Observational Study/Post Authorization Safety Study (PASS) Information

Acronym/Title	Real-world comparative effectiveness of stroke prevention in patients with atrial fibrillation treated with Factor Xa non-vitamin-K oral anticoagulants (NOACs) vs. Phenprocoumon (ReLoaDeD)
Protocol version and date	v1.0, 01.06. 2018
IMPACT study number	20031
Study type / Study phase	Observational, Phase IV Post marketing surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01) Direct factor XA inhibitor, Apixaban (B01AF02) Direct factor XA inhibitor, Edoxaban (B01AF03)
Medicinal product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Product reference	N/A
Procedure number	N/A
Comparator / Reference therapy	Vitamin-K antagonist, Phenprocoumon (B01AA04)
Study Initiator and Funder	Bayer AG 13353 Berlin, Germany
Research question and objectives	The primary objectives of this study are: • To describe the risk of ischemic stroke (IS)/ systemic embolism (SE) and intracranial hemorrhage (ICH) in patients with non-valvular atrial fibrillation (NVAF) and renal impairment initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon The secondary objectives of this study are: • To describe the risk of ischemic stroke (IS)/ systemic

	embolism (SE) and intracranial hemorrhage (ICH) in patients with non-valvular atrial fibrillation (NVAF) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon • To describe the risk of IS, SE, kidney failure, acute kidney injury (AKI), fatal bleeding, recurrent hospitalization, recurrent IS/SE, severe IS as well as to describe treatment persistence in patients with NVAF (overall population as well as in specific subpopulations of interest) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon Other objectives of this study are: • To describe the risk of IS/ SE, severe IS, fatal bleeding and ICH as combined effectiveness outcome in patients with NVAF (overall population as well as in specific subpopulations of interest) initiating treatment with reduced dose of individual NOACs (rivaroxaban, apixaban, edoxaban) compared to standard dose in a subpopulation of patients without renal impairment
Country(-ies) of study	This study will be conducted using secondary data from German sick funds.
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
MAH contact person	[redacted]

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

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2. List of abbreviations

AAI	Amount of active ingredient
AG	Andersen-Gill
AF	Atrial fibrillation
AKI	Acute kidney injury
ATC	Anatomical Therapeutic Chemical (Classification System)
CPN	Central pharmaceutical number
DDD	Defined Daily Dose
EBM	Einheitlicher Bewertungsmaßstab
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
ET	Exposure time
EU	European Union
ICD-10 GM	German Modification of the 10th revision of the International Classification of Diseases
INR	International normalized ratio
ICH	Intracranial hemorrhage
IPTW	Inverse probability of treatment weighting
HEOR	Health Economics and Outcomes Research
HR	Hazard ratio
InGef	Institute for Applied Healthcare Research Berlin
IS	Ischemic stroke
IRB	Institutional Review Board
IT	Information Technology
MAH	Marketing Authorization Holder
NOAC	Novel oral anticoagulant
NVAF	Non-valvular atrial fibrillation
OPS	Operationen und Prozedurenschlüssel
OS	Observational Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PWP	Prentice, Williams and Peterson
QPPV	Qualified Person Responsible For Pharmacovigilance
SE	Systemic embolism
SHI	Statutory health insurance
VKA	Vitamin-K antagonists
VTE	Venous thromboembolism

3. Responsible parties

3.1 Study initiator and funder

Role: [redacted]
Name:
E-mail:

Role: [redacted]
Name: [redacted]

Role: [redacted]
Name: [redacted]

Role: [redacted]
Name: [redacted]

Role: [redacted]
Name: [redacted]

Role: [redacted]
Name: [redacted]

Contact details of the responsible parties at Bayer AG are available upon request.

3.2 Collaborator(s)/External partner(s)/Committee(s)

Name	**Function**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4. Abstract

Acronym/Title	Real-world comparative effectiveness of stroke prevention in patients with atrial fibrillation treated with Factor Xa non-vitamin-K oral anticoagulants (NOACs) vs. Phenprocoumon (ReLoaDeD)
Rationale and background	Supplementary to randomized controlled trials, generation of real-world evidence is of importance in reinforcing safety perceptions and gaining knowledge on differences between treatments used in routine clinical practice. Existing real-world studies have provided evidence that novel oral anticoagulants (NOACs) in general and rivaroxaban in particular are more effective and at least as safe as warfarin in non-valvular atrial fibrillation (NVAF) patients with renal impairment. Nevertheless, it is known that clinicians often hesitate to prescribe NOACs to patients with even moderate renal impairment. Therefore, it is important to investigate effectiveness and safety of rivaroxaban and other NOACs compared to vitamin-K antagonists in NVAF patients with renal dysfunction in real life setting. In addition, the majority of real-world studies investigated the outcomes ischemic stroke with or without systemic embolism and different definitions of bleeding events, e.g. major bleeding, gastrointestinal bleeding etc. However, the severity of IS and fatal bleedings across different NOACs versus vitamin-K antagonists has only rarely been studied until now. Similarly, data on safety and effectiveness of NOACs and vitamin-K antagonists used in subgroups that are often affected by NAVF and related sequelae such as frail patients is scarce.
Research question and objectives	The primary objectives of this study are: • To describe the risk of ischemic stroke (IS)/ systemic embolism (SE) and intracranial hemorrhage (ICH) in patients with non-valvular atrial fibrillation (NVAF) and renal impairment initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon The secondary objectives of this study are: • To describe the risk of ischemic stroke (IS)/ systemic embolism (SE) and intracranial hemorrhage (ICH) in patients with non-valvular atrial fibrillation (NVAF) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to

	phenprocoumon • To describe the risk of IS, SE, kidney failure, acute kidney injury (AKI), fatal bleeding, recurrent hospitalization, recurrent IS/SE, severe IS as well as to describe treatment persistence in patients with NVAF (overall population as well as in specific subpopulations of interest) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon Other objectives of this study are: • To describe the risk of IS/ SE, severe IS, fatal bleeding and ICH as combined effectiveness outcome in patients with NVAF (overall population as well as in specific subpopulations of interest) initiating treatment with reduced dose of individual NOACs (rivaroxaban, apixaban, edoxaban) compared to standard dose in a subpopulation of patients without renal impairment
Study design	Non-interventional cohort study based between January 2012 and December 2017. The enrollment period will be from 01 January 2013 to 30 June 2017. Data from 1 July to 31 December 2017 will be considered as follow-up only to allow a follow-up of at least 6 months.
Population	The source population of this study will include all insured members of approximately 64 German statutory health insurances (SHIs) contributing data to the InGef database. Patients must meet all of the following inclusion criteria to be eligible for the study: (i) first NOAC (rivaroxaban, apixaban, edoxaban) or phenprocoumon prescription (index drug) in the enrollment period between 1st January 2013 to 30th June 2017 (index date), (ii) age of at least 18 years at index date, (iii) continuous enrollment in the 12 months before the index date (baseline period) and (iv) a verified ambulatory or primary/ secondary hospital discharge diagnosis of NVAF in the previous or same quarter of the index date. Patients meeting any of the following exclusion criteria will be excluded from the analysis: • A verified ambulatory or primary/ secondary hospital discharge diagnosis of valvular atrial fibrillation, indicating pregnancy, transient cause of atrial fibrillation or venous thromboembolism (VTE). • A claim for hip or knee replacement surgery in the 60 days

	prior to or on the index date in the baseline period; • A prescription of heparin or fondaparinux in the 60 days prior to or on the index date; • A prescription of more than one oral anticoagulant (rivaroxaban, apixaban, edoxaban or phenprocoumon) on the index date; • A prescription of warfarin in the baseline period or on the index date; • A verified ambulatory or primary/ secondary hospital discharge diagnosis of end-stage kidney disease or a claim for dialysis in the baseline period; • Patients receiving an initial dose of rivaroxaban 10 mg/ 2.5 mg or edoxaban 15 mg (these dosages are not indicated for the treatment of NVAF).
Variables	As exposure, we will assess prescriptions of phenprocoumon and NOACs, i.e. rivaroxaban (15 mg or 20 mg once daily), apixaban (2.5 mg or 5 mg twice daily), edoxaban (30 mg or 60 mg once daily). As effectiveness outcomes, IS/SE (as combined endpoint and alone), recurrent IS/SE (as combined endpoint) and severe IS will be analyzed while safety outcomes include ICH, fatal bleeding, recurrent hospitalization, kidney failure and AKI. Covariates will include demographic and clinical characteristics will be assessed based on primary and secondary hospital diagnoses and verified ambulatory diagnoses (ICD-10 GM codes), OPS codes, EBM codes and ATC codes
Data sources	This study will be conducted based on the InGef (former HRI) database which is an anonymized healthcare claims database with longitudinal data from approx. 6.7 million Germans insured in one of approx. 64 German SHIs currently contributing data to the database (mainly company or guild health insurances).
Study size	Based on previous studies, we estimate a sample size of approximately 90,000 new users of oral anticoagulants (16,800 apixaban, 1,600 edoxaban, 30,200 rivaroxaban and 35,400 phenprocoumon) with NVAF between 1st January 2013 to 30th June 2017
Data analysis	Analyses will be conducted in line with good statistical practices. Models will use confounding factors to adjust for group differences. However, unmeasured confounding and resulting confounding bias affecting point estimates, confidence intervals and any p-values in the treatment group comparisons may remain. P-values and related confidence intervals must not be interpreted as confirmatory.

	In a first step, Cox proportional hazards regression models will be applied in in each treatment group compared to phenprocoumon (reference) to estimate crude and confounder adjusted hazard ratios (HRs) of the above mentioned outcomes as well as treatment discontinuation with accompanying 95% confidence intervals and *p*-values. In the analysis of reduced vs. standard dose of NOACs, the standard dose will be used as reference. Kaplan-Meier cumulative incidence plots will be generated to characterize risk of outcome events of interest over time. In a second step, we will use the stabilized inverse probability of treatment weighting (IPTW) approach based on the propensity score to adjust for potential confounding resulting from imbalances in the baseline characteristics of different treatment groups. In a third step, we will additionally conduct a propensity score matched analyses for each comparison. A 1:1 matching will be performed using the nearest-neighbor approach with a caliper of 0.2 without replacement. Again, the balance of patient characteristics between treatment groups will be checked in analogy to the description above.
Milestones	Start of data collection: 15 June 2018 End of data collection: 31 Oct 2018 Registration in the EU PAS register: 05 June 2018. Final report of study results: 31 Dec 2018

5. Amendments

None.

6. Milestones

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation, data release and analysis do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are kept as stand-alone document (Table 3, Annex 1) that is available upon request.

