Association of ticagrelor versus clopidogrel with net adverse clinical events in patients with acute coronary syndrome undergoing percutaneous coronary intervention in clinical practice

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2 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

3 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.

4 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
1.1	24 May 2019	SCYou	Revision of target and comparator cohort: Because there are databases do not have visit ID link between drug exposure and procedure, the primary inclusion criteria was revised to use time based rule rather than same visit based rule. Because many US patients take aspirin over-the-count, the constraint for the concomitant use of aspirin in target and comparator cohort was removed.
1.2	3 September 2019	SCYou	Changing primary analysis from variable ratio PS matching to unconditioned one-to-one PS matching
1.3	28 October 2019	SCYou	Revising the query to extract individual secondary outcome cohorts. The documented definitions were also changed to add ‘first time’ criteria to stroke and GI bleeding outcomes. Adding NACE or mortality outcome as a secondary outcome Adding variable-ratio matching and PS stratification with blanking period analysis

5 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.[7] Moreover, 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.

6 Study Objectives

6.1 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.

6.2 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.

6.3 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.

6.4 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

7 Research methods

7.1 Study Design

7.1.1 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.

7.2 Study population

7.2.1 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 PCI (index event) with exposure of ticagrelor or clopidogrel between 7 days before and 0 days after the PCI.
- 20 years old or older
- At least 365 days of observation time prior to the index date
- A diagnose of ACS between 7 days before and 0 days after the index date
- Without use of prasugrel or the opposing drug within previous 30 days from index date
- No diagnosis of ischemic stroke or intracranial hemorrhage preceding the index date
- No diagnosis of the GI bleeding preceding the index date

7.2.2 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 PCI (index event) with concomitant exposure of ticagrelor or clopidogrel 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 ACS between 7 days before and 0 days after the index date
- Without use of prasugrel or the opposing drug within previous 30 days from index date
- No diagnosis of ischemic stroke or intracranial hemorrhage preceding the index date
- No diagnosis of the GI bleeding preceding the index date

7.3 Exposures

7.3.1 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:

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

- and at least 1 occurrences of a drug exposure of ticagrelor

  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: 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 #2: 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 #3: 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.

7.3.2 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

- and at least 1 occurrences of a drug exposure of clopidogrel

  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: 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 #2: 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.

7.4 Outcomes

7.4.1 Outcomes

Primary outcome: Net Adverse Clinical Event

Primary outcome includes recurrent acute myocardial infarction, any revascularization (CABG or PCI), first-time ischemic stroke, first-time hemorrhagic stroke, and first-time gastrointestinal bleeding. All of these conditions should be accompanied by same-day hospitalization

Secondary outcome: Net Adverse Clinical Event or mortality

Index rule defining the index date:

- Occurrence of acute MI, any revascularization (CABG or PCI), or ischemic stroke event with same-day hospitalization (inpatient or emergency department visit) or any mortality

Secondary outcome: Ischemic event

Index rule defining the index date:

- Occurrence of acute MI, any revascularization (CABG or PCI), or ischemic stroke event with same-day hospitalization (inpatient or emergency department visit)

Secondary outcome: Hemorrhagic event

Index rule defining the index date:

- Occurrence of hemorrhagic stroke or gastrointestinal bleeding event with same-day hospitalization (inpatient or emergency department visit)

Secondary outcome: Recurrent myocardial infarction

Index rule defining the index date:

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

Secondary outcome: Any revascularization

Index rule defining the index date:

- Occurrence of PCI 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)
- Limited to the first event

Secondary outcome: Hemorrhagic stroke

Index rule defining the index date:

- Occurrence of hemorrhagic stroke code with same-day hospitalization (inpatient or emergency department visit)
- Limited to the first event

Secondary outcome: Gastrointestinal bleeding

Index rule defining the index date:

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

Secondary outcome: Dyspnea

Index rule defining the index date:

- Occurrence of dyspnea code

Secondary outcome: Death

Any death occurrence

7.4.2 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] 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

7.5 Covariates

7.5.1 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.

7.5.2 Other variables

None

8 Data Analysis Plan

8.1 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.

8.2 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.

8.2.1 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, one-to-one matching will be performed. 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 unconditioned Cox regression, with only the treatment variable as predictor.

8.2.2 Statistical model for sensitivity analyses

- Without matching: The Cox proportional hazard model will be applied without PS matching or stratification.
- Variable ratio PS matching: the two cohorts were matched with a maximum ratio of 10. 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.
- 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.

8.2.3 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 gender
- Old age (age >= 65 years)
- Black or African American race

- Concomitant myocardial infarction
- Concomitant proton pump inhibitor use
- High aspirin maintenance dose (>=300mg)

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

8.2.4 Pooling effect estimates across databases

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

8.3 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
- 11 x 2 outcomes: NACE, NACE or mortality, 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.
- 3x2 time-at-risk definitions: One-year risk window, On-treatment risk window, five-year risk window, one-year risk window with blanking period, on-treatment risk window with blanking period, and five-year risk window with blanking period
- 4 model: unconditioned Cox regression after 1:1 PS matching, Cox regression without matching, conditioned Cox regression after variable-ratio PS matching , and conditioned Cox regression after PS stratification
- Additional 6 interaction analysis for 11 outcomes

The total number of analyses is 1320 (2 comparisons x 11 x2 outcomes x 3x2 TAR x4 statistical models + 264 interaction analyses).

8.4 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.

8.5 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.

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.[13]

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.

8.6 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.

8.7 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. 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.

8.8 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.

9 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.

10 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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11 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