Exploring mediation through major bleeding between DOACs and CV events

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Table of Contents

[1 Introduction 3](#_Toc166637879)

[2 Study design 4](#_Toc166637880)

[2.1 Estimands of interest 4](#_Toc166637881)

[2.2 Confounding adjustment 5](#_Toc166637882)

[2.3 Negative controls 5](#_Toc166637883)

[3 Data sources 5](#_Toc166637884)

[3.1 IBM Health MarketScan® Commercial Claims and Encounters Database 5](#_Toc166637885)

[3.2 IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database 6](#_Toc166637886)

[3.3 Optum EHR 6](#_Toc166637887)

[3.4 Optum’s Clinformatics® Extended Data Mart – Date of Death (DOD) 6](#_Toc166637888)

[3.5 PharMetrics Plus 7](#_Toc166637889)

[4 References 7](#_Toc166637890)

[5 Appendix A: Cohort Definitions 7](#_Toc166637891)

[5.1 Target: Rivaroxaban 7](#_Toc166637892)

[5.1.1 Cohort Entry Events 7](#_Toc166637893)

[5.1.2 Inclusion Criteria 7](#_Toc166637894)

[5.1.3 Cohort Exit 8](#_Toc166637895)

[5.1.4 Cohort Eras 8](#_Toc166637896)

[5.1.5 Rivaroxaban 8](#_Toc166637897)

[5.1.6 Nonvalvular atrial fibrillation 8](#_Toc166637898)

[5.2 Target: DOACs 8](#_Toc166637899)

[5.2.1 Cohort Entry Events 8](#_Toc166637900)

[5.2.2 Inclusion Criteria 8](#_Toc166637901)

[5.2.3 Cohort Exit 9](#_Toc166637902)

[5.2.4 Cohort Eras 9](#_Toc166637903)

[5.2.5 DOAC 9](#_Toc166637904)

[5.2.6 Nonvalvular atrial fibrillation 9](#_Toc166637905)

[5.3 Comparator: Warfarin 9](#_Toc166637906)

[5.3.1 Cohort Entry Events 9](#_Toc166637907)

[5.3.2 Inclusion Criteria 9](#_Toc166637908)

[5.3.3 Cohort Exit 10](#_Toc166637909)

[5.3.4 Cohort Eras 10](#_Toc166637910)

[5.3.5 Warfarin 10](#_Toc166637911)

[5.3.6 Nonvalvular atrial fibrillation 10](#_Toc166637912)

[5.4 Mediator: Major bleeding IP 10](#_Toc166637913)

[5.4.1 Cohort Entry Events 10](#_Toc166637914)

[5.4.2 Inclusion Criteria 11](#_Toc166637915)

[5.4.3 Cohort Exit 11](#_Toc166637916)

[5.4.4 Cohort Eras 11](#_Toc166637917)

[5.4.5 [EPI\_1001] Bleeding 11](#_Toc166637918)

[5.4.6 [EPI\_1001] Bleeding related disorders 11](#_Toc166637919)

[5.4.7 Inpatient Visit 12](#_Toc166637920)

[5.4.8 [Phenotype Phebruary][Bleed] Intracranial hemorrhage no trauma - definite w desc 12](#_Toc166637921)

[5.4.9 [Phenotype Phebruary][Bleed] Intracranial hemorrhage trauma - definite w desc 13](#_Toc166637922)

[5.5 Mediator: Major bleeding IP or ER 16](#_Toc166637923)

[5.5.1 Cohort Entry Events 16](#_Toc166637924)

[5.5.2 Inclusion Criteria 16](#_Toc166637925)

[5.5.3 Cohort Exit 16](#_Toc166637926)

[5.5.4 Cohort Eras 16](#_Toc166637927)

[5.5.5 [EPI\_1001] Bleeding 17](#_Toc166637928)

[5.5.6 [EPI\_1001] Bleeding related disorders 17](#_Toc166637929)

[5.5.7 Inpatient Visit 17](#_Toc166637930)

[5.5.8 [Phenotype Phebruary][Bleed] Intracranial hemorrhage no trauma - definite w desc 17](#_Toc166637931)

[5.5.9 [Phenotype Phebruary][Bleed] Intracranial hemorrhage trauma - definite w desc 19](#_Toc166637932)

[5.5.10 [HowOften] Inpatient or ER visit 21](#_Toc166637933)

[5.6 Outcome: Acute MI 21](#_Toc166637934)

[5.6.1 Cohort Entry Events 21](#_Toc166637935)

[5.6.2 Inclusion Criteria 22](#_Toc166637936)

[5.6.3 Cohort Exit 22](#_Toc166637937)

[5.6.4 Cohort Eras 22](#_Toc166637938)

[5.6.5 Inpatient or Inpatient/ER visit 22](#_Toc166637939)

[5.6.6 Myocardial Infarction and complication 22](#_Toc166637940)

[5.7 Outcome: Ischemic stroke 23](#_Toc166637941)

[5.7.1 Cohort Entry Events 23](#_Toc166637942)

[5.7.2 Inclusion Criteria 24](#_Toc166637943)

[5.7.3 Cohort Exit 24](#_Toc166637944)

[5.7.4 Cohort Eras 24](#_Toc166637945)

[5.7.5 Inpatient or Inpatient/ER visit 24](#_Toc166637946)

[5.7.6 Cerebral infarction 24](#_Toc166637947)

[5.8 Outcome: Composite 25](#_Toc166637948)

[5.8.1 Cohort Entry Events 25](#_Toc166637949)

[5.8.2 Inclusion Criteria 25](#_Toc166637950)