Table 1: Milestones

Milestone	**Planned date**
Start of data collection	15 June 2018
End of data collection	31 Oct 2018
Registration in the EU PAS register	05 June 2018
Final report of study results	31 Dec 2018

7. Rationale and background

Non-valvular atrial fibrillation (NVAF) is the most common cardiac arrhythmia, with a prevalence of 1-2% in the general population. NVAF prevalence increases with age and is a major risk factor for stroke and death. NVAF confers a 5-fold risk of stroke compared to patients without NVAF patients (1,2). The appropriate and timely use of anticoagulant therapy for patients at risk of stroke is one of the core principles of modern NVAF management. Vitamin-K antagonists (VKA) have long been the standard of care of patients with NVAF. However, narrow therapeutic control, high inter and intrapersonal variation of VKA exposure, multiple drug und food interactions, the need of extensive monitoring, and the associated risk of bleeding limit their use in practice. Rivaroxaban (Xarelto®) is a Factor Xa inhibitor which is marketed for stroke prevention in patients with NVAF. The clinical phase III study ROCKET-AF has shown that rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism. However, all relevant efficacy endpoints showed a trend towards better efficacy (partly significant) of rivaroxaban compared to VKA in the on-treatment analysis. Regarding safety, a significant reduction in intracranial hemorrhage (ICH) was demonstrated in ROCKET-AF.

Supplementary to randomized controlled trials, generation of real-world evidence is of importance in reinforcing safety perceptions and gaining knowledge on differences between treatments used in routine clinical practice. Available real world studies investigated effectiveness and safety of non-vitamin-K oral anticoagulants (NOACs) irrespective of dose prescribed dealing partly with the drugs' off-label use, or focused not only on renal impairment but required a combination of that condition with other phenotypes. Failure to reduce the NOAC dose for NVAF patients with severe

kidney disease may increase bleeding risk, whereas off-label dose reduction may decrease the effectiveness of these drugs (3).

Existing real-world studies have provided evidence that NOACs in general and rivaroxaban in particular are more effective and at least as safe as warfarin in NVAF patients with renal impairment (4,5) Nevertheless, it is known that clinicians often hesitate to prescribe NOACs to patients with even moderate renal impairment. Therefore, it is important to investigate effectiveness and safety of the reduced dose rivaroxaban and other NOACs compared to vitamin-k antagonists in NVAF patients with renal dysfunction in real life setting.

The RELOAD study being conducted in 2017 was the largest database study of its kind to date in Germany and contributes to understanding of the real-world use of rivaroxaban in patients with NVAF. A subgroup analysis was conducted comparing the use of rivaroxaban and phenprocoumon in patients with NVAF and renal impairment. Although patient numbers in this subgroup were low, the results of this analysis were generally consistent with the trends observed in the main RELOAD analysis, showing evidence for the improved effectiveness and safety of rivaroxaban versus phenprocoumon in this patient population.

Description	Rivaroxaban 15 mg (n=2786)				Phenprocoumon (n=9871)				HR (95% CI)	HR (95% CI)	*p*-value
	Events, n	Days of follow-up Mean	Days of follow-up Median	Events/ 100 PY	Events, n	Days of follow-up Mean	Days of follow-up Median	Events/ 100 PY			
Exposure time estimated with 'one tablet per day' definition											
Ischaemic stroke (effectiveness)	90	347.27	238.5	3.40	201	219.56	148	3.39		0.84 (0.64–1.10)	0.21
ICH (safety)	21	354.76	247	0.78	59	220.82	149	0.99		0.61 (0.35–1.06)	0.08
Combined endpoint	108	346.96	238	4.08	255	219.21	148	4.31		0.78 (0.61–1.00)	0.05
Exposure time estimated with eDDD definition											
Ischaemic stroke (effectiveness)	90	347.27	238.5	3.4	276	415.4	308	2.46		1.02 (0.79–1.31)	0.91
ICH (safety)	21	354.76	247	0.78	98	420.54	312	0.86		0.64 (0.39–1.04)	0.074
Combined endpoint	108	346.96	238	4.08	357	414.5	306.62	3.19		0.93 (0.74–1.17)	0.54

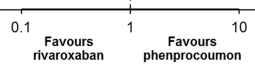

Figure 1 Multivariate regression analyses of the primary effectiveness and safety outcomes in patients with NVAF and renal impairment receiving rivaroxaban 15 mg od versus those receiving phenprocoumon (presented at ISPOR EU 2017)

CI, confidential interval; eDDD, empirical defined daily dose; HR, hazard ratio; ICH, intracranial haemorrhage; NVAF, non-valvular atrial fibrillation; od, once daily; PY, person years.

A recent publication by Hohnloser et al. (6) utilizing the same German data source provided insights into outcomes of all NOACs, compared to phenprocoumon. All three NOACs tested had significantly lower risks of stroke/SE compared with phenprocoumon (apixaban—HR: 0.77, 95% CI: 0.66–0.90; dabigatran—HR: 0.74, 95% CI: 0.60–0.91; rivaroxaban—HR: 0.86, 95% CI: 0.76–0.97). Apixaban (HR: 0.58, 95% CI: 0.49–0.69) and dabigatran (HR: 0.64, 95% CI: 0.50–0.80) were associated with lower bleeding risks than phenprocoumon, whereas the risk was similar for rivaroxaban and phenprocoumon. All three NOACs showed a reduced risk of (ICH) compared with

phenprocoumon. Unfortunately, important subgroups and subpopulations were not included in these analyses.

In addition, the majority of real-world studies investigated the outcomes IS with or without SE and different definitions of bleeding events, e.g. major bleeding, gastrointestinal bleeding etc. However, the severity of IS and fatal bleedings across different NOACs versus phenprocoumon has only rarely been studied until now. Similarly, data on safety and effectiveness of NOACs and phenprocoumon used in subgroups that are often affected by NVAF and related sequelae such as frail patients is scarce. The topic of renal function while an anticoagulation therapy is indicated has also only be studied rarely. Recent US data (7) showed that renal function decline is common among patients with NVAF treated with oral anticoagulant agents. NOACs, particularly rivaroxaban, may be associated with lower risks of adverse renal outcomes than warfarin. So far, German data are not yet available on this topic.

The increasing number of patients using NOACs in Germany over the last year, now allows addressing more detailed research questions including rare event endpoints as well as the to look into specific subgroups and subpopulations for analyses using claims databases.

8. Research questions and objectives

8.1 Primary objective

The primary objectives of this study are:

- To describe the risk of ischemic stroke (IS) and systemic embolism (SE) as combined effectiveness outcome in patients with NVAF and renal impairment initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon
- To describe the risk of intracranial hemorrhage (ICH) as safety outcome in patients with NVAF and renal impairment initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon

8.2 Secondary objectives

The secondary objectives of this study are:

- To describe the risk of ischemic stroke (IS) and systemic embolism (SE) as combined effectiveness outcome in the overall population of patients with NVAF initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon
- To describe the risk of intracranial hemorrhage (ICH) as safety outcome in the overall population of patients with NVAF initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon
- To describe the risk of IS as effectiveness outcome in patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon
- To describe the risk of SE as effectiveness outcome in patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon

- To describe the risk of kidney failure as safety outcome in patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon
- To describe the risk of acute kidney injury (AKI) as safety outcome in patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon
- To describe the risk of fatal bleeding as safety outcome in patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon
- To describe the risk of recurrent hospitalization for any reason as safety outcome in patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon
- To describe the risk of recurrent IS/SE as combined effectiveness outcome patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon
- To describe the risk of severe IS as effectiveness outcome patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon
- To describe the treatment persistence in patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon

8.3 Other objectives

Other objectives of this study are:

- To describe the risk of IS/ SE as combined effectiveness outcome in patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with reduced dose of individual NOACs (rivaroxaban, apixaban, edoxaban) compared to standard dose in a subpopulation of patients without renal impairment
- To describe the risk of severe IS in patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with reduced dose of individual NOACs (rivaroxaban, apixaban, edoxaban) compared to standard dose in a subpopulation of patients without renal impairment
- To describe the risk of fatal bleedings in patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with reduced dose of individual NOACs (rivaroxaban, apixaban, edoxaban) compared to standard dose in a subpopulation of patients without renal impairment
- To describe the risk of intracranial hemorrhage (ICH) in patients with NVAF (overall population as well as patients with renal impairment) initiating treatment with reduced dose of individual NOACs (rivaroxaban, apixaban, edoxaban) compared to standard dose in a subpopulation of patients without renal impairment

9. Research methods

9.1 Study design

We will conduct a non-interventional retrospective cohort study based on German claims data from the InGef (Institute for Applied Healthcare Research Berlin) research database between January 2012 and December 2017. Data from 2012 will only be used for the assessment of demographic and clinical characteristics and to identify new users of NOACs and phenprocoumon. The enrollment period will be from 01 January 2013 to 30 June 2017. Data from 1 July to 31 December 2017 will considered as follow-up only to allow a follow-up of at least 6 months.

9.2 Setting

9.2.1 Study population and selection criteria

The source population of this study will include all insured members of approximately 64 German statutory health insurances (SHIs) contributing data to the InGef database.

9.2.2 Inclusion criteria

Patients must meet all of the following inclusion criteria (see Annex 3: Additional information for detailed operationalization) to be eligible for the study (a detailed definition:

- Patients with a first NOAC (rivaroxaban, apixaban, edoxaban) or phenprocoumon prescription (index drug) in the enrollment period between 1st January 2013 to 30th June 2017 (index date), i.e. without prior prescription of any NOAC or phenprocoumon in the 12 months before the first prescription in the enrollment period;
- Age of at least 18 years at index date;
- Continuous enrollment in the 12 months before the first NOAC (rivaroxaban, apixaban, edoxaban) or phenprocoumon prescription in the enrollment period (baseline period);
- A verified ambulatory or primary/ secondary hospital discharge diagnosis of NVAF in the 12 months before the first NOAC (rivaroxaban, apixaban, edoxaban) or phenprocoumon prescription in the enrollment period (baseline period);

9.2.3 Exclusion criteria

Patients meeting any of the following exclusion criteria (see Annex 3: Additional information) will be excluded from the analysis:

- A verified ambulatory or primary/ secondary hospital discharge diagnosis of valvular atrial fibrillation in the baseline period;

- A verified ambulatory or primary/ secondary hospital discharge diagnosis indicating pregnancy in the baseline period;
- A verified ambulatory or primary/ secondary hospital discharge diagnosis of a transient cause of atrial fibrillation in the baseline period;
- A verified ambulatory or primary/ secondary hospital discharge diagnosis of venous thromboembolism (VTE) in the previous or same quarter of the index date;
- A claim for hip or knee replacement surgery in the 60 days prior to or on the index date;
- A prescription of heparin or fondaparinux in the 60 days prior to or on the index date;
- A prescription of more than one oral anticoagulant (rivaroxaban, apixaban, edoxaban or phenprocoumon) on the index date;
- A prescription of warfarin or dabigatran in the baseline period or on the index date;
- A verified ambulatory or primary/ secondary hospital discharge diagnosis of end-stage kidney disease or a claim for dialysis in the baseline period;
- Patients receiving an initial dose of rivaroxaban 10 mg/ 2.5 mg or edoxaban 15 mg (these dosages are not indicated for the treatment of NVAF).
- A prescription of contraindicated drug for apixaban or rivaroxaban due to drug interactions (i.e. azole antifungals and HIV protease inhibitors) in the 60 days before or on the index date.

