OHDSI: Comparative risk of the incident cancer between histamine-2 receptor antagonists

**Version:** 0.1 (feasibility test)

**Authors:**

Seng Chan You, MD, Ajou University, Korea

Seung In Seo, MD, Kangdong Sacred Heart Hospital, Korea

Chan Hyuk Park, MD, Hanyang University College of Medicine, Korea

Rae Woong Park, MD PhD, Ajou University, Korea

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Table of contents

[2 List of abbreviations 3](#_Toc33704612)

[3 Abstract 3](#_Toc33704613)

[4 Amendments and Updates 4](#_Toc33704614)

[5 Rationale and Background 4](#_Toc33704615)

[6 Study Objectives 5](#_Toc33704616)

[6.1 Research Questions 5](#_Toc33704617)

[6.2 Objectives 6](#_Toc33704618)

[7 Research methods 6](#_Toc33704619)

[7.1 Study Design 6](#_Toc33704620)

[7.1.1 Overview 6](#_Toc33704621)

[7.2 Study population 7](#_Toc33704622)

[7.2.1 Primary study population 7](#_Toc33704623)

[7.2.2 Secondary study population for sensitivity analysis 7](#_Toc33704624)

[7.2.3 Subgroups 7](#_Toc33704625)

[7.3 Outcomes 8](#_Toc33704626)

[7.3.1 Primary outcome: Overall cancer without thyroid cancer 8](#_Toc33704627)

[7.3.2 Secondary outcome: Overall cancer 9](#_Toc33704628)

[7.3.3 Secondary outcome: Lip, oral cavity and pharynx cancer 9](#_Toc33704629)

[7.3.4 Secondary outcome: Esophagus cancer 11](#_Toc33704630)

[7.3.5 Secondary outcome: Stomach cancer 11](#_Toc33704631)

[7.3.6 Secondary outcome: Colon and rectum cancer 12](#_Toc33704632)

[7.3.7 Secondary outcome: Liver cancer 13](#_Toc33704633)

[7.3.8 Secondary outcome: Pancreas cancer 13](#_Toc33704634)

[7.3.9 Secondary outcome: Lung cancer 14](#_Toc33704635)

[7.3.10 Secondary outcome: Breast cancer 15](#_Toc33704636)

[7.3.11 Secondary outcome: Cervix uteri cancer 16](#_Toc33704637)

[7.3.12 Secondary outcome: Corpus uteri cancer 16](#_Toc33704638)

[7.3.13 Secondary outcome: Ovary cancer 17](#_Toc33704639)

[7.3.14 Secondary outcome: Prostate cancer 18](#_Toc33704640)

[7.3.15 Secondary outcome: Bladder cancer 19](#_Toc33704641)

[7.3.16 Secondary outcome: Leukemia 19](#_Toc33704642)

[7.3.17 Secondary outcome: Thyroid cancer 20](#_Toc33704643)

[7.3.18 Secondary outcome: Gall bladder and biliary tract cancer 20](#_Toc33704644)

[7.3.19 Secondary outcome: Cancer mortality 21](#_Toc33704645)

[7.3.20 Negative controls 21](#_Toc33704646)

[7.4 Covariates 25](#_Toc33704647)

[7.4.1 Propensity score covariates 25](#_Toc33704648)

[7.4.2 Other variables 26](#_Toc33704649)

[8 Data Analysis Plan 26](#_Toc33704650)

[8.1 Calculation of time-at-risk 26](#_Toc33704651)

[8.2 Model specification 26](#_Toc33704652)

[8.2.1 Statistical models 27](#_Toc33704653)

[8.2.2 Pooling effect estimates across databases 27](#_Toc33704654)

[8.3 Analyses to perform 27](#_Toc33704655)

[8.4 Output 28](#_Toc33704656)

[8.5 Evidence Evaluation 28](#_Toc33704657)

[8.6 Data Sources 29](#_Toc33704658)

[8.7 Quality control 29](#_Toc33704659)

[8.8 Strengths and Limitations of the Research Methods 30](#_Toc33704660)

[9 Protection of Human Subjects 30](#_Toc33704661)

[10 Plans for Disseminating and Communicating Study Results 30](#_Toc33704662)

[11 References 30](#_Toc33704663)

[12 Appendix: Concept Set Definitions 32](#_Toc33704664)

# List of abbreviations

NMDA N-nitrosodimethylamine

H2RA H2-receptor antagonist

FDA Food and Drug Administration

OHDSI Observational Health Data Sciences and Informatics

PS propensity score

# Abstract

Dietary N-nitrosodimethylamine (NDMA) has been shown to be carcinogenic in animals, however, evidence from population-based studies is inconlusive. The U.S. Food and Drug Administration has issued a statement on ranitidine because they may contain unacceptable levels of NDMA in 2019.

