Observational Study 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)
Report version and date	V1.0, 31 JUL 2020
IMPACT study number	20031
Study type / Study phase	Observational, Phase IV
Medicinal product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Study Initiator and Funder	Bayer AG 13353 Berlin, Germany
Research question and objectives	The primary objectives of this study were: • 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 • To assess the health care resource consumption in patients with non-valvular atrial fibrillation (NVAF) and renal impairment initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon • To assesses the overall and sector specific costs in patients with renal impairment who were treated with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon The secondary objectives of this study were: • 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 were: 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 was conducted using secondary data from German sick funds.
Author	[redacted]

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1. 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)
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Report version and date **Author**	v 1.0, 31 JUL 2020 [redacted]
Keywords	non-valvular atrial fibrillation; vitamin K antagonist; direct oral anticoagulant; renal impairment
Rationale and background	Factor Xa inhibiting non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) are increasingly used for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF).
Research question and objectives	To investigate comparative effectiveness and safety of Factor Xa NOACs versus phenprocoumon in patients with renal impairment.
Study design	Retrospective cohort study
Setting	Study based on German Statutory Health Insurance claims data from the InGef research database
Subjects and study size, including dropouts	17842 patients with renal impairment, initiating treatment with VKA or NOACs.

Variables and data sources	Study outcomes included ischemic stroke/systemic embolism, intracranial hemorrhage and other clinical outcomes. In addition, measures of health resource utilization (HRU) and HRU costs were analysed.
Results	As the study population of primary interest was a population with renal impairment (defined by several ICD-codes) results in this section will refer to this population. More details results on the overall patient population can be found in the respective section of this report. The risk of IS/SE was similar in patients treated with rivaroxaban or apixaban, compared to phenprocoumon. Intracranial hemorrhage and fatal bleeding occurred less frequently in users of rivaroxaban (HR=0.62; 95% 0.37-1.01) or apixaban (HR=0.41; 95% CI 0.23-0.74). For acute kidney injury, risk estimates for all NOACs were below 1, without being statistically significant. The risk of kidney failure (defined as the occurrence of end-stage renal disease or the need of dialysis) was lower for rivaroxaban (HR=0.27; 95% CI 0.16-0.43) or apixaban (HR=0.43; 95% CI 0.29-0.63) when compared to phenprocoumon. These effects were consistent across multiple patient subgroups. The outcomes were generally robust with respect to the method of analysis used. Overall indicators of health resource utilization (hospitalizations; EMR visits; hospital days; number of different drugs used) were similar in the different treatment groups. During follow-up, overall HRU costs were higher in patients treated with NOACs compared to phenprocoumon. PS matched differences in overall costs ranged between additional 1771€ per year for rivaroxaban and 5493€ per year for edoxaban. Main drivers for these differences were hospital costs and drug prescription costs. Costs associated with renal impairment were lower in patients treated with rivaroxaban or apixaban than in patients treated with phenprocoumon (Cost per person year (CPY) ratio 0.42; 95% CI 0.28-0.62 and 0.51; 95% CI 0.33-0.79). The lower costs associated with renal impairment were mainly attributable to lower dialysis-associated costs.
Discussion	In this observational study of patients with NVAF and renal impairment as primary analysis population, the use of factor Xa NOACs was associated with a similar risk with respect to measures of clinical effectiveness (i.e. IS/SE combined or separately; severe IS to phenprocoumon) when compared to phenprocoumon. Rivaroxaban and apixaban were associated with lower risks of ICH and kidney failure. While total health

	care costs were higher in patients treated with NOACs compared to phenprocoumon, costs associated with renal impairment were lower. Results indicated that the beneficial effect on renal outcomes and lower costs related to renal impairment was more prominent for rivaroxaban.

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 (procedure coding)
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. Investigators

NA.

4. Other responsible parties

[redacted]

5. Study background and research question

5.1 Milestones

Table 1 presents planned milestones for the project. These milestones were based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation, data release and analysis did 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	15 Jul 2020

5.2 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 is associated with a 5-fold increased 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, tight monitoring, high inter and intrapersonal variation of VKA exposure, multiple drug und food interactions, the need for 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 in the mITT population of rivaroxaban compared to VKA in the on-treatment analysis. Regarding safety, a significant reduction in intracranial hemorrhage (ICH) was demonstrated in ROCKET AF. Overall, the benefit risk profile of patients with and without renal impairment treated with rivaroxaban was considered positive.

Supplementary to randomized controlled trials, generation of real-world evidence is of importance in reinforcing safety and effectiveness in the daily practice and gaining knowledge regarding effectiveness and safety of treatments used in routine clinical practice. Published real world studies investigated effectiveness and safety of non-vitamin-K oral anticoagulants (NOACs), some specifically with a focus on renal impairment. (Yao et al. 2017a).

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) As of evidence gaps and guideline recommendations, 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 conducted in 2017 has been the largest database study of its kind in Germany and significantly contributed to the understanding of the use of rivaroxaban in patients with NVAF in routine clinical practice. In this study, 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 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

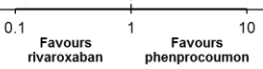


Figure 1 RELOAD: Multivariate regression analyses of the primary effectiveness and safety outcomes in patients with NVAF and renal impairment receiving rivaroxaban 15 mg od versus those receiving phenprocoumon (presented at ISPOR EU 2017)

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

A publication by Hohnloser et al. 2018 utilizing the same German data source provided insights into effectiveness and safety 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, other observational 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 regarding safety and effectiveness of NOACs and phenprocoumon with a clear focus on specific subgroups that have a high residual risk such as frail patients, is scarce. The effectiveness and safety including renal outcomes of patients with renal impairment has also only be studied rarely. Recent analyses from the US (Yao et al. 2017b) showed

that renal function decline was 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, there is no European evidence quantifying the risk of renal outcomes in NVAF patients treated with different anticoagulants.
The increasing number of patients using NOACs in Germany over the last year and accessibility of information from claims databases, now allows addressing more detailed research questions including rare endpoints as well as looking into specific subgroups and subpopulations of high residual risk.

5.3 Research questions and objectives

The primary objectives of this study were:

- 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
- To assess the health care resource consumption in patients with non-valvular atrial fibrillation (NVAF) and renal impairment initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon
- To assesses the overall and sector specific costs in patients with renal impairment who were treated with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon

The secondary objectives of this study were:

- 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

Other objectives of this study were:

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

5.4 Amendments and updates of the study protocol

10-Dec 2018 Change in outcome definition of fatal bleeding (section 9.3.2 and Annex 3 of study protocol)

The OPS code 8800 (blood transfusion) will no longer be considered for outcome definition of fatal bleeding, since explorative analyses showed that this code is also used in hospitalizations due to

severe injuries, sepsis or chronic diseases such as kidney failure or cancer, which are unrelated to anticoagulant use. Thus, this code has to be excluded to avoid outcome misclassification.