For the main analysis, patients will be followed from the index date until the first diagnosis of the respective outcome event, discontinuation of the index drug, death, end of continuous insurance in the SHI or the end of the study period (31 December 2017), whichever comes first. Patients will be censored in all analyses if they switch to phenprocoumon or another NOAC (including dabigatran), receive a prescription of heparin/ fondaparinux, warfarin, rivaroxaban 10 mg/ 2.5 mg, edoxaban 15mg or a contraindicated drug as defined above. For specific analyses, the end of follow-up may differ as described in 9.3.1.

9.3 Variables

9.3.1 Exposure definition

As exposure, we will assess prescriptions of phenprocoumon and NOACs, i.e. rivaroxaban (15 mg or 20 mg once daily), apixaban (2.5 mg or 5 mg twice daily), edoxaban (30 mg or 60 mg once daily). All prescriptions will be assessed based on the documented dispensation date. A detailed list of products with the corresponding central pharmaceutical number (CPN) of the study drugs is displayed in Annex 3: Additional information.

Each patient will be assigned to one of the four exposure groups based on the index drug: new users of phenprocoumon, rivaroxaban, apixaban or edoxaban.

Exposure time for phenprocoumon and NOACs starts on the index date and will be calculated as the sum of days of supply + a grace period of 14 days (in case of treatment discontinuation). A gap period of 30 days between the estimated end of supply and any following prescription of the index drug is allowed.

Since NOACs are prescribed in a fixed dose, the days of supply corresponds to the number of tablets in a dispensed package for rivaroxaban and edoxaban (used once daily) or half the number of tablets in a package for apixaban (used twice daily).

As of an international normalized ratio (INR) between 2 and 3, phenprocoumon patients are often asked to titrate or change their daily doses. Therefore, the exposure time calculation for phenprocoumon is not straightforward . In an anonymous empirical data collection using phenprocoumon diaries of anticoagulated NVAF patients in the university medical center of Schleswig-Holstein information on phenprocoumon dosing will be collected. The results of this survey will be used to calculate a median daily dose which will then be used as the basis for the phenprocoumon exposure time in this study.

As a sensitivity analysis, to account for the intra- and interpersonal variability of phenprocoumon treatment, a personalized defined daily dose (pDDD) based on the observed phenprocoumon prescriptions for each patient in the InGef database will be calculated. For this purpose, amount of active ingredient (AAI) dispensed to each patient of the phenprocoumon group will be obtained for each prescription. A prescribed personalized daily dose (pPDD) representing the average daily dose taken during follow-up will be computed for each patient i such that:

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

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

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 empirical DDD (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.

The exposure time (ET) corrected from the intra- and interpersonal variability of phenprocoumon treatments can be computed for each patient i as:

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

Patients will be considered as having discontinued treatment with the index drug, if they did not receive a subsequent prescription of the respective drug between the last prescription and a gap period of 30 days.

Patients will be considered as having switched from the index drug to phenprocoumon or another NOAC if they received a prescription of the respective drug during continuous exposure time to the index drug as described above. The date of the first prescription of phenprocoumon or another

NOAC will be defined as the date of treatment switch at which patients will be censored. For the comparison of the effectiveness outcomes in patients receiving reduced vs. standard doses of NOACs (other objectives), patients will also be censored if they switch from reduced to standard dose or vice versa.

9.3.2 Outcomes definition

As effectiveness outcomes, IS/SE (as combined endpoint and alone), recurrent IS/SE (as combined endpoint) and severe IS will be analyzed while safety outcomes include ICH, fatal bleeding, recurrent hospitalization, kidney failure and AKI. All study outcomes except kidney failure, fatal bleeding and hospitalizations will be defined based on primary hospital discharge diagnoses (ICD-10 GM codes) as defined in Annex 3: Additional information. The event date will be set to the admission date of the respective hospitalization.

Severe IS will be defined according to an approach proposed by Schubert et al. (8) as hospitalization with a primary hospital discharge diagnosis of IS in combination with an OPS (Operationen und Prozedurenschlüssel) code indicating one of the following: intubation, mechanical ventilation or percutaneous endoscopic gastronomy(see Annex 3: Additional information). In addition, IS cases will be considered as severe if the patients died during the respective hospitalization defined as documented death as reason for hospital discharge.

Cases of fatal bleeding will be defined as hospitalization with a primary hospital discharge diagnoses for bleeding with documented death as reason for hospital discharge or within 30 days after hospital discharge. The date of death will be set to the date of hospital discharge or date of disenrollment from the SHI, respectively.

Hospitalizations (in general and for IS/SE) will be considered as recurrent event if there was at least one day between hospital discharge date of the prior and the admission date of the respective hospitalization.

Kidney failure will also be assessed in the outpatient setting defined as verified ambulatory diagnosis for renal failure in combination with a claim for dialysis based on OPS codes and EBM (Einheitlicher Bewertungsmaßstab) codes in the same or following quarter (see Annex 3: Additional information). The event date for cases with renal failure in the outpatient setting will be set to the first documented claim for dialysis in the respective quarter.

9.3.3 Covariate definition

All demographic and clinical characteristics will be assessed based on primary and secondary hospital diagnoses and verified ambulatory diagnoses (ICD-10 GM codes), OPS codes, EBM codes and ATC codes as defined in Annex 3: Additional information. Unless otherwise mentioned, all information on covariates will be collected in the baseline period., i.e. in the 365 days prior to the index date). The assessment date for hospital diagnoses will be the admission date of the respective hospitalization and for ambulatory diagnoses the date of the first encounter with the diagnosing physician in the respective quarter (as ambulatory diagnoses are available on a quarterly basis only). Data derived from OPS codes and EBM codes will be assessed on the exact date.

Demographic characteristics

- Gender at index date
- Age at index date
- Age at index date categorized: 18–39, 40–44, 45–49, …, 85-89, 90+ years

Clinical characteristics

- $CHADS_2$ score
- CHA_2DS_2-VASc score
- modified HAS-BLED score (the INR will not be included in the calculation of the score because this information is not available in the InGef database, end-stage renal disease will not be considered as these patients will be excluded from the analysis)
- Comorbidities
    - Alcohol abuse
    - Anemia
    - Aortic plaque
    - Anemia
    - Coronary heart disease
        - Angina pectoris
        - Myocardial infarction
        - Acute ischemic heart diseases
        - Chronic ischemic heart disease
        - Coronary artery bypass graft(s)
        - Percutaneous coronary intervention
    - Dementia
    - Depression
    - Diabetes mellitus
    - Drug abuse
    - Gastric or peptic ulcer disease/diseases of gastrointestinal tract
    - Heart failure
    - History of major bleeding (hospitalization only)
    - Hypertension
    - Hypothyroidism

- Inflammatory bowel disease
- IS or transient ischemic attack
- Other cerebrovascular disease
- Liver disease
- Hyperlipidemia
- Volume depletion
- Other metabolic disorders
- Obesity
- Peripheral arterial disease
- Psychosis
- Pulmonary disease
- Rheumatoid arthritis/collagen vascular disease
- Tobacco abuse
- Other vascular disease
- Malignant cancer (except non-melanoma skin cancer)

- Comedications
  - Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers
  - Antiarrhythmics
  - Antidepressants
  - Antiplatelets
  - Antiulcer drugs (except proton-pump inhibitors)
  - Calcium channel blockers
  - Diabetes drugs
  - Diuretics
  - Erythropoietin-simulating agents
  - Estrogens
  - Lipid modifying agents
  - Non-steroidal anti-inflammatory drugs
  - Proton-pump inhibitors

- Other indicators of overall health status

- Number of hospitalizations
- Number of different medications used (based on 7 digit ATC codes)
- Number of ambulatory physician visits

Others

- Year of cohort entry
- Duration of follow-up in days
- Type of cohort exit (end of study period, switch, discontinuation, death, etc.)

9.3.4 Subpopulations and Subgroups

Subgroups and subpopulation are only build on the basis of conditions already present at index date.

The following subpopulations of special interest will be defined:

- Patients with renal impairment initiating either phenprocoumon or reduced doses of NOACs

Patients with renal impairment will be identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses in the baseline period according to Fleet et al. (9) and Nielsen et al. (4) (see definition of renal impairment as covariate in Annex 3: Additional information).

- Patients with chronic renal disease initiating either phenprocoumon or reduced dose of NOACs

Patients with chronic renal disease will be identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses (ICD 10 GM code N18.3 and N18.4) in the baseline period.

The following subgroups of special interest will be defined. Analyses will be conducted also including a test for effect modification (interaction):

- Frail patients

Frailty can be operationalized in several ways, but is commonly characterized by a set of signs and symptoms in geriatrics and gerontology research. While difficult to assess in administrative claims data, the recently validated claims based Frailty Indicator (10) will be used in this study. This algorithm is
validated using against the frailty phenotype, which is the most widely used instrument for assessing frailty. The frailty cut-off for this study will be 0.25 as the desire is to specifically identify frail individuals.

- Age group (<=79 vs. 80+ years)

Age will be assessed at the index date.

- Renal impairment

Patients with renal impairment will be identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses in the baseline period according to Fleet et al. (9) and Nielsen et al. (4) (see definition of renal impairment as covariate in Annex 3: Additional information).

- Prior IS or SE

Patients with IS, TIA or SE will be identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses in the baseline period according the definition for IS/TIA and SE as covariate (see Annex 3: Additional information).

- Reduced vs. standard dose of NOACs

For each respective NOAC, patients will be classified into reduced and standard dose initiators. Analyses will be conducted comparing reduced dose initiators vs. phenprocoumon and standard dose initiators vs. phenprocoumon.

- Malignant cancer (excl. non-melanoma skin cancer)

Patients with malignant cancer (excl. non-melanoma skin cancer) will be identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses in the baseline period according the definition for malignant cancer as covariate (see Annex 3: Additional information). For the subgroup of patients with cancer, the different underlying cancer-types will additionally be included as covariates in the respective statistical models.

9.4 Data sources

This study will be conducted based on the InGef (former HRI) database which is an anonymized healthcare claims database covering all geographic regions of Germany. It includes longitudinal data from approx. 6.7 million Germans insured in one of approx. 64 German SHIs currently contributing data to the database (mainly company or guild health insurances).

