**Research Protocol**

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

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# 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

# 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.

# 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. |

# 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.

# Aims and Objectives

This study is a cohort study which aims to:

1. Determine and compare the hazard of major adverse cardiovascular events (MACE)
2. 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.

# 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.

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.

## 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.

## 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 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 0 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 0 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

### Treatments of Interest

#### Target Drug: Ticagrelor

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

#### Comparator Drug: Prasugrel

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

## Outcomes

### 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]

### Primary Outcome

#### 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

### Secondary Outcomes

#### 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

#### All-cause Mortality

Outcome cohort entry on any death occurrence

#### 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.

#### 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

#### 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

#### 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

#### 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

#### 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

#### 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

### 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 |

# 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.

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.

#### 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.

#### Data Analysis Plan

##### **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

##### **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)
* 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

#### 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 ≤ F≤ 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 of the distribution of these results. | EASE <0.25 [11] |

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 |

#### 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.

#### 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

* 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.

## 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.

# 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.

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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 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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 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](http://10.19.10.241/atlas/#/concept/21600971) | 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 |