NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

Title	CARBOS E^{+} - comparative risk of major bleeding with new oral anticoagulants (NOACs) and phenprocoumon in patients with atrial fibrillation – effectiveness analyses added
Protocol number	B0661096
Version identifier of the final study report	Final
Date of last version of the final study report	30 November 2017
EU Post Authorisation Study (PAS) register number	EUPAS18323
Active substance	Apixaban (B01AF02) Phenprocoumon (B01AA04) Rivaroxaban (B01AF01) Dabigatran (B01AX06, B01AE07) Edoxaban (B01AF03)
Product reference	EU/1/11/691/006

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Procedure number	Not applicable
Marketing Authorisation Holder (MAH)	Pfizer Pharma GmbH
Joint PASS	No
Research question and objectives	The aim of this study was to investigate whether there are differences in the occurrence of strokes or systemic embolism (SE) and major bleeding events in patients with AF and prescribed oral anticoagulation therapies in a real-world setting. It was investigated whether the occurrence of strokes/SE as well as major bleeding events differs between AF patients treated with the VKA (phenprocoumon) vs. AF patients treated with apixaban, dabigatran or rivaroxaban, respectively.

Country of study	Germany
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1. ABSTRACT

Title:

Comparative risk of major bleeding with new oral anticoagulants (NOACs) and Phenprocoumon in patients with atrial fibrillation – effectiveness analyses added: a retrospective claims database study in Germany

Rationale and Background:

Atrial fibrillation (AF), the most common cardiac arrhythmia worldwide, it affects approximately 1-2% of the general population and is a major risk factor for ischemic stroke. In order to reduce AF related stroke risk, Vitamin-K-Antagonists (VKA) have long constituted the standard treatment of patients with AF. However, several clinical disadvantages, including their narrow therapeutic range and their high inter- and intrapersonal variation, limits their use in daily clinical practice. Novel oral anticoagulants (NOAC) have been shown to be at least as effective and safe as VKA for stroke prevention in patients with AF. Currently four NOACs are approved for stroke patients with AF in Germany: apixaban, dabigatran, rivaroxaban and edoxaban. The efficacy of these drugs has been proven in prospective randomized multicenter studies. However, outcomes achieved in clinical trials may not translate to routine practice.

Research question and objectives:

The aim of this study was to evaluate the effectiveness and safety of apixaban, dabigatran, and rivaroxaban by comparing each drug with phenprocoumon. It was investigated whether the occurrence of strokes or systemic embolism and major bleeding events in non-valvular AF patients differed between patients treated with phenprocoumon and patients under apixaban, dabigatran or rivaroxaban, respectively. As of the recent market entry of edoxaban, data were not yet available to include patients treated with this specific NOAC in the study.

Study design:

To address the objectives of this study, a non-interventional retrospective new-user analysis was conducted using insurance claims data research database of the Institute for applied health research (InGef), formerly Health Risk Institute (HRI).

Population (Setting and study population):

The study population consisted of AF patients who were newly treated with an oral anticoagulant therapy between 01.01.2013 and 31.12.2015[1]. Patients were identified from the InGef research database, a complete longitudinal dataset of patients under statutory health insurance in Germany.

Variables (exposures, outcomes, key-covariables):

Based on their initial prescription, patients were assigned to one of the following treatment groups: apixaban, dabigatran, rivaroxaban, or phenprocoumon. The main outcomes of interest were ischemic or hemorrhagic stroke or systemic embolism and major bleeding events in the patient individual study period. Key-covariates included comorbidities at baseline, age and the risk factors for stroke and for bleeding.

Data sources:

The study was conducted using data from the InGef research database. This database includes information about the utilization of services on a case-by-case individual level. To support claims, indications (ICD10-GM) and procedure codes were provided together with costs.

Study Size:

A total of 61.205 therapy naïve patients were included in the study population, thereof 23.823 phenprocoumon, 10.117 apixaban, 5.122 dabigatran and 22.143 rivaroxaban patients.

Data Analysis:

[1] In a sensitivity analyses only patients starting treatment until 31.03.2015 were included in the analyses to allow for a follow up times of at least one year in all patients.

After a descriptive characterization of the four treatment groups, adjusted hazard ratios of the risk of ischemic or hemorrhagic stroke or systemic embolism and major bleeding were estimated by means of three different methods. In a main analysis, multiple outcome-specific Cox proportional-hazards regression models were used to estimate treatment effects (apixaban, dabigatran, and rivaroxaban using phenprocoumon as reference) on the outcome-specific hazard rates. Secondly, a marginal structural model was developed to compare the risk of all safety and effectiveness outcomes between the individual treatment groups.

In a sensitivity analysis Propensity Score Matching was performed followed by the calculation of hazard ratios by means of a univariate cox-proportional hazards model to estimate the risk of ischemic or hemorrhagic stroke or systemic embolism and major bleeding. Furthermore subgroup analyses were performed for patients who initiated NOAC treatment on the reduced dose (apixaban 2.5 mg, dabigatran 110mg, rivaroxaban 15mg) and patients who used the standard dose of these substances.

Results

The four treatment groups differed with regard to socio-demographic and clinical baseline characteristics. Phenprocoumon and apixaban patients were older and had a higher baseline risk of stroke (CHA2DS2-VASc score) and bleeding (HAS BLED score) compared to patients treated with rivaroxaban and dabigatran.

After adjusting for baseline confounders, all 3 NOACs had significantly lower risks of stroke/SE compared to phenprocoumon (apixaban HR 0.77, 95% CI 0.66-0.90; dabigatran HR 0.74, 95% CI 0.60-0.91; rivaroxaban HR 0.86, 95% CI 0.76-0.97). Apixaban (HR 0.58, 95% CI 0.49-0.69) and dabigatran (HR 0.64, 95% CI 0.50-0.80) were associated with lower bleeding risks than phenprocoumon whereas the risk was similar for rivaroxaban and phenprocoumon. All 3 NOACs showed reduced risk of intracranial bleeding compared to phenprocoumon.

The performed sensitivity and subgroup analyses largely confirmed the results of the multiple cox regression model.

Conclusion

Results from this large real world data analysis demonstrate that NOACs have better effectiveness and safety characteristics than phenprocoumon. Reduced NOAC dosing regimens were prescribed preferentially to patients with advanced age and comorbidities. The reduced dosing regimens of apixaban and rivaroxaban showed a similar effectiveness and safety profile compared to phenprocoumon as the standard dose regimens.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Events
AF	Atrial Fibrillation
ATC	Anatomical Therapeutic Chemical Classification System
CCI	Charlson Comorbidity Index
CI	Confidence Interval
DDD	Defined Daily Dose
DVT	Deep Vein Thrombosis
EBM	Einheitlicher Bewertungsmaßstab
EU	European Union
FDA	Food and Drug Administration
GI	Gastrointestinal
GOP	Gebührenordnungsposition
HR	Hazard ratio
ICD-10 GM	International Classification of Diseases, 10th Revision, German Modification
ICH	Intracerebral Hemorrhage
InGef	Institute for applied health research [Institut für angewandte Gesundheitsforschung]
INR	International Normalized Ration
NI	Non-Interventional
NOAC	Novel Oral Anticoagulants
NSAID	Non-Steroidal Anti-Inflammatory Drug
OAC	Oral Anticoagulation
OPS	Operationen- und Prozedurenschlüssel
PE	Pulmonary Embolism
SE	Systemic Embolism

SGB	Sozialgesetzbuch
SHI	State Health Insurance
UK	United Kingdom
US	United States
TIA	Transitory Ischemic Attack
VKA	Vitamin-K Antagonist
VTE	Venous Thromboembolism

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
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Dr. Eva Hradetzky	Scientific Advisor Internal Medicine	Pfizer Pharma GmbH

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual date
Compilation of the study protocol	31 December 2016	27 February 2017
Start of data collection	01 January 2017	01 January 2017
End of data collection	28 February 2017	28 February 2017
Registration in the EU PASS register	28 April 2017	28 April 2017
Final report of study results	30 June 2017	30 November 2017

6. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a prevalence of about 1-2% in the general population (1). AF prevalence increases with age and therefore, will further increase in the future (2,3). AF is a major risk factor for stroke and death. While death rates are twice as high in AF patients, AF confers a 5-fold risk to suffer a stroke compared to non AF patients (4,5). The appropriate and timely anticoagulant therapy of AF patients at risk of stroke is one of the core principles of modern AF management (2).

Vitamin-K antagonists (VKA) have long been the standard treatment of patients with AF, reducing the risk of stroke in AF patients by approximately two thirds compared to placebo (6). However, narrow therapeutic range, high inter- and intrapersonal variation of VKA exposure, multiple drug und food interactions, the subsequent need of extensive monitoring, and the associated risk of bleeding limit their use in practice (6,7). Novel oral anticoagulants (NOAC) have been shown to be equivalent or superior to treatment with warfarin, a VKA commonly used in the US and the UK. Fixed dosing and no need for frequent monitoring are two major advantages of NOACs. Since 2009, four NOACs have been tested and approved for stroke prevention in AF. These large randomized controlled trials have demonstrated that NOAC therapy is at least as effective and probably safer than treatment with VKA (6,8–10). All pivotal trials have evaluated NOACs against therapy with warfarin. However, in some regions of the world, the most commonly used VKA is phenprocoumon, for instance in Germany. Phenprocoumon differs in pharmacokinetic and pharmacodynamic properties from warfarin; most notably, phenprocoumon has a very long elimination half-life (110-130 hours) compared to warfarin (35-40 hours) (11).

The aim of this real-world study was to assess and compare effectiveness and bleeding profiles among German patients with non-valvular AF who were new users of phenprocoumon, apixaban, dabigatran, or rivaroxaban. Market approval for edoxaban was granted in June 2015. Due to the expected insufficient number of patients treated with edoxaban within the study period, patients treated with edoxaban were only be identified but not included in this study.

This non-interventional study was designated as a Post-Authorisation Safety Study (PASS) and was conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The main research question was to assess whether there are differences in the risk of stroke (ischemic or hemorrhagic) or systemic embolism and major bleeding events among AF patients prescribed phenprocoumon or one of the NOACs in a real-world setting.

The primary objectives were to investigate whether

1. the rate of ischemic or hemorrhagic stroke or systemic embolism in AF patients under anticoagulant therapy differed between:
    a. patients treated with phenprocoumon and patients treated with apixaban.
    b. patients treated with phenprocoumon and patients treated with rivaroxaban.
    c. patients treated with phenprocoumon and patients treated with dabigatran.
2. the rate of major bleeding events in AF patients under anticoagulant therapy differed between:
    a. patients treated with phenprocoumon and patients treated with apixaban.
    b. patients treated with phenprocoumon and patients treated with rivaroxaban.
    c. patients treated with phenprocoumon and patients treated with dabigatran.

Secondary objectives were to investigate whether

3. the rate of all strokes (ischemic or hemorrhagic), the rate of a ischemic stroke, the rate of hemorrhagic stroke and the rate of all-cause mortality in AF patients under anticoagulant therapy differed between:
    a. patients treated with phenprocoumon and patients treated with apixaban.

b. patients treated with phenprocoumon and patients treated with rivaroxaban.

c. patients treated with phenprocoumon and patients treated with dabigatran.

4. the rate of gastrointestinal bleeding events, intracranial bleeding events and any bleeding events in AF patients under anticoagulant therapy differed between:

   a. patients treated with phenprocoumon and patients treated with apixaban.

   b. patients treated with phenprocoumon and patients treated with rivaroxaban.

   c. patients treated with phenprocoumon and patients treated with dabigatran.

8. AMENDMENTS AND UPDATES

Not applicable.

9. RESEARCH METHODS

9.1. Study design

A non-interventional retrospective new user analysis was conducted using insurance claims data from the Institute for applied health research (InGef) research database. For an insured person to be included in the study, he/she must have been prescribed an oral anticoagulant (OAC) therapy between 01.01.2013 and 31.12.2015 because of documented AF in the same or in the quarter before treatment initiation.

9.1.1. Sensitivity Analysis I – Study design

In a sensitivity analysis the inclusion period was limited to the time period between 01.01.2013 and 31.03.2015. Unadjusted hazard ratios are provided for all treatment groups based on patients initiating their treatment in that respective time period. This was done to allow a follow up period of at least 365 days after treatment initiation or until death in all treatment groups.

9.2. Setting

The InGef database, from which patients were selected for inclusion in the study population, is a complete, longitudinal claims dataset of approximately 6.7 million patients, comprising data of approximately 10% of the statutory health insured population between 2009 and 2015. The InGef database contains complete data for the following data elements: demographics (e.g. age, gender, date of death), outpatient care (e.g. ICD 10 diagnoses, procedures performed), pharmacy (e.g. drugs dispensed by PZN, prescription date, quantity dispensed), hospital care (e.g. ICD 10 main and secondary diagnoses, procedures performed, admission and discharge date) and remedies and aids (e.g. type of therapy, quantity prescribed, prescription date).

Claims data are transferred directly from health care providers to a specialized data center owned by SHIs, which provides data warehouse and IT services. In the data center (acting as a trust center), data is anonymized before entering the InGef database. Data are anonymized with respect to individual insurants, health care providers (e.g. physicians, practices, hospitals, pharmacies), and the respective SHI.

9.2.1. Inclusion criteria

To be representative of the real world daily care situation, a group of AF patients newly initiating OAC therapy was identified for this study. Patients had to fulfill all of the following inclusion criteria to have been eligible for inclusion in the study:

1. Patients with a newly initiated a OAC therapy (apixaban, dabigatran, rivaroxaban, edoxaban[2] or phenprocoumon) within the study period (01.01.2013 - 31.12.2015[3]), i.e. no prior prescription for any of the above listed substances in the 12 months before the first

[2] Patients initiating treatment with edoxaban were only identified for completeness reasons. Due to the low sample size, the number of patients in this treatment group are reported. However, descriptives and event rates are provided for this treatment group.

[3] In a sensitivity analyses patients starting treatment until 31.03.2015 were included in the analyses only to allow for a follow up times of at least one year in all patients. Unadjusted event rates for the primary outcomes and major bleeding were investigated in this subpopulation to determine whether there are differences between these event rates and the event rates in the main analysis due to the varying length of follow up. See also section 9.1.1.

prescription in the study period (for relevant Anatomical Therapeutic Chemical Classification System (ATC) Codes please refer to Table 18 in the appendix of this report);

2. An ambulatory verified or primary or secondary hospital discharge diagnosis of AF (ICD-10 GM I48.0/ I48.1/I48.2/I48.9) in the previous or same quarter of the index date;

3. ≥ 18 years of age at index date;

4. continuous enrolment in the four quarters pre-index.

9.2.2. Exclusion criteria

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

1. Patients receiving more than one anticoagulant substance (apixaban, dabigatran, rivaroxaban, edoxaban or phenprocoumon) or more than one dosage of a substance on the index date;

2. At least one dialysis in the four quarters before or on the index date. Dialysis patients are identified using the Operationen- und Prozedurenschlüssel (OPS) and Gebührenordnungsposition (GOP) codes depicted in Table 19 in the appendix of this report;

3. Patients receiving a NOAC/VKA and heparin on the index date (for relevant ATC Codes please see Table 20 in the appendix of this report);

4. Patients receiving an initial dose of Dabigatran 75 mg or Rivaroxaban 10 mg (these dosages are not indicated for the treatment of AF)

5. Individuals with documented cardiac valve surgery in the four quarters prior to or on index date (for relevant ICD and OPS codes please refer to Table 21 in the appendix of this report);

6. Patients who present any evidence of pregnancy in the four quarters prior to or on index date (for relevant ICD Codes please refer to Table 21 in the appendix of this report)

7. Patients with a thrombosis or a pulmonary embolism in the four quarters prior to or on index date (for relevant ICD Codes please refer to Table 21 in the appendix of this report).

9.2.3. Observation periods

The following observation periods were applied throughout this study:

Index date - The index date was the first date of OAC dispensation (dispensation date) documented in the observation period between 01.01.2013 and 31.12.2015[4] for all patients.

Baseline period - 365 days prior to index date for hospital diagnoses and prescriptions and four quarters prior to the index OAC prescription for ambulatory diagnosis. This period was used to determine whether patients had an AF diagnosis, to verify that patients were new OAC users and to assess baseline demographic and clinical characteristics of the patients included in the study population, necessary for the multivariate analysis.

Gap period - A gap period was allowed when treatment was discontinued before censoring the patient for discontinuation. Patients were considered as exposed until 30 days after the end of supply. The rationale behind this choice was that in clinical studies adverse events are often assessed and documented for 30 days after the end of treatment.

Days of supply - since NOACs are prescribed in a fixed dose, the number of days of supply strictly corresponded to the size of the package, or the number of days until the new prescription, if smaller. Assessing VKA's number of days of supply was not straightforward. Doses were standardized among VKA patients for the estimation. The approach is further described in section 9.6.3.3.

[4] In sensitivity analysis I patients were included until 31.03.2015 only; hence index dates could range from 01.01.2013 until 31.03.2015.

Exposure time – From the date of initial prescription: Days of supply + Days of hospitalization + Gap or wash-out period (if no prescription immediately followed). Any potential treatment related hospitalizations (bleeding events) were considered as either outcome event or time dependent covariate.

Date of switch - Patients who receive a prescription for an OAC[5] other than the index OAC prescription during the follow- up period were considered as switchers if the new prescription occurred either before the end of supply of the current prescription or within the gap period after the end of supply. The date on which the changed prescription was redeemed was defined as the date of the switch.

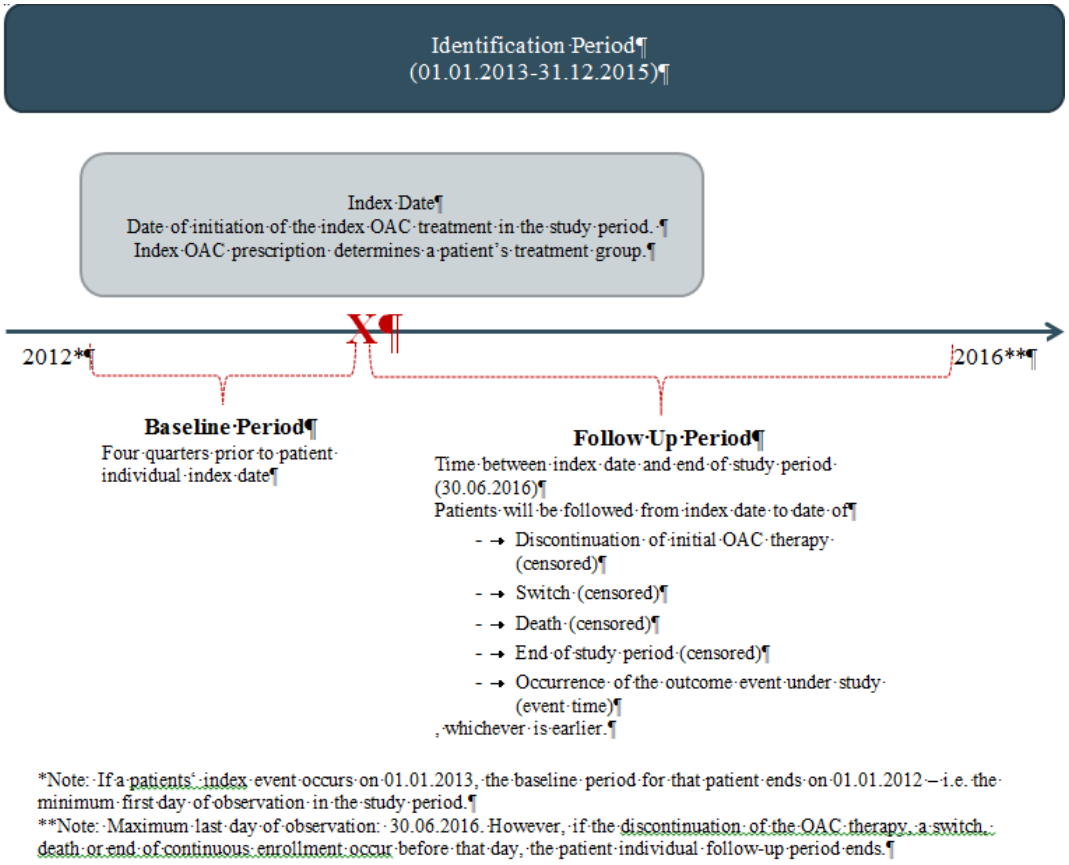
Date of discontinuation - Discontinuation was defined as no evidence of a follow up prescription for any of the OAC therapies at the end of the gap period after the end of supply. Patients who received prescriptions for warfarin or an NOAC in the wrong dosage (Dabigatran 75 mg or Rivaroxaban 10 mg) were also considered to have terminated the treatment. The last day of the exposure time was defined as the date of discontinuation and patients were censored.

9.2.3.1. Censoring scenario Cox proportional hazards model

A patients' initial OAC prescription determined treatment group affiliation, i.e. if a patient's first OAC prescription during the identification period was for apixaban, she/he was assigned to the apixaban treatment group. Censoring occurred when a patient switched to a different OAC treatment (date of censoring = date of switch) or when a patient discontinued the treatment. Further events ending the patient individual follow-up time included the death, end of continuous enrollment or the end of the study period, whichever occurred first. Figure 1 provides an overview about the observation periods that were applied.

[5] Including switches to edoxaban in the follow up period.

