NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Post Authorisation Safety Studies (PASS) information

Title	CARBOS – Comparative risk of major bleeding with new oral anticoagulants (NOACs) and Phenprocoumon in patients with atrial fibrillation: a retrospective claims database study in Germany
Protocol number	B0661069
Protocol version identifier	Update 1.0
Date of last version of protocol	08 January 2016
EU Post Authorisation Study (PAS) register number	ENCEPP/SDPP/11313
Active substance	Apixaban (B01AF02) Phenprocoumon (B01AA04) Rivaroxaban (B01AX06; B01AF01) Dabigatran (B01AX06)
Product reference	EU/1/11/691/006 EU/1/11/691/007 EU/1/11/691/008 EU/1/11/691/009 EU/1/11/691/010 EU/1/11/691/011

	EU/1/11/691/012 EU/1/11/691/014
Procedure number	Not Available
Marketing Authorisation Holder (MAH)	Pfizer Pharma GmbH
Joint PASS	No
Research question and objectives	The aim of this study is to investigate whether there are differences in the occurrence of major bleeding events in patients with NVAF and prescribed oral anticoagulation therapies in a real-world setting. It will be investigated whether the occurrence of major bleeding events in NVAF patients under anticoagulant therapy differs between patients treated with VKA (e.g. Phenprocoumon) and patients treated with Apixaban, Dabigatran or Rivaroxaban respectively.
Country of study	Germany
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Events
NVAF	Non-Valvular 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
EHA	Elsevier Health Analytics
EU	European Union
FDA	Food and Drug Administration

GI	Gastrointestinal
GOP	Gebührenordnungsposition
HRI	Health Risk Institute
ICD-10 GM	International Classification of Diseases, 10th Revision, German Modification
ICH	Intracerebral Hemorrhage
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

2. RESPONSIBLE PARTIES

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Country Coordinating Investigators

Not applicable

3. ABSTRACT

Title:

Comparative risk of major bleeding with new oral anticoagulants (NOACs) and Phenprocoumon in patients with non-valvular atrial fibrillation: a retrospective claims database study in Germany.

Rationale and Background:

Non-Valvular Atrial fibrillation (NVAF), the most common cardiac arrhythmia worldwide, affects approximately 1-2% of the general population and is a major risk factor for ischemic stroke. In order to reduce NVAF related stroke risk, Vitamin-K-Antagonists (VKA) have long constituted the standard treatment of patients with NVAF. 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 superior to VKA with regard to stroke prevention in patients with NVAF. Currently four NOACs are approved for stroke patients with NVAF in Germany: Apixaban, Dabigatran, Rivaroxaban and Edoxaban. The efficacy of these drugs has been proven in prospective randomized multicenter studies. Moreover, these trials have demonstrated a favorable safety profile of NOACs compared to VKA.

Research question and objectives:

The aim of this study is to investigate whether there are differences in the occurrence of major bleeding events in patients with a dispensed prescription of NVAF oral anticoagulation therapy in a real-world setting. It will be investigated whether the occurrence of major bleeding events in NVAF patients differs among patients with underVKA (e.g. Phenprocoumon) and patients under Apixaban, Dabigatran or Rivaroxaban, respectively. As of the recent market entry of Edoxaban, data are not yet available to include this NOAC in the study,

Study design:

To address the objectives of this study, a non-interventional retrospective user analysis will be conducted using insurance claims data from the Health Risk Institute's (HRI) research database.

Population (Setting and study population):

The study population will consist of NVAF patients who were treated with an oral anticoagulant therapy within 01.01.2013 and 31.12.2014. Patients will be identified from the HRI 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 will be assigned to one of the following treatment groups: Apixaban, Dabigatran, Rivaroxan or Phenprocoumon. The main outcome of interest is a major bleeding event in the patient individual study period. Key-covariates include comorbidities at baseline, age and the risk factor for bleeding.

Data sources:

The study will be conducted using data from the HRI 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 are provided together with costs. The size of the dataset has been reduced to a sample of approximately 4 million patients per year, representative of the German population in terms of age and gender (as of 31.12.2013).

Study Size:

A preliminary feasibility study identified a total of approximately 36,700 therapy naïve patients and approximately 85,000 experienced users eligible for the planned analysis.

Data Analysis:

After a descriptive characterization of the four treatment groups, adjusted hazard ratios of the risk of major bleeding will be estimated by means of two different models. In a first approach, a cox-proportional hazards model will be used to determine differences in the risk of major bleeding between treatment groups. Furthermore a marginal structural model (MSM) will be built in order to account for time-varying confounders and exposures.

Milestones:

- Compilation of data protocol: 30.08.2015
- End of preparation phase (study protocol): 17.09.2015
- Registration in the EU PAS register: 15.09.2015
- Start of data collection: 28.09.2015
- End of data collection: 12.10.2015
- End of data analysis: 15.01.2016

4. AMENDMENTS AND UPDATES

4.1. Update 1: Update of original study protocol from September, 9th 2015:

- Refined definition of the primary outcome major bleeding (see section 8.3.1 Outcomes/ Endpoint Variable)

- Bleeding events in experienced NVAF and phenprocoumon users will not be included in multivariate regression analyses due to very small sample size (see section 15.2.1 Setting)

- Definition of additional outcomes intracerebral bleeding (see section 15.2.2 Variables)

- Additional Cox regression analyses for patients starting their NVAF therapy on a low dose and for patients starting their NVAF therapy on a high dose (see section 15.3.1 Additional analyses – dosage analyses)

- Study timelines and final deliverables of analyses changed (see section 5)

All changes and amendments are described in more detail in section 15.

5. MILESTONES

Milestone	**Planned date**
Compilation of the study protocol	30 August 2015
Start of data collection - Preparation of the analysis dataset - Identification of the study population	28 September 2015
End of data collection (the minimum set of data required to perform the statistical analysis for the primary objective(s) will be first completely available).	12 October 2015
Analyses according to study protocol (Part I) - Definition and generation of covariates (clinical and demographic characteristics of the patients in the study population) - Definition and generation of the outcome variable (major bleeding)	12 - 18 October 2015
Analyses according to study protocol (Part II) - Analysis 'OT' - Analysis 'TS'	19 October – 15 January 2016

Registration in the European Union (EU) PAS register	15 September 2015
Quality management, editing of the results, final study report	15 - 31 January 2016

6. RATIONALE AND BACKGROUND

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

Vitamin-K antagonists (VKA) have long been the standard treatment of patients with NVAF, reducing the risk of stroke in NVAF patients by approximately two thirds compared to placebo (3). 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 (3,4). 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. Currently three NOACs are available for stroke prevention in patients with NVAF in Germany: Dabigatran – (a direct thrombin inhibitor) as well as Apixaban and Rivaroxaban (direct factor Xa inhibitors). Three randomized controlled trials (RCTs) found that NOACs are non-inferior or even superior compared to warfarin in preventing stroke and systemic embolisms, while the results regarding relevant safety outcomes such as bleeding were heterogeneous (3,5–7). A meta-analysis of these RCTs demonstrated a significantly lower risk of intracranial bleeding in NVAF patients taking NOACs compared to those taking warfarin. The findings regarding major bleeds or gastrointestinal bleeds were inconclusive (5). The ARISTOTLE trial, a double-blind, 1:1 randomized clinical trial demonstrated that Apixaban caused significantly less bleeding events as well as a lower mortality rate compared to warfarin (8).

The aim of this study is to gain further insight into the safety profile of VKAs compared to NOACs with a focus on major bleeding events in German NVAF patients.

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

7. RESEARCH QUESTION AND OBJECTIVES

The main research question is to assess whether there are differences in the risk of major bleeding events among NVAF patients prescribed VKA or one of the NOACs in a real-world setting.

The primary objective is to investigate whether the rate of major bleeding events in NVAF patients under anticoagulant therapy differs between:

1. patients treated with Phenprocoumon and patients treated with Apixaban.
2. patients treated with Phenprocoumon and patients treated with Rivaroxaban.
3. patients treated with Phenprocoumon and patients treated with Dabigatran.

Secondary objectives are to investigate whether the rate of gastrointestinal bleeding events and any bleeding events in NVAF patients under anticoagulant therapy differs between:

1. patients treated with Phenprocoumon and patients treated with Apixaban.
2. patients treated with Phenprocoumon and patients treated with Rivaroxaban.
3. patients treated with Phenprocoumon and patients treated with Dabigatran.

The tertiary objective is to investigate whether of the composite end point (net clinical benefit) in NVAF patients under anticoagulant therapy differs between:

1. patients treated with Phenprocoumon and patients treated with Apixaban.
2. patients treated with Phenprocoumon and patients treated with Rivaroxaban.
3. patients treated with Phenprocoumon and patients treated with Dabigatran.

The tertiary outcome net clinical benefit is a composite endpoint of ischemic stroke, systemic embolism, major bleeding or death from any cause.

8. RESEARCH METHODS

8.1. Study design

A non-interventional retrospective new user analysis will be conducted using insurance claims data from the Health Risk Institute's (HRI) research database. For an insured person to be included in the study, he/she must have been prescribed an oral anticoagulant (OAC) therapy within 01.01.2013 and 31.12.2014 because of documented NVAF in the same or preceding quarter of treatment initiation.

8.2. Setting

The HRI 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 within 2008 and 2014. The size of the dataset has been reduced to a sample of approximately 4 million patients per year in order to get a representative sample of the German population in terms of age and gender (as of 31.12.2013). This subset of patients will be used for the purposes of this study.

8.2.1. Inclusion criteria

To be representative of the real world daily care situation, two different groups of NVAF patients will be identified for this study, namely those with (i) novel and (ii) experienced OAC patients (see below for a description). The outcomes will be separately assessed for the two groups of patients meeting the inclusion criteria:

8.2.1.1. Therapy naive patients:

NVAF Patients who have been newly prescribed OAC therapy (Apixaban, Dabigatran, Rivaroxaban or Phenprocoumon) within the study period (01.01.2013 - 31.12.2014), i.e. no prior prescription for any of the above listed substances in the 12 months before index date

(for relevant Anatomical Therapeutic Chemical Classification System (ATC) Codes please refer to Table 6 in ANNEX 3).

