OHDSI: Net Adverse Clinical Event between ticagrelor and clopidogrel in patients with Acute Coronary Syndrome

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Table of contents

[2 List of abbreviations 3](#_Toc8307679)

[3 Abstract 3](#_Toc8307680)

[4 Amendments and Updates 4](#_Toc8307681)

[5 Rationale and Background 4](#_Toc8307682)

[6 Study Objectives 5](#_Toc8307683)

[6.1 Primary Hypothesis 5](#_Toc8307684)

[6.2 Secondary Hypotheses 5](#_Toc8307685)

[6.3 Primary objectives 6](#_Toc8307686)

[6.4 Secondary objectives 6](#_Toc8307687)

[7 Research methods 6](#_Toc8307688)

[7.1 Study Design 6](#_Toc8307689)

[7.1.1 Overview 6](#_Toc8307690)

[7.2 Study population 7](#_Toc8307691)

[7.2.1 Primary Study population 7](#_Toc8307692)

[7.2.2 Study population for sensitivity analysis 7](#_Toc8307693)

[7.3 Exposures 8](#_Toc8307694)

[7.3.1 Target: Ticagrelor user with percutaneous coronary intervention due to acute coronary syndrome 8](#_Toc8307695)

[7.3.2 Comparator: Clopidogrel user with percutaneous coronary intervention due to acute coronary syndrome 9](#_Toc8307696)

[7.4 Outcomes 11](#_Toc8307697)

[7.4.1 Outcomes 11](#_Toc8307698)

[7.4.2 Negative controls 13](#_Toc8307699)

[7.5 Covariates 15](#_Toc8307700)

[7.5.1 Propensity score covariates 15](#_Toc8307701)

[7.5.2 Other variables 17](#_Toc8307702)

[8 Data Analysis Plan 17](#_Toc8307703)

[8.1 Calculation of time-at-risk 17](#_Toc8307704)

[8.2 Model specification 17](#_Toc8307705)

[8.2.1 Statistical model for primary analysis 18](#_Toc8307706)

[8.2.2 Statistical model for sensitivity analyses 18](#_Toc8307707)

[8.2.3 Additional details for interaction term analysis 18](#_Toc8307708)

[8.2.4 Pooling effect estimates across databases 18](#_Toc8307709)

[8.3 Analyses to perform 19](#_Toc8307710)

[8.4 Output 19](#_Toc8307711)

[8.5 Evidence Evaluation 20](#_Toc8307712)

[8.6 Data Sources 20](#_Toc8307713)

[8.7 Quality control 20](#_Toc8307714)

[8.8 Strengths and Limitations of the Research Methods 21](#_Toc8307715)

[9 Protection of Human Subjects 21](#_Toc8307716)

[10 Plans for Disseminating and Communicating Study Results 21](#_Toc8307717)

[11 References 22](#_Toc8307718)

[12 Appendix: Concept Set Definitions 24](#_Toc8307719)

# List of abbreviations

ACC American College of Cardiology

AHA American Heart Association

ESC European Society of Cardiology

EACTS European Association for Cardio-Thoracic Surgery

ACS acute coronary syndrome

RCT randomized clinical trial

PLATO PLATelet inhibition and patient Outcomes

OHDSI Observational Health Data Sciences and Informatics

PCI percutaneous coronary intervention

NACE net adverse clinical event

GI gastrointestinal

MI myocardial infarction

CABG coronary artery bypass graft surgery

PS propensity score

# Abstract

The 2016 American College of Cardiology / American Heart Association (ACC/AHA) guideline and 2017 European Society of Cardiology (ESC) / European Association for Cardio-Thoracic Surgery (EACTS) guideline recommended to use ticagrelor on top of aspirin in preference to clopidogrel for patients with acute coronary syndrome (ACS) based on the results from randomized clinical trials (RCT).1,2 The PLATelet inhibition and patient Outcomes (PLATO) trial demonstrated the ticagrelor reduced the rate of death from vascular causes, myocardial infarction, or death, with an increase in the rate of non-procedural-related bleeding.3 Following meta-analysis also concluded in consistent with the PLATO trial.