[5.8.3 Cohort Exit 26](#_Toc166637951)

[5.8.4 Cohort Eras 26](#_Toc166637952)

[5.8.5 Inpatient or Inpatient/ER visit 26](#_Toc166637953)

[5.8.6 Cerebral infarction 26](#_Toc166637954)

[5.8.7 Myocardial Infarction and complication 27](#_Toc166637955)

[6 Appendix B: Negative controls 28](#_Toc166637956)

# 1 Introduction

Anticoagulant therapies have undergone significant evolution with the development of direct oral anticoagulants (DOACs), which have been increasingly favored over traditional warfarin due to their promising safety profiles, fewer dietary restrictions, and reduced need for monitoring. While DOACs are associated with a lower risk of major bleeding compared to warfarin, their overall impact on cardiovascular (CV) outcomes remains a subject of intense research. Major bleeding is a critical concern in anticoagulant therapy and can profoundly influence patient outcomes and treatment efficacy.

This real-world study aims to dissect the complex interplay between anticoagulant type, major bleeding events, and cardiovascular outcomes. This protocol outlines the methodology for an observational study that will estimate the extent to which the effect of DOACs versus warfarin on cardiovascular outcomes is mediated through their differential impact on major bleeding rates. By leveraging real-world data, the study will contribute valuable insights into the comparative effectiveness and safety of these anticoagulants, guiding clinical decision-making and potentially informing future guidelines.

This study will utilize novel advanced statistical techniques to model the mediation effects, controlling for a range of confounding factors that could influence both bleeding risk and cardiovascular outcomes.

# 2 Study design

This study will employ a new-user comparative cohort design, comparing a target cohort (rivaroxaban or the entire class of DOACs) to a comparator cohort (warfarin). Both target and cohort are defined as first exposure to drug of interest, requiring 365 days of prior observation. Followup starts on the day of treatment initiation, and ends at end of continuous exposure (allowing for 30-day gaps) or occurrence of the outcome, whichever comes first. A single mediator - major bleeding - is defined and included in the model. We evaluate 2 variants of this mediator, one only considering inpatient (IP) visitings, and one considering both IP and emergency room (ER) visits. This table lists all the comparisons that will be made:

| Target | Comparator | Mediator | Outcome |
| --- | --- | --- | --- |
| Rivaroxaban | Warfarin | Major bleeding IP or ER | Acute MI |
| Rivaroxaban | Warfarin | Major bleeding IP or ER | Ischemic stroke |
| Rivaroxaban | Warfarin | Major bleeding IP or ER | Composite |
| DOACs | Warfarin | Major bleeding IP or ER | Acute MI |
| DOACs | Warfarin | Major bleeding IP or ER | Ischemic stroke |
| DOACs | Warfarin | Major bleeding IP or ER | Composite |
| Rivaroxaban | Warfarin | Major bleeding IP | Acute MI |
| Rivaroxaban | Warfarin | Major bleeding IP | Ischemic stroke |
| Rivaroxaban | Warfarin | Major bleeding IP | Composite |
| DOACs | Warfarin | Major bleeding IP | Acute MI |
| DOACs | Warfarin | Major bleeding IP | Ischemic stroke |
| DOACs | Warfarin | Major bleeding IP | Composite |

The model is a Cox proportional hazards model, with the mediator as time-varying covariate. Cohort definitions of the targets, comparator, mediator and outcomes are provided in Appendix A.

## 2.1 Estimands of interest

For each target-comparator-outcome triplet, two Cox modes will be fitted, one with the mediator and one without. From these two models, the following estimands will be reported, each on the hazard ratio scale, including their 95% confidence intervals: (VanderWeele 2011)

* **Main effect**: The effect of the target on the outcome, relative to the comparator.
* **Direct effect**: The effect of the target on the outcome, relative to the comparator, *not* mediated by the mediator.
* **Indirect effect**: The effect of the target on the outcome, relative to the comparator, mediated by the mediator.

The indirect effect is estimated using the difference method, subtracting the (log) direct effect from the (log) main effect.

## 2.2 Confounding adjustment

Adjustment for confounding between target and comparator is achieved by large-scale propensity scores (LSPS), (Tian, Schuemie, and Suchard 2018) used for variable ratio PS matching. (Rassen et al. 2012)

Adjustment for confounding between those with the mediator and those without is achieved by a large-scale mediator risk score (MRS). The MRS is fitted as a Poisson regression by using the same set of baseline covariates used in the LSPS, including all demographics, drug exposures, conditions, procedures, etc. observed on or in the year prior to treatment initiation. Similar to the LSPS, the MRS model is fitted using L2 regularization, using 10-fold cross-validation to select the optimal hyperparameter by optimizing out-of-sample likelihood. The MRS is included in the outcome model using a 5-knot bicubic spline.

## 2.3 Negative controls

A set of 50 negative control outcomes - outcomes believed to be caused by neither the target nor the comparator - has been defined. (See Appendix B). We assume that these controls are negative both for the direct effect and the mediated effect. The negative control summary estimates will be used to estimate residual systematic error for all estimands of interest.

# 3 Data sources

The DatabaseDiagnostics package was used to select those databases that appear to have the elements needed for the example estimation questions:

## 3.1 IBM Health MarketScan® Commercial Claims and Encounters Database

The IBM(R) MarketScan(R) Commercial Database (CCAE) includes health insurance claims across the continuum of care (e.g. inpatient, outpatient, outpatient pharmacy, carve-out behavioral healthcare) as well as enrollment data from large employers and health plans across the United States who provide private healthcare coverage for more than 155 million employees, their spouses, and dependents. This administrative claims database includes a variety of fee- for-service, preferred provider organizations, and capitated health plans.

