NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Post Authorisation Safety Studies (PASS) information

Title	CARBOS E^+ - comparative risk of major bleeding with new oral anticoagulants (NOACs) and Phenprocoumon in patients with atrial fibrillation – effectiveness analyses added
Protocol number	B0661096
Protocol version identifier	Final 1.0
Date of last version of protocol	16 March 2017
EU Post Authorisation Study (PAS) register number	EUPAS18323
Active substance	Apixaban (B01AF02) Phenprocoumon (B01AA04) Rivaroxaban (B01AF01) Dabigatran (B01AX06, B01AE07) Edoxaban (B01AF03)
Product reference	EU/1/11/691/006 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

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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 strokes or systemic embolism (SE) and major bleeding events in patients with AF and prescribed oral anticoagulation therapies in a real-world setting. It will be investigated whether the occurrence of strokes/SE as well as major bleeding events differs between AF patients treated with the VKA (phenprocoumon) vs. AF patients treated with apixaban, dabigatran or rivaroxaban, respectively.
Country of study	Germany
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1. LIST OF ABBREVIATIONS

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

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

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 atrial fibrillation – effectiveness analyses added: a retrospective claims database study in Germany

Rationale and Background:

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

Research question and objectives:

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

Study design:

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

Population (Setting and study population):

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

Variables (exposures, outcomes, key-covariables):

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

Data sources:

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

Study Size:

A preliminary feasibility study identified a total of approximately 75,000 therapy naïve patients.

Data Analysis:

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

After a descriptive characterization of the four treatment groups, adjusted hazard ratios of the risk of ischemic or hemorrhagic stroke or systemic embolism and major bleeding will be estimated by means of three different methods. In a first approach, a cox-proportional hazards model will be used to determine differences in the risk of major ischemic and major bleeding between treatment groups. Secondly, a marginal structural model will be developed to compare the risk of all safety and effectiveness outcomes between the individual treatment groups.

In a Sensitivity Analysis a Propensity Score Matching will be performed followed by the calculation of hazard ratios by means of a univariate cox-proportional hazards model to estimate the risk of ischemic or hemorrhagic stroke or systemic embolism and major bleeding.

Milestones:

- Compilation of study protocol: 16.03.2017
- End of preparation phase (study protocol): 30.03.2017
- Registration in the EU PAS register: 28.04.2017
- Start of data collection: 13.04.2017
- End of data collection: 28.04.2017
- End of data analysis: 31.07.2017
- Final study report: 31.10.2017

4. AMENDMENTS AND UPDATES

5. MILESTONES

Milestone	**Planned date**
Compilation of the study protocol	16 March 2017
Start of data collection - Preparation of the analysis dataset - Identification of the study population	13 April 2017
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).	28 April 2017
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 variables	02 May 2017
Analyses according to study protocol (Part II) - Analysis Cox-proportional hazards model - Analysis marginal structural models	15 May – 15 July 2017

- Propensity Score Matching	
Registration in the European Union (EU) PAS register	
Quality management, editing of the results, final study report	31 October 2017

6. RATIONALE AND BACKGROUND

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

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

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

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 ischemic or hemorrhagic stroke or systemic embolism and major bleeding events among AF patients prescribed phenprocoumon or one of the NOACs in a real-world setting.

The primary objectives are to investigate whether

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

Secondary objectives are to investigate whether

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

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

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

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

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

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

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

8. RESEARCH METHODS

8.1. Study design

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

8.1.1. Sensitivity Analysis I – Study design

In a Sensitivity Analysis the inclusion period will be limited to 01.01.2013 until 31.03.2015. Unadjusted event rates will be provided for all treatment groups based on patients initiating their treatment in that respective time period. This is done to allow a follow up period of 365 days after treatment initiation or until death in all treatment groups. After investigating whether there are differences in the unadjusted event rates for the primary outcomes and major bleeding the further course of analysis will be determined by the project team.

8.2. Setting

The InGef database, from which patients will be selected for inclusion in the study population, is a complete, longitudinal claims dataset of approximately 6.7 million patients,

comprising approximately 10% of the statutory health insured population within 2010 and 2015.

8.2.1. Inclusion criteria

To be representative of the real world daily care situation, a group of novel OAC AF patients will be identified for this study. Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. AF Patients who have newly initiated a OAC therapy (apixaban, dabigatran, rivaroxaban, edoxaban[2] or phenprocoumon) within the study period (01.01.2013 - 31.12.2015[3]), i.e. no prior prescription for any of the above listed substances in the 12 months before the first prescription in the study period (for relevant Anatomical Therapeutic Chemical Classification System (ATC) Codes please refer to Table 6 in ANNEX 3)

AND

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

AND

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:

[2] Patients initiating treatment with edoxaban will only be identified for completeness reasons. Due to the expected low sample size, we will provide the number of patients in this treatment group. However, descriptives and event rates will not be provided for this treatment group.

[3] In a sensitivity analyses only patients starting treatment until 31.03.2015 will be included in the analyses only to allow for a follow up times of at least one year in all patients. See also section 8.1.1.

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

2. At least one dialysis in the four quarters before or on the index date. Dialysis patients are identified using the Operationen- und Prozedurenschlüssel (OPS) and Gebührenordnungsposition (GOP) codes depicted in Table 7 in ANNEX 3;

3. Patients receiving a NOAC/VKA and heparin on the index date (for relevant ATC Codes please see

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

		Wohnort **VALID UNTIL Q4 2012**
40802	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes mellitus, **VALID UNTIL Q4 2012**
40803	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes mellitus, bei einer Feriendialyse während des Ferienaufenthalts am Ferienort oder bei Dialysen wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID UNTIL Q4 2012**
40804	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung mit manifestem behandlungspflichtigen Diabetes mellitus **VALID UNTIL Q4 2012**
40805	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung mit manifestem behandlungspflichtigen Diabetes mellitus, bei einer Feriendialyse während des Ferienaufenthalts am Ferienort oder bei Dialysen wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID UNTIL Q4 2012**
40806	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse,

		Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr bis zum vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes mellitus bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können **VALID UNTIL Q4 2012**
40807	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes mellitus bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können. **VALID UNTIL Q4 2012**
40808	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung mit manifestem behandlungspflichtigen Diabetes mellitus bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können. **VALID UNTIL Q4 2012**
40810	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40800, 40802 oder 40804 für die Infektionsdialyse (bei Patienten mit Hepatitis B und/oder Hepatitis C und/oder mit HIV-Infektion und/oder mit MRSA-Infektion) **VALID UNTIL Q4 2012**
40811	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40801, 40803 oder 40805 bis 40808 für die Infektionsdialyse (bei Patienten mit Hepatitis B und/oder Hepatitis C und/oder mit HIV-Infektion und/oder mit MRSA-Infektion) **VALID UNTIL Q4 2012**
40812	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40800, 40802 oder 40804 für die intermittierende Peritonealdialyse (IPD)

		VALID UNTIL Q4 2012
40813	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40801, 40803 oder 40805 bis 40808 für die intermittierende Peritonealdialyse (IPD) **VALID UNTIL Q4 2012**
40820	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr **VALID UNTIL Q4 2012**
40821	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr bei einer Feriendialyse während des Ferienaufenthalts am Ferienort oder bei Dialysen wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID UNTIL Q4 2012**
40822	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können **VALID UNTIL Q4 2012**
40815	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei Dialysen am Wohnort **VALID FROM Q1 2013**
40816	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung **VALID FROM Q1 2013**
40817	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei Dialysen am

		Wohnort, die nicht mindestens 4 von 7 Peritonealdialysetage in der Behandlungswoche umfassen **VALID FROM Q1 2013**
40818	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei einer Feriendialyse während des Ferienaufenthalts am Ferienort, bei Dialyse wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID FROM Q1 2013**
40819	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei einer Feriendialyse während des Ferienaufenthalts am Ferienort, bei Dialyse wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID FROM Q1 2013**
40823	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen als Zentrums- bzw. Praxisdialyse oder zentralisierte Heimdialyse,einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung **VALID FROM Q1 2013**
40824	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen als Zentrums- bzw. Praxisdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können **VALID FROM Q1 2013**
40825	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen (z. B. CAPD, CCPD, IPD) oder Heimhämodialysen, bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung **VALID FROM Q1 2013**
40826	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen (z. B. CAPD, CCPD, IPD) oder Heimhämodialysen, bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung

		VALID FROM Q1 2013
40827	EBM	Kostenpauschale für Sachkosten bei Durchführung von intermittierenden Peritonealdialysen (IPD) oder Heimhämodialysen, bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können **VALID FROM Q1 2013**
40828	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämo- oder Peritonealdialysen, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung, bei einer Feriendialyse während des Ferienaufenthalts am Ferienort, bei Dialyse wegen beruflich oder sonstiger Abwesenheit vom Wohnort **VALID FROM Q1 2013**
40829	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40823 oder 40825 bei Versicherten ab dem vollendeten 59. Lebensjahr bis zum vollendeten 69. Lebensjahr **VALID FROM Q1 2013**
40830	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40824, 40826 und 40827 bei Versicherten ab dem vollendeten 59. Lebensjahr bis zum vollendeten 69. Lebensjahr
40831	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40823 oder 40825 bei Versicherten ab dem vollendeten 69. Lebensjahr bis zum vollendeten 79. Lebensjahr **VALID FROM Q1 2013**
40832	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40824, 40826 und 40827 bei Versicherten ab dem vollendeten 69. Lebensjahr bis zum vollendeten 79. Lebensjahr **VALID FROM Q1 2013**
40833	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40823 oder 40825 bei Versicherten ab dem vollendeten 79. Lebensjahr **VALID FROM Q1 2013**
40834	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40824, 40826 und 40827 bei Versicherten ab dem vollendeten 79. Lebensjahr

		VALID FROM Q1 2013
40835	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40816, 40823 oder 40825 für die Infektionsdialyse (bei Patienten mit Infektionserkrankungen mit Problemkeimen gemäß der mit der Kommission für Krankenhaushygiene und Infektionsprävention beim Robert Koch-Institut (KRINKO) abgestimmten Hygieneleitlinie als Ergänzung zum Dialysestandard) **VALID FROM Q1 2013**
40836	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40815, 40817, 40818, 40819, 40824, 40826 bis 40828 für die Infektionsdialyse (bei Patienten mit Infektionserkrankungen mit Problemkeimen gemäß der mit der Kommission für Krankenhaushygiene und Infektionsprävention beim Robert Koch-Institut (KRINKO) abgestimmten Hygieneleitlinie als Ergänzung zum Dialysestandard) **VALID FROM Q1 2013**
40837	EBM	Zuschlag zu der Kostenpauschale nach der Nr. 40816 oder 40825 für die intermittierende Peritonealdialyse (IPD) **VALID FROM Q1 2013**
40838	EBM	Zuschlag zu der Kostenpauschale nach der Nr. 40817, 40819, 40827 oder 40828 für die intermittierende Peritonealdialyse (IPD) **VALID FROM Q1 2013**
04562	EBM	Zusatzpauschale kontinuierliche Betreuung eines dialysepflichtigen Patienten **VALID FROM Q1 2013**
04561	EBM	Zusatzpauschale kindernephrologische Behandlung eines dialysepflichtigen Patienten **VALID FROM Q1 2013**
04564	EBM	Zusatzpauschale kindernephrologische Betreuung bei Durchführung der Hämodialyse **VALID FROM Q1 2013**
04565	EBM	Zusatzpauschale kindernephrologische Betreuung bei Durchführung einer Peritonealdialyse **VALID FROM Q1 2013**
13602	EBM	Zusatzpauschale kontinuierliche Betreuung eines dialysepflichtigen Patienten **VALID FROM Q1 2013**

13610	EBM	Zusatzpauschale ärztliche Betreuung bei Hämodialyse, Peritonealdialyse und Sonderverfahren **VALID FROM Q1 2013**
13611	EBM	Zusatzpauschale ärztliche Betreuung bei Peritonealdialyse **VALID FROM Q1 2013**

5. Table 8 in ANNEX 3);

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

7. 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

8. 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

9. Table 9 in ANNEX 3);

10. Patients who present any evidence of pregnancy in the four quarters prior to or on index (for relevant ICD Codes please refer to

11. 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

12. Table 9 in ANNEX 3).

13. Patients with a thrombosis or a pulmonary embolism in the four quarters prior to or on index date (for relevant ICD Codes please refer to

14. 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

15. Table 9 in ANNEX 3).

8.2.3. Observation periods

The following observation periods are defined throughout this study:

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

Baseline period - 365 days prior to index date for hospital diagnoses and prescriptions and four quarters prior to the index OAC prescription for ambulatory diagnosis. This period will be used to determine whether patients have an AF 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.

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 the 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.

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

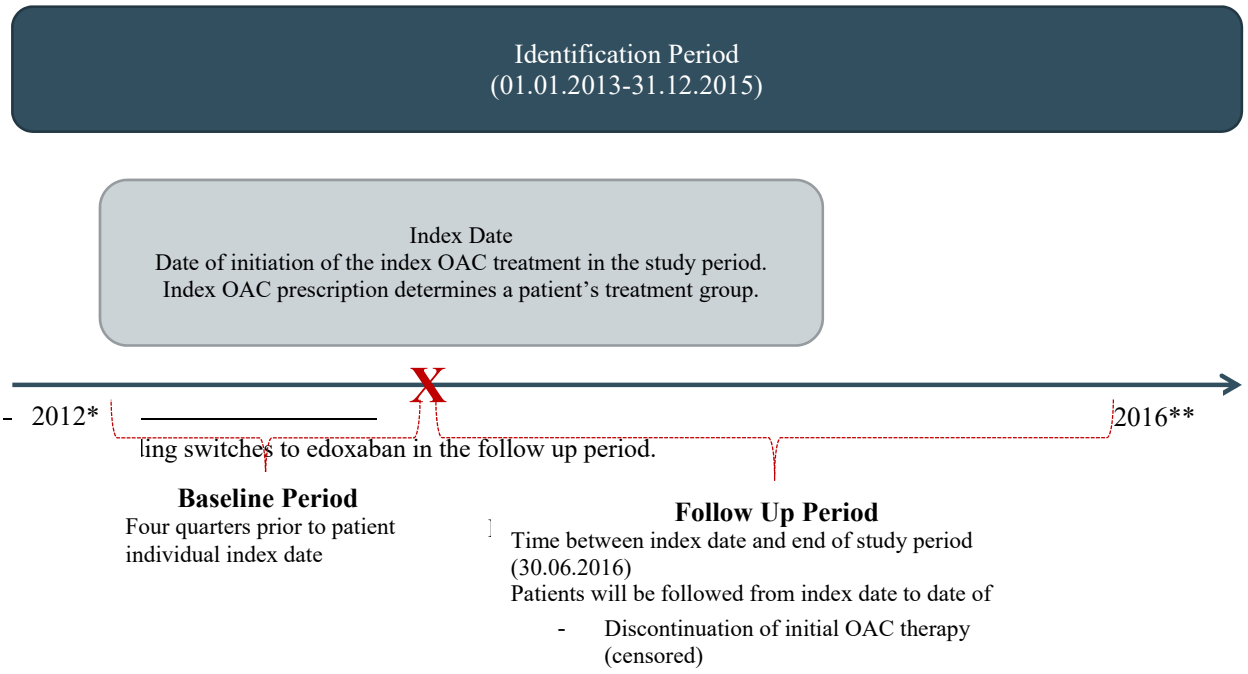
Date of switch - Patients who receive a prescription for an OAC other[5] than the index OAC prescription during the follow- up period will be considered as switchers if the new prescription occurred either before the end of supply of the current prescription or within the gap period after the end of 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. Censoring Scenario Cox Proportional Hazards Model

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 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.