Still, the real-world evidence evaluating net clinical benefit of ticagrelor over clopidogrel has been scarce. Furthermore, there is a concern that non-White patients, especially Asians and Black people, might be susceptible to anti-thrombotic therapy because of excessive bleeding risk.4,5 In PLATO trial, indeed, Caucasian patients formed most of the enrolled patients, up to 92%.3 The meta-analysis using RCT of East Asian patients reported that ticagrelor was associated with higher risk of major bleeding without significant lower risk of vascular death, myocardial infarction, or stroke.6

Therefore, we aimed to conduct observational study investigating clinical benefit and harm of ticagrelor and clopidogrel in patients with acute control syndrome from various countries and health care systems through observational health data sciences and informatics (OHDSI) network.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | 11 December 2018 | SC You | Initial draft |
| 0.2 | 16 February 2019 | SC You | Revision of definition in outcome definition  More covariates were added for estimation of propensity score. |
| 0.3 | 3 March 2019 | SC You | Revision of the manuscript of statistical analytic plan.  Statistical method of primary analysis was changed from 1-to-1 matching to variable ratio matching to avoid inferior covariate balance and bias reduction.  Sensitivity analyses, which includes only those who start the clopidogrel or ticagrelor from 2013 to 2017, and outcome with narrow definition were added. |
| 1.0 | 9 May 2019 | SC You | Revision of index event for the study population from drug initiation to PCI due to ACS  Positive control section was removed. Some negative controls, which have potential relationship with cardiovascular diseases or antiplatelet drug were removed.  Adding sensitivity analysis with 28-day blanking period of 28 days to exclude duplicated coding for the outcomes |

# Rationale and Background

The 2016 ACC/AHA guideline and 2017 ESC / EACTS guideline recommended to use ticagrelor on top of aspirin in preference to clopidogrel for patients with ACS based on the results from RCTs.1,2 The PLATO trial demonstrated the ticagrelor reduced the rate of death from vascular causes, myocardial infarction, or death, with an increase in the rate of non-procedural-related bleeding.3

Still, the real-world evidence evaluating net clinical benefit of ticagrelor over clopidogrel has been scarce. The internal validity of RCTs is achieved at the expense of limited generalizability. These trials are usually carried out under highly controlled conditions. The enrolled patients in trials are strictly selected by complicated inclusion and exclusion criteria, and they usually obtain exceptional care from medical staffs and show better compliance.7Moreover, inter-ethnic or inter-regional difference in overall net effect can exist because innate genetic or environmental difference can affect the risk/benefit ratio in real-world practice.8 Real-world evidence can provide complementary information to validate the findings from RCTs externally.9

In PLATO trial, the beneficial effect of ticagrelor was not evident in US patients.3 Even though the high maintenance dose of aspirin more than 300mg in US was pointed as responsible culprit for this phenomenon,10 it is worthwhile to evaluate the clinical benefit and harm of ticagrelor in real-world practice. Another small RCT, PHILO study failed to demonstrate clinical benefit of ticagrelor compared to clopidogrel in East Asian patients with ACS, either.11

Hence, we aimed to conduct comparative effectiveness research to establish real-world evidences for benefits and harms of ticagrelor and clopidogrel in patients with acute coronary syndrome through OHDSI network.

# Study Objectives

## Primary Hypothesis

This study’s hypotheses are:

* There is no difference in the incidence of net adverse clinical event between subjects taking ticagrelor and clopidogrel with percutaneous coronary intervention (PCI) for the treatment of acute coronary syndrome within 1 year.

## Secondary Hypotheses

* There is no difference in the incidence of hemorrhagic event between subjects taking ticagrelor and clopidogrel with PCI for the treatment of acute coronary syndrome.
* There is no difference in the incidence of ischemic event between subjects taking ticagrelor and clopidogrel with PCI for the treatment of acute coronary syndrome.
* There is no difference in the incidence of dyspnea event between subjects taking ticagrelor and clopidogrel with PCI for the treatment of acute coronary syndrome.
* There is no difference in the mortality event between subjects taking ticagrelor and clopidogrel with PCI for the treatment of acute coronary syndrome.

## Primary objectives

The overall goal of this protocols is conducting comparative effectiveness research to establish evidences for benefits and harms of ticagrelor and clopidogrel in patients with acute coronary syndrome through OHDSI network.

The primary objective is comparing the risk of net adverse clinical event (NACE) which composed of recurrent myocardial infarction, any revascularization, ischemic stroke, and major bleeding, within 1 year between ticagrelor and clopidogrel user among patients undertook percutaneous coronary intervention due to acute coronary syndrome.

