**Research Protocol**

**Title:** Comparative Effectiveness of Ticagrelor vs. Prasugrel in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

# Study Lead:

Chang Hoon Han, MD

Seng Chan You, MD, PhD

Contents

[1. List of abbreviations 4](#_Toc181715633)

[2. Abstract 4](#_Toc181715634)

[3. Amendments and Updates 4](#_Toc181715635)

[4. Rationale and Background 4](#_Toc181715636)

[5. Aims and Objectives 5](#_Toc181715637)

[6. Research Methods 5](#_Toc181715638)

[6.1. Study Design 5](#_Toc181715639)

[6.2. Study Population 5](#_Toc181715640)

[6.2.1. Cohort Definitions 5](#_Toc181715641)

[6.2.2. Treatments of Interest 7](#_Toc181715642)

[6.2.2.1. Target Drug: Ticagrelor 7](#_Toc181715643)

[6.2.2.2. Comparator Drug: Prasugrel 8](#_Toc181715644)

[6.2.2.3. Drugs to Exclude 8](#_Toc181715645)

[6.3. Outcomes 8](#_Toc181715646)

[6.3.1. Primary Outcome 8](#_Toc181715647)

[6.3.1.1. Net Adverse Clinical Event (NACE) 8](#_Toc181715648)

[6.3.2. Secondary Outcomes 9](#_Toc181715649)

[6.3.2.1. Major Adverse Cardiovascular Event (MACE) 9](#_Toc181715650)

[6.3.2.2. All-cause Mortality 9](#_Toc181715651)

[6.3.2.3. Cardiovascular Mortality 9](#_Toc181715652)

[6.3.2.4. Ischemic Event 9](#_Toc181715653)

[6.3.2.5. Hemorrhagic Event 9](#_Toc181715654)

[6.3.3. Negative Control Outcomes 10](#_Toc181715655)

[7. Data Analysis Plan 11](#_Toc181715656)

[7.1. Population Level Estimation 11](#_Toc181715657)

[7.1.1. Overview 11](#_Toc181715658)

[7.1.2. Propensity Score Generation 11](#_Toc181715659)

[7.1.3. Data Analysis Plan 12](#_Toc181715660)

[7.1.4. Output 13](#_Toc181715661)

[8. Strengths and Limitations of the Research Methods 13](#_Toc181715662)

[8.1. Strength 13](#_Toc181715663)

[8.2. Limitations 13](#_Toc181715664)

[9. Protection of Human Subjects 13](#_Toc181715665)

[10. Plans for Disseminating and Communicating Study Results 13](#_Toc181715666)

[11. Reference 13](#_Toc181715667)

# List of abbreviations

* ACS: acute coronary syndrome
* PCI: percutaneous coronary intervention
* RCT: randomized controlled trial
* NACE: net adverse clinical events
* EHR: electronic health record
* OMOP-CDM: Observational Medical Outcomes Partnership Common Data Model
* GI: gastrointestinal
* PS: Propensity score
* aSMD: Absolute standardized mean difference
* HR: Hazard ratio
* CI: Confidence interval

# Abstract

This study aims to compare ticagrelor and prasugrel, P2Y12 antiplatelet agents commonly used in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). By conducting a direct, head-to-head comparison, this research will provide valuable insights into their associations with various ischemic and hemorrhagic outcomes. The findings are expected to inform and guide clinical decision-making, helping to optimize treatment strategies for patients with ACS.

# Amendments and Updates

# Rationale and Background

Mortality due to acute coronary syndrome (ACS) accounts for approximately 20% of all deaths from cardiovascular disease, making it a significant cause of death.[1] In patients with ACS undergoing percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor forms the cornerstone of treatment. Research has been ongoing to determine which P2Y12 inhibitor among clopidogrel, ticagrelor, and prasugrel is more advantageous, in terms of efficacy (preventing ischemic events) and safety (minimizing bleeding risks).

