OHDSI Comparison of ticagrelor and clopidogrel in patients with Acute Coronary Syndrome

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# List of abbreviations

ACC American College of Cardiology

AHA American Heart Association

ESC European Society of Cardiology

EACTS European Association for Cardio-Thoracic Surgery

RCT Randomized Clinical Trial

ACS Acute Coronary Syndrome

PLATO PLATelet inhibition and patient Outcomes

OHDSI Observational Health Data Sciences and Informatics

# 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 study of 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 informatidcs (OHDSI) network.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | 11 December 2018 | SC You | Initial draft |

# Rationale and Background

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 study of 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 In post-hoc analysis, the significant interaction between treatment and trial region was identified, which suggested worse clinical effect of ticagrelor in North America than in the rest of the world. 7

The real-world evidence evaluating net clinical benefit of ticagrelor over clopidogrel across countries or races has been scarce. Furthermore, there is a concern that non-White patients, especially Asians and Black people, might be susceptible to anti-thrombotic therapy in real word 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

# Research Questions and Objectives

## Research Questions

Primary research questions

* Is febuxostat associated with increased risk of sudden cardiac death compared to febuxostat in real-world practice? What is the event rate difference?

Secondary objectives:

* Is febuxostat associated with increased risk of cardiovascular disease compared to febuxostat in real-world practice? What is the event rate difference?
* Is febuxostat associated with increased risk of gout flare compared to febuxostat in real-world practice? What is the event rate difference?
* Is febuxostat associated with lower risk of drug hypersensitivity compared to febuxostat in real-world practice? What is the event rate difference?

## Objectives

The 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.

**Primary objective**:

-Assess the adjusted hazard ratio for use of ticagrelor vs clopidogrel on net adverse clinical event (NACE) which composed of recurrent myocardial infarction, any revascularization, ischemic stroke, and major bleeding

**Secondary objectives**:

-Assess the adjusted hazard ratio for use of ticagrelor vs clopidogrel on risk of recurrent myocardial infarction

-Assess the adjusted hazard ratio for use of ticagrelor vs clopidogrel on risk of any revascularization: PCI or CABG

-Assess the adjusted hazard ratio for use of ticagrelor vs clopidogrel on risk of ischemic stroke

-Assess the adjusted hazard ratio for use of ticagrelor vs clopidogrel on risk of sudden cardiac death

-Assess the adjusted hazard ratio for use of ticagrelor vs clopidogrel on risk of intracranial hemorrhage

-Assess the adjusted hazard ratio for use of ticagrelor vs clopidogrel on risk of GI bleeding

-Assess the adjusted hazard ratio for use of ticagrelor vs clopidogrel on risk of ischemic event including recurrent MI, any revascularization, and ischemic stroke

-Assess the adjusted hazard ratio for use of ticagrelor vs clopidogrel on risk of major bleeding event including intracranial hemorrhage and GI bleeding

# 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 percutaneous coronary intervention (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. First, a propensity model will be fitted and used to create propensity scores (PS). These PS will be used to match the treatment and comparator cohorts, and the proportional hazards outcome models will be conditioned on the matched sets of strata respectively.

### Study population

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the first exposure to febuxostat or allopurinol)

* Exposure to ticagrelor or clopidogrel
* 20 years old or older
* At least 365 days of observation time prior to the index date
* A procedure of PCI between 7 days before and 7 days after the index date
* A diagnose of ACS between 7 days before and 7 days after the index date
* Concomitant aspirin use between 7 days before and 7 days after the index date
* Without use of prasugrel or the opposing drug within previous 30 days from index date
* No diagnosis of the stroke preceding the index date
* No diagnosis of the GI bleeding preceding the index date

### Additional analysis details

The propensity model will be fitted using a regularized logistic regression with a LaPlace prior. The regularization hyperparameter will be selected by optimizing the likelihood in a 10-fold cross-validation.

Variable-ratio propensity score matching will be performed using greedy matching3. A caliper of 0.25 times the standard deviation of the propensity score distribution will be used. The outcome model will be fitted using a Cox regression conditioned on the matched sets, with only the treatment variable as predictor.