To date, there have been several studies regarding association between NDMA exposure and risk of cancer, however, real-world evidence of cancer risk in relation with ranitidine is scarce. We aim to evaluate the comparative risk of incident cancer in patients exposed to various H2 receptor antagonists (H2RAs).

We will conduct systematic, multinational study to estimate the relative risk of primary outcome (overall cancer except thyroid cancer) and secondary outcomes (overall cancer, 16 types of cancer, and cancer mortality) in ranitidine cohort. We will 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 after propensity score adjustment.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0. 1 | February 28 2020 | SC You | Initial draft for feasibility test |

# Rationale and Background

Ranitidine is a histamine H2-receptor antagonist (H2RAs) commonly have been used to treat gastroesophageal reflux disease and peptic ulcer disease and it was top over-the-counter H2RA brand in the USA in 2013. Recent study confirmed that oral intake of ranitidine increases urinary execretion of N-nitrosodimethylamine (NDMA) by nitrosation of ranitidine under stomach-relevant pH conditions in vitro, and the potential cancer risk from ranitidine was suggested.1

In 2019, The US Food and Drug Administration (FDA) has asked doctors and patients to withdraw all ranitidine products from the market as of September 2019, after low levels of the probable human carcinogen NDMA were detected.2 NDMA is known as one of the most potent animal carcinogens and has been shown to be a potent carcinogen across all species that have been investigated.3–7 Hence, the International Agency for Research on Cancer has classified NDMA as “probably carcinogenic to humans” (group 2A).

To date, there have been several studies regarding association between NDMA exposure and risk of cancer,5,8–12 however, real-world evidence of cancer risk in relation with ranitidine is scarce. Recent Danish nationwide cohort study assessed the potential cancer risk associated with NDMA exposure in contaminated valsartan, however, they found no evidence of overall risk of cancer.5 It means that the real-world evidence could be uncertain.

In this study we will generate population-level estimates for comparative risk of malignancy across various H2RAs. We perform every possible pairwise comparison between H2RA treatments for diverse outcome definition related with malignancy.

# Study Objectives

## Research Questions

In this study, we are interested in every pairwise comparison between any two treatments in table 1 (e.g. comparing ranitidine to cimetidine). Only comparison where each treatment cohort has more than 1,000 subjects will be performed.

|  |  |
| --- | --- |
| Drug | OMOP Concept ID |
| Ranitidine | 961047 |
| Cimetidine | 997276 |
| Nizatidine | 950696 |
| roxatidine | 19011685 |
| Famotidine | 953076 |
| lafutidine | 43009003 |

**Table 1**. List of H2 antagonists considered in this study

For each comparison of two treatments, we are interested in the comparative effect on each of the outcomes listed in table 2.

|  |  |  |
| --- | --- | --- |
| Outcome | ICD-9-CM | ICD-10 |
| Overall cancer without thyroid cancer |  |  |
| Overall cancer |  |  |
| Lip, oral cavity and pharynx cancer | 140-149; 160-16113 | C00-C1414 |
| Esophagus cancer | 15015 | C1514 |
| Stomach cancer | 15115 | C1614 |
| Colon and rectum cancer | 153.x; 154.0-154.1, 154.816 | C18-C2114 |
| Liver cancer | 15517,18 | C2214 |
| Pancreas cancer | 15719 | C2514 |
| Lung cancer | 162.x16,20 | C33-C3414 |
| Breast cancer | 174.x16,20 | C5014 |
| Cervix uteri cancer | 18020 | C5314 |
| Corpus uteri cancer | 18221 | C5414 |
| Ovary cancer | 18322 | C5614 |
| Prostate cancer | 18520 | C6114 23 |
| Bladder cancer | 18824 | C6714 |
| Leukemia | 204-20525 | C91-C9514 |
| Thyroid cancer | 19326 | C7323 |
| Gall bladder and biliary tract cancer | 15619 | C23-C2423 |
| Cancer mortality |  |  |

**Table 2**. Outcomes of interest. Supporting references are cited for each outcome.

Primary research question

* Is there any significant difference in incidence of cancers except thyroid cancer between users of ranitidine and cimetidine?

