Non-Interventional Study Protocol
<B0661181>

Safety and effectiveness of apixaban in very elderly patients with NVAF compared to warfarin using administrative claims data

Statistical Analysis Plan(SAP)

Version: Ver.2.0

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

From version 1.0 to version 1.1, no substantial changes have been made and only asministrative changes including correction of typos as follows; 1) in CCI [redacted] 2) in 7.2.4 Summary of analysis, "time course of proportion of stroke-free" was changed to "time course of proportion of stroke/SE-free". Both changes are considered to be just administrative ones and little impact on the results would be expected.

From version 1.1 to version 2.0, two major changes have been made. Firstly, patient registration period descried in the section 2.1.1 was changed from “2008 to 2021” to “February 26, 2013 to December 31, 2021” to consider the launch date of apixaban in Japan. This change will make concurrent active control (i.e., warfarin cohort) for apixaban cohort. Secondly, calculation of propensity score was modified in the section “7.1.2.1” to adjust effect of time on treament selection (i.e., warfarin or apixaban). Propensity scores will be calculated by calendar year of index date.

2. INTRODUCTION

The number of patients with atrial fibrillation (AF) has been in the elderly patients has been increasing worldwide[1]. Especially, *Japan is a very elderly society compared to other countries in Europe and the United States, and there are many very elderly patients with NVAF who are treated with any of anticoagulant and there are considerable number of patients who are newly diagnosed with NVAF even in their 80’s and 90’s.* In the previous real-world database study conducted in Japan (CER3 study), the mean age of patients with non-valvular AF (NVAF) were 75-78 years old[2]. *Most of these very elderly people have many complications, including severe ones, and take many medications chronically. In addition, many elderly patients have low body weight, sarcopenia, low ADL, frailty or frail-like characteristics, or high risk of falls. There has been much debate and inconclusive evidence on the value of anticoagulation for these very elderly patients with NVAF*[1, 3, 4,]. *ARISTOTLE study has shown that apixaban is superior or equivalent to warfarin in various populations including populations at higher risk. However, there are few studies in the real-world settings regarding very elderly patients who are at higher risk.*

Research question and objectives：

The ARISTOTLE study and various real-world evidence (RWE) have shown that apixaban is superior or equivalent to warfarin in safety and effectiveness profile. Subgroup analyses of the ARISTOTLE study suggested that superiority over warfarin could be consistent in most populations including high risk populations. Study hypothesis and clinical questions in this study is apixaban is superior to warfarin in both safety and effectiveness even in the very elderly patients with NVAF in the real-world settings.

The clinical question of this study is that apixaban has a superior effectiveness and safety profile compared to warfarin, even in very elderly patients who are at particularly high risk, such as those with CCI *, frail or frail patients, those with significant comorbidities, those with polypharmacy, and those at high risk of falls.*

The objective of this study is to investigate safety and effectiveness of apixaban compared to warfarin in very elderly patients with NVAF. CCI [redacted]