10-Dec 2018 Change of inclusion criteria (section 9.2.2 of study protocol)

The period to assess diagnoses of NVAF as inclusion criterion was extended to the whole baseline period to account for possible undercoding.

10 Dec 2018 Change of exclusion criteria (section 9.2.3 and Annex 3 of study protocol)

1. Definition of (ICD-10 codes) for valvular atrial fibrillation was relaxed, since preliminary results showed that a substantial amount of patients were excluded from the analyses due to unspecific codes. Exclusion of these patients may have resulted in selection bias.

2. Prescriptions of heparin/fondaparinux in the 60 days before the index date are no longer considered as exclusion criterion. Explorative analyses showed that the majority of these patients had a diagnosis for atrial fibrillation and were most likely treated with heparin before cardioversion. Therefore, these patients had to be included to avoid selection bias. Instead, heparin/fondaparinux in the 60 days before the index date is considered as covariate.

3. Patients receiving both reduced and standard dose NOACs at the index date were also excluded, since no dose group could be assigned for this group as required for analyses.

4. Patients with documented cardiac valve surgery in the baseline period were excluded from the analyses, since NOACs are not indicated in these patients.

10 Dec 2018 Exposure assessment and duration of follow-up (section 9.3.1 of study protocol)

1. Hospitalized person time was considered as exposed to the most recent anticoagulant used as patients usually receive their drugs from the hospital. Therefore it appears reasonable to assume that treatment is continued to avoid exposure misclassification.

2. Start of follow-up for effectiveness outcomes was shifted from the index date to the day after the index date, i.e. the first anticoagulant prescription. This was done to avoid protopathic bias, since it remains unclear whether the outcome event occurred under treatment or drug treatment was started after the event.

10 Dec 2018 Additional subgroup analyses (section 9.3.4 of study protocol)

Additional subgroup analyses of interest in patients with diabetes (yes. vs. no) and chronic renal disease (yes. vs. no) were included

10 Dec 2018 Extended data analyses (section 9.7.2 of study protocol)

Propensity-score-matched analyses as well as IPTW analyses were extended to analyses of all safety and effectiveness outcomes in patients with renal impairment and the overall population.

01 Apr 2019 Extended data analyses (section 9.7.2 of study protocol)

AKI will also be analyzed as recurrent event based on two different case definition: 1. Inpatient and outpatient diagnoses and 2. Inpatient diagnoses only

01 Apr 2019 Assessment of additional covariates (Annex 3 of study protocol)

AKI and latest CKD stage will be assessed as additional covariates.

01 Apr 2019 Re-analysis based on different approach to identify patients with renal impairment (section 9.7.3 of study protocol)

A different approach for the identification of patients with renal impairment will be used and the outcomes IS/SE, ICH, renal failure, AKI will be re-analyzed for this subgroup.

01 Apr 2019 Feasibility assessment of kidney transplantation (section 9.3.2 of study protocol)

The event rate of kidney transplantation will be assessed as feasibility analysis.

20 Sep 2019 Add-on analysis for healthcare resource consumption and overall and sector specific costs (section 8.1, 8.2, 9.2, 9.3, 9.7, Annex 3 of study protocol)

Inclusion of the following study objectives as add-on analyses:

- To assess the health care resource consumption in patients with non-valvular atrial fibrillation (NVAF) and renal impairment initiating treatment with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon
- To assesses the overall and sector specific costs in patients with renal impairment who were treated with individual NOACs (rivaroxaban, apixaban, edoxaban) compared to phenprocoumon

20 Sep 2019 Additional subgroup analyses (section 9.3.4 of study protocol)

- Additional subgroup analyses of interest in patients with chronic renal disease (yes. vs. no) and renal impairment + diabetes + reduced dose

6. Research methods

6.1 Study design

This was 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 were only be used for the assessment of demographic and clinical characteristics and to identify new users of NOACs and phenprocoumon. The enrollment period was from 01 January 2013 to 30 June 2017. Data from 1 July to 31 December 2017 was considered as follow-up only to allow a follow-up of at least 6 months.

6.2 Setting

6.2.1 Study population and selection criteria

The source population of this study included all insured members of more than 60 German statutory health insurances (SHIs) contributing data to the InGef database.

6.2.2 Inclusion criteria

Patients met all of the following inclusion criteria:

- 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).

6.2.3 Exclusion criteria

Patients with any of the following exclusion criteria were excluded from the analysis:

- A verified ambulatory or primary/ secondary hospital discharge diagnosis of valvular atrial fibrillation in the baseline period;
- Individuals with documented cardiac valve surgery in the 365 days prior to or on the index date,
- 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 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).
- Patients receiving reduced and standard dose of apixaban, rivaroxaban or edoxaban on the index date
- 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 were 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 came first. Patients were censored in all analyses if they switched to phenprocoumon or another NOAC (including dabigatran), warfarin, rivaroxaban 10 mg/ 2.5 mg, edoxaban 15mg, reduced and standard dose at the same date or a contraindicated drug as defined above. For some of the specific analyses, the end of follow-up has differed as described in the sections below (related to the respective endpoints).

For the comparative add-on analysis on healthcare resource consumption and costs, patients were followed from the index date discontinuation of the index drug, death, end of continuous insurance in the SHI, one year after the index date or the end of the study period (31 December 2017), whichever came first. Patients were also censored as defined above. In sensitivity analyses, a modified intention-to-treat approach was used as defined below.

6.3 Variables

6.3.1 Exposure definition

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) were used to define main exposures of interest. All prescriptions were assessed based on the documented dispensation date.

Each patient were 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 started on the index date for analyses of safety outcomes and the day after the index date for analyses of effectiveness outcomes and were 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 was 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).

In-hospital stays during exposed person-time were considered as exposed to the most recent anticoagulant used, as patients usually receive their drugs from the hospital (assuming treatment is continued).

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 were collected. The results of this survey were used to define a median daily dose (0.606 tablets per day), which was 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 was calculated (separately for patients with and without renal impairment, since the estimated dose is assumed to differ substantially between both

groups). For this purpose, amount of active ingredient (AAI) dispensed to each patient of the phenprocoumon group was obtained for each prescription. A prescribed personalized daily dose pPDD) representing the average daily dose taken during follow-up was computed for each patient i such that:

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

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

For the sake of simplicity, only prescriptions of patients who were solely treated with phenprocoumon during follow-up were included in the computation of the empirical DDD (eDDD). Patients with a pDDD below the 5th or above the 95th percentile and patients with only one prescription for phenprocoumon were assigned the median pDDD (=eDDD) over all patients.