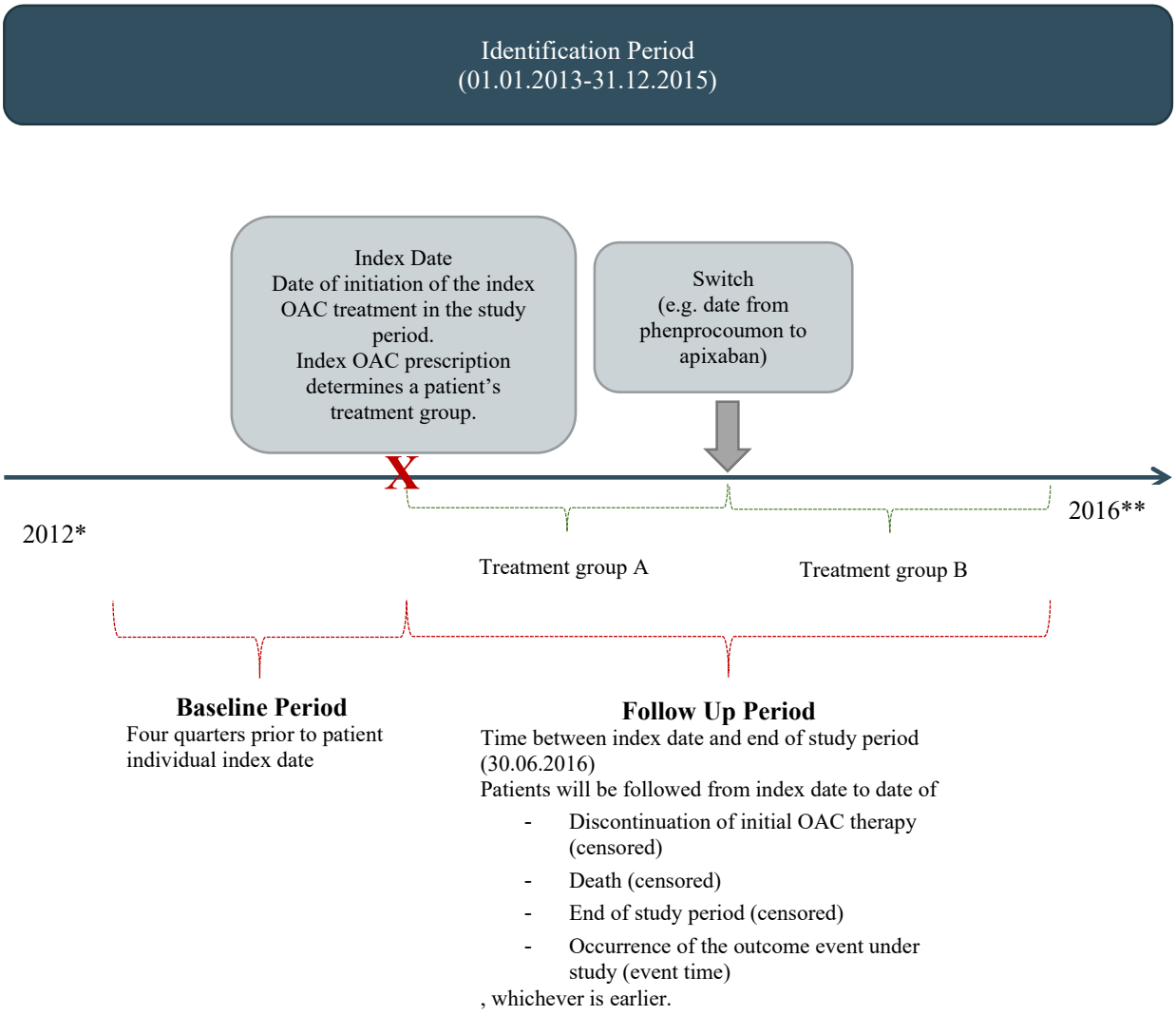
Figure 1 Observation Periods Scenario I Cox Proportonial Hazard Model



8.2.3.2. Censoring Scenario Marginal Structural models

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. However, in contrast to the scenario in section 8.2.3.1, the date of a switch 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 provides an overview about the observation periods which will be applied.

Figure 2 Observation Periods Scenario II – MSM



*Note: If a patients' index event occurs on 01.01.2013, the baseline period for that patient ends on 01.01.2012 – i.e. the minimum first day of observation in the study period.
**Note: Maximum last day of observation: 30.06.2016. However, if the discontinuation of the OAC therapy, a switch, death or end of continuous enrollment occurs 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: (i) a combined endpoint of ischemic or hemorrhagic stroke or systemic embolism and (ii) major bleeding events. Secondary outcomes of interest include (iii) all strokes (ischemic or hemorrhagic), (iv) hemorrhagic stroke, (v) ischemic stroke, (vi) all-cause mortality, (vii) gastrointestinal, (viii) intracranial and (ix) any bleeding. All ischemic events are effectiveness outcomes while all bleeding outcomes are safety outcomes.

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 ischemic or bleeding events described below.

Table 1 Definition of the outcomes

Variable	Objective	Operational definition
Ischemic stroke/ hemorrhagic stroke/ systemic embolism	Primary	Composite endpoint of ischemic stroke or hemorrhagic stroke or systemic embolism (whichever occurs first) during the **Exposure time**. The respective events will be defined based on primary or secondary ICD10 GM hospital discharge diagnoses. Ischemic stroke and hemorrhagic stroke will be defined accordingly using the following ICD-10 GM codes: - I63* Cerebral infarction - I61* Intracerebral haemorrhage - I64* Stroke, not specified as haemorrhage or

		infarction - I74* Arterial embolism and thrombosis
Major bleeding event	Primary	Major bleeding events are will be defined as A. (hospital case in which the : • hospital admission was labelled as an emergency admission AND • an any bleeding (except D62*), gastrointestinal, intracerebral ICD 10 codes in • Table 10 validated by OPS 8-800 (blood transfusion) or the ICD 10 diagnosis D62* (Acute posthaemorrhagic anaemia) have been documented in the same case with one of the) **OR** B. A hospital case with one of the ICD 10 codes labelled as a major bleeding event in the last column of C. Table 10 was documented as primary or secondary discharge diagnosis. For a complete list of all major bleeding events and their operationalization using ICD-10 GM codes please see

		column *major bleeding* in Table 10 in ANNEX 3.
Ischemic stroke/ hemorrhagic stroke	Secondary	Composite endpoint of ischemic stroke or hemorrhagic stroke (whichever occurs first) during the **Exposure time**. The respective events will be defined based on primary or secondary ICD10 GM hospital discharge diagnoses. Ischemic stroke and hemorrhagic stroke will be defined accordingly using the following ICD-10 GM codes: - I63* Cerebral infarction - I61* Intracerebral haemorrhage - I64* Stroke, not specified as haemorrhage or infarction
Ischemic stroke	Secondary	An ischemic stroke will be defined as any ischemic stroke occurring anytime during the **Exposure time**. Ischemic strokes will be defined based on primary and secondary ICD-10 GM hospital discharge diagnoses I63* (cerebral infarction) in the patient individual follow-up period.
Hemorrhagic stroke	Secondary	A hemorrhagic stroke will be defined as any hemorrhagic stroke occurring anytime during the **Exposure time**. Hemorrhagic strokes will be defined based on primary and secondary ICD-10 GM hospital discharge diagnoses I61* (intracebral haemorrhage) in

		the patient individual follow-up period.
All-cause mortality	Secondary	Death from any cause during the **Exposure time**.
Gastrointestinal bleeding event	Secondary	A gastrointestinal bleeding event 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 column bleeding category in Table 10 in ANNEX 3.
Intracranial bleeding event	Secondary	An intracranial bleeding event will be defined as a bleeding event occurring anytime during the **Exposure time**. Intracranial bleeding events will be defined based on the following primary or secondary ICD10 GM hospital discharge diagnoses. For a complete list of all intracranial bleeding events and their operationalization using ICD-10 GM codes please see column bleeding category in Table 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 column bleeding category in 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.

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 AF to Dabigatran 75mg or Rivaroxaban 10mg will be censored, because neither of these treatment regimens are indicated for the stroke prevention in AF patients. Patients switching to Warfarin will also be censored. The number of patients censored due to treatment discontinuation

	will be reported.
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**. Patients will also be censored if a prescription for edoxaban is issued within 30 days after the end of the **Exposure time**. The date on which the changed prescription was dispensed will be defined as the date of the switch. If a prescription, which differs from the initial OAC prescription, is dispensed before the end of the previous prescription, the date of the follow-up dispensation 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).
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 InGef 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 following 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: (01.01. of the index 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.
Days of hospitalization	continuous	Total number of hospital days, independent of admission diagnosis, during the Baseline period.
Days between last hospitalization prior to index	continuous	Distance in days between the last hospitalization prior to the index date and the index date.
Number of ambulatory physician visits	continuous	Total number of ambulatory physician visits, independent of the reason for the visit, during the Baseline period.
No of unique medications	continuous	Number of unique pharmaceutical substances (unique ATC 5 Codes) per patient received during the Baseline period, based on the prescriptions

		documented in the database.
CHA_2DS_2-VASc Score	continuous	The CHA_2DS_2-VASc score 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 (12). 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 (12). 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 InGef database does not contain any laboratory parameters, the international normalized

		ratio (INR) will not be included in the HAS-BLED score. For a complete list of all ICD codes which will be used to form the HAS-BLED score please refer to Table 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 to 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 to 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 to 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 to 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 to 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 to 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 to 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 to 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 to 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 to 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 to 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 to

		to 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 to 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 to 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 to 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 to 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 to 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 to 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 to 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 to 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 to assess whether patients suffered from a 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 to 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 to 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 to 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 to 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 are will be defined

		as A. (hospital case in which the : • hospital admission was labelled as an emergency admission AND • an any bleeding (except D62*), gastrointestinal, intracerebral ICD 10 codes in • Table 10 validated by OPS 8-800 (blood transfusion) or the ICD 10 diagnosis D62* (Acute posthaemorrhagic anaemia) have been documented in the same case with one of the) **OR** B. A hospital case with one of the ICD 10 codes labelled as a major bleeding event in the last column of C. 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	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.
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. Furthermore it will be assessed whether patients were still under therapy on the index date. For that purpose it will be tested whether the drug supply of last prescription prior to the index date lasted at least

		as long as the index date. For a complete list of all relevant ATC Codes please refer to Table 15.
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. Furthermore it will be assessed whether patients were still under therapy on the index date. For that purpose it will be tested whether the drug supply of last prescription prior to the index date lasted at least as long as 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 it will be assessed whether patients were still under therapy on the index date. For that purpose it will be tested whether the drug supply of last prescription prior to the index date lasted at least as long as the index date.
Prescription of non-steroidal anti-inflammatory drugs	categorical	It will be assessed whether patients received at least one prescription for NSAIDs (ATC Code: M01A*)