2.1. STUDY DESIGN

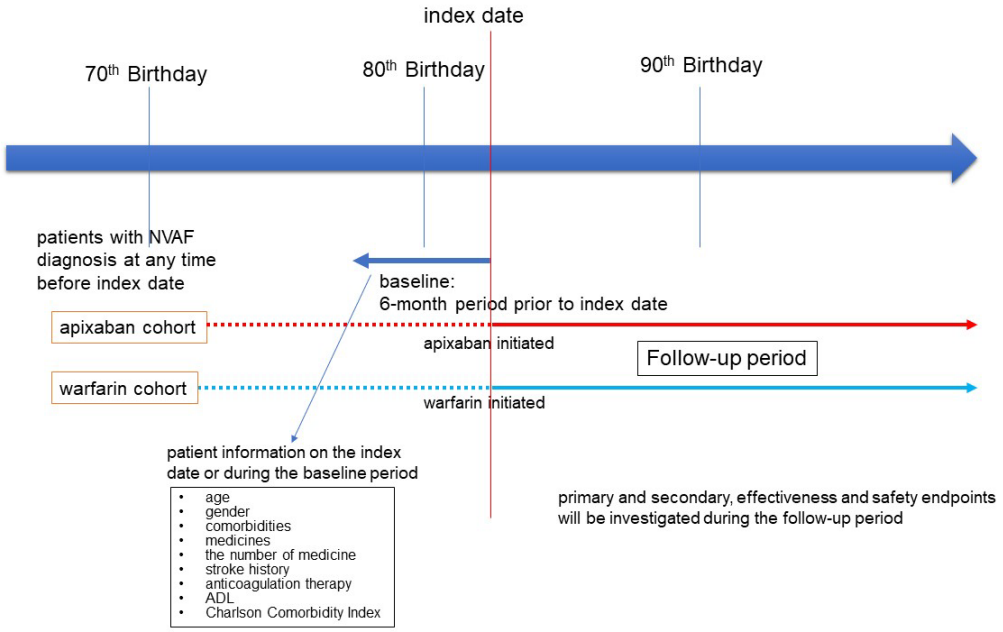
This is a retrospective non-intervention observational study to evaluate the difference in safety and effectiveness between apixaban and warfarin using a database provided by Medical Data Vision Co. Ltd. (MDV Co. Ltd.). Eligible patients will be extracted from the database and allocated to the pre-defined cohorts based on the actual age, age of NVAF diagnosis and types of anticoagulant therapy.

Based on the age category and anticoagulants on the index date (a date when patients initiated an anticoagulant for prevention of stroke/SE), eligible patients will be allocated to some cohorts. Patient characteristics will be balanced by an Inverse probability of treatment weighting (IPTW) method, and risk of stroke/SE (primary effectiveness endpoint) and major bleeding (primary safety endpoint) will be compared. Hazard ratios and 95% confident intervals will be calculated by using a Cox proportional hazard method with a robust sandwich variance estimator to account for induced correlations among weighted patients.

2.1.1. Study population

Patients registered in the MDV database from February 26, 2013 to December 31, 2021 will be used. First, patients with a NVAF diagnosis and received apixaban or warfarin as an anticoagulant after the NVAF diagnosis will be identified and then among them only patients who are 80 or older when they initiated these medications.

Based on the first anticoagulant prescribed, eligible patients will be allocated to one of two cohorts, an apixaban or warfarin cohort. Comparison will be made between these cohorts after balancing of the patient characteristics by a IPTW with stabilized weights (s-IPTW) method.



2.1.2. Data source

Medical Data Vision database, commercially available administrative claims database from hospitals introducing DPC (Diagnosis Procedure Combination) system, which comprises administrative data pertaining to approximately 39 million individuals (as of 2021 Dec.) managed in the inpatient and outpatient settings. In this database, all patients have been de-identified and no personal information resulting the identification of individuals.

2.1.3. Treatment/cohort labels

1. Apixaban cohort: patients diagnosed with non-valvular atrial fibrillation who are 80 or older when they initiated apixaban as an anticoagulant.
2. Warfarin cohort: patients diagnosed with non-valvular atrial fibrillation who are 80 or older when they initiated warfarin as an anticoagulant.

2.2. STUDY OBJECTIVES

The objective of this study is to investigate safety and effectiveness of apixaban compared to warfarin in very elderly patients with NVAF. CCI [redacted]

The purposes of this study are 1) to characterize the primary and secondary prevention patients, 2) incidence rates of stroke/SE or major bleeding in each cohort and 3) is to investigate for Japanese secondary prevention patients as RWE on the effectiveness and safety of apixaban compared to warfarin in patients with NVAF.

3. HYPOTHESES AND DECISION RULES

3.1. STATISTICAL HYPOTHESES

Not applicable

3.2. STATISTICAL DECISION RULES

When the effect of factors in an analysis is statistically evaluated, the alpha level of 0.05 will be referred.