## 3.2 IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database

The IBM(R) MarketScan(R) Medicare Supplemental Database (MDCR) represents the health services of approximately 10 million retirees in the United States with Medicare supplemental coverage through employer-sponsored plans. This database contains primarily fee-for-service plans and includes health insurance claims across the continuum of care (e.g. inpatient, outpatient and outpatient pharmacy).

## 3.3 Optum EHR

Optum‘s longitudinal EHR repository is derived from dozens of healthcare provider organizations in the United States, that include more than 700 Hospitals and 7000 Clinics; treating more than 102 million patients receiving care in the United States. The data is certified as de-identified by an independent statistical expert following HIPAA statistical de-identification rules, and managed according to Optum(R) customer data use agreements. Clinical, claims and other medical administrative data is obtained from both Inpatient and Ambulatory electronic health records (EHRs), practice management systems and numerous other internal systems. Information is processed, normalized, and standardized across the continuum of care from both acute inpatient stays and outpatient visits. Optum(R) data elements include: demographics, medications prescribed and administered, immunizations, allergies, lab results (including microbiology), vital signs and other observable measurements, clinical and inpatient stay administrative data and coded diagnoses and procedures. In addition, Optum(R) uses natural language processing (NLP) computing technology to transform critical facts from physician notes into usable datasets. The NLP data provides detailed information regarding signs and symptoms, family history, disease related scores (i.e. RAPID3 for RA, or CHADS2 for stroke risk), genetic testing, medication changes, and physician rationale behind prescribing decisions that might never be recorded in the EHR.

## 3.4 Optum’s Clinformatics® Extended Data Mart – Date of Death (DOD)

Optum‘s Clinformatics(R) Data Mart is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans.The database includes approximately 17-19 million annual covered lives, for a total of over 65 million unique lives over a 12 year period (1/2007 through 12/2019). Clinformatics(R) Data Mart is statistically de-identified under the Expert Determination method consistent with HIPAA and managed according to Optum(R) customer data use agreements. CDM administrative claims submitted for payment by providers and pharmacies are verified, adjudicated and de-identified prior to inclusion. This data, including patient-level enrollment information, is derived from claims submitted for all medical and pharmacy health care services with information related to healthcare costs and resource utilization. The population is geographically diverse, spanning all 50 states. Optum Clinformatics(R) Data Mart Data of Death (Optum DOD) also provides date of death (month and year only) for members with both medical and pharmacy coverage from the Social Security Death Master File (however after 2011 reporting frequency changed due to changes in reporting requirements) and location information for patients is at the US state level.

## 3.5 PharMetrics Plus

Data is from 2015 - 2023 and comprises of fully adjudicated medical and pharmacy claims. It contains a longitudinal view of inpatient and outpatient services, prescription and office/outpatient administered drugs, costs and enrollment information. With IQVIA Adjudicated Health Plan Claims, an enrolled patient can be tracked across all sites of care: hospital, specialist, emergency room, pharmacy, primary care, and more.<U+FFFD>

# 4 References

Rassen, Jeremy A, Abhi A Shelat, Jessica Myers, Robert J Glynn, Kenneth J Rothman, and Sebastian Schneeweiss. 2012. “One-to-Many Propensity Score Matching in Cohort Studies.” *Pharmacoepidemiol. Drug Saf.* 21 Suppl 2 (May): 69–80.

Tian, Yuxi, Martijn J Schuemie, and Marc A Suchard. 2018. “Evaluating Large-Scale Propensity Score Performance Through Real-World and Synthetic Data Experiments.” *Int. J. Epidemiol.* 47 (6): 2005–14.

VanderWeele, Tyler J. 2011. “Causal Mediation Analysis with Survival Data.” *Epidemiology* 22 (4): 582–85.

# 5 Appendix A: Cohort Definitions

## 5.1 Target: Rivaroxaban

### 5.1.1 Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of ‘Rivaroxaban’ for the first time in the person’s history.

Limit cohort entry events to the earliest event per person.

### 5.1.2 Inclusion Criteria

#### 5.1.2.1 1. Aged 18 or older

Entry events with the following event criteria: who are >= 18 years old. #### 2. Non-valvular atrial fibrillation in prior 365 days

Entry events having at least 1 condition occurrence of ‘Nonvalvular atrial fibrillation’, starting between 365 days before and 0 days after cohort entry start date.

### 5.1.3 Cohort Exit

The cohort end date will be based on a continuous exposure to ‘Rivaroxaban’: allowing 30 days between exposures, adding 30 days after exposure ends, and using days supply and exposure end date for exposure duration.

### 5.1.4 Cohort Eras

Remaining events will be combined into cohort eras if they are within 0 days of each other.

### 5.1.5 Rivaroxaban

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 40241330 | rivaroxaban | 1114195 | RxNorm | NO | YES | NO |

### 5.1.6 Nonvalvular atrial fibrillation

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 313217 | Atrial fibrillation | 49436004 | SNOMED | NO | YES | NO |
| 319843 | Mitral valve disorder | 11851006 | SNOMED | YES | YES | NO |
| 37395820 | Familial atrial fibrillation | 715395008 | SNOMED | YES | YES | NO |

## 5.2 Target: DOACs

### 5.2.1 Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug era of ‘DOAC’ for the first time in the person’s history.

