OHDSI: Impact of concomitant use of proton pump inhibitors and antiplatelet agents on cardiovascular adverse outcomes- A multicenter, multinational study using common data model

**Version:** 0.3

**Authors:**

Seonji Kim1,2, Kyung Joo Lee3, Seng Chan You1,2\*, Seung In Seo4,5\*

1 Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Korea

2 Institute for Innovation in Digital Healthcare, Yonsei University, Seoul, Korea

3 University Industry Foundation, Hallym University, Chuncheon, South Korea

4 Institute for Liver and Digestive Diseases, Hallym University, Chuncheon, Korea

5 Department of Internal Medicine, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea.

**Date:** August 3, 2023

**Acknowledgement:** The analysis is based in part on work from the Observational Health Sciences and Informatics collaborative. OHDSI (<http://ohdsi.org>) is a multi-stakeholder, interdisciplinary collaborative to create open-source solutions that bring out the value of observational health data through large-scale analytics.

Table of contents

[2 List of abbreviations 3](#_Toc144826393)

[3 Abstract 3](#_Toc144826394)

[4 Amendments and Updates 4](#_Toc144826395)

[5 Rationale and Background 4](#_Toc144826396)

[6 Study Objectives 4](#_Toc144826397)

[6.1 Primary Hypothesis 4](#_Toc144826398)

[6.2 Secondary Hypotheses 5](#_Toc144826399)

[6.3 Primary objectives 5](#_Toc144826400)

[6.4 Secondary objectives 5](#_Toc144826401)

[7 Research methods 6](#_Toc144826402)

[7.1 Study Design 6](#_Toc144826403)

[7.1.1 Overview 6](#_Toc144826404)

[7.2 Study population 6](#_Toc144826405)

[7.2.1 Primary Study population 6](#_Toc144826406)

[7.2.2 Subgroups 6](#_Toc144826407)

[7.3 Exposures 6](#_Toc144826408)

[7.3.1 Target: Inhibiting PPI user in patient with receiving clopidogrel 6](#_Toc144826409)

[7.3.2 Comparator: Other PPI user in patient with receiving clopidogrel 7](#_Toc144826411)

[7.4 Outcomes 8](#_Toc144826412)

[7.4.1 Outcomes 8](#_Toc144826413)

[7.4.2 Negative controls 8](#_Toc144826414)

[7.5 Covariates 14](#_Toc144826415)

[7.5.1 Propensity score covariates 14](#_Toc144826416)

[7.5.2 Other variables 15](#_Toc144826417)

[8 Data Analysis Plan 15](#_Toc144826418)

[8.1 Calculation of time-at-risk 15](#_Toc144826419)

[8.2 Model specification 15](#_Toc144826420)

[8.2.1 Statistical model for primary analysis 16](#_Toc144826421)

[8.2.2 Statistical model for sensitivity analyses 16](#_Toc144826422)

[8.2.3 Subgroup analysis 16](#_Toc144826423)

[8.2.4 Pooling effect estimates across databases 17](#_Toc144826424)

[8.3 Analyses to perform 17](#_Toc144826425)

[8.4 Output 17](#_Toc144826426)

[8.5 Evidence Evaluation 18](#_Toc144826427)

[8.6 Data Sources 19](#_Toc144826428)

[8.7 Quality control 19](#_Toc144826429)

[8.8 Strengths and Limitations of the Research Methods 19](#_Toc144826430)

[9 Protection of Human Subjects 20](#_Toc144826431)

[10 Plans for Disseminating and Communicating Study Results 20](#_Toc144826432)

[11 References 20](#_Toc144826433)

[12 Appendix: Concept Set Definitions 22](#_Toc144826434)

# List of abbreviations

PPI proton pump inhibitor

ACS acute coronary syndrome

FDA Food and Drug Administration

OHDSI Observational Health Data Sciences and Informatics

PCI percutaneous coronary intervention

MACE major adverse cardiac event

MI myocardial infarction

PS propensity score

# Abstract

It is still controversial regarding the interaction between proton pump inhibitors (PPIs) and clopidogrel. Both PPIs and clopidogrel are metabolized by hepatic cytochrome P450 (CYP) enzymes, and in the presence of CYP2C19 inhibition, PPIs could reduce the efficacy of clopidogrel's protective roles in cardiovascular events. Hence, The US Food and Drug Administration (FDA) issued safety announcements between January 2009 and October 2010 warning against concomitant use of clopidogrel and PPIs, especially omeprazole and esomeprazole, due to a potential drug interaction that may attenuate clopidogrel’s antiplatelet activity. After the FDA’s warnings against the use of clopidogrel with strong competitive inhibitor for CYP2C19 (inhibiting PPIs, omeprazole and esomeprazole), treatment with inhibiting PPIs and clopidogrel has continued to decrease since 2010, however, the real-world evidence has not been fully evaluated about whether inhibiting PPIs lead to more severe cardiovascular outcomes compared with weak competitive inhibitor for CYP2C19 (other PPIs, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole). This study will compare the major adverse cardiovascular events of inhibiting PPIs with other PPIs in patients who receiving clopidogrel.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | July 4, 2022 | SI Seo | Initial draft |
| 0.2 | May 23, 2023 | SI Seo | Revised |
| 0.3 | August 3, 2023 | SJ Kim | Added more negative control outcomes, since we could not identify many negative control outcomes in Korean databases from the feasibility test. |

# Rationale and Background

A proton pump inhibitor (PPI) is frequently co-prescribed with clopidogrel to reduce the risk of gastrointestinal bleeding. The role of clopidogrel after percutaneous coronary intervention (PCI) has been well established. However, antiplatelet effects of clopidogrel could be diminished by the concurrent use of PPIs, attributed to the competitive inhibition by PPIs of one of the cytochrome P450 isoenzymes, CYP2C19, involved in the metabolic activation of clopidogrel. Hence, the US Food and Drug Administration (FDA) issued three safety announcements between January 2009 and October 2010 warning against concomitant use of clopidogrel and PPIs, especially omeprazole and esomeprazole.