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

6.3.2 Outcomes definition

As effectiveness outcomes, IS/SE (as combined endpoint and alone), recurrent IS/SE (as combined endpoint) and severe IS were analyzed while safety outcomes included ICH, fatal bleeding, recurrent hospitalization, kidney failure, AKI and kidney transplant (feasibility only). All study outcomes except kidney failure, fatal bleeding, AKI and hospitalizations were defined based on primary hospital discharge diagnoses only (ICD-10 GM codes). The event date was set to the admission date of the respective hospitalization.

Severe IS was defined according to an approach proposed by Schubert et al. (Costs associated with renal impairment were lower 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. In addition,

IS cases were considered as severe if the patients died during the respective hospitalization defined as documented death as reason for hospital discharge.

Cases of fatal bleeding were 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 was set to the date of hospital discharge or date of disenrollment from the SHI, respectively.

Hospitalizations (in general and for IS/SE) were 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 was also 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. The event date for cases with renal failure in the outpatient setting was set to the first documented claim for dialysis in the respective quarter.

Kidney transplantation was defined based on OPS-Codes and the event date was assessed on the exact date of procedure.

Besides the primary case definition based on hospitalizations, AKI was also analyzed as recurrent event taking into account outpatients diagnoses. The event date for cases with AKI in the outpatient setting was set to the first documented EBM code of the respective case in ambulatory care in the respective quarter.

Further outcomes included the number of hospitalizations (with at least one day between discharge from previous hospitalization), number of hospital days, number of emergency room visits defined as hospital admissions with “emergency” as reason for admission, number of distinct drugs used on the seven digit ATC-Code level. Overall costs were defined as sum of hospital costs, ambulatory care costs, drug prescription costs, and remedies and aids costs. Costs for each of the mentioned healthcare sectors were also analyzed as separate outcome. In addition, costs associated with renal impairment including hospital costs and ambulatory care costs for dialysis were assessed. To account for cost inflation over the study period, costs in each year were standardized to the year 2017 for all analyses assuming the following inflation from 2013 onwards: 2012-2013: 1.5%, 2013-2014: 0.9%, 2014-2015: 0.5%, 2015-2016: 0.5%, 2016-2017: 1.5% (Source: https://data.oecd.org/price/inflation-cpi.htm).

6.3.3 Covariate definition

All demographic and clinical characteristics were assessed based on primary and secondary hospital diagnoses and verified ambulatory diagnoses (ICD-10 GM codes), OPS codes, EBM codes and ATC codes. In addition, healthcare resource consumption, i.e. number of hospitalizations, number of hospital days, number of emergency room visits, number of distinct drugs used on the seven digit ATC-Code level, as well as the overall costs and hospital costs, ambulatory care costs, drug prescription costs, remedies and aids costs and costs associated with renal impairment were assessed. Unless otherwise mentioned, all information on covariates were collected in the baseline period., i.e. in the 365 days prior to the index date. The assessment date for hospital diagnoses was 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 were 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
- Federal State at the index date

Clinical characteristics

- $CHADS_2$ score
- CHA_2DS_2-VASc score
- modified HAS-BLED score (INR was not included in the calculation of the score because this information is not available in the InGef database, and end-stage renal disease was not be considered as these patients were excluded from the analysis)
- Comorbidities
    - Alcohol abuse
    - Anemia
    - Aortic plaque
    - Acute kidney injury
    - 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
- Systemic embolism
- Tobacco abuse
- Other vascular disease
- Malignant cancer (except non-melanoma skin cancer)
- Last reported CKD stage
- Hospitalized CKD

- Comedications
  - Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers
  - Antiarrhythmics
  - Antidepressants
  - Antiplatelets
  - Antiulcer drugs (except proton-pump inhibitors)
  - Beta Blockers
  - Calcium channel blockers
  - Diabetes drugs
  - Diuretics
  - Erythropoietin-simulating agents

  - Estrogens
  - Lipid modifying agents
  - Non-steroidal anti-inflammatory drugs
  - Proton-pump inhibitors
  - Heparin or fondaparinux in the 60 days prior to or on the index date

- 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

Healthcare resource consumption and costs

- Overall costs
  - Hospital costs
  - Ambulatory care costs
  - Drug prescription costs
  - Remedies and aids costs
  - Costs associated with renal impairment
- Healthcare resource consumption
  - Number of hospitalizations
  - Number of hospital days
  - Number of emergency room visits
  - Number of unique drugs used on a seven digit ATC code level

<u>Others</u>

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

6.3.4 Subpopulations and Subgroups

Subgroups and subpopulation were only build on the basis of conditions already present at index date. The following subpopulations of special interest were defined:

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

Patients with renal impairment were identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses in the baseline period according to Fleet et al. 2013 and Nielsen et al. 2017.

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

Patients with chronic renal disease were 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 were defined:

- Frail patients

The validated claims based Frailty Indicator (Segal JB et al. 2017) was used in this study. This algorithm is validated against the frailty phenotype, which is the most widely used instrument for assessing frailty. The frailty cut-off for this study was 0.25 as the desire is to specifically identify frail individuals.

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

Age was assessed at the index date.

- Renal impairment

Patients with renal impairment were identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses in the baseline period according to Fleet et al. 2013 and Nielsen et al. 2017.

- Chronic renal disease

Patients with chronic renal disease were identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses in the baseline period according the definition for chronic renal disease as covariate.

- Prior IS or SE

Patients with IS, TIA or SE were 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.

- Reduced vs. standard dose of NOACs

For each respective NOAC, patients were classified into reduced and standard dose initiators. Analyses were 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) were identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses in the baseline period according the definition for malignant cancer as covariate. For the subgroup of patients with cancer, the different underlying cancer-types were additionally included as covariates in the respective statistical models.

- Diabetes

Patients with diabetes were identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses in the baseline period according the definition for diabetes as covariate.

For the healthcare resource consumption and costs analysis, the following subgroups were analyzed: patients with renal impairment, patients with diabetes, patients with chronic kidney disease, patients with renal impairment initiating either phenprocoumon or reduced doses of NOACs, patients with chronic kidney disease initiating either phenprocoumon or reduced doses of NOACs, patients with chronic kidney disease and diabetes initiating either phenprocoumon or reduced doses of NOACs.