## Secondary objectives

-Comparing use of ticagrelor vs clopidogrel on risk of recurrent myocardial infarction

-Comparing use of ticagrelor vs clopidogrel on risk of any revascularization including PCI and CABG

-Comparing use of ticagrelor vs clopidogrel on risk of ischemic stroke

-Comparing use of ticagrelor vs clopidogrel on risk of intracranial hemorrhage

-Comparing use of ticagrelor vs clopidogrel on risk of gastrointestinal (GI) bleeding

-Comparing use of ticagrelor vs clopidogrel on risk of ischemic event including recurrent MI, any revascularization, and ischemic stroke

-Comparing use of ticagrelor vs clopidogrel on risk of major bleeding event including intracranial hemorrhage and GI bleeding

-Comparing use of ticagrelor vs clopidogrel on risk of dyspnea

-Comparing use of ticagrelor vs clopidogrel on risk of death

# Research methods

## Study Design

### Overview

This study will be a retrospective, observational cohort study. 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 ‘cohort study’ we mean two cohorts, a treatment 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.

The treatment cohort will be users of ticagrelor. The comparator cohort will be users of clopidogrel. For both groups we restrict to people with acute coronary syndrome and underwent PCI, one of the main indications for the drugs of interest. The primary outcome of is net adverse clinical event. Proportional hazard models will be used to assess the hazard ratios between the two exposure cohorts. Adjustment for baseline confounders will be done using propensity scores.

## Study population

### Primary Study population

All subjects in the database will be included who meet the following criteria: (note: the index date is the day of PCI)

* A procedure of PCI1 (index event) with concomitant exposure of ticagrelor2 or clopidogrel3 within same visit for the first time
* 20 years old or older
* At least 365 days of observation time prior to the index date
* A diagnose of ACS4 between 7 days before and 0 days after the index date
* Concomitant aspirin5 use between 7 days before and 0 days after the index date
* Without use of prasugrel6 or the opposing drug within previous 30 days from index date
* No diagnosis of ischemic stroke7 or intracranial hemorrhage8 preceding the index date
* No diagnosis of the GI bleeding9 preceding the index date

### Study population for sensitivity analysis

In Korea, ticagrelor was covered by insurance from March 2013. Additional sensitivity analysis will only those starts the drug from 2013-03-01 to 2016-12-31 for study population.

* A procedure of PCI1 (index event) with concomitant exposure of ticagrelor2 or clopidogrel3 within same visit for the first time
* 20 years old or older
* At least 365 days of observation time prior to the index date
* A diagnose of ACS4 between 7 days before and 0 days after the index date
* Concomitant aspirin5 use between 7 days before and 0 days after the index date
* Without use of prasugrel6 or the opposing drug within previous 30 days from index date
* No diagnosis of ischemic stroke7 or intracranial hemorrhage8 preceding the index date
* No diagnosis of the GI bleeding9 preceding the index date

## Exposures

### Target: Ticagrelor user with percutaneous coronary intervention due to acute coronary syndrome

**Initial Event Cohort**

People having any of the following: 

* a procedure of PCI
  + for the first time in the person's history
  + with age >= 20

Having all of the following criteria:

* + - at least 1 occurrences of a drug exposure of ticagrelor

where event starts between 7 days Before and 0 days After index start date   
occurring within the same visit

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of ACS

where event starts between 7 days Before and 0 days After index start date

Limit cohort of initial events to: earliest event per person.

Inclusion Rules

Inclusion Criteria #1: aspirin

concomittant aspirin

Having all of the following criteria:

* at least 1 occurrences of a drug exposure of aspirin

where event starts between 7 days Before and 0 days After index start date

Inclusion Criteria #2: Without clopidogrel or prasugrel on the day of PCI

Having all of the following criteria:

* at most 0 occurrences of a drug exposure of clopidogrel

where event starts between 30 days Before and 0 days After index start date

* and at most 0 occurrences of a drug exposure of Prasugrel

where event starts between 30 days Before and 0 days After index start date

Inclusion Criteria #3: Without previous stroke

Having all of the following criteria:

* at most 0 occurrences of a condition occurrence of Ischemic stroke

where event starts between all days Before and 0 days After index start date

* and at most 0 occurrences of a condition occurrence of ICH

where event starts between all days Before and 0 days After index start date

Inclusion Criteria #4: Without previous GI bleeding

Having all of the following criteria:

* at most 0 occurrences of a condition occurrence of GI bleeding

where event starts between all days Before and 0 days After index start date

Limit qualifying cohort to: earliest event per person.