We further consider the following subgroups of interest:

* Female
* Elderly (age >=65)
* Users with cumulative drug dose more than 365 units
* Users with cumulative drug dose more than 730 units
* Users with cumulative drug dose more than 1095 units

Secondary research question

* For each comparison between two H2RAs, for each of the outcomes of interest, what is the hazard ratio?
* For each comparison between two H2RAs, for each of the outcomes of interest, how does the hazard ratio change within 5 subgroups of interest?

## Objectives

Primary objective

* Generate evidence for comparative safety of incident cancer for each pairwise comparison

Secondary objectives

* Assess the bias inherent in each analysis by including negative control outcomes.

# 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.

## Study population

In this study, we are interested in every pairwise comparison between any two treatments in table 1. Treatments will be compared among primary study population, but also among secondary study population without gastric ulcer.

### Primary study population

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment of H2RAs)

* Exposure to one of the treatments of interest longer than 30 days with allowing gaps between the treatment
* At least 365 days of observation time prior to the index date
* Without use of other H2RAs except the treatment of interest during a previous year
* Without use of sucralfate or bismuth from 30 days before to 30 days after the index date
* No diagnosis of cancer preceding the 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 H2RAs other than the drug of interest.

### Secondary study population for sensitivity analysis

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment of H2RAs)

* Exposure to one of the treatments of interest longer than 30 days with allowing gaps between the treatment
* At least 365 days of observation time prior to the index date
* Without use of other H2RAs except the treatment of interest during a previous year
* Without use of sucralfate or bismuth from 30 days before to 30 days after the index date
* Without diagnosis of gastric ulcer during a previous year
* No diagnosis of cancer preceding the index date

### Subgroups

Interaction effects will be estimates with the following subgroups:

* Female
* Elderly (age >=65)
* Users with cumulative drug dose more than 365 units
* Users with cumulative drug dose more than 730 units
* Users with cumulative drug dose more than 1095 units

**Gender = female**

Defined as having gender = female (concept ID 8532).

**Elderly (age >=65)**

Defined as having index year – year of birth >= 65.

**Users with cumulative drug dose more than 365 units**

Defined as cumulative quantity of the H2RAs more than 365 during on-treatment period.

**Users with cumulative drug dose more than 730 units**

Defined as cumulative quantity of the H2RAs more than 730 during on-treatment period.

**Users with cumulative drug dose more than 1095 units**

Defined as cumulative quantity of the H2RAs more than 1095 during on-treatment period.

## Outcomes

### Primary outcome: Overall cancer without thyroid cancer

Index rule defining the index date:

* Occurrence of malignant neoplasm except thyroid cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for the malignant neoplasm except thyroid cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Malignant neoplasm except thyroid cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443392 | Malignant neoplastic disease | Condition | SNOMED | NO | YES | NO |
| 4178976 | Malignant tumor of thyroid gland | Condition | SNOMED | YES | YES | NO |
| 4201622 | Metastasis from malignant tumor of thyroid | Condition | SNOMED | YES | NO | NO |
| 36717298 | Secondary malignant neoplasm of lymph nodes of neck from thyroid | Condition | SNOMED | YES | NO | NO |

### Secondary outcome: Overall cancer

Index rule defining the index date:

* Occurrence of malignant neoplasm for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for the malignant neoplasm as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Malignant neoplasm

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443392 | Malignant neoplastic disease | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Lip, oral cavity and pharynx cancer

Index rule defining the index date:

* Occurrence of lip, oral cavity and pharynx cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for the lip, oral cavity and pharynx cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Lip, oral cavity and pharynx cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 22557 | Malignant tumor of submandibular gland | Condition | SNOMED | NO | NO | NO |
| 22839 | Overlapping malignant neoplasm of larynx | Condition | SNOMED | NO | NO | NO |
| 25189 | Malignant tumor of oral cavity | Condition | SNOMED | NO | NO | NO |
| 26052 | Primary malignant neoplasm of larynx | Condition | SNOMED | NO | NO | NO |
| 28083 | Primary malignant neoplasm of pharynx | Condition | SNOMED | NO | NO | NO |
| 28356 | Overlapping malignant neoplasm of major salivary gland | Condition | SNOMED | NO | NO | NO |
| 31509 | Primary malignant neoplasm of tonsil | Condition | SNOMED | NO | NO | NO |
| 132258 | Primary malignant neoplasm of frontal sinus | Condition | SNOMED | NO | NO | NO |
| 132565 | Primary malignant neoplasm of vermilion border of lower lip | Condition | SNOMED | NO | NO | NO |
| 132832 | Primary malignant neoplasm of inner aspect of lip | Condition | SNOMED | NO | NO | NO |

### Secondary outcome: Esophagus cancer

Index rule defining the index date:

* Occurrence of esophagus cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for esophagus cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Esophagus cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4181343 | Malignant tumor of esophagus | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Stomach cancer

Index rule defining the index date:

* Occurrence of stomach cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for stomach cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Stomach Cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443387 | Malignant tumor of stomach | Condition | SNOMED | NO | YES | NO |
| 46271647 | Malignant carcinoid tumor of stomach | Condition | SNOMED | YES | YES | NO |

### Secondary outcome: Colon and rectum cancer

Index rule defining the index date:

* Occurrence of colon cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for colon cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Colon and rectum cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443390 | Malignant tumor of rectum | Condition | SNOMED | NO | YES | NO |
| 443391 | Malignant tumor of cecum | Condition | SNOMED | NO | YES | NO |
| 4180790 | Malignant tumor of colon | Condition | SNOMED | NO | YES | NO |
| 40481907 | Carcinoid tumor | Condition | SNOMED | YES | YES | NO |
| 44501937 | Goblet cell carcinoid of Ascending colon | Condition | ICDO3 | YES | NO | NO |
| 44502103 | Carcinoid tumor of Colon | Condition | ICDO3 | YES | NO | NO |

### Secondary outcome: Liver cancer

Index rule defining the index date:

* Occurrence of liver cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for liver cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Liver Cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 198700 | Secondary malignant neoplasm of liver | Condition | SNOMED | YES | YES | NO |
| 4246127 | Malignant neoplasm of liver | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Pancreas cancer

Index rule defining the index date:

* Occurrence of liver cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for liver cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Pancreas Cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4178966 | Malignant tumor of ampulla of Vater | Condition | SNOMED | YES | YES | NO |
| 4180793 | Malignant tumor of pancreas | Condition | SNOMED | NO | YES | NO |

Showing 1 to 2 of 2 entries

Previous1Next

### Secondary outcome: Lung cancer

Index rule defining the index date:

* Occurrence of lung cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for lung cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Lung Cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 254583 | Kaposi's sarcoma of lung | Condition | SNOMED | YES | YES | NO |
| 254591 | Secondary malignant neoplasm of lung | Condition | SNOMED | YES | YES | NO |
| 443388 | Malignant tumor of lung | Condition | SNOMED | NO | YES | NO |
| 4157333 | Malignant neoplasm of main bronchus | Condition | SNOMED | NO | YES | NO |
| 4177112 | Malignant tumor of trachea | Condition | SNOMED | NO | YES | NO |
| 4311499 | Primary malignant neoplasm of respiratory tract | Condition | SNOMED | NO | NO | NO |

### Secondary outcome: Breast cancer

Index rule defining the index date:

* Occurrence of breast cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for breast cancer as a primary diagnosis on or after the index date
* Only female gender

Appendix 1: Concept Set Definitions

1. Breast cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 135489 | Primary malignant neoplasm of male breast | Condition | SNOMED | YES | YES | NO |
| 140960 | Secondary malignant neoplasm of female breast | Condition | SNOMED | YES | YES | NO |
| 442178 | Secondary malignant neoplasm of male breast | Condition | SNOMED | YES | YES | NO |
| 4112853 | Malignant tumor of breast | Condition | SNOMED | NO | YES | NO |
| 4157448 | Carcinoma of male breast | Condition | SNOMED | YES | YES | NO |
| 4244051 | Malignant melanoma of skin of breast | Condition | SNOMED | YES | YES | NO |
| 4247348 | Primary malignant neoplasm of skin of breast | Condition | SNOMED | YES | YES | NO |
| 4313931 | Secondary malignant neoplasm of skin of breast | Condition | SNOMED | YES | YES | NO |