Claims data are transferred directly from health care providers to a specialized data center owned by SHIs, which provides data warehouse and IT services. In the data center (acting as a trust center), data is anonymized before entering the InGef database. Data are anonymized with respect to individual insured members, health care providers (e.g. physicians, practices, hospitals, pharmacies), and the respective SHI. The most important data elements included in the database are displayed in Table 2. The time period covered by the database is limited to a look-back period of 6 years starting with the most current complete year of data (11).

Table 2 Information included in the InGef Database

Demographics	Age
	Gender
	Date of death

	Region for place of living
	Insurance status (e.g. retired, family insurance)
	Date of insurance start and end (observation period)
Outpatient Care	Diagnosis (ICD 10-GM Codes) and quarter in which the diagnosis was documented
	Procedures performed (e.g. laboratory, radiology, echocardiography) (EBM-Codes) and day of performance
	Type of specialist that documented the diagnosis and performed the procedure (e.g. cardiologist, general practitioner)
	Costs of outpatient care
Pharmacy	Drug dispensed by central pharmaceutical number (package level) – this is mapped to ATC codes and DDD's by InGef
	Quantity dispensed
	Day of prescription
	Day of dispensing
	Type of doctor prescribing (e.g. cardiologist, general practitioner)
	Costs of drugs dispensed from SHI perspective (without individual rebates between single sickness funds and pharmaceutical companies)
Hospital care	Main diagnosis (ICD 10-GM Codes) and additional diagnoses
	Performed procedures and surgeries (e.g. pacemaker implant, implantable cardioverter defibrillator
	Date of hospital admission
	Reason for admission (e.g. accident, emergency, normal)
	Date of end of hospital stay
	Reason of end of hospital stay (e.g. death in hospital, normal end)

	DRG-Code
	Type of hospital: psychiatric vs. somatic
Remedies and aids	Type of therapy (e.g. massage, occupational therapy, walker, wheel chair)
	Quantity prescribed
	Type of care provider
	Start date
	End date
	Costs of therapy/aids

9.5 Study size

Based on previous studies, we estimate a sample size of approximately 90,000 new users of oral anticoagulants (16,800 apixaban, 6,800 dabigatran, 1,600 edoxaban, 30,200 rivaroxaban and 35,400 phenprocoumon) with NVAF between 1st January 2013 to 30th June 2017. We used the event rates from a previous study based on the InGef research database (6) to estimate the expected number of ICH and IS/SE as primary study outcomes and the precision of the estimated expected events in users of all study drugs assuming an average follow-up time of 1 year per person. As edoxaban was not included in this study, we assumed the lowest event rate obtained for all NOACs to obtain conservative estimates

Table 3 Expected number of primary outcome events and corresponding precision assuming an average follow-up of one year per patient

Overall		**Intracranial hemorrhage**				**Ischemic stroke/systemic embolism**			
Oral anticoagulant	**Estimated number of drug users**	**Estimated incidence rate**	**Expected events**	**Lower 95%-CI**	**Upper 95%-CI**	**Estimated incidence rate**	**Expected number of events**	**Lower 95%-CI**	**Upper 95%-CI**
Phenprocoumon	35,400	0.007	248	218	279	0.025	885	828	944
Apixaban	16,800	0.004	67	52	84	0.027	454	413	496
Rivaroxaban	30,200	0.005	151	128	176	0.022	664	614	715
Edoxaban	1,600	0.004	6	2	12	0.022	35	24	48

9.6 Data management

Completely anonymized analysis datasets comprising all observations and variables required for the planned analyses will be created from the information contained exclusively within the InGef database. The analytic datasets will be person-level, and will contain variables as specified in 9.3.

It is required that all analyses are conducted on the site of the data provider due to data protection requirements. The central statistical software programs used by InGef to evaluate data are R and SAS Enterprise Guide.

9.7 Data analysis

9.7.1 Descriptive analysis

Descriptive statistics will be generated to summarize the baseline characteristics of the study population. For continuous variables, the mean, median as well as the corresponding standard deviation, upper and lower quartiles and the minimum and maximum will be reported. For categorical variables, absolute counts and proportions of patients with given characteristics will be calculated relative to the total sample size of each treatment group.

The incidence rates of IS/ SE (as combined endpoint), ICH, IS, SE, kidney failure, AKI, fatal bleeding, and severe IS will be reported overall as well as in all subgroups as the number of events per 100 person-years. Corresponding 95%-confidence intervals will be calculated assuming a Poisson distribution.

9.7.2 Main analysis

Analyses will be conducted in line with good statistical practices. Models will use confounding factors to adjust for group differences. However, unmeasured confounding and resulting confounding bias affecting point estimates, confidence intervals and any p-values in the treatment group comparisons may remain.

In a first step, Cox proportional hazards regression models will be applied in in each treatment group compared to phenprocoumon (reference) to estimate crude and confounder adjusted hazard ratios (HRs) of the above mentioned outcomes as well as treatment discontinuation (persistence) with accompanying 95% confidence intervals and *p*-values. Persistence (risk of non-persistence) will also be calculated separately for specific time points of interest (months 3, 6, 9, 12, 18 and 24).
In the analysis of reduced vs. standard dose of NOACs, the standard dose will be used as reference.
Kaplan-Meier cumulative incidence plots will be generated to characterize risk of outcome events of interest over time.

Information on confounding factors which are planned to be included in the models as well as in the estimation of the propensity score can be found in section 9.3.3.

In a second step, we will use the stabilized inverse probability of treatment weighting (IPTW) approach based on the propensity score to adjust for potential confounding resulting from imbalances in the baseline characteristics of different treatment groups. The objective of IPTW

based analysis is to create a weighted sample, for which the distribution of possible confounding variables is approximately the same between comparison groups (12,13). The propensity score is defined as the patient's probability to receive a treatment under investigation (i.e. phenprocoumon for main analyses and standard dose for the analyses of reduced vs. standard dose of NOACs) given a set of known patient's baseline characteristics. Propensity scores will be calculated using multiple logistic regression on a relevant set of patient characteristics listed in section 9.3.1 for each 1:1 comparison separately, e.g. rivaroxaban vs. phenprocoumon, rivaroxaban 15 mg vs. rivaroxaban 20 mg etc.

Let Z be an indicator variable relating to the treatment received by a patient, $Z = 1$ for an active treatment (e.g. rivaroxaban), $Z = 0$ for a control treatment (warfarin), and let X denote a vector of observed patient baseline characteristics. Then the propensity score is $e = P(Z = 1 \mid X)$. The inverse probability of treatment weight is defined as $w = \frac{Z}{e} + \frac{1-Z}{1-e}$, i.e.

$w = \frac{1}{e}$ for patients receiving the active treatment, and

$w = \frac{1}{1-e}$ for patients receiving the control treatment.

Weighting by the inverse probability of treatment results in an artificial population or synthetic sample, in which treatment assignment is independent of measured baseline characteristics. Of note, a very low propensity score of subjects receiving an active treatment, or a propensity score close to 1 of subjects receiving a control treatment result in large weights. Such weights increase the variability of the estimated treatment effect (12). Moreover, it is known that the sample size of the synthetic sample is always greater that the sample size of the original data. Consequently, regression estimates with IPTW tend to have smaller confidence intervals because of the inflated sample sizes. In our analysis we will use IPTW with stabilized weights (12,13) which ensure more robust effect estimates. The stabilized weight is defined as $sw = \frac{P(Z=1)*Z}{e} + \frac{(1-P(Z=1))*(1-Z)}{1-e}$. The use of stabilized weights in the synthetic data preserves the sample size of the original data set (12).
The application of propensity score methods via stabilized weights requires overlap of the propensity score distribution in the active and control treatment group. Therefore distributions of propensity scores will be inspected for original data and the synthetic sample. Furthermore, the distribution of stabilized weights in the original data will be examined to determine, if large weights remain after stabilization of weights. By applying IPTW method using the propensity score assessment needs to be done, whether weighting procedure succeeded to balance patient characteristics between treatment groups. The distributions of propensity scores and stabilized weights will be inspected for original data and the synthetic sample. The balance of patient characteristics between treatment groups will be checked by using standardized mean differences (SMD). An absolute SMD of 0.1 or less will be considered as a negligible difference between groups. For continuous variables, the SMD is calculated via

$$SMD_{cont} = \frac{\overline{X_T} - \overline{X_C}}{\sqrt{\frac{S_T^2 + S_C^2}{2}}},$$

Where $\overline{X_T}, S_T^2$ and $\overline{X_C}, S_C^2$ denote the weighted sample mean and weighted sample variance of the variable in the treated and control patients, respectively. For binary variables, the SMD is calculated by

$$SMD_{cat} = \frac{100(P_T - P_C)}{\sqrt{(P_T(1-P_T) + P_C(1-P_C))/2}},$$

Where P_T and P_C denote the weighted sample prevalence of the variable in the treated and control patients, respectively.

In a third step, we will additionally conduct a propensity score matched analyses for each comparison. A 1:1 matching will be performed using the nearest-neighbor approach with a caliper of 0.2 without replacement. Again, the balance of patient characteristics between treatment groups will be checked in analogy to the description above.

For the analysis of IS /SE as combined endpoint and ICH (primary objectives) as well as for the comparison of reduced vs. standard dose of NOACs (other objectives) all three approaches will be used, i.e. Cox proportional hazards regression models, IPTW and propensity-score matching. For all other analyses (secondary objectives) only Cox proportional hazards regression models and IPTW will be applied.

To describe the risk of recurrent hospitalizations and IS/ SE, the following analyses will be conducted. Analyses of recurrent events will be conducted for the unadjusted, matched as well as IPTW populations:

1) Mean cumulative function (MCF)

An important quantity is the mean number of recurrent events per subject by a certain time, i.e. the mean cumulative function (MCF) which is defined as

$$\mu(t) = E\big(N(t)\big).$$

The MCF is a marginal quantity, i.e. independent of the history of the event process. The common Nelson-Aalen estimator for survival analysis can be used as a non-parametric estimator for the MCF under the assumption of independent censoring, i.e. patients remaining are representative of the population.

Let $Y_i(t)$ indicate whether patient $i = 1, \dots, m$ is "at risk" for an event at time t and $Y_\Sigma(t) = \sum_{i=1}^{m} Y_i(t)$ the total number of patients at risk at time t. With $dN_\Sigma(t) = \sum_{i=1}^{m} Y_i(t) dN_i(t)$ being the total number of events at time t and H distinct event times across all m patients denoted as $t_1 \leq \cdots \leq t_H$ the Nelson-Aalen estimator is given as

$\hat{\mu}(t) = \sum_{h:t_h \leq t} \frac{dN_\Sigma(t_h)}{Y_\Sigma(t_h)}$.

