Non-Interventional Study Protocol
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Safety and effectiveness of apixaban compared to warfarin in NVAF patients at higher risk of bleeding

Statistical Analysis Plan
(SAP)

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable since this is the first version and no amendment

2. INTRODUCTION

Atrial fibrillation (AF) is characterized by a rapid, irregular heartbeat which can cause blood to pool in the atria and increase the risk of the formation of blood clots. AF affects 0.6% to 1.6% of the general population and up to 14% in cardiovascular clinics in Japan[1-3]. AF can be categorized into three main categories based on patient characteristics: lone atrial fibrillation – AF in the absence of overt cardiovascular disease or precipitating illness non-valvular AF (NVAF) – presence of AF without concurrent rheumatic mitral valve disease or history of mitral valve repair or prosthetic heart valve; and secondary AF-AF that occurs in the setting of acute myocardial infarction (MI), cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute pulmonary disease. Anticoagulation therapy is important to prevent thromboembolism in patients with NVAF. Warfarin, a vitamin K antagonist, is the first oral anticoagulant approved for the treatment and prevention of thromboembolism in Japan in 1962 and it had long been the only oral anticoagulant until the first non-vitamin K antagonist oral anticoagulants (NOACs), dabigatran, was introduced with approval for NVAF treatment in March 2011[4]. Apixaban was approved in December 2012 in Japan and demonstrated superiority compared to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality in patients with atrial fibrillation in Phase 3 clinical trial[5].

Although randomized control trials (RCTs) aimed at head-to-head comparison with placebo or a reference drug may provide evidence of safety and efficacy of treatments at the highest level, there are potential limitations derived from a limited number of pre-selected patients and strict patient eligibility criteria with regard to age, comorbidities, and concomitant medications. Accordingly, these studies may not accurately represent what happens when drugs are used in general clinical practice. Especially data for Japanese NVAF patients are limited due to limited number of Japanese patients recruited in the RCT. Also patients with higher risk from a safety perspective, for instance patients with active caner, are generally excluded from RCT and further limited data are existed.
Previously we have shown that bleeding risks as well as stroke/SE risks are less in real world clinical practice in Japan compared to warfarin[6-8], but there are still little data for Japanese NVAF patients who has higher bleeding risks such as components of HAS-BLED risk score factors, active cancer, uncontrolled hypertension etc. The objectives of this study is to compare the risk of incidence of

stroke and bleeding among NVAF patients with such higher bleeding risk(s) newly prescribed apixaban or warfarin using a nation-wide administrative claims database.

2.1. STUDY DESIGN

This is a retrospective observational study using data from Medical Data Vision Co. Ltd. (MDV Co. Ltd.) database (data set from 1 March, 2011 to 31 Jun, 2021). Among patients registered in the database, patients are selected based on the inclusion and exclusion criteria (see below).

Study measures include: (1) for safety evaluation: major bleeding (primary safety endpoint, defined as any bleeding requiring hospitalization for treatment); (2) for effectiveness evaluation: a composite of ischemic stroke, hemorrhagic stroke or SE (primary effectiveness endpoint).

The primary purpose of this study is to investigate the safety and effectiveness of apixaban compared to warfarin in patients who are prone to bleeding, with at least one known risk factor for bleeding.
The analyses will be conducted using the 3-step procedure shown below,

- First, all patients with NVAF who are newly diagnosed and initiated apixaban or warfarin will be extracted from the database. Among these patients, patients with at least one predetermined high bleeding risks will be extracted. *In this study, predetermined high bleeding risks are 1) patients with hypertension diagnosis, 2) patients with liver dysfunction, 3) patients with renal dysfunction diagnosis, 4) patients with a history of bleeding, 5) patients with hemorrhagic stroke, 6) patients with alcohol abuse, 7) patients with concomitamt used of antiplatelet drugs, 8) patients with chronic (continuously for longer than 90 days) concomitant use of Non-steroidal anti-inflammatory drug (NSAID), 9) highly elderly (> 80 years old) , 10) patients with refractory hypertension, 11) patients with a history of peptic ulcer diagnosis, 12) patients with active cancer, 13) patients with diabetes mellitus, 14) patients whose body weight is <40kg, 15) patients with polypharmacy (sea Section 5.4 for the definition).* Patients with at least one predetermined high bleeding risk factor will be divided into two cohorts, apixaban and warfarin cohorts, based on the first prescribed drug just after the NVAF diagnosis. Patient characteristics will be balanced by using an inverse probability of treatment weighting (IPTW) method to create balanced apixaban and balanced warfarin cohorts. Comparisons will be conducted by using these balanced warfarin and apixaban cohorts (Kaplan-meier curves, incidence rates per 1,000 person-year and hazard ratio with 95% confident intervals). The primary safety and effectiveness analyses are comparison of apixaban with warfarin in patients with at least one predetermined risk factor for bleeding.

- Second, after the first analysis, we will conduct separate interaction analysis of the treatment (apixaban vs. warfarin) and one of the 15 risk factors (e.g., hypertension yes vs no, etc) to see if treatment effects are consistent among patients with or without each specific factor
- Third, patients will be stratified by risk factors into 15 subgroups, and same IPTW analyses as described in the step 1 will be conducted only in the subgroups with adequate sample sizes.

The follow-up period is variable, and will begin on the next day of the index date and continue until the earliest of the following scenarios – occurrence of target outcome event (details available in Subsection 5)*; discontinuation of apixaban or warfarin; switching from apixaban or warfarin; withdrawal from the database.*

2.1.1. Study population

The study population will consist of adults with NVAF who are newly prescribed apixaban or warfarin with at least one high bleeding risk. Further information on patient selection and enrolment and follow-up time periods are available in Subsection 9.2 of the protocol.

2.1.2. Data source

The analysis will be based on administrative data from MDV Co. Ltd., a longitudinal database based on health insurance claims and medical records obtained from the hospitals in which the DPC payment system for utilization of both inpatient and outpatient hospital claims (percentage of inpatients is about 20%). The database provides claims data from 449 hospitals (as of Aug 2021) using the DPC system for medical service claims (26% of general hospitals in Japan is under the DPC system) including approximately 36.7 million patient data.

2.1.3. Treatment/cohort labels

For primary analysis,

- IPTW-balanced apixaban cohort: NVAF patients de novo diagnosis with NVAF and initiate apixaban and have at least one risk factor(s) of bleeding.
- IPTW-balanced warfarin cohort: NVAF patients de novo diagnosis with NVAF and initiate warfarin and have at least one risk factor(s) of bleeding.

Patients will be assigned to each cohort based on the first prescription of oral anticoagulants after the diagnosis of NVAF (warfarin or apixaban). If the 1st prescribed oral anticoagulants are not warfarin

nor apixaban, the patients will be excluded. Patient clinical and demographic characteristics will be balanced by using IPTW methods.

2.2. STUDY OBJECTIVES

2.2.1. The research questions:

1. *Are there any differences in the risk of major bleeding between apixaban and warfarin for patients with higher bleeding risk(s) in the general practice settings in Japan?*
2. *Are there any differences in the risk of stroke/systemic embolism(SE) between apixaban and warfarin for patients with higher bleeding risk(s) in the general practice settings in Japan?*

2.2.2. The primary objective of the study

To compare effectiveness (a composite risk of stroke/SE) and safety (major bleeding events) of warfarin and apixaban among NVAF patients with at least one bleeding risk (that is, patients at higher risk of bleeding)

2.2.3. The secondary objectives are

1. *To compare the risk of major gastrointestinal or intracranial bleeding between warfarin-initiators and apixaban-initiators in patients with at least one bleeding risk.*
2. *To compare the risk of ischemic stroke, hemorrhagic stroke or SE between warfarin-initiators and apixaban-initiators in patients with at least one bleeding risk.*

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2.2.4. Objectives of other exploratory analysis are

To explore the risk of major bleeding and stroke/SE in the specific populations at higher bleeding risk(s).

As shown above (see 2.1), after interaction analyses of the treatment and risk factors, patients will be stratified to subgroups by each of above mentioned 15 predetermined risk factors separately. Subgroups with adequate sample size will be selected for IPTW analyses.

In the previous feasibility analysis, we found that the numbers of patients with hemorrhagic stroke, alcohol abuse, chronic concomitant used of NSAIDs (for continuously > 90 days), and refractory hypertension were less than 2,000. Due to the insufficient statistical power, these subgroups could be eliminated from the further subgroup analysis. Again, the final decision will be based on the formal evaluation of the number of sample sizes N in those subgroups.