Several studies addressed these issue, but it is controversial issue. Recent systematic review and meta-analysis reported that combined use of clopidogrel and PPI is associated with significantly higher adverse cardiovascular events such as major adverse cardiac event (MACE), stent thrombosis, and myocardial infarction following PCI, however, long-term mortality was not statistically significant. Despite this, the comparative impact of PPIs on risk of cardiovascular events by inhibiting CYP2C19 has been controversial in patients treating clopidogrel up to date.

In fact, inter-individual variability in antiplatelet drug response may also be explained by inter-ethnic differences in the distribution of functional CYP2C19 genes. CYP2C19 poor metabolic phenotypes are found in 13–23% of healthy East Asian populations but in only 2–5% of Caucasians. Thus, it is needed to perform multinational study to evaluate the clopidogrel with PPI considering ethnic differences.

# Study Objectives

## Primary Hypothesis

This study’s hypotheses are:

There would be no significant difference in the incidence of MACE which included cardiovascular mortality, and hospitalization or emergency department visit for myocardial infarction (MI), stroke between inhibiting PPI group and other PPI group in patients receiving clopidogrel.

## Secondary Hypotheses

* There would be no difference in the incidence of all-cause mortality, MI, stroke, and cardiovascular mortality between clopidogrel-inhibiting PPI combination group and clopidogrel-other PPI group.
* There would be no difference in the incidence of MACE, all-cause mortality, MI, stroke, and cardiovascular mortality between clopidogrel-inhibiting PPI combination group and clopidogrel-other PPI group without MI and stroke history before 1-year index date.

**Table 1**. List of PPI considered in this study

|  |  |  |
| --- | --- | --- |
| Drug | | OMOP Concept ID |
| Clopidogrel | | 1322184 |
| Inhibiting PPI | Omeprazole | 923645 |
| Esomeprazole | 904453 |
| Other PPI | Lansoprazole | 929887 |
| Pantoprazole | 948078 |
| Rabeprazole | 911735 |
| Dexlansoprazole | 19039926 |

## Primary objectives

* The overall goal of this protocols is conducting comparative effectiveness research to establish evidences for cardiovascular outcomes of concomitant clopidogrel with inhibiting PPI. The primary outcome is comparing the risk of MACE which composed of cardiovascular death, MI and stroke.

## Secondary objectives

* Comparing the incidence of all-cause death, MI, stroke and cardiovascular mortality between clopidogrel-inhibiting PPI combination group and clopidogrel-other PPI group.
* Comparing the incidence of MACE, all-cause death, MI, stroke and cardiovascular mortality between clopidogrel-inhibiting PPI combination group and clopidogrel-other PPI group without MI and stroke history before 1-year index date.

# Research methods

## Study Design

### Overview

This study will be a retrospective, observational cohort study. By ‘retrospective’ we mean the study will use data already collected at the start of the study. By ‘observational’ we mean no intervention will take place in the course of this study. By ‘cohort study’ we mean two cohorts, a treatment and comparator cohort, will be followed from index date (start of first exposure) to some end date, and assessed for the occurrence of the outcomes of interest. Proportional hazard models will be used to assess the hazard ratios between the two exposure cohorts. Adjustment for baseline confounders will be done using propensity scores (PSs).

## Study population

### Primary Study population

All subjects in the database will be included who meet the following criteria: (note: the index date is the day of acute coronary syndrome {ACS})

* 18 years old or older
* At least 365 days of observation time prior to the index date
* Users with clopidogrel more than 30 days
* No diagnosis of prespecified outcome before index date

The end of on-treatment duration is defined as the end of the exposure of the drug of interest, allowing for 30-day gaps between consecutive prescriptions or start of PPIs other than the drug of interest.

### Subgroups

* Without MI and stroke history before 1-year index date
* With ACS history before 1-year index date
* without gastrointestinal bleeding history before 1-year index date

## Exposures

### Target: Inhibiting PPI user in patient with receiving clopidogrel

### Cohort Entry Events

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

drug eras of 'Inhibiting PPI', who are >= 18 years old. Limit cohort entry events to the earliest event per person.

1. Inclusion Criteria
   1. with both drugs: Entry events having at least 1 drug era of 'Clopidogrel', starting anytime up to 30 days before cohort entry start date and ending between 0 days after cohort entry start date; with era length >= 30 days.
2. Cohort Exit
   1. The cohort end date will be based on a continuous exposure to 'Inhibiting PPI': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.
   2. The person exits the cohort when encountering any of the following events: drug exposures of 'Other PPI'.
3. Cohort Eras
   1. Entry events will be combined into cohort eras if they are within 0 days of each other.

### Comparator: Other PPI user in patient with receiving clopidogrel

1. Cohort Entry Events
   1. People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

drug eras of 'Other PPI', who are >= 18 years old. Limit cohort entry events to the earliest event per person.

1. Inclusion Criteria
   1. with both drugs: Entry events having at least 1 drug era of 'Clopidogrel', starting anytime up to 30 days before cohort entry start date and ending between 0 days after cohort entry start date; with era length >= 30 days.
2. Cohort Exit
3. The cohort end date will be based on a continuous exposure to 'Other PPI': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.
4. The person exits the cohort when encountering any of the following events: drug exposures of ' Inhibiting PPI'.
5. Cohort Eras
6. Entry events will be combined into cohort eras if they are within 0 days of each other.