In addition, analyses of all safety and effectiveness outcomes were also conducted in patients with chronic renal disease (yes vs.no) and patients with chronic kidney disease and diabetes initiating either phenprocoumon or reduced doses of NOACs.

6.4 Data source

This study was 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 (Andersohn F et al. 2016).

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

6.5 Study size

Based on previous studies, we estimated 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 (Hohnloser SH et al. 2018) 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

6.6 Data management

Completely anonymized analysis datasets comprising all observations and variables required for the planned analyses were created from the information contained exclusively within the InGef database. The analytic datasets were person-level, with variables contained as specified above.

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

6.7 Data analysis

6.7.1 Descriptive analysis

Descriptive statistics were 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 were reported. For categorical variables, absolute counts and proportions of patients with given characteristics were 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 (outpatient + inpatient diagnoses and inpatient only), kidney transplantation, fatal bleeding, and severe IS were reported overall as well as in all subgroups as the number of events per 100 person-years. Corresponding 95%-confidence intervals were calculated assuming a Poisson distribution. In addition, the mean number of hospitalizations and other healthcare consumption outcomes per patient per year as well as mean overall and sector specific costs per patient per year were calculated with corresponding 95%-confidence intervals.

6.7.2 Main analysis

Analyses were conducted in line with good statistical practices. Models used 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 were 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) was also 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 was used as reference.

For the analyses of healthcare resource consumption, negative binomial regression models were applied to estimate adjusted rate ratios of healthcare resource consumption per day with 95%-confidence intervals during the follow-up period between NOACs and phenprocoumon as the reference category. For the costs analyses, multivariate gamma regression models were applied to

estimate adjusted ratios of total cost per day with 95%-confidence intervals during the follow-up period between NOACs and phenprocoumon as the reference category. In case of zero costs, a two-part model composed of a logistic regression model in patients with an indicator of non-zero costs as a dependent variable, and a gamma regression model patients with costs greater than zero and the total cost per day as a dependent variable was applied. In addition, the absolute difference in mean costs between NOAC vs. phenprocoumon users per person year was calculated with 95% confidence intervals.

Information on confounding factors which were planned to be included in the multivariate models as well as in the estimation of the propensity score are described above. We uses forward selection ($p<0.1$ to enter the model) to select appropriate covariates. Potential instrumental variables such as Federal State, which are not independent risk factors of the outcome, were not included in the respective models.

In a second step, we used a 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 were calculated using multiple logistic regression on a relevant set of patient characteristics 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 $e=P(Z=1|X)$. 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 (Xu et al. 2010). 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 used 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 (Xu et al. 2010).

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 were inspected for original data and the synthetic sample. Furthermore, the distribution of stabilized weights in the original data was 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 were inspected for original data and the synthetic sample. The balance of patient characteristics between treatment groups was checked by using standardized mean differences (SMD). An absolute SMD of 0.1 or less was 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

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

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

For the analysis of each outcome in the population with renal impairment and the overall population as well as for the comparison of reduced vs. standard dose of NOACs (other objectives) as well as all healthcare resource consumption and cost analyses all three approaches were used, i.e. Cox proportional hazards regression models, negative binomial regression (for healthcare resource consumption) or gamma regression (for cost analyses), IPTW and propensity-score matching with subsequent negative binomial regression (for healthcare resource consumption) or gamma regression (for cost analysis). For all other analyses only Cox proportional hazards regression models and IPTW were applied.

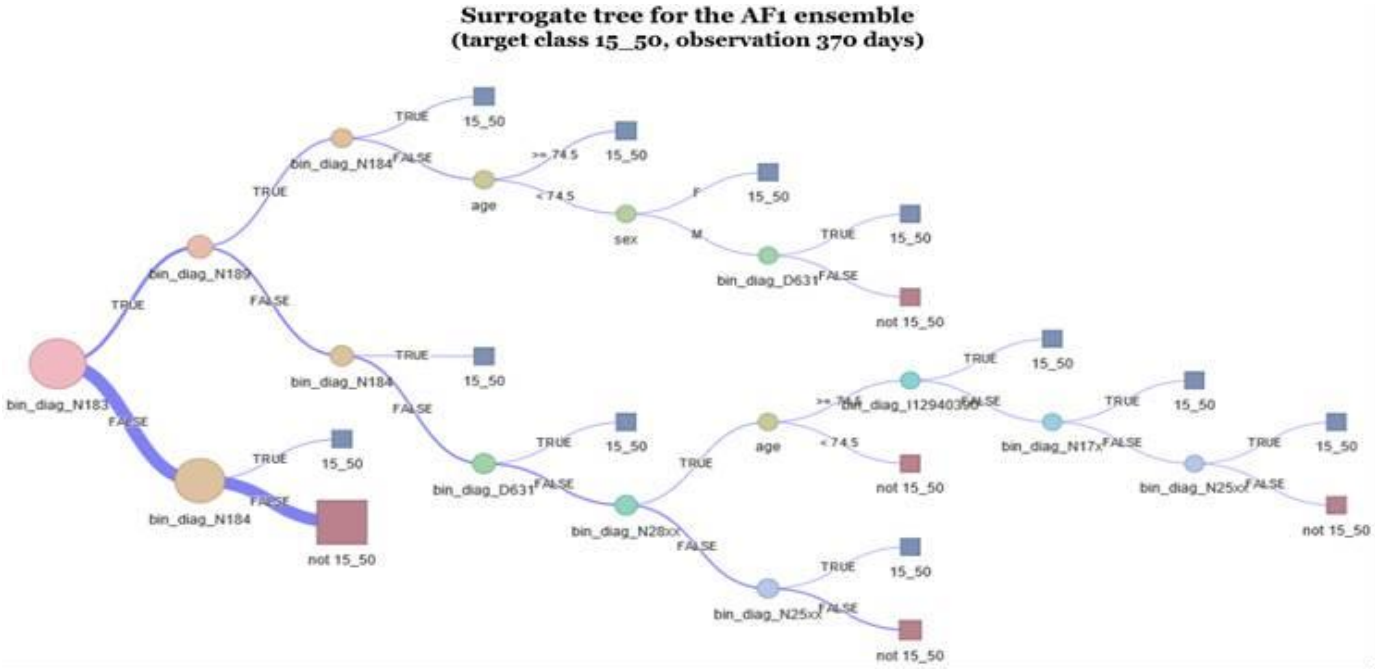
6.7.3 Sensitivity analyses

Pre-defined sensitivity analyses were performed to evaluate the consistency of main results. First, we repeated 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 was added to following prescription. Second,

performed the Cox regression analysis for the outcomes ICH, IS, SE, severe IS, 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. Third, we repeated the Cox regression analysis for IS/ SE as combined endpoint and ICH analyses using the pDDD to calculate the supply for phenprocoumon as defined above.

