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

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2 List of abbreviations

NMDA	N-nitrosodimethylamine
H_2RA	H_2-receptor antagonist
FDA	Food and Drug Administration
OHDSI	Observational Health Data Sciences and Informatics
PS	propensity score

3 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 H_2 receptor antagonists (H_2RAs).

We will conduct systematic, multinational study to estimate the relative risk of primary outcome (overall cancer except non-melanoma skin cancer) and secondary outcomes (overall cancer, overall cancer except thyroid 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.

4 Amendments and Updates

0.1	February 28 2020	SC You	Initial draft for feasibility test
0.2	May 24 2020	SC You	According to the review from SIDIAP scientific committee, we revised the primary outcome to malignant cancer except non-melanoma skin cancer. Empirical equipoise will be identified to assess the feasibility of the research
0.3	July 3 2020	SC You	We found that cimetidine users are not in equipoise with ranitidine user. So we decided to exclude cimetidine from the other H_2 blockers in the primary analysis as comparator of ranitidine users. We added details for the meta-analysis and diagnostics.
0.4	October 26 2020	SC You	We added more negative control outcomes, since we could not identify many negative control outcomes in Korean databases from the feasibility test.
0.5	January 13, 2021	SC You	We made following changes: -Limiting study population to adult -Primary outcome does not require hospitalization because this information is not available in many databases including UK CPRD. Rather, cancer diagnosis precipitating hospitalization remains as secondary outcomes for sensitivity analysis. -The criteria for concomitant use of bismuth and sucralfate was changed to avoid immortal time bias. -Redundant time-at-risk (TAR) settings were removed. Updated protocol will use only four TARs.

5 Rationale and Background

Ranitidine is a histamine H_2-receptor antagonist (H_2RAs) commonly have been used to treat gastroesophageal reflux disease and peptic ulcer disease and it was top over-the-counter H_2RA 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 H_2RAs. We perform every possible pairwise comparison between H_2RA treatments for diverse outcome definition related with malignancy.

6 Study Objectives

6.1 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).

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; 160-161[13]	C00-C14[14]
Esophagus cancer	150[15]	C15[14]
Stomach cancer	151[15]	C16[14]
Colon and rectum cancer	153.x; 154.0-154.1, 154.8[16]	C18-C21[14]
Liver cancer	155[17,18]	C22[14]
Pancreas cancer	157[19]	C25[14]
Lung cancer	162.x[16,20]	C33-C34[14]
Breast cancer	174.x[16,20]	C50[14]
Cervix uteri cancer	180[20]	C53[14]
Corpus uteri cancer	182[21]	C54[14]
Ovary cancer	183[22]	C56[14]
Prostate cancer	185[20]	C61[14 23]
Bladder cancer	188[24]	C67[14]
Leukemia	204-205[25]	C91-C95[14]
Thyroid cancer	193[26]	C73[23]
Gall bladder and biliary tract cancer	156[19]	C23-C24[23]
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 (1 unit means use of 1 ample or 1 pill of the drug)
- 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 H_2RAs, for each of the outcomes of interest, what is the hazard ratio?
- For each comparison between two H_2RAs, for each of the outcomes of interest, how does the hazard ratio change within 5 subgroups of interest?

6.2 Objectives

Primary objective

- Generate evidence for comparative safety of incident cancer of ranitidine compared with other H_2RAs

Secondary objectives

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

7 Research methods

7.1 Study Design

7.1.1 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.

7.2 Study population

In this study, we are interested in every pairwise comparison between any two treatments in table 1.

7.2.1 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 H_2RAs)

- 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 0 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 H_2RAs other than the drug of interest.

7.2.2 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 H_2RAs more than 365 during on-treatment period.

Users with cumulative drug dose more than 730 units

Defined as cumulative quantity of the H_2RAs more than 730 during on-treatment period.

Users with cumulative drug dose more than 1095 units

Defined as cumulative quantity of the H_2RAs more than 1095 during on-treatment period.