4. ANALYSIS SETS/POPULATIONS

4.1. FULL ANALYSIS SET

4.1.1. Inclusion criteria

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

1. *Diagnosed with AF anytime in the baseline period or on the index date, also have definitive diagnosis of AF anytime in the baseline period, on the index date, or post-index period.*

2. *Prescribed apixaban or warfarin on or after the day of AF diagnosis. The first observed prescription will be used to identify the patient's index date and treatment cohort*
3. *No use of the any OACs during the baseline period (the 180 days before the index date)*
4. *Age of 18 years or older on the index date.*
5. *Index date is at age 80 or older*

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 cardiac surgery procedure record during the baseline period*
3. *Having a joint replacement procedure record during the baseline period*
4. *Having a procedure of prosthetic heart valve during the baseline period*
5. *Having a diagnosis of venous thromboembolism during the baseline period*
6. *Female patients with pregnancy during the follow-up period*
7. *Patients prescribed "off-label" doses of OACs (per Japanese package insert of each OAC) or patients treated with OAC but in "off-label" or "contraindicated" manners.*

4.2. SAFETY ANALYSIS SET

Bleeding other than safety-related reactions will not be investigated here. Bleeding events will be evaluated using the same analysis set as effectiveness.

4.3. OTHER ANALYSIS SET

Not applicable. All eligible patients will be used for the analysis except the pre-designated subanalysis.

CCI [redacted]

[redacted]

4.5. SAMPLE SIZE CALCULATION

This study is a retrospective analysis of the structured data in the database and all eligible patients will be used for analysis.

The results of the feasibility assessment are shown below,

Table 1. The number of patients

Patient group	Number of patients
Patients diagnosed with NVAF at 80 years or an age older than 80 and data when patients are 80 or older are available.	
Treated with apixaban	76,260
Treated with warfarin	62,453

Note that not all of these patients are eligible for this study because no inclusion and exclusion criteria were applied when the number of patients was estimated.

In the previous study (CER3)[2], incidence rate of major bleeding and stroke/SE were 2.5% for warfarin and 1.18 % for apixaban and 1.92% for warfarin and 0.98% for apixaban, respectively. Hazard ratios for major bleeding and stroke/SE were 0.58 and 0.57, respectively. In CER3 subgroup analysis on age, hazard ratios in sub-cohort of ages ≥ 80 years were 0.59 and 0.53 for major bleeding and stroke/SE, respectively. Although populations used for analysis are different (in the CER3 study, warfarin and apixaban could be started at any age, whereas in this study, the starting date for warfarin and apixaban was restricted to ages 80 years and older), difference may not be very large because the mean age of populations in CER3 is around 77 years old in both warfarin and apixaban cohorts. Sample size calculation was performed based on the CER3 results of older age subgroup analysis.

Table 2. 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	0.59	
N ratio in apixaban and warfarin cohorts	1:1	
Event rate for warfarin	2.5%/year	
Event rate for apixaban	1.18%/year	
Total events needed		113
Estimated number of patients		6,141
For Stroke/SE		
Type I error rate	0.05	
Type II error rate	0.2	
Hazard ratio	0.53	
N ratio in apixaban and warfarin cohorts	1:1	
Event rate for warfarin	1.92%/year	
Event rate for apixaban	0.98%/year	
Total events needed		78
Estimated number of patients		5,379

Even allowing for the fact that 1) event rate may be higher because only patients whose index date is at 80 years or older (that is, high risk population for both stroke/SE and major

bleeding) and 2) not all of patients in Table 1 above are eligible for this study, the number of eligible patients could be enough for primary safety and effectiveness analyses with appropriate statistical power.

5. ENDPOINTS AND COVARIATES

5.1. EFFICACY/EFFECTIVENESS ENDPOINT(S)

5.1.1. Primary effectiveness endpoint and primary analyses

Primary effectiveness endpoint is incidence of a composite of Stroke/SE ("cardiogenic cerebral embolism", "cerebral infarction", hemorrhagic stroke or SE) in NVAF patients treated with warfarin or apixaban. TIA is not included in the outcome (not regarded as stroke).