8.2.1.2. Non-therapy naive patients / experienced user

Patients who have been prescribed any of the above listed substances in the 12 months prior to a first prescription within 01.01.2013 and 31.12.2014 will be defined as experienced users.

8.2.1.3. Inclusion criteria for therapy naive patients and experienced user

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

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

   OR

2. At least two ambulatory verified or secondary hospital discharge diagnoses in two quarters or one hospital discharge diagnosis in the period between 01 January 2010 and index date)

3. ≥ 18 years of age at index date;

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

8.2.2. Exclusion criteria

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

1. Patients receiving more than one anticoagulant substance (Apixaban, Dabigatran, Rivaroxaban 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 7 in ANNEX 3;

3. Patients receiving a NOAC and heparin on the index date (for relevant ATC Codes please see Table 8 in ANNEX 3);

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

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 9 in ANNEX 3);

6. Patients who present any evidence of pregnancy in the four quarters prior to or on index (for relevant ICD Codes please refer to Table 9 in ANNEX 3).

8.2.3. Observation periods

The objectives of this study are planned to be answered using two different analysis scenarios. The events that determine a patients' individual end of the follow up (i.e. censoring times) differs between the two scenarios and are described in more detail in the following section. For the sake of clarity, the entire study design, including the different groups of patients observed, the endpoints, the statistical options and sensitivity analyses is summarized graphically in ANNEX 5.

Index date - The index date will be the first date of OAC prescription documented in the observation period 01.01.2013 and 31.12.2014 for all patients. Patients who have been under OAC therapy in the four quarters prior to the index date will be assigned to the experienced user group, while patients without any prior OAC prescriptions are assigned to the therapy naïve user group.

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 will be used to determine whether patients have an NVAF diagnosis, to verify that patients are new OAC users and to assess baseline demographic and clinical characteristics of the patients included in the study population, necessary for the planned multivariate analysis.

Gap period - A gap period is allowed when treatment is discontinued before censoring the patient for discontinuation. Patients will be considered as being exposed until 30 days after the end of supply. The rationale behind this choice is that in clinical studies adverse events will be assessed and documented for 30 days after the end of treatment. Additionally to this conservative approach, a sensitivity analysis will be conducted using a more restricted approach: The gap period will then be considered as only the wash-out period (see below).

Wash-out period – The wash-out period will be used as a sensitivity analysis regarding the gap period. It will be added to the exposure to account for the time patients are still under the influence of the substance AFTERter discontinuation of the treatment (pharmacokinetic). A wash-out period of 2 days will be added to the exposure time for all patients with NOAC therapy. A wash-out period of 10 days will be added to the exposure time for all patients with VKA therapy.

Days of supply - since NOACs are prescribed in a fixed dose, the number of days of supply strictly corresponds to the size of the package, or the number of days until new prescription, if smaller. Assessing VKA's number of days of supply is not straightforward. Doses were standardized among VKA patients for the estimation. The approach is further described in 8.7.4 – VKA Days of Supply.

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

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

Date of discontinuation - Discontinuation will be 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.

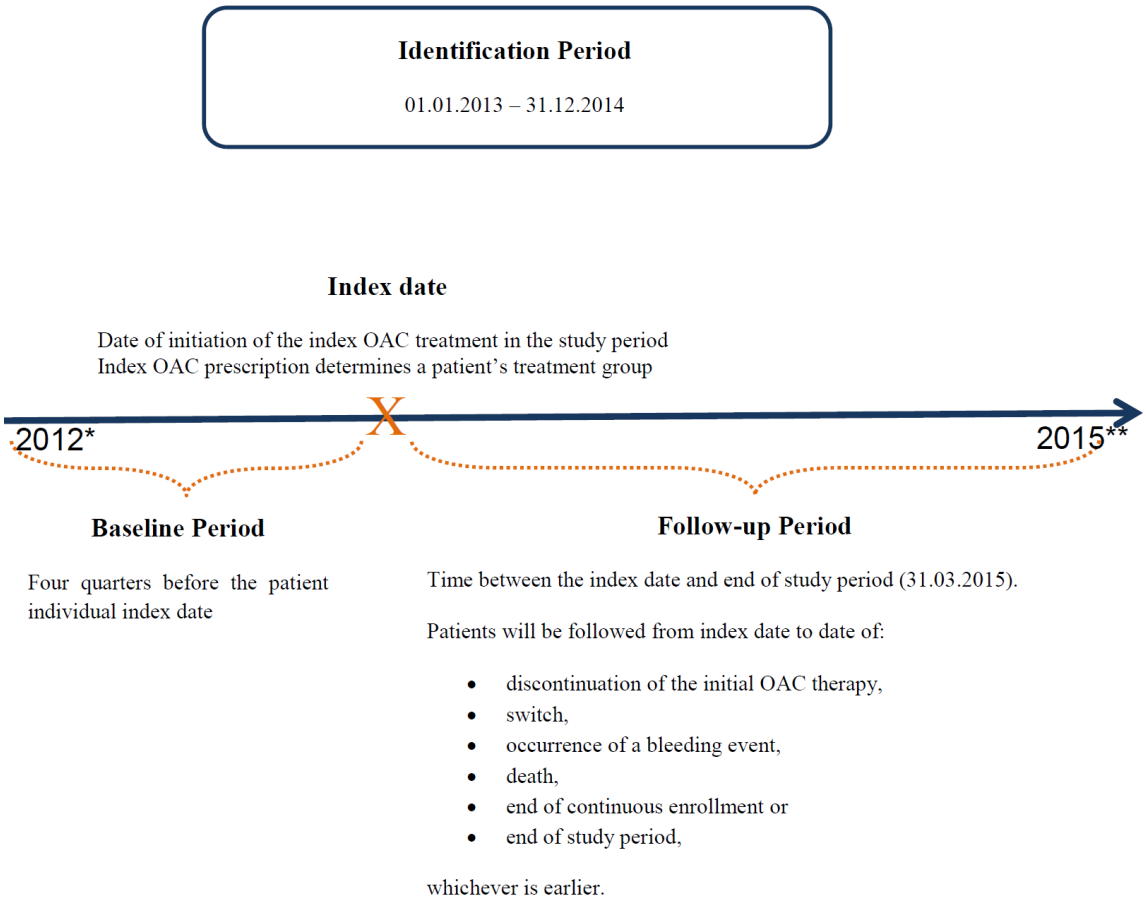
Patients receiving prescriptions for warfarin or an NOAC in the wrong dosage (Dabigatran 75 mg or Rivaroxaban 10 mg) will also be considered to have terminated the treatment.

The last day of the exposure time will be defined as the date of discontinuation and patients will be censored.

8.2.3.1. Scenario I – 'On Treatment (OT)'

In this scenario a patients' initial OAC prescription determines treatment group affiliation, i.e. if a patient's first OAC prescription during the identification period is for Apixaban, she/he will be assigned to the Apixaban treatment group. Censoring occurs when a patient switches to a different OAC treatment (date of censoring = date of switch) or when a patient discontinues the treatment. Further events ending the patient individual follow-up time include the occurrence of a bleeding event, death, end of continuous enrollment or the end of the study period, whichever is first. Figure 1 provides an overview about the observation periods which will be applied in this scenario.

Figure 1 Observation Periods Scenario I 'OT'



*Note: For example, 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.

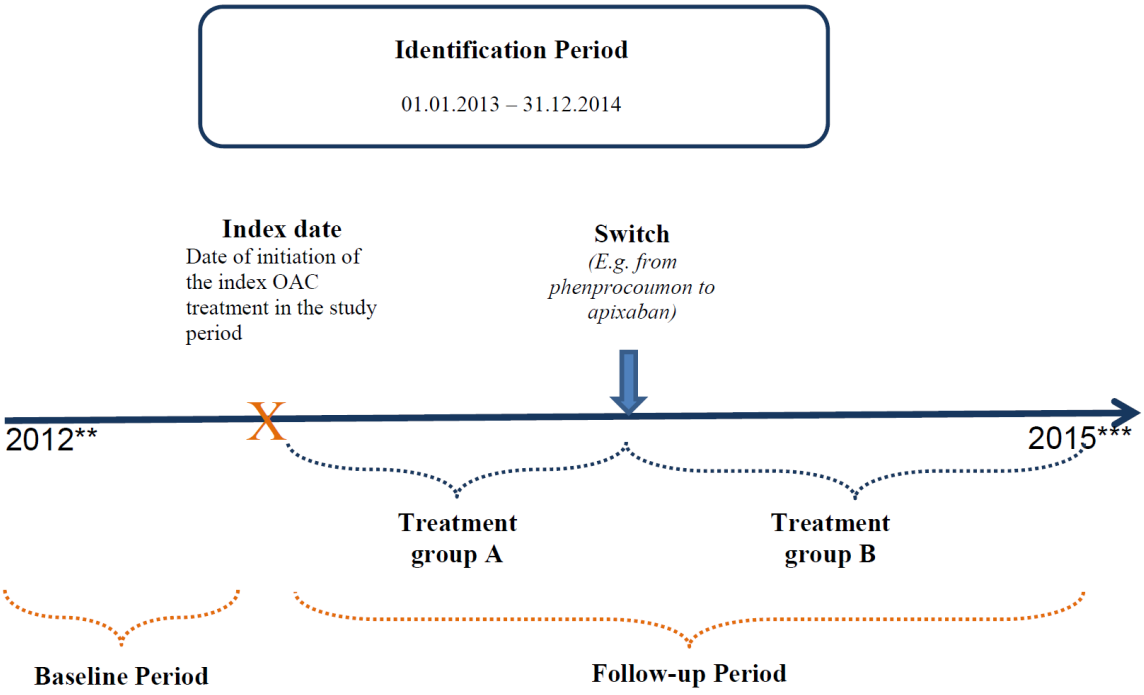
**Note: Maximum last day of observation: 31.03.2015. However if the discontinuation of the OAC therapy, a switch, the occurrence of a bleeding event, death or the end of continuous enrollment occur before that day, the patient individual follow-up period ends.

