 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)

aaa

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

aaa

## 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 trial
* Replication study 2: DECLARE-TIMI 58 trial
* Replication study 3: EMPA-REG OUTCOME trial
* Replication study 4: CANVAS trial
* Replication study 5: NCT01505426 trial
* Replication study 6: CARMELINA trial
* Replication study 7: TECOS trial
* Replication study 8: SAVOR-TIMI 53 trial
* Replication study 9: CAROLINA trial
* Replication study 10: TRITON-TIMI 38 trial
* Replication study 11: PLATO trial
* Replication study 12: ROCKET AF trial
* Replication study 13: ARISTOTLE trial
* Replication study 14: ENGAGE AF-TIMI 48 trial
* Replication study 15: ORAL trial
* Replication study 16: STRA-RA trial

### 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 first treatment for type 2 diabetes)

* With age greater or equal to 18
* A diagnose of T2DM on or preceding the index date
* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure of any T2DM treatment before the index date
* No diagnose of the outcome of interest preceding the index date

#### Exposures: replication study 1

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of interest (liraglutide [GLP-1] and DPP-4).

Inclusion rules based on the index date:

* At least 365 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 T2DM on or preceding the index date

### 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 first treatment for T2DM)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure of any T2DM treatment before the index date
* A diagnose of T2DM 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 2

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of interest (dapagliflozin [SGLT-2] and DPP-4).

Inclusion rules based on the index date:

* At least 365 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 T2DM on or preceding the index date

### 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 first treatment for T2DM)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure of any T2DM treatment before the index date
* A diagnose of T2DM 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 3

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of interest (empagliflozin [SGLT-2] and DPP-4).

Inclusion rules based on the index date:

* At least 365 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 T2DM on or preceding the index date

### 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 first treatment for T2DM)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure of any T2DM treatment before the index date
* A diagnose of T2DM on or preceding the index date
* No diagnose of the outcome of interest preceding the index date
* No diagnose of ??? preceding the index date
* With age greater or equal to 18

#### Exposures: replication study 4

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of interest (canagliflozin [SGLT-2] and DPP-4).

Inclusion rules based on the index date:

* At least 365 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 T2DM on or preceding the index date

### Replication study 5 (NCT01505426 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 T2DM)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure of any T2DM treatment before the index date
* A diagnose of T2DM 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 5

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of interest (ipragliflozin [SGLT-2] and DPP-4).

Inclusion rules based on the index date:

* At least 365 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 T2DM on or preceding the index date

### Replication study 6 (CARMELINA 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 T2DM)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure of any T2DM treatment before the index date
* A diagnose of T2DM 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 6

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of interest (linagliptin [DPP-4] and SU).

Inclusion rules based on the index date:

* At least 365 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 T2DM on or preceding the index date

### Replication study 7 (TECOS 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 T2DM)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure of any T2DM treatment before the index date
* A diagnose of T2DM 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 7

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of interest (sitagliptin [DPP-4] and SU).

Inclusion rules based on the index date:

* At least 365 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 T2DM on or preceding the index date

### Replication study 8 (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 first treatment for T2DM)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure of any T2DM treatment before the index date
* A diagnose of T2DM 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 8

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of interest (saxagliptin [DPP-4] and SU).

Inclusion rules based on the index date:

* At least 365 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 T2DM on or preceding the index date

### Replication study 9 (CAROLINA 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 T2DM)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure of any T2DM treatment before the index date
* A diagnose of T2DM 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 9

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient(s) or ATC 4th class of interest (linagliptin [DPP-4] and SU).

Inclusion rules based on the index date:

* At least 365 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 T2DM on or preceding the index date

### Replication study 10 (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 first treatment for ACS)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure of any ACS treatment before the index date
* A diagnose of ACS 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 10

Index rule defining the index date:

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

Inclusion rules based on the index date:

* At least 365 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 ACS on or preceding the index date

### Replication study 11 (PLATO 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 ACS)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure of any ACS treatment before the index date
* A diagnose of ACS 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 11

Index rule defining the index date:

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

Inclusion rules based on the index date:

* At least 365 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 ACS on or preceding the index date

### Replication study 12 (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 first treatment for atrial fibrillation)

* Exposure to one of the treatments of interest
* At least 365 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 12

Index rule defining the index date:

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

Inclusion rules based on the index date:

* At least 365 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 (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 365 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 365 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 14 (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 first treatment for atrial fibrillation)

* Exposure to one of the treatments of interest
* At least 365 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 14

Index rule defining the index date:

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

Inclusion rules based on the index date:

* At least 365 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 15 (ORAL 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 rheumatoid arthritis)

* Exposure to one of the treatments of interest
* At least 365 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
* No diagnose of the outcome of interest preceding the index date
* With age greater or equal to 18

#### 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 365 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 16 (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 first treatment for rheumatoid arthritis)

* Exposure to one of the treatments of interest
* At least 365 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
* No diagnose of the outcome of interest preceding the index date
* With age greater or equal to 18

#### Exposures: replication study 16

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 365 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

### HHF + cardiovascular death

### Type 2 diabetes remission

### Stroke + systemic embolism

### Stroke + MI

### Cancer

### 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

* ? comparison between two anti-hypertensive treatments
  + Target drug\*Outcome of interest\*Analysis settings (16\*1\*?) =?
  + Target class\*Outcome of interest\*Analysis settings (9\*1\*?) =?
* One outcome of interest corresponding to each replicate study
* 2 time-at-risk definitions: on-treatment and intent-to-treat
* ?? 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:

* n cohorts of interest:
  + ??
* One outcome of interest corresponding to each replicate study
* 2 time-at-risk definitions: on-treatment and intent-to-treat
* databases: ??

## 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.

# References