### 5.2.2 Inclusion Criteria

#### 5.2.2.1 1. Aged 18 or older

Entry events with the following event criteria: who are >= 18 years old. #### 2. Non-valvular atrial fibrillation in prior 365 days

Entry events having at least 1 condition occurrence of ‘Nonvalvular atrial fibrillation’, starting between 365 days before and 0 days after cohort entry start date.

### 5.2.3 Cohort Exit

The cohort end date will be based on a continuous exposure to ‘DOAC’: allowing 30 days between exposures, adding 30 days after exposure ends, and using days supply and exposure end date for exposure duration.

### 5.2.4 Cohort Eras

Remaining events will be combined into cohort eras if they are within 0 days of each other.

### 5.2.5 DOAC

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 43013020 | apixaban | 1364430 | RxNorm | NO | YES | NO |
| 45892850 | edoxaban | 1599538 | RxNorm | NO | YES | NO |
| 45775370 | dabigatran | 1546356 | RxNorm | NO | YES | NO |
| 40241330 | rivaroxaban | 1114195 | RxNorm | NO | YES | NO |
| 40228150 | dabigatran etexilate | 1037042 | RxNorm | NO | YES | NO |

### 5.2.6 Nonvalvular atrial fibrillation

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 313217 | Atrial fibrillation | 49436004 | SNOMED | NO | YES | NO |
| 319843 | Mitral valve disorder | 11851006 | SNOMED | YES | YES | NO |
| 37395820 | Familial atrial fibrillation | 715395008 | SNOMED | YES | YES | NO |

## 5.3 Comparator: Warfarin

### 5.3.1 Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug era of ‘Warfarin’ for the first time in the person’s history.

### 5.3.2 Inclusion Criteria

#### 5.3.2.1 1. Aged 18 or older

Entry events with the following event criteria: who are >= 18 years old. #### 2. Non-valvular atrial fibrillation in prior 365 days

Entry events having at least 1 condition occurrence of ‘Nonvalvular atrial fibrillation’, starting between 365 days before and 0 days after cohort entry start date.

### 5.3.3 Cohort Exit

The cohort end date will be based on a continuous exposure to ‘Warfarin’: allowing 30 days between exposures, adding 30 days after exposure ends, and using days supply and exposure end date for exposure duration.

### 5.3.4 Cohort Eras

Remaining events will be combined into cohort eras if they are within 0 days of each other.

### 5.3.5 Warfarin

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 1310149 | warfarin | 11289 | RxNorm | NO | YES | NO |

### 5.3.6 Nonvalvular atrial fibrillation

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 313217 | Atrial fibrillation | 49436004 | SNOMED | NO | YES | NO |
| 319843 | Mitral valve disorder | 11851006 | SNOMED | YES | YES | NO |
| 37395820 | Familial atrial fibrillation | 715395008 | SNOMED | YES | YES | NO |

## 5.4 Mediator: Major bleeding IP

### 5.4.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of ‘[EPI\_1001] Bleeding’, a condition status that is: “primary diagnosis”.
2. condition occurrences of ‘[EPI\_1001] Bleeding related disorders’, a condition status that is: “primary diagnosis”; having at least 1 condition occurrence of ‘[EPI\_1001] Bleeding’, starting between 0 days before and 0 days after ‘[EPI\_1001] Bleeding related disorders’ start date.

### 5.4.2 Inclusion Criteria

#### 5.4.2.1 1. During IP visit

Entry events having at least 1 visit occurrence of ‘Inpatient Visit’, starting anytime on or before cohort entry start date and ending between 0 days after and all days after cohort entry start date.

#### 5.4.2.2 2. no ICH

Entry events with all of the following criteria:

1. having no condition occurrences of ‘[Phenotype Phebruary][Bleed] Intracranial hemorrhage no trauma - definite w desc’, starting between 0 days before and 0 days after cohort entry start date.
2. having no condition occurrences of ‘[Phenotype Phebruary][Bleed] Intracranial hemorrhage trauma - definite w desc’, starting between 0 days before and 0 days after cohort entry start date.

### 5.4.3 Cohort Exit

The cohort end date will be offset from index event’s start date plus 30 days.

### 5.4.4 Cohort Eras

Remaining events will be combined into cohort eras if they are within 0 days of each other.

### 5.4.5 [EPI\_1001] Bleeding

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 437312 | Bleeding | 131148009 | SNOMED | NO | YES | NO |

### 5.4.6 [EPI\_1001] Bleeding related disorders

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 195562 | Hemorrhoids | 70153002 | SNOMED | NO | YES | NO |
| 193252 | Diverticulosis of small intestine | 8114009 | SNOMED | NO | YES | NO |
| 42535740 | Diverticulosis of colon | 733657002 | SNOMED | NO | YES | NO |
| 439777 | Anemia | 271737000 | SNOMED | NO | YES | NO |
| 4027663 | Peptic ulcer | 13200003 | SNOMED | NO | YES | NO |
| 30753 | Esophagitis | 16761005 | SNOMED | NO | YES | NO |
| 201340 | Gastritis | 4556007 | SNOMED | NO | YES | NO |
| 4306267 | Coag./bleeding tests abnormal | 165563002 | SNOMED | NO | YES | NO |
| 433516 | Duodenitis | 72007001 | SNOMED | NO | YES | NO |

### 5.4.7 Inpatient Visit

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 9201 | Inpatient Visit | IP | Visit | NO | YES | NO |