In addition, a different approach to identify patients with renal impairment (eGFR between 15 and 50) and analyses for the outcomes IS/SE, ICH, renal failure, AKI was conducted for this new subgroup (incl. multiple Cox regression, PS matching and IPTW).

The following diagram displays the algorithm to identify patients with renal impairment based on different patient characteristics:



In addition, the following sensitivity analyses were conducted for the healthcare resource consumption and cost analyses: First, we used a modified intention-to-treat approach with a maximum follow-up of one year, i.e. patients were not censored at treatment discontinuation or switch. Second, we applied the modified intention-to-treat approach with a maximum follow-up of two years to account for possible differences in long-term costs including patients. Third, patients with extreme overall baseline costs defined as 75th percentile + 5*inter-quartile range of the overall costs of the underlying study population (for cost analysis only) were excluded from the cost analysis.

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

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

6.8 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 outputs 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

7. Results

The main study results are presented in the following sections. Full results tables (e.g. results for all subgroups under study) are available as embedded EXCEL files in Annex 4.

7.1 Participants

From N=165.605 patients with at least one prescription of NOACs or phenprocoumon between January 2013 and June 2017, at total of 64920 were included in the *overall study population*. The majority of patients that were excluded did not fulfil the inclusion criterion on a diagnosis of NVAF. N=17842 patients of the overall study population (27.5%) fulfilled the criteria of renal impairment and were included in the *renal impairment population*, representing the primary study population for this study (Figure 2). During the total inclusion period, most patients of the primary study population initiated phenprocoumon (N=7289), followed by rivaroxaban (N=5121), apixaban (N=4750) and edoxaban (n=682). Due to the low number of patients treated with edoxaban in the renal impairment population, only few analyses could be performed for this NOAC. Over the years, there was a shift towards the use of NOACs instead of phenprocoumon: While in 2013, 2706 of 4180 initiators (64.7%) used phenprocoumon, this proportion dropped to 15.8% in 2017 (331 of 2098 initiators).

The baseline characteristics of included NVAF patients with renal impairment are displayed in Table 4. Patients treated with phenprocoumon received the prescription less often from cardiologists than patients treated with NOACs. The descriptive analysis of measures of disease risk (e.g. CHADS2 scores; HAS-BLED scores); health resource use; and proportion of patients with comorbidities did not reveal substantial imbalances between the four treatment groups. The majority of included patients for whom information on the last stage of chronic kidney disease (CKD) was available in the baseline period had CKD stage 3. CKD stage 4 was observed more often in patients who initiated phenprocoumon treatment.

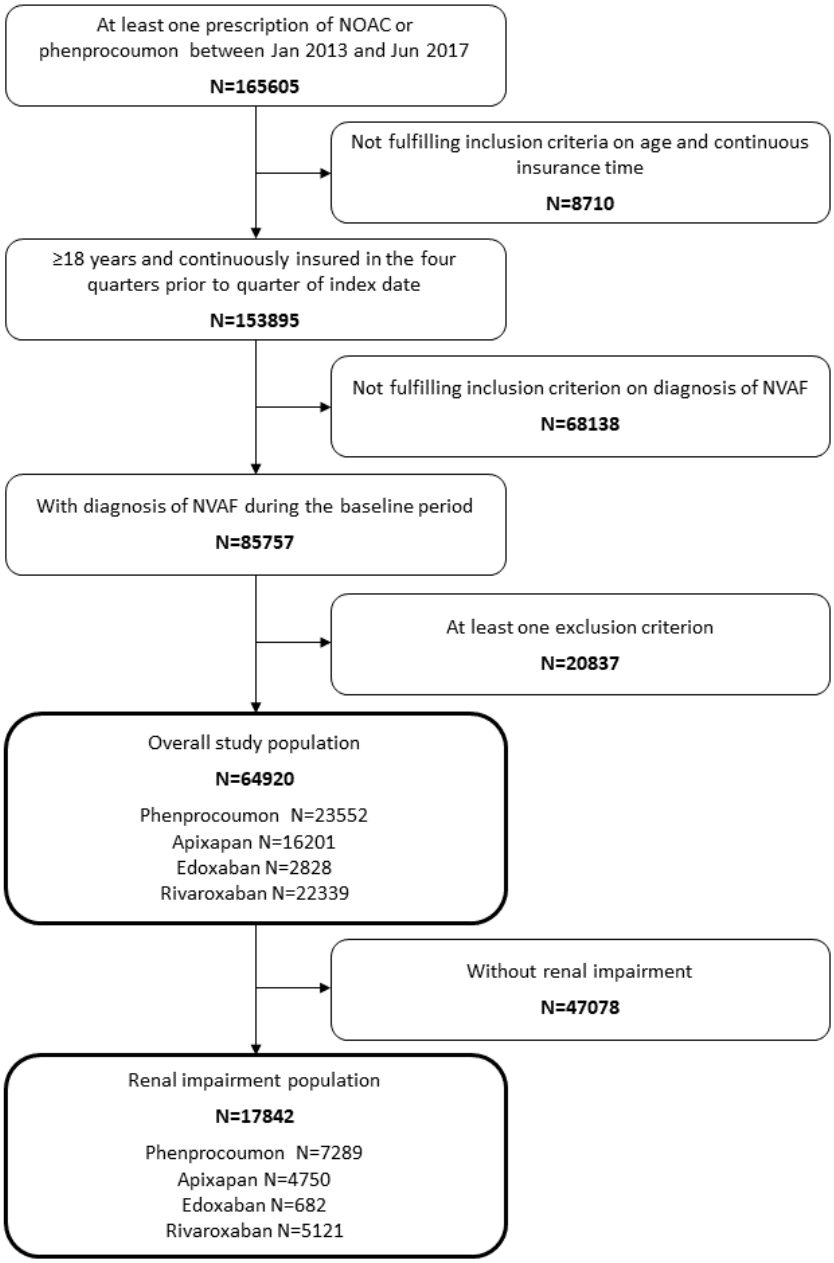


Figure 2 Flowchart of patient selection

Table 4 Baseline characteristics of NVAF patients with renal impairment, initiating treatment with phenprocoumon or NOACs