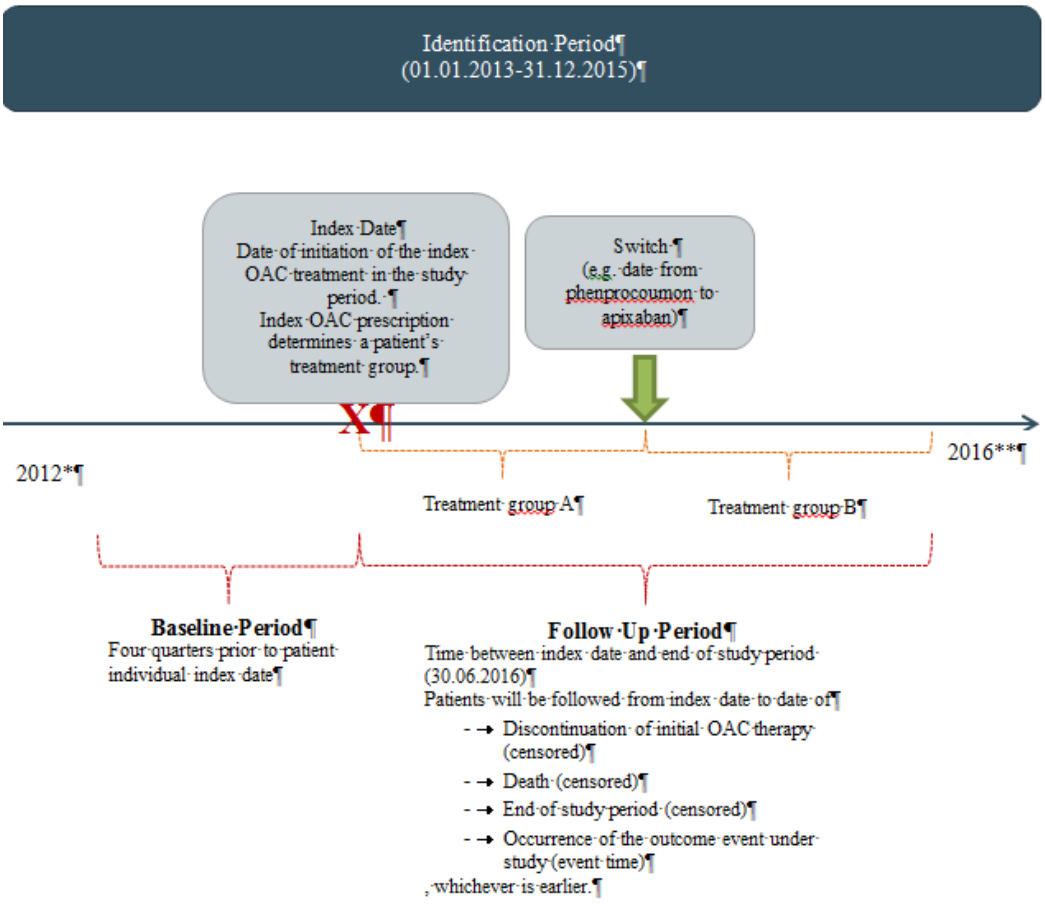
Figure 1 Observation periods scenario I Cox proportional hazards model



9.2.3.2. Censoring scenario marginal structural model (MSM)

A patients' initial OAC prescription determined treatment group affiliation, i.e. if a patient's first OAC prescription during the identification period was for apixaban, she/he was assigned to the apixaban treatment group. However, in contrast to the scenario in section 9.2.3.1, the date of a switch of the OAC treatment was not used as a censoring date. Instead, the exposure times of patients who switch from one substance to another was categorized based on the substance they received during certain intervals of the follow-up period. For example, if a patient was treated with phenprocoumon for the first three months of the follow-up period and switches to apixaban for the rest of the time, she/he was assigned to phenprocoumon treatment group for the first three months, and to the apixaban treatment group for the rest of the follow-up period. Figure 2 provides an overview about the observation periods which were applied.

Figure 2 Observation periods scenario II marginal structural models



*Note: If a patients' index event occurs on 01.01.2013, the baseline period for that patient ends on 01.01.2012 – i.e. the minimum first day of observation in the study period.
**Note: Maximum last day of observation: 30.06.2016. However, if the discontinuation of the OAC therapy, a switch, death or end of continuous enrollment occur before that day, the patient individual follow-up period ends.

9.3. Variables

In this section the demographic and clinical characteristics, outcome as well as any other key variables which were used in the analysis are identified and operationalized.

9.3.1. Outcomes/ Endpoint Variable

The primary outcomes of interest were: (i) a combined endpoint of ischemic or hemorrhagic stroke or systemic embolism and (ii) major bleeding events. Secondary outcomes of interest included (iii) all strokes (ischemic or hemorrhagic), (iv) hemorrhagic stroke, (v) ischemic stroke, (vi) all-cause mortality, (vii) gastrointestinal, (viii) intracranial and ix) any bleeding.

All ischemic events were effectiveness outcomes while all bleeding outcomes were safety outcomes.

All primary outcomes were identified by using inpatient hospital data in the form of primary and secondary discharge diagnoses indicative of any of the ischemic or bleeding events described below.

Table 1 Definition of the outcomes

Variable	**Objective**	**Operational definition**
Ischemic stroke/ hemorrhagic stroke/ systemic embolism	Primary	Composite endpoint of ischemic stroke or hemorrhagic stroke or systemic embolism (whichever occurs first) during the **Exposure time**. The respective events were defined based on primary or secondary ICD10 GM hospital discharge diagnoses. Ischemic stroke and hemorrhagic stroke were defined using the following ICD-10 GM codes: - I63* Cerebral infarction - I61* Intracerebral haemorrhage - I64* Stroke, not specified as haemorrhage or infarction - I74* Arterial embolism and thrombosis
Major bleeding event	Primary	Major bleeding events were defined as A. (hospital case in which the : • hospital admission was labelled as an

		emergency admission AND • an any bleeding (except D62*), gastrointestinal, intracerebral ICD 10 codes in Table 22 validated by OPS 8-800 (blood transfusion) or the ICD 10 diagnosis D62* (Acute posthaemorrhagic anaemia) have been documented in the same case with one of the) **OR** B. A hospital case with one of the ICD 10 codes labelled as a major bleeding event in the last column of Table 22_was documented as primary or secondary discharge diagnosis. For a complete list of all major bleeding events and their operationalization using ICD-10 GM codes please see column *major bleeding* in Table 22 in the appendix of this report.
Ischemic stroke/ hemorrhagic stroke	Secondary	Composite endpoint of ischemic stroke or hemorrhagic stroke (whichever occurs first) during the **Exposure time**. The respective events were defined based on primary or secondary ICD10 GM hospital discharge diagnoses. Ischemic stroke and hemorrhagic stroke were defined using the following ICD-10 GM codes: - I63* Cerebral infarction

		- I61* Intracerebral haemorrhage - I64* Stroke, not specified as haemorrhage or infarction
Ischemic stroke	Secondary	An ischemic stroke was defined as any ischemic stroke occurring anytime during the **Exposure time**. Ischemic strokes were defined based on primary and secondary ICD-10 GM hospital discharge diagnoses I63* (cerebral infarction) in the patient individual follow-up period.
Hemorrhagic stroke	Secondary	A hemorrhagic stroke was defined as any hemorrhagic stroke occurring anytime during the **Exposure time**. Hemorrhagic strokes were defined based on primary and secondary ICD-10 GM hospital discharge diagnoses I61* (intracebral haemorrhage) in the patient individual follow-up period.
All-cause mortality	Secondary	Death from any cause during the **Exposure time**.
Gastrointestinal bleeding event	Secondary	A gastrointestinal bleeding event was defined as a bleeding event occurring anytime during the **Exposure time**. Gastrointestinal bleeding events were defined based on primary or secondary ICD10 GM hospital discharge diagnoses. For a complete list of all gastrointestinal bleeding events and their operationalization using ICD-10 GM codes please see column bleeding category in Table 22 in the appendix of

		this report.
Intracranial bleeding event	Secondary	An intracranial bleeding event was defined as a bleeding event occurring anytime during the **Exposure time**. Intracranial bleeding events were defined based on the primary or secondary ICD10 GM hospital discharge diagnoses. For a complete list of all intracranial bleeding events and their operationalization using ICD-10 GM codes please see column bleeding category in Table 22 in the appendix of this report.
Any bleeding event	Secondary	Any bleeding event was defined as a bleeding event occurring anytime during the **Exposure time**. Any bleeding event was defined based on primary or secondary ICD10 GM hospital discharge diagnoses. For a complete list of all any bleeding events and their operationalization using ICD-10 GM codes please see column bleeding category in Table 22 in the appendix of this report. Severe, intracerebral and gastrointestinal bleeding events are part of this composite endpoint, i.e. all ICD 10 GM codes listed in Table 22 in the appendix of this report will be used for the definition of this endpoint.

9.3.2. Factors affecting censoring during follow up

Table 2 Definition of censoring events

Variable	**Operational definition**

Discontinuation	Discontinuation was defined as no evidence of the index OAC prescription or switching to another OAC throughout the gap period after the end of supply after the end of the **Exposure time** of the previous prescription. The last day of the **Exposure time** was defined as the date of discontinuation. Note: Any patient who switched from any dose of NOACs indicated for the treatment of AF to dabigatran 75mg or rivaroxaban 10mg were censored, because neither of these treatment regimens is indicated for the stroke prevention in AF patients. Patients switching to warfarin were censored.
Switch of OAC	Patients who receive a prescription for an OAC other than the index OAC prescription during the follow- up period were considered switchers if this switch occurred within 30 days after the end of the **Exposure time**. Patients were also censored if a prescription for edoxaban was issued within 30 days after the end of the **Exposure time**. The date on which the changed prescription was dispensed was defined as the date of the switch. If a prescription, which differed from the initial OAC prescription, was dispensed before the end of the previous prescription, the date of the follow-up dispensation was defined as the switch date and the patient was considered to be on the changed treatment from that date onwards.
Death	Patients who died during the follow up period. Date of death = date

	of censoring (i.e. end of follow-up).
End of enrollment	For patients who switched to a different health insurer during the follow up period, claims data were no longer available in the InGef database. The date of the end of the enrollment determined the date of censoring (i.e. end of the follow up) for these patients.

9.3.3. Exposure variables

Patients were allocated to the following four treatment groups listed below based on their index prescription:

- apixaban
- dabigatran
- rivaroxaban
- phenprocoumon.

9.3.4. Other covariates

The covariates included in the analysis were chosen based on biological plausibility, a literature or expert recommendation. They include comorbidities in the baseline period, age and the risk factors associated with bleeding and stroke.

Table 3 Definition of covariates

Variable	Category	Operational definition
Age	continuous	Age on the index date.
Gender	categorical	Sex on the index date.
Insurance status	categorical	Insurance status on the index date.

		• regular insurance • retired • family insured • unknown
Region	categorical	Place of residence on the index date: (01.01. of the index year) • east/west • urban/rural • unknown Patients were assigned to the groups based on the municipality key which was documented for each patient on Dec, 31st in the year before the index date. The municipality key can be traced back to the region of residence and hence it is possible to determine whether patients live in urban or rural areas or in the east or the west. However, for a small proportion of patient, the municipality key was not available. These patients were placed in the unknown category.
Number of hospitalizations	continuous	Total number of hospitalizations, independent of admission diagnosis, during the baseline period.
Days of hospitalization	continuous	Total number of hospital days, independent of admission diagnosis, during the baseline period.
Days between last hospitalization and index date	continuous	Distance in days between the last hospitalization prior to the index date and the index date.

Number of ambulatory physician visits	continuous	Total number of ambulatory physician visits, independent of the reason for the visit, during the baseline period.
No of unique medications	continuous	Number of unique pharmaceutical substances (unique ATC 5 Codes) per patient received during the baseline period, based on the prescriptions documented in the database.
CHA_2DS_2-VASc Score	continuous	The CHA_2DS_2-VASc score was calculated by assigning one point each for hypertension, diabetes mellitus, heart failure, vascular disease (peripheral artery disease, myocardial infarction, aortic plaque), age 65-74 years, female sex and two points for age 75 years or older, previous stroke or transient ischemic attack (TIA), with a total possible score of nine (12). Ambulatory verified as well as primary and secondary hospital discharge diagnoses within in the 12 months before the index date were used to assess the CHA_2DS_2-VASc score. For a complete list of all ICD-10 codes which were used to form the CHA_2DS_2-VASc score please refer to Table 23 in the appendix of this report.
$CHADS_2$ Score	continuous	The $CHADS_2$ Score was calculated by assigning one point each for hypertension, heart failure, age 75 years and older, diabetes mellitus. A preliminary stroke/TIA was assigned two points, with a total possible score of six (12). Ambulatory verified as well as primary and secondary hospital discharge diagnoses within in the 12 months before the index date were used to assess the $CHADS_2$ score.

		For a complete list of all ICD-10 codes which were used to form the $CHADS_2$ score please refer to Table 24 in the appendix of this report.
Charlson Comorbidity Index (CCI)	continuous	The Charlson Comorbidity Index (CCI) was used to weigh comorbidities in the baseline period depending on their severity (13–15). Ambulatory verified as well as primary and secondary hospital discharge diagnoses within the 12 months before the index date were used to calculate the CCI score. A list of included conditions and their assigned weights can be found in Table 25 in the appendix of this report.
Comorbidity Index (modified Charlson Comorbidity Index)	continuous	In order to avoid a high degree of correlation between some covariates a separate Comorbidity Index was defined, which included only disease categories which are not already measured by the HAS BLED score. This modified Comorbidity Index contains all Charlson disease categories except hypertension, congestive heart failure, cerebrovascular disease, mild, moderate or severe liver disease and moderate or severe renal disease.
Bleeding history (modified HAS BLED Score)	continuous	The HAS-BLED score was calculated for each patient in the baseline period by assigning one point and summing the score across the following conditions: hypertension, renal disease, cirrhosis, and stroke, major bleeding event, age 65 and older, use of non-steroidal anti-inflammatory drug, intake of antiplatelet agents, alcohol abuse. Since the InGef database does not contain any laboratory parameters, the international normalized ratio (INR) will not be included in the HAS-BLED score. For a complete list of all ICD codes which will be

		used to form the HAS-BLED score please refer to Table 26 in the appendix of this report.
Myocardial infarction (MI)	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from a previous myocardial infarction. MI was defined using the ICD-10 GM code I21.* and I22.*.
Chronic renal insufficiency	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from a chronic renal insufficiency. Chronic renal insufficiency was defined using the ICD-10 GM code N18.*.
Chronic renal insufficiency stage I	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage I was defined using the ICD-10 GM code N18.1.
Chronic renal insufficiency stage II	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage II was defined using the ICD-10 GM code N18.2.

Chronic renal insufficiency stage III	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage III was defined using the ICD-10 GM code N18.3.
Chronic renal insufficiency stage IV	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage IV was defined using the ICD-10 GM code N18.4.
Chronic renal insufficiency stage V	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage V was defined using the ICD-10 GM code N18.5.
Other chronic renal insufficiency	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from other chronic renal insufficiency. Other chronic renal insufficiency was be defined using the ICD-10 GM code N18.8.
Unspecified chronic	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and

renal insufficiency		secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from an unspecified renal insufficiency. Unspecified chronic renal insufficiency was be defined using the ICD-10 GM code N18.9.
Diabetes	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from diabetes mellitus. Diabetes mellitus was defined using the ICD-10 GM code E10.*-E14.*.
Hypertension	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from hypertension. Hypertension was defined using the ICD-10 GM code I10.*.
Congestive heart failure	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the Index date index date were used to assess whether patients suffered from congestive heart failure. Congestive heart failure was defined using the ICD-10 GM code I50.*.
Artherosclerosis of arteries of extremities	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from peripheral vascular disease. Peripheral vascular disease was

		defined using the ICD-10 GM code I70.2.
Ischemic stroke or TIA during baseline	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were be used to assess whether patients suffered from ischemic stroke or TIA. Ischemic stroke or TIA was defined using the ICD-10 GM code I63, I64, G45.9 and G45.8.
Coronary heart disease	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were be used to assess whether patients suffered from coronary heart disease. Coronary heart disease was defined using the ICD-10 GM code I20*(angina pectoris), I24.*(other acute ischemic heart diseases) and I25* (chronic ischaemic heart disease).
Liver disease		
Mild liver disease	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from a mild liver disease. Mild liver disease was defined using the ICD-10 GM codes according to the Charlson Comorbidity Index (Table 25).
Moderate or severe liver disease	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from a moderate or

		severe liver disease. Moderate or severe liver disease was defined using the ICD-10 GM codes according to the Charlson Comorbidity Index (Table 25).
Severe liver disease	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were be used to assess whether patients suffered from a severe liver disease. Severe liver disease was defined using the ICD-10 GM codes K70.4 Alcoholic hepatic disease K71.1 Toxic liver disease with hepatic necrosis K72.1 Chronic hepatic failure K72.9 Hepatic failure, unspecified K76.5 Hepatic veno-occlusive disease K76.6 Portal hypertension K76.7 Hepatorenal syndrome I85.0 Oesophageal varices with bleeding I85.9 Oesophageal varices without bleeding I86.4 Gastric varices I98.2 Oesophageal varices without bleeding in diseases classified elsewhere
Smoking	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients used tobacco. Tobacco use was defined using the ICD-10 GM codes F17*,

		Z71.6, Z72.0.
Alcohol abuse	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients abused alcohol. Alcohol abuse was defined using the ICD-10 GM codes F10*, Z71.4, Z50.2, Z72.1.
Depression	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from depression. Depression was defined using the ICD-10 GM codes F32*, F33*, F34.1.
Somatoform disorder	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from a somatoform disorder. Somatoform disorder was defined using the ICD-10 GM codes F45*.
Anxiety disorder	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were be used to assess whether patients suffered from anxiety disorder. Anxiety disorder was defined using the ICD-10 GM codes F40* and F41*.
Substance abuse	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the

		365 days before or on the index date were used to assess whether patients suffered from substance abuse. Substance abuse was defined using the ICD-10 GM codes F11*, F12*, F13*, F14*, F15*, F16*, F18*, F19*.
Dementia	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from dementia. Dementia was defined using the ICD-10 GM codes F00*, F01*, F02*, F03.
Cancer	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used to assess whether patients suffered from cancer. Cancer was defined using the ICD-10 GM code C*.
Obesity	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date were used assess whether patients suffered from obesity. Obesity was defined using the ICD-10 GM codes E66.
Major bleeding event	categorical	It was assessed whether patients suffered from a major bleeding event 365 days before or on the index date. Major bleeding events were defined as A. (hospital case in which the : • hospital admission was labelled as an

		emergency admission AND • an any bleeding (except D62*), gastrointestinal, intracerebral ICD 10 codes in Table 22 validated by OPS 8-800 (blood transfusion) or the ICD 10 diagnosis D62* (Acute posthaemorrhagic anaemia) have been documented in the same case with one of the) **OR** B. A hospital case with one of the ICD 10 codes labelled as a major bleeding event in the last column of Table 22 was documented as main or secondary discharge diagnosis. For a complete list of all major bleeding events and their operationalization using ICD-10 GM codes please see column *major bleeding* Table 22 in the appendix of this report.
Gastrointestinal bleeding event	categorical	It was assessed whether patients suffered from a gastrointestinal bleeding event in the 365 days before or on the Index date. Gastrointestinal bleeding events were defined based on primary or secondary ICD10 GM hospital discharge diagnoses and ambulatory verified diagnosis in the patient individual baseline period. For a complete list of all gastrointestinal bleeding events please see Table 22 in the appendix of this report. This covariate was only incorporated in the analysis

		when the outcome gastrointestinal bleeding is investigated.
Any bleeding event	categorical	It was assessed whether patients suffered from any bleeding event in the 365 days before or on the Index date. Any bleeding event was defined based on primary or secondary ICD10 GM hospital discharge diagnoses and ambulatory verified diagnosis in the patient individual baseline period. For a complete list of all any bleeding events please see Table 22 in the appendix of this report. This covariate was incorporated in the analysis when the outcome any bleeding event is investigated.
Proton-pump-inhibitors (omeprazol)	categorical	It was assessed whether patients received at least one prescription for proton-pump-inhibitors in the 365 days before or on the index date. Furthermore it was assessed whether patients were still under therapy on the index date. For that purpose it was calculated whether the drug supply of the last prescription prior to the index date lasted at least as long as the index date. For a complete list of all relevant ATC Codes please refer to Table 27 in the appendix of this report.
Coronary angioplasty	categorical	It was assessed whether patients underwent a percutaneous transluminal coronary angioplasty (PTCA) in the 365 days before or on the index date. The OPS Code 8837 (*perkutan-transluminale Gefäßintervention an Herz und Koronargefäßen*) was used to determine whether the procedure has been performed in the patient individual baseline period.
Antiplatelet	categorical	It was assessed whether patients received at least one

medication		prescription for antiplatelet medications in the 365 days before or on the index date. Furthermore it was assessed whether patients were still under therapy on the index date. For that purpose it was tested whether the drug supply of the last prescription prior to the index date lasted at least as long as the index date. The relevant ATC code that was used is B01ACx.
Prescription of acetylsalicylic acid (ASS)	categorical	It was assessed whether patients received at least one prescription for ASS (ATC Code: B01AC06) in the 365 days before or on the index date. Furthermore it was assessed whether patients were still under therapy on the index date. For that purpose it was tested whether the drug supply of the last prescription prior to the index date lasted at least as long as the index date.
Prescription of non-steroidal anti-inflammatory drugs (NSAIDs)	categorical	It was assessed whether patients received at least one prescription for NSAIDs (ATC Code: M01A*) in the 365 days before or on the index date. Furthermore it was assessed whether patients were still under therapy on the index date. For that purpose it was tested whether the drug supply of the last prescription prior to the index date lasted at least as long as the index date.

For a list of all covariates, their labels and definition please refer to Table 28 in the appendix of this report.

9.4. Data sources and measurement

The InGef database, from which patients will be selected for inclusion in the study population, is a complete, longitudinal claims dataset of approximately 6.7 million patients, comprising approximately 10% of the statutory health insured population between 2010 and 2016.

Data on patients and physicians is anonymized, as are the providers and the sickness funds, before data is made available to the InGef. No regions smaller than federal states or cohorts with less than 100 patients are identified. The InGef functions as the safe haven for data processing, statistics, predictive analytics, and outcomes research, ensuring the highest levels of patient data security.

The InGef research database includes information about the utilization of services on a case-by-case individual level. To support claims, indications (ICD10-GM) and procedure codes are provided together with costs.

The claims database does not contain any direct clinical parameters (e.g. lab test results, results of bone density tests, quality of life data, severity grade of a disease, symptom scores etc.).

9.5. Study Size

A preliminary feasibility analysis was conducted. Table 4 provides an estimate of the patient count which can be expected in the respective groups. However this preliminary assessment did not consider all of the above listed in- and exclusion criteria. We estimate that the number of study patients might be up to 25% lower because of the chosen in – and exclusion criteria.