In SAS the Nelson-Aalen estimator for the MCF can be calculated by means of the PHREG procedure. The following code plots the estimated MCFs of several treatment groups in one graph:

```
PROC PHREG DATA=dataset PLOTS(OVERLAY=ROW)=MCF;
     MODEL (TStart,TStop) * Status(0)= ;
     * start/stop time of inter-event times and censoring
       identifier;
     STRATA trt; * treatment group identifier;
RUN;
```

2) Andersen-Gill Model (AG) with robust standard errors (Wei Lin Weissfeld Model)

The Wei Lin Weissfeld (WLW) model models the total time from randomization to 1st, 2nd, 3rd, …, k-th event. Before applying the WLW model one has to pre-specify the maximum number of events k one wants to analyze. Therefore, one has to arrange the data in the right structure (a semi-restricted risk set) and also make sure to create 'dummy' events for patients with fewer than the maximal number of events k.

Semi-restricted risk sets

Semi-restricted risk sets have event-specific baseline hazards but allow subjects who have less than (k-1) events to be at risk for the k-th event through the creation of 'dummy' risk intervals. Thus a subject who has had none or one event can be considered at risk of a fourth event. However, a semi-restricted risk set does not allow information from the k-th event risk interval to contribute to the risk set for an earlier event. This risk set only applies to the total time and counting process formulation with event-specific baseline hazards.

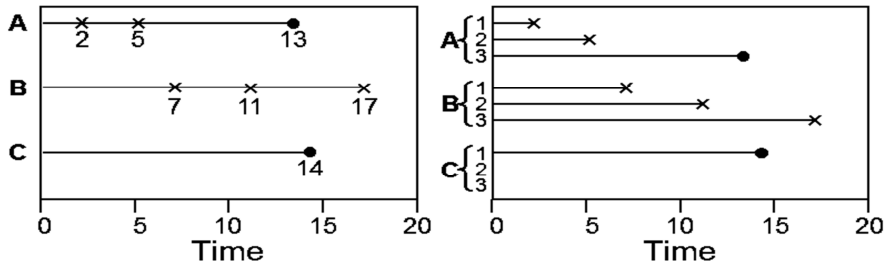

Figure 2 Hypothetical example with total time risk intervals

ID	time	num	event	total		cp	
				start	stop	start	stop
A	2	1	1	0	2	0	2
A	5	2	1	0	5	2	5
A	13	3	0	0	13	5	13
B	7	1	1	0	7	0	7
B	11	2	1	0	11	7	11
B	17	3	1	0	17	11	17
C	14	1	0	0	14	0	14
C	14	2	0	0	14	0	14
C	14	3	0	0	14	0	14

Figure 3 Semi-restricted risk sets in dataset representation

For example, in total time subject B is included with the second event time and subject C is included with a 'dummy' risk interval in the risk set for the second event of subject A (Figure 1). In the example above the maximum number of events per patient is three (for subject B). Accordingly, two dummy risk intervals need to be included for subject C for 'dummy' event number two and three. This results in a dataset as displayed in Figure 2.

One treatment effect estimate, which can be seen as an 'average effect' will be obtained. This average effect, however, is difficult to interpret, as for example the effect on the second event already includes the effect on the first event. Averaging the WLW treatment effects for first and second event would thus seem to double-count the effect on the first event.

Therefore, it is generally more advisable to obtain event-specific estimates by means of specifying interactions in the PROC PHREG call routine, i.e. treatment by event number. The following code gives an example of this for $k = 3$.

```
PROC PHREG DATA=<dataset> COVSANDWICH(AGGREGATE);
     MODEL totstop*event(0) = treat1 treat2 treat3;
     treat1 = treat*(num=1);
     treat2 = treat*(num=2);
     treat3 = treat*(num=3);
     STRATA num;
     ID pid;
RUN;
```

The event-specific estimate for the first event then coincides with the estimate of the Cox proportional hazards model for time-to-first event.

The distinctive feature of the WLW model is that each individual's time at risk for each event is considered to study entry, so that study entry is 'preserved' for all event-specific analyses.

9.7.3 Sensitivity analysis

We will conduct three pre-defined sensitivity analyses to prove the consistency of our results. First, we will repeat the Cox regression analysis for IS/ SE as combined endpoint and ICH (primary objectives) as well as for the analysis of treatment discontinuation allowing for stockpiling of phenprocoumon and NOACs, i.e. if a prescription of the index drug is refilled before the estimated end of supply, the remaining supply of the prescription will be added to following prescription. Second, we will perform the Cox regression analysis for the outcomes ICH, IS, SE, severe IS, kidney failure, AKI and fatal bleeding excluding patients with a prior outcome event in the baseline period, i.e. major bleeding for ICH and fatal bleeding, IS or SE for IS and severe IS, SE (see covariate definition in Annex 3: Additional information). Third, we will repeat the Cox regression analysis for IS/ SE as combined endpoint and ICH analyses using the pDDD to calculate the supply for phenprocoumon as defined in section 9.3.1.

No actions will be taken to deal with missing data, since data from all dimensions is assumed to be complete.

All analysis will be performed using SAS Enterprise guide version 7.1 or R.

The statistical concept of the study described above will be supplemented by the more detailed statistical analysis plan.

9.8 Quality control

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

Data quality management is built in to the core processing systems. In addition SAS/R 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:
- Quality control processes around reference data.
- Rules for raw data checks for completeness reasonability and volume
- Control processes for production files and outputs.
- Process flow and maintenance processes including standard operating procedures.
- Database metrics including quality and completeness
- 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:

- File Completeness Check
- File format versus the predefined standard
- Data content – are all fields present with corresponding values?

Data-processing checks include:

- Control for correctness of the format and any input files format transformations
- Control of correctness of the bridged data

Processed-data checks include:

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

Data quality management is built in to the core processing systems, however, SAS/R 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:

- Rules for raw data checks for completeness reasonability and volume
- Control processes for production files and outputs.
- Process flow and maintenance processes including standard operating procedures.
- Database metrics including quality and completeness
- 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:

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

9.9 Limitations of the research methods

Although the analysis dataset obtained from the InGef database covers more than 6 million insured members of SHIs all over Germany, representativeness for all phenprocoumon and NOAC users in Germany cannot be guaranteed if differences exist for instance by socioeconomic status or region. However, this will not affect the internal validity of the study results as the objectives of the study are related to relative risks rather than absolute risk estimates. Representativeness of the underlying data is therefore not a requirement.

As our study does not include a review of individual patient files to confirm the occurrence of individual outcomes such as IS and ICH, which for data protection reasons is generally not feasible, case validation is not possible and outcome misclassification cannot be ruled out. Therefore, only primary hospital diagnoses will be used to identify effectiveness and study outcomes to minimize the amount of false-positive case.

The recurrent event analysis for hospitalizations can only take into account those events which are recorded in the claims database. Therefore, patients could have deceased before any hospitalization.

Since no laboratory data and detailed clinical information are available in the InGef database, patients with an estimated glomerular filtration rate of 15-49 mL/min/1.73m^2, i.e. with an indication for the reduced dose of rivaroxaban, cannot be identified exactly.

With regard to drug usage, it has to be noted that the dispensation the respective drug does not necessarily imply that the patient actually took the medication. Therefore, exposure misclassification is generally possible; however, in case of continuous drug dispensations to the same patient the amount of misclassification is expected to be low.

In addition, unmeasured or residual confounding may affect the study results because several factors associated with the study outcomes cannot be measured adequately in claims data, e.g. laboratory values, physical activity, smoking. laboratory values and over the counter medications such as aspirin.

Patient populations underlying the common comparator can be different in every comparison planned, so that indirect comparisons of individual NOACs via the common comparator cannot be made.

9.10 Other aspects

Not applicable.

10. Protection of human subjects

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. Since this study is based on anonymized claims data, informed consent of the patient is not required.

11. Management and reporting of adverse events/adverse reactions

For non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. Reports of adverse events/reactions will be summarized in the study report, where applicable.

12. Plans for disseminating and communicating study results

The results of this study will be summarized in a study report. It further planned to submit at least one publication based on the results of this study to an international peer-reviewed journal.

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Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)*
SAP	tbd

* Draft versions are indicated by <draft> in brackets and date. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Please check for the current version of the ENCePP checklist for study protocols at http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml.

Annex 3: Additional information

Section 9.2.2. Inclusion criteria

- NVAF:

  ICD-10 GM Codes: I48.0, I48.1, I48.2, I48.9

Section 9.2.3. Exclusion criteria

- Valvular atrial fibrillation:

  ICD-10 GM: I05 – I08, I09.1, I09.9, I34 – I39, Q23.0 – Q23.3, Z95.2 – Z95.4
- Pregnancy:

  ICD-10 GM: O00 – O99, Z34 – Z39
- Transient cause of atrial fibrillation

  ICD-10 GM: I97.0, I97.1
- VTE (pulmonary embolism or deep vein thrombosis):

  ICD-10 GM: I26, I80, I81, I82.2, I82.9
- Hip or knee replacement:

  OPS: 5820, 5821, 5822, 5823
- Heparin or fondaparinux:

  ATC: B01AB, B01AX05
- Warfarin

  ATC: B01AA03
- Dabigatran

  ATC: B01AE07
- Azole antifungals

  ATC: J02AB, J02AC
- HIV protease inhibitors

  ATC: J05AE
- End-stage kidney disease or dialysis

ICD-10 GM: N18.5, Z49, Z94.0 OR

OPS: 8853, 8854, 8855, 8857 OR

EBM: (**valid from until Q4 2012**) 40800, 40801, 40802, 40803, 40805,40806, 40807, 40808, 40810, 40811, 40812, 40813; 40820, 40821, 40822, (**valid from Q1 2013 onwards**) 13602, 13610,

13611, 40815, 40816, 40817, 40818, 40819,40823, 40824, 40825, 40826, 40827, 40828, 40829, 40830, 40831, 40832, 40833, 40834, 40835, 40836, 40837, 40838

- NOAC dosages not approved for use in NVAF:

ATC Code	**NOAC**	**CPN**	**Name**
B01AF01	Rivaroxaban	05459513	Xarelto 10 mg Eurim
B01AF01	Rivaroxaban	05748766	Xarelto 10 mg Kohl Ph.
B01AF01	Rivaroxaban	05995074	Xarelto 10 mg
B01AF01	Rivaroxaban	05995080	Xarelto 10 mg
B01AF01	Rivaroxaban	05995097	Xarelto 10mg
B01AF01	Rivaroxaban	06410420	Xarelto 10 mg CC Ph.
B01AF01	Rivaroxaban	06454481	Xarelto 10 mg Westen Ph.
B01AF01	Rivaroxaban	07536850	Xarelto 10 mg
B01AF01	Rivaroxaban	07536927	Xarelto 10 mg
B01AF01	Rivaroxaban	07572633	Xarelto 10 mg Gerke Ph.
B01AF01	Rivaroxaban	07572662	Xarelto 10 mg Gerke Ph.
B01AF01	Rivaroxaban	07610606	Xarelto 10 mg Kohl Ph.
B01AF01	Rivaroxaban	07799012	Xarelto 10 mg Emra
B01AF01	Rivaroxaban	07799029	Xarelto 10 mg Emra
B01AF01	Rivaroxaban	08461261	Xarelto 2,5 mg Filmtabletten
B01AF01	Rivaroxaban	08461290	Xarelto 2,5 mg Filmtabletten 1x10x10
B01AF01	Rivaroxaban	08717186	Xarelto 2,5 mg Filmtabletten
B01AF01	Rivaroxaban	09154791	Xarelto 10 mg
B01AF01	Rivaroxaban	09647915	Xarelto 2,5 mg Filmtabletten
B01AF01	Rivaroxaban	09676408	Xarelto 2,5 mg Filmtabletten
B01AF01	Rivaroxaban	09721534	Xarelto 10 mg CC Ph.