1. Incidence of stroke/SE (per 1,000 person-year)
2. Survival curves of stroke/SE-free patients (Kaplan-Meier curves) will be drawn for apixaban and warfarin cohorts. Difference in the two curves will be evaluated by a Log-rank test.

Risk of stroke/SE in each cohort will be compared between balanced warfarin and balanced apixaban cohorts by using Cox proportional hazard analysis. Hazard ratio with 95% confident intervals will be calculated.

5.1.2. Secondary effectiveness endpoint and secondary analyses

Secondary effectiveness endpoints are the incidence of "cardiogenic cerebral embolism" or "ischemic stroke" during the follow-up period in NVAF patients treated with warfarin or apixaban.

For each secondary endpoint, like the primary analysis, incidence of the secondary endpoint, Kaplan Meier curves and Hazard ratios with 95% confident intervals will be calculated

5.2. SAFETY ENDPOINTS

5.2.1. Primary safety endpoint and primary analyses

Primary safety endpoint is incidence of major bleeding, which is defined as any bleeding requiring hospitalization.

1. Incidence of Major bleeding (per 1,000 person-year)

2. Survival curves of major bleeding-free patients (Kaplan-Meier curves) will be drawn for apixaban and warfarin cohorts. Difference in the two curves will be evaluated by a Log-rank test.
3. Risk of major bleeding in each cohort will be compared between balanced warfarin and balanced apixaban cohorts by using Cox proportional hazard analysis. Hazard ratio with 95% confident intervals will be calculated.

5.2.2. Secondary safety endpoint and secondary analyses

Secondary safety endpoints are the incidence of “intracranial hemorrhage”, “gastrointestinal bleeding” or “intraocular bleeding” during the follow-up period in NVAF patients treated with warfarin or apixaban.

For each secondary endpoint (“intracranial hemorrhage”, “gastrointestinal bleeding” or “intraocular bleeding”), like the primary analysis, incidence of each secondary endpoint, Kaplan-Meier curves and Hazard ratios with 95% confident intervals will be calculated

5.3. OTHER ENDPOINTS

None

5.4. COVARIATES

Items	***definitions***	***roles***
Gender	*Male or female*	*Patient characteristics*
[redacted]	[redacted]	CCI [redacted]
Body weight	*≥ 60 kg or < 60 kg*	*Patient characteristics*
eGFR (continuous)	*Value in the baseline If a patient has multiple eGFR values, the values closest to the index date will be adopted*	*Patient characteristics*
eGFR (categorical)	*≥ 50 ml/min or < 50 ml/min*	*Patient characteristics*
Serum creatinine (continuous)	*Value in the baseline If a patient has multiple eGFR values, the values closest to the index date will be adopted*	*Patient characteristics*

Serum creatinine (categorical)	*≥ 1.5mg/mL or < 1.5 mg/mL*	*Patient characteristics*
CHADS2	*CHADS2 score will be calculated based on age and the presence of congestive heart failure, hypertension, diabetes, and stroke or TIA.*	*Patient characteristics*
CHA2DS2-VASc	*CHA2DS2-VASc score will be calculated based on age and the presence of congestive heart failure, hypertension, diabetes, stroke or TIA, vascular disease and sex category.*	*Patient characteristics*
CCI [redacted]		
[redacted]	[redacted]	[redacted]

[redacted]	CCI [redacted]	[redacted]
Medications		
CCI [redacted]		
Treated with antiplatelet drug in baseline	*Defined using prespecified drug-specific codes: Yes or No*	*Patient characteristics*