7.3 Outcomes

7.3.1 Primary outcome: Overall cancer except non-melanoma skin cancer

Index rule defining the index date:

- Occurrence of malignant neoplasm except non-melanoma skin 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

Appendix 1: Concept Set Definitions

1. Malignant neoplasm except non-melanoma skin cancer

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
443392	Malignant neoplastic disease	Condition	SNOMED	NO	YES	NO
4111921	Squamous cell carcinoma of skin	Condition	SNOMED	YES	YES	NO
4112752	Basal cell carcinoma of skin	Condition	SNOMED	YES	NO	NO

7.3.2 Secondary outcome: Overall cancer except 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

7.3.3 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

7.3.4 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

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
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

7.3.5 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

7.3.6 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

7.3.7 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

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
44501937	Goblet cell carcinoid of Ascending colon	Condition	ICDO3	YES	NO	NO
44502103	Carcinoid tumor of Colon	Condition	ICDO3	YES	NO	NO

7.3.8 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

7.3.9 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

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7.3.10 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

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4177112	Malignant tumor of trachea	Condition	SNOMED	NO	YES	NO
4311499	Primary malignant neoplasm of respiratory tract	Condition	SNOMED	NO	NO	NO

7.3.11 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

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
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

7.3.12 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

7.3.13 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

7.3.14 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

7.3.15 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

7.3.16 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

7.3.17 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

7.3.18 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

7.3.19 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

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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

7.3.20 Secondary outcome: Additional hospitalization with primary diagnosis of cancer

As a sensitivity analysis, stricter outcomes requiring hospitalization with primary diagnosis of cancer for all 19 outcomes above are investigated.

7.3.21 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

7.3.22 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[27]. 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 119 negative outcomes is described in Table 3.

Concept ID	Concept Name
443698	Abnormal anal Papanicolaou smear
443585	Abrasion and/or friction burn of multiple sites
380818	Acquired deformity of head
31668	Acquired deformity of neck
4319325	Acquired deformity of trunk
432411	Acquired equinus deformity of foot
439673	Acute hepatitis B with delta-agent (coinfection) without hepatic coma
441481	Adult victim of abuse
4218106	Alcoholism
4303805	Allergic reaction to bite and/or sting
4101660	Amputated below knee
4198962	Amputated thumb
4171556	Ankle ulcer
77650	Aseptic necrosis of bone
439237	Assault
141797	Black piedra
79232	Burn of ankle
4172458	Candidiasis of skin
42709838	Cellulitis of lower limb
439674	Chronic viral hepatitis B without delta-agent
4047787	Colles' fracture
134734	Compartment syndrome
72995	Contracture of joint of hand
80492	Contracture of knee joint
439666	Contracture of multiple joints
199978	Contusion of lower limb
433071	Contusion of multiple sites
201606	Crohn's disease
75389	Current tear of lateral cartilage AND/OR meniscus of knee
80242	Current tear of medial cartilage AND/OR meniscus of knee

73575	Deformity of toe
436906	Disease caused by rickettsiae
4135080	Dislocation of radial head
78834	Effusion of joint of hand
4247710	Effusion of joint of pelvic region
72407	Effusion of joint of shoulder region
4150043	Epididymitis
197607	Excessive and frequent menstruation
374801	Foreign body in ear
4131595	Fracture of radius
441487	Frostbite
40481632	Ganglion cyst
74855	Genital herpes simplex
437744	Heat exhaustion
440021	Herpes simplex without complication
437489	Herpes zoster with complication
440329	Herpes zoster without complication
435511	Hypercalcemia
77364	Hypermobility of coccyx
74731	Hypertrophic osteoarthropathy
440129	Hypertrophy of nasal turbinates
440072	Hypogammaglobulinemia
4344500	Impingement syndrome of shoulder region
434872	Infection by Trichomonas
440053	Infestation by insect
4057662	Infestation by Phthirus
4168222	Intra-abdominal and pelvic swelling, mass and lump
72994	Jaccoud's syndrome
78512	Joint contracture of the ankle and/or foot
78228	Joint derangement
77072	Joint effusion of ankle AND/OR foot
72404	Joint stiffness
435903	Juvenile osteochondrosis of foot
438527	Juvenile osteochondrosis of lower extremity, excluding foot
435633	Juvenile osteochondrosis of upper extremity