End Date Strategy

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of ticagrelor

* allowing 7 days between exposures
* adding 0 days after exposure end

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

### Comparator: Clopidogrel user with percutaneous coronary intervention due to acute coronary syndrome

**Initial Event Cohort**

People having any of the following: 

* a procedure of PCI
  + for the first time in the person's history
  + with age >= 20

Having all of the following criteria:

* + - at least 1 occurrences of a drug exposure of clopidogrel

where event starts between 7 days Before and 0 days After index start date   
occurring within the same visit

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of ACS

where event starts between 7 days Before and 0 days After index start date

Limit cohort of initial events to: earliest event per person.

Inclusion Rules

Inclusion Criteria #1: aspirin

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Having all of the following criteria:

* at least 1 occurrences of a drug exposure of aspirin

where event starts between 7 days Before and 0 days After index start date

Inclusion Criteria #2: Without ticagrelor or prasugrel on the day of PCI

Having all of the following criteria:

* at most 0 occurrences of a drug exposure of ticagrelor

where event starts between 30 days Before and 0 days After index start date

* and at most 0 occurrences of a drug exposure of prasugrel

where event starts between 30 days Before and 0 days After index start date

Inclusion Criteria #3: Without previous stroke

Having all of the following criteria:

* at most 0 occurrences of a condition occurrence of Ischemic stroke

where event starts between all days Before and 0 days After index start date

* and at most 0 occurrences of a condition occurrence of ICH

where event starts between all days Before and 0 days After index start date

Inclusion Criteria #4: Without previous GI bleeding

Having all of the following criteria:

* at most 0 occurrences of a condition occurrence of GI bleeding

where event starts between all days Before and 0 days After index start date

Limit qualifying cohort to: earliest event per person.

End Date Strategy

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of ticagrelor

* allowing 7 days between exposures
* adding 0 days after exposure end

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

## Outcomes

### Outcomes

#### Primary outcome: Net Adverse Clinical Event

Primary outcome includes recurrent acute myocardial infarction9, any revascularization (CABG10 or PCI1), ischemic stroke7, intracranial hemorrhage8, and gastrointestinal bleeding9. All of these conditions should be accompanied by same-day hospitalization

#### Secondary outcome: Ischemic event

Index rule defining the index date:

* Occurrence of acute MI9, any revascularization (CABG10 or PCI1), or ischemic stroke7 event with same-day hospitalization (inpatient or emergency department visit)

#### Secondary outcome: Bleeding event

Index rule defining the index date:

* Occurrence of intracranial hemorrhage8 or gastrointestinal bleeding9 event with same-day hospitalization (inpatient or emergency department visit)

#### Secondary outcome: Recurrent myocardial infarction

Index rule defining the index date:

* Occurrence of acute MI9 code with same-day hospitalization (inpatient or emergency department visit)

#### Secondary outcome: Any revascularization

Index rule defining the index date:

* Occurrence of PCI1 or CABG10 code with same-day hospitalization (inpatient or emergency department visit)

#### Secondary outcome: Ischemic stroke

Index rule defining the index date:

* Occurrence of ischemic stroke7 code with same-day hospitalization (inpatient or emergency department visit)
* Limited to the earliest event

#### Secondary outcome: Intracranial hemorrhage

Index rule defining the index date:

* Occurrence of intracranial hemorrhage8 code with same-day hospitalization (inpatient or emergency department visit)
* Limited to the earliest event

#### Secondary outcome: Gastrointestinal bleeding

Index rule defining the index date:

* Occurrence of GI bleeding9 code with same-day hospitalization (inpatient or emergency department visit)
* Limited to the earliest event

#### Secondary outcome: Dyspnea

Index rule defining the index date:

* Occurrence of dyspnea11 code

#### Secondary outcome: Death

Any death occurrence

### Negative controls

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. [[12](#_ENREF_12)].We believe that negative controls are necessary for confidentiality of study design and statistical method. The concept ids for negative control is described below