8.2.3.2. Scenario II – 'Treatment switching (TS)'

In this scenario a patients' initial OAC prescription determines treatment group affiliation, i.e. if a patient's first OAC prescription during the identification period is for Apixaban, the patient will be assigned to the Apixaban treatment group. However, in contrast to the OT scenario, the date of a switch or of discontinuation of the OAC treatment will not be used as a censoring date. Instead, the exposure times of patients who switch from one substance to another will be categorized based on the substance they received during certain intervals of the follow-up period. For example, if a patient is 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 will be 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 Observation Periods Scenario II 'TS'



Four quarters before the patient individual index date

Time between the index date and end of study period (31.03.2015).

Patients will be followed from index date to date of:

- occurrence of a bleeding event,
- death,
- end of continuous enrollment,
- end of study period,

whichever is earlier.

*Note: In this scenario time dependent exposure changes are allowed

**Note: For example, 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: 31.03.2015. However if the occurrence of a bleeding event, death or the end of continuous enrollment occur before that day, the patient individual follow-up period ends.

8.3. Variables

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

8.3.1. Outcomes/ Endpoint Variable

The primary outcomes of interest are major bleeding events. Secondary outcomes of interest include gastrointestinal and any bleeding events. These outcomes are safety outcomes.

In addition, in the sense of a tertiary endpoint for this safety study, a "net clinical" combined outcome consisting of ischemic stroke, systemic embolism, major bleeding or death from any cause will be investigated. This composite outcome was used in most RCT on NOAC representing the overall freedom from death, embolic and hemorrhagic complications as well in NVAF-patients under OAC therapy (descriptive character to the safety endpoints).

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

Table 1 Definition of the outcomes

Variable	Objective	Operational definition
Major bleeding event[1]	Primary	A major bleeding event will be defined as a bleeding event occurring anytime during the **Exposure time** Major bleeding events are will be defined as A. (hospital case in which the : • hospital admission was labelled as an

1 This outcome has been specified throughout the course of the project when it became apparent that the previous definition was not defined a strict as necessary to truly depict a major bleeding event (e.g. a single transfusion OPS code was originally defined as sufficient to define a major bleeding event, while these could also have been part of a regular treatment regime following an elective surgery).

		emergency admission AND • an any bleeding (except D62*), gastrointestinal, intracerebral ICD 10 codes in Table 10 validated by OPS code 8-800 (blood transfusion) or the ICD 10 diagnosis D62* (Acute posthaemorrhagic anaemia) documented in the same hospital case) **OR** B. A hospital case with one of the ICD 10 codes labelled as a major bleeding event in the last column of Table 10 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* in Table 10 in ANNEX 3.
Gastrointestinal bleeding event	Secondary	A gastrointestinal bleeding event will be defined as a bleeding event occurring anytime during the **Exposure time**. Gastrointestinal bleeding events will be 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 Table 10 in ANNEX 3.

Any bleeding event	Secondary	Any bleeding event will be defined as a bleeding event occurring anytime during the **Exposure time**. Any bleeding event will be 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 Table 10 in ANNEX 3. Severe, intracerebral and gastrointestinal bleeding events are part of this composite endpoint, i.e. all ICD 10 GM codes listed in Table 10 will be used for the definition of this endpoint.
Net clinical benefit	Tertiary Endpoint	Composite endpoint of ischemic stroke, systemic embolism, major bleeding or death from any cause (whichever occurs first) during the **Exposure time**. Major bleeding events will be defined as defined as described above on primary or secondary ICD10 GM hospital discharge diagnoses. Stroke and systemic embolism will be defined accordingly using the following ICD-10 GM codes: - I63* Cerebral infarction - I74* arterial embolism and thrombosis

8.3.2. Factors affecting censoring during follow up

Table 2 Definition of censoring events

Variable	Operational definition
Discontinuation	Discontinuation will be 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** will be defined as the date of discontinuation. Note: Any patient who switches from any dose of NOACs indicated for the treatment of NVAF to Dabigatran 75mg or Rivaroxaban 10mg will be censored, because neither of these treatment regimens are indicated for the stroke prevention in NVAF patients. Patients switching to Warfarin will also be censored. It will be reported how many patients are censored due to treatment discontinuation.
Switch of OAC	Patients who receive a prescription for an OAC other than the index OAC prescription during the follow- up period will be considered switchers if this switch occurred within 30 days after the end of the **Exposure time**. The date on which the changed prescription was issued will be defined as the date of the switch. If a prescription, which differs from the initial OAC prescription, is prescribed before the end of the previous prescription, the date of the follow-up prescription will be defined as the switch date and the

	patient will be considered to be on the changed treatment from that date onwards. The number and proportion of patients switching from one substance to another, as well as the number and proportion of patients switching between different dosages of the same substance will be depicted.
Death	Patients who died during the follow up period. Date of death = date of censoring (i.e. end of follow-up, a potential issue with informative censoring will be assessed in the analysis of the combined endpoint).
End of enrollment	For patients who switched to a different health insurer during the follow up period, claims data will no longer be available in the HRI database. The date of the end of the enrollment will determine the date of censoring (i.e. end of the follow up) for these patients.

8.3.3. Exposure Variables / Independent Variables of Interest

Patients will be allocated to the four treatment groups listed below based on their index prescription.

- Apixaban
- Dabigatran
- Rivaroxaban
- Phenprocoumon

8.3.4. Other Covariates

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

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: (31.12. of the previous year) • east/west • urban/rural • unknown Patients are 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 is not available. These patients will be placed in the unknown category.
Number of hospitalizations	continuous	Total number of hospitalizations, independent of admission diagnosis, during the Baseline period.
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 will be derived by assigning one point each for hypertension, diabetes mellitus, and 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 (9). Ambulatory verified as well as primary and secondary hospital discharge diagnoses within in the 12 months before the Index date will be used to assess the CHA_2DS_2-VASc score. For a complete list of all ICD-10 codes which will be used to form the CHA_2DS_2-VASc score please refer to Table 11 of ANNEX 3.
$CHADS_2$ Score	continuous	The $CHADS_2$ Score will be derived by assigning one point each for hypertension, heart failure, age 75

		years and older, diabetes mellitus. A preliminary stroke/TIA will be assigned two points, with a total possible score of six (9). Ambulatory verified as well as primary and secondary hospital discharge diagnoses within in the 12 months before the Index date will be used to assess the $CHADS_2$ score. For a complete list of all ICD-10 codes which will be used to form the $CHADS_2$ score please refer to Table 12 of ANNEX 3.
Charlson Comorbidity Index (CCI)	continuous	The Charlson Comorbidity Index (CCI) will be used to weigh comorbidities in the Baseline period depending on their severity. Ambulatory verified as well as primary and secondary hospital discharge diagnoses within the 12 months before the Index date will be used to build the CCI score. A list of included conditions and their assigned weights can be found in Table 13 of ANNEX 3. Please consider the following publications for further information regarding the applied methodology: - Charlson ME, Pompei P, Ales KL, MacKenzie CR. "A new method of classifying prognostic comorbidity in longitudinal studies: development and validation", Journal of Chronic Disease, 1987, Vol. 40(5), pp. 373-383. - Quan et al., "Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data", Medical Care, Nov 2005, Vol. 43(11), pp. 1130-1139.
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 includes 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 is derived 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 HRI 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 14 in ANNEX 3.
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 will be used to assess whether patients suffered from a previous myocardial infarction. MI will be 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 will be used assess whether patients suffered from a chronic renal insufficiency. Chronic renal insufficiency will be 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 will be used assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage I will be 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 will be used assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage II will be 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 will be used assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage III will be 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 will be used assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage IV will be 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 will be used assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage V will be 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 will be used assess whether patients suffered from other chronic renal insufficiency. Other chronic renal insufficiency will be defined using the ICD-10 GM code N18.8.
Unspecified 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 will be used assess whether patients suffered from an unspecified renal insufficiency. Unspecified chronic renal insufficiency will 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 will be used assess whether patients suffered from diabetes mellitus. Diabetes mellitus will be 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 will be used assess whether patients suffered from hypertension. Hypertension will be 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 will be used assess whether patients suffered from congestive heart failure. Congestive heart failure will be 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 will be used assess whether patients suffered from peripheral vascular disease. Peripheral vascular disease will be 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 will be used assess whether patients suffered from ischemic stroke or TIA. Ischemic stroke or TIA will be 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 will be used assess whether patients suffered from coronary heart disease. Coronary heart disease will be 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 diagnosis 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 will be used assess whether patients suffered from a mild liver disease. Mild liver disease will be defined using the ICD-10 GM codes according to the Charlson Comorbidity Index (Table 13).
Moderate or severe liver disease	categorical	Ambulatory verified diagnosis 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 will be used assess whether patients suffered from a moderate or severe liver disease. Moderate or severe liver disease will be defined using the ICD-10 GM codes according to the Charlson Comorbidity Index (Table 13).
Severe liver disease	categorical	Ambulatory verified diagnosis 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 will be used assess whether patients suffered from a severe liver disease. Severe liver disease will be 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 diagnosis 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 will be used assess whether patients used tobacco. Tobacco use will be defined using the ICD-10 GM codes F17.*, Z71.6, Z72.0.
Alcohol abuse	categorical	Ambulatory verified diagnosis 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 will be used assess whether patients abused alcohol. Alcohol abuse will be defined using the ICD-10 GM codes F10.*, Z71.4, Z50.2, Z72.1.
Depression	categorical	Ambulatory verified diagnosis 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 will be used assess whether patients suffered from depression. Depression will be defined using the ICD-10 GM

