Research Protocol

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

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Contents

1. List of abbreviations

- ACS: acute coronary syndrome
- PCI: percutaneous coronary intervention
- RCT: randomized controlled trial
- OHDSI: Observational Health Data Sciences and Informatics
- NACE: net adverse clinical events
- EHR: electronic health record
- OMOP-CDM: Observational Medical Outcomes Partnership Common Data Model
- GI: gastrointestinal
- DOAC: direct oral anticoagula
- 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). Given ongoing uncertainty from prior trials, mixed guideline recommendations, and the limitations of previous observational research, additional rigorous real-world evidence is needed to clarify optimal treatment strategies for ACS. By conducting a direct, head-to-head comparison, this research will provide valuable insights into their comparative effectiveness and safety.

3. Amendments and Updates

Version	Date	Update
1.0	2025.04.24	Initial version
2.0	2025.06.05	1. Rationale and background updated to better describe this study. 2. Description for concept sets and vocabulary added. 3. Primary endpoint changed to MACE. NACE was moved to secondary endpoints. 4. Method for validating endpoint definitions described. 5. Concept set tables moved to Appendix
2.1	2025.06.17	1. Time frames in cohort definition were minorly adjusted. 2. Negative controls revised to more clinically understandable concepts. 3. Study design terms (e.g. intention-to-treat) revised to better represent comparative effectiveness study.

4. Rationale and Background

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is a cornerstone of treatment for patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Among the available P2Y12 inhibitors, ticagrelor and prasugrel are both recommended over clopidogrel, but direct comparative evidence between them remains mixed and inconclusive.[1, 2]

Initial randomized controlled trials (RCTs) established each drug's superiority over clopidogrel: The Study of Platelet Inhibition and Patient Outcomes (PLATO) showed ticagrelor reduced cardiovascular mortality without increasing major bleeding,[3] while the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel - Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 study demonstrated prasugrel reduced ischemic events but increased bleeding.[4] On the other hand, the Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction (PRAGUE-18) study found no significant difference between ticagrelor and prasugrel in composite ischemic or bleeding endpoints, though this study was greatly limited by early termination due to futility and inadequate power.[5]

The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5 (ISAR-

REACT 5) trial, originally designed to test ticagrelor's superiority, unexpectedly showed prasugrel significantly reduced the risk of death, myocardial infarction, and stroke, without increasing major bleeding.[6] This result influenced the 2023 European Society of Cardiology (ESC) guidelines to favor prasugrel as the first-line agent.[1] Yet, the updated 2025 American College of Cardiology/American Heart Association (ACC/AHA) guidelines continue to recommend either agent, reflecting discrepancy of interpretations and ongoing clinical equipoise.[2]

While ISAR-REACT 5 prompted increased adoption of prasugrel, its uptake remains limited compared to ticagrelor, requiring further rigorous investigation.[7] Although several observational comparative effectiveness studies have attempted to address this gap, many have failed to properly address residual confounding, had limitations in cohort definitions or had confined study populations.[8, 9] This study aims to provide additional robust evidence for clinical decision-making by comparing ticagrelor and prasugrel in ACS patients undergoing PCI, using real-world data accessible through multi-national Observational Health Data Sciences and Informatics (OHDSI) data network.

5. Aims and Objectives

This study is a cohort study which aims to:

I. Determine and compare the hazard of major adverse cardiovascular events (MACE)
II. Determine and compare the incidence rate of net adverse clinical events (NACE) 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.

This protocol outlines two distinct comparative designs based on differing time-at-risk definitions. First, an initiator analysis will be conducted on various timeframes to approximate the intention-to-treat principle in trial-based study designs. In parallel, an as-treated analysis will also be performed to emulate the on-treatment principle.

6.2. Vocabulary and Concept Sets

All definitions of conditions, drugs, and procedures are based on "concept sets", which are groups of concept IDs. Each concept ID represents a certain clinical entity defined through various published vocabulary systems and is universal under OMOP-CDM across databases.

Each category of concept sets in this study is built as follows:

- **Conditions**: Each concept ID in condition domain represents a term in **SNOMED Clinical Terms (CT)**. Each definition originates from a set of **ICD-10** based identification of a clinical condition, then a set of concept IDs that best represent this condition is compiled to form a concept set.
- **Drugs**: Each concept ID in drug domain represents a term in **RxNorm** or **Anatomical Therapeutic Chemical (ATC) classification 5th**. The ingredient or classification of drugs are mainly used to define a concept set.
- **Procedures**: Each concept ID in procedure domain represents a term in **SNOMED CT**.

For each concept set, a table is provided in the **Appendix** describing which concepts are used, how they are joined, and what ICD-10 codes are the basis (for concept sets describing clinical conditions).