Candidates of exploratory subgroups listed based on the preliminary feasibility analysis

- *Exploratory analysis regarding hypertension*
- *Exploratory analysis regarding liver dysfunction.*
- *Exploratory analysis regarding renal impairment.*
- *Exploratory analysis regarding bleeding including intracranial hemorrhage*
- *Exploratory analysis regarding concomitant use of antiplatelet drug*
- *Exploratory analysis by age*
  - ✓ > 80 y
  - ✓ > 90 y
- *Exploratory analysis regarding peptic ulcer*
- *Exploratory analysis regarding active cancer*
- *Exploratory analysis regarding low body weight (<40kg)*
- *Exploratory analysis regarding diabetes mellitus*
- *Exploratory analysis regarding polypharmacy (≥6 medicines)*

3. HYPOTHESES AND DECISION RULES

3.1. STATISTICAL HYPOTHESES

This study includes specific hypotheses to be tested. The null hypothesis for each objective is as follows:

Null: The risks of each of the following endpoints do not differ between NVAF patients treated with warfarin and patients treated with apixaban even if the patients have at least one bleeding risk.

- Major Bleeding
- A composite of stroke/SE

3.2. STATISTICAL DECISION RULES

For primary safety and effectiveness analyses, all statistical tests will be performed at p=0.05 (two-sided) with no adjustment for multiplicity. Since we will conduct various multiple subgroup analyses, which lead to the "Multiple Testing Problem". Here these subgroup analyses will be conducted with an exploratory purpose and we do not plan to conclude anything from the results here. Therefore, we will not adjust the p values and still the use p<0.05 to indicate the statistical significance.

4. ANALYSIS SETS/POPULATIONS

4.1. FULL ANALYSIS SET

This study uses data from the MDV database, which includes the data used for both inpatient and outpatient insurance claims by hospitals according to the Diagnosis Procedure Combination (DPC) procedure.

The study population will consist of adults with NVAF who are newly prescribed apixaban or warfarin. Follow-up time period starts from the next day of the index date, and ends depending on following outcomes which observed first.

4.1.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. *Patients with diagnosis with NVAF anytime in the baseline period or on the index date,*
2. *The first prescribed anticoagulant is apixaban or warfarin after the index date.*
3. *No use of the any oral anticoagulants (OACs) during the baseline period (the 180 days before the index date)*
4. *Age of 18 years or older on the index date.*

4.1.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. *Having a diagnosis of valvular atrial fibrillation, post-operative atrial fibrillation, rheumatic atrial fibrillation or mechanical-valvular atrial fibrillation during the baseline and post-index period*
2. *Having a procedure of prosthetic heart valve during the baseline period*
3. *Having a cardiac surgery procedure record during the baseline period*
4. *Having a diagnosis of venous thromboembolism during the baseline period*
5. *Having a hemodialysis during the baseline period*
6. *Female patients with pregnancy during the baseline and follow-up period*
7. *Patients prescribed apixaban other than approved daily dose (<5 mg or >10 mg)*
8. *Patients prescribed OACs during baseline period*

4.1.3. Definitions

4.1.3.1. Follow-up period

Follow-up time period starts from the next day of the index date, and ends depending on following outcomes which observed first.

1. *Major bleeding when the target outcome for the analysis is major bleeding.*
2. *Composite of (ischemic or hemorrhagic) stroke and SE when the target outcome for the analysis is the composite endpoint.*
3. *Discontinuation of apixaban or warfarin: The index treatment will be considered to be "discontinued" if apixaban or warfarin is not prescribed within 45 days after prescription refill date (calculated from the last refill date plus days of supply) of apixaban or warfarin, even though the patient has >1 medical encounter records after more than 45 days following the prescription refill date. The supposed prescription refill date is regarded as the last day of the follow-up for discontinued patients.*
4. *Switching from apixaban or warfarin: The index treatment is regarded as "switched" if the OAC is prescribed within 45 days after prescription refill date of apixaban or warfarin when the patient has 1> medical encounter records after more than 45 days following the prescription refill date. The switched day is regarded as the last day of the follow-up for the switched patients.*
5. *Withdrawal from the database: The patients are regarded as "withdrawal" from the database if apixaban or warfarin is not prescribed within 45 days after prescription refill date of the apixaban or warfarin and there is no data of the patient on the database after prescription refill date. The last medical encounter is regard as the last day of the follow-up for patients withdrawn from the database.*
6. *An elapse of 2 years from the index date without any of the event above.*

4.1.3.2. Index date

The date when patients initiated warfarin or apixaban

4.2. SAFETY ANALYSIS SET

Safety-related events other than bleeding will not be collected for this analysis. As mentioned above, bleeding will be investigated as safety-related primary endpoints. However, other adverse events,

serious AE or non-serious AE will not be collected in this analysis because the dataset provided by MDV will not contain the AE-related information.

4.3. OTHER ANALYSIS SET

None

4.4. SUBGROUPS

Following subgroups will be created and exploratory analyses for primary endpoints (major bleeding or stroke/SE) will be performed.

Variable	categories
Hypertension diagnosis	Yes or No
Liver dysfunction diagnosis	Yes or No
Renal impairment diagnosis	Yes or No
Bleeding diagnosis including intracranial hemorrhage	Yes or No
Treated with antiplatelet drug (>28d)	Yes or No
Age	>80 years >90years
Peptic ulcer diagnosis	Yes or No
Cancer diagnosis	Yes or No
Low body weight	<40 kg
Diabetes mellitus diagnosis	Yes or No
Polypharmacy	≧6 concomitant drugs

5. ENDPOINTS AND COVARIATES

5.1. EFFICACY/EFFECTIVENESS ENDPOINT(S)

Variable	Role	Operational definition
Stroke/SE (composite) event after index date	Outcome (primary endpoint)	Operational definition of Stroke and SE will follow the operational definition of Stroke event after index date and SE event after index date. Time to events will be defined as the number of days from the index date to the occurrence of the first stroke or SE.
Ischemic stroke event after index date	Outcome (secondary endpoint)	Ischemic stroke after index date not including the index date will be identified using hospital claims which had an ischemic stroke diagnosis code as the first listed ICD-10 diagnosis code (Appendix, 10.3.3). An event occurrence of ischemic stroke is defined as a case that “01: Disease name which input the most medical resources”, “02:Sub-disease name”, “11: Main disease name”, “21: Disease name behind hospitalization”, or “31: Disease name which input the second most medical resources” in DPC database. Time to ischemic

Variable	Role	Operational definition
		stroke will be defined as the number of days from the index date to the occurrence of the first ischemic stroke.
Hemorrhagic stroke event after index date	Outcome (secondary endpoint)	Hemorrhagic stroke after index date not including the index date will be identified using hospital claims which had a hemorrhagic stroke diagnosis code as the first listed ICD-10 diagnosis code (Appendix, 10.3.3). An event occurrence of hemorrhagic stroke is defined as a case that "01: Disease name which input the most medical resources", "02:Sub-disease name", "11: Main disease name", "21: Disease name behind hospitalization", or "31: Disease name which input the second most medical resources" in DPC database. Time to hemorrhagic stroke will be defined as the number of days from the index date to the occurrence of the first hemorrhagic stroke.
SE event after index date	Outcome (secondary endpoint)	SE after index date not including the index date will be identified using hospital claims which had a SE diagnosis code as the first listed ICD-10 diagnosis code (Appendix, 10.3.3). An event occurrence of SE is defined as a case that "01: Disease name which input the most medical resources", "02:Sub-disease name", "11: Main disease name", "21: Disease name behind hospitalization", or "31: Disease name which input the second most medical resources" in DPC database. Time to SE will be defined as the number of days from the index date to the occurrence of the first SE event.

5.2. SAFETY ENDPOINTS

Variable	Role	Operational definition
Major bleeding event after index date	Outcome (primary endpoint)	Major bleeding after index date will be identified using hospital claims which had a bleeding diagnosis code as the first listed ICD-10 or disease code (Appendix 10.3.5). An event occurrence of major bleeding is defined as a case that "21: Disease name behind hospitalization" in DPC database. Time-to-major bleeding will be defined as the number of days from the index date to the occurrence of the first major bleeding event.
Major ICH bleeding event after index date	Outcome (secondary endpoint)	Major ICH bleeding after index date will be identified using hospital claims which had an ICH bleeding diagnosis code as the first listed ICD-10 or disease code (Appendix, 10.3.4). An event occurrence of major bleeding is defined as a case that "21: Disease name behind hospitalization" in DPC database. Time-to-major ICH bleeding will be defined as the number of days from the index date to the occurrence of the first major ICH bleeding event.
Major GI bleeding event after index date	Outcome (secondary endpoint)	Any GI bleeding after index date will be identified using hospital claims which had a GI bleeding diagnosis code as the first listed ICD-10 or disease code (Appendix, 10.3.4). Time-to-any GI bleeding will be defined as the number of days from the index date to the occurrence of the first any GI bleeding event.

5.3. OTHER ENDPOINTS

None

5.4. COVARIATES

Demographic and clinical characteristics are collected during the baseline period, at the index date or during follow-up period.