		codes F32*, F33.*, F34.1.
Somatoform disorder	categorical	Ambulatory verified diagnosis 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 will be used assess whether patients suffered from somatoform disorder. Somatoform disorder will be defined using the ICD-10 GM codes F45.*.
Anxiety disorder	categorical	Ambulatory verified diagnosis 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 will be used assess whether patients suffered from anxiety disorder. Anxiety disorder will be defined using the ICD-10 GM codes F40.* and F41.*.
Substance abuse	categorical	Ambulatory verified diagnosis 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 will be used assess whether patients suffered from substance abuse. Substance abuse will be defined using the ICD-10 GM codes F11*, F12*, F13*, F14*, F15*, F16*, F18*, F19*.
Dementia	categorical	Ambulatory verified diagnosis 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 will be used assess whether patients suffered from dementia. Dementia will be defined using the ICD-10 GM codes F00, F01, F02, F03.
Cancer	categorical	Ambulatory verified diagnosis 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 will be used assess whether patients suffered from cancer. Cancer will be defined using the ICD-10 GM code C*.
Obesity	categorical	Ambulatory verified diagnosis 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 will be used assess whether patients suffered from obesity. Obesity will be defined using the ICD-10 GM codes E66.
Major bleeding event	categorical	It will be assessed whether patients suffered from a major bleeding event 365 days before or on the Index date. Major bleeding events will be defined based on primary or secondary ICD10 GM hospital discharge diagnoses in the patient individual Baseline period. For a complete list of all major bleeding events please see Table 10 in ANNEX 3.
Gastrointestinal bleeding event	categorical	It will be assessed whether patients suffered from a gastrointestinal bleeding event in the 365 days before or on the Index date. Gastrointestinal bleeding events will be 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 10 in ANNEX 3. This covariate will only be incorporated in the analysis when the outcome gastrointestinal bleeding is investigated.
Any bleeding event	categorical	It will be assessed whether patients suffered from any bleeding event in the 365 days before or on the Index date. Any bleeding events will be 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 10 in ANNEX 3. This covariate will only be incorporated in the analysis when the outcome any bleeding event is investigated.
Interaction with other medications probably inhibiting the OAC concentration	categorical	In all treatment groups it will be assessed whether patients initiating OAC therapy concurrently receive medication that inhibits the effect of these substances. In order to determine whether patients were concurrently treated with OACs and medication inhibiting this therapy, it will be assessed whether patients received any of the relevant substances in the 90 days before the Index date. For a list of pharmaceuticals inhibiting the effect of each substance please refer to Table 15 in ANNEX 3.
Interaction other medications probably enhancing the OAC concentration	categorical	In all treatment groups it will be assessed whether patients initiating OAC therapy concurrently receive medication that enhances the effect of these substances. In order to determine whether patients were concurrently treated with OACs and medication enhancing this therapy, it will be assessed whether patients received any of the relevant substances in the 90 days before the Index date. For a list of pharmaceuticals inhibiting the effect of each substance please refer to Table 15 in ANNEX 3.

Proton-pump-inhibitors (omeprazol)	categorical	It will be assessed whether patients received at least one prescription for proton-pump-inhibitors in the 365 days before or on the Index date. For a complete list of all relevant ATC Codes please refer to Table 16.
Coronary angioplasty	categorical	It will be 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*) will be used to determine whether the procedure has been performed in the patient individual baseline period.
Antiplatelet medication	categorical	It will be assessed whether patients received at least one prescription for antiplatelet medications in the 365 days before or on the index date. The relevant ATC code that will be used is B01AC.
Prescription of acetylsalicylic acid (ASS)	categorical	It will be assessed whether patients received at least one prescription for ASS (ATC Code: B01AC06) in the 365 days before or on the Index date. Furthermore, this covariate will be included as a time dependent confounder in the 'Switching' scenario. For this purpose it will be checked whether patients received an ASS prescription in the 10 days prior to the date of the therapy switch.
Prescription of non-steroidal anti-inflammatory drugs (NSAIDs)	categorical	It will be assessed whether patients received at least one prescription for NSAIDs (ATC Code: M01A*) in the 365 days before or on the Index date. Furthermore, this covariate will be included as a time dependent confounder in the 'Switching' scenario.

		For this purpose it will be checked whether patients received an NSAID prescription in the 10 days prior to the date of the therapy switch.
Switching	Categorical (descriptive analysis only)	The number and proportion of patients switching from one substance to another, as well as the number and proportion of patients switching between different dosages of the same substance will be depicted.

8.4. Data sources

In 2011, SpectrumK, a subsidiary of 75 German SHIs (State Health Insurance), and Elsevier founded the HRI to pool sickness funds' claims data so as to develop patient-level risk predictions and to conduct outcomes research. The data is provided in accordance with paragraphs 287 SGB V and 75 Sozialgesetzbuch (SGB) X of German law. The HRI 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 2008 and 2014. The size of the dataset has been reduced to a sample of approximately 4 million patients per year, representative of the German population in terms of age and gender (as of 31.12.2013). This subset of patients will be used for the purposes of this study.
Data on patients and physicians is anonymized, as are the providers and the sickness funds, before data is made available to the HRI. No regions smaller than federal states or cohorts with less than 100 patients are identified. The HRI functions as the safe haven for data processing, statistics, predictive analytics, and outcomes research, ensuring the highest levels of patient data security.

The HRI 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.).

8.5. Study size

This study is based on claims and the final sample size will ultimately be determined by the number of patients who fulfill all inclusion criteria.

8.5.1. Preliminary feasibility study -- sample size assessment and power analysis

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 number 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	~3,500
Dabigatran	~3,200
Rivaroxaban	~13,000
Phenprocoumon	~17,000
Total	~36,700

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 3 NOACs therapy groups. The method of Freedman for time-to-event analysis that satisfies the proportional-hazards assumption was used (10). It is relatively easy to implement and has proved well in comparative simulation studies (11). 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 (6,7). 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 Table 5. For major bleeding, defined as primary outcome here, the study has enough power in all therapy groups to detect the expected effects using a Cox Proportional Hazard Model. The power for a reduced sample size (higher dropout rate of 25%) would however be weak for Dabigatran. For the combined endpoint, the results indicated sufficient power for Apixaban using the full and reduced count estimates. No equivalent endpoint was observed in RE-LY and ROCKET-AF, and therefore no power estimation could be made. Finally, no power assessment could be made for Rivaroxaban regarding safety and effectiveness endpoints. The study design (non-inferiority trial) of ROCKET-AF was too different to the ARISTOTLE study. Power of the sample size for Apixaban is still strongly insufficient to detect the expected treatment effects. Stroke was therefore not considered as an endpoint in this study, but it remains an objective for the future.

Table 5 Power analyses for the endpoints major bleeding, stroke and net clinical benefit (Abbreviations: C: Control; T: Therapy; SE: Systematic embolism; HR: Hazard Ratio; Api: Apixaban, Dabi: Dabigatran; Riva: Rivaroxaban)

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.	17.000	3.500	0,05	0,035	0,690	0,001	0,98	0,93	-	-
	Dabi.	17.000	3.200	0,066	0,0535	0,8	0,003	0.79	0,66	17.781	3.429
	Riva.	17.000	13.000	-	-	1.04	0,58	-	-	-	-
Net clinical benefit	Api.	17.000	3.500	0,13	0,11	0,850	<0,001	0,85	0,8	-	-
	Dabi.**	17.000	3.200	-	-	-	-	-	-	-	-
	Riva.***	17.000	13.000	-	-	-	-	-	-	-	-
Ischemic Stroke/SE	Api.	17.000	3.500	0,027	0,022	0,788	0,0122	0,50	0,41	33.453	7108
	Dabi**	17.000	3.200	-	-	-	-	-	-	-	-
	Riva.	17.000	13.000	-	-	-	-	-	-	-	-

**In Rocket AF no Net Clinical outcome was considered.
***In RE-LY, Net Clinical Outcome comprised stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major hemorrhage and is therefore not comparable.
#This calculation was based on a conservative dropout rate of 25%

8.6. Data management

A completely anonymized file comprising all observations and variables required for planned analyses will be created from the information contained exclusively within the source material (i.e., the full HRI research database). The analytic file will be person-level, and will include data on demographic and clinical characteristics, information on medical care encounters for NVAF and associated costs.

It is required that all analyses be conducted on the site of the data provider due to data protection requirements. The central statistical software program used by HRI to evaluate data is SAS Enterprise Guide, version 9.2.

Retention of study-related data, documents, and other materials will be governed by Pfizer Policy on Records and Information Management, and per this policy, will remain effective for a period of five years from the date of project initiation. Amendments must be made only with the prior approval of Pfizer. Agreement from all study collaborators must be obtained for all amendments.

8.7. Data analysis

This section will provide a detailed overview about the statistical methods that will be 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 this section and there will not be a separate SAP.

8.7.1. Demographic and clinical characteristics

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

For continuous variables, such as age and number of hospitalizations, the mean, median, minimum (min), maximum (max) and the standard deviation (SD) will be reported. The differences between the treatment groups will be estimated by calculating the standardized difference in means (SMD):

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

Phenprocoumon will serve as the reference group. For a table shell please refer to Table 16 in ANNEX 4.

For categorical variables the absolute number and relative proportion of patients with the respective characteristic will be reported. Proportions will be relative to the total sample size in each treatment group. The differences between the treatment groups will be estimated by calculating the standardized difference in means (SMD). Phenprocoumon will serve as the reference group. For a table shell please refer to Table 17. All covariates described in Table 3 will be depicted in a descriptive manner.

8.7.2. Time to bleeding – Scenario I 'On treatment'

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

Baseline covariates are considered time-independent, i.e. only their values at baseline will 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 is:

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

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, will be compared to Phenprocoumon. Hence, Phenprocoumon will be the reference category in the analysis. A subset of the variables depicted in Table 3, which were selected on an empirical basis, will be included as covariates in the Cox proportional hazards model.

We will report the event rate per 100 patient years and the corresponding 95% confidence intervals per treatment group for the outcome major bleeding events. For a template table shell please see Table 18.

The adjusted hazard ratios based on a multivariate proportional hazard cox model, the corresponding 95% confidence intervals and the regression coefficients will be reported. For a table shell please see Table 19.

Kaplan-Meier curves will be generated to evaluate the time-to-first major bleeding event associated with the initial OAC treatment.