Table 4 Results preliminary feasibility study

Initial OAC prescription	**N**
apixaban	~9,500
dabigatran	~4,500
rivaroxaban	~22,000
phenprocoumon	~25,000
Total	~61,000

Based on the full sample size depicted in Table 4 and its reduced version, power analysis were conducted to find out whether the sample size had enough power to detect clinically meaningful differences with regard to the primary and secondary endpoints in the three

NOACs therapy groups. The method of Freedman for time-to-event analysis that satisfies the proportional-hazards assumption was used (16). It is relatively easy to implement and has proved well in comparative simulation studies (17). In this approach, the power depends on the expected number of patients in both groups, the probability of events combined across years in both groups and a postulated hazard ratio (expression of the effect-size when time-to-events are to be reported). The HR and probability of events used were those previously reported in the ARISTOTLE, RE-LY and ROCKET-AF clinical trials for apixaban, dabigatran and rivaroxaban respectively (8,9). Calculations were performed using a power of 80% and an α level of 0.05 (two sided). It was hypothesized that patients presenting with a high risk of bleeding were prescribed the lowest dose of apixaban (2.5 mg) in daily clinical practice, despite of not fulfilling the predefined criteria in this regard. To assess the impact of a possible bias in the assessment of the probability of event for both groups on power estimates, three different scenarios were identified, where we attributed: (i) the highest risk level to the entire sample, (ii) the same risk distribution as in the clinical trial (10-90% for the highest and lowest risk groups respectively) and (iii) a changing distribution, where the proportion belonging the high-risk group varied between 5% and 60%. Power estimates obtained under the different scenarios did not vary much and a representative medium value was presented here.

The results are presented in **Fehler! Verweisquelle konnte nicht gefunden werden.**. For ischemic or hemorrhagic stroke or systemic embolism and major bleeding, defined as primary outcomes here, the study has enough power in all therapy groups to detect the expected effects using a Cox Proportional Hazard Model. The same holds also for a reduced sample size (higher dropout rate of 20%).

Table 5 Power analyses for the endpoints ischemic or hemorrhagic stroke or systemic embolism, major bleeding

Endpoints	NOAC	Data			Power Analysis	
		No. of patients (observed in the database)	Probability of event (from RCT)	HR	Power vs VKA	Expected sample size

		C	T	C	T	HR	p-value	Full Size	Reduced size#	C	T
Major bleed	Api.	25.000	9.500	0,051	0,036	0,690	0,001	0,99	0,98	-	-
	Dabi.	25.000	4.500	0,066	0,0535	0,80	0,003	0.91	0,85	-	-
	Riva.	25.000	22.000	0,054	0,055	1.04	0,58	-	-	-	-
Stroke/SE	Api.	25.000	9.500	0,029	0,023	0,788	0,012	0,88	0,80	-	-
	Dabi	25.000	4.500	0,033	0,030	0,91	0,34	-	-	-	-
	Riva.	25.000	22.000	0,034	0,027	0,79	0,02	0,99	0,97	-	-

#This calculation was based on a conservative dropout rate of 20%
Abbreviations: C: Control; T: Therapy; SE: Systematic embolism; HR: Hazard Ratio; Api: Apixaban, Dabi: Dabigatran; Riva: Rivaroxaban

9.6. Statistical methods

This section provides a detailed overview about the statistical methods that were applied in order to answer each research question. The core statistical elements (analysis populations, definition and measurement of endpoints and other key variables and statistical methodology) are adequately detailed within the study report and in this section and no separate SAP was compiled.

9.6.1. Demographic and clinical characteristics

In a first step the demographic and clinical characteristics of the patients in all treatment groups were determined. All variables were derived based on claims data in the baseline period. Table 3 provides an overview about all variables which were formed for the description of the study population and for the inclusion in the multivariate models.

For continuous variables, the mean, median, minimum (min), maximum (max) and the standard deviation (SD) are reported. For categorical variables the absolute number and relative proportion of patients with the respective characteristic are reported. Proportions are relative to the total sample size in each treatment group. The differences between the treatment groups is estimated by calculating the standardized difference in means (SMD), using a threshold of 0.1 to indicate imbalance:

$$\frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{(n_1-1)S_1^2 + (n_2-1)S_2^2}{n_1+n_2-2}}} \quad \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{(n_1-1)S_1^2 + (n_2-1)S_2^2}{n_1+n_2-2}}}$$

Phenprocoumon is used as the reference group. All covariates described in Table 3 are depicted in a descriptive manner.

9.6.2. Time to event – Cox proportional hazards model

The adjusted risk of a major bleeding event was estimated using a Cox proportional hazards model. In this scenario, the independent exposure of interest was the type of drug exposure at treatment initiation.

Baseline covariates were considered time-independent, i.e. only their values at baseline were be considered. If we define T as the subject's time of event since follow-up or treatment regime changes with time measured in days, A_p a subject's treatment with drug p up to t and V be a vector of time-independent baseline covariates, the conditional hazard of event given treatment history and covariates at baseline was:

$$\lambda_T(t|A,V) = \lambda_0(t)\exp(\sum_{p=1}^{P-1} \beta_{1_p} A_p + \beta_2 V)$$

with $\lambda_0(t)$ the unspecified baseline hazard; the row vectors β_1 and β_2 the unknown parameters to be estimated; P the number of alternative drugs (A is a categorical variable).

Each of the NOACs, namely apixaban, dabigatran and rivaroxaban, were compared to phenprocoumon. Hence, phenprocoumon was the reference category in the analysis. A subset of the variables depicted in Table 3, which were selected on an empirical basis, was included as covariates in the Cox proportional hazards model.

We report the event rate per 100 patient years and the corresponding 95% confidence intervals per treatment group for the outcome major bleeding events.

The adjusted hazard ratios based on a multiple proportional hazard Cox model, the corresponding 95% confidence intervals and the regression coefficients are reported.

9.6.2.1. Censoring

Patients were followed from the index date to date of:

- discontinuation of treatment,
- switch of treatment,
- death (a potential issue of informative censoring will be assessed by analyzing the combined endpoint of stroke, systematic embolism, major bleeding or death),
- end of continuous enrollment,
- end of study period,

whichever occurs earlier.

Censoring occurred if a subject either withdrew or reached the end of follow-up without experiencing any event. If we defined E_i and c_i the (independent) event time and censoring time of individual i respectively, then the time of event $T_i = \min_i\{E_i, c_i\}$. We defined a censoring variable C_i taking values 1 if $E_i \leq c_i$ and 0 otherwise which was included in the partial likelihood function of the Cox model.

9.6.3. Time to event –Marginal structural model

In order to account for changes in the treatment regime throughout the patient-individual follow-up period (time-dependent exposure), as well as for the presence of time-dependent covariates that may simultaneously be confounders (possibly affected by prior treatment) and intermediate variables (predict both subsequent treatment and subsequent outcome), a marginal structural model Cox proportional hazards model with inverse probability treatment weighting (Cox PH MSM) was fitted. By fitting the final Cox PH model using inverse-probability-of-treatment weighted (IPTW) estimators, MSM allowed us to obtain unbiased estimates of treatment effects of ischemic events and major bleeding events, when (i) the treatment changed over time and (ii) in the presence of confounding covariates. Weighting each subject with the inverse probability of having his own treatment given his covariates and confounder profile gives more weight to individuals with small treatment probabilities

(less likely to be confounded). In this pseudo-population, the treatment is unconfounded but the causal relationship treatment/outcome remains the same as in the actual population. The true causal effect of the treatment on the outcome can therefore be unbiasedly estimated from the pseudo-population using a standard PH Cox model.

A two-step estimation strategy was necessary to separate the controlling for confounding from the estimation of the (unbiased) risk parameters in the marginal structural model.

1. In the first step the weights for each subject and occasion were derived, i.e., the same subject is assigned different weights at different occasions. Specifically, the IPWT weight for occasion p was based on the overall probability of the subject receiving his or her own observed sequence of treatments for all previous occasions $A(1)$ to $A(k)$, i.e., the product of the occasion-specific probabilities of the observed treatments. The weights were based on the estimated probability that a subject received his own observed treatment, given his baseline covariates, past treatments, and confounder history. In this study we used stabilized weights which were defined as:

$$sw_K = \prod_{k=0}^{K} \frac{P(A_k|A_{k-1}, V)}{P(A_k|A_{k-1,}L_{k-1}, V)}, \quad A_{-1} = 0$$

   where L is a vector of time dependent confounders. By accounting for both treatment history and baseline covariates in both the numerator and denominator, the stabilized weight reflected an incremental effect of the time-varying confounders on the current treatment choice, over and above the other determinants of the treatment. Furthermore, it has been shown that the use of stabilized weights leads to more efficient estimates of the treatment effects, especially to CI for the outcome having reasonable variance estimates, in comparison to those obtained with highly variable unstabilized weights. For the estimation of the probabilities $P(A_k|A_{k-1}, L_{k-1}, V)$ and $P(A_k|A_{k-1}, V)$ we used multinomial logistic regression.

2. In the second step the causal treatment effect was estimated using a Cox-Regression, including the weights derived in the first step as a time-dependent covariate, i.e,

$$\lambda(t|A,V) = \lambda_0(t)\exp(\sum_{p=1}^{P-1}\beta_{1_p}A_p + \beta_2 V)$$

Ultimately only the treatment variable was included as a time dependent variable. Further time dependent covariates were not included in the final MSM.

9.6.3.1. Censoring weights

Censoring variable for the MSM model were the same as for the classical Cox model. Unbiased estimates of the causal parameters β_1 were then obtained by fitting the final weighted Cox model in which for a subject at risk at time t, the weight is the product $sw_K \times sw_K{}'$, where

$$sw'_K = \prod_{k=0}^{K} \frac{P(C_k = 1|C_{k-1} = 1, A_{k-1}, V)}{P(C_k = 1|C_{k-1} = 1, A_{k-1,}L_{k-1}, V)}, \quad A_{-1} = 0, C_{-1} = 1$$

was the weight when no event occurred before t. If the event occurs at t, then the weight was calculated by

$$sw'_K = \prod_{k=0}^{K-1} \frac{P(C_k = 1|C_{k-1} = 1, A_{k-1}, V)}{P(C_k = 1|C_{k-1} = 1, A_{k-1,}L_{k-1}, V)} \cdot \frac{P(C_k = 0|C_{k-1} = 1, A_{k-1}, V)}{P(C_k = 0|C_{k-1} = 1, A_{k-1,}L_{k-1}, V)}$$

Those weights accounted for confounded censoring and time-varying selection bias due to loss to follow-up. As for the treatment, probabilities in the numerator and the denominator were estimated using a pooled logistic regression model. The denominator represents the patient's conditional probability of remaining uncensored up to k given his observed treatment and covariate history. The product $sw_K \times sw_K{}'$ then represent the conditional probability for a patient to have his own treatment and censoring history. The weighted estimator of the final Cox model can be referred to as "inverse-probability-of-treatment-and-censoring" weighted (IPTCW).

9.6.3.2. Censoring

Patients were followed from the index date to date of:

- death (a potential issue of informative censoring will be assessed by analyzing the combined endpoint of stroke, systemic embolism, major bleeding or death),
- end of continuous enrollment,
- end of study period,
- discontinuation of treatment

whichever occurs earlier.

9.6.3.3. Days of VKA supply – empirical DDD

In order to estimate the time period in which patients were under oral anticoagulative treatment a two-step approach was implemented.

First, in an attempt to account for the intra- and interpersonal variability of the phenprocoumon treatment regime a personalized DDD (pDDD) based on the observed phenprocoumon prescription patterns for each patient in the InGef database was calculated.

For this purpose the PZN code ("Pharmazentralnummer") was used to compute the amount of active ingredient (AAI) dispensed to each patient of the phenprocoumon group for each prescription. A pPDD representing the average daily dose taken during follow-up was computed for each patient i such that:

$$pPDD_i = \frac{\sum_{k=1}^{K-1} AAI_{i,k}}{T_i}$$

- k = index of the prescriptions received during follow-up ($k \in \{1, K\}$)
- T= number of days between the first and the last prescription during follow-up.

For the sake of simplicity, only prescriptions of patients who were solely treated with phenprocoumon during follow-up were included in the computation of the eDDD. Patients with a pDDD below the 5th or above the 95th percentile and patients with only one

prescription for phenprocoumon were assigned the median pDDD (eDDD) over all patients[6]. The Exposure Time (ET) corrected from the intra- and interpersonal variability of Phenprocoumon treatments (pDDD) can be computed for each patient i as:

$$ET_i = \frac{\sum_{k=1}^{K} AAI_{i,k}}{pDDD}$$

Secondly, for each phenprocoumon patient, the median of the distribution of the pPDD estimated over all patients was used to calculate exposure times for the phenprocoumon patients. For the sake of simplicity, only prescriptions of patients who were solely treated with phenprocoumon during follow-up were included in the computation of the eDDD.

The Exposure Time (ET) corrected from the intra- and interpersonal variability of Phenprocoumon treatments was computed for each patient i as:

$$ET_i = \frac{\sum_{k=1}^{K} AAI_{i,k}}{eDDD}$$

The eDDD was used to estimate exposure times for all phenprocoumon patients in the main analysis.

9.6.4. Missing values

None

9.6.5. Sensitivity analysis early user

In this sensitivity analysis the inclusion period was limited to 01.01.2013 until 31.03.2015. This is done to allow a follow up period of 365 days after treatment initiation or until death in all treatment groups.

9.6.6. Sensitivity analysis propensity score matching

In order to test the robustness of the results estimated by means of the multivariate Cox regression, the group of patients treated with OAC's and the group of patients treated with

[6] Unadjusted event rates will also be provided for a scenario in which patients with a pDDD below the 5th or above the 95th percentile will not be assigned the median pDDD, but their true estimated pDDD. Patients with only one prescription will be assigned the median pDDD estimated over all patients.

apixaban, rivaroxaban and dabigatran respectively, was compared by means of propensity score matching (PSM).

For each apixaban, rivaroxaban and dabigatran case, a control was selected from the pool of subjects in the phenprocoumon group. Controls will be matched 1:1 according to the propensity score (PS) (the same control subjects can only be matched once), age, and sex using nearest-neighbor matching. The matching criteria were assessed in the year prior to the index quarter. The propensity score was calculated using logistic regression as the probability of being assigned to the respective NOAC group (apixaban, dabigatran or rivaroxaban) conditional on a set of given covariables. Three separate PSM's will be conducted to match the following groups:

- phenprocoumon and apixaban
- phenprocoumon and dabigatran
- phenprocoumon and rivaroxaban.

The distribution of the outcome variables in the baseline period in the matched groups was checked to evaluate the matching performance. For continuous variables, the mean, median, minimum (min), maximum (max) and the standard deviation (SD) are investigated. For categorical variables the absolute number and relative proportion of patients with the respective characteristic are reported. Proportions are relative to the total sample size in each treatment group. The differences between the treatment groups were estimated by calculating the standardized difference in means (SMD), using a threshold of 0.1 to indicate imbalance:

$$\frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}}}$$

Following the PSM a univariate Cox Regression Model, with treatment group was estimated to calculate hazard ratios for all outcomes under study comparing patients treated with phenprocoumon and patients treated with apixaban, dabigatran and rivaroxaban, respectively.

9.6.7. Subgroup analysis dosing

To assess the impact of different dosages on the primary findings the risk of effectiveness and safety endpoints was compared to phenprocoumon only for those patients who received the reduced dose of NOACs (2x2.5mg/d for apixaban, 2x110 mg/d for dabigatran, 1x15 mg/d for rivaroxaban), and standard approved dose of NOACs only (2x5mg/d for apixaban, 2x150 mg/d for dabigatran, 1x20 mg/d for rivaroxaban), respectively.

9.7. Quality control

Data quality management comprises data collection, management, and verification process, including quality control processes and documentation of the quality control steps.

Data quality management is built in to the core processing systems. In addition SAS is used to process data extracted from the production process to determine quality metrics.

As part of the management strategy the InGef documents and implements:

1. Quality control processes around reference data.
2. Rules for raw data checks for completeness reasonability and volume
3. Control processes for production files and outputs.
4. Process flow and maintenance processes including standard operating procedures.
5. Database metrics including quality and completeness
6. Procedures for handling internal inquiries

The InGef routinely applies data quality assurance across data life-cycle stages. The following process is typical:

Data acquisition

The acquisition of the data follows a predefined statistical data-collection design/plan. The first control is the assurance that this plan is executed, i.e. all the required data items have been acquired and are in the collected-data-repository.

The data is then checked for compliance and completeness:

1. File Completeness Check
2. File format versus the predefined standard

3. Data content – are all fields present with corresponding values?

Data-processing checks include:

1. Control for correctness of the format and any input files format transformations
2. Control of correctness of the bridged data

Processed-data checks include:

1. Control of individual data-suppliers - total data volume versus expected and previous periods
2. Checks for missing data estimations
3. Check for aggregated data by analysis unit, e.g. values for surgeries, hospitals, PCTs, Regions

Data quality management is built in to the core processing systems, however, SAS is also used to process data extracted from the production process to determine quality metrics.

As part of the management strategy InGef documents and implements:

1. Rules for raw data checks for completeness reasonability and volume
2. Control processes for production files and outputs.
3. Process flow and maintenance processes including standard operating procedures.
4. Database metrics including quality and completeness
5. Procedures for handling internal inquiries

Indicator Quality Assurance:

The InGef will output a series of descriptive statistics derived from the underlying data to validate the integrity of the field content. A sample of these statistics includes but is not limited to:

1. Record counts with each data table
2. Unique counts of patients
3. Unique counts of patients continuously enrolled for specified one year increments
4. Percentage of missing values in key data fields (e.g. patient date of birth, patient gender, billing and diagnosis codes, dates of service, etc.)

5. Percentage of valid values in key data fields:

6. Verify that a unique patient identifier is linked to only one individual.

9.8. Protection of human subjects

Not applicable.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in *Guidelines for Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

10. RESULTS

10.1. Participants

A total of 242.316 patients with at least one prescription for an oral anticoagulant, i.e. phenprocoumon, apixaban, dabigatran, rivaroxaban, edoxaban or warfarin, between 01.01.2013 and 31.12.2015 were identified in the InGef research database. After applying all of the defined in- and exclusion criteria 61.205 patients remained in the selected study population, thereof 23.823 phenprocoumon patients, 10.117 apixaban patients, 5.122 dabigatran and 22.143 rivaroxaban patients. Table 6 provides a detailed overview of the selection of the study population.

Table 6 Attrition table selection of the study population

Inclusion criteria	***Treatment group***	***N***
1. insurants with OAC prescription in 2013 / 2014 / 2015		242.316
2. thereof observable in pre-index period and at least one day after index		236.842

3. thereof new OAC user in 2013 / 2014 / 2015		127.711
4. thereof with spec I48		73.026
5. thereof age >= 18 at index		73.025
6. thereof without dialyses / valvular / thrombosis / pregnancy in pre-index period (4 quarter before index)		66.828
7. thereof without heparin dispensation at index day		62.709
8. thereof with clear assignment of ingredient and dose		62.563
9. thereof without dose indicated for thrombosis (dabigatran 75 mg, rivaroxaban 2.5 mg, rivaroxaban 10mg)		61.585
10. thereof phenprocoumon, apixaban, dabigatran or rivaroxaban as initial ingredient (exclusion of warfarin and edoxaban user)		61.205
a. thereof with an initial prescription for	phenprocoumon	23.823
b. thereof with an initial prescription for	apixaban	10.117
c. thereof with an initial prescription for	dabigatran	5.122
d. thereof with an initial prescription for	rivaroxaban	22.143

10.2. Baseline characteristics

Patients prescribed phenprocoumon or apixaban were older, had a higher CHA2DS2-VASc score and had a higher Charlson Comorbidity Index compared to those who initiated treatment with dabigatran or rivaroxaban. The proportion of patients with a history of stroke or SE was higher among patients being newly initiated on apixaban and dabigatran indicating preferential use of these 2 substances for secondary stroke prevention (Table 7).