Variable	Role	Data source(s)	Operational definition
Sex Category	*Baseline characteristic*	*Index date*	Dichotomous variable equals 1 if sex is male and 2 if female
Age	*Baseline characteristic*	*Index date*	Age (in years) at the index date
Age (> 80y, >90 y)	*Sub-group identifier*	*Index date*	Age (in years) at the index date
Body weight	*Baseline characteristic*	*Baseline period*	≥ 60 kg or < 60 kg
eGFR (continuous)	*Baseline characteristic*	*Baseline period*	Value in the baseline If a patient has multiple eGFR values, the values closest to the index date will be adopted If a patient does not have eGFR values, but has serum creatinine values, an eGFR value is

Variable	Role	Data source(s)	Operational definition
			calculated from a serum creatinine value using fomulas.
eGFR (categorical)	*Baseline characteristic*	*Baseline period*	≥ 50 ml/min or < 50 ml/min If a patient does not have eGFR values, but has serum creatinine values, an eGFR value is calculated from a serum creatinine value using fomulas.
Serum creatinine (continuous)	*Baseline characteristic*	*Baseline period*	Value in the baseline If a patient has multiple eGFR values, the values closest to the index date will be adopted If a patient does not have serum creatinine values but has eGFR values, a serum creatinine value is calculated from eGFR value using fomulas
Serum creatinine (categorical)	*Baseline characteristic*	*Baseline period*	≥ 1.5mg/mL or < 1.5 mg/mL If a patient does not have serum creatinine values but has eGFR values, a serum creatinine value is calculated from eGFR value using fomulas
CHADS2	*Baseline characteristic*	*Baseline period*	CHADS2 score will be calculated based on age and the presence of congestive heart failure, hypertension, diabetes, and stroke or TIA.
CHA2DS2-VASc	*Baseline characteristic*	*Baseline period*	Score calculated by appointing 1 point each for congestive heart failure/left ventricle dysfunction, hypertension, diabetes, vascular disease (prior MI, peripheral arterial disease, or aortic plaque), age between 65-74, female gender; and 2 points each for age >75 years and prior stroke, TIA, or thromboembolism.
Heart failure diagnosis	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for heart failure ICD-10 or disease codes during the baseline period.
Coronary heart disease diagnosis	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for coronary heart disease ICD-10 or disease codes during the baseline period.
Peripheral arterial disorder diagnosis	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for peripheral arterial disorder ICD-10 or disease codes during the baseline period.
Myocardial infarction diagnosis	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for myocardial infarction ICD-10 or disease codes during the baseline period.
Hyperthyroidism or thyrotoxicosis	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for hyperthyroidism ICD-10 or disease codes during the baseline period.
Stroke, TIA or SE diagnosis	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for Stroke, TIA or systemic embolism ICD-10 or disease codes during the baseline period.
Renal dysfunction diagnosis	*Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for renal dysfunction ICD-10 or disease codes during the baseline period.
Liver dysfunction diagnosis	*Baseline characteristic* *Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for liver dysfunction ICD-10 or disease codes during the baseline period.
Bleeding diagnosis	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for bleeding ICD-10 or disease codes during the baseline period.

Variable	Role	Data source(s)	Operational definition
Hypertension diagnosis	*Baseline characteristic Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for hypertension ICD-10 or disease codes during the baseline period.
Refractory hypertension diagnosis	*Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are prescriptions of ATC codes or receipt codes for all of the following 4 drugs during the baseline period; calcium channel blocker, ACE inhibitor/ARB, thiazide diuretics and MR antagonist/a-blocker/b-blocker
Diabetes mellitus diagnosis	*Baseline characteristic Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for diabetes mellitus ICD-10 or disease codes during the baseline period.
Cancer diagnosis	*Baseline characteristic Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for diabetes mellitus ICD-10 or disease codes during the baseline period.
Treated with antiplatelet drug	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 prescriptions of antiplatelet drug ATC or receipt codes during the baseline period.
Treated with antiplatelet drug (>28 d)	*Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 prescriptions of antiplatelet drug ATC or receipt codes during the baseline period.
Treated with NSAIDs	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 prescriptions of NSAIDs ATC or receipt codes during the baseline period.
Treated with NSAIDs (>90 d)	*Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 prescriptions of NSAIDs ATC or receipt codes during the baseline period.
Treated with gastric secretion inhibitor	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 prescriptions of gastric secretion inhibitor drug ATC or receipt codes during the baseline period.
Treated with statin-based drug	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 prescriptions of statin-based drug ATC or receipt codes during the baseline period.
Treated with anti-hypertensives	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 prescriptions of anti-hypertensive ATC or receipt codes during the baseline period.
Treated with anti-arrhythmics	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 prescriptions of anti-arrythmics ATC or receipt codes during the baseline period.
Treated with beta-blockers	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 prescriptions of beta-blockers ATC or receipt codes during the baseline period.
Treated with heparins	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 prescriptions of heparins ATC or receipt codes during the baseline period.
Cardioversion	*Baseline characteristic*	*Baseline period*	Dichotomous variable equals 1 if there is ≥1 operation of cardioversion receipt codes during the baseline period.
Alcohol abuse	*Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for Alcohol abuse ICD-10 or disease codes during the baseline period.
Bleeding diagnosis	*Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for major or any bleeding ICD-10 or disease codes during the baseline period

Variable	Role	Data source(s)	Operational definition
Peptic ulcer diagnosis	*Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for peptic ulcer ICD-10 or disease codes during the baseline period
Hemorrhagic stroke diagnosis	*Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are ≥1 diagnoses for hemorrhagic stroke ICD-10 or disease codes during the baseline period
Low body weight (<40 kg)	*Sub-group identifier*	*Baseline period*	Body weight during baseline period
Polypharmacy	*Sub-group identifier*	*Baseline period*	Dichotomous variable equals 1 if there are ≥6 prescriptions of oral drug ATC or receipt codes during the baseline period.
PT-INR (Prothrombin time-international normalized ratio)	*potential confounder*	*Baseline period*	Continuous variable. * Only available for patients treated with warfarin
Physician specialty	*potential confounder*	*Index date*	Dichotomous variable equals 1 if a physician specialty on the index date is categorized into a cardiac specialty and 0 if others. Following specialties will be categorized as the cardiac specialty: cardiology stroke, cardiovascular surgery, pediatric cardiology, neurosurgery, cardiovascular medicine, and neurology. If there are ≥1 specialties but including the cardiac specialty, the physician specialty will be regarded as the cardiac specialty.
Hospital size (<500 beds or not)	*potential confounder*	*Index date*	Dichotomous variable equals 1 if hospital size on the index date is <500 beds and 0 if ≥500 beds.
Hospitalization status on index date	*potential confounder*	*Index date*	Dichotomous variable equals 1 if hospitalization status is inpatient and 0 if outpatient.
INR (warfarin cohort)	*Baseline characteristic*	*Baseline period*	Continuous variable. * Only available for patients treated with warfarin
Apixaban dose (2.5 g BID)	*Baseline characteristic*	*Baseline period*	2.5 mg BID or 5mg BID * Only available for patients treated with apixaban

6. HANDLING OF MISSING VALUES

Patients without all required data will be excluded from the analysis.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1. STATISTICAL METHODS

7.1.1. Calculation of Propensity Score

In this study, balanced cohorts (apixaban vs. warfarin) will be created by an IPTW method. Propensity scores will be estimated by unconditional logistic regression analyses that incorporate potential predictors of therapy as independent variables in the regression and cohort status as the outcome. Using calculated propensity score an IPTW method will be applied to balance the warfarin and apixaban cohorts, which will be used for the comparisons of all endpoints (sections 5.1 and 5.2). The following covariates will be included in the logistic regression for calculation of propensity score:

- age on index date

- gender
- CHADS2 score in baseline
- CHA2DS2-VASc score in baseline
- heart failure diagnosis in baseline
- coronary heart disease diagnosis in baseline
- peripheral arterial disorder diagnosis in baseline
- myocardial infarction diagnosis in baseline
- hyperthyroidism or thyrotoxicosis in baseline
- TIA diagnosis in baseline
- stroke or SE diagnosis in baseline
- renal dysfunction diagnosis in baseline
- liver dysfunction diagnosis in baseline
- bleeding diagnosis in baseline
- hypertension diagnosis in baseline
- diabetes mellitus diagnosis in baseline
- treated with antiplatelet drug in baseline
- treated with NSAIDs in baseline
- treated with gastric secretion inhibitor in baseline
- treated with statin-based drug in baseline
- treated with anti-hypertensives in baseline
- treated with anti-arrhythmics in baseline
- treated with beta-blockers in baseline
- treated with heparins in baseline
- cardioversion in baseline

The operational definitions for the above covariates are shown in the Section 5.4.

7.1.2. Inverse probability treatment weighting (IPTW)

IPTW with stabilized weights will be used to balance patient characteristics between two groups using propensity score calculated by using a multivariable logistic model as mentioned above (see above 7.1.2.1). However, if a treated patient has a very low propensity score, a very large weight can be created, which leads to increased variability of the estimated treatment effect. In order to address this, the weights can be stabilized by using a formula shown below, by multiplying the treatment and control weights by a constant, equal to the expected value of being in the treatment or comparison cohorts, respectively.

$W_i = \frac{Z}{PS_i} + \frac{1-Z}{1-PS_i}$, z: probability of treatment without considering covariates

The distribution of the stabilized weight will be reviewed. If there are extreme outliers, the large weights could be set to a less extreme value (e.g. recoding all weights that are outside 5th and 95th percentile). If needed, truncation can be done after stabilizing the weights. After the weights are applied, the balance of the baseline covariates will be assessed. First, the means and proportions of baseline variables are compared. The standardized difference compares the difference in means in units of the standard deviation. If the standardized difference is less than 10%, the covariates are considered balanced.