	Phenprocoumon (N=7289)	Apixaban (N=4750)	Rivaroxaban (N=5121)	Edoxaban (N=682)
Gender				
Female	2901 (39.8%)	2095 (44.1%)	2067 (40.4%)	261 (38.3%)
Male	4388 (60.2%)	2655 (55.9%)	3054 (59.6%)	421 (61.7%)
Age in years (Mean±SD)	77.2±8.4	78.5±9.1	75.9±9.4	77±9.2
Year of index date				
2013	2706 (37.1%)	214 (4.5%)	1260 (24.6%)	0 (0%)
2014	1883 (25.8%)	703 (14.8%)	1258 (24.6%)	0 (0%)
2015	1391 (19.1%)	1190 (25.1%)	1187 (23.2%)	40 (5.9%)
2016	978 (13.4%)	1621 (34.1%)	975 (19%)	338 (49.6%)
2017	331 (4.5%)	1022 (21.5%)	441 (8.6%)	304 (44.6%)
Dose at index date				
Reduced	N/A	2507 (52.8%)	2221 (43.4%)	292 (42.8%)
Standard	N/A	2243 (47.2%)	2900 (56.6%)	390 (57.2%)
Speciality of physician initiating treatment				
General practitioners	6805 (93.4%)	4235 (89.2%)	4509 (88.1%)	558 (81.8%)
Cardiologists	293 (4%)	347 (7.3%)	359 (7%)	100 (14.7%)
Other	141 (1.9%)	121 (2.6%)	172 (3.4%)	20 (2.9%)
Unknown	50 (0.7%)	47 (1%)	81 (1.6%)	<5
Frailty score				
<0.25	4536 (62.2%)	2364 (49.8%)	3171 (61.9%)	419 (61.4%)
≥0.25	2753 (37.8%)	2386 (50.2%)	1950 (38.1%)	263 (38.6%)
Last stage of chronic kidney disease (if reported)				
1	180 (2.5%)	116 (2.4%)	153 (3%)	31 (4.6%)
2	967 (13.3%)	648 (13.6%)	814 (15.9%)	109 (16%)
3	2759 (37.9%)	1946 (41%)	1680 (32.8%)	219 (32.1%)
4	565 (7.8%)	245 (5.2%)	167 (3.3%)	25 (3.7%)
unspecified	530 (7.3%)	286 (6%)	350 (6.8%)	41 (6%)
CHA2DS2-VASc Score				
Mean±SD	4.9±1.6	5.1±1.7	4.6±1.7	4.6±1.6
0	10 (0.1%)	6 (0.1%)	24 (0.5%)	<5
1	73 (1%)	70 (1.5%)	146 (2.9%)	16 (2.4%)
≥2	7206 (98.9%)	4674 (98.4%)	4951 (96.7%)	665 (97.5%)
CHADS2 Score				
Mean±SD	3.1±1.2	3.3±1.3	3±1.3	2.9±1.3
0	41 (0.6%)	32 (0.7%)	64 (1.3%)	10 (1.5%)
1	548 (7.5%)	349 (7.4%)	585 (11.4%)	68 (10%)
≥2	6700 (91.9%)	4369 (92%)	4472 (87.3%)	604 (88.6%)
Modified HAS-BLED Score				
Mean±SD	3.7±0.8	3.8±0.9	3.6±0.9	3.6±0.8
0 to 2	390 (5.4%)	272 (5.7%)	412 (8.1%)	49 (7.2%)
≥3	6899 (94.7%)	4478 (94.3%)	4709 (92%)	633 (92.8%)
Number of hospitalizations (Mean±SD)	1.5±1.5	1.7±1.5	1.6±1.5	1.3±1.4

	Phenprocoumon (N=7289)	Apixaban (N=4750)	Rivaroxaban (N=5121)	Edoxaban (N=682)
Number of ambulatory physician contacts (Mean±SD)	17.9±8.6	17±8.3	17.4±8.7	17.9±8.7
Number of different medications used (Mean±SD)	10.9±5.6	10.6±5.7	10.3±5.8	10.1±5.6
Renal morbidity				
Chronic renal disease	3513 (48.2%)	2300 (48.4%)	1967 (38.4%)	259 (38%)
Unspecified kidney failure	2315 (31.8%)	1417 (29.8%)	1381 (27%)	186 (27.3%)
Cystic kidney disease	1188 (16.3%)	794 (16.7%)	942 (18.4%)	134 (19.7%)
Glomerular disorders in diseases classified elsewhere	1215 (16.7%)	791 (16.7%)	815 (15.9%)	107 (15.7%)
Acute kidney injury	582 (8%)	436 (9.2%)	342 (6.7%)	61 (8.9%)
Recurrent and persistent haematuria	70 (1%)	41 (0.9%)	53 (1%)	10 (1.5%)
Chronic nephritic syndrome	33 (0.5%)	14 (0.3%)	22 (0.4%)	<5
Nephrotic syndrome	33 (0.5%)	23 (0.5%)	24 (0.5%)	<5
Unspecified nephritic syndrome	60 (0.8%)	33 (0.7%)	44 (0.9%)	5 (0.7%)
Hereditary nephropathy, not elsewhere classified	<5	<5	<5	0 (0%)
Drug- and heavy-metal-induced tubulo-interstitial and tubular conditions	16 (0.2%)	5 (0.1%)	8 (0.2%)	0 (0%)
Type 1 diabetes mellitus with renal complications	54 (0.7%)	28 (0.6%)	45 (0.9%)	5 (0.7%)
Type 2 diabetes mellitus with renal complications	1130 (15.5%)	749 (15.8%)	756 (14.8%)	113 (16.6%)
Other specified diabetes mellitus with renal complications	9 (0.1%)	12 (0.3%)	13 (0.3%)	<5
Hypertensive renal disease	574 (7.9%)	277 (5.8%)	269 (5.3%)	46 (6.7%)
Hypertensive heart and renal disease	515 (7.1%)	295 (6.2%)	313 (6.1%)	49 (7.2%)
Comorbidity				
Alcohol abuse	207 (2.8%)	121 (2.6%)	157 (3.1%)	21 (3.1%)
Anemia	1416 (19.4%)	1024 (21.6%)	933 (18.2%)	121 (17.7%)
Aortic plaque	456 (6.3%)	318 (6.7%)	314 (6.1%)	57 (8.4%)
Coronary heart disease	4317 (59.2%)	2466 (51.9%)	2629 (51.3%)	325 (47.7%)
Angina pectoris	926 (12.7%)	465 (9.8%)	561 (11%)	69 (10.1%)
Myocardial infarction	1573 (21.6%)	834 (17.6%)	881 (17.2%)	115 (16.9%)
Acute ischemic heart diseases	144 (2%)	72 (1.5%)	67 (1.3%)	13 (1.9%)
Chronic ischemic heart disease	4110 (56.4%)	2314 (48.7%)	2452 (47.9%)	298 (43.7%)
Coronary artery bypass graft(s)	841 (11.5%)	422 (8.9%)	448 (8.8%)	60 (8.8%)
Percutaneous coronary intervention	688 (9.4%)	248 (5.2%)	238 (4.7%)	25 (3.7%)
Dementia	445 (6.1%)	515 (10.8%)	457 (8.9%)	49 (7.2%)
Depression	1809 (24.8%)	1365 (28.7%)	1412 (27.6%)	183 (26.8%)