Table 7 Baseline characteristics of the study population

Characteristic	Phenpro-coumon *n* = 23,823	Any NOAC *n* = 37,382	Apixaban *n* = 10,117	Dabigatran *n* = 5,122	Rivaroxaban *n* = 22,143
Patient demographics					
Age (mean ± SD)	75.2 (9.5)	72.7 (11.7)	74.5 (11.4)	71.7 (11.6)	72.1 (11.8)
Male (%)	53.3	53.8	51.4	55.1	54.7
Medical history					

Characteristic	Phenpro-coumon *n* = 23,823	Any NOAC *n* = 37,382	Apixaban *n* = 10,117	Dabigatran *n* = 5,122	Rivaroxaban *n* = 22,143
CHA_2DS_2-VASc score (mean ± SD)	4.0 (1.6)	3.7 (1.8)	4.0 (1.8)	3.7 (1.8)	3.5 (1.8)
modified HAS-BLED score (mean ± SD)	2.8 (1.1)	2.6 (1.2)	2.8 (1.2)	2.6 (1.2)	2.5 (1.2)
Charlson Comorbidity Index (mean ± SD)	3.4 (2.6)	3.0 (2.6)	3.4 (2.7)	2.9 (2.5)	2.9 (2.5)
Ambulatory care visits (mean ± SD)	13.8 (7.5)	12.6 (7.2)	12.9 (7.2)	12.4 (7.1)	12.5 (7.2)
Number of hospital days (mean ± SD)	11.1 (17.7)	11.4 (18.7)	12.8 (20.1)	10.7 (17.4)	10.9 (18.4)
Number of hospitalizations (mean ± SD)	1.2 (1.3)	1.3 (1.3)	1.3 (1.3)	1.3 (1.2)	1.2 (1.3)
Hospitalization within the 30 days before first dispensation (%)	46.3	61.0	62.3	62.6	60.0
Hospitalization due to stroke/SE within the 30 days before first dispensation (%)	3.6	6.9	10.2	11.2	4.4
Comorbidities					
Ischemic stroke or TIA (%)	11.9	15.0	20.1	21.7	11.2
Myocardial Infarction (%)	8.3	5.1	5.7	5.5	4.8
Renal insufficiency (%)	23.6	16.8	21.0	12.3	15.9
Congestive heart failure (%)	39.7	36.7	35.5	30.7	32.5
Coronary heart disease (%)	46.6	36.7	38.3	36.0	36.1
Hypertension (%)	88.2	84.8	87.0	84.4	83.8
Cancer (%)	19.7	18.5	19.8	17.5	18.2
Moderate or severe liver disease (%)	0.6	0.4	0.6	0.2	0.4
Dementia (%)	7.1	8.5	10.8	6.5	7.9
Atherosclerosis (%)	7.5	5.7	6.3	5.3	5.6
Hemiplegia (%)	6.2	9.3	12.9	12.7	6.9
Thyroid dysfunction (%)	28.6	28.5	29.9	27.8	28.0
COPD (%)	29.9	27.5	27.7	26.1	27.8
Diabetes mellitus (%)	37.0	32.3	33.4	30.2	32.2
Obesity (%)	24.9	23.6	22.9	22.4	24.3
Mobility and gait disorders (%)	10.5	11.7	15.4	9.9	10.4
Senility (%)	5.6	6.3	8.9	4.5	5.5

Characteristic	Phenpro-coumon *n* = 23,823	Any NOAC *n* = 37,382	Apixaban *n* = 10,117	Dabigatran *n* = 5,122	Rivaroxaban *n* = 22,143
Any bleeding event (%)	8.8	8.0	9.3	7.2	7.6
Concomitant medications					
Number of unique substances prescribed (mean ± SD)	9.9 (5.3)	9.2 (5.3)	9.7 (5.4)	8.9 (5.2)	9.1 (5.3)
Antiplatelet drugs (%)	25.3	23.9	26.5	25.1	22.5
ASA (%)	19.3	19.1	21.2	19.3	18.1
NSAIDs (%)	35.4	36.4	35.8	35.5	36.9
β-blocker (%)	82.2	82.4	81.9	82.3	82.6
Amiodarone (%)	6.5	4.9	5.0	4.1	5.1
Diuretics (%)	54.3	44.8	48.5	41.6	43.9
Antipsychotics (%)	4.4	5.7	7.3	4.7	5.2
Proton-pump-inhibitors (%)	43.9	44.1	46.0	44.0	43.6

ASA acetylsalicylic acid, ATC anatomical therapeutic chemical, CHA2DS2-VASc congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA, vascular disease, age, sex category, modified HAS-BLED hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, elderly, drugs/alcohol concomitantly, NSAIDs non-steroidal anti-inflammatory drugs, TIA transient ischemic attack, COPD chronic obstructive pulmonary disease

10.3. Outcome data

10.3.1. Unadjusted and adjusted event rates

Table 8 displays the number of effectiveness outcome events, and the crude and adjusted event rates per 100 person-years according to treatment. There were 1,383 stroke/SE events during follow-up. Of these, 968 were coded as ischemic strokes. Slightly higher crude event rates of stroke or systemic embolism were observed for apixaban and phenprocoumon. The highest crude event rates of death from all causes were observed for patients on apixaban which, however, comprised the subgroup of patients with the highest mean age, CHA2DS2-VASc, HAS-BLED, and comorbidity scores (Table 7).

Table 9 displays the number of events, and the crude and adjusted event rates per 100 person-years according to initiated treatment for safety outcomes. A total of 336 patients experienced an intracranial bleeding event. For apixaban and dabigatran, crude event rates of all safety outcomes were lower than that for phenprocoumon and rivaroxaban.

Table 8 Number of effectiveness events, crude event rates, and adjusted event rates per 100 person-years according to initiated treatment

Outcome	Phenprocoumon			Apixaban			Dabigatran			Rivaroxaban		
	Events	Crude rate	Adjusted rate	Events	Crude rate	Adjusted rate	Events	Crude rate	Adjusted rate	Events	Crude rate	Adjusted rate
Stroke/SE	597	2.5	2.2	226	2.7	1.7	104	2.2	1.5	456	2.2	1.8
Stroke	510	2.1	1.9	196	2.3	1.4	91	1.9	1.3	396	1.9	1.5
Ischemic stroke	399	1.7	1.4	165	1.9	1.2	82	1.7	1.2	322	1.6	1.2
Hemorrhagic stroke	119	0.5	0.4	25	0.3	0.2	10	0.2	0.1	78	0.4	0.3
Death any cause	1595	6.7	4.6	804	9.4	4.4	253	5.2	3.7	1509	7.2	4.6

Table 9 Number of safety events, crude event rates, and adjusted event rates per 100 person-years according to initiated treatment

Outcome	Phenprocoumon			Apixaban			Dabigatran			Rivaroxaban		
	Events	Crude rate	Adjusted rate	Events	Crude rate	Adjusted rate	Events	Crude rate	Adjusted rate	Events	Crude rate	Adjusted rate
Major bleeding	692	2.9	2.3	167	2.0	1.4	80	1.7	1.5	568	2.7	2.3
Intracranial bleeding	175	0.7	0.6	35	0.4	0.3	20	0.4	0.3	106	0.5	0.4
Gastrointestinal bleeding	730	3.0	2.4	213	2.5	1.7	123	2.6	2.2	759	3.7	2.9
Any bleeding	2573	11.4	9.8	822	10.0	7.7	393	8.5	7.9	2276	11.5	10.1

10.4. Main results after multivariate Cox proportional hazards model

After adjusting for baseline confounders apixaban and dabigatran use was associated with lower risks for both primary endpoints, namely for the combined outcome of hemorrhagic stroke, ischemic stroke and systemic embolism as well as for major bleeding. Adjusted hazard ratios for all outcomes and all treatment groups are depicted Table 10. Primary outcomes are highlighted in grey.

Table 10 Adjusted hazard ratios with 95% confidence intervals for primary and secondary outcomes (reference group=phenprocoumon)

Outcome	Apixaban HR (95% CI) p-value	Dabigatran HR (95% CI) p-value	Rivaroxaban HR (95% CI) p-value
Hemorrhagic / ischemic stroke / systemic embolism	0.77 (0.66-0.90) p=0.001	0.74 (0.6-0.91) p=0.005	0.86 (0.76-0.97) p=0.018
Major bleeding	0.58 (0.49-0.69) p<0.001	0.64 (0.50-0.80) p<0.001	0.99 (0.88-1.10) p=0.805
Any bleeding	0.78 (0.72-0.84) p=0	0.82 (0.74-0.92) p=0	1.05 (0.99-1.11) p=0.084
Intracranial bleeding	0.44 (0.3-0.64) p<0.001	0.52 (0.33-0.84) p=0.007	0.68 (0.53-0.88) p=0.003
Gastrointestinal bleeding	0.71 (0.6-0.82) p<0.001	0.96 (0.79-1.17) p=0.683	1.26 (1.13-1.40) p<0.001
Hemorrhagic stroke	0.47 (0.3-0.73) p=0.001	0.38 (0.2-0.74) p=0.004	0.75 (0.56-1.00) p=0.053
Ischemic stroke	0.82 (0.68-0.99) p=0.036	0.85 (0.67-1.08) p=0.188	0.91 (0.78-1.05) p=0.208
Hemorrhagic / ischemic stroke	0.76 (0.64-0.90) p=0.002	0.74 (0.59-0.93) p=0.01	0.87 (0.76-0.99) /p=0.036

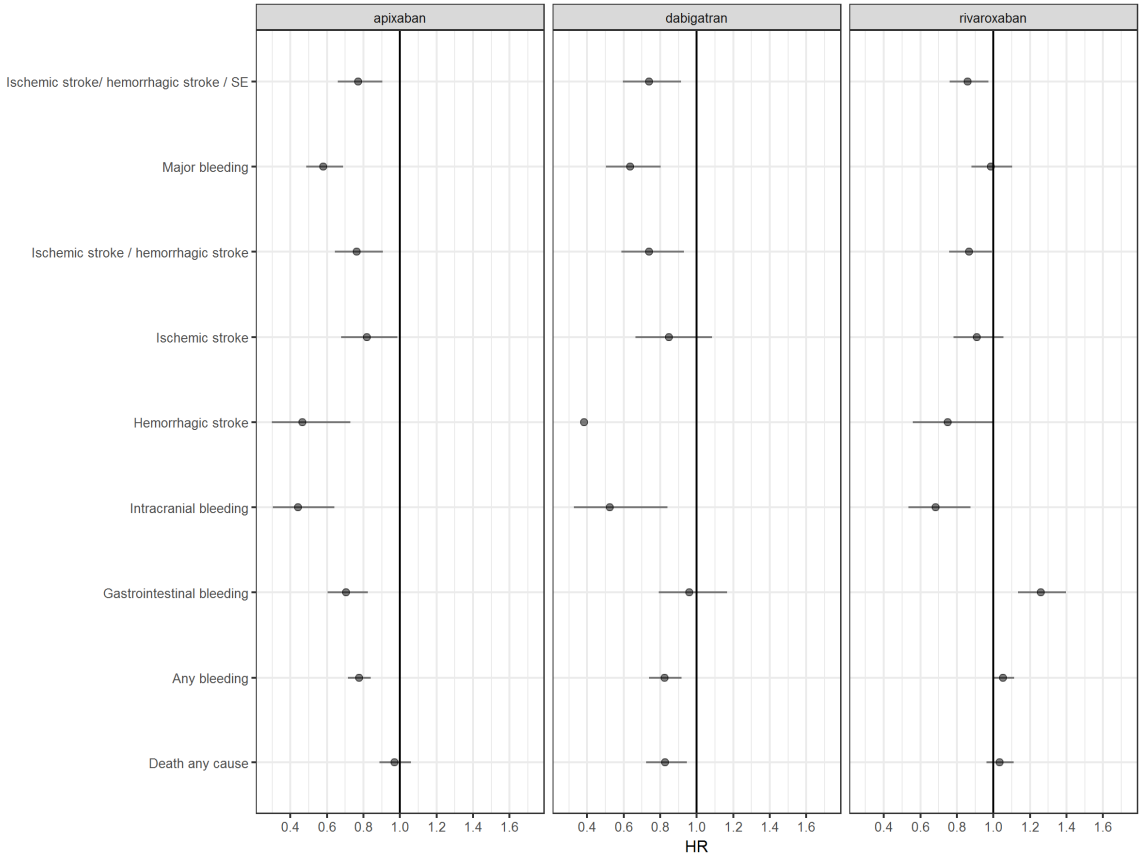
Death any cause	0.97 (0.89-1.06) p=0.506	0.83 (0.72-0.95) p=0.006	1.03 (0.96-1.11) p=0.366

HR hazard ratio; CI confidence interval;

The hazard ratios for the primary effectiveness outcome were 0.77 (95% CI 0.66-0.90, p=0.001) and 0.74 (95% CI 0.60-0.91, p=0.005) for apixaban and dabigatran, respectively. Apixaban patients had a 42% lower risk for major bleeding compared to patients treated with phenprocoumon (HR 0.58, 95% CI 0.49-0.69, p <0.001). Therapy with rivaroxaban was associated with lower risks of stroke/SE compared to phenprocoumon (HR 0.86, 95% CI 0.76-0.97, p=0.018), while the risk of major bleeding was similar between rivaroxaban and phenprocoumon users (HR 0.99, 95% CI 0.88-1.10, p=0.805).

Apixaban patients had a lower risk for all other safety outcomes studied, namely for any bleeding (HR 0.78, 95% CI 0.72-0.84, p <0.001), intracranial bleeding (HR 0.44, 95% CI 0.30-0.64, p < 0.001), and gastrointestinal bleeding (HR 0.71, 95% CI 0.60-0.82, p < 0.001). Apixaban was also associated with a lower risk for hemorrhagic stroke (HR 0.47, 95% CI 0.30-0.73, p=0.001), ischemic stroke (0.82, 95% CI 0.68-0.99, p=0.036) and the combined endpoint of both (HR 0.76, 95% CI 0.64-0.90, p=0.002). The risk for all cause death in apixaban and rivaroxaban patients was similar compared to that of phenprocoumon patients. Dabigatran was associated with lower risks of death from any cause compared to phenprocoumon (HR 0.83, 95% CI 0.72-0.95, p=0.006). Rivaroxaban was associated with a higher risk for gastrointestinal bleeding (HR 1.26, 95% CI 1.13-1.40, p < 0.001).

Figure 3: Adjusted hazard ratios with 95% confidence intervals for all outcomes (reference group=phenprocoumon)

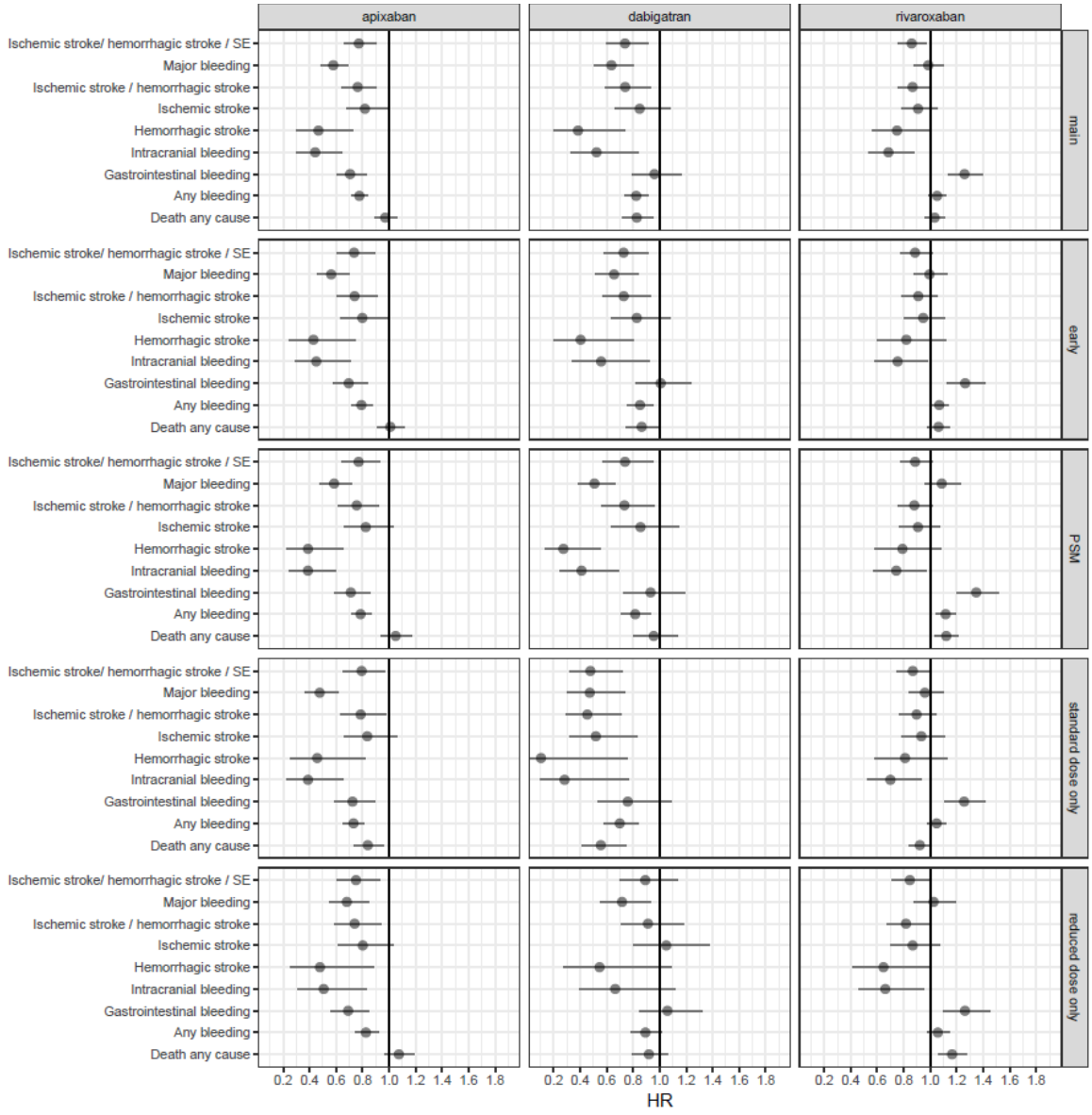


10.5. Other analyses

In the following section the results of the sensitivity analyses performed will be presented. In the study protocol two sensitivity analyses regarding the calculation of the exposure time of phenprocoumon patients had been planned. Results from these analyses were similar to the results of the main analysis and will not be reported.

Figure 4 provides an overview of the adjusted hazard ratios of all sensitivity analyses, which enables a visual comparison of all performed analyses. The following subsections each contain a more detailed description of the results, including p-values.

Figure 4: Adjusted hazard ratios with 95% confidence intervals for all outcomes and all analyses scenarios (reference group=phenprocoumon)



10.5.1. Sensitivity analysis early user

In this sensitivity analysis only patients initiating the therapy until 31.03.2015 were included in the analysis. Table 11 displays the selection of this specific study population. A total of 47.407 patients were included in the study population, thereof 20.276 phenprocoumon, 5.786 apixaban, 4.291 dabigatran and 17.054 rivaroxaban patients. Baseline characteristics of early user were similar to those of the main analysis and will not be reported separately.

Table 11 Attrition table selection of the study population initiating treatment until 31 March 2015

Inclusion criteria	*Treatment group*	*N*
1. Insurants with OAC prescription in 2013 / 2014 / 2015		242.316
2. thereof observable in pre-index period and at least one day after index		236.842
3. thereof new OAC user in 2013 / 2014 / 2015		127.711
4. thereof with spec I48		73.026
5. thereof age >= 18 at index		73.025
6. thereof without dialyses / valvular / thrombosis / pregnancy in pre-index period (4 quarter before index)		66.828
7. thereof without heparin dispensation at index day		62.709
8. thereof with clear assignment of ingredient and dose		62.563
9. thereof without dose indicated for thrombosis (dabigatran 75 mg, rivaroxaban 2.5 mg, rivaroxaban 10mg)		61.585
10. thereof phenprocoumon, apixaban, dabigatran or rivaroxaban as initial ingredient (exclusion of warfarin and edoxaban)		61.205
11. thereof with an initial prescription before 31 March 2015		47.407
a. thereof with an initial prescription for	phenprocoumon	20.276
b. thereof with an initial prescription for	apixaban	5.786
c. thereof with an initial prescription for	dabigatran	4.291
d. thereof with an initial prescription for	rivaroxaban	17.054

Unadjusted and adjusted event rates were similar to rates in the main analysis (see section 10.3.1) and are not reported here.

After adjusting for baseline confounders the risks for the occurrence of all studied outcomes were similar to the risks reported in the main analysis. The risks for the combined endpoint

of stroke/SE and for major bleeding were lower for patients treated with apixaban and dabigatran compared to patients treated with phenprocoumon. For early rivaroxaban user no significant risk reduction regarding the occurrence of both primary outcomes was found (Table 12).

The adjusted hazard ratios for the secondary outcomes were similar to the ones reported in the main analysis. Rivaroxaban patients initiating treatment until 31 March 2015 also had a significantly higher risk of gastrointestinal bleeding (HR 1.26, 95% CI 1.13-1.41, p<0.001).

Table 12 Adjusted hazard ratios with 95% confidence intervals for primary and secondary outcomes for sensitivity analysis including early user only (reference group=phenprocoumon)

Outcome	Apixaban HR (95% CI) p-value	Dabigatran HR (95% CI) p-value	Rivaroxaban HR (95% CI) p-value
Hemorrhagic / ischemic stroke / systemic embolism	0.74 (0.61-0.89) p=0.002	0.73 (0.58-0.91) p=0.006	0.89 (0.78-1.01) p=0.075
Major bleeding	0.56 (0.46-0.70) p<0.001	0.66 (0.51-0.84) p=0.001	0.99 (0.88-1.13) p=0.932
Any bleeding	0.79 (0.72-0.87) p=0	0.85 (0.76-0.95) p=0.006	1.07 (1.00-1.14) p=0.039
Intracranial bleeding	0.45 (0.29-0.71) p<0.001	0.56 (0.34-0.92) p=0.022	0.75 (0.58-0.98) p=0.036
Gastrointestinal bleeding	0.7 (0.58-0.84) p<0.001	1.01 (0.82-1.23) p=0.94	1.26 (1.13-1.41) p<0.001
Hemorrhagic stroke	0.43 (0.25-0.75) p=0.003	0.4 (0.2-0.81) p=0.01	0.82 (0.6-1.12) p=0.211
Ischemic stroke	0.8 (0.64-1.00) p=0.049	0.83 (0.64-1.08) p=0.156	0.95 (0.81-1.11) p=0.506
Hemorrhagic ischemic stroke	0.74 (0.6-0.91) p=0.004	0.73 (0.57-0.93) p=0.012	0.91 (0.79-1.05) p=0.197
Death any cause	1.01 (0.91-1.12) p=0.871	0.86 (0.75-1.00) p=0.043	1.06 (0.98-1.15) p=0.125

HR hazard ratio; CI confidence interval;

10.5.2. Sensitivity analysis propensity score matching

10.5.2.1. Baseline characteristics after PSM

A propensity score matching was used to adjust for possible differences in baseline characteristics. Three matched cohorts using 1:1 PSM were created: phenprocoumon versus apixaban ($n_{per\ group}$=9448), phenprocoumon versus dabigatran ($n_{per\ group}$=5005) and phenprocoumon versus rivaroxaban ($n_{per\ group}$=18.056). Baseline characteristics and clinical features, including risk scores (CHA2DS2-VASc and modified HAS-BLED), were balanced with all standardized differences less than 10% between the matched cohorts (compare Table 13).