### 5.4.8 [Phenotype Phebruary][Bleed] Intracranial hemorrhage no trauma - definite w desc

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 4319328 | Brain stem hemorrhage | 95454007 | SNOMED | NO | YES | NO |
| 376713 | Cerebral hemorrhage | 274100004 | SNOMED | NO | YES | NO |
| 43530850 | Chronic non-traumatic intracranial subdural hemorrhage | 609382000 | SNOMED | NO | YES | NO |
| 4176892 | Cortical hemorrhage | 49422009 | SNOMED | NO | YES | NO |
| 4110186 | Intracerebral hemorrhage, multiple localized | 195169004 | SNOMED | NO | YES | NO |
| 439847 | Intracranial hemorrhage | 1386000 | SNOMED | NO | YES | NO |
| 436430 | Nontraumatic extradural hemorrhage | 397809001 | SNOMED | NO | YES | NO |
| 4144154 | Non-traumatic intracerebral ventricular hemorrhage | 425957003 | SNOMED | NO | YES | NO |
| 4111709 | Non-traumatic subdural hemorrhage | 195176009 | SNOMED | NO | YES | NO |
| 43530670 | Spontaneous cerebellar hemorrhage | 142851000119103 | SNOMED | NO | YES | NO |
| 43530730 | Spontaneous cerebral hemorrhage | 291571000119106 | SNOMED | NO | YES | NO |
| 42535430 | Spontaneous hemorrhage of cerebral hemisphere | 291531000119108 | SNOMED | NO | YES | NO |
| 4148906 | Spontaneous subarachnoid hemorrhage | 270907008 | SNOMED | NO | YES | NO |
| 432923 | Subarachnoid hemorrhage | 21454007 | SNOMED | NO | YES | NO |
| 4108952 | Subarachnoid hemorrhage from carotid siphon and bifurcation | 195155004 | SNOMED | NO | YES | NO |
| 4111708 | Subarachnoid hemorrhage from vertebral artery | 195160000 | SNOMED | NO | YES | NO |
| 4049659 | Subcortical hemorrhage | 20908003 | SNOMED | NO | YES | NO |
| 439040 | Subdural hemorrhage | 35486000 | SNOMED | NO | YES | NO |

### 5.4.9 [Phenotype Phebruary][Bleed] Intracranial hemorrhage trauma - definite w desc

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 4014781 | Closed traumatic subdural hemorrhage | 209947002 | SNOMED | NO | YES | NO |
| 4306943 | Epidural hemorrhage | 82999001 | SNOMED | NO | YES | NO |
| 42873160 | Intracranial hemorrhage following injury | 450410005 | SNOMED | NO | YES | NO |
| 444197 | Intracranial hemorrhage following injury with brief loss of consciousness | 127309004 | SNOMED | NO | YES | NO |
| 444198 | Intracranial hemorrhage following injury with loss of consciousness | 127308007 | SNOMED | NO | YES | NO |
| 444196 | Intracranial hemorrhage following injury with moderate loss of consciousness | 127310009 | SNOMED | NO | YES | NO |
| 436526 | Intracranial hemorrhage following injury with prolonged loss of consciousness AND return to pre-existing conscious level | 127311008 | SNOMED | NO | YES | NO |
| 437106 | Intracranial hemorrhage following injury with prolonged loss of consciousness without return to pre-existing conscious level | 127312001 | SNOMED | NO | YES | NO |
| 4134162 | Subarachnoid hemorrhage due to traumatic injury | 262955000 | SNOMED | NO | YES | NO |
| 438595 | Subdural hemorrhage following injury without open intracranial wound AND with no loss of consciousness | 40135004 | SNOMED | NO | YES | NO |
| 4196276 | Traumatic extradural hematoma without open intracranial wound | 315048006 | SNOMED | NO | YES | NO |
| 37205200 | Traumatic intracranial extradural hemorrhage | 784573006 | SNOMED | NO | YES | NO |
| 4154699 | Traumatic intracranial subdural hematoma with brief loss of consciousness | 371050006 | SNOMED | NO | YES | NO |
| 4196275 | Traumatic subdural hematoma without open intracranial wound | 315046005 | SNOMED | NO | YES | NO |
| 4017107 | Traumatic subdural hemorrhage | 209987007 | SNOMED | NO | YES | NO |

## 5.5 Mediator: Major bleeding IP or ER

### 5.5.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of ‘[EPI\_1001] Bleeding’, a condition status that is: “primary diagnosis”.
2. condition occurrences of ‘[EPI\_1001] Bleeding related disorders’, a condition status that is: “primary diagnosis”; having at least 1 condition occurrence of ‘[EPI\_1001] Bleeding’, starting between 0 days before and 0 days after ‘[EPI\_1001] Bleeding related disorders’ start date.

### 5.5.2 Inclusion Criteria

#### 5.5.2.1 1. During ER-IP visit

Entry events having at least 1 visit occurrence of ‘[HowOften] Inpatient or ER visit’, starting anytime on or before cohort entry start date and ending between 0 days after and all days after cohort entry start date.

#### 5.5.2.2 2. no ICH

Entry events with all of the following criteria:

1. having no condition occurrences of ‘[Phenotype Phebruary][Bleed] Intracranial hemorrhage no trauma - definite w desc’, starting between 0 days before and 0 days after cohort entry start date.
2. having no condition occurrences of ‘[Phenotype Phebruary][Bleed] Intracranial hemorrhage trauma - definite w desc’, starting between 0 days before and 0 days after cohort entry start date.

### 5.5.3 Cohort Exit

The cohort end date will be offset from index event’s start date plus 30 days.

### 5.5.4 Cohort Eras

Remaining events will be combined into cohort eras if they are within 0 days of each other.