## Outcomes

### Outcomes

#### Primary outcome: MACE (cardiovascular death, MI and stroke)

* Occurrence of acute MI, stroke event with same-day hospitalization (inpatient or emergency department visit) or cardiovascular mortality
* Limited to the first event

#### Secondary outcome: all cause mortality

Index rule defining the index date:

* Occurrence of death record

#### Secondary outcome: MI

Index rule defining the index date:

* Occurrence of acute MI code with same-day hospitalization (inpatient or emergency department visit)
* Limited to the first event

#### Secondary outcome: stroke

Index rule defining the index date:

* Occurrence of stroke code with same-day hospitalization (inpatient or emergency department visit)
* Limited to the first event

#### Secondary outcome: Cardiovascular Death

* Death record with at least 1 cardiovascular-related condition record (MI, stroke, sudden cardiac death) between 30 days and 7 days prior to death or hospitalization for heart failure with hospitalization record (inpatient or emergency department visit) prior to death 14

### Negative controls

Negative controls are concepts known to not be associated with the target or comparator cohorts, such that we can assume the true relative risk between the two cohorts is 1. Negative controls are selected using a similar process to that outlined by Voss et al.12 We believe that negative controls are necessary for confidentiality of study design and statistical method. The concept ids for negative control is described below

|  |  |  |
| --- | --- | --- |
| **Concept ID** | **Concept Code** | **Concept Name** |
| 4175583 | 297231002 | 3-Methylglutaconic aciduria type 2 |
| 443698 | 439855007 | Abnormal anal Papanicolaou smear |
| 375824 | 60331006 | Abnormal auditory perception |
| 435574 | 110333006 | Abnormal form of root of tooth |
| 4262562 | 361136003 | Abnormal heart beat |
| 439935 | 43029002 | Abnormal posture |
| 436409 | 274093008 | Abnormal pupil |
| 443702 | 440574002 | Abnormal response to nerve stimulation |
| 443585 | 429562001 | Abrasion and/or friction burn of multiple sites |
| 4088768 | 248820000 | Absent nipple |
| 44783954 | 698065002 | Acid reflux |
| 380818 | 111270009 | Acquired deformity of head |
| 31668 | 72082009 | Acquired deformity of neck |
| 4319325 | 95428004 | Acquired deformity of trunk |
| 432411 | 37718006 | Acquired equinus deformity of foot |
| 439673 | 186626002 | Acute hepatitis B with delta-agent (coinfection) without hepatic coma |
| 441481 | 406137001 | Adult victim of abuse |
| 435720 | 405656000 | Adverse anesthesia outcome |
| 4218106 | 7200002 | Alcoholism |
| 4254371 | 409033001 | Altered growth and development |
| 434916 | 191843004 | Amphetamine or psychostimulant dependence, continuous |
| 4101660 | 299652006 | Amputated below knee |
| 4198962 | 299217009 | Amputated thumb |
| 4155909 | 271805006 | Anesthesia of skin |
| 4171556 | 419193008 | Ankle ulcer |
| 45757682 | 3.2335E+14 | Anomaly of jaw size |
| 4060259 | 169653006 | Antenatal amniocentesis - abnormal |
| 4061157 | 169665005 | Antenatal ultrasound scan abnormal |
| 77650 | 398199007 | Aseptic necrosis of bone |
| 439237 | 52684005 | Assault |
| 76744 | 48188009 | Azoospermia |
| 4216219 | 80670004 | Bizarre personal appearance |
| 141797 | 33666009 | Black piedra |
| 433813 | 399072004 | Bladder neck obstruction |
| 436230 | 166318006 | Blood chemistry abnormal |
| 74698 | 6096002 | Breech presentation |
| 256449 | 12295008 | Bronchiectasis |
| 79232 | 40993007 | Burn of ankle |
| 134765 | 238108007 | Cachexia |
| 4172458 | 49883006 | Candidiasis of skin |
| 4228429 | 421784001 | Carnitine deficiency |
| 42709838 | 449710006 | Cellulitis of lower limb |
| 4213540 | 417347005 | Cervical somatic dysfunction |
| 443570 | 416030007 | Cervicovaginal cytology: Low grade squamous intraepithelial lesion |
| 439674 | 186639003 | Chronic viral hepatitis B without delta-agent |
| 438262 | 91098006 | Chyluria |
| 4066505 | 202606004 | Clicking hip |
| 196454 | 197238009 | Colostomy and enterostomy malfunction |
| 4201390 | 302112009 | Colostomy present |
| 134734 | 111245009 | Compartment syndrome |
| 46269889 | 1.0859E+15 | Complication due to Crohn's disease |
| 4173078 | 47988006 | Complication due to immunization |
| 434675 | 309773000 | Complication of gastrostomy |
| 438624 | 33603003 | Complication of renal dialysis |
| 72995 | 86414002 | Contracture of joint of hand |
| 80492 | 239739005 | Contracture of knee joint |
| 439666 | 202264009 | Contracture of multiple joints |
| 199978 | 91603007 | Contusion of lower limb |
| 433071 | 111721009 | Contusion of multiple sites |
| 4022071 | 105499002 | Convalescence |
| 432729 | 162214009 | Crying infant |
| 75389 | 308849005 | Current tear of lateral cartilage AND/OR meniscus of knee |
| 80242 | 307945003 | Current tear of medial cartilage AND/OR meniscus of knee |
| 73575 | 299567001 | Deformity of toe |
| 436233 | 274625009 | Delayed milestone |
| 443737 | 416673002 | Dental restoration lost |
| 438183 | 278621009 | Denture occlusion incorrect |