Table 13 Baseline characteristics of the matched treatment groups

	Phenprocoumon - Apixaban Cohort		**Phenprocoumon - Dabigatran Cohort**		**Phenprocoumon - Rivaroxaban Cohort**	
Characteristic	**Phenpro-coumon *n* = 9448**	**Apixaban *n* = 9448**	**Phenpro-coumon *n* = 5005**	**Dabigatran *n* = 5005**	**Phenpro-coumon *n* = 18,056**	**Rivaroxaban *n* = 18,056**
Patient demographics						
Age (mean ± SD)	74.4 (10.8)	74.6 (10.9)	72.0 (11.3)	72.1 (11.2)	74.2 (9.9)	74.0 (10.2)
Male (%)	51.3	51.5	55.5	54.8	53.6	53.3
Medical history						
CHA_2DS_2-VASc score (mean ± SD)	4.0 (1.7)	3.9 (1.8)	3.7 (1.7)	3.7 (1.8)	3.9 (1.6)	3.8 (1.7)
modified HAS-BLED score (mean ± SD)	2.8 (1.2)	2.7 (1.2)	2.6 (1.2)	2.6 (1.2)	2.7 (1.1)	2.6 (1.1)
Charlson Comorbidity Index (mean ± SD)	3.3 (2.6)	3.3 (2.7)	2.9 (2.4)	2.9 (2.5)	3.1 (2.5)	3.1 (2.6)
Ambulatory care visits (mean ± SD)	13.3 (7.3)	13.0 (7.2)	12.5 (7.1)	12.5 (7.2)	13.3 (7.3)	12.8 (7.2)
Number of hospital days	12.7 (18.3)	12.3 (19.6)	11.5 (16.6)	10.7 (17.4)	11.3 (17.5)	11.2 (18.8)
Number of hospitalizations (mean ± SD)	1.3 (1.3)	1.3 (1.3)	1.3 (1.2)	1.3 (1.2)	1.2 (1.3)	1.2 (1.3)
hospitalisation within the 30 days before first despensions (%)	61.2	61.2	62.0	61.9	54.8	55.5
hospitalisation due to stroke/SE within the 30 days before first despensions (%)	7.5	7.6	10.3	10.5	4.5	4.5

	Phenprocoumon - Apixaban Cohort		Phenprocoumon - Dabigatran Cohort		Phenprocoumon - Rivaroxaban Cohort	
Characteristic	**Phenpro-coumon *n* = 9448**	**Apixaban *n* = 9448**	**Phenpro-coumon *n* = 5005**	**Dabigatran *n* = 5005**	**Phenpro-coumon *n* = 18,056**	**Rivaroxaban *n* = 18,056**
Comorbidities						
Ischemic stroke or TIA (%)	17.2	17.0	20.5	20.9	12.7	11.5
Myocardial Infarction (%)	5.9	5.9	5.1	5.6	6.1	5.5
Renal insufficiency (%)	20.8	21.2	12.8	12.5	18.8	18.1
Congestive heart failure (%)	35.1	36.0	31.2	31.2	35.7	35.5
Coronary heart disease (%)	38.6	39.4	35.8	36.3	41.1	40.0
Hypertension	88.2	87.1	85.9	84.7	87.7	85.5
Cancer (%)	18.8	20.2	16.6	17.6	18.7	19.3
Moderate or severe liver disease (%)	0.6	0.6	0.1	0.2	0.5	0.5
Dementia (%)	9.9	9.6	6.5	6.5	7.7	7.8
Artherosclerosis (%)	7.1	6.3	5.7	5.3	6.8	6.0
Hemiplegia (%)	9.5	10.7	10.9	12.3	6.7	7.0
Thyroid dysfunction (%)	29.0	30.1	27.6	28.1	28.1	28.6
COPD (%)	29.1	28.0	26.3	26.2	29.3	28.4
Diabetes mellitus (%)	35.4	33.7	32.5	30.3	35.5	33.9
Obesity (%)	25.4	23.2	25.1	22.5	25.3	24.3
Any bleeding event (%)	8.9	8.9	7.6	7.2	8.3	8.1
Concomitant medications						
Number of unique substances prescribed	9.8	9.7	9.0 (5.0)	8.9 (5.2)	9.6 (5.2)	9.4 (5.4)
Antiplatelet drugs (%)	24.6	26.5	23.5	25.1	24.2	24.3
ASA (%)	18.9	21.1	17.8	19.4	18.6	19.5
NSAIDs (%)	36.2	35.9	35.4	35.7	36.4	37.1
β-blocker (%)	82.5	82.4	82.3	82.3	82.3	82.6
Amiodarone (%)	4.9	5.2	3.9	4.2	5.6	5.5
Diuretics (%)	50.4	48.9	45.0	42.1	50.7	47.0
Antipsychotics (%)	6.2	6.2	4.7	4.6	5.0	4.9

	Phenprocoumon - Apixaban Cohort		Phenprocoumon - Dabigatran Cohort		Phenprocoumon - Rivaroxaban Cohort	
Characteristic	**Phenpro-coumon *n* = 9448**	**Apixaban *n* = 9448**	**Phenpro-coumon *n* = 5005**	**Dabigatran *n* = 5005**	**Phenpro-coumon *n* = 18,056**	**Rivaroxaban *n* = 18,056**
Proton-pump-inhibitors (%)	44.2	46.0	41.9	42.1	42.8	44.1

ASA acetylsalicylic acid, ATC anatomical therapeutic chemical, CHA2DS2-VASc congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA, vascular disease, age, sex category, modified HAS-BLED hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, elderly, drugs/alcohol concomitantly, NSAIDs non-steroidal anti-inflammatory drugs, TIA transient ischemic attack, COPD chronic obstructive pulmonary disease

10.5.2.2. Adjusted hazard ratios after PSM

The hazard ratios after PSM were similar to the hazard ratios reported in the main analysis. The risk of both primary outcomes was lower for apixaban and dabigatran user compared to phenprocoumon user (Table 14). Both apixaban and dabigatran users showed significant risk reduction of stroke/SE compared to phenprocoumon users (HR 0.77, 95% CI 0.64-0.93, p=0.006; HR 074, 95% 0.57-0.95, p=0.018). After PSM no significant risk reduction for the occurrence of both primary outcomes was observed in rivaroxaban users compared to phenprocoumon users.

The hazard ratios after PSM for the secondary outcomes studied were similar to the risks found in the main analysis. Apixaban treatment was associated with a lower risk of any bleeding (HR 0.78, 95% CI 0.71-0.86, p<0.001), intracranial bleeding (HR 0.39, 95% CI 0.25-0.60, p<0.001), gastrointestinal bleeding (HR 0.71, 95% CI 0.59-0.85, p<0.001) and hemorrhagic stroke (HR 0.39, 95% CI 0.23-0.66, p<0.001). Similar hazards were found for comparison of dabigatran and phenprocoumon patients. However, dabigatran was not associated with a significantly lower risk of gastrointestinal bleeding (HR0.93, 95% CI 0.73-1.19, p=0.571).

After PSM the risk of any bleeding (HR 1.12, CI 1.05-1.19, p=0.001), gastrointestinal bleeding (HR 1.35, 95% CI 1.20-1.51, p<0.001) and all cause death (HR 1.12, 95% CI 1.04-1.21, p=0.005) was significantly higher in rivaroxaban patients compared to phenprocoumon patients.

Table 14 Adjusted hazard ratios with 95% confidence intervals for primary and secondary outcomes for sensitivity analysis PSM (reference group=phenprocoumon)

Outcome	Apixaban HR (95% CI) p-value	Dabigatran HR (95% CI) p-value	Rivaroxaban HR (95% CI) p-value
Hemorrhagic / ischemic stroke / systemic embolism	0.77 (0.64-0.93) p=0.006	0.74 (0.57-0.95) p=0.018	0.89 (0.77-1.02) p=0.083
Major bleeding	0.58 (0.48-0.71) p<0.001	0.51 (0.39-0.67) p<0.001	1.09 (0.96-1.23) p=0.187
Any bleeding	0.78 (0.71-0.86) p<0.001	0.82 (0.71-0.93) p=0.003	1.12 (1.05-1.19) p=0.001
Intracranial bleeding	0.39 (0.25-0.60) p<0.001	0.41 (0.24-0.69) p=0.001	0.74 (0.57-0.97) p=0.03
Gastrointestinal bleeding	0.71 (0.59-0.85) p<0.001	0.93 (0.73-1.19) p=0.571	1.35 (1.2-1.51) p<0.001
Hemorrhagic stroke	0.39 (0.23-0.66) p<0.001	0.27 (0.14-0.55) p<0.001	0.79 (0.58-1.08) p=0.143
Ischemic stroke	0.82 (0.66-1.03) p=0.086	0.86 (0.64-1.15) p=0.297	0.91 (0.77-1.07) p=0.246
Hemorrhagic / ischemic stroke	0.76 (0.62-0.92) p=0.006	0.73 (0.56-0.96) p=0.024	0.88 (0.76-1.02) p=0.088
Death any cause	1.05 (0.94-1.17) p=0.38	0.96 (0.8-1.14) p=0.611	1.12 (1.04-1.21) p=0.005

HR hazard ratio; CI confidence interval;

10.5.3. Subgroup analysis dosing

10.5.3.1. Baseline characteristics according to NOAC dose

Among patients who received apixaban, dabigatran and rivaroxaban, 37% (n=3741), 51% (n=2596), and 28% (n=6220), respectively, initiated treatment at a reduced dose. There were important differences in baseline characteristics of patients receiving reduced and standard NOAC dosing: Patients receiving the reduced dose regimens were older by 9.8 to 11.3 years and had more comorbidities resulting in higher CHA2DS2-VASc and higher modified HAS-

BLED scores. Table 15 depicts baseline characteristics for both dosages and all treatment groups.

Table 15 Baseline characteristics according to NOAC dose

Characteristic	Phenpro-coumon	Apixaban		Dabigatran		Rivaroxaban	
		(5 mg)	(2.5 mg)	(150 mg)	(110 mg)	(20 mg)	(15 mg)
	n=23,823	n=6376	n=3741	n=2526	n=2596	n=15,923	n=6220
Patient demographics							
Age (mean ± SD)	75.2 (9.5)	70.4 (10.9)	81.6 (8.2)	66.0 (10.7)	77.3 (9.5)	69.3 (11.6)	79.1 (9.0)
Male (%)	53.3	57.6	40.7	63.5	46.9	58.3	45.5
Medical history							
CHA_2DS_2-VASc score (mean ± SD)	4.0 (1.6)	3.5 (1.8)	4.9 (1.5)	2.9 (1.7)	4.4 (1.7)	3.2 (1.7)	4.5 (1.6)
modified HAS-BLED score (mean ± SD)	2.8 (1.1)	2.5 (1.2)	3.2 (1.1)	2.2 (1.1)	3.0 (1.2)	2.3 (1.1)	3.0 (1.1)
Charlson Comorbidity Index (mean ± SD)	3.4 (2.6)	2.8 (2.5)	4.4 (2.8)	2.2 (2.0)	3.6 (2.7)	2.4 (2.3)	4.0 (2.8)
Ambulatory care visits (mean ± SD)	13.8 (7.5)	12.7 (7.3)	13.1 (7.1)	11.9 (7.0)	12.9 (7.2)	12.3 (7.1)	13.1 (7.3)
Number of hospital days (mean ± SD)	11.1 (17.7)	10.1 (18.4)	17.3 (22.0)	7.3 (12.4)	14.0 (20.7)	9.2 (16.5)	15.2 (21.8)
Number of hospitalizations (mean ± SD)	1.2 (1.3)	1.2 (1.2)	1.6 (1.5)	1.1 (1.1)	1.4 (1.4)	1.2 (1.2)	1.4 (1.4)
hospital case within the 30 days before first despensions (%)	46.3	59.4	67.4	62.0	63.2	60.3	59.2
hospital case due to stroke/SE within the 30 days before first despensions (%)	3.6	9.2	11.9	10.0	12.3	3.9	5.7
Number of unique ATC codes (mean ± SD)	9.9 (5.3)	8.8 (5.2)	11.2 (5.5)	7.6 (4.6)	10.1 (5.4)	8.5 (5.1)	10.8 (5.6)
Comorbidities							
Previous Ischemic stroke or TIA (%)	11.9	18.0	23.6	18.6	24.7	9.6	15.4
Myocardial Infarction (%)	8.3	4.2	8.2	3.4	7.6	3.8	7.4

Characteristic	Phenpro-coumon	Apixaban		Dabigatran		Rivaroxaban	
		(5 mg)	(2.5 mg)	(150 mg)	(110 mg)	(20 mg)	(15 mg)
	n=23,823	n=6376	n=3741	n=2526	n=2596	n=15,923	n=6220
Renal insufficiency (%)	23.6	12.6	35.2	5.5	19.0	9.3	32.6
Congestive heart failure (%)	39.7	27.6	49.0	22.0	39.2	27.0	46.6
Coronary heart disease (%)	46.6	32.9	47.4	28.3	43.5	32.1	46.2
Hypertension	88.2	84.6	91.1	80.1	88.7	81.9	88.7
Cancer (%)	19.7	17.7	23.2	14.4	20.5	16.5	22.5
Moderate or severe liver disease (%)	0.6	0.5	0.7	0.2	0.2	0.4	0.6
Dementia (%)	7.1	5.7	19.5	2.3	10.6	5.1	15.0
Artherosclerosis (%)	7.5	5.1	8.4	3.3	7.4	4.5	8.2
Hemiplegia (%)	6.2	11.3	15.8	10.0	15.4	5.5	10.2
Thyroid dysfunction (%)	28.6	28.8	32.0	26.6	29.0	27.4	29.8
COPD (%)	29.9	26.8	29.2	24.1	28.0	26.9	30.1
Diabetes mellitus (%)	37.0	30.0	39.4	25.1	35.1	29.0	40.5
Obesity (%)	24.9	24.8	19.6	24.4	20.4	24.9	22.7
Mobility and gait disorders (%)	10.5	10.0	24.6	5.2	14.4	7.7	17.3
Any bleeding event (%)	8.8	6.5	13.9	3.9	10.3	5.9	12.0
Concomitant medications							
Number of unique substances prescribed (mean ± SD)	9.9 (5.3)	8.8 (5.2)	11.2 (5.5)	7.6 (4.6)	10.1 (5.4)	8.5 (5.1)	10.8 (5.6)
Antiplatelet drugs (%)	25.3	20.9	36.1	17.4	32.5	18.7	32.2
ASA (%)	19.3	16.9	28.7	14.1	24.5	15.2	25.6
NSAIDs (%)	35.4	37.4	33.1	35.1	35.9	37.7	34.8
β-blocker (%)	82.2	82.0	81.8	82.5	82.1	82.8	82.1
Amiodarone (%)	6.5	5.1	4.8	4.3	4.0	4.9	5.7
Diuretics (%)	54.3	39.4	64.0	31.7	51.3	37.2	61.1
Antipsychotics (%)	4.4	4.7	11.7	2.2	7.0	3.9	8.6

Characteristic	Phenpro-coumon	Apixaban		Dabigatran		Rivaroxaban	
		(5 mg)	(2.5 mg)	(150 mg)	(110 mg)	(20 mg)	(15 mg)
	n=23,823	n=6376	n=3741	n=2526	n=2596	n=15,923	n=6220
Proton-pump-inhibitors (%)	43.9	41.7	53.9	35.6	48.4	40.2	49.9

10.5.3.2. Adjusted hazard ratios according to NOAC dose

The adjusted hazards for the primary outcomes stroke/SE and major bleeding were significantly lower in both apixaban subgroups, i.e. in patients treated with the standard or the low dose of apixaban, compared to phenprocoumon patients. The same was found for all secondary outcomes studied with the exception of any cause death. While apixaban patients treated with the standard dose had a significantly lower risk of death from any cause (HR 0.84, 95% CI 0.74-0.96, p=0.009), no significant risk reduction was found for patients treated with the reduced dose (HR 1.07, 95% CI 0.97-1.19, p=0.177). The adjusted hazard ratios for all outcomes and according to NOAC dose are displayed in Table 16.

The significant risk reduction for all effectiveness outcomes in dabigatran patients initiating treatment on the standard dose was not found in patients taking the reduced dose. While the risk of stroke/SE was significantly lower in dabigatran patients on the standard dose compared to phenprocoumon treatment (HR 0.48, 95% CI 0.32-0.72, p<0.001), no significant risk reduction was found for patients on the reduced dose (HR 0.89, 95% CI 0.70-1.13, p=0.349). The adjusted hazard ratio for major bleeding was significantly lower compared to phenprocoumon treatment in patients on the standard dabigatran dose (HR 0.47, 95% CI 0.30-0.74, p<0.001) and on the reduced dabigatran dose (0.72, 95% CI 0.55-0.94, p=0.014).

In rivaroxaban patients the adjusted risk for all outcomes under study was similar in patients treated with the standard dose or with the reduced dose compared to patients treated with phenprocoumon. The only exception was any cause death. The risk for any cause death (HR 1.17, 95% CI 1.07-1.27, p=0.001) of patients treated with the reduced dose of rivaroxaban was significantly higher compared to phenprocoumon patients, whereas no significant difference was found for patients on the standard dose.

Table 16 Adjusted hazard ratios with 95% confidence intervals for primary and secondary outcomes according to NOAC dose (reference group=phenprocoumon)

Outcome	Apixaban		Dabigatran		Rivaroxaban	
	HR (95% CI) / p-value		HR (95% CI) / p-value		HR (95% CI) / p-value	
	5mg	**2.5mg**	**150mg**	**110mg**	**20mg**	**15mg**
Hemorrhagic / ischemic stroke / systemic embolism	0.79 (0.65-0.97) /p=0.023	0.75 (0.6-0.93) /p=0.01	0.48 (0.32-0.72) /p<0.001	0.89 (0.70-1.13) /p=0.349	0.87 (0.75-1) /p=0.056	0.85 (0.71-1.01) /p=0.062
Major bleeding	0.48 (0.37-0.61) /p<0.001	0.68 (0.55-0.84) / p<0.001	0.47 (0.3-0.74) /p=0.001	0.72 (0.55-0.94) /p=0.014	0.96 (0.84-1.1) /p=0.553	1.03 (0.88-1.19) /p=0.745
Any bleeding	0.73 (0.66-0.81) /p<0.001	0.83 (0.74-0.92) /p<0.001	0.70 (0.58-0.84) /p<0.001	0.89 (0.79-1.01) /p=0.079	1.05 (0.98-1.12) /p=0.164	1.06 (0.98-1.14) /p=0.165
Intracranial bleeding	0.39 (0.23-0.65) /p<0.001	0.51 (0.31-0.83) /p=0.007	0.28 (0.1-0.77) /p=0.013	0.66 (0.39-1.12) /p=0.124	0.70 (0.53-0.93) /p=0.015	0.66 (0.46-0.95) /p=0.024
Gastrointestinal bleeding	0.72 (0.59-0.89) /p=0.002	0.69 (0.56-0.85) /p<0.001	0.76 (0.53-1.09) /p=0.132	1.06 (0.85-1.32) /p=0.613	1.26 (1.11-1.42) /p<0.001	1.26 (1.10-1.45) /p=0.001
Hemorrhagic stroke	0.46 (0.26-0.82) /p=0.008	0.48 (0.26-0.88) /p=0.018	0.1 (0.01-0.75) /p=0.025	0.55 (0.27-1.09) /p=0.085	0.81 (0.58-1.13) /p=0.215	0.65 (0.42-1.01) /p=0.054
Ischemic stroke	0.83 (0.66-1.06) /p=0.133	0.80 (0.62-1.04) /p=0.09	0.52 (0.32-0.83) /p=0.006	1.05 (0.80-1.38) /p=0.725	0.93 (0.79-1.11) /p=0.433	0.87 (0.70-1.07) /p=0.189
Hemorrhagic / ischemic stroke	0.79 (0.63-0.97) /p=0.027	0.74 (0.59-0.93) /p=0.012	0.45 (0.29-0.71) /p<0.001	0.91 (0.71-1.18) /p=0.479	0.90 (0.77-1.05) /p=0.169	0.82 (0.68-0.99) /p=0.039
Death any cause	0.84 (0.74-0.96) /p=0.009	1.07 (0.97-1.19) /p=0.177	0.56 (0.41-0.75) /p<0.001	0.92 (0.79-1.06) /p=0.259	0.92 (0.84-1.01) /p=0.078	1.17 (1.07-1.27) /p=0.001

10.5.4. Sensitivity analysis marginal structural model

After adjusting for baseline confounders and time varying treatment apixaban and dabigatran use was associated with lower risks for both primary endpoints, namely for the combined outcome of hemorrhagic stroke, ischemic stroke and systemic embolism as well as for major bleeding. Adjusted hazard ratios for all outcomes and all treatment groups are depicted Table 17.

Table 17 Adjusted hazard ratios with 95% confidence intervals for primary and secondary outcomes for sensitivity analysis MSM (reference group=phenprocoumon)

Outcome	Apixaban HR (95% CI) p-value	Dabigatran HR (95% CI) p-value	Rivaroxaban HR (95% CI) p-value
Hemorrhagic / ischemic stroke / systemic embolism	0.80 (0.69-0.93) /p=0.003	0.77 (0.62-0.94) /p=0.012	0.89 (0.79-1.00) /p=0.057
Major bleeding	0.59 (0.51-0.70) /p<0.001	0.68 (0.55-0.84) /p<0.001	1.01 (0.91-1.12) /p=0.887
Any bleeding	0.77 (0.72-0.83) /p<0.001	0.84 (0.76-0.93) /p=0.001	1.05 (0.99-1.11) /p=0.092
Intracranial bleeding	0.45 (0.32-0.64) /p<0.001	0.49 (0.31-0.79) /p=0.003	0.66 (0.52-0.84) /p=0.001
Gastrointestinal bleeding	0.71 (0.61-0.82) /p<0.001	0.98 (0.82-1.18) /p=0.832	1.26 (1.15-1.39) /p<0.001
Hemorrhagic stroke	0.48 (0.32-0.73) /p=0.001	0.32 (0.17-0.64) /p=0.001	0.75 (0.56-0.99) /p=0.041
Ischemic stroke	0.87 (0.73-1.04) /p=0.128	0.92 (0.72-1.16) /p=0.462	0.97 (0.84-1.12) /p=0.666
Hemorrhagic / ischemic stroke	0.80 (0.68-0.94) /p=0.008	0.78 (0.63-0.97) /p=0.027	0.91 (0.8-1.03) /p=0.148
Death any cause	1.03 (0.95-1.12) /p=0.516	0.85 (0.75-0.97) /p=0.014	1.05 (0.98-1.13) /p=0.136

HR hazard ratio; CI confidence interval;

The hazard ratios for the primary effectiveness outcome stroke/SE were 0.80 (95% CI 0.69-0.93, p=0.003) and 0.77 (95% CI 0.62-0.94, p=0.012) for apixaban and dabigatran, respectively. Apixaban patients had a 41% lower risk for major bleeding compared to phenprocoumon users (HR 0.59, 95% CI 0.51-0.70, p <0.001). Rivaroxaban use was not associated with a lower risk for stroke/SE (HR 0.89, 95% CI 0.79-1.00, p=0.057) or major bleeding events (HR 1.01, 95% 0.91-1.12, p=0.887).