### Secondary outcome: Cervix uteri cancer

Index rule defining the index date:

* Occurrence of cervix uteri cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for cervix uteri cancer as a primary diagnosis on or after the index date
* Only female gender

Appendix 1: Concept Set Definitions

1. Cervix uteri cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 198984 | Malignant tumor of cervix | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Corpus uteri cancer

Index rule defining the index date:

* Occurrence of corpus uteri cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for corpus uteri cancer as a primary diagnosis on or after the index date
* Only female gender

Appendix 1: Concept Set Definitions

1. Corpus uteri cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 197230 | Malignant neoplasm of uterus | Condition | SNOMED | NO | YES | NO |
| 198984 | Malignant tumor of cervix | Condition | SNOMED | YES | YES | NO |
| 4048225 | Neoplasm of endometrium | Condition | SNOMED | NO | YES | NO |
| 4241777 | Carcinoma in situ of endometrium | Condition | SNOMED | YES | YES | NO |
| 4303970 | Endometrial intraepithelial neoplasia | Condition | SNOMED | YES | NO | NO |

### Secondary outcome: Ovary cancer

Index rule defining the index date:

* Occurrence of ovary cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for ovary cancer as a primary diagnosis on or after the index date
* Only female gender

Appendix 1: Concept Set Definitions

1. Ovary Cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 199752 | Secondary malignant neoplasm of ovary | Condition | SNOMED | YES | YES | NO |
| 200052 | Primary malignant neoplasm of uterine adnexa | Condition | SNOMED | NO | YES | NO |
| 4181351 | Malignant tumor of ovary | Condition | SNOMED | NO | YES | NO |
| 4312824 | Secondary malignant neoplasm of broad ligament | Condition | SNOMED | YES | YES | NO |
| 40486213 | Malignant neoplasm of broad ligament of uterus | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Prostate cancer

Index rule defining the index date:

* Occurrence of prostate cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for prostate cancer as a primary diagnosis on or after the index date
* Only male gender

Appendix 1: Concept Set Definitions

1. Prostate cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4163261 | Malignant tumor of prostate | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Bladder cancer

Index rule defining the index date:

* Occurrence of bladder cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for bladder cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Bladder cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 197508 | Malignant tumor of urinary bladder | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Leukemia

Index rule defining the index date:

* Occurrence of leukemia for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for leukemia as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Leukemia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 133169 | Myelofibrosis | Condition | SNOMED | NO | YES | NO |
| 135214 | Polycythemia vera | Condition | SNOMED | NO | YES | NO |
| 317510 | Leukemia | Condition | SNOMED | NO | YES | NO |
| 4297355 | Aggressive NK-cell leukemia involving skin | Condition | SNOMED | NO | YES | NO |
| 40492268 | Myelodysplastic/myeloproliferative disease | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Thyroid cancer

Index rule defining the index date:

* Occurrence of thyroid cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for thyroid cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Thyroid cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4178976 | Malignant tumor of thyroid gland | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Gall bladder and biliary tract cancer

Index rule defining the index date:

* Occurrence of gall bladder and biliary tract cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for gall bladder and biliary tract cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Gall bladder and biliary tract cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4181345 | Malignant tumor of biliary tract | Condition | SNOMED | NO | YES | NO |
| 40490929 | Primary malignant neoplasm of intrahepatic bile duct | Condition | SNOMED | YES | YES | NO |

### Secondary outcome: Cancer mortality

Index rule defining the index date:

* A death occurrence from cancer

Appendix 1: Concept Set Definitions

1. Cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443392 | Malignant neoplastic disease | Condition | SNOMED | NO | YES | NO |

### 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 al27. Once potential negative control candidates were selected, manual clinical review to exclude any pairs that may still be in a causal relationship or similar to the study outcome was be performed to select the top concepts by patient exposure. The final list of 99 negative outcomes is described in Table 3.