7.1.3. Analysis of Continuous Data

Continuous data will be summarized using descriptive statistics, including the mean, standard deviation, median, first and third quartiles, and minimum and maximum. Baseline characteristics (before and after IPTW weighting) will be compared between patients treated with warfarin and patients treated with apixaban, using the standardized difference.

7.1.4. Analysis of Categorical Data

Counts and percentages will be provided for dichotomous and polychotomous variables of baseline patient characteristics when performing descriptive analysis. Standardized difference will be calculated for each variable (before and after IPTW weighting). For calculation of standardized differences, categorical variables will be converted into a set of binary indicators, one for each non-reference level of the variable.

7.1.5. Kaplan-Meier Method

For each endpoint, Kaplan-Meier curves will be plotted for the time from the index date to first event by index OAC treatment in each of the propensity-score-weighted cohorts. The log-rank test will be used for comparison between two curves.

7.1.6. Cox proportional hazards model

Cox proportional hazards model will be used to compare endpoints (time-to-endpoint) in the propensity-score-weighted cohorts with robust sandwich estimates to account for the potential clustering within weighted sets. The Cox proportional hazards model will include only index OAC treatment as the independent variable if patient characteristics are balanced between groups... If not balanced, the unbalanced variable will be also included to the model in addition to the index OAC

treatment. The hazard ratios with corresponding 95% confidence intervals and p-values will be reported.

7.1.7. Exploratory subgroup analysis

For subgroup analyses, hazard ratios with 95% confident intervals (95% CI) will be calculated using the Cox proportional hazards model as in primary analysis. As mentioned above, subgroup analyses are exploratory, no definitive conclusions from these subgroup analyses would be drawn.

7.1.8. Sensitivity analysis

For the primary effectiveness and safety analysis, E-values[10] (evidence for causality) will be calculated based on calculated hazard ratios and 95% confident intervals to assess the extent of unmeasured confounding. The E-value is defined as the minimum strength of association for an unmeasured confounder with both the treatment and the outcome to explain away the observed significant (if any) treatment-outcome association.

7.1.9. Power calculation

Incidence rates of stroke/SE and major bleeding in the primary analysis population here (that is, de novo NVAF patients initiating an anticoagulant therapy with warfarin or apixaban who have at least one bleeding risk factor) have not been investigated yet and hazard ratios of stroke/SE and major bleeding in apixaban users relative to warfarin users also have not been investigated yet. Therefore, we estimated the needed sample size to achieve adequate statistical power (e.g., 0.80) based on the major previous RCT and RWE conducted so far.

Stroke/SE

Study	Subgroup	HR	Incidence rate (%/year)	
			Warfarin	Apixaban
ARISTOTLE	-	0.79	1.60	1.27
	≥ 75 years		2.2	1.6
	≤ 60kg		3.2	2.0
	Prior stroke or TIA		3.2	2.5
	Diabetes		1.9	1.4
	Severe to moderate renal dysfunction		2.7	2.1
	Aspirin		1.9	1.3
CER3		0.66	2.87	1.55

	≥ 80 years		4.04	2.06
	< 60 kg		3.47	2.45
	Severe to moderate renal dysfunction		2.50	1.33
	Anti-platelet		3.61	1.93

Major bleeding

Study	Subgroup	HR	Incidence rate (%/year)	
			Warfarin	Apixaban
ARISTOTLE	-	0.69	3.09	2.13
	≥ 75 years		5.2	3.3
	≤ 60kg		3.0	2.1
	Prior stroke or TIA		3.9	2.8
	Diabetes		3.1	3.0
	Severe to moderate renal dysfunction		6.4	3.2
	Aspirin		3.7	2.7
CER3		0.74	2.81	1.69
	≥ 80 years		3.94	2.35
	< 60 kg		3.67	2.61
	Severe to moderate renal dysfunction		3.32	2.21
	Anti-platelets		3.07	1.91

As shown in Tables above, absolute incidence rates of stroke/SE and major bleeding could be higher in patients with (a) risk factor(s) associated with bleeding. However, the ARISTOTLE study has revealed that P-value for interaction was mostly >0.05 and relative risk (HR) may not be changed in the specific subgroups compared to the entire cohorts

Based on the incidence rates and HRs shown above, sample size required for adequate statistical power (e.g., power=0.8) was estimated as follows,

Sample size calculation

	Assumption: Values used for calculation	**Calculated results**
For major bleeding		
Type I error rate	0.05	
Type II error rate	0.2	
Hazard ratio*	0.7	
N ratio in apixaban and warfarin cohorts	1:1	
Event rate for warfarin	3.77%/year**	
Event rate for apixaban	2.50%/year**	
Total events needed		246***
Estimated number of patients		**7,846**

For Stroke/SE		
Type I error rate	0.05	
Type II error rate	0.2	
Hazard ratio*	0.7	
N ratio in apixaban and warfarin cohorts	1:1	
Event rate for warfarin	2.77%/year**	
Event rate for apixaban	1.79%/year**	
Total events needed		246***
Estimated number of patients		**10,789**

* estimated from ARISTOTLE and CER studies

** averages of incidence rates shown in the Tables above

*** Calculated using an on-line calculator (Sample Size Survival Analysis (quesgen.com))

In the preliminary check to examine the feasibility of this study, we have obtained that the number of apixaban users and of warfarin users who were eligible for this study were both more than 10,000 patients. Considering that IPTW will be applied to balance the patient characteristics in this study, the number of patients eligible for this study would be adequate for the primary analysis.

7.2. STATISTICAL ANALYSIS

See sections 2~5.

7.2.1. Safety Analysis

See sections 2~5.

7.2.2. Analysis of Efficacy Analysis

See sections 2~5.

7.2.3. Summary of Analyses

Efficacy and safety analyses excluding descriptive summaries will be shown in the following table.

1) Unbalanced cohorts

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
The incidence rates of stroke/SE and major bleeding per 1,000 person-years	**Unbalanced patients** With high bleeding risk cohort vs without high bleeding risk cohort	NA	NA	1000 person-years (no statistical comparison)	Refer to 5.4	No imputation
Interaction analysis	**Unbalanced patients** With high bleeding risk cohort vs without high bleeding risk cohort	NA	NA	Cox proportional hazards model	With/without high bleeding risk, Warfarin/apixaban	No imputation

2) Balanced cohorts

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
Major bleeding	**Balanced patients** Warfarin vs. apixaban Cohorts	safety, primary	Whole cohort, primary analysis	Cox proportional hazards model	Refer to 5.4	No imputation
Major bleeding	**Balanced patients** Warfarin vs. apixaban Cohorts	safety, primary	Whole cohort, primary analysis	Plot of Kaplan-Meier Estimates		No imputation
Major bleeding	**Balanced patients** Warfarin vs. apixaban Cohorts	safety, primary	Whole cohort, primary analysis	Incidence rate (per 1000 patient-year)		No imputation
Major intracranial bleeding	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety Secondary	Whole cohort, secondary analysis	Cox proportional hazards model	Refer to 5.4	No imputation
Major intracranial bleeding	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety Secondary	Whole cohort, secondary analysis	Plot of Kaplan-Meier Estimates		No imputation
Major intracranial bleeding	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety Secondary	Whole cohort, secondary analysis	Incidence rate (per 1000 patient-year)		No imputation
Major GI bleeding	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety Secondary	Whole cohort, secondary analysis	Cox proportional hazards model	Refer to 5.4	No imputation
Major GI bleeding	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety Secondary	Whole cohort, secondary analysis	Plot of Kaplan-Meier Estimates		No imputation
Major GI bleeding	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety Secondary	Whole cohort, secondary analysis	Incidence rate (per 1000 patient-year)		No imputation

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
Stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Effectiveness Primary	Whole cohort, secondary analysis	Cox proportional hazards model	Refer to 5.4	No imputation
Stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Effectiveness Primary	Whole cohort, secondary analysis	Plot of Kaplan-Meier Estimates		No imputation
Stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Effectiveness Primary	Whole cohort, secondary analysis	Incidence rate (per 1000 patient-year)		No imputation
Stroke	**Balanced patients** Warfarin vs. apixaban Cohorts	Effectiveness Secondary	Whole cohort, secondary analysis	Cox proportional hazards model	Refer to 5.4	No imputation
Stroke	**Balanced patients** Warfarin vs. apixaban Cohorts	Effectiveness Secondary	Whole cohort, secondary analysis	Plot of Kaplan-Meier Estimates		No imputation
Stroke	**Balanced patients** Warfarin vs. apixaban Cohorts	Effectiveness Secondary	Whole cohort, secondary analysis	Incidence rate (per 1000 patient-year)		No imputation
SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Effectiveness Secondary	Whole cohort, secondary analysis	Cox proportional hazards model	Refer to 5.4	No imputation
SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Effectiveness Secondary	Whole cohort, secondary analysis	Plot of Kaplan-Meier Estimates		No imputation
SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Effectiveness Secondary	Whole cohort, secondary analysis	Incidence rate (per 1000 patient-year)		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Hypertension subgroup, exploratory analysis	1000 person-years	Refer to 5.4	No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Hypertension subgroup, exploratory analysis	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Hypertension subgroup, exploratory analysis	Plot of Kaplan-Meier Estimates		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Liver dysfunction subgroup, exprolatory analysis	1000 person-years	Refer to 5.4	No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Liver dysfunction subgroup, exprolatory analysis	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Liver dysfunction subgroup, exprolatory analysis	Plot of Kaplan-Meier Estimates		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Renal impairment, exploratory analysis	1000 person-years	Refer to 5.4	No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Renal impairment, exploratory analysis	Incidence rate (per 100 patient-year)		No imputation