8.7.2.1. Censoring

Patients will be censored in the follow-up period as follows:

Patients will be 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 occurs if a subject either withdraws or reached the end of follow-up without experiencing any event. It we define 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 can define a censoring variable C_i taking values 1 if $E_i \leq c_i$ and 0 otherwise that will be included in the partial likelihood function of the Cox model.

8.7.3. Time to bleeding – scenario II 'Treatment Switching'

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) will be fitted. By fitting the final Cox PH model using inverse-probability-of-treatment weighted (IPTW) estimators, MSM enables to obtain unbiased estimates of treatment effects of major bleeding, when (i) the treatment changes 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 is 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 are derived, i.e., the same subject is assigned different weights at different occasions. Specifically, the IPWT weight for occasion p is 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 are 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 will use stabilized weights which are 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 reflects 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 lead 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 will use multinomial logistic regression.

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

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

As time dependent covariates CHA_2DS_2-VASc score, HASB(L)ED score and the medications interacting with the OAC therapy (compare Table 14) that will be considered.

For a table shell of the results that will be presented as a result of this analysis please refer to Table 20.

8.7.3.1. Censoring weights

Censoring variable for the MSM model is the same as for the classical Cox model. Unbiased estimates of the causal parameters β_1 are 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

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

is the weight when no event occurred before t. If the event occurs at t, then the weight is 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 account for confounded censoring and time-varying selection bias due to lost to follow-up. As for the treatment, probabilities in the numerator and the denominator can be 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).

8.7.3.2. Censoring

Patients will be censored in the follow-up period as follows: Patients will be 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, systematic embolism, major bleeding or death),
- end of continuous enrollment,
- end of study period,
- discontinuation of treatment

whichever occurs earlier.

8.7.4. Days of VKA supply – Global Option

In an attempt to account for the intra- and interpersonal variability of the Phenprocoumon treatment regime an empirical DDD (eDDD) based on the observed Phenprocoumon prescription patterns in the HRI database will be calculated.

For this purpose the PZN code ("Pharmazentralnummer") will be used to compute the Amount of Active Ingredient (AAI) dispensed to each patient of the Phenprocoumon group for each prescription. A personalized prescribed daily dose (pPDD) representing the average daily dose taken during follow-up will be 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

The eDDD corresponds to the median of the distribution of the pPDD estimated over all patients. For the sake of simplicity, only prescriptions of patients who were solely treated with Phenprocoumon during follow-up will be included in the computation of the eeDDD.

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

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

8.7.5. Additional analyses – pairwise comparisons

In addition to the primary objectives of this study for which Phenprocoumon will be used as a reference category, all models will also be estimated with the time to bleeding will also be estimated by means of a Cox PH MSM in which all pairwise comparisons will be estimated. All of the following possible pairwise comparisons will be tested for the primary and secondary endpoints, without any sensitivity analysis:

- Phenprocoumon vs. Apixaban
- Phenprocumon vs. Rivaroxaban
- Phenprocoumon vs. Dabigatran
- Apixaban vs. Rivaroxaban
- Apixaban vs. Dabigatran
- Rivaroxaban vs. Dabigatran

8.7.6. Additional analyses – NOAC comparison

All previously described models will also be estimated using one of the NOAC treatment groups as the reference group instead of Phenprocoumon.

8.8. Quality control

8.8.1. HRI Data quality management

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 HRI 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 HRI 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 HRI 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 HRI 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

8.9. Limitations of the research methods

Although the HRI database covers approximately four million patients, representativeness cannot be guaranteed since the sample is not stratified by geographic dimensions such as county or federal state. Thus, if NVAF is correlated with geographical factors (e.g. higher prevalence north of Germany) and if these factors are systematically distorted in the analytic subsample (e.g. under coverage of northern German areas), biased estimates may be the result. There is, however, little evidence of systematic variation at least in terms of geography in NVAF.

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.

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

The use of MSM to model the adjusted risk of major bleeding events is based on the assumption that there are no unmeasured confounders. However, while the covariates included in the model were selected on an empirical basis, it cannot be ascertained that unmeasured confounders do not distort the findings of this analysis. Residual confounding therefore remains a source of possible bias.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

Informed consent is not required for this study, since this analysis is based on anonymized claims data.

9.2. Patient withdrawal

Not applicable.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

All patient-level data in the HRI research database are de-identified to comply with German data protection regulations. Use of the study database for health services research is therefore fully compliant with German federal law and, accordingly, IRB/ethical approval is not needed.

9.4. Ethical Conduct of the Study

The study will be 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), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological

Standards in Pharmacoepidemiology, and Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study does not include unstructured data. In the data source, it is not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events (AE) are not reportable as individual AE reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

The results of this study will be comprehensively summarized in a final report. It is furthermore planned to publish the findings in a peer-reviewed journal.

12. REFERENCES

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1

List of standalone documents

None

ANNEX 2

ENCePP checklist for study protocols

ANNEX 3

Additional information

Table 6 ATC and PZN Codes for all substances under study

ATC Code	PZN	Active ingredient	Name	Class	DDD (mg)
B01AA04	10269507	Phenprocoumon	PHENPROCOUMON 3MG Tabletten	VKA	3
B01AA04	10269513	Phenprocoumon	PHENPROCOUMON 3MG Tabletten	VKA	3
B01AA04	10269542	Phenprocoumon	PHENPROCOUMON 3MG Tabletten	VKA	3
B01AA04	972890	Phenprocoumon	FALITHROM 1.5 MITE	VKA	3
B01AA04	972915	Phenprocoumon	FALITHROM 1.5 MITE	VKA	3
B01AA04	1300649	Phenprocoumon	MARCUMAR	VKA	3
B01AA04	2021408	Phenprocoumon	MARCUMAR	VKA	3
B01AA04	2059517	Phenprocoumon	PHENPRO ABZ 3MG TABLETTEN	VKA	3
B01AA04	2499417	Phenprocoumon	MARCUMAR	VKA	3
B01AA04	2704892	Phenprocoumon	PHENPROGAMMA 3	VKA	3
B01AA04	2704900	Phenprocoumon	PHENPROGAMMA 3	VKA	3
B01AA04	2704917	Phenprocoumon	PHENPROGAMMA 3	VKA	3
B01AA0	321554	Phenprocoumo	MARCUMAR	VKA	3

4	0	n			
B01AA04	3352194	Phenprocoumon	MARCOUMAR	VKA	3
B01AA04	3352202	Phenprocoumon	MARCOUMAR	VKA	3
B01AA04	3422262	Phenprocoumon	MARCOUMAR	VKA	3
B01AA04	4334620	Phenprocoumon	MARCOUMAR	VKA	3
B01AA04	4334637	Phenprocoumon	MARCOUMAR	VKA	3
B01AA04	4386479	Phenprocoumon	MARCOUMAR	VKA	3
B01AA04	4421721	Phenprocoumon	FALITHROM	VKA	3
B01AA04	4421738	Phenprocoumon	FALITHROM	VKA	3
B01AA04	4421744	Phenprocoumon	FALITHROM	VKA	3
B01AA04	4582128	Phenprocoumon	PHENPRO RATIOPHARM 3MG TAB	VKA	3
B01AA04	4582134	Phenprocoumon	PHENPRO RATIOPHARM 3MG TAB	VKA	3
B01AA04	4582140	Phenprocoumon	PHENPRO RATIOPHARM 3MG TAB	VKA	3
B01AA04	4958705	Phenprocoumon	MARCOUMAR	VKA	3
B01AA04	4958711	Phenprocoumon	MARCOUMAR	VKA	3
B01AA04	5541315	Phenprocoumon	MARCUMAR	VKA	3

B01AA04	5541321	Phenprocoumon	MARCUMAR	VKA	3
B01AA04	5541338	Phenprocoumon	MARCUMAR	VKA	3
B01AA04	6575233	Phenprocoumon	PHENPRO RATIOPHARM 3MG TAB	VKA	3
B01AA04	6588626	Phenprocoumon	MARCUPHEN - CT 3MG TAB	VKA	3
B01AA04	6811219	Phenprocoumon	PHENPRO ABZ 3MG TABLETTEN	VKA	3
B01AA04	7636008	Phenprocoumon	MARCUPHEN - CT 3MG TAB	VKA	3
B01AA04	7636014	Phenprocoumon	MARCUPHEN - CT 3MG TAB	VKA	3
B01AA04	7636020	Phenprocoumon	MARCUPHEN - CT 3MG TAB	VKA	3
B01AA04	7768135	Phenprocoumon	MARCUMAR	VKA	3
B01AA04	7768170	Phenprocoumon	MARCUMAR	VKA	3
B01AA04	8874885	Phenprocoumon	MARCOUMAR	VKA	3
B01AA04	8874891	Phenprocoumon	MARCOUMAR	VKA	3
B01AA04	9404207	Phenprocoumon	PHENPROGAMMA 3	VKA	3
B01AA04	9726170	Phenprocoumon	MARCOUMAR	VKA	3
B01AF02	3643804	Apixaban	ELIQUIS 2.5MG FILMTABL	NOAC	5
B01AF0	470050	Apixaban	ELIQUIS 2.5MG FILMTABL	NOA	5

2	4			C	
B01AF02	4700510	Apixaban	ELIQUIS 2.5MG FILMTABL	NOAC	5
B01AF02	4700527	Apixaban	ELIQUIS 2.5MG FILMTABL	NOAC	5
B01AF02	4712163	Apixaban	ELIQUIS 2.5MG FILMTABL	NOAC	5
B01AF02	4712186	Apixaban	ELIQUIS 2.5MG FILMTABL	NOAC	5
B01AF02	10218496	Apixaban	ELIQUIS 5MG FILMTABL	NOAC	10
B01AF02	10232906	Apixaban	ELIQUIS 5MG FILMTABL	NOAC	10
B01AF02	8400012	Apixaban	ELIQUIS 2,5 mg Filmtabletten	NOAC	5
B01AF02	8400029	Apixaban	ELIQUIS 2,5 mg Filmtabletten	NOAC	5
B01AF02	8400035	Apixaban	ELIQUIS 2,5 mg Filmtabletten	NOAC	5
B01AF02	8400041	Apixaban	ELIQUIS 2,5 mg Filmtabletten	NOAC	5
B01AF02	1647784	Apixaban	ELIQUIS 5 mg Filmtabletten	NOAC	10
B01AF02	1647755	Apixaban	ELIQUIS 5 mg Filmtabletten	NOAC	10
B01AF02	1647778	Apixaban	ELIQUIS 5 mg Filmtabletten	NOAC	10
B01AF02	1647821	Apixaban	ELIQUIS 5 mg Filmtabletten	NOAC	10
B01AF02	1647809	Apixaban	ELIQUIS 5 mg Filmtabletten	NOAC	10