|  |  |
| --- | --- |
| **Concept ID** | **Concept Name** |
| 4218106 | Alcoholism |
| 439237 | Assault |
| 4172458 | Candidiasis of skin |
| 4047787 | Colles' fracture |
| 4131595 | Fracture of radius |
| 4297984 | Local infection of wound |
| 4215978 | Onychomycosis |
| 4171915 | Orchitis |
| 4295888 | Prolapse of intestine |
| 4195698 | Tenosynovitis |
| 4339088 | Testicular mass |
| 133141 | Tinea pedis |
| 4092565 | Uterine prolapse |
| 140648 | Onychomycosis due to dermatophyte |
| 4245252 | Raised prostate specific antigen |
| 74719 | Ulcer of foot |
| 78228 | Joint derangement |
| 435511 | Hypercalcemia |
| 4115991 | Knee joint effusion |
| 80242 | Current tear of medial cartilage AND/OR meniscus of knee |
| 137967 | Muscle, ligament and fascia disorders |
| 4295261 | Postmenopausal state |
| 4168222 | Intra-abdominal and pelvic swelling, mass and lump |
| 77650 | Aseptic necrosis of bone |
| 4171556 | Ankle ulcer |
| 315361 | Orthopnea |
| 201606 | Crohn's disease |
| 77364 | Hypermobility of coccyx |
| 4319325 | Acquired deformity of trunk |
| 72404 | Joint stiffness |
| 4101660 | Amputated below knee |
| 77139 | Open wound of finger without complication |
| 380818 | Acquired deformity of head |
| 440129 | Hypertrophy of nasal turbinates |
| 31668 | Acquired deformity of neck |
| 437359 | Osteochondritis dissecans |
| 435903 | Juvenile osteochondrosis of foot |
| 75920 | Osteitis condensans |
| 435633 | Juvenile osteochondrosis of upper extremity |
| 438527 | Juvenile osteochondrosis of lower extremity, excluding foot |
| 74731 | Hypertrophic osteoarthropathy |
| 75389 | Current tear of lateral cartilage AND/OR meniscus of knee |
| 199876 | Prolapse of female genital organs |
| 443698 | Abnormal anal Papanicolaou smear |
| 77421 | Open wound of hand except fingers without complication |
| 77072 | Joint effusion of ankle AND/OR foot |
| 432798 | Mechanical complication of internal orthopedic device, implant AND/OR graft |
| 72994 | Jaccoud's syndrome |
| 4163280 | Tinea of perianal region |
| 438120 | Opioid dependence |
| 438297 | Mechanical complication of cardiac device, implant AND/OR graft |
| 435516 | Lipoprotein deficiency disorder |
| 444426 | Open wound of foot except toes without complication |
| 77356 | Pathological dislocation of joint |
| 443593 | Ulcer of thigh |
| 73575 | Deformity of toe |
| 435723 | Wound seroma |
| 439666 | Contracture of multiple joints |
| 435131 | Victim of neglect |
| 4094448 | Pregnancy test negative |
| 197607 | Excessive and frequent menstruation |
| 137426 | Open wound of forearm without complication |
| 198715 | Premature menopause |
| 440638 | Lyme disease |
| 134734 | Compartment syndrome |
| 440072 | Hypogammaglobulinemia |
| 72407 | Effusion of joint of shoulder region |
| 440021 | Herpes simplex without complication |
| 80946 | Tinea manus |
| 433071 | Contusion of multiple sites |
| 261599 | Vocal cord paralysis |
| 132834 | White piedra |
| 72995 | Contracture of joint of hand |
| 199978 | Contusion of lower limb |
| 81930 | Transient arthropathy |
| 141797 | Black piedra |
| 432411 | Acquired equinus deformity of foot |
| 4271024 | Musculoskeletal fibromatosis |
| 80492 | Contracture of knee joint |
| 443585 | Abrasion and/or friction burn of multiple sites |
| 78512 | Joint contracture of the ankle and/or foot |
| 378160 | Otorrhea |
| 72413 | Nontraumatic rupture of muscle |
| 4247710 | Effusion of joint of pelvic region |
| 74080 | Orthostatic proteinuria |
| 78834 | Effusion of joint of hand |
| 4198962 | Amputated thumb |
| 74855 | Genital herpes simplex |
| 4303805 | Allergic reaction to bite and/or sting |
| 441481 | Adult victim of abuse |
| 437489 | Herpes zoster with complication |
| 42709838 | Cellulitis of lower limb |
| 4209423 | Nicotine dependence |
| 253796 | Pneumothorax |
| 4051004 | Open wound of scalp |
| 4129404 | Open wound of upper arm |
| 40481632 | Ganglion cyst |
| 4150043 | Epididymitis |
| 194997 | Prostatitis |