### 5.5.5 [EPI\_1001] Bleeding

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 437312 | Bleeding | 131148009 | SNOMED | NO | YES | NO |

### 5.5.6 [EPI\_1001] Bleeding related disorders

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 195562 | Hemorrhoids | 70153002 | SNOMED | NO | YES | NO |
| 193252 | Diverticulosis of small intestine | 8114009 | SNOMED | NO | YES | NO |
| 42535740 | Diverticulosis of colon | 733657002 | SNOMED | NO | YES | NO |
| 439777 | Anemia | 271737000 | SNOMED | NO | YES | NO |
| 4027663 | Peptic ulcer | 13200003 | SNOMED | NO | YES | NO |
| 30753 | Esophagitis | 16761005 | SNOMED | NO | YES | NO |
| 201340 | Gastritis | 4556007 | SNOMED | NO | YES | NO |
| 4306267 | Coag./bleeding tests abnormal | 165563002 | SNOMED | NO | YES | NO |
| 433516 | Duodenitis | 72007001 | SNOMED | NO | YES | NO |

### 5.5.7 Inpatient Visit

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 9201 | Inpatient Visit | IP | Visit | NO | YES | NO |

### 5.5.8 [Phenotype Phebruary][Bleed] Intracranial hemorrhage no trauma - definite w desc

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 4319328 | Brain stem hemorrhage | 95454007 | SNOMED | NO | YES | NO |
| 376713 | Cerebral hemorrhage | 274100004 | SNOMED | NO | YES | NO |
| 43530850 | Chronic non-traumatic intracranial subdural hemorrhage | 609382000 | SNOMED | NO | YES | NO |
| 4176892 | Cortical hemorrhage | 49422009 | SNOMED | NO | YES | NO |
| 4110186 | Intracerebral hemorrhage, multiple localized | 195169004 | SNOMED | NO | YES | NO |
| 439847 | Intracranial hemorrhage | 1386000 | SNOMED | NO | YES | NO |
| 436430 | Nontraumatic extradural hemorrhage | 397809001 | SNOMED | NO | YES | NO |
| 4144154 | Non-traumatic intracerebral ventricular hemorrhage | 425957003 | SNOMED | NO | YES | NO |
| 4111709 | Non-traumatic subdural hemorrhage | 195176009 | SNOMED | NO | YES | NO |
| 43530670 | Spontaneous cerebellar hemorrhage | 142851000119103 | SNOMED | NO | YES | NO |
| 43530730 | Spontaneous cerebral hemorrhage | 291571000119106 | SNOMED | NO | YES | NO |
| 42535430 | Spontaneous hemorrhage of cerebral hemisphere | 291531000119108 | SNOMED | NO | YES | NO |
| 4148906 | Spontaneous subarachnoid hemorrhage | 270907008 | SNOMED | NO | YES | NO |
| 432923 | Subarachnoid hemorrhage | 21454007 | SNOMED | NO | YES | NO |
| 4108952 | Subarachnoid hemorrhage from carotid siphon and bifurcation | 195155004 | SNOMED | NO | YES | NO |
| 4111708 | Subarachnoid hemorrhage from vertebral artery | 195160000 | SNOMED | NO | YES | NO |
| 4049659 | Subcortical hemorrhage | 20908003 | SNOMED | NO | YES | NO |
| 439040 | Subdural hemorrhage | 35486000 | SNOMED | NO | YES | NO |

### 5.5.9 [Phenotype Phebruary][Bleed] Intracranial hemorrhage trauma - definite w desc

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 4014781 | Closed traumatic subdural hemorrhage | 209947002 | SNOMED | NO | YES | NO |
| 4306943 | Epidural hemorrhage | 82999001 | SNOMED | NO | YES | NO |
| 42873160 | Intracranial hemorrhage following injury | 450410005 | SNOMED | NO | YES | NO |
| 444197 | Intracranial hemorrhage following injury with brief loss of consciousness | 127309004 | SNOMED | NO | YES | NO |
| 444198 | Intracranial hemorrhage following injury with loss of consciousness | 127308007 | SNOMED | NO | YES | NO |
| 444196 | Intracranial hemorrhage following injury with moderate loss of consciousness | 127310009 | SNOMED | NO | YES | NO |
| 436526 | Intracranial hemorrhage following injury with prolonged loss of consciousness AND return to pre-existing conscious level | 127311008 | SNOMED | NO | YES | NO |
| 437106 | Intracranial hemorrhage following injury with prolonged loss of consciousness without return to pre-existing conscious level | 127312001 | SNOMED | NO | YES | NO |
| 4134162 | Subarachnoid hemorrhage due to traumatic injury | 262955000 | SNOMED | NO | YES | NO |
| 438595 | Subdural hemorrhage following injury without open intracranial wound AND with no loss of consciousness | 40135004 | SNOMED | NO | YES | NO |
| 4196276 | Traumatic extradural hematoma without open intracranial wound | 315048006 | SNOMED | NO | YES | NO |
| 37205200 | Traumatic intracranial extradural hemorrhage | 784573006 | SNOMED | NO | YES | NO |
| 4154699 | Traumatic intracranial subdural hematoma with brief loss of consciousness | 371050006 | SNOMED | NO | YES | NO |
| 4196275 | Traumatic subdural hematoma without open intracranial wound | 315046005 | SNOMED | NO | YES | NO |
| 4017107 | Traumatic subdural hemorrhage | 209987007 | SNOMED | NO | YES | NO |

### 5.5.10 [HowOften] Inpatient or ER visit

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | ERIP | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | ER | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | IP | Visit | NO | YES | NO |

## 5.6 Outcome: Acute MI

### 5.6.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of ‘Myocardial Infarction and complication’.

Restrict entry events to having at least 1 visit occurrence of ‘Inpatient or Inpatient/ER visit’, starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

### 5.6.2 Inclusion Criteria

#### 5.6.2.1 1. has no events in prior ‘clean window’ - 365 days

Entry events having no condition occurrences of ‘Myocardial Infarction and complication’, starting in the 365 days prior to cohort entry start date; allow events outside observation period; having at least 1 visit occurrence of ‘Inpatient or Inpatient/ER visit’, starting anytime on or before ‘Myocardial Infarction and complication’ start date and ending between 0 days before and all days after ‘Myocardial Infarction and complication’ start date.