Treated with NSAIDs in baseline	*Defined using prespecified drug-specific codes: Yes or No*	*Patient characteristics*
Treated with gastric secretion inhibitor in baseline	*Defined using prespecified drug-specific codes: Yes or No*	*Patient characteristics*
Treated with statin-based drug in baseline	*Defined using prespecified drug-specific codes: Yes or No*	*Patient characteristics*
Treated with anti-hypertensives in baseline	*Defined using prespecified drug-specific codes: Yes or No*	*Patient characteristics*
Treated with anti-arrhythmics in baseline	*Defined using prespecified drug-specific codes: Yes or No*	*Patient characteristics*
Treated with beta-blockers in baseline	*Defined using prespecified drug-specific codes: Yes or No*	*Patient characteristics*
Procedures		
Cardioversion	*Defined using prespecified medical procedure codes: Yes or No*	*Patient characteristics*
Cardiac ablation	*Defined using prespecified medical procedure codes: Yes or No*	*Patient characteristics*
Anticogulation		
INR (warfarin cohort)	*Continuous variable. * Only available for patients treated with warfarin*	*Patient characteristics*
Apixaban doses	*2.5 mg BID or 5mg BID * Only available for patients treated with apixaban*	*Patient characteristics*

Chronically prescribed medicines

Medicines that had been prescribed at least for 30 days during the baseline period.

6. HANDLING OF MISSING VALUES

No imputation for missing values will be conducted.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1. STATISTICAL METHODS

7.1.1. Patient characteristics

Means with standard deviations or medians with quartile values (25% and 75% values) will be provided for continuous variables when performing descriptive analysis of continuous data. Numbers and percentages will be provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data. Bivariate comparisons of baseline characteristics and outcomes measures will be provided. Appropriate tests (unpaired t-test or Mann-Whitney U-test, categorical variables: Chi-square or Fisher's exact test) will be used based on the distribution of the measure.

7.1.2. Patient characteristics balancing

In this study, cohorts with balanced patient characteristics (s-IPTW warfarin cohort and s-IPTW apixaban cohort) will be created from raw cohorts (raw warfarin and raw apixaban cohorts). A propensity score will be calculated based on multivariable logistic regressions in order to account for confounding effects and to ensure that patient characteristics will be balanced between the warfarin cohort and apixaban cohort. An inverse probability of treatment weighting (IPTW) method using the calculated propensity score will be applied. To avoid sample size inflation and to ensure appropriate estimation of variances, s-IPTW (stabilized IPTW) will be used here.

7.1.2.1. Calculation of propensity score

Propensity scores will be estimated by calendar year of index date based on multivariable logistic regression analyses that incorporate potential predictors of therapy as independent variables in the regression and cohort status (prescription of warfarin or apixaban) as the outcome. Consecutive calendar years of index dates may be collapsed to build logistic regression model with robustness. The following covariates will be included in the logistic regression:

- age on index date
- age at NVAF diagnosis
- gender

- $CHADS_2$ score in baseline
- CHA_2DS_2-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

7.1.2.2. IPTW with stabilized weights[6]

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. Large weights can increase the variability of estimated treatment effect. In order to address this, the weights can be stabilized. Stabilized weights will be calculated 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.

7.1.2.3. Calculation of event rate

Patients who experience a clinical endpoint event after the earlier of their discontinuation of the index OAC, switching from the index OAC, withdrawal from the database, or the end of intended follow-up period will be censored. Patients who do not experience a clinical endpoint event will be censored at the earlier of their discontinuation of the index OAC, switching from the index OAC or withdrawal from the database will be censored.

Using the number of patients who experience each endpoints and the total observation period, incidence rate of each endpoint will be calculated and be presented as per 1,000 person-years.

7.1.2.4. 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 IPTW cohorts. The log-rank test is used for comparison between two curves.

7.1.2.5. Calculation of hazard ratio with 95% confident intervals

Cox proportional hazards model will be used to compare endpoints in each of the sIPTW cohorts, with robust sandwich estimates to account for the clustering within balanced sets. The Cox proportional hazards model will include only index OAC treatment (apixaban or warfarin) as the independent variable if patient characteristics are well balanced between groups based on standardized difference in components of the PS. 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.

CCI [redacted]

7.2. STATISTICAL ANALYSIS

7.2.1. Safety Analysis

This is a database study and safety analyses will not be performed because it is not possible to identify adverse events directly caused by the drug or suspected to be related to the drug. Only incidence of major bleeding, occurred during the follow-up periods, will be compared between s-IPTW apixaban and warfarin cohorts. See 5.2.1 and 7.1 above.