**Table 3**. Negative control outcomes

## Covariates

### Propensity score covariates

Propensity scores (PS) will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score 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 propensity score model will be:

* Demographics
  + Gender
  + Age group (5-year bands)
  + Index year
  + Race
* Conditions
  + In prior 30d
  + In prior 365d
* Condition aggregation
  + SNOMED
* Drugs
  + In prior 30d
  + In prior 365d
  + Overlapping index date
* Drug aggregation
  + Ingredient
  + ATC Class
* Procedure
  + In prior 365d
* Observation
  + In prior 365d
* Risk scores
  + Charlson comorbidity index

Specific covariates to be excluded from the propensity score model are labelled **concepts to exclude,** which composed of drug use of H2RAs.

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

Six time-at-risk periods will be used:

* Intent-to-treat: Starting on the day of treatment initiation and stopping at the end of observation.
* Intent-to-treat with one-year blanking period: Starting 365 days after the day of treatment initiation and stopping at the end of observation.
* On-treatment: Starting on the day of treatment initiation, and stopping at treatment end or at starting H2RAs other than the target drug, allowing for a maximum gap of 30 days between prescriptions.
* On-treatment with one-year blanking period: Starting 365 days after the day of treatment initiation, and stopping at treatment end or at starting H2RAs other than the target drug, allowing for a maximum gap of 30 days between prescriptions.
* On-treatment with one-year lag period: Starting on the day of treatment initiation, and stopping 1 year after treatment end or starting H2RAs other than the target drug, allowing for a maximum gap of 30 days between prescriptions.
* On-treatment with one-year lag period and one-year blanking period: Starting 365 days after treatment initiation, and stopping 1 year after treatment end or starting H2RAs other than the target drug, allowing for a maximum gap of 30 days between prescriptions.

## 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 will be computed for each outcome in each exposure group

### Statistical models

Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score 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 7.4.1.

* One-to-one PS matching: After estimating the PS, one-to-one matching will be performed. 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 an unconditioned Cox regression, with only the treatment variable as predictor.
* Variable ratio PS matching: 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.
* 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.
* Without matching: The Cox proportional hazard model will be applied without PS matching or stratification.

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.

Interactions between the treatment effect and the predefined subgroups will be evaluated in separate outcome models, one per subgroup. For efficiency reasons, only one-to-one PS matching will be used when investigating effect interactions

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

### 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 comparative analyses will be performed if sufficient data is present (e.g. if at least 1,000 subjects are observed in both target and comparator cohort):

* 6x5x2 comparisons: Pairwise comparison among six H2RA users. Additionally, H2RA users without gastric ulcer will be compared.
* 19 outcomes
* 6 time-at-risk definitions
* 4 model: unconditioned Cox regression after 1:1 PS matching, Cox regression without matching, conditioned Cox regression after variable-ratio PS matching, and conditioned Cox regression after PS stratification
* Additional 6 interaction analysis for 19 outcomes

The total number of analyses is 17,100 (30 comparisons x 19 outcomes x 6 TAR x4 statistical models + 30x6x19 interaction analyses) in each database.

Among these analyses, the result from meta-analysis using balanced results from the one-to-one PS matching using to-treat time-at-risk with one-year blanking period between ranitidine and cimetidine users regardless of history of gastric ulcer will be reported as the primary outcome.

## 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 propensity score distributions for both cohorts after matching will be provided. Covariate balance will be evaluated by plotting the standardized mean difference of each covariate before propensity score matching against the standardized mean difference for each covariate after propensity score 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:

* Propensity score distribution
* Covariate balance before and after propensity score matching
* Estimation for negative 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 ticagrelor nor clopidogrel, 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.28

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 misspecified 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.

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# Appendix: Concept Set Definitions

1. Bismuth or sucralfate

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 1036228 | Sucralfate | Drug | RxNorm | NO | NO | NO |
| 958134 | bismuth subcitrate | Drug | RxNorm | NO | NO | NO |

2. Cancer

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 443392 | Malignant neoplastic disease | Condition | SNOMED | NO | YES | NO |

3. Gastric ulcer

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 4265600 | Gastric ulcer | Condition | SNOMED | NO | YES | NO |

ICD10: K25.x; K28.x

ICD9-CM: 531.x; 533.3x; 534.x