| 438759 | 193821003 | Descemet's membrane fold |
| 4101282 | 190660003 | Dietary selenium deficiency |
| 4115402 | 301345002 | Difficulty sleeping |
| 4019971 | 105515007 | Discord in school |
| 4022078 | 105520007 | Discord with counselor |
| 436906 | 37246009 | Disease caused by rickettsiae |
| 4135080 | 263023008 | Dislocation of radial head |
| 201091 | 199398004 | Disproportion - major pelvic abnormality |
| 372329 | 86485009 | Dissociated deviation |
| 4155818 | 284097000 | Does climb |
| 4196636 | 8011004 | Dysarthria |
| 433441 | 8659000 | Ectopic production of endocrine substance |
| 433111 | 212966005 | Effects of hunger |
| 78834 | 16711001 | Effusion of joint of hand |
| 4247710 | 9363005 | Effusion of joint of pelvic region |
| 72407 | 40884005 | Effusion of joint of shoulder region |
| 439791 | 309838005 | Emotional upset |
| 4150043 | 31070006 | Epididymitis |
| 4029271 | 238114000 | Essential fatty acid deficiency |
| 197607 | 266601003 | Excessive and frequent menstruation |
| 40480271 | 444655009 | Extra unidentified structurally abnormal chromosome |
| 193598 | 274732007 | Extravasation of urine |
| 439128 | 276658003 | Extreme prematurity of infant |
| 4059015 | 161898004 | Falls |
| 4092896 | 249625002 | Feces contents abnormal |
| 4182437 | 429744008 | Female genital cutting |
| 4118057 | 206038006 | Fetal or neonatal effect of maternal oligohydramnios |
| 4229403 | 404675003 | Flat anterior chamber of eye |
| 4069540 | 203569006 | Flexion deformity of knee |
| 374801 | 75441006 | Foreign body in ear |
| 4096540 | 249254001 | Foreskin deficient |
| 441487 | 370977006 | Frostbite |
| 73564 | 202843000 | Full thickness rotator cuff tear |
| 40481568 | 444951002 | Fussy infant |
| 439788 | 190745006 | Galactosemia |
| 40481632 | 445008009 | Ganglion cyst |
| 435775 | 47986005 | Genetic anomaly of leukocyte |
| 74855 | 33839006 | Genital herpes simplex |
| 437744 | 95868006 | Heat exhaustion |
| 440021 | 111853008 | Herpes simplex without complication |
| 437489 | 49183009 | Herpes zoster with complication |
| 440329 | 111859007 | Herpes zoster without complication |
| 4012570 | 102947004 | High risk sexual behavior |
| 435511 | 66931009 | Hypercalcemia |
| 77364 | 202809009 | Hypermobility of coccyx |
| 441829 | 267446004 | Hyperosmolality and or hypernatremia |
| 4287416 | 68528007 | Hyperphenylalaninemia |
| 192298 | 58381000 | Hypersplenism |
| 74731 | 203357004 | Hypertrophic osteoarthropathy |
| 440129 | 17467004 | Hypertrophy of nasal turbinates |
| 4029280 | 238146000 | Hypervitaminosis B6 |
| 435522 | 27712000 | Hypervitaminosis D |
| 434004 | 21639008 | Hypervolemia |
| 4024266 | 19577007 | Hypocupremia |
| 440072 | 119250001 | Hypogammaglobulinemia |
| 437390 | 389087006 | Hypoxemia |
| 443447 | 408668005 | Iatrogenic hypotension |
| 432596 | 71922006 | Immune defect |
| 4344500 | 239960007 | Impingement syndrome of shoulder region |
| 4090353 | 252025007 | Incompetent urethral closure mechanism |
| 441417 | 281016006 | Incoordination |
| 434485 | 248301008 | Increase in body fat |
| 440276 | 31871009 | Infection AND/OR inflammatory reaction due to internal prosthetic device, implant AND/OR graft |
| 434872 | 56335008 | Infection by Trichomonas |
| 4057662 | 19690006 | Infestation by Phthirus |
| 440053 | 71571008 | Infestation by insect |
| 442120 | 95384003 | Injection site extravasation |
| 4168222 | 274719002 | Intra-abdominal and pelvic swelling, mass and lump |
| 440710 | 247136003 | Intraretinal microvascular abnormality |
| 72994 | 84801008 | Jaccoud's syndrome |
| 78228 | 398993007 | Joint derangement |
| 77072 | 4819006 | Joint effusion of ankle AND/OR foot |
| 72404 | 84445001 | Joint stiffness |
| 435903 | 203392007 | Juvenile osteochondrosis of foot |
| 438527 | 354223006 | Juvenile osteochondrosis of lower extremity, excluding foot |
| 435633 | 62100001 | Juvenile osteochondrosis of upper extremity |
| 4115991 | 202381003 | Knee joint effusion |
| 4093346 | 249607009 | Large prostate |
| 133088 | 30401009 | Late amputation stump complication |
| 436041 | 64351000 | Leech infestation |
| 4228331 | 89013002 | Leukokeratosis nicotina palati |
| 377873 | 89893000 | Lid lag |
| 4027782 | 10741005 | Lipid storage disease |
| 435516 | 267436001 | Lipoprotein deficiency disorder |
| 4297984 | 76844004 | Local infection of wound |
| 440638 | 23502006 | Lyme disease |
| 4083487 | 247154004 | Macular drusen |
| 438067 | 61462000 | Malaria |
| 4051630 | 23268009 | Malingering |
| 436426 | 51662008 | Malleus mobility reduced |
| 44783760 | 697944008 | Mammographic calcification of breast |
| 258540 | 19346006 | Marfan's syndrome |
| 438297 | 75446001 | Mechanical complication of cardiac device, implant AND/OR graft |
| 432798 | 5285008 | Mechanical complication of internal orthopedic device, implant AND/OR graft |
| 439082 | 123756000 | Menopausal syndrome |
| 436940 | 237602007 | Metabolic syndrome X |
| 435247 | 52276000 | Metallosis |
| 45757258 | 1.0899E+15 | Minimal keratinized residual ridge mucosa |
| 40480000 | 441628001 | Multiple complications due to diabetes mellitus |