	Phenprocoumon (N=7289)	Apixaban (N=4750)	Rivaroxaban (N=5121)	Edoxaban (N=682)
Diabetes mellitus	3669 (50.3%)	2331 (49.1%)	2469 (48.2%)	332 (48.7%)
Drug abuse	540 (7.4%)	348 (7.3%)	351 (6.9%)	53 (7.8%)
Gastric or peptic ulcer disease	2731 (37.5%)	1813 (38.2%)	1934 (37.8%)	271 (39.7%)
Heart failure	4372 (60%)	2717 (57.2%)	2855 (55.8%)	324 (47.5%)
Hyperlipidemia	4895 (67.2%)	3083 (64.9%)	3266 (63.8%)	441 (64.7%)
Hypertension	7023 (96.4%)	4568 (96.2%)	4870 (95.1%)	635 (93.1%)
Hypothyroidism	1269 (17.4%)	968 (20.4%)	940 (18.4%)	119 (17.5%)
Inflammatory bowel disease	401 (5.5%)	285 (6%)	279 (5.5%)	45 (6.6%)
Ischemic stroke or transient ischemic attack	1302 (17.9%)	1226 (25.8%)	872 (17%)	101 (14.8%)
Ischemic stroke	627 (8.6%)	794 (16.7%)	479 (9.4%)	68 (10%)
Liver disease	1350 (18.5%)	895 (18.8%)	1016 (19.8%)	139 (20.4%)
Cancer (excl. non-melanoma skin cancer)	1471 (20.2%)	1045 (22%)	1054 (20.6%)	148 (21.7%)
Obesity	2367 (32.5%)	1488 (31.3%)	1632 (31.9%)	239 (35%)
Other cerebrovascular disease	1812 (24.9%)	1383 (29.1%)	1234 (24.1%)	162 (23.8%)
Other metabolic disorders	2110 (29%)	1531 (32.2%)	1486 (29%)	164 (24.1%)
Other vascular disease	2729 (37.4%)	1532 (32.3%)	1540 (30.1%)	209 (30.7%)
Peripheral artery disease	2059 (28.3%)	1258 (26.5%)	1257 (24.6%)	190 (27.9%)
Psychosis	153 (2.1%)	164 (3.5%)	141 (2.8%)	21 (3.1%)
Pulmonary disease	2099 (28.8%)	1272 (26.8%)	1344 (26.2%)	196 (28.7%)
Rheumatoid arthritis	1507 (20.7%)	972 (20.5%)	1066 (20.8%)	156 (22.9%)
Systemic embolism	183 (2.5%)	89 (1.9%)	114 (2.2%)	12 (1.8%)
Tobacco abuse	139 (1.9%)	86 (1.8%)	108 (2.1%)	12 (1.8%)
Volume depletion	677 (9.3%)	676 (14.2%)	600 (11.7%)	84 (12.3%)
History of major bleeding	499 (6.9%)	345 (7.3%)	339 (6.6%)	36 (5.3%)
Co-medication				
Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers	5820 (79.9%)	3653 (76.9%)	3873 (75.6%)	520 (76.3%)
Antiarrhythmics	455 (6.2%)	194 (4.1%)	288 (5.6%)	31 (4.6%)
Antidepressants	1136 (15.6%)	787 (16.6%)	784 (15.3%)	115 (16.9%)
Antiplatelets	2161 (29.7%)	1592 (33.5%)	1510 (29.5%)	188 (27.6%)
Antiulcer drugs (except proton-pump inhibitors)	140 (1.9%)	73 (1.5%)	103 (2%)	10 (1.5%)
Beta blockers	5391 (74%)	3248 (68.4%)	3507 (68.5%)	457 (67%)
Calcium channel blockers	2741 (37.6%)	1768 (37.2%)	1826 (35.7%)	235 (34.5%)
Diabetes drugs (incl. insulin)	2350 (32.2%)	1494 (31.5%)	1594 (31.1%)	229 (33.6%)
Diuretics	4488 (61.6%)	2661 (56%)	2666 (52.1%)	356 (52.2%)
Erythropoietin-simulating agents	61 (0.8%)	33 (0.7%)	18 (0.4%)	<5
Estrogens	167 (2.3%)	117 (2.5%)	126 (2.5%)	17 (2.5%)
Lipid modifying agents	3652 (50.1%)	2116 (44.6%)	2189 (42.8%)	286 (41.9%)
Non-steroidal anti-inflammatory drugs	2521 (34.6%)	1569 (33%)	1886 (36.8%)	239 (35%)
Proton-pump-inhibitors	3340 (45.8%)	2259 (47.6%)	2364 (46.2%)	312 (45.8%)
Heparin or fondaparinux	1653 (22.7%)	361 (7.6%)	414 (8.1%)	43 (6.3%)

Data on scores, comorbidities, and co-medication use were retrieved from the 12 months prior to index date (baseline period).

7.2 Effectiveness and safety outcomes

7.2.1 Patients with renal impairment

The adjusted risk of IS/SE was similar in patients treated with rivaroxaban or apixaban, compared to phenprocoumon (

Table 5). For important safety outcomes (intracranial hemorrhage, fatal bleeding), users of rivaroxaban or apixaban had lower risks than users of phenprocoumon, effects were more pronounced for apixaban over phenprocoumon. For acute kidney injury, adjusted risk estimates for all NOACs were below 1, particularly being statistically significant for rivaroxaban. The risk for kidney failure was lower for rivaroxaban and apixaban, being more pronounced for rivaroxaban. The same pattern of results was observed after restricting the NOAC study population to users of reduced doses of NOACs (Table 6).

Rivaroxaban and apixaban were similar to phenprocoumon in terms of additional effectiveness outcomes ischemic stroke, systemic embolism and severe ischemic stroke (Table 7). Treatment discontinuations occurred less frequently with all NOACs under study (Table 7). The results for these outcomes were similar when the NOAC study population was restricted to users of reduced doses of NOACs (Table 8).