The Study of Platelet Inhibition and Patient Outcomes (PLATO) compared clopidogrel and ticagrelor through a randomized controlled trial (RCT) and found that ticagrelor significantly reduced cardiovascular mortality compared to clopidogrel, without an increased risk of overall bleeding.[2] Additionally, the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel - Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 study compared clopidogrel and prasugrel and demonstrated that prasugrel significantly lowered the risk of ischemic events compared to clopidogrel but was associated with an increased risk of bleeding.[3] On the other hand, the Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction (PRAGUE-18) study compared the composite endpoint of death, reinfarction, stroke, and bleeding between patients treated with prasugrel and those treated with ticagrelor in an RCT, finding no significant difference.[4]

Based on these studies, the 2021 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend ticagrelor or prasugrel over clopidogrel for initiating DAPT in patients with ACS undergoing PCI, except in cases where there are concerns about bleeding complications, such as a history of stroke, where prasugrel is advised against.[5] However, the 2019 results of the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial indicated that prasugrel significantly reduced the combined risk of death, myocardial infarction, and stroke compared to ticagrelor, with no difference in bleeding risk.[6] This has led to an incomplete consensus regarding the superiority between prasugrel and ticagrelor. Despite acknowledging limitations such as the open-label design of this study, the 2023 European Society of Cardiology (ESC) guidelines have recommended prasugrel as the first choice based on these findings, though this has not yet been reflected in the ACC/AHA guidelines, highlighting the need for further validation.[5, 7]

This study aims to provide additional evidence for clinical decision-making by comparing ticagrelor and prasugrel in ACS patients undergoing PCI using real-world data.

# Aims and Objectives

This study is a cohort study which aims to:

1. Determine and compare the incidence rate of net adverse clinical events (NACE), a composite outcome including cardiovascular deaths, ischemic and hemorrhagic events of ticagrelor and prasugrel in ACS patients undergoing PCI.
2. Determine and compare the incidence rate of major adverse cardiovascular events (MACE) and individual outcomes, including all-cause mortality, cardiovascular mortality, ischemic events, and hemorrhagic events of ticagrelor and prasugrel in ACS patients undergoing PCI.

# Research Methods

## Study Design

This is a retrospective cohort study, comparing the incidence rates of effectiveness and safety outcomes. Data sources will be electronic health record (EHR) data & claims data in Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM) format.

## Study Population

### Cohort Definitions

The study population includes patients aged 18 or higher diagnosed with ACS undergoing PCI, administered with either ticagrelor or prasugrel. T**he index date** is defined as the date of PCI, with the minimum date 2009-07-10 (the day of FDA approval of prasugrel). Patients with previous history of other major ischemic or hemorrhagic events, including stroke and gastrointestinal (GI) bleeding are excluded. Specific rules defining the index date are described below.

The target group consists of patients who were initiated with ticagrelor and who meet the criteria below. The comparator group consists of patients who were initiated with prasugrel and who meet the criteria below.

As primary analysis, intention-to-treat design will be applied to derive 1-year outcomes.

As sensitivity analysis, on-treatment design will be applied. The cohort exit rule described below will be applied.

Index rule defining the index date:

* First procedure occurrence of **PCI** (Table 1)
* With age greater or equal to 18 at the index date.
* With continuous observation of at least 90 days before the event index date.
* At least 1 occurrence of a condition occurrence of **ACS** (Table 2) between 7 days before and 0 days after index start date
* At least 1 occurrence of a drug exposure to the drug of interest between 7 days before and 0 days after index start date

Inclusion rules based on the index date:

* With no exposure to the comparator/target drug between 30 days before and 0 days after index start date
* With no condition occurrence of **ischemic stroke** (Table 3) or **hemorrhagic stroke** (Table 4) before and 0 days after index start date
* With no condition occurrence of **GI bleeding** (Table 5) before and 0 days after index start date

Exit rules defining the cohort end date (on-treatment):

* Event will persist until the end of a continuous drug exposure of interest.
* Allowance for 14-day gaps between exposure records of the drug of interest.
* No additional period of surveillance after the end of the era of persistent exposure
* Censored with an exposure of **clopidogrel** (Table 8), **cangrelor** (Table 9) or the drug of the other group

Table 1. Percutaneous Coronary Intervention (PCI) Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4283892 | Placement of stent in coronary artery | Procedure | FALSE | TRUE | FALSE |
| 4139198 | Percutaneous transluminal thrombolysis of artery | Procedure | FALSE | TRUE | FALSE |
| 4006788 | Percutaneous transluminal coronary angioplasty | Procedure | FALSE | TRUE | FALSE |
| 4264286 | Percutaneous rotational coronary endarterectomy | Procedure | FALSE | TRUE | FALSE |
| 4337738 | Percutaneous endarterectomy of coronary artery | Procedure | FALSE | FALSE | FALSE |
| 44789455 | Insertion of drug-eluting coronary artery stent | Procedure | FALSE | FALSE | FALSE |

Table 2. Acute Coronary Syndrome (ACS) Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 315296 | Preinfarction syndrome | Condition | FALSE | TRUE | FALSE |
| 4329847 | Myocardial infarction | Condition | FALSE | TRUE | FALSE |
| 314666 | Old myocardial infarction | Condition | TRUE | TRUE | FALSE |
| 4215140 | Acute coronary syndrome | Condition | FALSE | TRUE | FALSE |

Table 3. Ischemic Stroke Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4310996 | Ischemic stroke | Condition | FALSE | TRUE | FALSE |
| 4159140 | Thrombotic stroke | Condition | FALSE | TRUE | FALSE |
| 4153352 | Embolic stroke | Condition | FALSE | TRUE | FALSE |
| 441874 | Cerebral thrombosis | Condition | FALSE | TRUE | FALSE |
| 443454 | Cerebral infarction | Condition | FALSE | TRUE | FALSE |
| 375557 | Cerebral embolism | Condition | FALSE | TRUE | FALSE |
| 372924 | Cerebral artery occlusion | Condition | FALSE | TRUE | FALSE |
| 4045734 | CVA - cerebrovascular accident due to cerebral artery occlusion | Condition | FALSE | TRUE | FALSE |
| 43531605 | Occlusion of cerebral artery with stroke | Condition | FALSE | FALSE | FALSE |
| 761790 | Nonpyogenic cerebral venous thrombosis with stroke | Condition | FALSE | FALSE | FALSE |
| 762344 | Cerebrovascular accident due to thrombus of right vertebral artery | Condition | FALSE | FALSE | FALSE |
| 42535458 | Cerebrovascular accident due to stenosis of right vertebral artery | Condition | FALSE | FALSE | FALSE |
| 42535459 | Cerebrovascular accident due to stenosis of left vertebral artery | Condition | FALSE | FALSE | FALSE |
| 37309657 | Cerebrovascular accident due to stenosis of bilateral vertebral arteries | Condition | FALSE | FALSE | FALSE |
| 37209562 | Cerebrovascular accident due to stenosis of bilateral carotid arteries | Condition | FALSE | FALSE | FALSE |
| 42535460 | Cerebrovascular accident due to right vertebral artery occlusion | Condition | FALSE | FALSE | FALSE |
| 37395575 | Cerebrovascular accident due to right carotid artery stenosis | Condition | FALSE | FALSE | FALSE |
| 37395574 | Cerebrovascular accident due to right carotid artery occlusion | Condition | FALSE | FALSE | FALSE |
| 42535147 | Cerebrovascular accident due to occlusion of right pontine artery | Condition | FALSE | FALSE | FALSE |
| 42535149 | Cerebrovascular accident due to occlusion of right cerebellar artery | Condition | FALSE | FALSE | FALSE |
| 42535461 | Cerebrovascular accident due to occlusion of left vertebral artery | Condition | FALSE | FALSE | FALSE |
| 42535146 | Cerebrovascular accident due to occlusion of left pontine artery | Condition | FALSE | FALSE | FALSE |
| 42535148 | Cerebrovascular accident due to occlusion of left cerebellar artery | Condition | FALSE | FALSE | FALSE |
| 42539262 | Cerebrovascular accident due to occlusion of left carotid artery | Condition | FALSE | FALSE | FALSE |
| 619802 | Cerebrovascular accident due to occlusion of bilateral vertebral arteries | Condition | FALSE | FALSE | FALSE |
| 37309665 | Cerebrovascular accident due to occlusion of bilateral pontine arteries | Condition | FALSE | FALSE | FALSE |
| 609301 | Cerebrovascular accident due to occlusion of bilateral cerebellar arteries | Condition | FALSE | FALSE | FALSE |
| 37395576 | Cerebrovascular accident due to left carotid artery stenosis | Condition | FALSE | FALSE | FALSE |
| 37312014 | Cerebral ischemic stroke due to hypercoagulable state | Condition | FALSE | FALSE | FALSE |
| 37312015 | Cerebral ischemic stroke due to global hypoperfusion with watershed infarct | Condition | FALSE | FALSE | FALSE |
| 37312017 | Cerebral ischemic stroke due to dissection of artery | Condition | FALSE | FALSE | FALSE |

Table 4. Hemorrhagic Stroke Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 35609033 | Haemorrhagic stroke | Condition | FALSE | TRUE | FALSE |
| 376713 | Cerebral hemorrhage | Condition | FALSE | TRUE | FALSE |
| 432923 | Subarachnoid hemorrhage | Condition | FALSE | TRUE | FALSE |
| 439847 | Intracranial hemorrhage | Condition | FALSE | TRUE | FALSE |

Table 5. Gastrointestinal (GI) Bleeding Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4103703 | Melena | Condition | FALSE | TRUE | FALSE |
| 443530 | Hematochezia | Condition | FALSE | TRUE | FALSE |
| 26727 | Hematemesis | Condition | FALSE | TRUE | FALSE |
| 192671 | Gastrointestinal hemorrhage | Condition | FALSE | TRUE | FALSE |
| 4242106 | Occult blood in stools | Clinical Finding | FALSE | TRUE | FALSE |

### Treatments of Interest

#### Target Drug: Ticagrelor

Table 6. Ticagrelor Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 40241186 | ticagrelor | Drug | FALSE | TRUE | FALSE |
| 40252640 | ticagrelor; oral | Drug | FALSE | TRUE | FALSE |

#### Comparator Drug: Prasugrel

Table 7. Prasugrel Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 40163718 | prasugrel | Drug | FALSE | TRUE | FALSE |
| 21601004 | prasugrel; oral | Drug | FALSE | TRUE | FALSE |

#### Drugs to Exclude

Patients using clopidogrel and cangrelor are excluded in accordance with inclusion and exit rules specified in 6.2.1. Cohort Definitions section.

Table 8. Clopidogrel Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 1322184 | clopidogrel | Drug | FALSE | TRUE | FALSE |
| 21600989 | clopidogrel; oral | Drug | FALSE | TRUE | FALSE |

Table 9. Cangrelor Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 46275677 | cangrelor | Drug | FALSE | TRUE | FALSE |
| 45893522 | Cangrelor; parenteral | Drug | FALSE | TRUE | FALSE |

## Outcomes

### Primary Outcome

#### Net Adverse Clinical Event (NACE)

The primary outcome of this study is **NACE**, which is defined as a composite outcome of cardiovascular mortality, acute myocardial infarction (AMI), stroke (ischemic and hemorrhagic), and GI bleeding.

Among the components, **cardiovascular mortality** is operationally defined as death occurrence with a condition occurrence of sudden cardiac death, AMI, stroke (ischemic or hemorrhagic), or hospitalization from heart failure. Specific rules for this definition are described below.

A death occurrence with any of the following criteria:

* At least 1 condition occurrence of **sudden cardiac death** (Table 10) between 30 days before and 0 days after the day of the death event.
* At least 1 condition occurrence of **AMI** (Table 11) between 30 days before and 0 days after the day of the death event.
* At least 1 condition occurrence of **ischemic stroke** (Table 3) between 30 days before and 0 days after the day of the death event.
* At least 1 condition occurrence of **hemorrhagic stroke** (Table 4) between 30 days before and 0 days after the day of the death event.
* At least 1 condition occurrence of **heart failure** (Table 12) between 30 days before and 0 days after the day of the death event, with at least 1 **hospitalization** (Table 13) visit occurrence starting before and ending after the condition occurrence.

Table 10 Sudden Cardiac Death Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4317150 | Sudden cardiac death | Condition | FALSE | TRUE | FALSE |
| 4132309 | Sudden death | Condition | FALSE | TRUE | FALSE |
| 442289 | Death in less than 24 hours from onset of symptoms | Condition | FALSE | FALSE | FALSE |
| 321042 | Cardiac arrest | Condition | FALSE | TRUE | FALSE |

Table 11 Acute Myocardial Infarction (AMI) Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 312327 | Acute myocardial infarction | Condition | FALSE | TRUE | FALSE |
| 314666 | Old myocardial infarction | Condition | TRUE | TRUE | FALSE |

Table 12 Heart Failure Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 316139 | Heart failure | Condition | FALSE | TRUE | FALSE |
| 315295 | Congestive rheumatic heart failure | Condition | TRUE | TRUE | FALSE |

Table 13 Hospitalization Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 9203 | Emergency Room Visit | Visit | FALSE | TRUE | FALSE |
| 9201 | Inpatient Visit | Visit | FALSE | TRUE | FALSE |

Considering the definitions of the components specified above, the outcome cohort definition for NACE is described below.

Outcome cohort entry on any of the following events:

* A death occurrence that follows the criteria of **cardiovascular mortality** described above
* An inpatient condition occurrence of **AMI** (Table 11)
* An inpatient condition occurrence of **ischemic stroke** (Table 3)
* An inpatient condition occurrence of **hemorrhagic stroke** (Table 4)
* An inpatient condition occurrence of **GI bleeding** (Table 5)

Cohort exit on fixed duration (1 day) relative to initial event

### Secondary Outcomes

#### Major Adverse Cardiovascular Event (MACE)

MACE is defined as a composite outcome of cardiovascular mortality, AMI, and stroke. The outcome cohort definition is described below.

Outcome cohort entry on any of the following events:

* A death occurrence that follows the criteria of **cardiovascular mortality** described above
* An inpatient condition occurrence of **AMI** (Table 11)
* An inpatient condition occurrence of **ischemic stroke** (Table 3)
* An inpatient condition occurrence of **hemorrhagic stroke** (Table 4)

Cohort exit on fixed duration (1 day) relative to initial event

#### All-cause Mortality

Outcome cohort entry on any death occurrence

#### Cardiovascular Mortality

Outcome cohort entry on any death occurrence that follows the criteria of **cardiovascular mortality** described above

#### Ischemic Event

An ischemic event is defined as a composite outcome of AMI and ischemic stroke. The outcome cohort definition is described below.

Outcome cohort entry on any of the following events:

* An inpatient condition occurrence of **AMI** (Table 11)
* An inpatient condition occurrence of **ischemic stroke** (Table 3)

Cohort exit on fixed duration (1 day) relative to initial event

#### Hemorrhagic Event

A hemorrhagic event is defined as a composite outcome of hemorrhagic stroke and GI bleeding. The outcome cohort definition is described below.

Outcome cohort entry on any of the following events:

* An inpatient condition occurrence of **hemorrhagic stroke** (Table 4)
* An inpatient condition occurrence of **GI bleeding** (Table 5)

Cohort exit on fixed duration (1 day) relative to initial event

### Negative Control Outcomes

A total of 96 concepts were selected as negative controls that were not associated with both the target and comparator drugs and study outcomes.

Table 14 Negative controls outcomes

|  |  |  |  |
| --- | --- | --- | --- |
| Concept ID | Concept Name | Concept ID | Concept Name |
| 378256 | Abnormal reflex | 4095288 | Ketoacidotic coma due to diabetes mellitus |
| 4218106 | Alcoholism | 4297984 | Local infection of wound |
| 440424 | Aphasia | 4018050 | Localized infection |
| 439237 | Assault | 439840 | Lymphangitis |
| 378424 | Astigmatism | 4163232 | Mastitis |
| 261880 | Atelectasis | 440389 | Mental retardation |
| 134118 | Atrophic condition of skin | 436100 | Narcolepsy |
| 4224118 | Bladder dysfunction | 4262178 | Neurogenic dysfunction of the urinary bladder |
| 80509 | Bone cyst | 4044391 | Neuropathy due to diabetes mellitus |
| 434626 | Borderline personality disorder | 193874 | Nocturnal enuresis |
| 438407 | Bulimia nervosa | 4171549 | Nodular goiter |
| 134765 | Cachexia | 442274 | Oligomenorrhea |
| 4172458 | Candidiasis of skin | 4215978 | Onychomycosis |
| 436740 | Cervical incompetence | 4171915 | Orchitis |
| 381581 | Chalazion | 380731 | Otitis externa |
| 4307254 | Closed fracture | 378160 | Otorrhea |
| 4047787 | Colles' fracture | 192606 | Paraplegia |
| 198075 | Condyloma acuminatum of the anogenital region | 253796 | Pneumothorax |
| 73302 | Curvature of spine | 195501 | Polycystic ovaries |
| 4242416 | Cutis laxa | 4164337 | Polyp of large intestine |
| 433163 | Deficiency of macronutrients | 4153877 | Post-traumatic wound infection |
| 4047269 | Deformity of foot | 434319 | Premature ejaculation |
| 133228 | Dental caries | 373478 | Presbyopia |
| 4147672 | Disease due to Papilloma virus | 199876 | Prolapse of female genital organs |
| 443767 | Disorder of eye due to diabetes mellitus | 4295888 | Prolapse of intestine |
| 4140510 | Disorder of lymphatic vessel | 194997 | Prostatitis |
| 433440 | Dysthymia | 4146239 | Pruritus of genital organs |
| 376132 | Ectropion | 4285569 | Pupillary disorder |
| 440695 | Encopresis | 81336 | Rectal prolapse |
| 438872 | Excessive eating - polyphagia | 380395 | Retinal dystrophy |
| 78804 | Fibrocystic disease of breast | 141825 | Simple goiter |
| 4131595 | Fracture of radius | 137054 | Skin striae |
| 74855 | Genital herpes simplex | 434630 | Sleep-wake schedule disorder |
| 441788 | Human papilloma virus infection | 4195698 | Tenosynovitis |
| 76737 | Hydrocele | 4339088 | Testicular mass |
| 4029582 | Hyperandrogenization syndrome | 133141 | Tinea pedis |
| 195212 | Hypercortisolism | 440814 | Torticollis |
| 438134 | Hypersomnia | 435140 | Toxic effect of alcohol |
| 45768449 | Hypertensive crisis | 4270490 | Tracheitis |
| 140362 | Hypoparathyroidism | 4028970 | Tracheobronchitis |
| 4322737 | Infection of tooth | 4114197 | Tumor of hypothalamus |
| 4207688 | Infectious enteritis | 193326 | Urge incontinence of urine |
| 79072 | Inflammatory disorder of breast | 4092565 | Uterine prolapse |
| 139099 | Ingrowing nail | 140641 | Verruca vulgaris |
| 4288544 | Inguinal hernia | 197036 | Vesicoureteric reflux |
| 444191 | Injury of face | 133551 | Vesicular eczema of hands and/or feet |
| 444130 | Injury of foot | 4223947 | Viral hepatitis, type A |
| 134222 | Injury of forearm | 261326 | Viral pneumonia |

# Data Analysis Plan

## Population Level Estimation

#### Overview

Propensity score (PS) adjustment methods will be used to adjust for potential confounding biases originating from differences in baseline covariates. Absolute standardized mean differences (aSMD) before and after PS adjustment will be calculated to estimate the difference in patient characteristics in the two groups and how they are adjusted. Based on PS distribution, quantification of empirical equipoise will be achieved.

Incidence rates will be estimated for each group. Cox proportional hazards models will be used to estimate the hazard ratios (HR) and 95% confidence intervals (CI). Furthermore, negative control outcomes specified in 6.3.3. Negative Control Outcomes section will be used for empirical calibration and minimization of potential unmeasured confounding biases.

#### Propensity Score Generation

Large-scale L1-regularized logistic regression is used to formulate the PS model.

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

* Demographics
  + Gender
  + Age groups (5-year bands)
  + Race
  + Ethnicity
  + Index Year/Month
* Condition
  + In prior 7d or 365d
  + Group in prior 7d or 365d
* Drug
  + In prior 7d or 365d
  + Group in prior 7d or 365d
* Procedure
  + In prior 7d or 365d
* Device
  + In prior 7d or 365d
* Measurement
  + In prior 7d or 365d
  + Range Group in prior 365d
* Observation
  + In prior 7d or 365d
* Index score
  + CHA2DS2VASc
  + DCSI
  + Charlson

The concepts used in the definitions of the target and comparator cohorts are excluded from the propensity score model.

#### Data Analysis Plan

##### **Definition of Time at Risk**

Per analysis, time at risk is defined as below.

Primary analysis: Intention-to-treat (1 year)

* Time at risk start: Index date +1 day
* Time at risk end: Index date +365 day
* Minimum time at risk: 1day

Sensitivity analysis: On-treatment

* Time at risk start: Index date +1 day
* Time at risk end: Cohort end date
* Minimum time at risk: 1day

##### **Statistical Model Specification**

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. Incidence rates will be computed for each outcome in each exposure group.

Propensity score adjustment: PS stratification

* The target cohort and comparator cohorts will be stratified into 5 stratums of the PS distribution.

Sensitivity analysis: PS matching

* The target cohort and comparator cohorts will be matched 1:1 on PS.

Outcome model settings will be:

* Cox proportional hazards model will be used to estimate the risk of outcome between target and comparator cohorts.

##### **Analysis to Perform**

The following comparative analysis will be performed:

* One comparison:
  + Ticagrelor group (Target) vs. Prasugrel group (Comparator)
* 6 outcomes:
  + NACE
  + MACE
  + All-cause mortality
  + Cardiovascular mortality
  + Ischemic event
  + Hemorrhagic event
* 2 time-at-risks:
  + Intention-to-treat (1-year)
  + On-treatment
* 2 adjustment strategies
  + PS stratification
  + PS 1:1 matching
* One model: Cox-regression after PS adjustment

#### Output

|  |  |
| --- | --- |
| Output | Description |
| Propensity score distribution Plot | The propensity score distribution for both cohorts will be provided. |
| Propensity model | The propensity model will show the table that reports the covariates selected from propensity score models, with associated coefficients. |
| Covariate balance scatter plot | Covariate balance scatter plot will show the absolute standardized difference of mean before and after PS adjustment. |
| Attrition diagram | Attrition diagram will show the counts to meet the inclusion and exclusion criteria. |
| Kaplan-Meier plot | Kaplan-Meier plot will display the survival over time in both cohorts. |
| Population characteristics table | A table which lists some select population characteristics before and after PS adjustment will be created. |

# Strengths and Limitations of the Research Methods

## Strength

* The new-user design can appropriately capture early events following treatment exposures while avoiding confounding from previous treatment effects.
* Rigorous methods to minimize potential biases including PS adjustment and empirical calibration allows balancing on many potential confounders.

## Limitations

* Due to the inherent nature of observational studies, even though many potential confounders will be accounted for in this study, there may be residual bias due to unmeasured variables.

# Protection of Human Subjects

In this study, we will use only de-identified data from CDM. Only the results of study will be aggregated, and the data will not identify individual subjects. The study was approved by the institutional review board of Yonsei University Health System, Severance Hospital. (No.4-2024-0718)

# Plans for Disseminating and Communicating Study Results

At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

# Reference

1. Timmis, A., et al., *Global epidemiology of acute coronary syndromes.* Nat Rev Cardiol, 2023. **20**(11): p. 778-788.

2. Wallentin, L., et al., *Ticagrelor versus clopidogrel in patients with acute coronary syndromes.* N Engl J Med, 2009. **361**(11): p. 1045-57.

3. Wiviott, S.D., et al., *Prasugrel versus clopidogrel in patients with acute coronary syndromes.* N Engl J Med, 2007. **357**(20): p. 2001-15.

4. Motovska, Z., et al., *Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Multicenter Randomized PRAGUE-18 Study.* Circulation, 2016. **134**(21): p. 1603-1612.

5. Lawton, J.S., et al., *2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.* Circulation, 2022. **145**(3): p. e18-e114.

6. Schupke, S., et al., *Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes.* N Engl J Med, 2019. **381**(16): p. 1524-1534.

7. Byrne, R.A., et al., *2023 ESC Guidelines for the management of acute coronary syndromes.* Eur Heart J, 2023. **44**(38): p. 3720-3826.