|  |  |  |
| --- | --- | --- |
| **Concept ID** | **Concept Code** | **Concept Name** |
| 378256 | 46670006 | Abnormal reflex |
| 4218106 | 7200002 | Alcoholism |
| 440424 | 87486003 | Aphasia |
| 439237 | 52684005 | Assault |
| 378424 | 82649003 | Astigmatism |
| 261880 | 46621007 | Atelectasis |
| 134118 | 400190005 | Atrophic condition of skin |
| 4224118 | 40492006 | Bladder dysfunction |
| 80509 | 203465002 | Bone cyst |
| 434626 | 20010003 | Borderline personality disorder |
| 438407 | 78004001 | Bulimia nervosa |
| 134765 | 238108007 | Cachexia |
| 4172458 | 49883006 | Candidiasis of skin |
| 436740 | 17382005 | Cervical incompetence |
| 381581 | 1482004 | Chalazion |
| 4307254 | 423125000 | Closed fracture |
| 4047787 | 123971006 | Colles' fracture |
| 198075 | 240542006 | Condyloma acuminatum |
| 73302 | 64217002 | Curvature of spine |
| 4242416 | 58588007 | Cutis laxa |
| 433163 | 238107002 | Deficiency of macronutrients |
| 4047269 | 229844004 | Deformity of foot |
| 133228 | 80967001 | Dental caries |
| 4095288 | 26298008 | Diabetic coma with ketoacidosis |
| 4044391 | 230572002 | Diabetic neuropathy |
| 443767 | 25093002 | Diabetic oculopathy |
| 4147672 | 30415006 | Disease due to Papilloma virus |
| 4140510 | 3305006 | Disorder of lymphatic vessel |
| 433440 | 78667006 | Dysthymia |
| 376132 | 62909004 | Ectropion |
| 440695 | 302690004 | Encopresis |
| 438872 | 267023007 | Excessive eating - polyphagia |
| 78804 | 27431007 | Fibrocystic disease of breast |
| 4131595 | 12676007 | Fracture of radius |
| 74855 | 33839006 | Genital herpes simplex |
| 441788 | 240532009 | Human papilloma virus infection |
| 76737 | 55434001 | Hydrocele |
| 4029582 | 237793004 | Hyperandrogenization syndrome |
| 195212 | 47270006 | Hypercortisolism |
| 438134 | 77692006 | Hypersomnia |
| 45768449 | 706882009 | Hypertensive crisis |
| 140362 | 36976004 | Hypoparathyroidism |
| 4322737 | 427898007 | Infection of tooth |
| 4207688 | 55184003 | Infectious enteritis |
| 79072 | 266579006 | Inflammatory disorder of breast |
| 139099 | 400097005 | Ingrowing nail |
| 4288544 | 396232000 | Inguinal hernia |
| 444191 | 125593007 | Injury of face |
| 444130 | 125604000 | Injury of foot |
| 134222 | 125597008 | Injury of forearm |
| 4297984 | 76844004 | Local infection of wound |
| 4018050 | 10443009 | Localized infection |
| 439840 | 1415005 | Lymphangitis |
| 4163232 | 45198002 | Mastitis |
| 440389 | 91138005 | Mental retardation |
| 436100 | 60380001 | Narcolepsy |
| 4262178 | 397732007 | Neurogenic dysfunction of the urinary bladder |
| 193874 | 8009008 | Nocturnal enuresis |
| 4171549 | 419153005 | Nodular goiter |
| 442274 | 52073004 | Oligomenorrhea |
| 4215978 | 414941008 | Onychomycosis |
| 4171915 | 274718005 | Orchitis |
| 380731 | 3135009 | Otitis externa |
| 378160 | 65668001 | Otorrhea |
| 192606 | 60389000 | Paraplegia |
| 253796 | 36118008 | Pneumothorax |
| 195501 | 69878008 | Polycystic ovaries |
| 4164337 | 399505005 | Polyp of large intestine |
| 4153877 | 269406001 | Post-traumatic wound infection |
| 434319 | 44001008 | Premature ejaculation |
| 373478 | 41256004 | Presbyopia |
| 199876 | 73998008 | Prolapse of female genital organs |
| 4295888 | 76641005 | Prolapse of intestine |
| 194997 | 9713002 | Prostatitis |
| 4146239 | 267802000 | Pruritus of genital organs |
| 4285569 | 68633000 | Pupillary disorder |
| 81336 | 57773001 | Rectal prolapse |
| 380395 | 314407005 | Retinal dystrophy |
| 141825 | 267369002 | Simple goiter |
| 137054 | 201066002 | Skin striae |
| 434630 | 3745000 | Sleep-wake schedule disorder |
| 4195698 | 67801009 | Tenosynovitis |
| 4339088 | 87860000 | Testicular mass |
| 133141 | 6020002 | Tinea pedis |
| 440814 | 70070008 | Torticollis |
| 435140 | 67426006 | Toxic effect of alcohol |
| 4270490 | 62994001 | Tracheitis |
| 4028970 | 13617004 | Tracheobronchitis |
| 4114197 | 254968009 | Tumor of hypothalamus |
| 193326 | 87557004 | Urge incontinence of urine |
| 4092565 | 24976005 | Uterine prolapse |
| 140641 | 57019003 | Verruca vulgaris |
| 197036 | 197811007 | Vesicoureteric reflux |
| 133551 | 402567004 | Vesicular eczema of hands and/or feet |
| 4223947 | 40468003 | Viral hepatitis, type A |
| 261326 | 75570004 | Viral pneumonia |