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
				(no statistical comparison)		
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Renal impairment Renal impairment, exprolatory analysis	Plot of Kaplan-Meier Estimates		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Bleeding history subgroup, exploratory analysis	1000 person-years	Refer to 5.4	No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Bleeding history subgroup, exploratory analysis	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Bleeding history subgroup, exploratory analysis	Plot of Kaplan-Meier Estimates		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Concomitant use of antiplatelet drug, exploratory analysis	1000 person-years	Refer to 5.4	No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Concomitant use of antiplatelet drug, exploratory analysis	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Concomitant use of antiplatelet drug, exploratory analysis	Plot of Kaplan-Meier Estimates		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Age ✓ >80 y ✓ >90 y exploratory analysis	1000 person-years	Refer to 5.4	No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Age ✓ >80 y ✓ >90 y exploratory analysis	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Age ✓ >80 y ✓ >90 y exploratory analysis	Plot of Kaplan-Meier Estimates		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Peptic ulcer, exploratory analysis	1000 person-years	Refer to 5.4	No imputation

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Peptic ulcer, exploratory analysis	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Peptic ulcer, exploratory analysis	Plot of Kaplan-Meier Estimates		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Active cancer, exploratory analysis	1000 person-years	Refer to 5.4	No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Active cancer, exploratory analysis	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Active cancer, exploratory analysis	Plot of Kaplan-Meier Estimates		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Low body weight, exploratory analysis	1000 person-years	Refer to 5.4	No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Low body weight, exploratory analysis	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Low body weight, exploratory analysis	Plot of Kaplan-Meier Estimates		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Diabetes mellitus, exploratory analysis	1000 person-years	Refer to 5.4	No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Diabetes mellitus, exploratory analysis	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Diabetes mellitus, exploratory analysis	Plot of Kaplan-Meier Estimates		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Polypharmacy, exploratory analysis	1000 person-years	Refer to 5.4	No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Polypharmacy, exploratory analysis	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Safety: Major Bleeding Effectiveness: stroke/SE	**Balanced patients** Warfarin vs. apixaban Cohorts	Safety/effectiveness Exploratory	Polypharmacy, exploratory analysis	Plot of Kaplan-Meier Estimates		No imputation

8. LIST OF TABLES AND TABLE SHELLS

9. REFERENCES

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10. APPENDICES

10.1. APPENDIX 1: DATA DERIVATION DETAILS

Not applicable

10.2. APPENDIX 2: ADDITIONAL STATISTICAL METHODOLOGY DETAILS

Not applicable

10.3. APPENDIX 3: DIAGNOSIS AND PROCEDURE CODES USED IN THE STUDY

10.3.1. List of diagnosis code

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
Atrial fibrillation	I48	
Post-operative atrial fibrillation	8847772	Standard disease code
Valvular atrial fibrillation	8846941	Standard disease code
Rheumatic atrial fibrillation	I05	
	I06	
	I07	
	I08	
	I09	
Mechanical-valvular atrial fibrillation	T820	
Hyperthyroidism or thyrotoxicosis	E05	
Heart failure	I110	
	I500	
	I501	Exclude cardiac asthma
	I509	
Hypertension	H208	Include only hypertensive iridocyclitis
	H350	Include only hypertensive retinopathy and hypertensive neuroretinopathy
	I10	
	I110	
	I119	
	I120	
	I129	Include only hypertensive renal disease, hypertensive nephropathy and hypertensive nephrosclerosis
	I139	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	I150	
	I151	
	I152	
	I158	
	I159	
	I619	Include only hypertensive intracerebral hemorrhage
	I674	
Diabetes	E10	
	E11	
	E12	
	E13	
	E14	
Hemorrhage stroke	I60	
	I61	
	I62	Exclude non-traumatic extradural haemorrhage
Ischemic stroke	I63	
	3489032	standard disease code
	4371003	
	4379014	
	3448002	
	3448028	
	3489029	
	3489035	
	4379006	
TIA	H340	
	G450	
	G451	
	G458	
	G459	
Systemic embolism	I740	Include only abdominal aortic embolism
	I741	Include only aortic embolism
	I742	Include only acute arterial occlusive disease of arteries of upper extremities
	I743	Include only femoral arterial occlusion and acute arterial occlusive disease of arteries of lower extremities
	I744	
	I745	Include only iliac artery embolism

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	I748	Include only hepatic artery embolism
	I749	Include only thromboembolism, embolic infarction, aortic embolism
Peripheral vascular disorder	I702	Include only atherosclerosis and arteriosclerosis obliterans
	I709	
	I731	Include only Buerger's disease
	I739	Exclude peripheral circulatory failure, cerebrovascular spasm, and angiospasm pf the extremities
	I742	
	I743	
	I745	
	I748	Include only subclavian artery stenosis
Aortic plaque	4400011	Standard disease code
	8837393	Standard disease code
Coronary artery disease	I200	
	I201	
	I208	
	I209	
	I210	
	I211	
	I212	
	I213	
	I214	
	I240	
	I241	
	I248	
	I251	
	I252	Exclude calcification of coronary artery
	I255	
	I258	Exclude coronary arteritis
	I259	
Myocardial infarction	I200	Exclude intermediate angina syndrome, preinfarction syndrome, initial arbeits angina, intermediate coronary syndrome
	I210	
	I211	
	I212	
	I214	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	I240	
	I241	Exclude Dressler syndrome
Renal impairment	I120	
	I129	
	I139	
	N003	
	N009	
	N032	
	N033	
	N039	
	N040	
	N044	
	N049	
	N052	
	N055	
	N058	
	N059	
	N170	
	N171	
	N172	
	N178	
	N179	
	N189	
	N19	Exclude renal anemia, afunctional kidney, and alimentary proteinuria
Liver dysfunction	B150	
	B159	
	B162	
	B169	
	B171	
	B172	
	B178	
	B179	
	B181	
	B182	
	B189	
	B190	
	B199	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	C220	
	K700	
	K701	
	K703	
	K709	
	K716	
	K720	
	K721	
	K729	
	K730	
	K732	
	K738	
	K739	
	K740	
	K741	
	K743	
	K744	
	K745	
	K746	
	K750	
	K751	
	K754	
	K759	
	K760	
	K761	
	K762	
	K763	
	K766	
	K767	
	K768	
	K769	
Cancer	C00	
	C01	
	C02	
	C03	
	C04	
	C05	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	C06	
	C07	
	C08	
	C09	
	C10	
	C11	
	C12	
	C13	
	C14	
	C15	
	C16	
	C17	
	C18	
	C19	
	C20	
	C21	
	C22	
	C23	
	C24	
	C25	
	C26	
	C30	
	C31	
	C32	
	C33	
	C34	
	C37	
	C38	
	C40	
	C41	
	C43	
	C44	
	C45	
	C46	
	C47	
	C48	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	C49	
	C50	
	C51	
	C52	
	C53	
	C54	
	C55	
	C56	
	C57	
	C58	
	C60	
	C61	
	C62	
	C63	
	C64	
	C65	
	C66	
	C67	
	C68	
	C69	
	C70	
	C71	
	C72	
	C73	
	C74	
	C75	
	C76	
	C78	
	C79	
	C80	
	C81	
	C82	
	C83	
	C84	
	C85	
	C88	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	C90	
	C91	
	C92	
	C93	
	C94	
	C95	
	C96	
	C97	
	D00	
	D01	
	D02	
	D03	
	D04	
	D05	
	D06	
	D07	
	D09	
	D10	
	D11	
	D12	
	D13	
	D14	
	D15	
	D16	
	D17	
	D18	
	D19	
	D20	
	D21	
	D22	
	D23	
	D24	
	D25	
	D27	
	D28	
	D29	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	D30	
	D31	
	D32	
	D33	
	D34	
	D35	
	D36	
	D37	
	D38	
	D39	
	D40	
	D41	
	D42	
	D43	
	D44	
	D45	
	D46	
	D48	

10.3.2. List of procedure code

Procedure	Procedure Code
Cardiac surgery	150138210
	150138310
	150138410
	150138510
	150359210
	150138710
	150140510
	150140610
	150140710
	150139010
	150140810
	150318010
	150317810
	150318110
	150331450