### Analysis variations

The following variations of the analysis will be performed:

Primary analysis:

* Using a PS model and perform 1-on-1 matching. The outcome model will be condition on the matched sets, but will only contain the treatment as predictor. This is included to allow plotting of the Kaplan-Meier curve, which is not possible when using variable ratio matching.
* The outcome at one-year from the index year will be evaluated

Secondary analyses:

* No PS model, a simple outcome model with only the treatment as predictor.
* Using a PS model to match treated and comparator. The outcome model will be condition on the matched sets.
* All analyses will be repeated using an on-treatment + 7 day risk window definition, which starts on treatment initiation, and ends 7 days after when treatment ends.
* All analyses will be repeated using an on-treatment risk window definition, which starts on treatment initiation, and ends when treatment ends.

## Variables

### Exposures

#### Ticagrelor

Initial Event Cohort

People having any of the following: 

* a drug exposure of ticagrelor
  + with age >= 20

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 procedure of PCI

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

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

Inclusion Rules

Inclusion Criteria #1: ACS

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of ACS

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

Inclusion Criteria #2: 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 7 days After index start date

Inclusion Criteria #3: 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 #4: 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 #5: 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

#### Clopidogrel

Initial Event Cohort

People having any of the following: 

* a drug exposure of clopidogrel
  + with age >= 20

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 procedure of PCI

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

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

Inclusion Rules

Inclusion Criteria #1: ACS

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of ACS

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

Inclusion Criteria #2: 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 7 days After index start date

Inclusion Criteria #3: 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 #4: 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 #5: 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 clopidogrel

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

### Outcomes

#### Primary outcome: Net Adverse Clinical Event

Primary outcome includes recurrent myocardial infarction, any revascularization, ischemic stroke, intracranial hemorrhage, and gastrointestinal bleeding. All of these conditions should be accompanied by same-day hospitalization

#### Secondary outcome: Ischemic event

Index rule defining the index date:

* Occurrence of acute myocardial infarction, any revascularization, or ischemic stroke code with same-day hospitalization (inpatient or emergency department visit)

#### Secondary outcome: Bleeding event

Index rule defining the index date:

* Occurrence of intracranial hemorrhage or gastrointestinal bleeding code with same-day hospitalization (inpatient or emergency department visit)

#### Secondary outcome: Recurrent myocardial infarction

Index rule defining the index date:

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

#### Secondary outcome: Any revascularization

Index rule defining the index date:

* Occurrence of percutaneous coronary intervention or CABG code with same-day hospitalization (inpatient or emergency department visit)

#### Secondary outcome: Ischemic stroke

Index rule defining the index date:

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

#### Secondary outcome: Intracranial hemorrhage

Index rule defining the index date:

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

#### Secondary outcome: Gastrointestinal bleeding

Index rule defining the index date:

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

#### Secondary outcome: Sudden cardiac death

Index rule defining the index date:

* Occurrence of sudden cardiac death code with same-day hospitalization (inpatient or emergency department visit)

### Potential confounders

The following will be included as potential covariates: (note: Long-term covariates are assessed on or in the 365 days prior to index date. Short-term covariates are assessed on or in the 7 days prior to index date.)

* Demographics (age in 5-year increments, gender, race, ethnicity, year of index date, month of index date)
* Short-term Condition occurrence (one or more variables per diagnose code)
* Long-term and Short-term Condition group (one or more variables per MedDRA group or SNOMED groups)
* Long-term and Short-term Drug group (one or more variables per ATC group)
* Long-term and Short-term Procedure occurrence (one or more variables per procedure code)

For the full details see the OHDSI CohortMethod package (<https://github.com/OHDSI/CohortMethod>).

Variables with less than 100 non-zero values are discarded. All covariates were used in both the propensity model and the outcome model.

### Negative controls

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 |
| 317585 | 67362008 | Aortic aneurysm |
| 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 |
| 4174977 | 4855003 | Diabetic retinopathy |
| 4132130 | 26660001 | Dilatation of aorta |
| 4147672 | 30415006 | Disease due to Papilloma virus |
| 4153380 | 371160000 | Disorder of carotid artery |
| 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 |
| 4029966 | 128609009 | Intracranial aneurysm |
| 437409 | 127296001 | Intracranial injury |
| 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 |

### Other variables

None

## 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>.

## Sample Size and Study Power

-

## 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.
* The outcome of interest, angioedema, is rare and typically captured only in inpatient settings, so we may have insufficient numbers of patients to generate reliable evidence on this drug-outcome association.

# 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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