## 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 group (5-year bands)
  + Index year
  + Index month
  + Race
* Condition
  + In prior 365d
  + In prior 30d
  + In prior 7d
* Primary condition during hospitalization
  + In prior 30d
* Aggregated conditions by SNOMED
  + Any time prior
  + In prior 365d
* Drugs
  + In prior 30d
  + In prior 7d
* Aggregated drug by ATC/Ingredient
  + Any time prior
  + In prior 30d
  + In prior 365d
  + In prior 7d
  + Overlapping index date
* Procedure
  + In prior 365d
  + In prior 30d
* Device exposure
  + In 365d
  + In 7d
* Measurement
  + In 30d
  + In 7d
* Measurement Value
  + In 30d
  + In 7d
* Visit count
  + In 365d

Specific covariates to be excluded from the propensity score model are labelled **concepts to exclude,** which composed of drug use of ticagrelor and clopidogrel.

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.

### Other variables

None

# Data Analysis Plan

## Calculation of time-at-risk

Primary analysis

-One-year risk window: outcome windows, or time-at-risk, for the primary analysis is one year from the index date, defined as intent-to-treat manner to start 1 day after index date to 365 days after the index date.

Secondary analysis

-One-year risk window with blanking period: outcome windows, or time-at-risk, for the primary analysis is one year from the index date, defined as intent-to-treat manner to start 29 day after index date to 365 days after the index date.

-On-treatment risk window: to avoid time-dependent bias, on-treatment risk window was added, of which time-at-risk starts on treatment (ticagrelor or clopidogrel) initiation, and ends when the treatment ends.

-On-treatment risk window with blanking period: to avoid time-dependent bias, on-treatment risk window was added, of which time-at-risk starts 29 days after the index (PCI) date, and ends when the treatment (ticagrelor or clopidogrel) ends.

-Five-year risk window: Five-year risk window starts from 1 day to 1825 days after index date, which is extended risk window from the one-year risk window.

-Five-year risk window with blanking period: Five-year risk window starts from 29 day to 1825 days after index date, which is extended risk window from the one-year risk window with blanking period.

## 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. A pre-specified *P*<0.05 was considered statistically significant for all two-sided tests.

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, and 3) the end of the observation period that spans the time-at-risk start.

### Statistical model for primary analysis

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 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 validation using 10 replications per fold, 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 7.5.1.

* Primary analysis (PS Matching): After estimating the PS, variable ratio propensity score matching instead of one-to-one matching will be performed to avoid inferior covariate balance and reduction of bias.13 A caliper of 0.2 times the standard deviation of the propensity score distribution, and a greedy matching will be used. The outcome model will be fitted using a stratified Cox regression conditioned on the matched sets, with only the treatment variable as predictor.

### Statistical model for sensitivity analyses

* Without matching: The Cox proportional hazard model will be applied without PS matching or stratification.
* PS stratification: The target cohort and comparator cohorts will be stratified into ten quantiles of the propensity score distribution. The final outcome model will apply a conditional Cox proportional hazard model, conditions on the propensity score strata.

### Additional details for interaction term analysis

Additionally, interaction term analysis will be conducted to assess the interaction for the primary analysis between outcomes and six characteristics described below

* Female gender14
* Old age (age >= 65 years)
* Black or African American race15
* Concomitant myocardial infarction
* Concomitant proton pump inhibitor use
* High aspirin maintenance dose (>=300mg)10

Based on the result from interaction term analysis, the additional subgroup analysis can be performed.

### Pooling effect estimates across databases

Random-effect model meta-analysis will be performed to calculate summary hazard ratio for pooling effect estimates across databases

## Analyses to perform

The following analyses will be performed:

* 2 comparisons: One primary comparison (ticagrelor vs clopidogrel group) and one secondary comparison limiting the index date from 2013-03-01 to 2016-12-31
* 10 x 2 outcomes: Net adverse clinical event, ischemic event, hemorrhagic event, ischemic stroke, any revascularization, recurrent acute myocardial infarction, intracranial hemorrhage, GI bleeding, dyspnea and any death, and their narrow definitions with constraints for primary condition.
* 3 time-at-risk definitions: One-year risk window, On-treatment risk window, and five-year risk window
* Additional time-at-risk definition with blanking period: One-year risk window with blanking period, On-treatment risk window with blanking period, and five-year risk window with blanking period
* 3 model: Cox regression using PS matching, Cox regression without matching, and Cox regression using PS stratification
* Additional 6 interaction analysis for 10 outcomes

The total number of analyses is therefore 2x10x2x3x3 + 2x10x2x3+ 6x10 = 540 analyses

## Output

Covariate balance will be summarized in tabular form by showing the mean value for all baseline covariates in the target and comparator cohort, with the associated standardized mean difference computed for each covariate.