In this sensitivity analysis apixaban patients had a lower risk for all other safety outcomes studied, namely for any bleeding (HR 0.77, 95% CI 0.72-0.83, p <0.001), intracranial bleeding (HR 0.45, 95% CI 0.32-0.64, p < 0.001), gastrointestinal bleeding (HR 0.71, 95% CI 0.61-0.82, p < 0.001). Apixaban was also associated with a lower risk for hemorrhagic stroke (HR 0.48, 95% CI 0.32-0.73, p=0.001) and for the combined endpoint of hemorrhagic and ischemic stroke (HR 0.80, 95% CI 0.68-0.94, p=0.008), but not with a significant risk reduction for ischemic stroke (0.87, 95% CI 0.73-1.04, p=0.128). The risk for all cause death in apixaban and rivaroxaban patients was similar compared to phenprocoumon patients. Dabigatran use was associated with a lower risk of all-cause death (HR 0.85, 95% CI 0.75-0.97, p=0.014). Rivaroxaban was associated with a higher risk for gastrointestinal bleeding (HR 1.26, 95% CI 1.15-1.39, p < 0.001).

11. DISCUSSION

11.1. Key results

In patients with NVAF the use of apixaban, as compared with phenprocoumon, significantly reduced the risk of stroke/SE by 23% and major bleeding by 42%. The results were largely consistent throughout all sensitivity and subgroup analyses. The presented findings for apixaban were in accordance with reported findings in ARISTOTLE, which reported a lower adjusted risk for the primary efficacy outcome stroke or systemic embolism (HR 0.79, 95% CI 0.66-0.95, p=0.01) (6). The reported hazard estimates for the major bleeding were also comparable between this study and ARISTOTLE. However, in contrast to ARISTOTLE, risk of death from any cause was significantly reduced in patients receiving standard dose apixaban, while being similar to phenprocoumon in patients receiving reduced dose apixaban. This is not surprising given the very advanced age and the multiple comorbidities of these patients making age by itself increasingly important as the main driver of mortality. The results of this study are also in line with previous real-world studies comparing the effectiveness and safety of NOACs and warfarin (21,22).

NVAF patients treated with dabigatran had a 26% lower risk of stroke/SE and a 36% lower risk of major bleeding, as compared to patients treated with phenprocoumon. The findings of this study were generally in line with the findings of the RE-LY trial which reported relative risks for the two dabigatran 110mg and 150mg separately only (8). RE-LY reported a significantly lower risk for the primary efficacy outcome stroke or systemic embolism for dabigatran patients treated with the standard and similar risk for those treated with the reduced dose (8). This study also found a significant risk reduction for patients on the standard dose and similar risk for patients treated with the reduced dose. The results regarding the risk for a major bleeding event were slightly different between RE-LY and this study. The use of dabigatran standard dose was associated with reduced risk of major bleeding when compared to phenprocoumon users while in the RE-LY trial similar risk between dabigatran and warfarin patients was reported. For patients on dabigatran reduced dose consistent results between our study and the RE-LY trial were observed. In addition, the increased risk of gastrointestinal bleeding in dabigatran patients treated with the standard dose reported in RE-LY (RR 1.50, 95% CI 1.19-1.89, p<0.001) was not reaffirmed in our study. It should be noted, however, that the high dose dabigatran regimen was used in the

youngest patient subgroup with the lowest CHA_2DS_2-VASc, HAS-BLED, and comorbidity scores. These more favorable effectiveness and safety outcomes in younger patients are in line with the findings of the RE-LY trial.

The use of rivaroxaban, as compared to phenprocoumon, in NVAF patients was associated with a 14% lower risk of stroke/SE, which is in line with the findings for the "on protocol population" reported in the ROCKET-AF trial (9). The adjusted risk of major bleeding was similar in rivaroxaban and phenprocoumon patients in this study. The risk for gastrointestinal bleeding was significantly higher in rivaroxaban patients compared to phenprocoumon patients in all sensitivity and subgroup analyses. For rivaroxaban, the observed higher risk of gastrointestinal bleeding along with similar risks of major bleeding compared to phenprocoumon is in line with the results of the ROCKET-AF trial.

11.2. Limitations

This study is subject to a number of limitations which are inherent to retrospective claims data analyses. Despite extensive attempts to adjust for all relevant baseline confounders by applying various statistical methods and sensitivity analyses, residual confounding cannot be excluded. However, the consistency of our results with previously published studies indicates that this study yielded reliable results (6,21,22).

Exposure misclassification may have been a source of bias in this study. The time under exposure, especially for patients treated with phenprocoumon, was subject to a number of assumptions. In order to account for the large intra- and interpersonal variability of the phenprocoumon therapy, three options of determining the exposure time for patients treated with phenprocoumon were applied, which lead to similar results. However, uncertainty remains whether the days of supply could in in fact be over or underestimated, which could have had an impact on the attribution of an outcome event to the phenprocoumon treatment, when in fact this treatment might have been stopped or paused before the event occurred.

Furthermore the presence of a claim for a dispensed prescription does not indicate that the medication was used by the patient, nor does it indicate that is was taken as prescribed or that it was taken as recommended by the label indication. Again patients might have stopped or

paused the treatment before the event occurred and might have been misclassified as exposed in this study.

The lack of INR measurements and laboratory data on renal function represents another inherent limitation of our study.

11.3. Interpretation

In the real world scenario of this study NOACs are prescribed in patients that are on average younger, have less ambulatory physician contacts and more hospitalizations compared to patients receiving VKA. Nevertheless, a group of NOAC patients with higher burden of disease and/or increased risk of thromboembolic/bleeding events and a consecutive low dose treatment was analyzed, which was older than the average of phenprocoumon patients. High risk patients within the phenprocoumon group were not separately analyzed. However, different statistical methods were used to adjust for differences in patient's characteristics.

The findings from the present large real-world patient population are in general consistent with the observations made in the three respective phase III trials of the studied NOACs, suggesting that in real-world conditions efficacy and safety levels similar to what has been seen in the controlled clinical trials can be achieved. Given the similarity of the comparative efficacy and safety data in the NOAC trials and this real-world comparison with phenprocoumon, it seems unlikely that the predominant use of phenprocoumon in Germany would be responsible for differences in the comparative efficacy and safety. Therefore, there is no reason to assume that the results of the clinical trials of the NOACs cannot be extrapolated to daily practice when phenprocoumon is used as a predominant VKA.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

The efficacy and safety of NOACs have been proven in prospective randomized multicenter studies (6,8,9,10). Moreover, NOACs have demonstrated a better or at least comparable safety and efficacy profile to warfarin in these trials.

Results from this large real world data analysis demonstrate that NOACs have better effectiveness and safety characteristics than phenprocoumon. Reduced NOAC dosing regimens were prescribed preferentially to patients with advanced age and comorbidities and displayed similar effectivity and safety benefits relative to phenprocoumon as the standard dose NOAC regimens.

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APPENDIX

Table 18 PZN Codes and days of supply per PZN for all substances under study

PZN	grp	NAME_PACKUNG	tablets_pckg	days_supply
1647755	Apixaban	Eliquis 5 mg	20	10
1647778	Apixaban	Eliquis 5 mg	60	30
1647784	Apixaban	Eliquis 5 mg	100	50
1647809	Apixaban	Eliquis 5 mg	200	100
1647821	Apixaban	Eliquis 5 mg 5x20	100	50
3643804	Apixaban	Eliquis 2,5 mg CC Ph.	60	30
4700504	Apixaban	Eliquis 2,5 mg Emra	10	5
4700510	Apixaban	Eliquis 2,5 mg Emra	20	10
4700527	Apixaban	Eliquis 2,5 mg Emra	60	30
4712163	Apixaban	Eliquis 2,5 mg Kohl Ph.	20	10
4712186	Apixaban	Eliquis 2,5 mg Kohl Ph.	60	30
5117273	Apixaban	Eliquis 5 mg Eurim	200	100
8400012	Apixaban	Eliquis 2,5 mg	10	5
8400029	Apixaban	Eliquis 2,5 mg	20	10
8400035	Apixaban	Eliquis 2,5 mg	60	30
8400041	Apixaban	Eliquis 2,5 mg	60	30
10218496	Apixaban	Eliquis 5 mg Kohl Ph.	60	30
10232906	Apixaban	Eliquis 5 mg CC Ph.	60	30
10250465	Apixaban	Eliquis 2,5 mg Filmtabletten	200	100
10273130	Apixaban	Eliquis 5 mg Eurim	60	30
11174884	Apixaban	Eliquis 5 mg Emra	60	30

11341537	Apixaban	Eliquis 2,5 mg Filmtabletten Docpharm	60	30
11376429	Apixaban	Eliquis 2,5 mg Filmtabletten Milinda	60	30
11376435	Apixaban	Eliquis 2,5 mg Filmtabletten Milinda	200	100
11376441	Apixaban	Eliquis 5 mg Filmtabletten Milinda	60	30
11376458	Apixaban	Eliquis 5 mg Filmtabletten Milinda	200	100
2531523	Dabigatran	Pradaxa 110 mg Kohl Ph.	10	5
2531546	Dabigatran	Pradaxa 110 mg Kohl Ph.	30	15
3420607	Dabigatran	Pradaxa 75 mg	10	5
3420613	Dabigatran	Pradaxa 75 mg	30	15
3420754	Dabigatran	Pradaxa 110 mg	10	5
3420760	Dabigatran	Pradaxa 110 mg	30	15
5704071	Dabigatran	Pradaxa 75 mg	180	90
5704088	Dabigatran	Pradaxa 110 mg	180	90
6115862	Dabigatran	Pradaxa 75 mg CC Ph.	30	15
6115879	Dabigatran	Pradaxa 110 mg CC Ph.	30	15
6141724	Dabigatran	Pradaxa 75 mg CC Ph.	10	5
6141730	Dabigatran	Pradaxa 110 mg CC Ph.	10	5
6312284	Dabigatran	Pradaxa 75 mg Kohl Ph.	30	15
6561863	Dabigatran	Pradaxa 75 mg	200	100
6561892	Dabigatran	Pradaxa 110 mg	60	30
6561900	Dabigatran	Pradaxa 110 mg Hartkapseln	180	90

6561917	Dabigatran	Pradaxa 110 mg	200	100
6561946	Dabigatran	Pradaxa 150 mg	30	15
6561952	Dabigatran	Pradaxa 150 mg	60	30
6561969	Dabigatran	Pradaxa 150 mg Hartkapseln	180	90
6561981	Dabigatran	Pradaxa 150 mg	200	100
7520300	Dabigatran	Pradaxa 75 mg Emra	10	5
7525295	Dabigatran	Pradaxa 75 mg Gerke Ph.	10	5
7525303	Dabigatran	Pradaxa 75 mg Gerke Ph.	30	15
7525326	Dabigatran	Pradaxa 110 mg Gerke Ph.	10	5
7525390	Dabigatran	Pradaxa 110 mg Gerke Ph.	30	15
7544157	Dabigatran	Pradaxa 110 mg Emra	10	5
7544163	Dabigatran	Pradaxa 110 mg Emra	30	15
7544186	Dabigatran	Pradaxa 75 mg Emra	30	15
8797446	Dabigatran	Pradaxa 150 mg	10	5
8844364	Dabigatran	Pradaxa 75 mg Axicorp	30	15
8844370	Dabigatran	Pradaxa 110 mg Axicorp	30	15
8866839	Dabigatran	Pradaxa 110 mg Eurim	30	15
8866880	Dabigatran	Pradaxa 75 mg Eurim	30	15
9124100	Dabigatran	Pradaxa 75 mg Veron Ph.	10	5
9124117	Dabigatran	Pradaxa 75 mg Veron Ph.	30	15
9228199	Dabigatran	Pradaxa 110 mg Westen Ph.	60	30
9321102	Dabigatran	Pradaxa 110 mg Emra	60	30
9328156	Dabigatran	Pradaxa 110 mg Kohl Ph.	60	30
9707095	Dabigatran	Pradaxa 110 mg Hartkapseln	100	50

9707103	Dabigatran	Pradaxa 150 mg Hartkapseln	100	50
9947971	Dabigatran	Pradaxa 150 mg Hartkapseln CC Ph.	30	15
9947988	Dabigatran	Pradaxa 150 mg CC Pharma	60	30
10183585	Dabigatran	Pradaxa 110 mg Kohl Ph.	30	15
10193365	Dabigatran	Pradaxa 150 mg Eurim	30	15
10193371	Dabigatran	Pradaxa 150 mg Eurim	60	30
10206458	Dabigatran	Pradaxa 150 mg Hartkapseln CC Ph.	100	50
10218349	Dabigatran	Pradaxa 110 mg Hartkapseln Eurim	60	30
10218355	Dabigatran	Pradaxa 110 mg Hartkapseln Eurim	100	50
10218361	Dabigatran	Pradaxa 110 mg Hartkapseln Eurim	180	90
10249781	Dabigatran	Pradaxa 150 mg Hartkapseln Kohl Ph.	60	30
10251016	Dabigatran	Pradaxa 110 mg CC Ph.	60	30
10251022	Dabigatran	Pradaxa 110 mg CC Ph.	100	50
10261210	Dabigatran	Pradaxa 110 mg Hartkapseln Kohl Ph.	180	90
10261233	Dabigatran	Pradaxa 150 mg Hartkapseln Kohl Ph.	180	90
10288114	Dabigatran	Pradaxa 150 mg Hartkapseln Gerke Ph.	100	50
10288120	Dabigatran	Pradaxa 110 mg Hartkapseln Gerke Ph.	100	50
10339484	Dabigatran	Pradaxa 110 mg Hartkapseln Emra	60	30

10339509	Dabigatran	Pradaxa 110 mg Hartkapseln Emra	100	50
10339521	Dabigatran	Pradaxa 110 mg Hartkapseln Emra	180	90
10357542	Dabigatran	Pradaxa 150 mg Hartkapseln Emra	60	30
10390829	Dabigatran	Pradaxa 110 mg Hartkapseln Kohl Ph.	100	50
10390835	Dabigatran	Pradaxa 150 mg Hartkapseln Kohl Ph.	100	50
10395867	Dabigatran	Pradaxa 150 mg Hartkapseln Gerke Ph.	60	30
10402596	Dabigatran	Pradaxa 110 mg Hartkapseln Axicorp	100	50
10402604	Dabigatran	Pradaxa 110 mg Hartkapseln Axicorp	180	90
10402685	Dabigatran	Pradaxa 110 mg Hartkapseln Axicorp	60	30
10737084	Dabigatran	Pradaxa 110 mg Hartkapseln Haemato-Ph.	60	30
10783204	Dabigatran	Pradaxa 110 mg Hartkapseln Haemato-Ph.	100	50
10944541	Dabigatran	Pradaxa 110 mg Hartkapseln Orifarm	180	90
10989779	Dabigatran	Pradaxa 150 mg Hartkapseln Orifarm	180	90
11004550	Dabigatran	Pradaxa 150 mg Hartkapseln Emra	180	90
11009889	Dabigatran	Pradaxa 75 mg Hartkapseln Eurim	30	15
11027491	Dabigatran	Pradaxa 75 mg Hartkapseln	30	15

		Emra		
11038299	Dabigatran	Pradaxa 150 mg Hartkapseln Haemato-Ph.	60	30
11038307	Dabigatran	Pradaxa 150 mg Hartkapseln Haemato-Ph.	180	90
11127442	Dabigatran	Pradaxa 110 mg Hartkapseln Gerke Ph.	60	30
11130183	Dabigatran	Pradaxa 110 mg Hartkapseln Docpharm	60	30
11130378	Dabigatran	Pradaxa 110 mg Hartkapseln Docpharm	180	90
11130384	Dabigatran	Pradaxa 150 mg Hartkapseln Docpharm	60	30
11130409	Dabigatran	Pradaxa 150 mg Hartkapseln Docpharm	180	90
11291087	Dabigatran	Pradaxa 75 mg Hartkapseln Emra	60	30
11309114	Dabigatran	Pradaxa 110 mg Hartkapseln Docpharm	30	15
11309120	Dabigatran	Pradaxa 150 mg Hartkapseln Docpharm	30	15
11341916	Dabigatran	Pradaxa 110 mg Hartkapseln Milinda	60	30
11341922	Dabigatran	Pradaxa 110 mg Hartkapseln Milinda	180	90
11341939	Dabigatran	Pradaxa 150 mg Hartkapseln Milinda	60	30
11341945	Dabigatran	Pradaxa 150 mg Hartkapseln Milinda	180	90
10713994	Edoxaban	Lixiana 15 mg Filmtabletten	10	10

10714002	Edoxaban	Lixiana 15 mg Filmtabletten	10	10
10714031	Edoxaban	Lixiana 30 mg Filmtabletten	28	28
10714060	Edoxaban	Lixiana 30 mg Filmtabletten	98	98
10714083	Edoxaban	Lixiana 30 mg Filmtabletten	100	100
10714143	Edoxaban	Lixiana 30 mg Filmtabletten	10	10
10714172	Edoxaban	Lixiana 60 mg Filmtabletten	10	10
10714255	Edoxaban	Lixiana 60 mg Filmtabletten	28	28
10714284	Edoxaban	Lixiana 60 mg Filmtabletten	98	98
10714309	Edoxaban	Lixiana 60 mg Filmtabletten	100	100
972890	Phenprocoumon	Falithrom 1,5 mite	20	10
972909	Phenprocoumon	Falithrom 1,5 mite	50	25
972915	Phenprocoumon	Falithrom 1,5 mite	100	50
1294216	Phenprocoumon	Marcoumar Me-Pharma	50	50
1294222	Phenprocoumon	Marcoumar Me-Pharma	100	100
1300649	Phenprocoumon	Marcumar	30	30
1835787	Phenprocoumon	Marcoumar DOCPHARMA	50	50
1837390	Phenprocoumon	Marcoumar DOCPHARMA	100	100
2021408	Phenprocoumon	MARCUMAR	50	50
2059517	Phenprocoumon	Phenpro AbZ 3 mg	100	100
2499417	Phenprocoumon	MARCUMAR	20	20
2704892	Phenprocoumon	Phenprogamma 3	20	20
2704900	Phenprocoumon	Phenprogamma 3	50	50
2704917	Phenprocoumon	Phenprogamma 3	100	100
3011932	Phenprocoumon	Falithrom	20	20

3215540	Phenprocoumon	MARCUMAR	100	100
3352194	Phenprocoumon	MARCOUMAR BERAGENA	50	50
3352202	Phenprocoumon	MARCOUMAR BERAGENA	100	100
3422256	Phenprocoumon	MARCOUMAR OPTI ARZNEI	50	50
3422262	Phenprocoumon	MARCOUMAR OPTI ARZNEI	100	100
3462445	Phenprocoumon	Marcoumar Westen Ph.	50	50
3462451	Phenprocoumon	Marcoumar Westen Ph.	100	100
4334620	Phenprocoumon	MARCOUMAR EMRA MED	50	50
4334637	Phenprocoumon	MARCOUMAR EMRA MED	100	100
4386462	Phenprocoumon	Marcoumar Gerke Ph.	50	50
4386479	Phenprocoumon	Marcoumar Gerke Ph.	100	100
4421721	Phenprocoumon	FALITHROM	20	20
4421738	Phenprocoumon	FALITHROM	50	50
4421744	Phenprocoumon	FALITHROM	100	100
4446773	Phenprocoumon	Marcoumar GPP	50	50
4446796	Phenprocoumon	Marcoumar GPP	100	100
4582128	Phenprocoumon	Phenpro.-ratiopharm 3 mg	20	20
4582134	Phenprocoumon	Phenpro.-ratiopharm 3 mg	50	50
4582140	Phenprocoumon	Phenpro.-ratiopharm 3 mg	100	100
4658618	Phenprocoumon	MARCOUMAR EURIM PHARM	100	100
4958705	Phenprocoumon	Marcoumar Kohl Ph.	50	50

4958711	Phenprocoumon	Marcoumar Kohl	100	100
5541315	Phenprocoumon	Marcumar	14	14
5541321	Phenprocoumon	Marcumar	49	49
5541338	Phenprocoumon	Marcumar	98	98
6575233	Phenprocoumon	Phenpro.-ratiopharm 3 mg	98	98
6588626	Phenprocoumon	Marcuphen-CT 3 mg	98	98
6811219	Phenprocoumon	Phenpro AbZ 3 mg	98	98
6969475	Phenprocoumon	MARCOUMAR GrÃ?newald	50	50
6969481	Phenprocoumon	MARCOUMAR GrÃ?newald	100	100
7118762	Phenprocoumon	Marcoumar Alphamed 4x25	100	100
7532349	Phenprocoumon	Marcoumar Alpha Med	50	50
7614188	Phenprocoumon	Marcumar Eurim	50	50
7614194	Phenprocoumon	Marcumar Eurim	100	100
7636008	Phenprocoumon	marcuphen von ct	20	20
7636014	Phenprocoumon	marcuphen von ct	50	50
7636020	Phenprocoumon	marcuphen von ct	100	100
7646567	Phenprocoumon	Marcoumar AE Media	50	50
7646573	Phenprocoumon	Marcoumar AE Media	100	100
7768135	Phenprocoumon	Marcumar	56	56
7768170	Phenprocoumon	Marcumar	92	92
8874885	Phenprocoumon	Marcumar ACA/ADAG	50	50
8874891	Phenprocoumon	Marcumar ACA/ADAG	100	100
9404207	Phenprocoumon	Phenprogamma 3	14	14
9726170	Phenprocoumon	Marcoumar Eurim	100	100