B01AF01	Rivaroxaban	09777888	Xarelto 10 mg Haemato-Ph.
B01AF01	Rivaroxaban	09941276	Xarelto 10 mg
B01AF01	Rivaroxaban	10339455	Xarelto 10 mg Docpharm
B01AF01	Rivaroxaban	10381894	Xarelto 10 mg Milinda
B01AF01	Rivaroxaban	10381902	Xarelto 10 mg Milinda
B01AF01	Rivaroxaban	10402662	Xarelto 10 mg Axicorp Pharma
B01AF01	Rivaroxaban	10743771	Xarelto 10 mg Docpharm
B01AF01	Rivaroxaban	10764520	Xarelto 10 mg Orifarm
B01AF01	Rivaroxaban	10852626	Xarelto 10 mg Beragena
B01AF01	Rivaroxaban	10852632	Xarelto 10 mg Beragena
B01AF01	Rivaroxaban	11565001	Xarelto 10 mg Mevita
B01AF01	Rivaroxaban	11617270	Xarelto 10 mg Abacus
B01AF01	Rivaroxaban	11898174	Xarelto 10 mg Filmtabletten
B01AF01	Rivaroxaban	12407801	Xarelto 15 mg + 20 mg Starterpackung
B01AF01	Rivaroxaban	12590136	Xarelto 2,5 mg Filmtabletten
B01AF03	Edoxaban	10713994	Lixiana 15 mg Filmtabletten
B01AF03	Edoxaban	10714002	Lixiana 15 mg Filmtabletten

Section 9.3.1. Exposure definition

- Study drugs with categorization into standard vs. reduced dose:

ATC Code	**Drug**	**CPN**	**Name**	**Dose**
B01AA04	Phenprocoumon	00972890	Falithrom 1,5 mite	N/A
B01AA04	Phenprocoumon	00972915	Falithrom 1,5 mite	N/A
B01AA04	Phenprocoumon	01300649	Marcumar	N/A
B01AA04	Phenprocoumon	02059517	Phenpro AbZ 3 mg	N/A

B01AA04	Phenprocoumon	02704892	Phenprogamma 3	N/A
B01AA04	Phenprocoumon	02704900	Phenprogamma 3	N/A
B01AA04	Phenprocoumon	02704917	Phenprogamma 3	N/A
B01AA04	Phenprocoumon	03011932	Falithrom	N/A
B01AA04	Phenprocoumon	03352194	MARCOUMAR BERAGENA	N/A
B01AA04	Phenprocoumon	03352202	MARCOUMAR BERAGENA	N/A
B01AA04	Phenprocoumon	03422256	MARCOUMAR OPTI ARZNEI	N/A
B01AA04	Phenprocoumon	03422262	MARCOUMAR OPTI ARZNEI	N/A
B01AA04	Phenprocoumon	04334620	MARCOUMAR EMRA MED	N/A
B01AA04	Phenprocoumon	04334637	MARCOUMAR EMRA MED	N/A
B01AA04	Phenprocoumon	04386479	Marcoumar Gerke Ph.	N/A
B01AA04	Phenprocoumon	04421721	FALITHROM	N/A
B01AA04	Phenprocoumon	04421738	FALITHROM	N/A
B01AA04	Phenprocoumon	04421744	FALITHROM	N/A
B01AA04	Phenprocoumon	04582128	Phenpro.-ratiopharm 3 mg	N/A
B01AA04	Phenprocoumon	04582134	Phenpro.-ratiopharm 3 mg	N/A
B01AA04	Phenprocoumon	04582140	Phenpro.-ratiopharm 3 mg	N/A
B01AA04	Phenprocoumon	04958705	Marcoumar Kohl Ph.	N/A
B01AA04	Phenprocoumon	04958711	Marcoumar Kohl	N/A
B01AA04	Phenprocoumon	05541315	Marcumar	N/A
B01AA04	Phenprocoumon	05541321	Marcumar	N/A
B01AA04	Phenprocoumon	05541338	Marcumar	N/A
B01AA04	Phenprocoumon	06575233	Phenpro.-ratiopharm 3 mg	N/A
B01AA04	Phenprocoumon	06588626	Marcuphen-CT 3 mg	N/A

B01AA04	Phenprocoumon	06811219	Phenpro AbZ 3 mg	N/A
B01AA04	Phenprocoumon	07636008	marcuphen von ct	N/A
B01AA04	Phenprocoumon	07636014	marcuphen von ct	N/A
B01AA04	Phenprocoumon	07636020	marcuphen von ct	N/A
B01AA04	Phenprocoumon	07768135	Marcumar	N/A
B01AA04	Phenprocoumon	07768170	Marcumar	N/A
B01AA04	Phenprocoumon	08874885	Marcumar ACA/ADAG	N/A
B01AA04	Phenprocoumon	08874891	Marcumar ACA/ADAG	N/A
B01AA04	Phenprocoumon	09404207	Phenprogamma 3	N/A
B01AA04	Phenprocoumon	09726170	Marcoumar Eurim	N/A
B01AA04	Phenprocoumon	10269507	Phenprocoumon acis 3 mg	N/A
B01AA04	Phenprocoumon	10269513	Phenprocoumon acis 3 mg	N/A
B01AA04	Phenprocoumon	10269542	Phenprocoumon acis 3 mg	N/A
B01AA04	Phenprocoumon	12345626	Marcuphen AbZ 3 mg Tabletten	N/A
B01AA04	Phenprocoumon	12345655	Marcuphen AbZ 3 mg Tabletten	N/A
B01AA04	Phenprocoumon	12345661	Marcuphen AbZ 3 mg Tabletten	N/A
B01AA04	Phenprocoumon	12345690	Marcuphen AbZ 3 mg Tabletten	N/A
B01AA04	Phenprocoumon	12357664	Phenpro-ratiopharm 3 mg Tabletten	N/A
B01AA04	Phenprocoumon	13631050	Marcoumar ACA/ADAG	N/A
B01AF01	Rivaroxaban	04369423	Xarelto 15 mg Emra	Reduced
B01AF01	Rivaroxaban	04369452	Xarelto 15 mg Emra	Reduced
B01AF01	Rivaroxaban	04369475	Xarelto 15 mg Emra	Reduced
B01AF01	Rivaroxaban	04369481	Xarelto 20 mg Emra	Standard
B01AF01	Rivaroxaban	04369498	Xarelto 20 mg Emra	Standard

B01AF01	Rivaroxaban	07089598	Xarelto 15 mg Westen Ph.	Reduced
B01AF01	Rivaroxaban	07089606	Xarelto 20 mg Westen Ph.	Standard
B01AF01	Rivaroxaban	07605019	Xarelto 15 mg Orifarm	Reduced
B01AF01	Rivaroxaban	07605025	Xarelto 20 mg Orifarm	Standard
B01AF01	Rivaroxaban	08461344	Xarelto 15 mg	Reduced
B01AF01	Rivaroxaban	08461350	Xarelto 15 mg	Reduced
B01AF01	Rivaroxaban	08461367	Xarelto 15 mg	Reduced
B01AF01	Rivaroxaban	08461373	Xarelto 15 mg Filmtabletten	Reduced
B01AF01	Rivaroxaban	08461404	Xarelto 15 mg	Reduced
B01AF01	Rivaroxaban	08461410	Xarelto 20 mg	Standard
B01AF01	Rivaroxaban	08461427	Xarelto 20 mg	Standard
B01AF01	Rivaroxaban	08461433	Xarelto 20 mg	Standard
B01AF01	Rivaroxaban	08461456	Xarelto 20 mg Filmtabletten	Standard
B01AF01	Rivaroxaban	09333393	Xarelto 15 mg	Reduced
B01AF01	Rivaroxaban	09333401	Xarelto 20 mg	Standard
B01AF01	Rivaroxaban	09724515	Xarelto 15 mg CC Ph.	Reduced
B01AF01	Rivaroxaban	09724521	Xarelto 15 mg CC Ph.	Reduced
B01AF01	Rivaroxaban	09724538	Xarelto 15 mg CC Ph.	Reduced
B01AF01	Rivaroxaban	09724544	Xarelto 20 mg CC Ph.	Standard
B01AF01	Rivaroxaban	09724550	Xarelto 20 mg CC Ph.	Standard
B01AF01	Rivaroxaban	09941282	Xarelto 15 mg	Reduced
B01AF01	Rivaroxaban	09941299	Xarelto 20 mg	Standard
B01AF01	Rivaroxaban	10005926	Xarelto 15 mg Kohl Ph.	Reduced
B01AF01	Rivaroxaban	10005932	Xarelto 20 mg Kohl Ph.	Standard