| 137967 | 268006001 | Muscle, ligament and fascia disorders |
| 4271024 | 400148004 | Musculoskeletal fibromatosis |
| 134315 | 47739002 | Myelophthisis |
| 4195085 | 68235000 | Nasal congestion |
| 4209423 | 56294008 | Nicotine dependence |
| 4035269 | 237939006 | Non-ketotic hyperglycinemia |
| 434016 | 191912005 | Nondependent opioid abuse, continuous |
| 201792 | 84619001 | Nongonococcal urethritis |
| 40480893 | 441846005 | Nonspecific tuberculin test reaction |
| 72413 | 29191005 | Nontraumatic rupture of muscle |
| 198802 | 20018005 | Occlusion of ureter |
| 4215978 | 414941008 | Onychomycosis |
| 140648 | 402134005 | Onychomycosis due to dermatophyte |
| 4129408 | 125662003 | Open wound of ankle |
| 4053600 | 125650002 | Open wound of elbow |
| 77139 | 2630008 | Open wound of finger without complication |
| 444426 | 91368005 | Open wound of foot except toes without complication |
| 137426 | 85135003 | Open wound of forearm without complication |
| 77421 | 73059000 | Open wound of hand except fingers without complication |
| 4051004 | 210323002 | Open wound of scalp |
| 4129404 | 125648005 | Open wound of upper arm |
| 438130 | 5602001 | Opioid abuse |
| 438120 | 75544000 | Opioid dependence |
| 4171915 | 274718005 | Orchitis |
| 315361 | 62744007 | Orthopnea |
| 74080 | 32482005 | Orthostatic proteinuria |
| 75920 | 55413008 | Osteitis condensans |
| 437359 | 82562007 | Osteochondritis dissecans |
| 378160 | 65668001 | Otorrhea |
| 439035 | 11543004 | Otosclerosis |
| 77356 | 80406003 | Pathological dislocation of joint |
| 4022076 | 105507009 | Patient dependence on care provider |
| 375292 | 60442001 | Perforation of tympanic membrane |
| 78162 | 50438001 | Peripheral vertigo |
| 437092 | 274626005 | Physiological development failure |
| 253796 | 36118008 | Pneumothorax |
| 4295261 | 76498008 | Postmenopausal state |
| 4202045 | 51771007 | Postviral fatigue syndrome |
| 433542 | 51920004 | Precipitate labor |
| 4094448 | 250425007 | Pregnancy test negative |
| 434319 | 44001008 | Premature ejaculation |
| 198715 | 373717006 | Premature menopause |
| 439081 | 82639001 | Premenstrual tension syndrome |
| 46286594 | 9.8789E+14 | Problem related to lifestyle |
| 199876 | 73998008 | Prolapse of female genital organs |
| 4295888 | 76641005 | Prolapse of intestine |
| 194997 | 9713002 | Prostatitis |
| 439790 | 8971008 | Psychalgia |
| 440068 | 268637002 | Psychosexual dysfunction |
| 435028 | 200277008 | Puerperal pyrexia of unknown origin |
| 4245252 | 396152005 | Raised prostate specific antigen |
| 436246 | 8357008 | Reduced libido |
| 45772079 | 1.2411E+14 | Retinopathy of prematurity stage 0 |
| 436828 | 271867001 | Saliva abnormal |
| 435088 | 271873000 | Senility |
| 4052226 | 210962001 | Sequelae of injuries of lower limb |
| 4056577 | 210954009 | Sequelae of open wound of head |
| 4233565 | 360549009 | Severe protein-calorie malnutrition (Gomez: less than 60% of standard weight) |
| 4250163 | 74007000 | Sexual arousal disorder |
| 4096999 | 249696007 | Short rib |
| 4305303 | 130989002 | Sleep deprivation |
| 195926 | 84471002 | Slowing of urinary stream |
| 4125590 | 289195008 | Slurred speech |
| 4019836 | 105412007 | Social exclusion |
| 444127 | 125153001 | Specimen satisfactory for evaluation but limited |
| 4345332 | 240220009 | Spinal instability |
| 443172 | 211015001 | Splinter of face, without major open wound |
| 443082 | 212968006 | Starvation |
| 440233 | 18888002 | Strain of supraspinatus muscle AND/OR tendon |
| 135852 | 8004003 | Teething syndrome |
| 4195698 | 67801009 | Tenosynovitis |
| 4339088 | 87860000 | Testicular mass |
| 440457 | 54048003 | Threatened miscarriage |
| 374907 | 192848006 | Tics of organic origin |
| 80946 | 48971001 | Tinea manus |
| 4163280 | 399172001 | Tinea of perianal region |
| 133141 | 6020002 | Tinea pedis |
| 433244 | 25540007 | Tooth loss |
| 440268 | 17383000 | Toxic effect of carbon monoxide |
| 81930 | 66191007 | Transient arthropathy |
| 4029731 | 237959005 | Trimethylaminuria |
| 40482801 | 443694000 | Type II diabetes mellitus uncontrolled |
| 74719 | 95345008 | Ulcer of foot |
| 443593 | 428194005 | Ulcer of thigh |
| 4199550 | 302043000 | Unable to mobilize |
| 4002572 | 10028000 | Uncomplicated sedative, hypnotic AND/OR anxiolytic withdrawal |
| 4092743 | 249990003 | Unsteady when standing |
| 195591 | 252020002 | Urethral overactivity |
| 4216708 | 71820002 | Urgent desire for stool |
| 80070 | 267441009 | Uric acid urolithiasis |
| 4088910 | 248911005 | Uterine cervix absent |
| 4092565 | 24976005 | Uterine prolapse |
| 4088920 | 248942000 | Uterus absent |
| 435131 | 95930005 | Victim of neglect |
| 261599 | 302912005 | Vocal cord paralysis |
| 4104132 | 300366003 | Vomit contains feces |
| 439405 | 228158008 | Walking disability |
| 314754 | 56018004 | Wheezing |
| 132834 | 35586003 | White piedra |
| 435723 | 239159001 | Wound seroma |
| 440193 | 59349003 | Wristdrop |
| 4303805 | 418484009 | Allergic reaction to bite and/or sting |
| 78512 | 267931000 | Joint contracture of the ankle and/or foot |