7.2.2. Analysis of Efficacy Analysis

See 7.1 above

7.2.3. Sensitivity analysis

E-values will be calculated to assess the extent of unmeasured confounding on findings from primary analyses of effectiveness and safety outcomes. E-value is a measure developed by VanderWeele and Ding (2017) as the minimal strength of association between a hypothetical unmeasured confounder with both the treatment and outcome to explain away the identified association between treatment and the outcome.

7.2.4. Summary of Analyses

Outcome	Analysis Set	Endpoint	Subgroup	Statistical Method	Covariates/Strata	Missing Data
Incidence rate of stroke/SE	Balanced cohorts	Primary effectiveness	None	1000 person-years	Refer to 5.1.1	No imputation
Incidence of cardiogenic cerebral embolism	Balanced cohorts	Secondary effectiveness	None	1000 person-years	Refer to 5.1.2	No imputation
Incidence of cerebral infarction	Balanced cohorts	Secondary effectiveness	None	1000 person-years	Refer to 5.1.2	No imputation
Incidence rate of major bleeding	Balanced cohorts	Primary safety	None	1000 person-years	Refer to 5.2.1	No imputation
Incidence rate of intracranial hemorrhage	Balanced cohorts	Secondary safety	None	1000 person-years	Refer to 5.2.2	No imputation
Incidence rate of gastrointestinal bleeding	Balanced cohorts	Secondary safety	None	1000 person-years	Refer to 5.2.2	No imputation
Incidence of rate of intraocular bleeding	Balanced cohorts	Secondary safety	None	1000 person-years	Refer to 5.2.2	No imputation
Time course of proportion of stroke/SE -free NVAF patients	Balanced cohorts	Primary effectiveness	None	Kaplan-Meier curves	Refer to 5.1.1	No imputation
Time course of proportion of cardiogenic cerebral embolism-free NVAF patients	Balanced cohorts	Secondary effectiveness	None	Kaplan-Meier curves	Refer to 5.1.2	No imputation
Time course of proportion of cerebral infarction”-free NVAF patients	Balanced cohorts	Secondary effectiveness	None	Kaplan-Meier curves	Refer to 5.1.2	No imputation

Time course of proportion of major bleeding-free NVAF patients	Balanced cohorts	Primary safety	None	Kaplan-Meier curves	Refer to 5.2.1	No imputation
Time course of proportion of intracranial hemorrhage-free NVAF patients	Balanced cohorts	Secondary safety	None	Kaplan-Meier curves	Refer to section 5.2.2	No imputation
Time course of proportion of gastrointestinal bleeding-free NVAF patients	Balanced cohorts	Secondary safety	None	Kaplan-Meier curves	Refer to section 5.2.2	No imputation
Time course of proportion of intraocular bleeding-free NVAF patients	Balanced cohorts	Secondary safety	None	Kaplan-Meier curves	Refer to section 5.2.2	No imputation
Risk of stroke/SE during the follow-up period in NVAF patients (Hazard ratio, apixaban versus warfarin)	Balanced cohorts	Primary endpoint	None	Cox proportional hazards regression model	Refer to 5.1.1	No imputation
Risk of cardioembolic stroke during the follow-up period in NVAF patients (Hazard ratio, apixaban versus warfarin)	Balanced cohorts	Secondary effectiveness	None	Cox proportional hazards regression model	Refer to 5.1.2	No imputation
Risk of cerebral infarction during the follow-up period in NVAF patients (Hazard ratio, apixaban versus warfarin)	Balanced cohorts	Secondary effectiveness	None	Cox proportional hazards regression model	Refer to 5.1.2	No imputation
Risk of major bleeding during the follow-up period in NVAF patients (Hazard ratio, apixaban versus warfarin)	Balanced cohorts	Primary safety	None	Cox proportional hazards regression model	Refer to 5.2.1	No imputation
Risk of intracranial hemorrhage during the follow-up period in NVAF patients (Hazard ratio, apixaban versus warfarin)	Balanced cohorts	Secondary safety	None	Cox proportional hazards regression model	Refer to 5.2.2	No imputation
Risk of gastrointestinal tract bleeding during the follow-up period in NVAF patients (Hazard ratio, apixaban versus warfarin)	Balanced cohorts	Secondary safety	None	Cox proportional hazards regression model	Refer to 5.2.2	No imputation