Procedure	Procedure Code
	150331550
	150331950
	150332050
	150317910
	150318210
	150140010
	150139210
	150153910
	150374910
	150375010
	150375110
	150260350
	150284310
	150359310
	150263310
	150375210
	150375310
	150375410
	160107550
	150139810
	150139910
	150318310
	150145710
	150145810
	150145910
	150146010
	150318410
	150318510
	150302770
	150143010
	150143110
	150331650
	150332150
	150318710
	150319010
	150319310
	150318810
	150319110

Procedure	Procedure Code
	150319410
	150328750
	150328850
	150331750
	150331850
	150332250
	150332350
	150318910
	150319210
	150319510
	150318610
	150141010
	150279510
	150279610
	150141410
	150141610
	150369950
	150141710
	150359470
	150143610
	150260050
	150143710
	150143810
	150141510
	150375570
	150375670
	150375770
	150319610
	150292910
	150139310
	150140910
	150242550
	150244910
	150245010
	150359510
	150359610
	150381150
	150381250

Procedure	Procedure Code
	150381350
	150381450
	150150010
	150381550
	150275910
	150359710
	150359810
	150359910
	150381650
	150381750
	150381850
	150381950
	150150110
	150382050
	150245110
	150245210
	150375870
	150375970
	150376070
	150141210
	150301310
	150267850
	150319710
	150151810
	150376110
	150139110
	150319810
	150138810
	150151910
	150320010
	150346410
	150320110
	150147150
	150144110
	150320210
	150320310
	150142710
	150139410

Procedure	Procedure Code
	150320410
	150142910
	150320510
	150260150
	150346510
	150145110
	150145010
	150376210
	150376310
	150143250
	150143350
	150143450
	150143550
	150283250
	150283350
	150283450
	150283550
	150144910
	150139610
	150142410
	150141810
	150141910
	150320610
	150142050
	150142110
	150142210
	150142310
	150142810
	150144010
	150320710
	150144210
	150144550
	150147410
	150147510
	150320810
	150320910
	150144410
	150144650

Procedure	Procedure Code
	150144750
	150146510
	150146610
	150321010
	150321110
	150321210
	150376470
	150146910
	150146810
	150321310
	150142510
	150329810
	150145310
	150329910
	150139510
	150330010
	150147010
	150330110
	150376570
	150321410
	150321510
	150376670
	150147310
	150145650
	150141310
	150321810
	150321610
	150321910
	150146710
	150321710
	150330210
	150330310
	150376770
	150293010
	150330410
	150145510
	150302870
	150145410

Procedure	Procedure Code
	150322010
	150322110
	150144310
	150147250
	150346610
	150144810
	150253810
	150253910
	150275610
	150346710
	150262810
	150303310
	150267310
	150140110
	150140210
	150140410
	150346910
	150347010
	150303210
	150322210
	150275210
	150275310
	150336910
	150337010
	150360010
	150148010
	150148110
	150147610
	150147910
	150147770
	150147870
	150347170
	150275870
	150262910
	150275710
	150266110
	150382650
	150266210

Procedure	Procedure Code
	150382750
	150301810
	150382850
	150303410
	150303510
	150360110
	150360210
	150360310
	150360410
	150303610
	150303710
	150322410
	150322610
Ablation	150346710
	150262810
	150303310
	150346870
	150370050
Electrical defibrillation	140051410
	140010310
	140055010
	150275210
	150275310
	150336910
	150337010
	150370550
Heart valve prosthesis implantation surgery	150141410
	150141610
	150141710
	150359470
	150369950
	150331950
	150332050
	150332150
	150328850
	150332250
	150332350
	150141510

Procedure	Procedure Code
	150375570
	150375670
	150375770
	150244910
	150359510
	150381150
	150381250
	150359710
	150359810
	150381650
	150381750
	150283450

10.3.3. Effectiveness endpoints

Disease	ICD10 code	Standard disease code	Note
Hemorrhage stroke	I60		
	I61		
	I62		Exclude non-traumatic extradural haemorrhage
Ischemic stroke	I63		
		3489032	
		4371003	
		4379014	
		3448002	
		3448028	
		3489029	
		3489035	
		4379006	
TIA	H340		
	G450		
	G451		
	G458		
	G459		
Systemic embolism	I740		Include only abdominal aortic embolism
	I741		Include only aortic embolism
	I742		Include only acute arterial occlusive disease of arteries of upper extremities
	I743		Include only femoral arterial occlusion and acute arterial occlusive disease of arteries of lower extremities
	I744		
	I745		Include only iliac artery embolism
	I748		Include only hepatic artery embolism
	I749		Include only thromboembolism, embolic infarction, aortic embolism

Disease	ICD10 code	Standard disease code	Note
	I748		Include only subclavian artery stenosis

10.3.4. Safety endopoints

Disease	ICD10 code	Standard disease code	Note
Major bleeding			Refer to 10.3.5
Intracranial bleeding	I600		Subarachnoid haemorrhage from carotid siphon and bifurcation
	I601		Subarachnoid haemorrhage from middle cerebral artery
	I602		Subarachnoid haemorrhage from anterior communicating artery
	I603		Subarachnoid haemorrhage from posterior communicating artery
	I604		Subarachnoid haemorrhage from basilar artery
	I605		Subarachnoid haemorrhage from vertebral artery
	I606		Subarachnoid haemorrhage from other intracranial arteries
	I607		Subarachnoid haemorrhage from intracranial artery, unspecified
	I608		Other subarachnoid haemorrhage
	I609		Subarachnoid haemorrhage, unspecified
	I610		Intracerebral haemorrhage in hemisphere, subcortical
	I611		Intracerebral haemorrhage in hemisphere, cortical
	I613		Intracerebral haemorrhage in brain stem
	I614		Intracerebral haemorrhage in cerebellum
	I615		Intracerebral haemorrhage, intraventricular
	I616		Intracerebral haemorrhage, multiple localized
	I618		Other intracerebral haemorrhage
	I619		Intracerebral haemorrhage, unspecified
	I620		Subdural haemorrhage (acute)(nontraumatic)
	I621		Nontraumatic extradural haemorrhage
	I629		Intracranial haemorrhage (nontraumatic), unspecified
	I690		Sequelae of subarachnoid haemorrhage
	I691		Sequelae of intracerebral haemorrhage
	S064		Epidural haemorrhage
	S065		Traumatic subdural haemorrhage
	S066		Traumatic subarachnoid haemorrhage
	S068		Other intracranial injuries
GI bleeding	I850		Oesophageal varices with bleeding
	K226		Gastro-oesophageal laceration-haemorrhage syndrome
	K228		Other specified diseases of oesophagus
	K250		Acute with haemorrhage
	K252		Gastric ulcer, Acute with both haemorrhage and perforation
	K254		Gastric ulcer, Chronic or unspecified with haemorrhage
	K256		Gastric ulcer, Chronic or unspecified with both haemorrhage and perforation
	K260		Duodenal ulcer, Acute with haemorrhage

Disease	ICD10 code	Standard disease code	Note
	K262		Duodenal ulcer, Acute with both haemorrhage and perforation
	K264		Duodenal ulcer, Chronic or unspecified with haemorrhage
	K266		Duodenal ulcer, Chronic or unspecified with both haemorrhage and perforation
	K270		Acute duodenal tumor with haemorrhage
	K284		Gastrojejunal ulcer, Chronic or unspecified with haemorrhage
	K290		Acute haemorrhagic gastritis
	K625		Haemorrhage of anus and rectum
	K920		Haematemesis
	K921		Melaena
	K922		Gastrointestinal haemorrhage, unspecified

10.3.5. bleeding

Procedure for definition of "bleeding"
Step 1. To extract the following group A or group B from MDV data base.

Group A: ICD-10 name includes "出血 (bleeding)" or "血腫 (ecchymoma)"

Group B: Disease name includes "出血 (bleeding)" or "血腫 (ecchymoma)"

Step 2. To select disease names considered to be relevant to side effect of OAC individually from disease names excluded in Step 1.
Step 3. To exclude disease names which are not considered to be relevant to side effect of OAC from the disease names included in Step 1.