## Covariates

### Propensity score covariates

PSs will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The PS is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates.

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

* Demographics
  + Gender
  + Age
  + Age group (5-year bands)
  + Index year
  + Race
* Condition
  + In prior 30d
* Condition group
  + In prior 365d
  + In prior 30d
* Drug group
  + In prior 365d
  + In prior 30d
* Procedure
  + In prior 365d
  + In prior 30d
* Measurement
  + In prior 365d
* Measurement - Value
  + In prior 30d
* Measurement - Range Group
  + In prior 365d
* Device
  + In prior 365d
* Risk scores
  + Charlson comorbidity index

Specific covariates to be excluded from the PS model are labelled **concepts to exclude,** which composed of drug use of clopidogrel and PPI.

All covariates that occur in fewer than 0.1% of the persons between the target and comparator cohorts combined will be excluded prior to model fitting for computational efficiency.

### Other variables

None

# Data Analysis Plan

## Calculation of time-at-risk

**Primary analysis**

* On treatment: To avoid time-dependent bias, on-treatment risk window of which time-at-risk starts on treatment initiation, and ends when the treatment ends.

**Secondary analysis**

* Intent-to-treat: Time-at-risk starts after the index date, and ends when the database ends.
* Time-at-risk windows (30-day): Starting on the day of treatment initiation and stopping at the 30 days after treatment initiation.
* Time-at-risk windows (1-year): Starting on the day of treatment initiation and stopping at the 1 year after treatment initiation.

## Model specification

In this study, 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. A pre-specified *P*<0.05 was considered statistically significant for all two-sided tests.

The time-to-event of outcome among patients in the target and comparator cohorts is determined by calculating the number of days from the start of the time-at-risk window (the cohort start date), until the earliest event among 1) the first occurrence of the outcome, 2) the end of the time-at-risk window, and 3) the end of the observation period that spans the time-at-risk start.

Incidence rates are computed for each outcome in each exposure group

### Statistical model for primary analysis

PSs will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The PS is estimated for each patient, using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross validation using 10 replications per fold, a starting variance of 0.01 and a tolerance of 2e-7. Covariates to be used in the propensity score model are listed in section 7.5.1.

* Primary analysis (variable ratio PS Matching): After estimating the PS, variable matching ratio will be performed. The two cohorts were matched with a maximum ratio of 10. A caliper of 0.2 times the standard deviation of the propensity score distribution, and a greedy matching will be used. The outcome model will be fitted using a stratified Cox regression conditioned on the matched sets, with only the treatment variable as predictor.

### Statistical model for sensitivity analyses

The Cox proportional hazard model will be applied with PS matching or stratification.

* 1:1 PS matching: the two cohorts were matched with 1:1 ratio. A caliper of 0.2 times the standard deviation of the propensity score distribution, and a greedy matching will be used.
* PS stratification: The target cohort and comparator cohorts will be stratified into ten quantiles of the propensity score distribution. The final outcome model will apply a conditional Cox proportional hazard model, conditions on the propensity score strata.

If there is any covariate with standardized differences greater than 0.1 between target and comparator cohort after PS adjustment, then the PS adjustment will be considered as sub-optimal or non-balanced. And these results will be considered as results for sensitivity analysis.

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

### Subgroup analysis

Additionally, interaction term analysis will be conducted to assess the interaction for the primary analysis between outcomes and 3 characteristics described below

* Without MI and stroke history before 1-year index date
* With ACS history before 1-year index date
* without gastrointestinal bleeding history before 1-year index date

Based on the result from interaction term analysis, the additional subgroup analysis can be performed.

### Pooling effect estimates across databases

Random-effect model meta-analysis will be performed to calculate summary hazard ratio for pooling effect estimates across databases

The only balanced results after PS adjustment will be aggregated to the primary analysis.

## Analyses to perform

The following analyses will be performed:

* 2 comparisons: primary comparison (clopidogrel with inhibiting PPI vs. clopidogrel with other PPI), primary comparison without MI and stroke history before 1-year index date
  + 3 subgroups: secondary comparison (clopidogrel with inhibiting PPI vs. clopidogrel with H2RA), without gastrointestinal bleeding history, and with ACS history
* 5 outcomes: MACE, all-cause death, MI, stroke and cardiovascular mortality
* 4 time-at-risk definitions: On-treatment, Intent-to-treat, Time-at-risk windows (30-day and 1-year)
* 3 models: Conditioned Cox regression after variable-ratio PS matching, unconditioned Cox regression after 1:1 PS matching, and conditioned Cox regression after PS stratification

The total number of analyses is 160 (2 comparisons x {1 comparison + 3 subgroups} x 5 outcomes x 4 TAR x 3 statistical models) in each database (**Table 2**).

**Table 2**. Analyses to perform

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Target | Comparator | Stratification | Outcomes | Time-at-risk | Statistical model | Subgroup analysis |
| Concomitant use of clopidogrel with inhibiting PPI | Concomitant use of clopidogrel with other PPI | Based on previous 1-year history of MI and stroke history | \*Primary outcome: MACE  \*Secondary outcome:  - Overall mortality  - MI  - Stroke  - Cardiovascular mortality | \*Intent-to-treat  \*On-treatment  \* Time-at-risk windows (30-day)  \* Time-at-risk windows (1-year) | \*Variable ratio PS matching  \* One-to-one PS matching  \*PS stratification | \* Secondary comparison (clopidogrel with inhibiting PPI vs. clopidogrel with H2RA)  \* Without gastrointestinal bleeding history  \* With ACS history |

## Output

Covariate balance will be summarized in tabular form by showing the mean value for all baseline covariates in the target and comparator cohort, with the associated standardized mean difference computed for each covariate.

Once the propensity score model is fit, we will plot the propensity score distribution of the target and comparator cohorts to evaluate the comparability of the two cohorts. The plot will be scaled to the preference score, normalizing for any imbalance in cohort size. The covariates selected within the propensity score model, with associated coefficients will also be reported.

A plot showing the PS distributions for both cohorts after matching will be provided. Covariate balance will be evaluated by plotting the standardized mean difference of each covariate before PS matching against the standardized mean difference for each covariate after PS matching.

An attrition diagram will be provided to detail the loss of patients from the original target cohort and comparator cohort to the subpopulations that remain after all design considerations have been applied.

The final outcome model, a Cox proportional hazards model, will be summarized by providing the hazards ratio and associated 95% confidence interval. The number of persons, amount of time-at-risk, and number of outcomes in each cohort will also be reported.

## Evidence Evaluation

We have executed diagnostics to determine if the analysis can be appropriately conducted. The diagnostics include:

* PS distribution
* Covariate balance before and after PS matching
* Estimation for negative and positive controls, to assess residual error
* Negative control exposures and outcomes will be used to evaluate the potential impact of residual systematic error in the study design, and to facilitate empirical calibration of the p-value and confidence interval for the exposures and outcome of interest.

Negative control outcomes in the context of this study are outcomes that are not believed to be caused by neither clopidogrel nor PPI, and where therefore the true hazard ratio is equal to 1. We will execute the same analysis used for the primary hypothesis to produce hazard ratio estimates for the negative controls. The distribution of effect estimates across all negative controls will be used to fit an empirical null distribution which models the observed residual systematic error. The empirical null distribution will then be applied to the target exposures and outcome of interest to calibrate the p-value.