Risk of intraocular bleeding during the follow-up period in NVAF patients (Hazard ratio, apixaban versus warfarin)	Balanced cohorts	Secondary safety	None	Cox proportional hazards regression model	Refer to 5.2.2	No imputation

8. LIST OF TABLES AND TABLE SHELLS

None

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

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
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	
	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

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
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
	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	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	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	
	I240	
	I241	Exclude Dressler syndrome
Renal impairment	I120	
	I129	
	I139	
	N003	
	N009	
	N032	
	N033	
	N039	
	N040	
	N044	
	N049	
	N052	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	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	
	C220	
	K700	
	K701	
	K703	
	K709	
	K716	
	K720	
	K721	
	K729	
	K730	
	K732	
	K738	
	K739	
	K740	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	K741	
	K743	
	K744	
	K745	
	K746	
	K750	
	K751	
	K754	
	K759	
	K760	
	K761	
	K762	
	K763	
	K766	
	K767	
	K768	
	K769	
Cancer	C00	
	C01	
	C02	
	C03	
	C04	
	C05	
	C06	
	C07	
	C08	
	C09	
	C10	
	C11	
	C12	
	C13	
	C14	
	C15	
	C16	
	C17	
	C18	
	C19	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	C20	
	C21	
	C22	
	C23	
	C24	
	C25	
	C26	
	C30	
	C31	
	C32	
	C33	
	C34	
	C37	
	C38	
	C40	
	C41	
	C43	
	C44	
	C45	
	C46	
	C47	
	C48	
	C49	
	C50	
	C51	
	C52	
	C53	
	C54	
	C55	
	C56	
	C57	
	C58	
	C60	
	C61	
	C62	
	C63	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	C64	
	C65	
	C66	
	C67	
	C68	
	C69	
	C70	
	C71	
	C72	
	C73	
	C74	
	C75	
	C76	
	C78	
	C79	
	C80	
	C81	
	C82	
	C83	
	C84	
	C85	
	C88	
	C90	
	C91	
	C92	
	C93	
	C94	
	C95	
	C96	
	C97	
	D00	
	D01	
	D02	
	D03	
	D04	
	D05	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	D06	
	D07	
	D09	
	D10	
	D11	
	D12	
	D13	
	D14	
	D15	
	D16	
	D17	
	D18	
	D19	
	D20	
	D21	
	D22	
	D23	
	D24	
	D25	
	D27	
	D28	
	D29	
	D30	
	D31	
	D32	
	D33	
	D34	
	D35	
	D36	
	D37	
	D38	
	D39	
	D40	
	D41	
	D42	
	D43	

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
	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
	150331550
	150331950
	150332050
	150317910
	150318210
	150140010
	150139210
	150153910
	150374910
	150375010
	150375110
	150260350
	150284310
	150359310
	150263310

Procedure	Procedure Code
	150375210
	150375310
	150375410
	160107550
	150139810
	150139910
	150318310
	150145710
	150145810
	150145910
	150146010
	150318410
	150318510
	150302770
	150143010
	150143110
	150331650
	150332150
	150318710
	150319010
	150319310
	150318810
	150319110
	150319410
	150328750
	150328850
	150331750
	150331850
	150332250
	150332350
	150318910
	150319210
	150319510
	150318610
	150141010
	150279510
	150279610
	150141410