Once the propensity score model is fit, we will plot the propensity score distribution of the target and comparator cohorts to evaluate the comparability of the two cohorts. The plot will be scaled to the preference score, normalizing for any imbalance in cohort size. The covariates selected within the propensity score model, with associated coefficients will also be reported.

A plot showing the propensity score distributions for both cohorts after matching will be provided. Covariate balance will be evaluated by plotting the standardized mean difference of each covariate before propensity score matching against the standardized mean difference for each covariate after propensity score matching.

An attrition diagram will be provided to detail the loss of patients from the original target cohort and comparator cohort to the subpopulations that remain after all design considerations have been applied.

The final outcome model, a Cox proportional hazards model, will be summarized by providing the hazards ratio and associated 95% confidence interval. The number of persons, amount of time-at-risk, and number of outcomes in each cohort will also be reported.

## 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 and positive 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 denosumab nor zoledronic acid, and where therefore the true hazard ratio is equal to 1. We will execute the same analysis used for the primary hypothesis 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.16

The negative control will be used to estimate an empirical systematic error model, which will inform whether systematic error changes as a function of true effect size. The empirical systematic error model will then be applied to the target the target exposures and outcome of interest to calibrate the confidence interval.12

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.

## Data Sources

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>.

## Quality control

We will evaluate the PS by

* Inspection of the fitted PS model for large coefficients (indicative of model-misspecification) and predictors that we cannot explain (post-hoc).
* Inspection of the PS distribution.
* Evaluation of covariate balance after matching using the standardized difference in means between treatment and comparator cohort before and after matching [[5](#_ENREF_5)]. Standardized differences greater than 0.2 will be reported and investigated.

We will investigate the outcome model by

* Inspection of the fitted outcome model for large coefficients and predictors that we cannot explain (post-hoc).

The error distribution estimated using the negative controls will be used to estimate residual bias after adjustments.

The CohortMethod package itself, as well as other OHDSI packages on which CohortMethod depends, use unit tests for validation.

## 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 and full outcome models allow balancing on a large number of baseline potential confounders.
* Use of negative 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.

# 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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# Appendix: Concept Set Definitions

1. Percutaneous coronary intervention

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 4006788 | Percutaneous transluminal coronary angioplasty | Procedure | SNOMED | NO | YES | NO |
| 4020653 | Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery | Procedure | SNOMED | NO | YES | NO |
| 4139198 | Percutaneous transluminal thrombolysis of artery | Procedure | SNOMED | NO | YES | NO |
| 4175997 | Percutaneous transluminal thrombolysis and reconstruction of artery | Procedure | SNOMED | NO | YES | NO |
| 4178148 | Placement of stent in anterior descending branch of left coronary artery | Procedure | SNOMED | NO | YES | NO |
| 4181025 | Percutaneous transluminal balloon angioplasty with insertion of stent into coronary artery | Procedure | SNOMED | NO | YES | NO |
| 2000064 | Percutaneous transluminal coronary angioplasty [PTCA] | Procedure | ICD9Proc | NO | YES | NO |
| 2001505 | Insertion of non-drug-eluting coronary artery stent(s) | Procedure | ICD9Proc | NO | NO | NO |
| 2001506 | Insertion of drug-eluting coronary artery stent(s) | Procedure | ICD9Proc | NO | NO | NO |
| 4171077 | Fluoroscopic angiography of coronary artery and insertion of stent | Procedure | SNOMED | NO | NO | NO |

2. Ticagrelor

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 40241186 | Ticagrelor | Drug | RxNorm | NO | YES | NO |

3. Clopidogrel

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 1322184 | clopidogrel | Drug | RxNorm | NO | YES | NO |

4. Acute Coronary Syndrome

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 312327 | Acute myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 315296 | Preinfarction syndrome | Condition | SNOMED | NO | YES | NO |
| 434376 | Acute myocardial infarction of anterior wall | Condition | SNOMED | NO | YES | NO |
| 438170 | Acute myocardial infarction of inferior wall | Condition | SNOMED | NO | YES | NO |
| 444406 | Acute subendocardial infarction | Condition | SNOMED | NO | YES | NO |