(NSAIDs)		in the 365 days before or on the Index date. Furthermore it will be assessed whether patients were still under therapy on the index date. For that purpose it will be tested whether the drug supply of last prescription prior to the index date lasted at least as long as the index date.

8.4. Data sources

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

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

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

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

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 might be up to 20% lower because of the chosen in – and exclusion criteria.

Table 4 Results preliminary feasibility study

Initial OAC prescription	**N**
Apixaban	~13,000
Dabigatran	~6,500
Rivaroxaban	~28,000
Phenprocoumon	~27,500
Total	~75,000

Based on the full sample size depicted in Table 4 and its reduced version, power analysis were conducted to find out whether the sample size had enough power to detect clinically meaningful differences with regard to the primary and secondary endpoints in the 3 NOACs therapy groups. The method of Freedman for time-to-event analysis that satisfies the proportional-hazards assumption was used (13). It is relatively easy to implement and has proved well in comparative simulation studies (14). In this approach, the power depends on the expected number of patients in both groups, the probability of events combined across years in both groups and a postulated hazard ratio (expression of the effect-size when time-to-events are to be reported). The HR and probability of events used were those previously reported in the ARISTOTLE, RE-LY and ROCKET-AF clinical trials for Apixaban, Dabigatran and Rivaroxaban respectively (8,9). Calculations were performed using a power of 80% and an α level of 0.05 (two sided). It was hypothesized that patients presenting with a high risk of bleeding were prescribed the lowest dose of Apixaban (2.5 mg) in daily clinical practice, despite of not fulfilling the predefined criteria in this regard. To assess the impact of a possible bias in the assessment of the probability of event for both groups on power estimates, three different scenarios were identified, where we attributed: (i) the highest risk

level to the entire sample, (ii) the same risk distribution as in the clinical trial (10-90% for the highest and lowest risk groups respectively) and (iii) a changing distribution, where the proportion belonging the high-risk group varied between 5% and 60%. Power estimates obtained under the different scenarios did not vary much and a representative medium value was presented here.

The results are presented in Table 5. For ischemic or hemorrhagic stroke or systemic embolism and major bleeding, defined as primary outcomes here, the study has enough power in all therapy groups to detect the expected effects using a Cox Proportional Hazard Model. The same holds also for a reduced sample size (higher dropout rate of 20%).

Table 5 Power analyses for the endpoints ischemic or hemorrhagic stroke or systemic embolism, major bleeding(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.	25.000	9.500	0,051	0,036	0,690	0,001	0,99	0,98	-	-
	Dabi.	25.000	4.500	0,066	0,0535	0,80	0,003	0.97	0,92	-	-
	Riva.	25.000	22.000	0,054	0,055	1.04	0,58	-	-	-	-
Stroke/SE	Api.	25.000	9.500	0,029	0,023	0,788	0,012	0,94	0,88	-	-
	Dabi	25.000	4.500	0,033	0,030	0,91	0,34	-	-	-	-
	Riva.	25.000	22.000	0,034	0,027	0,79	0,02	0,99	0,98	-	-

#This calculation was based on a conservative dropout rate of 20%

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 InGef research database). The analytic file will be person-level, and will include data on demographic and clinical characteristics, information on medical care encounters for AF 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 InGef 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, the mean, median, minimum (min), maximum (max) and the standard deviation (SD) will be reported. 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), using a threshold of 0.1 to indicate imbalance:

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

Phenprocoumon will serve as the reference group. For a table shell please refer to Table 16 and Table 17 in ANNEX 4. All covariates described in Table 3 will be depicted in a descriptive manner.

8.7.2. Time to event – Cox proportional hazards model

The adjusted risk of an event of interest 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:

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

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 outcomes of interest. 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.

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 event –Marginal structural model

In order to account for changes in the treatment regime throughout the patient-individual follow-up period (time-dependent exposure), as well as for the presence of time-dependent covariates that may simultaneously be confounders (possibly affected by prior treatment) and intermediate variables (predict both subsequent treatment and subsequent outcome), a marginal structural model Cox proportional hazards model with inverse probability treatment weighting (Cox PH MSM) 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 ischemic events and major bleeding events, 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 3) that will be considered.

For a table shell of the results that will be presented as a result of this analysis please refer to **Fehler! Verweisquelle konnte nicht gefunden werden.**.

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, systemic 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 – Personalized DDD

In an attempt to account for the intra- and interpersonal variability of the Phenprocoumon treatment regime a personalized DDD (pDDD) based on the observed Phenprocoumon prescription patterns for each patient in the InGef database 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 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

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 eDDD. Patients with a pDDD below the 5th or above the 95th percentile and patients with only one prescription for phenprocoumon will be assigned the median pDDD (eDDD) over all patients[6].

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

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

Section 8.7.4.1 and 8.7.4.2 describe further sensitivity analyses to calculate the exposure time for phenprocoumon patients. In a first step differences in unadjusted event rates for the primary outcomes and major bleeding will be investigated before a final decision is made as to which scenario to use for the further analyses.

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

8.7.4.1. Days of VKA supply – Sensitivity Analysis II – empirical DDD

Within the scope of a sensitivity analyses an alternative option to calculate the days of supply will be implemented. Instead of using the pDDD for each phenprocoumon patient, the median of the distribution of the pPDD estimated over all patients will be used to calculate exposure times for the phenprocoumon patients. For the sake of simplicity, only prescriptions of patients who were solely treated with Phenprocoumon during follow-up will be included in the computation of the eDDD.

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 dosage dependent results

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

8.7.6. Time to event – Propensity Score Matching and Cox proportional hazards model (Sensitivity Analysis)

In order to test the robustness of the results estimated by means of the multivariate Cox Regression, the group of patients treated with OAC's and the group of patients treated with apixaban, rivaroxaban and dabigatran respectively, will be compared by means of Propensity Score Matching (PSM).

For each apixaban, rivaroxaban and dabigatran case, a control will be selected from the pool of subjects in the phenprocoumon group. Controls will be matched 1:1 according to the propensity score (PS) (the same control subjects can only be matched once), age, and sex using nearest-neighbor matching. The matching criteria will be assessed in the year prior to the index quarter. The propensity score will be calculated using logistic regression as the

probability of being assigned to the respective NOAC group (apixaban, dabigatran or rivaroxaban) conditional on a set of given covariables (defined in Table 3). Three separate PSM's will be conducted to match the following groups:

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

The distribution of the outcome variables in the baseline period in the matched groups will be checked to evaluate the matching performance. For continuous variables, the mean, median, minimum (min), maximum (max) and the standard deviation (SD) will be reported. 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), using a threshold of 0.1 to indicate imbalance:

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

Following the PSM a univariate Cox Regression Model, with treatment group as the only covariable, will be estimated to calculated hazard ratios for all outcomes under study comparing patients treated with Phenprocoumon and patients treated with Apixaban, Dabigatran and Rivaroxaban, respectively.

8.8. Quality control

8.8.1. InGef 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 InGef documents and implements:

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

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

Data acquisition

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

The data is then checked for compliance and completeness:

1. File Completeness Check
2. File format versus the predefined standard
3. Data content – are all fields present with corresponding values?