10269507	Phenprocoumon	Phenprocoumon acis 3 mg	20	20
10269513	Phenprocoumon	Phenprocoumon acis 3 mg	50	50
10269542	Phenprocoumon	Phenprocoumon acis 3 mg	100	100
2088536	Rivaroxaban	Xarelto 10 mg CC Ph.	5	5
4369423	Rivaroxaban	Xarelto 15 mg Emra	28	28
4369452	Rivaroxaban	Xarelto 15 mg Emra	42	42
4369475	Rivaroxaban	Xarelto 15 mg Emra	98	98
4369481	Rivaroxaban	Xarelto 20 mg Emra	28	28
4369498	Rivaroxaban	Xarelto 20 mg Emra	98	98
5459513	Rivaroxaban	Xarelto 10 mg Eurim	30	30
5748766	Rivaroxaban	Xarelto 10 mg Kohl Ph.	30	30
5995074	Rivaroxaban	Xarelto 10 mg	10	10
5995080	Rivaroxaban	Xarelto 10 mg	30	30
5995097	Rivaroxaban	Xarelto 10mg	100	100
6410420	Rivaroxaban	Xarelto 10 mg CC Ph.	30	30
6454481	Rivaroxaban	Xarelto 10 mg Westen Ph.	30	30
7089598	Rivaroxaban	Xarelto 15 mg Westen Ph.	98	98
7089606	Rivaroxaban	Xarelto 20 mg Westen Ph.	98	98
7536850	Rivaroxaban	Xarelto 10 mg	10	10
7536927	Rivaroxaban	Xarelto 10 mg	30	30
7572633	Rivaroxaban	Xarelto 10 mg Gerke Ph.	10	10
7572662	Rivaroxaban	Xarelto 10 mg Gerke Ph.	30	30
7605019	Rivaroxaban	Xarelto 15 mg Orifarm	28	28
7605025	Rivaroxaban	Xarelto 20 mg Orifarm	28	28

7610606	Rivaroxaban	Xarelto 10 mg Kohl Ph.	10	10
7799012	Rivaroxaban	Xarelto 10 mg Emra	10	10
7799029	Rivaroxaban	Xarelto 10 mg Emra	30	30
8461290	Rivaroxaban	Xarelto 2,5 mg Filmtabletten 1x10x10	100	100
8461344	Rivaroxaban	Xarelto 15 mg	14	14
8461350	Rivaroxaban	Xarelto 15 mg	28	28
8461367	Rivaroxaban	Xarelto 15 mg	98	98
8461404	Rivaroxaban	Xarelto 15 mg	42	42
8461410	Rivaroxaban	Xarelto 20 mg	14	14
8461427	Rivaroxaban	Xarelto 20 mg	28	28
8461433	Rivaroxaban	Xarelto 20 mg	98	98
8717186	Rivaroxaban	Xarelto 2,5 mg Filmtabletten	30	30
9154791	Rivaroxaban	Xarelto 10 mg	5	5
9333393	Rivaroxaban	Xarelto 15 mg	100	100
9333401	Rivaroxaban	Xarelto 20 mg	100	100
9721534	Rivaroxaban	Xarelto 10 mg CC Ph.	10	10
9724515	Rivaroxaban	Xarelto 15 mg CC Ph.	28	28
9724521	Rivaroxaban	Xarelto 15 mg CC Ph.	42	42
9724538	Rivaroxaban	Xarelto 15 mg CC Ph.	98	98
9724544	Rivaroxaban	Xarelto 20 mg CC Ph.	28	28
9724550	Rivaroxaban	Xarelto 20 mg CC Ph.	98	98
9777888	Rivaroxaban	Xarelto 10 mg Haemato-Ph.	30	30
9941276	Rivaroxaban	Xarelto 10 mg	100	100

9941282	Rivaroxaban	Xarelto 15 mg	100	100
9941299	Rivaroxaban	Xarelto 20 mg	100	100
10005926	Rivaroxaban	Xarelto 15 mg Kohl Ph.	98	98
10005932	Rivaroxaban	Xarelto 20 mg Kohl Ph.	98	98
10012139	Rivaroxaban	Xarelto 15 mg Gerke Ph.	14	14
10012145	Rivaroxaban	Xarelto 15 mg Gerke Ph.	28	28
10012151	Rivaroxaban	Xarelto 15 mg Gerke Ph.	42	42
10012168	Rivaroxaban	Xarelto 15 mg Gerke Ph.	98	98
10012174	Rivaroxaban	Xarelto 20 mg Gerke Ph.	14	14
10012180	Rivaroxaban	Xarelto 20 mg Gerke Ph.	28	28
10012197	Rivaroxaban	Xarelto 20 mg Gerke Ph.	98	98
10057490	Rivaroxaban	Xarelto 20 mg Eurim	14	14
10057509	Rivaroxaban	Xarelto 20 mg Eurim	28	28
10058590	Rivaroxaban	Xarelto 15 mg Eurim	14	14
10058609	Rivaroxaban	Xarelto 15 mg Eurim	28	28
10072093	Rivaroxaban	Xarelto 15 mg ACA/ADAG	28	28
10072101	Rivaroxaban	Xarelto 15 mg ACA/ADAG	98	98
10072118	Rivaroxaban	Xarelto 20 mg ACA/ADAG	28	28
10072124	Rivaroxaban	Xarelto 20 mg ACA/ADAG	98	98
10101682	Rivaroxaban	Xarelto 15 mg Filmtabletten Axicorp	14	14
10102144	Rivaroxaban	Xarelto 15 mg Filmtabletten Axicorp	42	42
10106863	Rivaroxaban	Xarelto 20 mg Filmtabletten Axicorp	14	14

10106886	Rivaroxaban	Xarelto 20 mg Filmtabletten Axicorp	28	28
10106892	Rivaroxaban	Xarelto 20 mg Filmtabletten Axicorp	98	98
10132139	Rivaroxaban	Xarelto 15 mg Filmtabletten Axicorp	98	98
10200906	Rivaroxaban	Xarelto 15 mg Eurim	42	42
10200912	Rivaroxaban	Xarelto 15 mg Eurim	98	98
10200929	Rivaroxaban	Xarelto 20 mg Eurim	98	98
10297679	Rivaroxaban	Xarelto 15 mg CC Ph.	14	14
10297685	Rivaroxaban	Xarelto 20 mg CC Ph.	14	14
10318631	Rivaroxaban	Xarelto 20 mg Kohl Ph.	28	28
10339455	Rivaroxaban	Xarelto 10 mg Docpharm	30	30
10381894	Rivaroxaban	Xarelto 10 mg Milinda	10	10
10381902	Rivaroxaban	Xarelto 10 mg Milinda	30	30
10381919	Rivaroxaban	Xarelto 15 mg Milinda	14	14
10381925	Rivaroxaban	Xarelto 15 mg Milinda	28	28
10381931	Rivaroxaban	Xarelto 15 mg Milinda	42	42
10381948	Rivaroxaban	Xarelto 15 mg Milinda	98	98
10381954	Rivaroxaban	Xarelto 20 mg Milinda	14	14
10381983	Rivaroxaban	Xarelto 20 mg Milinda	28	28
10382008	Rivaroxaban	Xarelto 20 mg Milinda	98	98
10393638	Rivaroxaban	Xarelto 20 mg Docpharm	28	28
10393644	Rivaroxaban	Xarelto 20 mg Docpharm	98	98
10393650	Rivaroxaban	Xarelto 15 mg Docpharm	28	28

10393667	Rivaroxaban	Xarelto 15 mg Docpharm	42	42
10393696	Rivaroxaban	Xarelto 15 mg Docpharm	98	98
10402662	Rivaroxaban	Xarelto 10 mg Axicorp Pharma	30	30
10743771	Rivaroxaban	Xarelto 10 mg Docpharm	10	10
10743794	Rivaroxaban	Xarelto 15 mg FD Pharma	98	98
10743802	Rivaroxaban	Xarelto 20 mg FD Pharma	98	98
10762403	Rivaroxaban	Xarelto 15 mg Abacus	98	98
10762426	Rivaroxaban	Xarelto 20 mg Abacus	98	98
10764520	Rivaroxaban	Xarelto 10 mg Orifarm	10	10
10852626	Rivaroxaban	Xarelto 10 mg Beragena	10	10
10852632	Rivaroxaban	Xarelto 10 mg Beragena	30	30
10852649	Rivaroxaban	Xarelto 15 mg Beragena	14	14
10852655	Rivaroxaban	Xarelto 15 mg Beragena	28	28
10852661	Rivaroxaban	Xarelto 15 mg Beragena	42	42
10852678	Rivaroxaban	Xarelto 15 mg Beragena	98	98
10852684	Rivaroxaban	Xarelto 20 mg Beragena	14	14
10852690	Rivaroxaban	Xarelto 20 mg Beragena	28	28
10852709	Rivaroxaban	Xarelto 20 mg Beragena	98	98
10853560	Rivaroxaban	Xarelto 15 mg Kohl Ph.	14	14
10853577	Rivaroxaban	Xarelto 20 mg Kohl Ph.	14	14
10948970	Rivaroxaban	Xarelto 15 mg Kohl Ph.	42	42
10948987	Rivaroxaban	Xarelto 15 mg Kohl Ph.	28	28
10964153	Rivaroxaban	Xarelto 15 mg Orifarm	14	14

10964176	Rivaroxaban	Xarelto 15 mg Orifarm	42	42
10964182	Rivaroxaban	Xarelto 20 mg Orifarm	14	14
10999312	Rivaroxaban	Xarelto 15 mg Axicorp	14	14
10999329	Rivaroxaban	Xarelto 15 mg Axicorp	42	42
10999335	Rivaroxaban	Xarelto 15 mg Axicorp	98	98
10999341	Rivaroxaban	Xarelto 20 mg Axicorp	14	14
10999358	Rivaroxaban	Xarelto 20 mg Axicorp	28	28
10999364	Rivaroxaban	Xarelto 20 mg Axicorp	98	98
11015708	Rivaroxaban	Xarelto 15 mg filmtabletten Emra	14	14
11015714	Rivaroxaban	Xarelto 20 mg Emra	14	14
11096606	Rivaroxaban	Xarelto 15 mg Euro DK	98	98
11096612	Rivaroxaban	Xarelto 20 mg Euro DK	98	98
11559348	Rivaroxaban	Xarelto 15 mg BB Farma	98	98
11559354	Rivaroxaban	Xarelto 20 mg BB Farma	98	98
11617270	Rivaroxaban	Xarelto 10 mg Abacus	30	30
245546	Warfarin	COUMADIN 5MG	100	66,667
8516358	Warfarin	Coumadin 5 mg	20	13,333
8516364	Warfarin	Coumadin 5 mg	50	33,333
9897078	Warfarin	Coumadin 5 mg Eurim	100	66,667
10066230	Warfarin	Coumadin 5 mg Emra	100	66,667
11054430	Warfarin	Coumadin 5 mg Kohl Ph.	100	66,667
11367761	Warfarin	Coumadin 5 mg Tabletten Kohl Ph.	50	33,333
11651054	Warfarin	Coumadin 5 mg Tabletten	50	33,333

		Emra		

Table 19 Codes Dialyses (exclusion criteria)

Code	Codetyp	Description
8853	Ops_code	Hämofiltration
8854	Ops_code	Hämodialyse
8855	Ops_code	Hämodiafiltration
8857	Ops_code	Peritonealdialyse
40800	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr bis zum vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes Mellitus **VALID UNTIL Q4 2012**
40801	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr bis zum vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes mellitus, bei einer Feriendialyse während des Ferienaufenthalts am Ferienort, bei Dialysen wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID UNTIL Q4 2012**
40802	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes mellitus, **VALID UNTIL Q4 2012**

40803	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes mellitus, bei einer Feriendialyse während des Ferienaufenthalts am Ferienort oder bei Dialysen wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID UNTIL Q4 2012**
40804	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung mit manifestem behandlungspflichtigen Diabetes mellitus **VALID UNTIL Q4 2012**
40805	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung mit manifestem behandlungspflichtigen Diabetes mellitus, bei einer Feriendialyse während des Ferienaufenthalts am Ferienort oder bei Dialysen wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID UNTIL Q4 2012**
40806	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr bis zum vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes mellitus bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können **VALID UNTIL Q4 2012**
40807	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl.

		Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes mellitus bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können. **VALID UNTIL Q4 2012**
40808	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung mit manifestem behandlungspflichtigen Diabetes mellitus bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können. **VALID UNTIL Q4 2012**
40810	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40800, 40802 oder 40804 für die Infektionsdialyse (bei Patienten mit Hepatitis B und/oder Hepatitis C und/oder mit HIV-Infektion und/oder mit MRSA-Infektion) **VALID UNTIL Q4 2012**
40811	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40801, 40803 oder 40805 bis 40808 für die Infektionsdialyse (bei Patienten mit Hepatitis B und/oder Hepatitis C und/oder mit HIV-Infektion und/oder mit MRSA-Infektion) **VALID UNTIL Q4 2012**
40812	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40800, 40802 oder 40804 für die intermittierende Peritonealdialyse (IPD) **VALID UNTIL Q4 2012**
40813	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40801, 40803 oder 40805 bis 40808 für die intermittierende Peritonealdialyse (IPD) **VALID UNTIL Q4 2012**
40820	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr

		VALID UNTIL Q4 2012
40821	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr bei einer Feriendialyse während des Ferienaufenthalts am Ferienort oder bei Dialysen wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID UNTIL Q4 2012**
40822	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können **VALID UNTIL Q4 2012**
40815	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei Dialysen am Wohnort **VALID FROM Q1 2013**
40816	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung **VALID FROM Q1 2013**
40817	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei Dialysen am Wohnort, die nicht mindestens 4 von 7 Peritonealdialysetage in der Behandlungswoche umfassen **VALID FROM Q1 2013**
40818	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei einer Feriendialyse während des Ferienaufenthalts am Ferienort, bei Dialyse wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID FROM Q1 2013**

40819	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei einer Feriendialyse während des Ferienaufenthalts am Ferienort, bei Dialyse wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID FROM Q1 2013**
40823	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen als Zentrums- bzw. Praxisdialyse oder zentralisierte Heimdialyse,einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung **VALID FROM Q1 2013**
40824	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen als Zentrums- bzw. Praxisdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können **VALID FROM Q1 2013**
40825	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen (z. B. CAPD, CCPD, IPD) oder Heimhämodialysen, bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung **VALID FROM Q1 2013**
40826	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen (z. B. CAPD, CCPD, IPD) oder Heimhämodialysen, bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung **VALID FROM Q1 2013**
40827	EBM	Kostenpauschale für Sachkosten bei Durchführung von intermittierenden Peritonealdialysen (IPD) oder Heimhämodialysen, bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können **VALID FROM Q1 2013**
40828	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämo- oder Peritonealdialysen, als Zentrums- bzw. Praxisdialyse, Heimdialyse

		oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung, bei einer Feriendialyse während des Ferienaufenthalts am Ferienort, bei Dialyse wegen beruflich oder sonstiger Abwesenheit vom Wohnort **VALID FROM Q1 2013**
40829	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40823 oder 40825 bei Versicherten ab dem vollendeten 59. Lebensjahr bis zum vollendeten 69. Lebensjahr **VALID FROM Q1 2013**
40830	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40824, 40826 und 40827 bei Versicherten ab dem vollendeten 59. Lebensjahr bis zum vollendeten 69. Lebensjahr
40831	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40823 oder 40825 bei Versicherten ab dem vollendeten 69. Lebensjahr bis zum vollendeten 79. Lebensjahr **VALID FROM Q1 2013**
40832	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40824, 40826 und 40827 bei Versicherten ab dem vollendeten 69. Lebensjahr bis zum vollendeten 79. Lebensjahr **VALID FROM Q1 2013**
40833	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40823 oder 40825 bei Versicherten ab dem vollendeten 79. Lebensjahr **VALID FROM Q1 2013**
40834	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40824, 40826 und 40827 bei Versicherten ab dem vollendeten 79. Lebensjahr **VALID FROM Q1 2013**
40835	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40816, 40823 oder 40825 für die Infektionsdialyse (bei Patienten mit Infektionserkrankungen mit Problemkeimen gemäß der mit der Kommission für Krankenhaushygiene und Infektionsprävention beim Robert Koch-Institut (KRINKO) abgestimmten Hygieneleitlinie als Ergänzung zum Dialysestandard) **VALID FROM Q1 2013**
40836	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40815, 40817, 40818, 40819, 40824, 40826 bis 40828 für die Infektionsdialyse (bei Patienten mit Infektionserkrankungen mit Problemkeimen gemäß der

		mit der Kommission für Krankenhaushygiene und Infektionsprävention beim Robert Koch-Institut (KRINKO) abgestimmten Hygieneleitlinie als Ergänzung zum Dialysestandard) **VALID FROM Q1 2013**
40837	EBM	Zuschlag zu der Kostenpauschale nach der Nr. 40816 oder 40825 für die intermittierende Peritonealdialyse (IPD) **VALID FROM Q1 2013**
40838	EBM	Zuschlag zu der Kostenpauschale nach der Nr. 40817, 40819, 40827 oder 40828 für die intermittierende Peritonealdialyse (IPD) **VALID FROM Q1 2013**
04562	EBM	Zusatzpauschale kontinuierliche Betreuung eines dialysepflichtigen Patienten **VALID FROM Q1 2013**
04561	EBM	Zusatzpauschale kindernephrologische Behandlung eines dialysepflichtigen Patienten **VALID FROM Q1 2013**
04564	EBM	Zusatzpauschale kindernephrologische Betreuung bei Durchführung der Hämodialyse **VALID FROM Q1 2013**
04565	EBM	Zusatzpauschale kindernephrologische Betreuung bei Durchführung einer Peritonealdialyse **VALID FROM Q1 2013**
13602	EBM	Zusatzpauschale kontinuierliche Betreuung eines dialysepflichtigen Patienten **VALID FROM Q1 2013**
13610	EBM	Zusatzpauschale ärztliche Betreuung bei Hämodialyse, Peritonealdialyse und Sonderverfahren **VALID FROM Q1 2013**
13611	EBM	Zusatzpauschale ärztliche Betreuung bei Peritonealdialyse **VALID FROM Q1 2013**

Table 20 ATC Codes Heparin

ATC_Code	Bezeichnung
B01AB01	Heparin

B01AB02	Antithrombin III, Antithrombin alfa
B01AB04	Dalteparin
B01AB05	Enoxaparin
B01AB06	Nadroparin
B01AB07	Parnaparin
B01AB08	Reviparin
B01AB09	Danaparoid
B01AB10	Tinzaparin
B01AB11	Sulodexid
B01AB12	Bemiparin
B01AB13	Certoparin
B01AB51	Heparin, Kombinationen
B01AB63	Certoparin, Kombinationen

Table 21 Codes used as exclusion criteria

Code	Type of Code	Label
I26.*	ICD-10	Pulmonary embolism
I80.1	ICD-10	Phlebitis and thrombophlebitis of femoral vein
I80.2	ICD-10	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
I80.3	ICD-10	Phlebitis and thrombophlebitis of lower extremities, unspecified
O*	ICD-10	Pregnancy, childbirth and puerperium
Z34	ICD-10	Supervision of a normal pregnancy
Z35	ICD-10	Supervision of a high-risk pregnancy
Z36	ICD-10	Antenatal screening
01770	EBM	'Versorgung einer Schwangeren'
5351*	OPS	Ersatz von Herzklappen durch Prothese
5352	OPS	Wechsel von Herzklappenprothesen
5353	OPS	Valvuloplastik
5358*	OPS	Operationen bei kongenitalen Klappenanomalien des Herzens
535a	OPS	Minimalinvasive Operationen an Herzklappen

Table 22 ICD Codes bleeding

ICD/OPS	Label (German)	Bleeding category	Major bleeding -
8-800	Transfusion von Blutzellen: Transfusion von Vollblut, Erythrozytenkonzentrat und Thrombozytenkonzentrat: Vollblut	any	Yes, but only in combination with an emergency hospital admission and any of the here listed ICD 10 codes except D62*.