Procedure	Procedure Code
	150141610
	150369950
	150141710
	150359470
	150143610
	150260050
	150143710
	150143810
	150141510
	150375570
	150375670
	150375770
	150319610
	150292910
	150139310
	150140910
	150242550
	150244910
	150245010
	150359510
	150359610
	150381150
	150381250
	150381350
	150381450
	150150010
	150381550
	150275910
	150359710
	150359810
	150359910
	150381650
	150381750
	150381850
	150381950
	150150110
	150382050
	150245110

Procedure	Procedure Code
	150245210
	150375870
	150375970
	150376070
	150141210
	150301310
	150267850
	150319710
	150151810
	150376110
	150139110
	150319810
	150138810
	150151910
	150320010
	150346410
	150320110
	150147150
	150144110
	150320210
	150320310
	150142710
	150139410
	150320410
	150142910
	150320510
	150260150
	150346510
	150145110
	150145010
	150376210
	150376310
	150143250
	150143350
	150143450
	150143550
	150283250
	150283350

Procedure	Procedure Code
	150283450
	150283550
	150144910
	150139610
	150142410
	150141810
	150141910
	150320610
	150142050
	150142110
	150142210
	150142310
	150142810
	150144010
	150320710
	150144210
	150144550
	150147410
	150147510
	150320810
	150320910
	150144410
	150144650
	150144750
	150146510
	150146610
	150321010
	150321110
	150321210
	150376470
	150146910
	150146810
	150321310
	150142510
	150329810
	150145310
	150329910
	150139510

Procedure	Procedure Code
	150330010
	150147010
	150330110
	150376570
	150321410
	150321510
	150376670
	150147310
	150145650
	150141310
	150321810
	150321610
	150321910
	150146710
	150321710
	150330210
	150330310
	150376770
	150293010
	150330410
	150145510
	150302870
	150145410
	150322010
	150322110
	150144310
	150147250
	150346610
	150144810
	150253810
	150253910
	150275610
	150346710
	150262810
	150303310
	150267310
	150140110
	150140210

Procedure	Procedure Code
	150140410
	150346910
	150347010
	150303210
	150322210
	150275210
	150275310
	150336910
	150337010
	150360010
	150148010
	150148110
	150147610
	150147910
	150147770
	150147870
	150347170
	150275870
	150262910
	150275710
	150266110
	150382650
	150266210
	150382750
	150301810
	150382850
	150303410
	150303510
	150360110
	150360210
	150360310
	150360410
	150303610
	150303710
	150322410
	150322610
Ablation	150346710
	150262810

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

10.3.3. Stroke related medical history

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
	I748		Include only subclavian artery stenosis

10.3.4. 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

ICD-10	ICD10Name
B303	Acute epidemic haemorrhagic conjunctivitis (enteroviral)
D500	Iron deficiency anaemia secondary to blood loss (chronic)
D62	Acute posthaemorrhagic 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
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

ICD-10	ICD10Name
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
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

ICD-10	ICD10Name
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
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

ICD-10	ICD10Name
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 newborn 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
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 newborn
P519	Umbilical haemorrhage of newborn, unspecified
P523	Unspecified intraventricular (nontraumatic) haemorrhage of fetus and newborn
P524	Intracerebral (nontraumatic) haemorrhage of fetus and newborn
P528	Other intracranial (nontraumatic) haemorrhages of fetus and newborn
P529	Intracranial (nontraumatic) haemorrhage of fetus and newborn, 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

ICD-10	ICD10Name
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
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

ICD-10	ICD10Name
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
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

10.3.5. other codes

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 thyroid bleeding
	E274		Include only adrenal bleeding

Subgroups	ICD10 code	Standard disease code	Note
	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		
	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		

Subgroups	ICD10 code	Standard disease code	Note
	I619		
	I620		
	I621		
	I629		
	I638		Include 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
	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		

Subgroups	ICD10 code	Standard disease code	Note
	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		
	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		

Subgroups	ICD10 code	Standard disease code	Note
	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
	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

Subgroups	ICD10 code	Standard disease code	Note
	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		
	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
CCI [redacted]			[redacted]