How the concept IDs are joined are based on the following rules:

- "Excluded": Whether the concept (and its descendent or mapped concepts) should be excluded from the set.
- "Descendent": Whether all the descendent concepts, which are hierarchically under the concept should be also included in the set.
- "Mapped": Whether all concepts (including non-standard vocabulary) mapped as equivalent to the concept should be also included in the set.

6.3. Study Population

6.3.1. 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 a primary analysis, initiators analysis will be done to derive **1-year outcomes**.
As sensitivity analysis, initiators analysis will be done to derive **1-month** and **3-month outcomes**.

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 365 days before the event index date.
- At least 1 occurrence of a condition occurrence of **ACS** (Table 2) between 7 days before and 0 day after index start date
- At least 1 occurrence of a drug exposure to the drug of interest between 1 day before and 1 day after index start date

Inclusion rules based on the index date:

- With no exposure to the drug of the other group between 180 days before and 1 days after index start date
- With no exposure to **warfarin or direct oral anticoagulants (DOAC)** (Table 6) between 180 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

As-treated analysis will also be done for a sensitivity analysis. In this case, the cohort exit rule described below will be applied for time at risk end.

Exit rules defining the cohort end date:

- 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 exposure to the drug of the other group

6.3.2. Treatments of Interest

6.3.2.1. Target Drug: Ticagrelor

Target cohort using **ticagrelor** (Table 7) is defined as above.

6.3.2.2. Comparator Drug: Prasugrel

Comparator cohort using **prasugrel** (Table 8) is defined as above.

6.4. Outcomes

6.4.1. Outcome Definition Validation

For individual outcomes, a sample of cohort (100 patients at most) defined with the following definitions will be compared against the results of chart review by a physician to determine the positive predictive value (PPV). PPV values will be cited from the previous study if the same concept set was already used and validated.[10]

6.4.2. Primary Outcome

6.4.2.1. Major Adverse Cardiovascular Event (MACE)

The primary outcome of this study is MACE, which is defined as a composite outcome of all-cause mortality, AMI, and stroke. The outcome cohort definition is described below.

Outcome cohort entry on any of the following events:

- Any death occurrence
- 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

6.4.3. Secondary Outcomes

6.4.3.1. Net Adverse Clinical Event (NACE)

NACE, which is defined as a composite outcome of all-cause mortality, acute myocardial infarction (AMI), stroke (ischemic and hemorrhagic), and GI bleeding, will be also explored. The outcome cohort definition for NACE is described below.

Composite of **NACE** and cardiovascular mortality will be also investigated as a secondary outcome.
The outcome cohort definition for this composite outcome is described below.

Outcome cohort entry on any of the following events:

- Any death occurrence
- 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

6.4.3.2. All-cause Mortality

Outcome cohort entry on any death occurrence

6.4.3.3. Cardiovascular Mortality

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 12) 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 13) between 30 days before and 0 days after the day of the death event, with at least 1 **hospitalization** (Table 14) visit occurrence starting before and ending after the condition occurrence.

6.4.3.4. 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

6.4.3.5. 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

6.4.3.6. Acute Myocardial Infarction (AMI)

Outcome cohort entry on any of the following events:

- An inpatient condition occurrence of **AMI** (Table 11)

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

6.4.3.7. Ischemic Stroke

Outcome cohort entry on any of the following events:

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

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

6.4.3.8. Hemorrhagic Stroke

Outcome cohort entry on any of the following events:

- An inpatient condition occurrence of **hemorrhagic stroke** (Table 4)

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

6.4.3.9. Stroke

Outcome cohort entry on any of the following events:

- 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

6.4.3.10. GI bleeding

Outcome cohort entry on any of the following events:

- An inpatient condition occurrence of **GI bleeding** (Table 5)

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

6.4.4. Negative Control Outcomes

A total of 100 concepts were selected as negative controls that were not associated with both the target and comparator drugs and study outcomes.