Data-processing checks include:

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

Processed-data checks include:

1. Control of individual data-suppliers - total data volume versus expected and previous periods
2. Checks for missing data estimations

3. Check for aggregated data by analysis unit, e.g. values for surgeries, hospitals, PCTs, Regions

Data quality management is built in to the core processing systems, however, SAS is also used to process data extracted from the production process to determine quality metrics.
As part of the management strategy InGef documents and implements:

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

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

1. Record counts with each data table
2. Unique counts of patients
3. Unique counts of patients continuously enrolled for specified one year increments
4. Percentage of missing values in key data fields (e.g. patient date of birth, patient gender, billing and diagnosis codes, dates of service, etc.)
5. Percentage of valid values in key data fields:
6. Verify that a unique patient identifier is linked to only one individual

8.9. Limitations of the research methods

Although the InGef 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 AF 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 AF.

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. Uncertainty remains whether the days of supply could in fact are over or underestimated, which could have an impact on the attribution of outcome events to the Phenprocoumon treatment, when in fact this treatment might have been stopped or paused before the event occurred.

Another concern may be the potential for coding errors inherent to retrospective analysis of claims databases. However, one can expect that residual bias associated with coding errors may be similar for all exposure groups and thus should not meaningfully influence the assessment of our outcomes.

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

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

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

11174884	Apixaban	Eliquis 5 mg Emra	60	30
11341537	Apixaban	Eliquis 2,5 mg Filmtabletten Docpharm	60	30
11376429	Apixaban	Eliquis 2,5 mg Filmtabletten Milinda	60	30
11376435	Apixaban	Eliquis 2,5 mg Filmtabletten Milinda	200	100
11376441	Apixaban	Eliquis 5 mg Filmtabletten Milinda	60	30
11376458	Apixaban	Eliquis 5 mg Filmtabletten Milinda	200	100
2531523	Dabigatran	Pradaxa 110 mg Kohl Ph.	10	5
2531546	Dabigatran	Pradaxa 110 mg Kohl Ph.	30	15
3420607	Dabigatran	Pradaxa 75 mg	10	5
3420613	Dabigatran	Pradaxa 75 mg	30	15
3420754	Dabigatran	Pradaxa 110 mg	10	5
3420760	Dabigatran	Pradaxa 110 mg	30	15
5704071	Dabigatran	Pradaxa 75 mg	180	90
5704088	Dabigatran	Pradaxa 110 mg	180	90
6115862	Dabigatran	Pradaxa 75 mg CC Ph.	30	15
6115879	Dabigatran	Pradaxa 110 mg CC Ph.	30	15
6141724	Dabigatran	Pradaxa 75 mg CC Ph.	10	5
6141730	Dabigatran	Pradaxa 110 mg CC Ph.	10	5
6312284	Dabigatran	Pradaxa 75 mg Kohl Ph.	30	15
6561863	Dabigatran	Pradaxa 75 mg	200	100
6561892	Dabigatran	Pradaxa 110 mg	60	30

6561900	Dabigatran	Pradaxa 110 mg Hartkapseln	180	90
6561917	Dabigatran	Pradaxa 110 mg	200	100
6561946	Dabigatran	Pradaxa 150 mg	30	15
6561952	Dabigatran	Pradaxa 150 mg	60	30
6561969	Dabigatran	Pradaxa 150 mg Hartkapseln	180	90
6561981	Dabigatran	Pradaxa 150 mg	200	100
7520300	Dabigatran	Pradaxa 75 mg Emra	10	5
7525295	Dabigatran	Pradaxa 75 mg Gerke Ph.	10	5
7525303	Dabigatran	Pradaxa 75 mg Gerke Ph.	30	15
7525326	Dabigatran	Pradaxa 110 mg Gerke Ph.	10	5
7525390	Dabigatran	Pradaxa 110 mg Gerke Ph.	30	15
7544157	Dabigatran	Pradaxa 110 mg Emra	10	5
7544163	Dabigatran	Pradaxa 110 mg Emra	30	15
7544186	Dabigatran	Pradaxa 75 mg Emra	30	15
8797446	Dabigatran	Pradaxa 150 mg	10	5
8844364	Dabigatran	Pradaxa 75 mg Axicorp	30	15
8844370	Dabigatran	Pradaxa 110 mg Axicorp	30	15
8866839	Dabigatran	Pradaxa 110 mg Eurim	30	15
8866880	Dabigatran	Pradaxa 75 mg Eurim	30	15
9124100	Dabigatran	Pradaxa 75 mg Veron Ph.	10	5
9124117	Dabigatran	Pradaxa 75 mg Veron Ph.	30	15
9228199	Dabigatran	Pradaxa 110 mg Westen Ph.	60	30
9321102	Dabigatran	Pradaxa 110 mg Emra	60	30
9328156	Dabigatran	Pradaxa 110 mg Kohl Ph.	60	30

9707095	Dabigatran	Pradaxa 110 mg Hartkapseln	100	50
9707103	Dabigatran	Pradaxa 150 mg Hartkapseln	100	50
9947971	Dabigatran	Pradaxa 150 mg Hartkapseln CC Ph.	30	15
9947988	Dabigatran	Pradaxa 150 mg CC Pharma	60	30
10183585	Dabigatran	Pradaxa 110 mg Kohl Ph.	30	15
10193365	Dabigatran	Pradaxa 150 mg Eurim	30	15
10193371	Dabigatran	Pradaxa 150 mg Eurim	60	30
10206458	Dabigatran	Pradaxa 150 mg Hartkapseln CC Ph.	100	50
10218349	Dabigatran	Pradaxa 110 mg Hartkapseln Eurim	60	30
10218355	Dabigatran	Pradaxa 110 mg Hartkapseln Eurim	100	50
10218361	Dabigatran	Pradaxa 110 mg Hartkapseln Eurim	180	90
10249781	Dabigatran	Pradaxa 150 mg Hartkapseln Kohl Ph.	60	30
10251016	Dabigatran	Pradaxa 110 mg CC Ph.	60	30
10251022	Dabigatran	Pradaxa 110 mg CC Ph.	100	50
10261210	Dabigatran	Pradaxa 110 mg Hartkapseln Kohl Ph.	180	90
10261233	Dabigatran	Pradaxa 150 mg Hartkapseln Kohl Ph.	180	90
10288114	Dabigatran	Pradaxa 150 mg Hartkapseln Gerke Ph.	100	50
10288120	Dabigatran	Pradaxa 110 mg Hartkapseln Gerke Ph.	100	50

10339484	Dabigatran	Pradaxa 110 mg Hartkapseln Emra	60	30
10339509	Dabigatran	Pradaxa 110 mg Hartkapseln Emra	100	50
10339521	Dabigatran	Pradaxa 110 mg Hartkapseln Emra	180	90
10357542	Dabigatran	Pradaxa 150 mg Hartkapseln Emra	60	30
10390829	Dabigatran	Pradaxa 110 mg Hartkapseln Kohl Ph.	100	50
10390835	Dabigatran	Pradaxa 150 mg Hartkapseln Kohl Ph.	100	50
10395867	Dabigatran	Pradaxa 150 mg Hartkapseln Gerke Ph.	60	30
10402596	Dabigatran	Pradaxa 110 mg Hartkapseln Axicorp	100	50
10402604	Dabigatran	Pradaxa 110 mg Hartkapseln Axicorp	180	90
10402685	Dabigatran	Pradaxa 110 mg Hartkapseln Axicorp	60	30
10737084	Dabigatran	Pradaxa 110 mg Hartkapseln Haemato-Ph.	60	30
10783204	Dabigatran	Pradaxa 110 mg Hartkapseln Haemato-Ph.	100	50
10944541	Dabigatran	Pradaxa 110 mg Hartkapseln Orifarm	180	90
10989779	Dabigatran	Pradaxa 150 mg Hartkapseln Orifarm	180	90
11004550	Dabigatran	Pradaxa 150 mg Hartkapseln Emra	180	90
11009889	Dabigatran	Pradaxa 75 mg Hartkapseln	30	15