B01AF02	3643804	Apixaban	ELIQUIS 2.5MG FILMTABL	NOAC	5
B01AF01	4369423	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOAC	15
B01AF01	4369481	Rivaroxaban	XARELTO 20 mg Filmtabletten	NOAC	20
B01AF01	5748766	Rivaroxaban	XARELTO 10 mg Filmtabletten	NOAC	10
B01AF01	5459513	Rivaroxaban	XARELTO 10 mg Filmtabletten	NOAC	10
B01AF01	7572662	Rivaroxaban	XARELTO 10 mg Filmtabletten	NOAC	10
B01AF01	6454481	Rivaroxaban	XARELTO 10 mg Filmtabletten	NOAC	10
B01AF01	7799012	Rivaroxaban	XARELTO 10 mg Filmtabletten	NOAC	10
B01AF01	5995074	Rivaroxaban	XARELTO 10 mg Filmtabletten	NOAC	10
B01AF01	5995080	Rivaroxaban	XARELTO 10 mg Filmtabletten	NOAC	10
B01AF01	9941276	Rivaroxaban	XARELTO 10 mg Filmtabletten	NOAC	10
B01AF01	9154791	Rivaroxaban	XARELTO 10 mg Filmtabletten	NOAC	10
B01AF01	6410420	Rivaroxaban	XARELTO 10 mg Filmtabletten	NOAC	0
B01AF01	8461344	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOAC	15
B01AF01	9724515	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOAC	15
B01AF0	100121	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOA	15

1	45			C	
B01AF01	8461350	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOAC	15
B01AF01	10012151	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOAC	15
B01AF01	9724521	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOAC	15
B01AF01	8461404	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOAC	15
B01AF01	7089598	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOAC	15
B01AF01	8461367	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOAC	15
B01AF01	10005926	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOAC	15
B01AF01	9724538	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOAC	15
B01AF01	9941282	Rivaroxaban	XARELTO 15 mg Filmtabletten	NOAC	15
B01AF01	8461410	Rivaroxaban	XARELTO 20 mg Filmtabletten	NOAC	20
B01AF01	9724544	Rivaroxaban	XARELTO 20 mg Filmtabletten	NOAC	20
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B01AF01	8461427	Rivaroxaban	XARELTO 20 mg Filmtabletten	NOAC	20
B01AF01	7089606	Rivaroxaban	XARELTO 20 mg Filmtabletten	NOAC	20
B01AF01	9724550	Rivaroxaban	XARELTO 20 mg Filmtabletten	NOAC	20

B01AF01	10005932	Rivaroxaban	XARELTO 20 mg Filmtabletten	NOAC	20
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B01AF01	9941299	Rivaroxaban	XARELTO 20 mg Filmtabletten	NOAC	20
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B01AF01	7536850	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AF01	7536927	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AF01	7572633	Rivaroxaban	XARELTO 10MG	NOAC	10
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B01AF01	9777888	Rivaroxaban	XARELTO 10MG FILMTABLETTEN	NOAC	10
B01AF01	10012139	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AF01	10012168	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AF01	10012174	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AF01	10012180	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AF01	10012197	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AF0	100574	Rivaroxaban	XARELTO 20MG	NOA	20

1	90			C	
B01AF01	10058590	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AF01	10058609	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AF01	2088536	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AF01	4369475	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AF01	4369498	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AF01	7536850	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AF01	7536927	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AF01	7572633	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AF01	7610606	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AF01	7799029	Rivaroxaban	XARELTO 10MG	NOAC	10
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B01AF01	9777888	Rivaroxaban	XARELTO 10MG FILMTABLETTEN	NOAC	10
B01AF01	10012139	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AF01	10012168	Rivaroxaban	XARELTO 15MG	NOAC	15

B01AF01	10012174	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AF01	10012180	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AF01	10012197	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AF01	10057490	Rivaroxaban	XARELTO 20MG	NOAC	20
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B01AF01	10102144	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AF01	10106863	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AF01	10106886	Rivaroxaban	XARELTO 20MG	NOAC	20
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B01AF01	10200906	Rivaroxaban	XARELTO 15MG	NOAC	15
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B01AF01	10200929	Rivaroxaban	XARELTO 20MG	NOAC	20
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B01AX06	7610606	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AX06	8461344	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AX06	8461350	Rivaroxaban	XARELTO 15MG	NOAC	15

B01AX06	8461367	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AX06	8461404	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AX06	8461410	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AX06	8461427	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AX06	8461433	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AX06	9154791	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AX06	9721534	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AX06	9724515	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AX06	9724521	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AX06	9724538	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AX06	9724544	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AX06	9724550	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AX06	9777888	Rivaroxaban	XARELTO 10MG FILMTABLETTEN	NOAC	10
B01AX06	5459513	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AX06	5748766	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AX0	599507	Rivaroxaban	XARELTO 10MG	NOA	10

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B01AX06	5995080	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AX06	6410420	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AX06	6454481	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AX06	7536850	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AX06	7610606	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AX06	8461344	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AX06	8461350	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AX06	8461367	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AX06	8461404	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AX06	8461410	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AX06	8461427	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AX06	8461433	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AX06	9154791	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AX06	9721534	Rivaroxaban	XARELTO 10MG	NOAC	10
B01AX06	9724515	Rivaroxaban	XARELTO 15MG	NOAC	15

B01AX06	9724521	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AX06	9724538	Rivaroxaban	XARELTO 15MG	NOAC	15
B01AX06	9724544	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AX06	9724550	Rivaroxaban	XARELTO 20MG	NOAC	20
B01AX06	9777888	Rivaroxaban	XARELTO 10MG FILMTABLETTEN	NOAC	10
B01AE07	9328156	Dabigatran	PRADAXA 110 MG KAPSELN	NOAC	220
B01AE07	9947988	Dabigatran	PRADAXA 150MG HARTKAPSELN	NOAC	300
B01AE07	10183585	Dabigatran	PRADAXA 110 MG KAPSELN	NOAC	220
B01AE07	10193365	Dabigatran	PRADAXA 150MG HARTKAPSELN	NOAC	300
B01AE07	10193371	Dabigatran	PRADAXA 150MG HARTKAPSELN	NOAC	300
B01AE07	10206458	Dabigatran	PRADAXA 150MG KAPSELN	NOAC	300
B01AE07	10218349	Dabigatran	PRADAXA 110 MG KAPSELN	NOAC	220
B01AE07	10218355	Dabigatran	PRADAXA 110 MG KAPSELN	NOAC	220
B01AE07	10218361	Dabigatran	PRADAXA 110 MG KAPSELN	NOAC	220
B01AE07	10249781	Dabigatran	PRADAXA 150MG KAPSELN	NOAC	300
B01AE0	102510	Dabigatran	PRADAXA 110 MG KAPSELN	NOA	220

7	16			C	
B01AE07	10251022	Dabigatran	PRADAXA 110 MG KAPSELN	NOAC	220
B01AE07	10261210	Dabigatran	PRADAXA 110 MG KAPSELN	NOAC	220
B01AE07	10261233	Dabigatran	PRADAXA 150MG KAPSELN	NOAC	300
B01AE07	10288114	Dabigatran	PRADAXA 150MG KAPSELN	NOAC	300
B01AE07	10288120	Dabigatran	PRADAXA 110 MG KAPSELN	NOAC	220
B01AE07	10339484	Dabigatran	PRADAXA 110 MG KAPSELN	NOAC	220
B01AE07	10339509	Dabigatran	PRADAXA 110 MG KAPSELN	NOAC	220
B01AE07	10339521	Dabigatran	PRADAXA 110 MG KAPSELN	NOAC	220
B01AE07	10357542	Dabigatran	PRADAXA 150MG KAPSELN	NOAC	300
B01AE07	10390829	Dabigatran	PRADAXA 110 MG KAPSELN	NOAC	220
B01AE07	10390835	Dabigatran	PRADAXA 150MG KAPSELN	NOAC	300
B01AE07	3420607	Dabigatran	PRADAXA 75 mg Hartkapseln	NOAC	150
B01AE07	3420613	Dabigatran	PRADAXA 75 mg Hartkapseln	NOAC	150
B01AE07	6561863	Dabigatran	PRADAXA 75 mg Hartkapseln	NOAC	150
B01AE07	3420754	Dabigatran	PRADAXA 110 mg Hartkapseln	NOAC	220

B01AE07	3420760	Dabigatran	PRADAXA 110 mg Hartkapseln	NOAC	220
B01AE07	6561892	Dabigatran	PRADAXA 110 mg Hartkapseln	NOAC	220
B01AE07	9707095	Dabigatran	PRADAXA 110 mg Hartkapseln	NOAC	220
B01AE07	6561900	Dabigatran	PRADAXA 110 mg Hartkapseln	NOAC	220
B01AE07	6561917	Dabigatran	PRADAXA 110 mg Hartkapseln	NOAC	220
B01AE07	8797446	Dabigatran	PRADAXA 150 mg Hartkapseln	NOAC	300
B01AE07	9947971	Dabigatran	PRADAXA 150 mg Hartkapseln	NOAC	300
B01AE07	6561946	Dabigatran	PRADAXA 150 mg Hartkapseln	NOAC	300
B01AE07	6561952	Dabigatran	PRADAXA 150 mg Hartkapseln	NOAC	300
B01AE07	9707103	Dabigatran	PRADAXA 150 mg Hartkapseln	NOAC	300
B01AE07	6561969	Dabigatran	PRADAXA 150 mg Hartkapseln	NOAC	300
B01AE07	6561981	Dabigatran	PRADAXA 150 mg Hartkapseln	NOAC	300
B01AE07	2531523	Dabigatran	PRADAXA 110MG KAPSELN	NOAC	220
B01AE07	2531546	Dabigatran	PRADAXA 110MG KAPSELN	NOAC	220
B01AE07	6115862	Dabigatran	PRADAXA 75MG KAPSELN	NOAC	150
B01AE0	611587	Dabigatran	PRADAXA 110MG KAPSELN	NOA	220