5. Aspirin

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 1112807 | Aspirin | Drug | RxNorm | NO | YES | NO |

6. Prasugrel

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 40163718 | prasugrel | Drug | RxNorm | NO | YES | NO |

7. Ischemic stroke

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 443454 | Cerebral infarction | Condition | SNOMED | NO | YES | NO |
| 4043731 | Infarction - precerebral | Condition | SNOMED | NO | YES | NO |

8. Intracranial hemorrhage

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 376713 | Cerebral hemorrhage | Condition | SNOMED | NO | NO | NO |
| 432923 | Subarachnoid hemorrhage | Condition | SNOMED | NO | NO | NO |
| 436430 | Nontraumatic extradural hemorrhage | Condition | SNOMED | NO | NO | NO |
| 439040 | Subdural hemorrhage | Condition | SNOMED | NO | NO | NO |
| 439847 | Intracranial hemorrhage | Condition | SNOMED | NO | NO | NO |
| 4049659 | Subcortical hemorrhage | Condition | SNOMED | NO | NO | NO |
| 4108952 | Subarachnoid hemorrhage from carotid siphon and bifurcation | Condition | SNOMED | NO | NO | NO |
| 4110185 | Intracerebral hemorrhage, intraventricular | Condition | SNOMED | NO | NO | NO |
| 4111708 | Subarachnoid hemorrhage from vertebral artery | Condition | SNOMED | NO | NO | NO |
| 4111709 | Non-traumatic subdural hemorrhage | Condition | SNOMED | NO | NO | NO |

9. Gastrointestinal bleeding

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 192671 | Gastrointestinal hemorrhage | Condition | SNOMED | NO | YES | NO |
| 443530 | Hematochezia | Condition | SNOMED | NO | YES | NO |
| 4103703 | Melena | Condition | SNOMED | NO | YES | NO |
| 194158 | Perinatal gastrointestinal hemorrhage | Condition | SNOMED | YES | NO | NO |
| 4048282 | Perinatal melena | Condition | SNOMED | YES | NO | NO |
| 4048286 | Neonatal rectal hemorrhage | Condition | SNOMED | YES | NO | NO |
| 4048601 | Perinatal hematemesis | Condition | SNOMED | YES | NO | NO |
| 4048602 | Perinatal rectal hemorrhage | Condition | SNOMED | YES | NO | NO |
| 4048608 | Neonatal melena | Condition | SNOMED | YES | NO | NO |
| 4071070 | Neonatal hematemesis | Condition | SNOMED | YES | NO | NO |

9. Acute myocardial infarction

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 312327 | Acute myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 434376 | Acute myocardial infarction of anterior wall | Condition | SNOMED | NO | YES | NO |
| 438170 | Acute myocardial infarction of inferior wall | Condition | SNOMED | NO | YES | NO |
| 444406 | Acute subendocardial infarction | Condition | SNOMED | NO | YES | NO |

10. Coronary artery bypass graft surgery

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 2001514 | Single internal mammary-coronary artery bypass | Procedure | ICD9Proc | NO | YES | NO |
| 2001515 | Double internal mammary-coronary artery bypass | Procedure | ICD9Proc | NO | YES | NO |
| 2001516 | Abdominal-coronary artery bypass | Procedure | ICD9Proc | NO | YES | NO |
| 2107216 | Coronary artery bypass, vein only; single coronary venous graft | Procedure | CPT4 | NO | YES | NO |
| 2107217 | Coronary artery bypass, vein only; 2 coronary venous grafts | Procedure | CPT4 | NO | YES | NO |
| 2107218 | Coronary artery bypass, vein only; 3 coronary venous grafts | Procedure | CPT4 | NO | YES | NO |
| 2107219 | Coronary artery bypass, vein only; 4 coronary venous grafts | Procedure | CPT4 | NO | YES | NO |
| 2107220 | Coronary artery bypass, vein only; 5 coronary venous grafts | Procedure | CPT4 | NO | YES | NO |
| 2107221 | Coronary artery bypass, vein only; 6 or more coronary venous grafts | Procedure | CPT4 | NO | YES | NO |
| 2107222 | Coronary artery bypass, using venous graft(s) and arterial graft(s); single vein graft (List separately in addition to code for primary procedure) | Procedure | CPT4 | NO | YES | NO |

11. Dyspnea

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 312437 | Dyspnea | Condition | SNOMED | NO | YES | NO |