### 5.6.3 Cohort Exit

The cohort end date will be offset from index event’s start date plus 1 day.

### 5.6.4 Cohort Eras

Remaining events will be combined into cohort eras if they are within 0 days of each other.

### 5.6.5 Inpatient or Inpatient/ER visit

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | ERIP | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | IP | Visit | NO | YES | NO |

### 5.6.6 Myocardial Infarction and complication

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 4329847 | Myocardial infarction | 22298006 | SNOMED | NO | YES | NO |
| 4108680 | Thrombosis of atrium, auricular appendage, and ventricle due to and following acute myocardial infarction | 194868001 | SNOMED | NO | YES | NO |
| 4108678 | Hemopericardium due to and following acute myocardial infarction | 194862000 | SNOMED | NO | YES | NO |
| 438172 | Atrial septal defect due to and following acute myocardial infarction | 194863005 | SNOMED | NO | YES | NO |
| 4124687 | Cardiac rupture due to and following acute myocardial infarction | 233847009 | SNOMED | NO | YES | NO |
| 45766210 | Mitral valve regurgitation due to and following acute myocardial infarction | 703326006 | SNOMED | NO | YES | NO |
| 37109910 | Ventricular aneurysm due to and following acute myocardial infarction | 723858002 | SNOMED | NO | YES | NO |
| 37109910 | Pulmonary embolism due to and following acute myocardial infarction | 723859005 | SNOMED | NO | YES | NO |
| 37109910 | Arrhythmia due to and following acute myocardial infarction | 723860000 | SNOMED | NO | YES | NO |
| 314666 | Old myocardial infarction | 1755008 | SNOMED | YES | YES | NO |

## 5.7 Outcome: Ischemic stroke

### 5.7.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of ‘Cerebral infarction’.

Restrict entry events to having at least 1 visit occurrence of ‘Inpatient or Inpatient/ER visit’, starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

### 5.7.2 Inclusion Criteria

#### 5.7.2.1 1. has no events in prior ‘clean window’ - 365 days

Entry events having no condition occurrences of ‘Cerebral infarction’, starting in the 365 days prior to cohort entry start date; allow events outside observation period; having at least 1 visit occurrence of ‘Inpatient or Inpatient/ER visit’, starting anytime on or before ‘Cerebral infarction’ start date and ending between 0 days before and all days after ‘Cerebral infarction’ start date.

### 5.7.3 Cohort Exit

The cohort end date will be offset from index event’s start date plus 1 day.

### 5.7.4 Cohort Eras

Remaining events will be combined into cohort eras if they are within 0 days of each other.

### 5.7.5 Inpatient or Inpatient/ER visit

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | ERIP | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | IP | Visit | NO | YES | NO |

### 5.7.6 Cerebral infarction

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 443454 | Cerebral infarction | 432504007 | SNOMED | NO | YES | NO |
| 40479570 | Infarct of cerebrum due to iatrogenic cerebrovascular accident | 441526008 | SNOMED | YES | YES | NO |
| 4046360 | Lacunar infarction | 230698000 | SNOMED | YES | YES | NO |
| 372435 | Periventricular leukomalacia | 230769007 | SNOMED | YES | NO | NO |
| 377254 | Multi-infarct dementia, uncomplicated | 70936005 | SNOMED | YES | NO | NO |
| 379778 | Multi-infarct dementia | 56267009 | SNOMED | YES | NO | NO |
| 443790 | Multi-infarct dementia with delusions | 25772007 | SNOMED | YES | NO | NO |
| 443864 | Multi-infarct dementia with depression | 14070001 | SNOMED | YES | NO | NO |
| 444091 | Multi-infarct dementia with delirium | 10349009 | SNOMED | YES | NO | NO |
| 4046089 | Vascular dementia of acute onset | 230285003 | SNOMED | YES | NO | NO |
| 4046090 | Mixed cortical and subcortical vascular dementia | 230287006 | SNOMED | YES | NO | NO |
| 4129534 | Pituitary apoplexy | 237701005 | SNOMED | YES | NO | NO |

## 5.8 Outcome: Composite

### 5.8.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of ‘Cerebral infarction’.
2. condition occurrences of ‘Myocardial Infarction and complication’.

Restrict entry events to having at least 1 visit occurrence of ‘Inpatient or Inpatient/ER visit’, starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

### 5.8.2 Inclusion Criteria

#### 5.8.2.1 1. has no events in prior ‘clean window’ - 365 days

Entry events with all of the following criteria:

1. having no condition occurrences of ‘Cerebral infarction’, starting in the 365 days prior to cohort entry start date; allow events outside observation period; having at least 1 visit occurrence of ‘Inpatient or Inpatient/ER visit’, starting anytime on or before ‘Cerebral infarction’ start date and ending between 0 days before and all days after ‘Cerebral infarction’ start date.
2. having at least 0 condition occurrences of ‘Myocardial Infarction and complication’, starting in the 365 days prior to cohort entry start date; allow events outside observation period; having at least 1 visit occurrence of ‘Inpatient or Inpatient/ER visit’, starting anytime on or before ‘Myocardial Infarction and complication’ start date and ending between 0 days before and all days after ‘Myocardial Infarction and complication’ start date.