Concept ID	Concept Name	Concept ID	Concept Name
4299544	Acanthosis nigricans	440129	Hypertrophy of nasal turbinates
77965	Acquired trigger finger	140362	Hypoparathyroidism
376707	Acute conjunctivitis	4207307	Infective meningitis
141323	Acute maxillary sinusitis	4288544	Inguinal hernia
4150372	Acute otitis media	75576	Irritable bowel syndrome
199074	Acute pancreatitis	439840	Lymphangitis
4280571	Acute pyelonephritis	316457	Mallory-Weiss syndrome
4218106	Alcoholism	374655	Mastoiditis
139902	Allergic urticaria	4304008	Memory impairment
141933	Alopecia areata	436100	Narcolepsy
437082	Ankylosing spondylitis	30234	Neck sprain
436675	Anorexia nervosa	376938	Neurofibromatosis syndrome
440424	Aphasia	201792	Nongonococcal urethritis
138463	Aphthous ulcer of mouth	4215978	Onychomycosis
378424	Astigmatism	4171915	Orchitis
261880	Atelectasis	4079750	Osteoarthritis of knee
81878	Benign paroxysmal positional vertigo	380731	Otitis externa
198803	Benign prostatic hyperplasia	433450	Paranoid schizophrenia
72576	Benign tumor of breast	192606	Paraplegia
80509	Bone cyst	199861	Perianal abscess
434626	Borderline personality disorder	253796	Pneumothorax
438407	Bulimia nervosa	40443308	Polycystic ovary syndrome
4108467	Burn of skin	4164337	Polyp of large intestine
134453	Bursitis	4153877	Post-traumatic wound infection
134765	Cachexia	436676	Posttraumatic stress disorder
4172458	Candidiasis of skin	373478	Presbyopia
380094	Carpal tunnel syndrome	4068482	Prolapsed lumbar intervertebral disc
436740	Cellulitis	194997	Prostatitis
381581	Chalazion	140168	Psoriasis
444367	Cholelithiasis without obstruction	4239381	Psychoactive substance abuse
435093	Closed fracture of femur	73300	Radial styloid tenosynovitis
4047787	Colles' fracture	81336	Rectal prolapse
198075	Condyloma acuminatum of the anogenital region	380395	Retinal dystrophy

381444	Contusion of eye	72418	Scoliosis deformity of spine
198202	Cystocele	374366	Sensorineural hearing loss
432590	Delusional disorder	30441	Sialolithiasis
133228	Dental caries	377535	Sleep walking disorder
377910	Deviated nasal septum	74189	Sprain of cruciate ligament of knee
4135082	Dislocation of distal radioulnar joint	42873169	Sprain of shoulder rotator cuff
194696	Dysmenorrhea	4339088	Testicular mass
433440	Dysthymia	440814	Torticollis
376132	Ectropion	134619	Toxic nodular goiter
433527	Endometriosis (clinical)	4028970	Tracheobronchitis
4001458	Fatigue fracture of vertebra	380839	Tuberous sclerosis syndrome
4131595	Fracture of radius	4114197	Tumor of hypothalamus
4142905	Fracture of rib	4092565	Uterine prolapse
318800	Gastroesophageal reflux disease	197036	Vesicoureteric reflux
74855	Genital herpes simplex	4049417	Vesicular eczema
135215	Hashimoto thyroiditis	4223947	Viral hepatitis, type A
195212	Hypercortisolism	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.

Cumulative incidence 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

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: 1- year outcomes
- Time at risk start: Index date +1 day
- Time at risk end: Index date +365 day
- Minimum time at risk: 1day

Sensitivity analysis 1: 3-month outcomes
- Time at risk start: Index date +1 day
- Time at risk end: Index date +90 day
- Minimum time at risk: 1day

Sensitivity analysis 2: 1-month outcomes
- Time at risk start: Index date +1 day
- Time at risk end: Index date +30 day
- Minimum time at risk: 1day

Sensitivity analysis 3: As-treated
- 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)
- 11 outcomes:
  - MACE
  - NACE
  - All-cause mortality
  - Cardiovascular mortality
  - Ischemic event
  - Hemorrhagic event
  - AMI
  - Ischemic stroke
  - Hemorrhagic stroke
  - Stroke
  - GI bleeding
- 4 time-at-risks:
  - 1-year
  - 3-month
  - 1-month
  - As-treated
- 2 adjustment strategies
  - PS stratification
  - PS 1:1 matching
- One model: Cox-regression after PS adjustment

7.1.4. Diagnostics

We will perform a series of study diagnostics to assess the reliability of analyses from each database. Estimates diagnosed as reliable based on pre-specified thresholds will be included in the final meta-analysis. This approach ensures a rigorous evaluation of potential biases within individual databases and helps safeguard the robustness of the overall evidence.

The details of diagnostics are detailed as follows:

Target	Metric	Description	Threshold
Covariate balance after PS adjustment	Standardized difference of means (SDM)	This is to determine whether the PS adjustment is sufficient to balance baseline patient characteristics. Characteristics specified below will be mainly observed, and covariate balance scatter plot will be generated for all covariates included in the PS model.	Max SDM < 0.1 [11]
Empirical equipoise	Preference score (F)	Good equipoise ensures that a sufficient portion of patients have the comparable probability of receiving either intervention. This is assessed by determining the overlap in preference score distribution between the target and comparator cohorts.	At least 20% patients $0.3 \leq F \leq 0.7$ [10]
Systematic error	Expected Absolute Systematic Error (EASE)	For each negative control outcome specified above, the primary analysis will be applied to derive an estimated result. This result is then compared to true HR, which is expected to be 1 in this case, and is quantified on a logarithmic scale. Overall systematic error is calculated from the absolute expected value	EASE <0.25 [11]

		of the distribution of these results.	