7	9			C	
B01AE07	6141724	Dabigatran	PRADAXA 75MG KAPSELN	NOAC	150
B01AE07	6312284	Dabigatran	PRADAXA 75MG KAPSELN	NOAC	150
B01AE07	7544163	Dabigatran	PRADAXA 110MG KAPSELN	NOAC	220
B01AE07	7544186	Dabigatran	PRADAXA 75MG KAPSELN	NOAC	150
B01AE07	8844364	Dabigatran	PRADAXA 75MG KAPSELN	NOAC	150
B01AE07	8866880	Dabigatran	PRADAXA 75MG KAPSELN	NOAC	150
B01AE07	9124117	Dabigatran	PRADAXA 75MG KAPSELN	NOAC	150
B01AE07	9228199	Dabigatran	PRADAXA 110MG	NOAC	220
B01AE07	9321102	Dabigatran	PRADAXA 110MG KAPSELN	NOAC	220
B01AE07	10206458	Dabigatran	PRADAXA 150MG KAPSELN	NOAC	300

Table 7 Codes Dialyses (exclusion criteria)

Code	Codety	Description
8853	Ops_code	Hämofiltration
8854	Ops_code	Hämodialyse
8855	Ops_code	Hämodiafiltration
8857	Ops_code	Peritonealdialyse
13602	EBM	Zusatzpauschale kontinuierliche Betreuung eines dialysepflichtigen Patienteb
13610	EBM	Zusatzpauschale ärztliche Betreuung bei Hämodialyse, Peritonealdialyse und Sonderverfahren
13611	EBM	Zusatzpauschale ärztliche Betreuung bei Peritonealdialyse
40826	EBM	Kostenpauschale für Dialyse bei Versicherten ab vollendetem 18. Lebensjahr
40823	EBM	Kostenpauschale für Dialyse bei Versicherten ab vollendetem 18. Lebensjahr
40824	EBM	Kostenpauschale für Dialyse bei Versicherten ab vollendetem 18. Lebensjahr
40825	EBM	Kostenpauschale für Peritonealdialyse bei Versicherten ab vollendetem 18. Lebensjahr
40826	EBM	Kostenpauschale für Peritonealdialyse bei Versicherten ab vollendetem 18. Lebensjahr am Wohnort
40827	EBM	Zuschlag zur Kostenpauschale 40817, 40819, 40827 oder 40828 für die intermittierende Peritonealdialyse
40828	EBM	Kostenpauschale für Dialyse ab dem vollendeten 18. Lebensjahr bei Ferien- oder berufsbedingtem Aufenthalt

Table 8 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 9 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 10 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	**any**	**yes**

	Aderhaut		
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	**intracerebral (also part of any**	**yes**

	bezeichneter intrakranieller Arterie ausgehend	**bleeding)**	
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 Blutung in die Großhirnhemisphäre, subkortikal	**intracerebral (also part of any bleeding)**	**yes**
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 extradurale Blutung	**intracerebral (also part of any bleeding)**	**yes**
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	**gastrointestinal (also part of any**	**Yes, but only in combination with an emergency hospital**

	Blutung	**bleeding)**	**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 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.
K57.11	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	**gastrointestinal**	**Yes, but only in combination**

	Dünndarmes als auch des Dickdarmes mit Perforation und Abszess Divertikulose mit Blutung	**(also part of any bleeding)**	**with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.**
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 näher bezeichnet, ohne Perforation oder 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**

	Divertikulose mit Blutung		**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 Innenmeniskus	**any**	**yes**
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 glomeruläre Läsionen	**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.**

N02.2	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	**any**	**Yes, but only in combination with an emergency hospital admission and a documented**

	Veränderungen		**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	**any**	**Yes, but only in combination with an emergency hospital**

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

	traumatisches Hämatom, Kontusion		

Table 11 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 12 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 13 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,M353,M360	1	1
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,K	1	0

	764,K768,K769,Z944		
Diabetes	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,C14,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,C	2	2

	60,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 14 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 15 Pharmaceutical substances interacting with the OAC therapy by treatment group

Treatment group	Effect	ATC_Code	Label
Phenprocoumon	Boost	B01AC	Thrombozytenaggregationshemmer
Phenprocoumon	Boost	M01A	Nichtsteroidale Antiphlogistika und Antirheumatika
Phenprocoumon	Boost	B01AB	Heparingruppe
Phenprocoumon	Boost	M04AA01	Allopurinol
Phenprocoumon	Boost	C01BD01	Amiodaron
Phenprocoumon	Boost	C01BA01	Chinidin
Phenprocoumon	Boost	C01BA51	Chinidin, Kombinationen exkl. Psycholeptika
Phenprocoumon	Boost	C01BA71	Chinidin, Kombinationen mit Psycholeptika
Phenprocoumon	Boost	C08DA81	Verapamil in Kombination mit Chinidin
Phenprocoumon	Boost	C01BC03	Propafenon
Phenprocoumon	Boost	J01G	Aminoglykosid Antibiotika
Phenprocoumon	Boost	S01AA01	Chloramphenicol
Phenprocoumon	Boost	J01A	Tetracycline
Phenprocoumon	Boost	J01E	Sulfonamid und Trimethoprim
Phenprocoumon	Boost	J01CF01	Cloxacillin
Phenprocoumon	Boost	J01FA	Makrolide
Phenprocoumon	Boost	J01DB	Cephalosporine der 1. Generation
Phenprocoumon	Boost	J01DC	Cephalosporine der 2. Generation
Phenprocoumon	Boost	J01DD	Cephalosporine der 3. Generation
Phenprocoumon	Boost	J01DE	Cephalosporine der 4. Generation
Phenprocoumon	Boost	C01AB	Fibrate
Phenprocoumon	Boost	G01AF	Imidazolderivate
Phenprocoumon	Boost	G01AG	Triaolderivate
Phenprocoumon	Boost	L04AA13	Leflunomid
Phenprocoumon	Boost	M01AA01	Phenylbutazon
Phenprocoumon	Boost	M01AA51	Phenylbutazon, Kombinationen
Phenprocoumon	Boost	M01AC01	Piroxicam
Phenprocoumon	Boost	M01AH	Coxibe
Phenprocoumon	Boost	N02AX02	Tramadol
Phenprocoumon	Boost	A14A	Andere anabole Steroide
Phenprocoumon	Boost	H03AA	Schilddrüsenhormone
Phenprocoumon	Boost	L02BA01	Tamoxifen
Phenprocoumon	Boost	L01BC06	Capecitabin
Phenprocoumon	Boost	N06AA	Nichtselektive Monoamin-Wiederaufnahmehemmer
Phenprocoumon	Attenuation	L04AX01	Azathioprin
Phenprocoumon	Attenuation	N01AF	Barbiturate, rein

Phenprocoumon	Attenuation	N01AG	Barbiturate in Kombination mit anderen Mitteln
Phenprocoumon	Attenuation	N03AF01	Carbamazepin
Phenprocoumon	Attenuation	C10AC01	Colestyramin
Phenprocoumon	Attenuation	C01AA	Digitalisglykoside
Phenprocoumon	Attenuation	C03	Diuretika
Phenprocoumon	Attenuation	H02	Corticosteroide zur systemischen Anwendung
Phenprocoumon	Attenuation	L01BB02	Mercaptopurin
Phenprocoumon	Attenuation	J04AB02	Verapamil in Kombination mit Chinidin
Phenprocoumon	Attenuation	A10BA02	Metformin
Phenprocoumon	Attenuation	H03BA	Thiouracile
Dabigatran	Boost	B01	Antithrombotische Mittel
Dabigatran	Boost	C01BD01	Amiodaron
Dabigatran	Boost	C08DA01	Verapamil
Dabigatran	Boost	C08DA51	Verapamil, Kombinationen
Dabigatran	Boost	C08DA81	Verapamil in Kombination mit Chinidin
Dabigatran	Boost	C01BA01	Chinidin
Dabigatran	Boost	C01BA51	Chinidin, Kombinationen exkl. Psycholeptika
Dabigatran	Boost	C01BA71	Chinidin, Kombinationen mit Psycholeptika
Dabigatran	Boost	G01AF11	Ketoconazol
Dabigatran	Boost	J02AB02	Ketoconazol
Dabigatran	Boost	J01FA09	Clarithromycin
Dabigatran	Boost	N06AB	selektive Serotonin-Wiederaufnahmehemmer
Dabigatran	Attenuation	J04AB02	Rifampicin
Dabigatran	Attenuation	J04AM02	Rifampicin und Isoniazid
Dabigatran	Attenuation	J04AM05	Rifampicin, Pyrazinamid und Isoniazid
Dabigatran	Attenuation	J04AM06	Rifampicin, Pyrazinamid, Ethambutol und Isoniazid
Dabigatran	Attenuation	N03AF01	Carbamazepin
Dabigatran	Attenuation	N03AB02	Phenytoin
Rivaroxaban	Boost	G01AF02	Clotrimazol
Rivaroxaban	Boost	G01AF05	Econazol
Rivaroxaban	Boost	J02AC01	Fluconazol
Rivaroxaban	Boost	J02AC02	Itraconazol
Rivaroxaban	Boost	G01AF11	Ketoconazol
Rivaroxaban	Boost	J02AB02	Ketoconazol
Rivaroxaban	Boost	G01AF17	Oxiconazol
Rivaroxaban	Boost	J02AC04	Posaconazol
Rivaroxaban	Boost	J02AC03	Voriconazol
Rivaroxaban	Boost	J05AE	Proteasehemmer