		Eurim		
11027491	Dabigatran	Pradaxa 75 mg Hartkapseln Emra	30	15
11038299	Dabigatran	Pradaxa 150 mg Hartkapseln Haemato-Ph.	60	30
11038307	Dabigatran	Pradaxa 150 mg Hartkapseln Haemato-Ph.	180	90
11127442	Dabigatran	Pradaxa 110 mg Hartkapseln Gerke Ph.	60	30
11130183	Dabigatran	Pradaxa 110 mg Hartkapseln Docpharm	60	30
11130378	Dabigatran	Pradaxa 110 mg Hartkapseln Docpharm	180	90
11130384	Dabigatran	Pradaxa 150 mg Hartkapseln Docpharm	60	30
11130409	Dabigatran	Pradaxa 150 mg Hartkapseln Docpharm	180	90
11291087	Dabigatran	Pradaxa 75 mg Hartkapseln Emra	60	30
11309114	Dabigatran	Pradaxa 110 mg Hartkapseln Docpharm	30	15
11309120	Dabigatran	Pradaxa 150 mg Hartkapseln Docpharm	30	15
11341916	Dabigatran	Pradaxa 110 mg Hartkapseln Milinda	60	30
11341922	Dabigatran	Pradaxa 110 mg Hartkapseln Milinda	180	90
11341939	Dabigatran	Pradaxa 150 mg Hartkapseln Milinda	60	30
11341945	Dabigatran	Pradaxa 150 mg Hartkapseln Milinda	180	90

10713994	Edoxaban	Lixiana 15 mg Filmtabletten	10	10
10714002	Edoxaban	Lixiana 15 mg Filmtabletten	10	10
10714031	Edoxaban	Lixiana 30 mg Filmtabletten	28	28
10714060	Edoxaban	Lixiana 30 mg Filmtabletten	98	98
10714083	Edoxaban	Lixiana 30 mg Filmtabletten	100	100
10714143	Edoxaban	Lixiana 30 mg Filmtabletten	10	10
10714172	Edoxaban	Lixiana 60 mg Filmtabletten	10	10
10714255	Edoxaban	Lixiana 60 mg Filmtabletten	28	28
10714284	Edoxaban	Lixiana 60 mg Filmtabletten	98	98
10714309	Edoxaban	Lixiana 60 mg Filmtabletten	100	100
972890	Phenprocoumon	Falithrom 1,5 mite	20	10
972909	Phenprocoumon	Falithrom 1,5 mite	50	25
972915	Phenprocoumon	Falithrom 1,5 mite	100	50
1294216	Phenprocoumon	Marcoumar Me-Pharma	50	50
1294222	Phenprocoumon	Marcoumar Me-Pharma	100	100
1300649	Phenprocoumon	Marcumar	30	30
1835787	Phenprocoumon	Marcoumar DOCPHARMA	50	50
1837390	Phenprocoumon	Marcoumar DOCPHARMA	100	100
2021408	Phenprocoumon	MARCUMAR	50	50
2059517	Phenprocoumon	Phenpro AbZ 3 mg	100	100
2499417	Phenprocoumon	MARCUMAR	20	20
2704892	Phenprocoumon	Phenprogamma 3	20	20
2704900	Phenprocoumon	Phenprogamma 3	50	50
2704917	Phenprocoumon	Phenprogamma 3	100	100

3011932	Phenprocoumon	Falithrom	20	20
3215540	Phenprocoumon	MARCUMAR	100	100
3352194	Phenprocoumon	MARCOUMAR BERAGENA	50	50
3352202	Phenprocoumon	MARCOUMAR BERAGENA	100	100
3422256	Phenprocoumon	MARCOUMAR OPTI ARZNEI	50	50
3422262	Phenprocoumon	MARCOUMAR OPTI ARZNEI	100	100
3462445	Phenprocoumon	Marcoumar Westen Ph.	50	50
3462451	Phenprocoumon	Marcoumar Westen Ph.	100	100
4334620	Phenprocoumon	MARCOUMAR EMRA MED	50	50
4334637	Phenprocoumon	MARCOUMAR EMRA MED	100	100
4386462	Phenprocoumon	Marcoumar Gerke Ph.	50	50
4386479	Phenprocoumon	Marcoumar Gerke Ph.	100	100
4421721	Phenprocoumon	FALITHROM	20	20
4421738	Phenprocoumon	FALITHROM	50	50
4421744	Phenprocoumon	FALITHROM	100	100
4446773	Phenprocoumon	Marcoumar GPP	50	50
4446796	Phenprocoumon	Marcoumar GPP	100	100
4582128	Phenprocoumon	Phenpro.-ratiopharm 3 mg	20	20
4582134	Phenprocoumon	Phenpro.-ratiopharm 3 mg	50	50
4582140	Phenprocoumon	Phenpro.-ratiopharm 3 mg	100	100
4658618	Phenprocoumon	MARCOUMAR EURIM PHARM	100	100

4958705	Phenprocoumon	Marcoumar Kohl Ph.	50	50
4958711	Phenprocoumon	Marcoumar Kohl	100	100
5541315	Phenprocoumon	Marcumar	14	14
5541321	Phenprocoumon	Marcumar	49	49
5541338	Phenprocoumon	Marcumar	98	98
6575233	Phenprocoumon	Phenpro.-ratiopharm 3 mg	98	98
6588626	Phenprocoumon	Marcuphen-CT 3 mg	98	98
6811219	Phenprocoumon	Phenpro AbZ 3 mg	98	98
6969475	Phenprocoumon	MARCOUMAR GrÃ?newald	50	50
6969481	Phenprocoumon	MARCOUMAR GrÃ?newald	100	100
7118762	Phenprocoumon	Marcoumar Alphamed 4x25	100	100
7532349	Phenprocoumon	Marcoumar Alpha Med	50	50
7614188	Phenprocoumon	Marcumar Eurim	50	50
7614194	Phenprocoumon	Marcumar Eurim	100	100
7636008	Phenprocoumon	marcuphen von ct	20	20
7636014	Phenprocoumon	marcuphen von ct	50	50
7636020	Phenprocoumon	marcuphen von ct	100	100
7646567	Phenprocoumon	Marcoumar AE Media	50	50
7646573	Phenprocoumon	Marcoumar AE Media	100	100
7768135	Phenprocoumon	Marcumar	56	56
7768170	Phenprocoumon	Marcumar	92	92
8874885	Phenprocoumon	Marcumar ACA/ADAG	50	50
8874891	Phenprocoumon	Marcumar ACA/ADAG	100	100
9404207	Phenprocoumon	Phenprogamma 3	14	14

9726170	Phenprocoumon	Marcoumar Eurim	100	100
10269507	Phenprocoumon	Phenprocoumon acis 3 mg	20	20
10269513	Phenprocoumon	Phenprocoumon acis 3 mg	50	50
10269542	Phenprocoumon	Phenprocoumon acis 3 mg	100	100
2088536	Rivaroxaban	Xarelto 10 mg CC Ph.	5	5
4369423	Rivaroxaban	Xarelto 15 mg Emra	28	28
4369452	Rivaroxaban	Xarelto 15 mg Emra	42	42
4369475	Rivaroxaban	Xarelto 15 mg Emra	98	98
4369481	Rivaroxaban	Xarelto 20 mg Emra	28	28
4369498	Rivaroxaban	Xarelto 20 mg Emra	98	98
5459513	Rivaroxaban	Xarelto 10 mg Eurim	30	30
5748766	Rivaroxaban	Xarelto 10 mg Kohl Ph.	30	30
5995074	Rivaroxaban	Xarelto 10 mg	10	10
5995080	Rivaroxaban	Xarelto 10 mg	30	30
5995097	Rivaroxaban	Xarelto 10mg	100	100
6410420	Rivaroxaban	Xarelto 10 mg CC Ph.	30	30
6454481	Rivaroxaban	Xarelto 10 mg Westen Ph.	30	30
7089598	Rivaroxaban	Xarelto 15 mg Westen Ph.	98	98
7089606	Rivaroxaban	Xarelto 20 mg Westen Ph.	98	98
7536850	Rivaroxaban	Xarelto 10 mg	10	10
7536927	Rivaroxaban	Xarelto 10 mg	30	30
7572633	Rivaroxaban	Xarelto 10 mg Gerke Ph.	10	10
7572662	Rivaroxaban	Xarelto 10 mg Gerke Ph.	30	30
7605019	Rivaroxaban	Xarelto 15 mg Orifarm	28	28