B01AF01	Rivaroxaban	10012139	Xarelto 15 mg Gerke Ph.	Reduced
B01AF01	Rivaroxaban	10012145	Xarelto 15 mg Gerke Ph.	Reduced
B01AF01	Rivaroxaban	10012151	Xarelto 15 mg Gerke Ph.	Reduced
B01AF01	Rivaroxaban	10012168	Xarelto 15 mg Gerke Ph.	Reduced
B01AF01	Rivaroxaban	10012174	Xarelto 20 mg Gerke Ph.	Standard
B01AF01	Rivaroxaban	10012180	Xarelto 20 mg Gerke Ph.	Standard
B01AF01	Rivaroxaban	10012197	Xarelto 20 mg Gerke Ph.	Standard
B01AF01	Rivaroxaban	10057490	Xarelto 20 mg Eurim	Standard
B01AF01	Rivaroxaban	10057509	Xarelto 20 mg Eurim	Standard
B01AF01	Rivaroxaban	10058590	Xarelto 15 mg Eurim	Reduced
B01AF01	Rivaroxaban	10058609	Xarelto 15 mg Eurim	Reduced
B01AF01	Rivaroxaban	10072093	Xarelto 15 mg ACA/ADAG	Reduced
B01AF01	Rivaroxaban	10072101	Xarelto 15 mg ACA/ADAG	Reduced
B01AF01	Rivaroxaban	10072118	Xarelto 20 mg ACA/ADAG	Standard
B01AF01	Rivaroxaban	10072124	Xarelto 20 mg ACA/ADAG	Standard
B01AF01	Rivaroxaban	10101682	Xarelto 15 mg Filmtabletten Axicorp	Reduced
B01AF01	Rivaroxaban	10102144	Xarelto 15 mg Filmtabletten Axicorp	Reduced
B01AF01	Rivaroxaban	10106863	Xarelto 20 mg Filmtabletten Axicorp	Standard
B01AF01	Rivaroxaban	10106886	Xarelto 20 mg Filmtabletten Axicorp	Standard
B01AF01	Rivaroxaban	10106892	Xarelto 20 mg Filmtabletten Axicorp	Standard
B01AF01	Rivaroxaban	10132139	Xarelto 15 mg Filmtabletten Axicorp	Reduced
B01AF01	Rivaroxaban	10200906	Xarelto 15 mg Eurim	Reduced
B01AF01	Rivaroxaban	10200912	Xarelto 15 mg Eurim	Reduced
B01AF01	Rivaroxaban	10200929	Xarelto 20 mg Eurim	Standard

B01AF01	Rivaroxaban	10297679	Xarelto 15 mg CC Ph.	Reduced
B01AF01	Rivaroxaban	10297685	Xarelto 20 mg CC Ph.	Standard
B01AF01	Rivaroxaban	10318631	Xarelto 20 mg Kohl Ph.	Standard
B01AF01	Rivaroxaban	10381919	Xarelto 15 mg Milinda	Reduced
B01AF01	Rivaroxaban	10381925	Xarelto 15 mg Milinda	Reduced
B01AF01	Rivaroxaban	10381931	Xarelto 15 mg Milinda	Reduced
B01AF01	Rivaroxaban	10381948	Xarelto 15 mg Milinda	Reduced
B01AF01	Rivaroxaban	10381954	Xarelto 20 mg Milinda	Standard
B01AF01	Rivaroxaban	10381983	Xarelto 20 mg Milinda	Standard
B01AF01	Rivaroxaban	10382008	Xarelto 20 mg Milinda	Standard
B01AF01	Rivaroxaban	10393638	Xarelto 20 mg Docpharm	Standard
B01AF01	Rivaroxaban	10393644	Xarelto 20 mg Docpharm	Standard
B01AF01	Rivaroxaban	10393650	Xarelto 15 mg Docpharm	Reduced
B01AF01	Rivaroxaban	10393667	Xarelto 15 mg Docpharm	Reduced
B01AF01	Rivaroxaban	10393696	Xarelto 15 mg Docpharm	Reduced
B01AF01	Rivaroxaban	10743794	Xarelto 15 mg FD Pharma	Reduced
B01AF01	Rivaroxaban	10743802	Xarelto 20 mg FD Pharma	Standard
B01AF01	Rivaroxaban	10762403	Xarelto 15 mg Abacus	Reduced
B01AF01	Rivaroxaban	10762426	Xarelto 20 mg Abacus	Standard
B01AF01	Rivaroxaban	10852649	Xarelto 15 mg Beragena	Reduced
B01AF01	Rivaroxaban	10852655	Xarelto 15 mg Beragena	Reduced
B01AF01	Rivaroxaban	10852661	Xarelto 15 mg Beragena	Reduced
B01AF01	Rivaroxaban	10852678	Xarelto 15 mg Beragena	Reduced
B01AF01	Rivaroxaban	10852684	Xarelto 20 mg Beragena	Standard

B01AF01	Rivaroxaban	10852690	Xarelto 20 mg Beragena	Standard
B01AF01	Rivaroxaban	10852709	Xarelto 20 mg Beragena	Standard
B01AF01	Rivaroxaban	10853560	Xarelto 15 mg Kohl Ph.	Reduced
B01AF01	Rivaroxaban	10853577	Xarelto 20 mg Kohl Ph.	Standard
B01AF01	Rivaroxaban	10948970	Xarelto 15 mg Kohl Ph.	Reduced
B01AF01	Rivaroxaban	10948987	Xarelto 15 mg Kohl Ph.	Reduced
B01AF01	Rivaroxaban	10964153	Xarelto 15 mg Orifarm	Reduced
B01AF01	Rivaroxaban	10964176	Xarelto 15 mg Orifarm	Reduced
B01AF01	Rivaroxaban	10964182	Xarelto 20 mg Orifarm	Standard
B01AF01	Rivaroxaban	10999312	Xarelto 15 mg Axicorp	Reduced
B01AF01	Rivaroxaban	10999329	Xarelto 15 mg Axicorp	Reduced
B01AF01	Rivaroxaban	10999335	Xarelto 15 mg Axicorp	Reduced
B01AF01	Rivaroxaban	10999341	Xarelto 20 mg Axicorp	Standard
B01AF01	Rivaroxaban	10999358	Xarelto 20 mg Axicorp	Standard
B01AF01	Rivaroxaban	10999364	Xarelto 20 mg Axicorp	Standard
B01AF01	Rivaroxaban	11015708	Xarelto 15 mg filmtabletten Emra	Reduced
B01AF01	Rivaroxaban	11015714	Xarelto 20 mg Emra	Standard
B01AF01	Rivaroxaban	11096606	Xarelto 15 mg Euro DK	Reduced
B01AF01	Rivaroxaban	11096612	Xarelto 20 mg Euro DK	Standard
B01AF01	Rivaroxaban	11559348	Xarelto 15 mg BB Farma	Reduced
B01AF01	Rivaroxaban	11559354	Xarelto 20 mg BB Farma	Standard
B01AF01	Rivaroxaban	11565018	Xarelto 15 mg Mevita	Reduced
B01AF01	Rivaroxaban	11724729	Xarelto 15 mg Axicorp	Reduced
B01AF01	Rivaroxaban	11864962	Xarelto 15 mg ADL Ph.	Reduced

B01AF01	Rivaroxaban	12645529	Xarelto 20 mg Orifarm	Standard
B01AF01	Rivaroxaban	12645535	Xarelto 20 mg Orifarm	Standard
B01AF01	Rivaroxaban	12868703	Xarelto 20 mg Abacus	Standard
B01AF01	Rivaroxaban	13155164	Xarelto 20 mg ADL Ph.	Standard
B01AF01	Rivaroxaban	13331135	Xarelto 15 mg 2Care	Reduced
B01AF01	Rivaroxaban	13331141	Xarelto 20 mg 2Care	Standard
B01AF01	Rivaroxaban	13502499	Xarelto 15 mg Medico	Reduced
B01AF01	Rivaroxaban	13502507	Xarelto 20 mg Medico	Standard
B01AF01	Rivaroxaban	13711866	Xarelto 15 mg Abacus	Reduced
B01AF01	Rivaroxaban	13721818	Xarelto 15 mg Abacus	Reduced
B01AF01	Rivaroxaban	13721830	Xarelto 20 mg Abacus	Standard
B01AF02	Apixaban	1647755	Eliquis 5 mg	Standard
B01AF02	Apixaban	1647778	Eliquis 5 mg	Standard
B01AF02	Apixaban	1647784	Eliquis 5 mg	Standard
B01AF02	Apixaban	1647809	Eliquis 5 mg	Standard
B01AF02	Apixaban	1647821	Eliquis 5 mg 5x20	Standard
B01AF02	Apixaban	3643804	Eliquis 2,5 mg CC Ph.	Reduced
B01AF02	Apixaban	04700504	Eliquis 2,5 mg Emra	Reduced
B01AF02	Apixaban	04700510	Eliquis 2,5 mg Emra	Reduced
B01AF02	Apixaban	04700527	Eliquis 2,5 mg Emra	Reduced
B01AF02	Apixaban	04712163	Eliquis 2,5 mg Kohl Ph.	Reduced
B01AF02	Apixaban	04712186	Eliquis 2,5 mg Kohl Ph.	Reduced
B01AF02	Apixaban	05117273	Eliquis 5 mg Eurim	Standard
B01AF02	Apixaban	08400012	Eliquis 2,5 mg	Reduced

B01AF02	Apixaban	08400029	Eliquis 2,5 mg	Reduced
B01AF02	Apixaban	08400035	Eliquis 2,5 mg	Reduced
B01AF02	Apixaban	08400041	Eliquis 2,5 mg	Reduced
B01AF02	Apixaban	10218496	Eliquis 5 mg Kohl Ph.	Standard
B01AF02	Apixaban	10232906	Eliquis 5 mg CC Ph.	Standard
B01AF02	Apixaban	10250465	Eliquis 2,5 mg Filmtabletten	Reduced
B01AF02	Apixaban	10273130	Eliquis 5 mg Eurim	Standard
B01AF02	Apixaban	11174884	Eliquis 5 mg Emra	Standard
B01AF02	Apixaban	11341537	Eliquis 2,5 mg Filmtabletten Docpharm	Reduced
B01AF02	Apixaban	11376429	Eliquis 2,5 mg Filmtabletten Milinda	Reduced
B01AF02	Apixaban	11376435	Eliquis 2,5 mg Filmtabletten Milinda	Reduced
B01AF02	Apixaban	11376441	Eliquis 5 mg Filmtabletten Milinda	Standard
B01AF02	Apixaban	11376458	Eliquis 5 mg Filmtabletten Milinda	Standard
B01AF02	Apixaban	11524829	Eliquis 5 mg Axicorp	Standard
B01AF02	Apixaban	11524841	Eliquis 5 mg Axicorp	Standard
B01AF02	Apixaban	13578924	Eliquis 2,5 mg Axicorp	Reduced
B01AF03	Edoxaban	10714031	Lixiana 30 mg Filmtabletten	Reduced
B01AF03	Edoxaban	10714060	Lixiana 30 mg Filmtabletten	Reduced
B01AF03	Edoxaban	10714083	Lixiana 30 mg Filmtabletten	Reduced
B01AF03	Edoxaban	10714143	Lixiana 30 mg Filmtabletten	Reduced
B01AF03	Edoxaban	10714172	Lixiana 60 mg Filmtabletten	Standard
B01AF03	Edoxaban	10714255	Lixiana 60 mg Filmtabletten	Standard
B01AF03	Edoxaban	10714284	Lixiana 60 mg Filmtabletten	Standard
B01AF03	Edoxaban	10714309	Lixiana 60 mg Filmtabletten	Standard