Baseline characteristics for evaluating covariate balance after PS adjustment are detailed as follows:

Characteristics	Detail
Age group	
Sex	
Race	
Medical history	Hypertensive disorder, DM, Hyperlipidemia, Obesity, Renal impairment, Atrial fibrillation, Heart failure, Peripheral vascular disease
Medication use	Aspirin, Abciximab, Statins, Beta blockers, Calcium channel blockers, ACE inhibitors, Angiotensin II antagonists, Proton pump inhibitors, Diuretics, Insulin and analogues, Blood glucose-lowering drugs excluding insulins

7.1.5. Meta-analysis

A Bayesian random-effects meta-analysis will be conducted to combine each site's hazard ratio estimate into a single aggregated hazard ratio using non-normal likelihood approximations.

7.1.6. 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

- Rigorous methods to minimize potential biases including PS adjustment and empirical calibration allows balancing on many potential confounders.
- Utilizing OHDSI data network framework to efficiently collaborate and collect data from multiple databases internationally.

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.
- Due to the inherent nature of CDM-based studies, individual code-based definitions may not ensure perfect representation of true clinical entity.

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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Appendix

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

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 Definition

Code	Basis for definition				
ICD-10	I20.0, I21.0-4, I21.9, I24.0, I24.8, I24.9				
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

Code	Basis for definition				
ICD-10	I63.0-6, I63.8, I63.9, G46.0-7, F01.0, F01.1, F01.3				
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	Condition	FALSE	FALSE	FALSE

	arteries				
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

Code	Basis for definition				
ICD-10	I60.0-9, I61.0-6, I61.8, I61.9, I62.0, I62.1, I62.9				
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

Code	Basis for definition				
ICD-10	K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K62.5, K92.0-2				
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

Table 6. Warfarin or Direct Oral Anticoagulants (DOAC) Concept Set Definitions

Concept ID	Concept Name	Domain	Excluded	Descendant	Mapped
21600965	warfarin; systemic	Drug	FALSE	TRUE	FALSE
1310149	warfarin	Drug	FALSE	TRUE	FALSE
21600971	tioclomarol; oral	Drug	FALSE	TRUE	FALSE
19018364	tioclomarol	Drug	FALSE	TRUE	FALSE
21600966	phenprocoumon; oral	Drug	FALSE	TRUE	FALSE
19035344	phenprocoumon	Drug	FALSE	TRUE	FALSE
21600964	phenindione; oral	Drug	FALSE	TRUE	FALSE
19033934	phenindione	Drug	FALSE	TRUE	FALSE
40252605	fluindione; oral	Drug	FALSE	TRUE	FALSE
19113013	fluindione	Drug	FALSE	TRUE	FALSE
21600963	dicoumarol; oral	Drug	FALSE	TRUE	FALSE
1325124	dicumarol	Drug	FALSE	TRUE	FALSE
21600967	acenocoumarol; oral	Drug	FALSE	TRUE	FALSE
19024063	acenocoumarol	Drug	FALSE	TRUE	FALSE
43534761	rivaroxaban; oral	Drug	FALSE	TRUE	FALSE
40241331	rivaroxaban	Drug	FALSE	TRUE	FALSE
1123891	edoxaban; oral	Drug	FALSE	TRUE	FALSE
45892847	edoxaban	Drug	FALSE	TRUE	FALSE
21601026	dabigatran etexilate; oral	Drug	FALSE	TRUE	FALSE
40228152	dabigatran etexilate	Drug	FALSE	TRUE	FALSE
715776	betrixaban; oral	Drug	FALSE	TRUE	FALSE
1592988	betrixaban	Drug	FALSE	TRUE	FALSE
43534762	apixaban; oral	Drug	FALSE	TRUE	FALSE
43013024	apixaban	Drug	FALSE	TRUE	FALSE

Table 7. 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

Table 8. 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

Table 9. 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 10. 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

Table 11 Acute Myocardial Infarction (AMI) Concept Set Definition

Code	Basis for definition				
ICD-10	I21.0-4, I21.9				
312327	Acute myocardial infarction	Condition	FALSE	TRUE	FALSE
314666	Old myocardial infarction	Condition	TRUE	TRUE	FALSE

Table 12 Sudden Cardiac Death Concept Set Definition

Code	Basis for definition				
ICD-10	I46.1, I46.9, R96.0, R96.1				
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 13 Heart Failure Concept Set Definition

Code	Basis for definition				
ICD-10	I50.0, I50.1, I50.9				
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 14 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