The negative control will be used to estimate an empirical systematic error model, which will inform whether systematic error changes as a function of true effect size. The empirical systematic error model will then be applied to the target the target exposures and outcome of interest to calibrate the confidence interval.

Empirical calibration serves as an important diagnostic tool to evaluate if the residual systematic error is sufficient to cast doubt on the accuracy of the unknown effect estimate. The calibration effect plot and calibration probability plots will be generated for review. We will report the traditional and empirically calibrated p-value and confidence interval for each negative control, as well as the hypothesis of interest.

## Data Sources

The analyses will be performed across a network of observational healthcare databases. All databases have been transformed into the OMOP Common Data Model, version 5. The complete specification for OMOP Common Data Model, version 5 is available at: <https://github.com/OHDSI/CommonDataModel>.

## Quality control

We will evaluate the PS by

* Inspection of the fitted PS model for large coefficients (indicative of model-misspecification) and predictors that we cannot explain (post-hoc).
* Inspection of the PS distribution.
* Evaluation of covariate balance after matching using the standardized difference in means between treatment and comparator cohort before and after matching. Standardized differences greater than 0.1 will be reported and investigated.

We will investigate the outcome model by

* Inspection of the fitted outcome model for large coefficients and predictors that we cannot explain (post-hoc).

The error distribution estimated using the negative controls will be used to estimate residual bias after adjustments.

The CohortMethod package itself, as well as other OHDSI packages on which CohortMethod depends, use unit tests for validation.

## Strengths and Limitations of the Research Methods

Strength

* Cohort studies allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date.
* PS matching and full outcome models allow balancing on a large number of baseline potential confounders.
* Use of negative control outcomes allow for evaluating the study design as a whole in terms of residual bias.

Limitations

* Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or mis-specified confounders.

# Protection of Human Subjects

The study is using only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

# Plans for Disseminating and Communicating Study Results

The study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

# References

1 Lee, Y. C., Lin, J. T., Wang, H. P., Chiu, H. M. & Wu, M. S. Influence of cytochrome P450 2C19 genetic polymorphism and dosage of rabeprazole on accuracy of proton-pump inhibitor testing in Chinese patients with gastroesophageal reflux disease. *Journal of gastroenterology and hepatology* **22**, 1286-1292, doi:10.1111/j.1440-1746.2007.04942.x (2007).

2 Pang, J. *et al.* Efficacy and safety of clopidogrel only vs. clopidogrel added proton pump inhibitors in the treatment of patients with coronary heart disease after percutaneous coronary intervention: A systematic review and meta-analysis. *Int J Cardiol Heart Vasc* **23**, 100317, doi:10.1016/j.ijcha.2018.12.016 (2019).

3 Han, Y. Y., Li, Z. X. & Duan, R. Efficacy and safety of proton pump inhibitors combined with clopidogrel in patients undergoing percutaneous coronary intervention: a meta-analysis. *Rev Cardiovasc Med* **22**, 167-174, doi:10.31083/j.rcm.2021.01.296 (2021).

4 Bundhun, P. K., Teeluck, A. R., Bhurtu, A. & Huang, W. Q. Is the concomitant use of clopidogrel and Proton Pump Inhibitors still associated with increased adverse cardiovascular outcomes following coronary angioplasty?: a systematic review and meta-analysis of recently published studies (2012 - 2016). *BMC Cardiovasc Disord* **17**, 3, doi:10.1186/s12872-016-0453-6 (2017).

5 Kim, M. S. *et al.* Effectiveness and Safety of Clopidogrel Co-administered With Statins and Proton Pump Inhibitors: A Korean National Health Insurance Database Study. *Clin Pharmacol Ther* **106**, 182-194, doi:10.1002/cpt.1361 (2019).

6 Choi, Y. J. *et al.* Pantoprazole Does Not Reduce the Antiplatelet Effect of Clopidogrel: A Randomized Controlled Trial in Korea. *Gut and liver* **11**, 504-511, doi:10.5009/gnl16352 (2017).

7 Muthiah, M. D. *et al.* Outcomes of a multi-ethnic Asian population on combined treatment with clopidogrel and omeprazole in 12,440 patients. *J Thromb Thrombolys*, doi:10.1007/s11239-021-02472-w (2021).

8 Koo, B.-K. *et al.* Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. *The Lancet*, doi:10.1016/s0140-6736(21)01063-1 (2021).

9 Goodman, S. G. *et al.* Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the platelet inhibition and patient outcomes trial. *Circulation* **125**, 978-986, doi:10.1161/CIRCULATIONAHA.111.032912 (2012).

10 You, S. C. *et al.* Association of Ticagrelor vs Clopidogrel With Net Adverse Clinical Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. *Jama* **324**, 1640-1650, doi:10.1001/jama.2020.16167 (2020).

11 Vashisht, R. *et al.* Association of Hemoglobin A1c Levels With Use of Sulfonylureas, Dipeptidyl Peptidase 4 Inhibitors, and Thiazolidinediones in Patients With Type 2 Diabetes Treated With Metformin: Analysis From the Observational Health Data Sciences and Informatics Initiative. *JAMA Netw Open* **1**, e181755, doi:10.1001/jamanetworkopen.2018.1755 (2018).

12 Suchard, M. A. *et al.* Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. *Lancet (London, England)*, doi:10.1016/s0140-6736(19)32317-7 (2019).

13 Prats-Uribe, A. *et al.* Use of repurposed and adjuvant drugs in hospital patients with covid-19: multinational network cohort study. *BMJ* **373**, n1038, doi:10.1136/bmj.n1038 (2021).

14 Martijn J. S. *et al.* Large-scale evidence generation and evaluation across a network of databases (LEGEND): assessing validity using hypertension as a case study. *J Am Med Inform Assoc.* **27**, 1268-1277, doi: 10.1093/jamia/ocaa256 (2020).