D62	Akute Blutungsanämie	any	Yes, but only in combination with an emergency hospital admission and any of the here listed ICD 10 codes.
D68.3	Hämorrhagische Diathese durch Antikoagulanzien und Antikörper	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
D69.8	Sonstige näher bezeichnete hämorrhagische Diathesen	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
D69.9	Hämorrhagische Diathese, nicht näher bezeichnet	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
H11.3	Blutung Konjunktiva	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
H21.0	Hyphäma	any	yes
H31.3	Blutung und Ruptur Aderhaut	any	yes
H31.30	Blutung und Ruptur der Aderhaut	any	yes
H31.31	Blutung und Ruptur der Aderhaut	any	yes
H35.6	Netzhautblutung	any	yes
H43.1	Glaskörperblutung	any	yes
H45.0	Glaskörperblutung bei sonst klassifiz. Krankheit	any	yes
H92.2	Blutung aus äußerem Gehörgang	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
I31.2	Hämoperikard, anderenorts nicht klassifiziert	any	yes

I60.0	Subarachnoidalblutung, vom Karotissiphon oder der Karotisbifurkation ausgehend	intracerebral (also part of any bleeding) (also part of any bleeding)	yes
I60.1	Subarachnoidalblutung, von der A. cerebri media ausgehend	intracerebral (also part of any bleeding)	yes
I60.2	Subarachnoidalblutung, von der A. communicans anterior ausgehend	intracerebral (also part of any bleeding)	yes
I60.3	Subarachnoidalblutung, von der A. communicans posterior ausgehend	intracerebral (also part of any bleeding)	yes
I60.4	Subarachnoidalblutung, von der A. basilaris ausgehend	intracerebral (also part of any bleeding)	yes
I60.5	Subarachnoidalblutung, von der A. vertebralis ausgehend	intracerebral (also part of any bleeding)	yes
I60.6	Subarachnoidalblutung, von sonstigen intrakraniellen Arterien ausgehend	intracerebral (also part of any bleeding)	yes
I60.7	Subarachnoidalblutung, von nicht näher bezeichneter intrakranieller Arterie ausgehend	intracerebral (also part of any bleeding)	yes
I60.8	Sonstige Subarachnoidalblutung	intracerebral (also part of any bleeding)	yes
I60.9	Subarachnoidalblutung, nicht näher bezeichnet	intracerebral (also part of any bleeding)	yes
I61.0	Intrazerebrale	intracerebral	yes

	Blutung in die Großhirnhemisphäre, subkortikal	(also part of any bleeding)	
I61.1	Intrazerebrale Blutung in die Großhirnhemisphäre, kortikal	intracerebral (also part of any bleeding)	yes
I61.2	Intrazerebrale Blutung in die Großhirnhemisphäre, nicht näher bezeichnet	intracerebral (also part of any bleeding)	yes
I61.3	Intrazerebrale Blutung in den Hirnstamm	intracerebral (also part of any bleeding)	yes
I61.4	Intrazerebrale Blutung in das Kleinhirn	intracerebral (also part of any bleeding)	yes
I61.5	Intrazerebrale intraventrikuläre Blutung	intracerebral (also part of any bleeding)	yes
I61.6	Intrazerebrale Blutung an mehreren Lokalisationen	intracerebral (also part of any bleeding)	yes
I61.8	Sonstige intrazerebrale Blutung	intracerebral (also part of any bleeding)	yes
I61.9	Intrazerebrale Blutung, nicht näher bezeichnet	intracerebral (also part of any bleeding)	yes
I62.00	Subdurale Blutung (nichttraumatisch) Akut	intracerebral (also part of any bleeding)	yes
I62.01	Subdurale Blutung (nichttraumatisch) Subakut	intracerebral (also part of any bleeding)	yes
I62.02	Subdurale Blutung (nichttraumatisch) Chronisch	intracerebral (also part of any bleeding)	yes
I62.09	Subdurale Blutung (nichttraumatisch) Nicht näher bezeichnet	intracerebral (also part of any bleeding)	yes
I62.1	Nichttraumatische	intracerebral	yes

	extradurale Blutung	(also part of any bleeding)	
I62.9	Intrakranielle Blutung (nichttraumatisch), nicht näher bezeichnet	intracerebral (also part of any bleeding)	yes
I85.0	Ösophagusvarizen mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
I98.21	Ösophagus- und Magenvarizen bei anderenorts klassifizierten Krankheiten Mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
J94.2	Hämatothorax	any	yes
K22.6	Mallory-Weiss-Syndrom, Schleimhautrisse in der Kardiaregion mit Hämorrhagie	any	yes
K22.8	Ösophagusblutung ohne nähere Angabe	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K25.0	Ulcus ventriculi akut mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K25.2	Ulcus ventriculi akut mit Blutung und Perforation	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K25.4	Ulcus ventriculi chronisch oder onA mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.

K25.6	Ulcus ventriculi chronisch oder onA mit Blutung und Perforation	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K26.0	Ulcus duodeni akut mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K26.2	Ulcus duodeni akut mit Blutung und Perforation	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K26.4	Ulcus duodeni chronisch oder onA mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K26.6	Ulcus duodeni chronisch oder onA mit Blutung und Perforation	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K27.0	Ulcus pepticum Lokalisation onA akut mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K27.2	Ulcus pepticum Lokalisation onA akut mit Blutung und Perforation	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K27.4	Ulcus pepticum Lokalisation onA chronisch oder onA mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K27.6	Ulcus pepticum Lokalisation onA chronisch oder onA mit Blutung und Perforation	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.

K28.0	Ulcus pepticum jejuni akut mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K28.2	Ulcus pepticum jejuni akut mit Blutung und Perforation	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K28.4	Ulcus pepticum jejuni chronisch oder onA mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K28.6	Ulcus pepticum jejuni chronisch oder onA mit Blutung und Perforation	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K29.0	Akute hämorrhagische Gastritis	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K31.82	Angiodysplasie des Magens und des Duodenums mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K55.22	Angiodysplasie des Kolons mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.01	Divertikulose des Dünndarmes mit Perforation und Abszess Divertikulose mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.03	Divertikulose des Dünndarmes mit Perforation und Abszess	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the

	Divertikulitis mit Blutung		same hospital case.
K57.11	Divertikulose des Dünndarmes ohne Perforation oder Abszess Divertikulose mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.13	Divertikulose des Dünndarmes ohne Perforation oder Abszess Divertikulitis mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.21	Divertikulose des Dickdarmes mit Perforation und Abszess Divertikulose mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.23	Divertikulose des Dickdarmes mit Perforation und Abszess Divertikulitis mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.31	Divertikulose des Dickdarmes ohne Perforation oder Abszess Divertikulose mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.33	Divertikulose des Dickdarmes ohne Perforation oder Abszess Divertikulitis mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.41	Divertikulose sowohl des Dünndarmes als auch des Dickdarmes mit Perforation und Abszess	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.

	Divertikulose mit Blutung		
K57.43	Divertikulose sowohl des Dünndarmes als auch des Dickdarmes mit Perforation und Abszess Divertikulitis mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.51	Divertikulose sowohl des Dünndarmes als auch des Dickdarmes ohne Perforation oder Abszess Divertikulose mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.53	Divertikulose sowohl des Dünndarmes als auch des Dickdarmes ohne Perforation oder Abszess Divertikulitis mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.81	Divertikulose des Darmes, Teil nicht näher bezeichnet, mit Perforation und Abszess Divertikulose mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.83	Divertikulose des Darmes, Teil nicht näher bezeichnet, mit Perforation und Abszess Divertikulitis mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.91	Divertikulose des Darmes, Teil nicht	gastrointestinal (also part of	Yes, but only in combination with an emergency hospital admission and a

	näher bezeichnet, ohne Perforation oder Abszess Divertikulose mit Blutung	any bleeding)	documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.93	Divertikulose des Darmes, Teil nicht näher bezeichnet, ohne Perforation oder Abszess Divertikulitis mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K62.5	Hämorrhagie des Anus und des Rektums	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K66.1	Hämoperitoneum	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K92.0	Hämatemesis	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K92.1	Meläna	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K92.2	Gastrointestinale Blutung onA	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
M25.0	Hämarthros	any	yes
M25.00	Hämarthros Mehrere Lokalisationen	any	yes
M25.01	Hämarthros Vorderes Kreuzband oder Vorderhorn des	any	yes

	Innenmeniskus		
M25.02	Hämarthros Hinteres Kreuzband oder Hinterhorn des Innenmeniskus	any	yes
M25.03	Hämarthros Innenband [Lig. collaterale tibiale] oder sonstiger u nicht näher bezeichneter Teil des Innenmeniskus	any	yes
M25.04	Hämarthros Außenband [Lig. collaterale fibulare] oder Vorderhorn des Außenmeniskus	any	yes
M25.05	Hämarthros Hinterhorn des Außenmeniskus	any	yes
M25.06	Hämarthros Sonstiger und nicht näher bezeichneter Teil des Außenmeniskus	any	yes
M25.07	Hämarthros Kapselband	any	yes
M25.09	Hämarthros Nicht näher bezeichnetes Band oder nicht näher bezeichneter Meniskus	any	yes
N02.0	Rezidivierende und persistierende Hämaturie Minimale glomeruläre Läsion	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N02.1	Rezidivierende und persistierende Hämaturie Fokale und segmentale	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the

	glomeruläre Läsionen		same hospital case.
N02.2	Rezidivierende und persistierende Hämaturie Diffuse membranöse Glomerulonephritis	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N02.3	Rezidivierende und persistierende Hämaturie Diffuse mesangioproliferative Glomerulonephritis	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N02.4	Rezidivierende und persistierende Hämaturie Diffuse endokapillär-proliferative Glomerulonephritis	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N02.5	Rezidivierende und persistierende Hämaturie Diffuse mesangiokapilläre Glomerulonephritis	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N02.6	Rezidivierende und persistierende Hämaturie Dense-deposit-Krankheit	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N02.7	Rezidivierende und persistierende Hämaturie Glomerulonephritis mit diffuser Halbmondbildung	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N02.8	Rezidivierende und persistierende Hämaturie Sonstige morphologische Veränderungen	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.

N02.9	Rezidivierende und persistierende Hämaturie Art der morphologischen Veränderung nicht näher bezeichnet	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N42.1	Kongestion und Blutung Prostata	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N83.6	Hämatosalpinx	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N85.7	Hämatometra	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N89.7	Hämatokolpos	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N93.0	Postkoitale Blutung und Kontaktblutung	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N93.8	Sonstige näher bezeichnete abnorme Uterus- oder Vaginalblutung	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N93.9	Abnorme Uterus- oder Vaginalblutung, nicht näher bezeichnet	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N95.0	Postmenopausenblutung	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the

			same hospital case.
R04.0	Epistaxis	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R04.1	Blutung aus dem Rachen	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R04.2	Hämoptoe	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R04.8	Blutung aus sonstigen Lokalisationen in den Atemwegen	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R04.9	Blutung aus den Atemwegen, nicht näher bezeichnet	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R23.3	Spontane Ekchymosen	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R31	Nicht näher bezeichnete Hämaturie	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R58	Blutung sonst nicht klassifiz.	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
S06.4	Epidurale Blutung	intracerebral (also part of any bleeding)	yes
S06.5	Traumatische	intracerebral	yes

	subdurale Blutung	(also part of any bleeding)	
S06.6	Traumatische subarachnoidale Blutung	intracerebral (also part of any bleeding)	yes
S06.8	Sonstige intrakranielle Verletzungen: Traumatische Blutung, traumatisches Hämatom, Kontusion	intracerebral (also part of any bleeding)	yes

Table 23 Comorbidities included in the CHA_2DS_2-VASc Score

Conditions	**ICD-10 GM code**	**Assigned weights**
Hypertension	I10.*, I11.*, I12.*, I13.*, I14.*, I15.*	1
Diabetes mellitus	E10.*, E11.*, E12.*, E13.*, E14.*	1
Heart failure	I50.*	1
Age between 65 and 74 years		1
Vascular disease (previous MI, peripheral arterial disease or aortic plaque)	I21.*, I22.*, I73.9, I70.2, I70.0	1
Stroke or TIA	G45.9, I63.*	2
Age ≥ 75 years		2
Female sex		1

Table 24 Comorbidities included in the $CHADS_2$ Score

Conditions	**ICD-10 GM code**	**Assigned weights**
Hypertension	I10.*, I11.*, I12.*, I13.*, I14.*, I15.*	1

Diabetes mellitus	E10.*, E11.*, E12.*, E13.*, E14.*	1
Heart failure	I50.*	1
Stroke or TIA	G45.9, I63.*	2
Age ≥ 75 years		1

Table 25 Comorbidities included in the Charlson Comorbidity Index (CCI) and modified comorbidity index

Conditions	**ICD-10 GM code**	**Assigned weights CCI**	**Assigned weights modified comorbidity index**
Myocardial Infarction	I21,I22,I252	1	1
Congestive heart failure	I43,I50,I099,I110,I130,I132,I255,I420,I425,I426,I427,I428,I429,P290	1	0
Peripheral vascular disease	I70,I71,I731,I738,I739,I771,I790,I792,K551,K558,K559,Z958,Z959	1	1
Cerebrovascular disease	G45,G46,I60,I61,I62,I63,I64,I65,I66,I67,I68,I69,H340	1	0
Dementia	F00,F01,F02,F03,G30,F051,G311	1	1
Chronic pulmonary disease	J40,J41,J42,J43,J44,J45,J46,J47,J60,J61,J62,J63,J64,J65,J66,J67,I278,I279,J684,J701,J703	1	1
Connective tissue disease	M05,M32,M33,M34,M06,M315,M351,M35	1	1

	3,M360		
Ulcer disease	K25,K26,K27,K28	1	1
Mild liver disease	B18,K73,K74,K700,K701,K702,K703,K709,K717,K713,K714,K715,K760,K762,K763,K764,K768,K769,Z944	1	0
Diabetes without complications	E100,E101,E106,E108,E109,E110,E111,E116,E118,E119,E120,E121,E126,E128,E129,E130,E131,E136,E138,E139,E140,E141,E146,E148,E149	1	1
Hemiplegia	G81,G82,G041,G114,G801,G802,G830,G831,G832,G833,G834,G839	2	2
Moderate or severe renal disease	N18,N19,N052,N053,N054,N055,N056,N057,N250,I120,I131,N032,N033,N034,N035,N036,N037,Z490,Z491,Z492,Z940,Z992	2	0
Diabetes with end organ damage	E102,E103,E104,E105,E107,E112,E113,E114,E115,E117,E122,E123,E124,E125,E127,E132,E133,E134,E135,E137,E142,E143,E144,E145,E147	2	2
Any tumor	C00,C01,C02,C03,C04,C05,C06,C07,C08,C09,C10,C11,C12,C13,C	2	2

	14,C15,C16,C17,C18,C19,C20,C21,C22,C23,C24,C25,C26,C30,C31,C32,C33,C34,C37,C38,C39,C40,C41,C43,C45,C46,C47,C48,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,C81,C82,C83,C84,C85,C88,C90,C91,C92,C93,C94,C95,C96,C97		
Moderate or severe liver disease	K704,K711,K721,K729,K765,K766,K767,I850,I859,I864,I982	3	0
Metastatic solid tumor or AIDS	C77,C78,C79,C80,B20,B21,B22,B24	6	6

Table 26 Operationalization HAS-BLED Score

Criteria	**ICD-10 GM code**
Hypertension	I10.*, I11.*, I12.*, I13.*, I14.*, I15.*
Renal disease	N18.*, N19.*
Cirrhosis	K70.3, K71.7, K74.*
Stroke	I63.*
Major bleeding event	According to outcome definition
Alcohol use	F10.*
Non-steroidal anti-inflammatory drug	M01A*

Antiplatelet agents	B01AC*
Age >65	

Table 27 ATC Codes Proton-pump-inhibitors

ATC Code	Label
A02BC01	Omeprazol
A02BC02	Pantoprazol
A02BC03	Lansoprazol
A02BC04	Rabeprazol
A02BC05	Esomeprazol
A02BC06	Dexlansoprazol

Table 28 List of covariates

Variable	Definition
male	proportion of male persons
age	age of the persons
initiation_kh	binary: prescription is initialized by hospital (1 if hospital discharge on day of dispensation or within three days before dispensation) ; (hospital > cardiologist > other)
initiation_amb_kardio	binary: prescription is initialised by ambulatory cardiologist (if if cardiologist prescriped the initial drug) ; (hospital > cardiologist > other)
initiation_amb_else	binary: prescription is initialised by other ambulatory physician ; (hospital > cardiologist > other)
urban	residence of the persons in region type urban
east_germany	residence of the person in east Germany
initiation_kh	initiation by hospital (hospital discharge diagnoses within 7 days prior to first dispensing)
initiation_amb_kardio	initiation by cardiologist in ambulatory setting
initiation_amb_else	initiation by any other physician in ambulatory setting
vers_stat_regular	insurance status: regular
vers_stat_family	insurance status: family insured
vers_stat_retired	insurance status: retired
n_hosp_cases	number of (full- and part time) hospital cases
n_hosp_days	sum of (full- and part time) hospital days
hosp	binary: hospitals case yes / no in baseline
hosp30	binary: hospital case yes / no within the 30 days before first despensions of vka
i_stroke_h_stroke_se_hosp30	binary: hospital case due to stroke yes / no within the 30 days before first despensions

mi_hosp30	binary: hospital case due to myocardial infarction yes / no within the 30 days before first despensions
days_since_last_hosp	days since last hospital stay (for all with at least one hospital stay in baseline, missing if no stay in baseline)
n_amb_efn_id_visits	number of ambulatory care visits (counted via efn_id)
n_amb_qtr_visits	number of quarters wirth ambulatory care visits
n_unique_lanr	number of unique physicians contacted
n_unique_atc7	number of unique atc-7- codes
n_verord	sum of prescriptions
antiplatelet	binary: antiplatelet in baseline
ass	binary: ass in baseline
nsaids	binary: nsaids in baseline
ppi	binary: proton pump inhibator in baseline
betablock	binary: betablocker in baseline
verapamil	binary: verapamil in baseline
amiodarone	binary: amiodarone in baseline
ace_inhibator	binary: ace_inhibator in baseline
antipsychotics	binary: antipsychotics in baseline
antidepressant	binary: antidepressant in baseline
diuretics	binary: diuretics in baseline
insulin	binary: insulin in baseline
antiplatelet_until_index	binary: antiplatelet prescription with range until day of first disepension of vka
ass_until_index	binary: ass in baseline with range until day of first disepension of vka
nsaid_until_index	binary: nsaids in baseline with range until day of first disepension of vka
ppi_until_index	binary: ppi in baseline with range until day of first disepension of vka
mod_has_bled_score	modified has bled score
CHADS2_SCORE	CHADS2 SCORE
CHA2DS2_VASC_SCORE	CHA2DS2 VASC SCORE
max_nyha	highest nyha stage in baseline based on icd codes (0 - none ; 0.5 - unspecific ; 1 - stage 1 ; 2 - stage 2 ; 3 stage 3 ; 4 stage 4)
max_niere	highest nyha stage in baseline based on icd codes (0 - none ; 0.5 - unspecific ; 1 - stage 1 ; 2 - stage 2 ; 3 stage 3 ; 4 stage 4 ; 5 - stage 5)
max_copd	highest copd obstuction stage in baseline based on icd codes (0 - none ; 0.5 - unspecific ; 1 - stage 1 ; 2 - stage 2 ; 3 stage 3 ; 4 stage 4)
frailty	binary: frailty diagnoses in baseline
thyroid_dysfunction	binary: thyroid dysfunction diagnoses in baseline

alzheimer_parkinson	binary: alzheimer or parkinson diagnoses in baseline
sleep_apnoea	binary: sellep apnoea diagnoses in baseline
ICD10_CH_MI	binary: charlson category for myocardial infarction
ICD10_CH_CHF	binary: charlson category for congestive heart failure
ICD10_CH_PVD	binary: charlson category for Peripheral vascular disease
ICD10_CH_CEVD	binary: charlson category for Cerebrovascular disease
ICD10_CH_DEM	binary: charlson category for Dementia
ICD10_CH_LUNGE	binary: charlson category for Chronic pulmonary disease
ICD10_CH_Rheum	binary: charlson category for Rheumatologic disease / chronic tissue disease
ICD10_CH_PUD	binary: charlson category for Peptic Ulcer disease
ICD10_CH_MILDLD	binary: charlson category for Mild liver disease
ICD10_CH_DIAB_noCOMP	binary: charlson category for Diabetes without chronic complications
ICD10_CH_DIAB_withCOMP	binary: charlson category for Diabetes with chronic complications
ICD10_CH_PARA	binary: charlson category for Hemiplegia
ICD10_CH_RD	binary: charlson category for Rheumatologic disease / chronic tissue disease
ICD10_CH_CANCER	binary: charlson category for any malignant tumor (excluding C42 and metastases)
ICD10_CH_METS	binary: charlson category for Metastatic solid tumor
ICD10_CH_MSLD	binary: charlson category for Moderate or severe liver disease
ICD10_CH_HIV	binary: charlson category for HIV
Charlson_index	charlson comorbidity index
como_index	comorbidity index
_alcohol	binary: alcohol yes / no
_anxiety_disorder	binary: anxiety_disorder yes / no
_artherosclerosis	binary: artherosclerosis yes / no
_cancer	binary: cancer yes / no
_chronic_renal_insuffiency	binary: chronic_renal_insuffiency yes / no
_congestive_heart_failure	binary: congestive_heart_failure yes / no
_coronary_heart_disease	binary: coronary_heart_disease yes / no
_dementia	binary: dementia yes / no
_depression	binary: depression yes / no
_diabetes	binary: diabetes yes / no
_hypertension	binary: hypertension yes / no
_ischemic_stroke_or_tia	binary: ischemic_stroke_or_tia yes / no

_mild_liver	binary: mild_liver yes / no
_moderate_severe_liver	binary: moderate_severe_liver yes / no
_myocardial_infarction	binary: myocardial_infarction yes / no
_obesity	binary: obesity yes / no
_smoking	binary: smoking yes / no
_somatoform_disorder	binary: somatoform_disorder yes / no
_substance_abuse	binary: substance_abuse yes / no
_chronic_renal	binary: chronic_renal desease yes / no
_chronic_renal_1	binary: chronic_renal desease stage 1yes / no
_chronic_renal_2	binary: chronic_renal desease stage 2 yes / no
_chronic_renal_3	binary: chronic_renal desease stage 3 yes / no
_chronic_renal_4	binary: chronic_renal desease stage 4 yes / no
_chronic_renal_5	binary: chronic_renal desease stage 5 yes / no
_chronic_renal_other	binary: othere chronic_renal desease yes / no
_chronic_renal_unspec	binary: unspecific chronic_renal desease yes / no
_chronic_renal_3_or_4_or_5	binary: chronic_renal desease stage 3 or higher yes / no
_chronic_renal_4_or_5	binary: chronic_renal desease stage 4 or higher yes / no
any_bleeding	binary: any bleeding event yes / no
gastro_bleeding	binary: gastro bleeding event yes / no
major_bleeding	binary: major bleeding event yes / no
intra_bleeding	binary: intra bleeding event yes / no
i_stroke_h_stroke_se	binary: i-stroke, h-stroke se yes / no
i_stroke_h_stroke	binary: i-stroke, h-stroke yes / no
i_stroke	binary: i-stroke yes / no
h_stroke	binary: h-stroke yes / no
max_nyha_pid_nyha	highest nyha stage in baseline based on icd codes for persons with nyha (missing - none ; 0.5 - unspecific ; 1 - stage 1 ; 2 - stage 2 ; 3 stage 3 ; 4 stage 4)
max_niere_pid_niere	highest nyha stage in baseline based on icd codes for persons with chronic renal disease (missing - none ; 0.5 - unspecific ; 1 - stage 1 ; 2 - stage 2 ; 3 stage 3 ; 4 stage 4 ; 5 - stage 5)
max_copd_pid_copd	highest copd obstuction stage in baseline based on icd codes for persons with copd (missing - none ; 0.5 - unspecific ; 1 - stage 1 ; 2 - stage 2 ; 3 stage 3 ; 4 stage 4)