### 5.8.3 Cohort Exit

The cohort end date will be offset from index event’s start date plus 1 day.

### 5.8.4 Cohort Eras

Remaining events will be combined into cohort eras if they are within 0 days of each other.

### 5.8.5 Inpatient or Inpatient/ER visit

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | ERIP | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | IP | Visit | NO | YES | NO |

### 5.8.6 Cerebral infarction

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 443454 | Cerebral infarction | 432504007 | SNOMED | NO | YES | NO |
| 40479570 | Infarct of cerebrum due to iatrogenic cerebrovascular accident | 441526008 | SNOMED | YES | YES | NO |
| 4046360 | Lacunar infarction | 230698000 | SNOMED | YES | YES | NO |
| 372435 | Periventricular leukomalacia | 230769007 | SNOMED | YES | NO | NO |
| 377254 | Multi-infarct dementia, uncomplicated | 70936005 | SNOMED | YES | NO | NO |
| 379778 | Multi-infarct dementia | 56267009 | SNOMED | YES | NO | NO |
| 443790 | Multi-infarct dementia with delusions | 25772007 | SNOMED | YES | NO | NO |
| 443864 | Multi-infarct dementia with depression | 14070001 | SNOMED | YES | NO | NO |
| 444091 | Multi-infarct dementia with delirium | 10349009 | SNOMED | YES | NO | NO |
| 4046089 | Vascular dementia of acute onset | 230285003 | SNOMED | YES | NO | NO |
| 4046090 | Mixed cortical and subcortical vascular dementia | 230287006 | SNOMED | YES | NO | NO |
| 4129534 | Pituitary apoplexy | 237701005 | SNOMED | YES | NO | NO |

### 5.8.7 Myocardial Infarction and complication

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 4329847 | Myocardial infarction | 22298006 | SNOMED | NO | YES | NO |
| 4108680 | Thrombosis of atrium, auricular appendage, and ventricle due to and following acute myocardial infarction | 194868001 | SNOMED | NO | YES | NO |
| 4108678 | Hemopericardium due to and following acute myocardial infarction | 194862000 | SNOMED | NO | YES | NO |
| 438172 | Atrial septal defect due to and following acute myocardial infarction | 194863005 | SNOMED | NO | YES | NO |
| 4124687 | Cardiac rupture due to and following acute myocardial infarction | 233847009 | SNOMED | NO | YES | NO |
| 45766210 | Mitral valve regurgitation due to and following acute myocardial infarction | 703326006 | SNOMED | NO | YES | NO |
| 37109910 | Ventricular aneurysm due to and following acute myocardial infarction | 723858002 | SNOMED | NO | YES | NO |
| 37109910 | Pulmonary embolism due to and following acute myocardial infarction | 723859005 | SNOMED | NO | YES | NO |
| 37109910 | Arrhythmia due to and following acute myocardial infarction | 723860000 | SNOMED | NO | YES | NO |
| 314666 | Old myocardial infarction | 1755008 | SNOMED | YES | YES | NO |

# 6 Appendix B: Negative controls

| Concept ID | Name |
| --- | --- |
| 437643 | Abnormal gait |
| 260139 | Acute bronchitis |
| 257007 | Allergic rhinitis |
| 442077 | Anxiety disorder |
| 4153359 | Arthritis of spine |
| 4324765 | Arthropathy of knee joint |
| 261880 | Atelectasis |
| 443344 | Barrett’s esophagus |
| 378425 | Blepharitis |
| 256449 | Bronchiectasis |
| 313791 | Bundle branch block |
| 435613 | Cellulitis |
| 257012 | Chronic sinusitis |
| 134441 | Chronic ulcer of skin |
| 4150614 | Communication disorder |
| 201606 | Crohn’s disease |
| 73302 | Curvature of spine |
| 4242416 | Cutis laxa |
| 74726 | Dislocation of joint |
| 192279 | Disorder of kidney due to diabetes mellitus |
| 443730 | Disorder of nervous system due to diabetes mellitus |
| 435657 | Dyssomnia |
| 197684 | Dysuria |
| 79903 | Effusion of joint |
| 4050747 | Fracture of upper limb |
| 196456 | Gallstone |
| 4007453 | Gammopathy |
| 441788 | Human papilloma virus infection |
| 197032 | Hyperplasia of prostate |
| 4208390 | Inflammation of sacroiliac joint |
| 139099 | Ingrowing nail |
| 4112853 | Malignant tumor of breast |
| 374919 | Multiple sclerosis |
| 24134 | Neck pain |
| 433736 | Obesity |
| 141663 | Osteomyelitis |
| 372328 | Otitis media |
| 78162 | Peripheral vertigo |
| 4002650 | Plantar fasciitis |
| 373478 | Presbyopia |
| 199876 | Prolapse of female genital organs |
| 436073 | Psychotic disorder |
| 4174977 | Retinopathy due to diabetes mellitus |
| 141932 | Senile hyperkeratosis |
| 141825 | Simple goiter |
| 313459 | Sleep apnea |
| 4077081 | Superficial mycosis |
| 193326 | Urge incontinence of urine |
| 81902 | Urinary tract infectious disease |
| 140641 | Verruca vulgaris |