# Appendix: Concept Set Definitions

1. Proton pump inhibitor

1.1. Inhibiting proton pump inhibitor

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 904453 | Esomeprazole | Drug | RxNorm | NO | YES | NO |
| 923645 | Omeprazole | Drug | RxNorm | NO | YES | NO |

1.2. Other proton pump inhibitor

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 19039926 | Dexlansoprazole | Drug | RxNorm | NO | YES | NO |
| 929887 | Lansoprazole | Drug | RxNorm | NO | YES | NO |
| 948078 | Pantoprazole | Drug | RxNorm | NO | YES | NO |
| 911735 | Rabeprazole | Drug | RxNorm | NO | YES | NO |

2. Clopidogrel

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1322184 | Clopidogrel | Drug | RxNorm | NO | YES | NO |

3. H2-receptor antagonist

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 997276 | Cimetidine | Drug | RxNorm | NO | YES | NO |
| 953076 | Famotidine | Drug | RxNorm | NO | YES | NO |
| 43009003 | Lafutidine | Drug | RxNorm | NO | YES | NO |
| 950696 | Nizatidine | Drug | RxNorm | NO | YES | NO |
| 961047 | Ranitidine | Drug | RxNorm | NO | YES | NO |
| 19011685 | Roxatidine | Drug | RxNorm | NO | YES | NO |

4. Myocardial infarction

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 4329847 | Myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 314666 | Old myocardial infarction | Condition | SNOMED | YES | YES | NO |

5. Stroke

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 372924 | Cerebral artery occlusion | Condition | | SNOMED | NO | NO | NO |
| 375557 | Cerebral embolism | Condition | | SNOMED | NO | NO | NO |
| 376713 | Cerebral hemorrhage | Condition | | SNOMED | NO | NO | NO |
| 432923 | Subarachnoid hemorrhage | Condition | | SNOMED | NO | NO | NO |
| 439847 | Intracranial hemorrhage | Condition | | SNOMED | NO | NO | NO |
| 441874 | Cerebral thrombosis | Condition | | SNOMED | NO | NO | NO |
| 443454 | Cerebral infarction | Condition | | SNOMED | NO | YES | NO |
| 4148906 | Spontaneous subarachnoid hemorrhage | Condition | | SNOMED | NO | NO | NO |
| 43530727 | Spontaneous cerebral hemorrhage | Condition | | SNOMED | NO | NO | NO |

6. Sudden cardiac death for cardiovascular mortality

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 321042 | Cardiac arrest | Condition | SNOMED | NO | YES | NO |
| 437894 | Ventricular fibrillation | Condition | SNOMED | YES | YES | NO |
| 442289 | Death in less than 24 hours from onset of symptoms | Observation | SNOMED | NO | YES | NO |
| 4048809 | Brainstem death | Condition | SNOMED | NO | YES | NO |
| 4132309 | Sudden death | Observation | SNOMED | NO | YES | NO |
| 4317150 | Sudden cardiac death | Condition | SNOMED | NO | YES | NO |

7. Heart failure for cardiovascular mortality

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 315295 | Congestive rheumatic heart failure | Condition | SNOMED | YES | YES | NO |
| 316139 | Heart failure | Condition | SNOMED | NO | YES | NO |

8. Acute coronary syndrome

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 312327 | Acute myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 315296 | Preinfarction syndrome | Condition | SNOMED | NO | YES | NO |
| 434376 | Acute myocardial infarction of anterior wall | Condition | SNOMED | NO | YES | NO |
| 438170 | Acute myocardial infarction of inferior wall | Condition | SNOMED | NO | YES | NO |
| 444406 | Acute subendocardial infarction | Condition | SNOMED | NO | YES | NO |

9. Gastrointestinal bleeding

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 28779 | Bleeding esophageal varices | Condition | SNOMED | NO | YES | NO |
| 192671 | Gastrointestinal hemorrhage | Condition | SNOMED | NO | YES | NO |
| 198798 | Dieulafoy's vascular malformation | Condition | SNOMED | NO | YES | NO |
| 2002608 | Control of hemorrhage and suture of ulcer of stomach or duodenum | Procedure | ICD9Proc | NO | YES | NO |
| 4027663 | Peptic ulcer | Condition | SNOMED | NO | YES | NO |
| 4112183 | Esophageal varices with bleeding, associated with another disorder | Condition | SNOMED | NO | YES | NO |
| 4147683 | Acute gastrojejunal ulcer without hemorrhage AND without perforation | Condition | SNOMED | NO | NO | NO |
| 4198381 | Ulcer of duodenum | Condition | SNOMED | NO | YES | NO |
| 4265600 | Gastric ulcer | Condition | SNOMED | NO | YES | NO |
| 40482685 | Angiodysplasia of duodenum | Condition | SNOMED | NO | YES | NO |
| 23808 | Chronic peptic ulcer without hemorrhage, without perforation AND without obstruction | Condition | SNOMED | YES | YES | NO |
| 24973 | Chronic peptic ulcer without hemorrhage AND without perforation but with obstruction | Condition | SNOMED | YES | YES | NO |
| 195584 | Acute peptic ulcer without hemorrhage AND without perforation but with obstruction | Condition | SNOMED | YES | YES | NO |
| 197925 | Hemorrhage of rectum and anus | Condition | SNOMED | YES | YES | NO |
| 200769 | Chronic gastric ulcer without hemorrhage, without perforation AND without obstruction | Condition | SNOMED | YES | YES | NO |
| 434400 | Chronic gastrojejunal ulcer without hemorrhage AND without perforation but with obstruction | Condition | SNOMED | YES | YES | NO |
| 438795 | Chronic gastrojejunal ulcer without hemorrhage, without perforation AND without obstruction | Condition | SNOMED | YES | YES | NO |
| 443530 | Hematochezia | Condition | SNOMED | YES | YES | NO |
| 4101104 | Gastrojejunal ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4138962 | Acute duodenal ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4163865 | Acute peptic ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4177387 | Chronic gastrojejunal ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4195231 | Acute gastric ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4204555 | Chronic peptic ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4209746 | Duodenal ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4222896 | Chronic duodenal ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4248429 | Gastric ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4291028 | Peptic ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4296611 | Chronic gastric ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |