Research Protocol

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

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1. 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

2. 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.

3. Amendments and Updates

4. 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.

5. Aims and Objectives

This study is a cohort study which aims to:

I. 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.

II. 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.

6. Research Methods

6.1. Study Design

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

6.2. Study Population

6.2.1. 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	Condition	FALSE	FALSE	FALSE

	right carotid artery occlusion				
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

6.2.2. Treatments of Interest

6.2.2.1. 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

6.2.2.2. 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

6.2.2.3. 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

6.3. Outcomes

6.3.1. Primary Outcome

6.3.1.1. 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

6.3.2. Secondary Outcomes

6.3.2.1. 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

6.3.2.2. All-cause Mortality

Outcome cohort entry on any death occurrence

6.3.2.3. Cardiovascular Mortality

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

6.3.2.4. 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

6.3.2.5. 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

6.3.3. 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	253796	Pneumothorax

	anogenital region		
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

7. Data Analysis Plan

7.1. Population Level Estimation

7.1.1. 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.

7.1.2. 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
  - CHA_2DS_2VASc
  - DCSI
  - Charlson

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

7.1.3. Data Analysis Plan

7.1.3.1. 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

7.1.3.2. 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.

7.1.3.3. 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

7.1.4. 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.

8. Strengths and Limitations of the Research Methods

8.1. 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.

8.2. 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.

9. 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)

10. 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.

11. Reference

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