ICD-10	ICD10Name
A162	Tuberculosis of lung, without mention of bacteriological or histological confirmation
A165	Tuberculous pleurisy, without mention of bacteriological or histological confirmation
B303	Acute epidemic haemorrhagic conjunctivitis (enteroviral)
D500	Iron deficiency anaemia secondary to blood loss (chronic)
D62	Acute post haemorrhagic anaemia
D66	Hereditary factor VIII deficiency
D683	Haemorrhagic disorder due to circulating anticoagulants
D698	Other specified haemorrhagic conditions
D699	Haemorrhagic condition, unspecified
E078	Other specified disorders of thyroid
E274	Other and unspecified adrenocortical insufficiency
G361	Acute and subacute haemorrhagic leukoencephalitis [Hurst]
G951	Vascular myelopathies
G968	Other specified disorders of central nervous system
H052	Exophthalmic conditions
H113	Conjunctival haemorrhage

ICD-10	ICD10Name
H168	Other keratitis
H208	Other iridocyclitis
H210	Hyphaema
H313	Choroidal haemorrhage and rupture
H350	Background retinopathy and retinal vascular changes
H356	Retinal haemorrhage
H357	Separation of retinal layers
H405	Glaucoma secondary to other eye disorders
H431	Vitreous haemorrhage
H448	Other disorders of globe
H470	Disorders of optic nerve, not elsewhere classified
H603	Other infective otitis externa
H669	Otitis media, unspecified
H738	Other specified disorders of tympanic membrane
H922	Otorrhagia
I213	Acute transmural myocardial infarction of unspecified site
I230	Haemopericardium as current complication following acute myocardial infarction
I312	Haemopericardium, not elsewhere classified
I600	Subarachnoid haemorrhage from carotid siphon and bifurcation
I601	Subarachnoid haemorrhage from middle cerebral artery
I602	Subarachnoid haemorrhage from anterior communicating artery
I603	Subarachnoid haemorrhage from posterior communicating artery
I604	Subarachnoid haemorrhage from basilar artery
I605	Subarachnoid haemorrhage from vertebral artery
I606	Subarachnoid haemorrhage from other intracranial arteries
I607	Subarachnoid haemorrhage from intracranial artery, unspecified
I608	Other subarachnoid haemorrhage
I609	Subarachnoid haemorrhage, unspecified
I610	Intracerebral haemorrhage in hemisphere, subcortical
I611	Intracerebral haemorrhage in hemisphere, cortical
I613	Intracerebral haemorrhage in brain stem
I614	Intracerebral haemorrhage in cerebellum
I615	Intracerebral haemorrhage, intraventricular
I616	Intracerebral haemorrhage, multiple localized
I618	Other intracerebral haemorrhage
I619	Intracerebral haemorrhage, unspecified
I620	Subdural haemorrhage (acute)(nontraumatic)
I621	Nontraumatic extradural haemorrhage
I629	Intracranial haemorrhage (nontraumatic), unspecified
I638	Other cerebral infarction
I690	Sequelae of subarachnoid haemorrhage
I691	Sequelae of intracerebral haemorrhage

ICD-10	ICD10Name
I780	Hereditary haemorrhagic telangiectasia
I788	Other diseases of capillaries
I841	Internal hemorrhoid with other complications
I844	External hemorrhoid with other complications
I848	Unspecified hemorrhoid with other complications
I850	Oesophageal varices with bleeding
I864	Gastric varices
J041	Acute tracheitis
J339	Nasal polyp, unspecified
J90	Pleural effusion, not elsewhere classified
J942	Haemothorax
J950	Tracheostomy malfunction
K049	Other and unspecified diseases of pulp and periapical tissues
K068	Other specified disorders of gingiva and edentulous alveolar ridge
K121	Other forms of stomatitis
K137	Other and unspecified lesions of oral mucosa
K148	Other diseases of tongue
K226	Gastro-oesophageal laceration-haemorrhage syndrome
K228	Other specified diseases of oesophagus
K250	Acute with haemorrhage
K252	Gastric ulcer, Acute with both haemorrhage and perforation
K254	Gastric ulcer, Chronic or unspecified with haemorrhage
K256	Gastric ulcer, Chronic or unspecified with both haemorrhage and perforation
K260	Duodenal ulcer, Acute with haemorrhage
K262	Duodenal ulcer, Acute with both haemorrhage and perforation
K264	Duodenal ulcer, Chronic or unspecified with haemorrhage
K266	Duodenal ulcer, Chronic or unspecified with both haemorrhage and perforation
K270	Acute duodenal tumor with haemorrhage
K284	Gastrojejunal ulcer, Chronic or unspecified with haemorrhage
K290	Acute haemorrhagic gastritis
K571	Diverticular disease of small intestine without perforation or abscess
K573	Diverticular disease of large intestine without perforation or abscess
K625	Haemorrhage of anus and rectum
K661	Haemoperitoneum
K762	Central haemorrhagic necrosis of liver
K768	Other specified diseases of liver
K85	Acute pancreatitis
K920	Haematemesis
K921	Melaena
K922	Gastrointestinal haemorrhage, unspecified
L508	Other urticaria
M250	Haemarthrosis

ICD-10	ICD10Name
N029	Recurrent and persistent haematuria, Unspecified
N288	Other specified disorders of kidney and ureter
N300	Acute cystitis
N304	Irradiation cystitis
N309	Cystitis, unspecified
N328	Other specified disorders of bladder
N368	Other specified disorders of urethra
N421	Congestion and haemorrhage of prostate
N488	Other specified disorders of penis
N501	Vascular disorders of male genital organs
N645	Other signs and symptoms in breast
N830	Follicular cyst of ovary
N831	Corpus luteum cyst
N836	Haematosalpinx
N837	Haematoma of broad ligament
N838	Other noninflammatory disorders of ovary, fallopian tube and broad ligament
N898	Other specified noninflammatory disorders of vagina
N908	Other specified noninflammatory disorders of vulva and perineum
N921	Excessive and frequent menstruation with irregular cycle
N922	Excessive menstruation at puberty
N923	Ovulation bleeding
N924	Excessive bleeding in the premenopausal period
N930	Postcoital and contact bleeding
N938	Other specified abnormal uterine and vaginal bleeding
N939	Abnormal uterine and vaginal bleeding, unspecified
N950	Postmenopausal bleeding
O208	Other haemorrhage in early pregnancy
O209	Haemorrhage in early pregnancy, unspecified
O441	Placenta praevia with haemorrhage
O469	Antepartum haemorrhage, unspecified
O679	Intrapartum haemorrhage, unspecified
O695	Labour and delivery complicated by vascular lesion of cord
O717	Obstetric haematoma of pelvis
O720	Third-stage haemorrhage
O721	Other immediate postpartum haemorrhage
O722	Delayed and secondary postpartum haemorrhage
O901	Disruption of perineal obstetric wound
O902	Haematoma of obstetric wound
P021	Fetus and new-born affected by other forms of placental separation and haemorrhage
P100	Subdural haemorrhage due to birth injury
P101	Cerebral haemorrhage due to birth injury
P102	Intraventricular haemorrhage due to birth injury

ICD-10	ICD10Name
P103	Subarachnoid haemorrhage due to birth injury
P109	Unspecified intracranial laceration and haemorrhage due to birth injury
P120	Cephalhaematoma due to birth injury
P269	Unspecified pulmonary haemorrhage originating in the perinatal period
P510	Massive umbilical haemorrhage of new-born
P519	Umbilical haemorrhage of new-born, unspecified
P523	Unspecified intraventricular (nontraumatic) haemorrhage of fetus and new-born
P524	Intracerebral (nontraumatic) haemorrhage of fetus and new-born
P528	Other intracranial (nontraumatic) haemorrhages of fetus and new-born
P529	Intracranial (nontraumatic) haemorrhage of fetus and new-born, unspecified
P540	Neonatal haematemesis
P542	Neonatal rectal haemorrhage
P543	Other neonatal gastrointestinal haemorrhage
P544	Neonatal adrenal haemorrhage
P545	Neonatal cutaneous haemorrhage
P546	Neonatal vaginal haemorrhage
P549	Neonatal haemorrhage, unspecified
P580	Neonatal jaundice due to bruising
P581	Neonatal jaundice due to bleeding
R040	Epistaxis
R041	Haemorrhage from throat
R042	Haemoptysis
R048	Haemorrhage from other sites in respiratory passages
R049	Haemorrhage from respiratory passages, unspecified
R18	Ascites
R195	Other faecal abnormalities
R233	Spontaneous ecchymoses
R31	Unspecified haematuria
R571	Hypovolaemic shock
R58	Haemorrhage, not elsewhere classified
S000	Superficial injury of scalp
S001	Contusion of eyelid and periocular area
S002	Other superficial injuries of eyelid and periocular area
S003	Superficial injury of nose
S004	Superficial injury of ear
S005	Superficial injury of lip and oral cavity
S007	Multiple superficial injuries of head
S008	Superficial injury of other parts of head
S013	Open wound of ear
S019	Open wound of head, part unspecified
S050	Injury of conjunctiva and corneal abrasion without mention of foreign body
S051	Contusion of eyeball and orbital tissues