Rivaroxaban	Boost	B01	Antithrombotische Mittel
Rivaroxaban	Boost	M01A	Nichtsteroidale Antiphlogistika und Antirheumatika
Apixaban	Boost	R05GB07	Erythromycin, Kombinationen
Apixaban	Boost	J01FA01	Erythromycin
Apixaban	Boost	S01AA17	Erythromycin
Apixaban	Boost	J01FA09	Clarithromycin
Apixaban	Boost	J01FA10	Azithromycin
Apixaban	Boost	S01AA26	Azithromycin
Apixaban	Boost	J01FA15	Telithromycin
Apixaban	Boost	G01AA05	Chloramphenicol
Apixaban	Boost	S01AA01	Chloramphenicol
Apixaban	Boost	S02AA01	Chloramphenicol
Apixaban	Boost	S03AA08	Chloramphenicol
Apixaban	Boost	J01BA01	Chloramphenicol
Apixaban	Boost	J02AC01	Fluconazol
Apixaban	Boost	G01AF11	Ketoconazol
Apixaban	Boost	J02AB02	Ketoconazol
Apixaban	Boost	J02AC02	Itraconazol
Apixaban	Boost	C08DA01	Verapamil
Apixaban	Boost	C08DA51	Verapamil, Kombinationen
Apixaban	Boost	C08DA81	Verapamil in Kombination mit Chinidin
Apixaban	Boost	A04AD12	Aprepitant, Fosaprepitant
Apixaban	Boost	N06AX06	Nefazodon
Apixaban	Boost	C01BD01	Amiodaron
Apixaban	Boost	J05AE	Proteasehemmer
Apixaban	Boost	M01A	Nichtsteroidale Antiphlogistika und Antirheumatika
Apixaban	Boost	B01AC	Thrombozytenaggregationshemmer
Apixaban	Attenuation	J04AB02	Rifampicin
Apixaban	Attenuation	J04AM02	Rifampicin und Isoniazid
Apixaban	Attenuation	J04AM05	Rifampicin, Pyrazinamid und Isoniazid
Apixaban	Attenuation	J04AM06	Rifampicin, Pyrazinamid, Ethambutol und Isoniazid
Apixaban	Attenuation	N03AA02	Phenobarbital
Apixaban	Attenuation	N03AF01	Carbamazepin
Apixaban	Attenuation	N03AB02	Phenytoin

Table 16 ATC Codes Proton-pump-inhibitors

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

ANNEX 4

Table Shells

Table 17 Table shell – descriptive statistics continuous variables (with age as an example)

Age	**Treatment group**			
	Apixaban	**Dabigatran**	**Rivaroxaban**	**Phenprocoumon**
Mean				
Median				
SD				
SMD*				

*reference category = Phenprocoumon

Table 18 Table shell – descriptive statistics categorical variables

Variable	**Treatment group**										
	Phenprocoumon		**Apixaban**			**Dabigatran**			**Rivaroxaban**		
	N	**%**	**N**	**%**	**SMD***	**N**	**%**	**SMD***	**N**	**%**	**SMD***
Gender											
- Female											
- Male											
Region											
- East-Urban											

- East-Rural											
- West-Urban											
- West-Rural											
History of MI											
…											

*reference category = Phenprocoumon

Table 19 Table shell – event rates per 100 patient years by treatment group

Bleeding event	**Treatment group**			
	Apixaban	**Dabigatran**	**Rivaroxaban**	**Phenprocoumon**
Major bleeding event				

Table 20 Table shell – Cox proportional hazards model

Predictor	**Coefficient**	**Hazard Ratio**	**95% confidence interval**	
			Lower limit	**Upper limit**
Treatment group				
- Phenprocoumon				
- Phenprocoumon vs. Apixaban				
- Phenprocoumon vs. Dabigatran				
- Phenprocoumon vs. Rivaroxaban				
Age				
Gender				

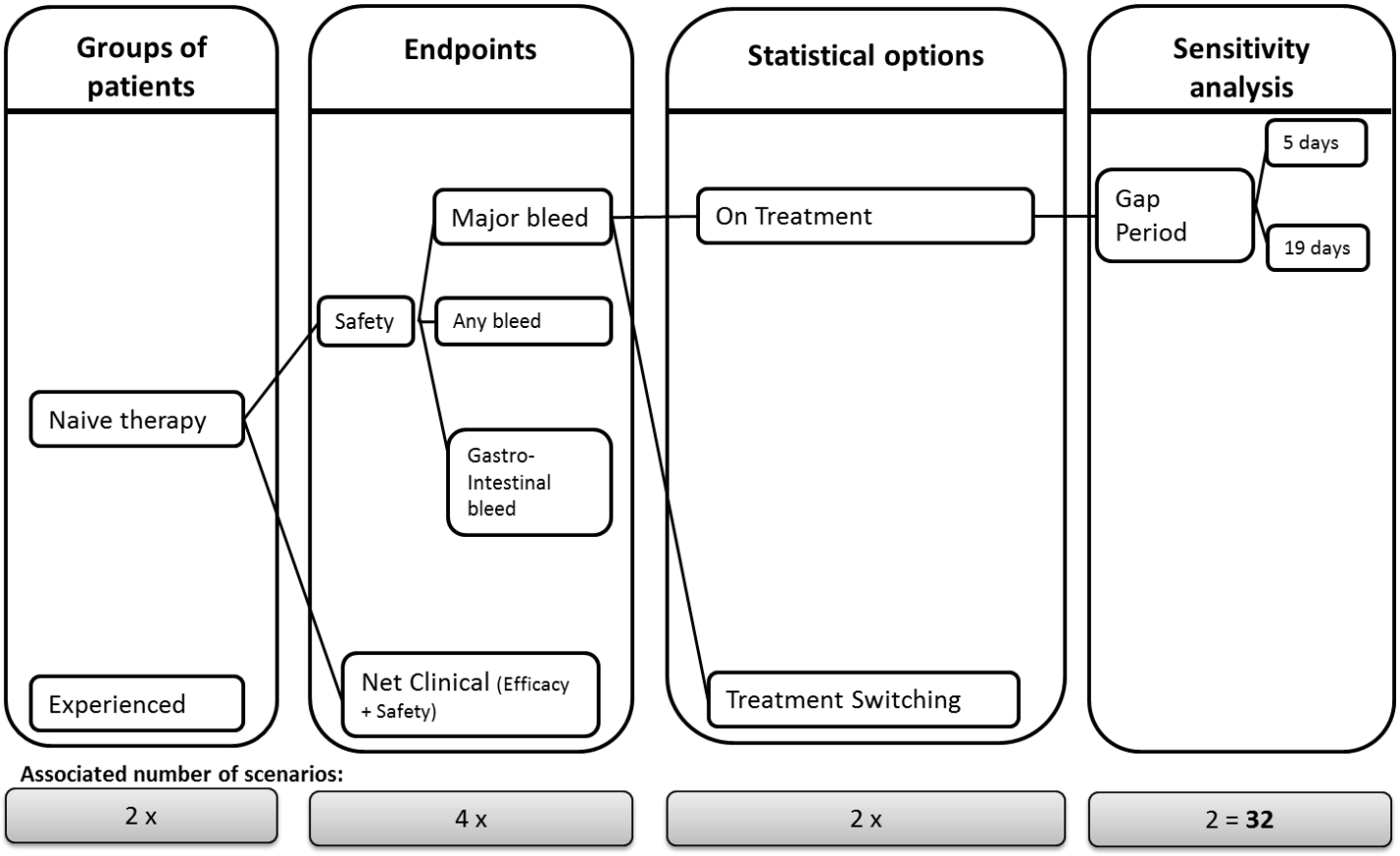
- male vs. female				
$CHADS_2$ VASC score				
…				

Table 21 Table shell – Results IPTW cox proportional hazards model (MSM)

Model	**No. of events**	**Person-years of follow up**	**Hazard ratio (HR)**	**95% CI**
Unadjusted				
Phenprocoumon				
Apixaban				
Dabigatran				
Rivaroxaban				
Adjusted and Weighted				
Phenprocoumon				
Apixaban				
Dabigatran				
Rivaroxaban				

ANNEX 5

Overview modelling scenarios



15. AMENDMENT

In the following section the changes made to the original study protocol will be defined.

15.1. Research questions and objectives

The following additional research questions have been defined throughout the course of the originally planned analyses.

A secondary objective is to investigate whether the rate of intracerebral bleeding events in NVAF patients under anticoagulant therapy differs between:

1. patients treated with Phenprocoumon and patients treated with Apixaban.
2. patients treated with Phenprocoumon and patients treated with Rivaroxaban.
3. patients treated with Phenprocoumon and patients treated with Dabigatran.

15.2. Research methods

15.2.1. Setting

Throughout the course of the analyses it became apparent that the number of experienced Apixaban users (N=94) was too small to allow for a multivariate comparison between all treatment groups. For that reason all planned analyses using the group of experienced users were not performed.

15.2.2. Variables

15.2.2.1. Outcomes / Endpoint Variable

The following outcome has newly defined throughout the course of the analysis.

Variable	Objective	Operational definition
Intracerebral bleeding events	Secondary	An intracerebral bleeding event will be defined as a bleeding event occurring anytime during the Exposure time. Intracerebral bleeding events will be defined based

		on primary or secondary ICD10 GM hospital discharge diagnoses (S06.4*, S06.5*, S06.6*, S06.7* S06.8*, I60*, I61* und I62*). For a complete list of all intracerebral bleeding events and their operationalization using ICD-10 GM codes please see column 3 in Table 10 in ANNEX 3.

15.3. Data analysis

15.3.1. Additional analyses – dosage analyses

It became apparent that a significant part of the patients initiating a NVAF therapy start their therapy on the lower dosage (i.e. Apixaban 2,5mg, Rivaroxaban 15mg and Dabigatran 150mg). Since these patients might be of particular risk of bleeding events and in order to assess the robustness of the results all Cox regression analyses will be performed separately for patients treated with the low and for patients treated with the normal dose of NVAF's.

The figure on the following page provides an overview about the updated number of modelling scenarios.

Overview modelling scenarios Update