B01AF03	Edoxaban	12749950	Lixiana 30 mg Axicorp	Reduced
B01AF03	Edoxaban	12749967	Lixiana 30 mg Axicorp	Reduced
B01AF03	Edoxaban	12749996	Lixiana 60 mg Axicorp	Standard
B01AF03	Edoxaban	12750002	Lixiana 60 mg Axicorp	Standard
B01AF03	Edoxaban	13695860	Lixiana 30 mg Kohl Ph.	Reduced
B01AF03	Edoxaban	13695877	Lixiana 60 mg Kohl Ph.	Standard

Section 9.3.2. Outcome definition

- Ischemic stroke (IS):

  ICD-GM: I63

- Severe ischemic stroke according to (8):

  ICD-GM: I63 in combination with

  OPS: 870, 871 (intubation/mechanical ventilation), 5431, 8017, 8018, 8123 (percutaneous endoscopic gastrostomy)

- Systemic embolism (SE):

  ICD-GM: I74

- Intracranial hemorrhage (ICH):

  ICD-GM: I60 – I62

- Acute kidney injury (AKI) according to (14):

  ICD-GM: N17

- Kidney failure:

  ICD-GM (hospital): N18.5, Z94.0

  ICD-GM (ambulatory): N18.5, N18.9, N19, Z94.0 in combination with

  OPS: 8853, 8854, 8855, 8857 OR

  EBM: (**valid from Q1 2013 onwards**) 13602, 13610, 13611, 40815, 40816, 40817, 40818, 40819,40823, 40824, 40825, 40826, 40827, 40828, 40829, 40830, 40831, 40832, 40833, 40834, 40835, 40836, 40837, 40838

- Fatal bleeding:

  OPS: 8800

  ICD-GM: D62, H11.3, H21.0, H31.3, H35.6, H43.1, H45.0, H92.2, I32.1, I60, I61, I62, I85.0, J94.2, K22.6, K22.8, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2,

K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K66.1 K92.0, K92.1. K92.2, M25.0, N02, N42.1, N83.6, N85.7, N89.7, N93.0, N93.8, N93.9, N95.0, R04.0, R04.1, R04.2, R04.8, R04.9, R23.3, R31, R58, S06.4, S06.5, S06.6, S06.8

Section 9.3.3. Covariate definition

Operational definition of CHA_2DS_2-VASc Score:

Conditions	ICD-10 GM code	Assigned weights
Hypertension	I10 – I15, I67.4	1
Diabetes mellitus	E10 – E14	1
Heart failure	I11.0, I13.0, I13.2, I25.5, I42, I43, I50, I09.9	1
Age between 65 and 74 years		1
Vascular disease (previous MI, peripheral arterial disease or aortic plaque)	I21 – I23, I25.2, I70.0, I70.2 – I70.9, I71, I73.9	1
Stroke or TIA	G45.0 – G45.2, G45.4 – G45.9, I63, I69.3, I69.4, I64	2
Age ≥ 75 years		2
Female sex		1

Operational definition of $CHADS_2$ Score:

Conditions	ICD-10 GM code	Assigned weights
Hypertension	I10 – I15, I67.4	1
Diabetes mellitus	E10 – E14	1
Heart failure	I11.0, I13.0, I13.2, I25.5, I42, I43, I50, I09.9	1
Stroke or TIA	G45.0 – G45.2, G45.4 – G45.9, I63, I69.3, I69.4, I64	2

Age ≥ 75 years		1

Operational definition of modified HAS-BLED Score:

Criteria	**ICD-10 GM / ATC /OPS code**	**Assigned weights**
Hypertension	I10 – I15, I67.4	1
Liver or renal disease	B18.0, B18.1, B18.2, I85, K70.0, K70.2, K70.3, K70.4, K70.9, K72.1, K73, K74, K75.4, K75.8, K76.0, K76.6, K76.9, Z94.4, D63.1, E10.2, E11.2, E13.2, I12, I13, N02, N03, N04, N05, N07, N08, N14, N18.1-N18.4, N18.9, N19, Q61	1
Stroke history	I63, I69.3, I69.4, I64	1
Major bleeding event	OPS: 8800 ICD-GM: D62, H21.0, H31.3, H35.6, H43.1, H45.0, I32.1, I60 - I62, J94.2, M25.0, S06.4, S06.5, S06.6, S06.8	1
Alcohol abuse	F10	1
Non-steroidal anti-inflammatory drugs or antiplatelet	B01AC, M01A*	1
Age >65		1

Operational definition of claims based frailty indicator (10):

Criteria	**ICD-10 GM / ATC /OPS code**	**Assigned weights**
Impaired mobility	U50, Z99.3	1
Depression	F31, F32 – F34, F39, F43.1, F43.2,	1
Congestive heart failure	I11.0, I13.0, I13.2, I25.5, I42, I43, I50	
Parkinson’s disease	G20-G22	

White race (yes vs. no)	N/A	
Arthritis (any type)	M05, M06, M08, L90.0, L94.0, L94.1, L94.3, M32 – M35, M45, M46, M48, M49	
Cognitive impairment	F01 – F05, F06.0, F06.7, F06.8, F07.0, F07.8, F09, G30, G31.0, G31.1, G31.8, R41	
Charlson comorbidity index (>0, 0)	As defined above	
Stroke	I60-I64, I69.0-4	1
Paranoia	F06.0, F06.2, F20, F22-F29, F32.3, F33.3, F44.8	
Chronic skin ulcer	I70.24, I70.25, I83.0, I83.2, I87.21, L89, L97	
Male (yes vs. no)		
Skin and soft tissue infection	L00-L06	
Mycoses	B35-B45	
Pneumonia	J10.0, J11.0, J12-J18	
Age (in 5 year categories)		
Hospital admission in past 6 months		
Gout or other crystal-induced arthropathy	M10, M11	1
Falls	N/A	1
Muscoskeletal problems	G45, M12-M14, M24, M25, M36, M43, M46, M47.1, M47.8, M50-M54, M67.8, M80, M81. M84.3, M84.4, M96.1, R26.2, R29.8, Z87.3	
Urinary tract infection	N10, N30, N34, N39.0	1

- Alcohol abuse:
  ICD-GM: F10

- Anemia:

  ICD-GM: D50 – D53, D63, D64.9
- Aortic plaque:

  ICD-GM: I70.0
- Coronary heart disease
  - Angina pectoris:

    ICD-GM: I20
  - Myocardial infarction:

    ICD-GM: I21 – I23, I25.2
  - Acute ischemic heart diseases:

    ICD-GM: I24
  - Chronic ischemic heart disease:

    ICD-GM: I25 (excl. I25.2)
  - Coronary artery bypass graft(s) :

    ICD-GM: Z95.1

    OPS: 5361, 5362
  - Percutaneous coronary intervention:

    OPS: 8837
- Dementia:

  ICD-GM: F01 – F03, G30, G31.0
- Depression:

  ICD-GM: F31, F32 – F34, F39, F43,1, F43.2
- Diabetes mellitus:

  ICD-GM: E10 - E14
- Drug abuse:

  ICD-GM: F11 – F19 (excl. F17.2)
- Gastric or peptic ulcer disease/diseases of gastrointestinal tract:

  ICD-GM: K21, K25.4 – K25.9, K26.4 – K26.9, K27.4 – K27.9, K28.4 – K28.9, K29, K30, K64
- Heart failure:

  ICD-GM: I11.0, I13.0, I13.2, I25.5, I42, I43, I50
- History of major bleeding (hospitalization only):

  OPS: 8800

ICD-GM: D62, H21.0, H31.3, H35.6, H43.1, H45.0, I32.1, I60 - I62, J94.2, M25.0, S06.4, S06.5, S06.6, S06.8

- Hypertension:

  ICD-GM: I10 - I15, I67.4

- Hypothyroidism:

  ICD-GM: E00, E01.8, E02, E03, E89.0

- Inflammatory bowel disease:

  ICD-GM: K51, K52

- Ischemic stroke or transient ischemic attack:

  ICD-GM: G45.0 – G45.2, G45.4 – G45.9, I63, I69.3, I69.4

- Systemic embolism:

  ICD-GM: I74

- Other cerebrovascular disease:

  ICD-GM: I64 - I69 (excl. I69.3, I69.4)

- Liver disease:

  ICD-GM: B18.0, B18.1, B18.2, I85, K70.0, K70.2, K70.3, K70.4, K70.9, K72.1, K73, K74, K75.4, K75.8, K76.0, K76.6, K76.9, Z94.4

- Hyperlipidemia:

  ICD-GM: E78.0 – E78.5

- Volume depletion:

  ICD-GM: E86

- Other metabolic disorders:

  ICD-GM: E87

- Obesity:

  ICD-GM: E66

- Peripheral artery disease:

  ICD-GM: I70.2 – I70.9, I71, I73.9

- Psychosis:

  ICD-GM: F20, F22 – F25, F28, F29 – F31, F32.3 – F32.5, F33.3, F33.4, F34.8, F34.9, F39, F44.8

- Pulmonary disease:

  ICD-GM: I27, I28.9, J44

- Rheumatoid arthritis/collagen vascular disease:

ICD-GM: M05, M06, M08, L90.0, L94.0, L94.1, L94.3, M32 – M35, M45, M46, M48, M49

- Renal impairment:

  ICD-GM: D63.1, E10.2, E11.2, E13.2, I12, I13, N02, N03, N04, N05, N07, N08, N14, N18.1-N18.4, N18.9, N19, Q61

- Acute kidney injury:
  ICD-GM: N17
- Tobacco abuse:
  ICD-GM: F17.2
- Other vascular disease:
  ICD-GM: I70.1, I72, I73.1, I73.8, I74, I79, K55.1, K55.8, K55.9, Z95
- Malignant cancer (excl. non-melanoma skin cancer) :
  ICD-GM: C00-C97 (excl. C44)
- Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers:
  ATC: C09
- Antiarrhythmics:
  ATC: C01B
- Antidepressants:
  ATC: N06A
- Antiplatelets:
  ATC: B01AC
- Antiulcer drugs (except proton-pump inhibitors):
  ATC: A02BA, A02BB, A02BX
- Beta blockers:
  ATC: C07
- Calcium channel blockers:
  ATC: C08
- Diabetes drugs (incl. insulin):
  ATC: A10A, A10B
- Diuretics:
  ATC: C03
- Erythropoietin-simulating agents:
  ATC: B03XA
- Estrogens:
  ATC: G03C, L02AA
- Lipid modifying agents:
  ATC: C10

- Non-steroidal anti-inflammatory drugs:

  ATC: M01A
- Proton-pump inhibitors:

  ATC: A02BC