7605025	Rivaroxaban	Xarelto 20 mg Orifarm	28	28
7610606	Rivaroxaban	Xarelto 10 mg Kohl Ph.	10	10
7799012	Rivaroxaban	Xarelto 10 mg Emra	10	10
7799029	Rivaroxaban	Xarelto 10 mg Emra	30	30
8461290	Rivaroxaban	Xarelto 2,5 mg Filmtabletten 1x10x10	100	100
8461344	Rivaroxaban	Xarelto 15 mg	14	14
8461350	Rivaroxaban	Xarelto 15 mg	28	28
8461367	Rivaroxaban	Xarelto 15 mg	98	98
8461404	Rivaroxaban	Xarelto 15 mg	42	42
8461410	Rivaroxaban	Xarelto 20 mg	14	14
8461427	Rivaroxaban	Xarelto 20 mg	28	28
8461433	Rivaroxaban	Xarelto 20 mg	98	98
8717186	Rivaroxaban	Xarelto 2,5 mg Filmtabletten	30	30
9154791	Rivaroxaban	Xarelto 10 mg	5	5
9333393	Rivaroxaban	Xarelto 15 mg	100	100
9333401	Rivaroxaban	Xarelto 20 mg	100	100
9721534	Rivaroxaban	Xarelto 10 mg CC Ph.	10	10
9724515	Rivaroxaban	Xarelto 15 mg CC Ph.	28	28
9724521	Rivaroxaban	Xarelto 15 mg CC Ph.	42	42
9724538	Rivaroxaban	Xarelto 15 mg CC Ph.	98	98
9724544	Rivaroxaban	Xarelto 20 mg CC Ph.	28	28
9724550	Rivaroxaban	Xarelto 20 mg CC Ph.	98	98
9777888	Rivaroxaban	Xarelto 10 mg Haemato-Ph.	30	30

9941276	Rivaroxaban	Xarelto 10 mg	100	100
9941282	Rivaroxaban	Xarelto 15 mg	100	100
9941299	Rivaroxaban	Xarelto 20 mg	100	100
10005926	Rivaroxaban	Xarelto 15 mg Kohl Ph.	98	98
10005932	Rivaroxaban	Xarelto 20 mg Kohl Ph.	98	98
10012139	Rivaroxaban	Xarelto 15 mg Gerke Ph.	14	14
10012145	Rivaroxaban	Xarelto 15 mg Gerke Ph.	28	28
10012151	Rivaroxaban	Xarelto 15 mg Gerke Ph.	42	42
10012168	Rivaroxaban	Xarelto 15 mg Gerke Ph.	98	98
10012174	Rivaroxaban	Xarelto 20 mg Gerke Ph.	14	14
10012180	Rivaroxaban	Xarelto 20 mg Gerke Ph.	28	28
10012197	Rivaroxaban	Xarelto 20 mg Gerke Ph.	98	98
10057490	Rivaroxaban	Xarelto 20 mg Eurim	14	14
10057509	Rivaroxaban	Xarelto 20 mg Eurim	28	28
10058590	Rivaroxaban	Xarelto 15 mg Eurim	14	14
10058609	Rivaroxaban	Xarelto 15 mg Eurim	28	28
10072093	Rivaroxaban	Xarelto 15 mg ACA/ADAG	28	28
10072101	Rivaroxaban	Xarelto 15 mg ACA/ADAG	98	98
10072118	Rivaroxaban	Xarelto 20 mg ACA/ADAG	28	28
10072124	Rivaroxaban	Xarelto 20 mg ACA/ADAG	98	98
10101682	Rivaroxaban	Xarelto 15 mg Filmtabletten Axicorp	14	14
10102144	Rivaroxaban	Xarelto 15 mg Filmtabletten Axicorp	42	42
10106863	Rivaroxaban	Xarelto 20 mg Filmtabletten	14	14

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

10393650	Rivaroxaban	Xarelto 15 mg Docpharm	28	28
10393667	Rivaroxaban	Xarelto 15 mg Docpharm	42	42
10393696	Rivaroxaban	Xarelto 15 mg Docpharm	98	98
10402662	Rivaroxaban	Xarelto 10 mg Axicorp Pharma	30	30
10743771	Rivaroxaban	Xarelto 10 mg Docpharm	10	10
10743794	Rivaroxaban	Xarelto 15 mg FD Pharma	98	98
10743802	Rivaroxaban	Xarelto 20 mg FD Pharma	98	98
10762403	Rivaroxaban	Xarelto 15 mg Abacus	98	98
10762426	Rivaroxaban	Xarelto 20 mg Abacus	98	98
10764520	Rivaroxaban	Xarelto 10 mg Orifarm	10	10
10852626	Rivaroxaban	Xarelto 10 mg Beragena	10	10
10852632	Rivaroxaban	Xarelto 10 mg Beragena	30	30
10852649	Rivaroxaban	Xarelto 15 mg Beragena	14	14
10852655	Rivaroxaban	Xarelto 15 mg Beragena	28	28
10852661	Rivaroxaban	Xarelto 15 mg Beragena	42	42
10852678	Rivaroxaban	Xarelto 15 mg Beragena	98	98
10852684	Rivaroxaban	Xarelto 20 mg Beragena	14	14
10852690	Rivaroxaban	Xarelto 20 mg Beragena	28	28
10852709	Rivaroxaban	Xarelto 20 mg Beragena	98	98
10853560	Rivaroxaban	Xarelto 15 mg Kohl Ph.	14	14
10853577	Rivaroxaban	Xarelto 20 mg Kohl Ph.	14	14
10948970	Rivaroxaban	Xarelto 15 mg Kohl Ph.	42	42
10948987	Rivaroxaban	Xarelto 15 mg Kohl Ph.	28	28

10964153	Rivaroxaban	Xarelto 15 mg Orifarm	14	14
10964176	Rivaroxaban	Xarelto 15 mg Orifarm	42	42
10964182	Rivaroxaban	Xarelto 20 mg Orifarm	14	14
10999312	Rivaroxaban	Xarelto 15 mg Axicorp	14	14
10999329	Rivaroxaban	Xarelto 15 mg Axicorp	42	42
10999335	Rivaroxaban	Xarelto 15 mg Axicorp	98	98
10999341	Rivaroxaban	Xarelto 20 mg Axicorp	14	14
10999358	Rivaroxaban	Xarelto 20 mg Axicorp	28	28
10999364	Rivaroxaban	Xarelto 20 mg Axicorp	98	98
11015708	Rivaroxaban	Xarelto 15 mg filmtabletten Emra	14	14
11015714	Rivaroxaban	Xarelto 20 mg Emra	14	14
11096606	Rivaroxaban	Xarelto 15 mg Euro DK	98	98
11096612	Rivaroxaban	Xarelto 20 mg Euro DK	98	98
11559348	Rivaroxaban	Xarelto 15 mg BB Farma	98	98
11559354	Rivaroxaban	Xarelto 20 mg BB Farma	98	98
11617270	Rivaroxaban	Xarelto 10 mg Abacus	30	30
245546	Warfarin	COUMADIN 5MG	100	66,667
8516358	Warfarin	Coumadin 5 mg	20	13,333
8516364	Warfarin	Coumadin 5 mg	50	33,333
9897078	Warfarin	Coumadin 5 mg Eurim	100	66,667
10066230	Warfarin	Coumadin 5 mg Emra	100	66,667
11054430	Warfarin	Coumadin 5 mg Kohl Ph.	100	66,667
11367761	Warfarin	Coumadin 5 mg Tabletten Kohl Ph.	50	33,333

11651054	Warfarin	Coumadin 5 mg Tabletten Emra	50	33,333

Table 7 Codes Dialyses (exclusion criteria)

Code	Codetyp	Description
8853	Ops_code	Hämofiltration
8854	Ops_code	Hämodialyse
8855	Ops_code	Hämodiafiltration
8857	Ops_code	Peritonealdialyse
40800	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr bis zum vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes Mellitus **VALID UNTIL Q4 2012**
40801	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr bis zum vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes mellitus, bei einer Feriendialyse während des Ferienaufenthalts am Ferienort, bei Dialysen wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID UNTIL Q4 2012**
40802	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 59. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung ohne manifesten behandlungspflichtigen Diabetes mellitus, **VALID UNTIL Q4 2012**
40803	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei

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

		die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können. **VALID UNTIL Q4 2012**
40808	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration), bei Versicherten ab dem vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung mit manifestem behandlungspflichtigen Diabetes mellitus bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können. **VALID UNTIL Q4 2012**
40810	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40800, 40802 oder 40804 für die Infektionsdialyse (bei Patienten mit Hepatitis B und/oder Hepatitis C und/oder mit HIV-Infektion und/oder mit MRSA-Infektion) **VALID UNTIL Q4 2012**
40811	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40801, 40803 oder 40805 bis 40808 für die Infektionsdialyse (bei Patienten mit Hepatitis B und/oder Hepatitis C und/oder mit HIV-Infektion und/oder mit MRSA-Infektion) **VALID UNTIL Q4 2012**
40812	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40800, 40802 oder 40804 für die intermittierende Peritonealdialyse (IPD) **VALID UNTIL Q4 2012**
40813	EBM	Zuschlag zu der Kostenpauschale nach den Nrn. 40801, 40803 oder 40805 bis 40808 für die intermittierende Peritonealdialyse (IPD) **VALID UNTIL Q4 2012**
40820	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr **VALID UNTIL Q4 2012**
40821	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl.

		Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr bei einer Feriendialyse während des Ferienaufenthalts am Ferienort oder bei Dialysen wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID UNTIL Q4 2012**
40822	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen, CAPD, CCPD, als Zentrums- bzw. Praxisdialyse, Heimdialyse oder zentralisierte Heimdialyse, einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr bei Dialysen am Wohnort, die nicht mindestens dreimal in der Behandlungswoche durchgeführt werden können **VALID UNTIL Q4 2012**
40815	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei Dialysen am Wohnort **VALID FROM Q1 2013**
40816	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung **VALID FROM Q1 2013**
40817	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei Dialysen am Wohnort, die nicht mindestens 4 von 7 Peritonealdialysetage in der Behandlungswoche umfassen **VALID FROM Q1 2013**
40818	EBM	Kostenpauschale für Sachkosten bei Durchführung von Hämodialysen einschl. Sonderverfahren (z. B. Hämofiltration, Hämodiafiltration) bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei einer Feriendialyse während des Ferienaufenthalts am Ferienort, bei Dialyse wegen beruflich bedingter oder sonstiger Abwesenheit vom Wohnort **VALID FROM Q1 2013**
40819	EBM	Kostenpauschale für Sachkosten bei Durchführung von Peritonealdialysen bei Patienten bis zum vollendeten 18. Lebensjahr mit einer dialysepflichtigen Nierenerkrankung bei einer Feriendialyse während des Ferienaufenthalts am Ferienort, bei Dialyse wegen

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

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

		VALID FROM Q1 2013
40837	EBM	Zuschlag zu der Kostenpauschale nach der Nr. 40816 oder 40825 für die intermittierende Peritonealdialyse (IPD) **VALID FROM Q1 2013**
40838	EBM	Zuschlag zu der Kostenpauschale nach der Nr. 40817, 40819, 40827 oder 40828 für die intermittierende Peritonealdialyse (IPD) **VALID FROM Q1 2013**
04562	EBM	Zusatzpauschale kontinuierliche Betreuung eines dialysepflichtigen Patienten **VALID FROM Q1 2013**
04561	EBM	Zusatzpauschale kindernephrologische Behandlung eines dialysepflichtigen Patienten **VALID FROM Q1 2013**
04564	EBM	Zusatzpauschale kindernephrologische Betreuung bei Durchführung der Hämodialyse **VALID FROM Q1 2013**
04565	EBM	Zusatzpauschale kindernephrologische Betreuung bei Durchführung einer Peritonealdialyse **VALID FROM Q1 2013**
13602	EBM	Zusatzpauschale kontinuierliche Betreuung eines dialysepflichtigen Patienten **VALID FROM Q1 2013**
13610	EBM	Zusatzpauschale ärztliche Betreuung bei Hämodialyse, Peritonealdialyse und Sonderverfahren **VALID FROM Q1 2013**
13611	EBM	Zusatzpauschale ärztliche Betreuung bei Peritonealdialyse **VALID FROM Q1 2013**

Table 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 Aderhaut	any	yes
H31.30	Blutung und Ruptur der Aderhaut	any	yes
H31.31	Blutung und Ruptur der Aderhaut	any	yes
H35.6	Netzhautblutung	any	yes

H43.1	Glaskörperblutung	any	yes
H45.0	Glaskörperblutung bei sonst klassifiz. Krankheit	any	yes
H92.2	Blutung aus äußerem Gehörgang	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
I31.2	Hämoperikard, anderenorts nicht klassifiziert	any	yes
I60.0	Subarachnoidalblutung, vom Karotissiphon oder der Karotisbifurkation ausgehend	intracerebral (also part of any bleeding) (also part of any bleeding)	yes
I60.1	Subarachnoidalblutung, von der A. cerebri media ausgehend	intracerebral (also part of any bleeding)	yes
I60.2	Subarachnoidalblutung, von der A. communicans anterior ausgehend	intracerebral (also part of any bleeding)	yes
I60.3	Subarachnoidalblutung, von der A. communicans posterior ausgehend	intracerebral (also part of any bleeding)	yes
I60.4	Subarachnoidalblutung, von der A. basilaris ausgehend	intracerebral (also part of any bleeding)	yes
I60.5	Subarachnoidalblutung, von der A. vertebralis ausgehend	intracerebral (also part of any bleeding)	yes
I60.6	Subarachnoidalblutung, von sonstigen intrakraniellen Arterien ausgehend	intracerebral (also part of any bleeding)	yes

I60.7	Subarachnoidalblutung, von nicht näher bezeichneter intrakranieller Arterie ausgehend	intracerebral (also part of any bleeding)	yes
I60.8	Sonstige Subarachnoidalblutung	intracerebral (also part of any bleeding)	yes
I60.9	Subarachnoidalblutung, nicht näher bezeichnet	intracerebral (also part of any bleeding)	yes
I61.0	Intrazerebrale 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)	intracerebral (also part of	yes

	Akut	any bleeding)	
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	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood

	und Perforation		transfusion (OPS codes 8-800) in the same hospital case.
K27.4	Ulcus pepticum Lokalisation onA chronisch oder onA mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K27.6	Ulcus pepticum Lokalisation onA chronisch oder onA mit Blutung und Perforation	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K28.0	Ulcus pepticum jejuni akut mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K28.2	Ulcus pepticum jejuni akut mit Blutung und Perforation	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K28.4	Ulcus pepticum jejuni chronisch oder onA mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K28.6	Ulcus pepticum jejuni chronisch oder onA mit Blutung und Perforation	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K29.0	Akute hämorrhagische Gastritis	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K31.82	Angiodysplasie des Magens und des Duodenums mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K55.22	Angiodysplasie des Kolons mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood

			transfusion (OPS codes 8-800) in the same hospital case.
K57.01	Divertikulose des Dünndarmes mit Perforation und Abszess Divertikulose mit Blutung	gastrointestinal (also part of any bleeding)	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.03	Divertikulose des Dünndarmes mit Perforation und Abszess 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	gastrointestinal	Yes, but only in combination with an

	Dickdarmes ohne Perforation oder Abszess Divertikulitis mit Blutung	(also part of any bleeding)	emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
K57.41	Divertikulose sowohl des Dünndarmes als auch des Dickdarmes mit Perforation und Abszess 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.
K57.43	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	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

	und Abszess Divertikulose mit Blutung		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 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.
K57.93	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	gastrointestinal	Yes, but only in combination with an

	Blutung onA	(also part of any bleeding)	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	any	yes

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

	abnorme Uterus- oder Vaginalblutung		documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N93.9	Abnorme Uterus- oder Vaginalblutung, nicht näher bezeichnet	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
N95.0	Postmenopausenblutung	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R04.0	Epistaxis	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R04.1	Blutung aus dem Rachen	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R04.2	Hämoptoe	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R04.8	Blutung aus sonstigen Lokalisationen in den Atemwegen	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R04.9	Blutung aus den Atemwegen, nicht näher bezeichnet	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R23.3	Spontane Ekchymosen	any	Yes, but only in combination with an emergency hospital admission and a documented D62* diagnosis or a blood transfusion (OPS codes 8-800) in the same hospital case.
R31	Nicht näher bezeichnete	any	Yes, but only in combination with an emergency hospital admission and a

	Hämaturie		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, traumatisches Hämatom, Kontusion	intracerebral (also part of any bleeding)	yes

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 without complications	E100,E101,E106,E108,E109,E110,E111,E116,E118,E119,E120,E121,E126,E128,E129,E130,E131,E136,E138,E139,E140,E141,E146,E148,E149	1	1
Hemiplegia	G81,G82,G041,G114,G801,G802,G830,G831,G832,G833,G834,G839	2	2
Moderate or severe renal disease	N18,N19,N052,N053,N054,N055,N056,N057,N250,I120,I131,N032,N033,N034,N035,N036,N037,Z490,Z491,Z492,Z940,Z992	2	0
Diabetes with end organ damage	E102,E103,E104,E105,E107,E112,E113,E114,E115,E117,E122,E123,E124,E125,E127,E132,E133,E134,E135,E137,E142,E143,E144,E145,E147	2	2
Any tumor	C00,C01,C02,C03,C04,C05,C06,C07,C08,C09,C10,C11,C12,C13,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 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 16 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 17 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 18 Table shell – event rates per 100 patient years by treatment group

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

Table 19 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				
…				