4115991	Knee joint effusion
435516	Lipoprotein deficiency disorder
4297984	Local infection of wound
440638	Lyme disease
438067	Malaria
438297	Mechanical complication of cardiac device, implant AND/OR graft
432798	Mechanical complication of internal orthopedic device, implant AND/OR graft
137967	Muscle, ligament and fascia disorders
4271024	Musculoskeletal fibromatosis
4209423	Nicotine dependence
201792	Nongonococcal urethritis
72413	Nontraumatic rupture of muscle
4215978	Onychomycosis
140648	Onychomycosis due to dermatophyte
4129408	Open wound of ankle
4053600	Open wound of elbow
77139	Open wound of finger without complication
444426	Open wound of foot except toes without complication
137426	Open wound of forearm without complication
77421	Open wound of hand except fingers without complication
4051004	Open wound of scalp
4129404	Open wound of upper arm
438120	Opioid dependence
4171915	Orchitis
315361	Orthopnea
74080	Orthostatic proteinuria
75920	Osteitis condensans
437359	Osteochondritis dissecans
378160	Otorrhea
77356	Pathological dislocation of joint
375292	Perforation of tympanic membrane
253796	Pneumothorax
4295261	Postmenopausal state
4094448	Pregnancy test negative
198715	Premature menopause

199876	Prolapse of female genital organs
4295888	Prolapse of intestine
194997	Prostatitis
4245252	Raised prostate specific antigen
4345332	Spinal instability
4195698	Tenosynovitis
4339088	Testicular mass
80946	Tinea manus
4163280	Tinea of perianal region
133141	Tinea pedis
440268	Toxic effect of carbon monoxide
81930	Transient arthropathy
74719	Ulcer of foot
443593	Ulcer of thigh
4092565	Uterine prolapse
435131	Victim of neglect
261599	Vocal cord paralysis
132834	White piedra
435723	Wound seroma

Table 3. Negative control outcomes

7.4 Covariates

7.4.1 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
  - Age group (5-year bands)
  - Index year
  - Race

- Conditions
  - Any time prior
  - 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
- Measurement
  - In prior 30d
  - In prior 365d
  - Range Group in prior 365d
- Observation
  - In prior 365d
- Risk scores
  - Charlson comorbidity index
- Visit count
  - In prior 365d

Specific covariates to be excluded from the propensity score model are labelled **concepts to exclude,** which composed of drug use of H_2RAs.

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.

7.4.2 Other variables

None

8 Data Analysis Plan

8.1 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 lag 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 H_2RAs other than the target drug, allowing for a maximum gap of 30 days between prescriptions.
- On-treatment with one-year lag period: Starting 365 days after treatment initiation, and stopping 1 year after treatment end or starting H_2RAs other than the target drug, allowing for a maximum gap of 30 days between prescriptions.

8.2 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

8.2.1 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.

8.2.2 Pooling effect estimates across databases

Random-effects 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.

8.3 Analyses to perform

The following comparative analyses will be performed:

- 6x2 comparisons: Pairwise comparison among six H_2RA users. Additionally, H_2RA users without gastric ulcer will be compared.
- 39 outcomes: 1 primary outcome + 18 secondary outcomes + 19 narrow outcomes requiring hospitalization with primary diagnosis of cancer + cancer mortality
- 4 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 20 outcomes

The total number of analyses is 8,928 (12 comparisons x 39 outcomes x 4 TAR x 4 statistical models + 12x6x20 interaction analyses) in each database (**Table 4**).

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.

Target	Comparator	Stratification	Outcomes	Time-at-risk	Statistical model	Subgroup analysis
Exposure to the ranitidine	H_2 Blocker exposure -Other H_2 blockers (roxatidine, famotidine, and lafutidine) -Cimetidine -Nizatidine -Roxatidine -Famotidine -Lafutidine	-Based on previous history of gastric ulcer	Primary outcome: Overall cancer except non-melanoma skin cancer Secondary outcome: - Overall cancer except thyroid cancer - Overall cancer - 16 subtypes of cancer - 19 additional outcomes requiring hospitalization - Cancer mortality	*Intent-to-treat *Intent-to-treat with one-year lag period *On-treatment *On-treatment with one-year lag period	* One-to-one PS matching *Variable ratio PS matching *PS stratification *Without matching	* 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

Table 4. Analyses to perform

8.4 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.

8.5 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.

8.6 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.

8.7 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 assess the feasibility of the study by identifying empirical equipoise

- Target and comparator cohorts are defined to stand in empirical equipoise, if the majority of patients in both carry preference scores between 0.3 and 0.7 and achieve sufficient balance if all after-adjustment baseline characteristics returned absolute standardized mean differences of less than 0.1[29]

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.

8.8 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.

9 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.

10 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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12 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