ICD-10	ICD10Name
S063	Focal brain injury
S064	Epidural haemorrhage
S065	Traumatic subdural haemorrhage
S066	Traumatic subarachnoid haemorrhage
S068	Other intracranial injuries
S098	Other specified injuries of head
S100	Contusion of throat
S101	Other and unspecified superficial injuries of throat
S141	Other and unspecified injuries of cervical spinal cord
S241	Other and unspecified injuries of thoracic spinal cord
S271	Traumatic haemothorax
S272	Traumatic haemopneumothorax
S278	Injury of other specified intrathoracic organs
S279	Injury of unspecified intrathoracic organ
S301	Contusion of abdominal wall
S302	Contusion of external genital organs
S341	Other injury of lumbar spinal cord
S361	Injury of liver or gallbladder
S368	Injury of other intra-abdominal organs
S369	Injury of unspecified intra-abdominal organ
S370	Injury of kidney
S378	Injury of other pelvic organs
S390	Injury of muscle and tendon of abdomen, lower back and pelvis
S400	Contusion of shoulder and upper arm
S408	Other superficial injuries of shoulder and upper arm
S500	Contusion of elbow
S501	Contusion of other and unspecified parts of forearm
S600	Contusion of finger(s) without damage to nail
S601	Contusion of finger(s) with damage to nail
S701	Contusion of thigh
S800	Contusion of knee
S801	Contusion of other and unspecified parts of lower leg
S901	Contusion of toe(s) without damage to nail
S902	Contusion of toe(s) with damage to nail
T009	Multiple superficial injuries, unspecified
T060	Injuries of brain and cranial nerves with injuries of nerves and spinal cord at neck level
T090	Superficial injury of trunk, level unspecified
T093	Injury of spinal cord, level unspecified
T140	Superficial injury of unspecified body region
T144	Injury of nerve(s) of unspecified body region
T145	Injury of blood vessel(s) of unspecified body region
T146	Injury of muscles and tendons of unspecified body region

ICD-10	ICD10Name
T794	Traumatic shock
T810	Haemorrhage and haematoma complicating a procedure, not elsewhere classified
T811	Shock during or resulting from a procedure, not elsewhere classified
T876	Other and unspecified complications of amputation stump
T905	Sequelae of intracranial injury
	Subgaleal hemorrhage
	Intracranial hemorrhage

10.3.6. Variables for subgroup analysis

Subgroups	ICD10 code	Standard disease code	Note
Hypertension			Refer to 10.3.1
Liver dysfunction			Refer to 10.3.1
Renal impairment			Refer to 10.3.1
Bleeding history	A162		Include only tubercular hemoptysis
	A165		Include only tubercular hemothorax
	B303		
	D500		
	D62		
	D66		Include only hemophiliac bleeding
	D683		Include only hemorrhagic disorder due to circulating anticoagulants
	D698		
	D699		
	E078		Include only tyroid bleeding
	E274		Include only adrenal bleeding
	G361		
	G951		Include only hematomyelia, spinal subdural hemorrhage, hematorrhachis, spinal epidural hemorrhage and spontaneous Cervical Epidural Hematoma
	G968		Include only spinal subarachnoid hemorrhage
	H052		Include only orbital fat hemorrhage
	H113		
	H168		Include only Hemorrhagic keratitis
	H208		Include only hemorrhagic iritis
	H210		
	H313		
	H350		Include only hemorrhagic retinitis and juvenile recurrent vitreoretinal hemorrhage
	H356		
	H357		Include only hemorrhagic retinal pigment epithelial detachment
	H405		Include only hemorrhagic glaucoma
	H431		

Subgroups	ICD10 code	Standard disease code	Note
	H448		Include only intraocular hemorrhage
	H470		Include only optic disc hemorrhage and optic nerve sheath hemorrhage
	H603		Include only otitis externa hemorrhagica
	H669		Include only hemorrhagic otitis media
	H738		Include only eardrum bleeding
	H922		
	I213		Include only Atrial thrombus as current complication following acute myocardial infarction
	I230		
	I312		
	I600		
	I601		
	I602		
	I603		
	I604		
	I605		
	I606		
	I607		
	I608		
	I609		
	I610		
	I611		
	I613		
	I614		
	I615		
	I616		
	I618		
	I619		
	I620		
	I621		
	I629		
	I638		Inculde only hemorrhagic cerebral infarction
	I690		
	I691		
	I780		
	I788		
	I850		
	I864		Include only gastric variceal bleeding
	J041		Include only hemorrhagic tracheitis
	J339		Include only bleeding polyp
	J90		Include only hemorrhagic pleural effusion
	J942		
	J950		Include only bleeding from a tracheostomy site
	K049		Include only hemorrhage in the pulp
	K068		Include only gingival hemorrhage
	K121		Include only hemorrhagic stomatitis
	K137		Include only oral hemorrhage

Subgroups	ICD10 code	Standard disease code	Note
	K148		Include only tongue root submucosal bleeding
	K226		
	K228		Include only esophageal hemorrhage
	K250		
	K252		
	K254		
	K256		
	K260		Exclude acute gastroduodenal mucosal lesion
	K262		
	K264		
	K266		
	K284		
	K290		
	K571		Include only Duodenal diverticulum bleeding
	K573		Include only bleeding from Sigmoid diverticulum, Transverse colon diverticulum, Descending colon diverticulum, Ascending colon diverticulum and Large intestine diverticulum
	K625		
	K649		Include only Hemorrhoidal external hemorrhoids, Hemorrhoids and Hemorrhoidal internal hemorrhoids
	K661		
	K762		
	K768		Include only hepatorrhagia
	K859		Include only acute hemorrhagic necrotizing pancreatitis
	K920		
	K921		
	K922		
	L508		Include only hemorrhagic urticaria
	M2506		
	M2509		
	N029		
	N288		Include only perirenal bleeding, nephrorrhagia and idiopathic hematuria
	N300		Include only acute hemorrhagic cystitis
	N304		Include only radiation-induced hemorrhagic cystitis
	N309		Include only hemorrhagic cystitis
	N328		Include only bladder hemorrhage
	N368		Include only urethremorrhagia
	N421		
	N488		Include only penile hemorrhage
	N501		Include only Scrotal hemorrhage and Spermatic cord hematoma
	N645		Include only thelorrhagia
	N830		Include only follicular hemorrhage and hemorrhagic follicular cyst
	N831		Exclude luteal cyst
	N836		

Subgroups	ICD10 code	Standard disease code	Note
	N837		
	N838		Include only ovarian hemorrhage
	N898		Include only vaginal hematoma
	N908		Include only vulval hemorrhage
	N921		
	N922		
	N923		
	N924		
	N930		
	N938		
	N939		
	N950		
	O717		
	O901		
	O902		
	R040		
	R041		
	R042		
	R048		
	R049		
	R18		Include only hemorrhagic ascites
	R195		Include only fecal occult blood
	R233		
	R31		
	R571		Include only hemorrhagic shock
	R58		
	S000		Include only ecchymoma, hematoma and hemorrhage
	S001		Include only hematoma and hemorrhage
	S002		Include only hematoma
	S003		Include only hematoma and hemorrhage
	S004		Include only hematoma and hemorrhage
	S005		Include only hematoma and hemorrhage
	S007		Include only hematoma and hemorrhage
	S008		Include only hematoma
	S013		Include only hemorrhage
	S050		Include only Corneal hematoma
	S051		Include only traumatic vitreous hemorrhage and traumatic hyphema
	S063		Include only hematoma and hemorrhage
	S064		
	S065		
	S066		
	S068		Include only hematoma, hemorrhage
	S098		Include only hemorrhage
	S100		Include only hematoma
	S101		
	S141		Include only hematoma
	S241		Include only hematoma

Subgroups	ICD10 code	Standard disease code	Note
	S271		
	S272		
	S278		Include only hematoma
	S279		Include only hematoma
	S301		Include only hematoma
	S302		Include only hematoma
	S341		Include only hematoma
	S361		Include only hematoma
	S368		Include only hemorrhage
	S369		Include only hematoma
	S370		Include only hematoma
	S378		Include only hemorrhage
	S390		Include only hematoma
	S400		Include only hematoma
	S408		Include only hematoma
	S500		Include only hematoma
	S501		Include only hematoma
	S600		Include only hematoma
	S601		Include only hematoma
	S701		Include only hematoma
	S800		Include only hematoma
	S801		Include only hematoma
	S902		Include only hematoma
	T009		Include only hematoma and hemorrage
	T060		Include only spinal subarachnoid hemorrhage
	T090		Including only hematoma
	T093		Including only hematoma
	T140		Including only hematoma
	T144		Include only traumatic hematomyelia
	T145		Include only traumatic arterial hematoma
	T146		Include only Intramuscular hematoma
	T794		Include only traumatic hemorrhagic shock
	T810		Include only hematoma and hemorrage
	T811		Include only hemorragic shock
	T876		Include only hematoma
	T905		Include only sequelae after
Hemorrhage stroke			Refer to 10.3.1
Alcohol abuse	E244		
	E52		Include only Alcoholic pellagra
	F100		
	G312		
	G405		Include only alcoholic epilepsy
	G621		
	G701		Include only alcoholic neuropathy
	G721		
	H470		Include only alcoholic optic neuropathy
	I426		

Subgroups	ICD10 code	Standard disease code	Note
	K292		
	K70		
	K852		
	K860		
	T519		
Antiplatelet drug			Refer to 5.4
NSAIDs			Refer to 5.4
Peptic ulcer	F54		Include only psychogenic gastric ulcer
	K221		
	K227		Include only Barrett's esophagus
	K25		
	K26		
	K27		
	K28		
	K51		
	K626		
	K633		
Active cancer			Refer to 10.3.1
Diabetes mellitus			Refer to 10.3.1
Polypharmacy			Refer to 5.4