Table 5 Effectiveness and safety outcomes in NVAF patients with renal impairment, initiating treatment with phenprocoumon or NOACs

	Person years at risk	Number of events	Incidence rate % per year (95% CI)	Hazard ratio crude (95% CI)	Hazard ratio adjusted (95% CI)
Ischemic stroke / systemic embolism					
Phenprocoumon	7654.9	132	1.72 (1.44 ; 2.04)	1.0	1.0
Rivaroxaban	5507.7	92	1.67 (1.35 ; 2.05)	1.00 (0.76 ; 1.30)	0.95 (0.73 ; 1.24)
Apixaban	4648.7	95	2.04 (1.65 ; 2.50)	1.17 (0.90; 1.52)	0.99 (0.74 ; 1.30)
Edoxaban			-[1]		
Intracranial hemorrhage					
Phenprocoumon	7699	50	0.65 (0.48 ; 0.86)	1.0	1.0
Rivaroxaban	5558	23	0.41 (0.26 ; 0.62)	0.65 (0.40 ; 1.07)	0.62 (0.37 ; 1.01)
Apixaban	4707.1	16	0.34 (0.19 ; 0.55)	0.52 (0.30 ; 0.91)	0.41 (0.23 ; 0.74)
Edoxaban			-[1]		
Fatal bleeding					
Phenprocoumon	7707.8	82	1.06 (0.85 ; 1.32)	1.0	1.0
Rivaroxaban	5563.3	34	0.61 (0.42 ; 0.85)	0.59 (0.4 ; 0.88)	0.63 (0.42 ; 0.95)
Apixaban	4708.6	24	0.51 (0.33 ; 0.76)	0.46 (0.29 ; 0.73)	0.39 (0.24 ; 0.62)
Edoxaban			-[1]		
Acute kidney injury					
Phenprocoumon	7635.4	155	2.03 (1.72 ; 2.38)	1.0	1.0
Rivaroxaban	5542.2	79	1.43 (1.13 ; 1.78)	0.73 (0.56 ; 0.96)	0.77 (0.58 ; 1.01)
Apixaban	4658.9	92	1.97 (1.59 ; 2.42)	0.96 (0.74 ; 1.24)	0.90 (0.69 ; 1.17)

Edoxaban	529.6	10	1.89 (0.91 ; 3.47)	0.84 (0.44 ; 1.60)	0.86 (0.45 ; 1.65)
Kidney failure					
Phenprocoumon	7647.4	134	1.75 (1.47 ; 2.08)	1.0	1.0
Rivaroxaban	5560.3	19	0.34 (0.21 ; 0.53)	0.20 (0.12 ; 0.32)	0.27 (0.16 ; 0.43)
Apixaban	4700.5	34	0.72 (0.50 ; 1.01)	0.41 (0.28 ; 0.60)	0.43 (0.29 ; 0.63)
Edoxaban			-[1]		

[1]No estimates possible due to low number of patients with events (n<5).

Table 6 Effectiveness and safety outcomes in NVAF patients with renal impairment, initiating treatment with phenprocoumon or reduced dose NOACs

	Person years at risk	Number of events	Incidence rate % per year (95% CI)	Hazard ratio crude (95% CI)	Hazard ratio adjusted (95% CI)
Ischemic stroke / systemic embolism					
Phenprocoumon	7654.9	132	1.72 (1.44 ; 2.04)	1.0	1.0
Rivaroxaban	2326.2	51	2.19 (1.63 ; 2.88)	1.31 (0.94 ; 1.81)	1.08 (0.78 ; 1.52)
Apixaban	2383.3	60	2.52 (1.92 ; 3.24)	1.44 (1.06 ; 1.95)	1.07 (0.76 ; 1.49)
Edoxaban			-[1]		
Intracranial hemorrhage					
Phenprocoumon	7699	50	0.65 (0.48 ; 0.86)	1.0	1.0
Rivaroxaban	2346.2	11	0.47 (0.23 ; 0.84)	0.74 (0.39 ; 1.42)	0.63 (0.32 ; 1.24)
Apixaban	2420.6	8	0.33 (0.14 ; 0.65)	0.51 (0.24 ; 1.07)	0.35 (0.16 ; 0.77)
Edoxaban			-[1]		
Fatal bleeding					
Phenprocoumon	7707.8	82	1.06 (0.85 ; 1.32)	1.0	1.0
Rivaroxaban	2347.8	23	0.98 (0.62 ; 1.47)	0.95 (0.60 ; 1.50)	0.70 (0.43 ; 1.14)
Apixaban	2421	14	0.58 (0.32 ; 0.97)	0.52 (0.29 ; 0.92)	0.30 (0.17 ; 0.55)
Edoxaban			-[1]		
Acute kidney injury					
Phenprocoumon	7635.4	155	2.03 (1.72 ; 2.38)	1.0	1.0
Rivaroxaban	2337.2	44	1.88 (1.37 ; 2.53)	0.96 (0.69 ; 1.35)	0.82 (0.58 ; 1.15)
Apixaban	2386.5	63	2.64 (2.03 ; 3.38)	1.28 (0.95 ; 1.71)	0.98 (0.72 ; 1.33)
Edoxaban	221.3	8	3.61 (1.56 ; 7.12)	1.60 (0.78 ; 3.27)	1.25 (0.61 ; 2.57)
Kidney failure					
Phenprocoumon	7647.4	134	1.75 (1.47 ; 2.08)	1.0	1.0
Rivaroxaban	2346.3	12	0.51 (0.26 ; 0.89)	0.3 (0.17 ; 0.54)	0.31 (0.17 ; 0.57)
Apixaban	2417.2	24	0.99 (0.64 ; 1.48)	0.56 (0.37 ; 0.87)	0.49 (0.32 ; 0.78)
Edoxaban			-[1]		

[1]No estimates possible due to low number of patients with events (n<5).

Table 7 Additional effectiveness and safety outcomes in NVAF patients with renal impairment

	Person years at risk	Number of events	Incidence rate % per year (95% CI)	Hazard ratio crude (95% CI)	Hazard ratio adjusted (95% CI)
Ischemic stroke					
Phenprocoumon	7660.8	118	1.54 (1.27 ; 1.84)	1.0	1.0
Rivaroxaban	5510	87	1.58 (1.26 ; 1.95)	1.05 (0.8 ; 1.39)	1.02 (0.77 ; 1.36)
Apixaban	4651.2	86	1.85 (1.48 ; 2.28)	1.18 (0.89 ; 1.56)	0.98 (0.73 ; 1.3)
Edoxaban		<5			
Systemic embolism					
Phenprocoumon	7702	14	0.18 (0.1 ; 0.3)	1.0	1.0
Rivaroxaban	5561	5	0.09 (0.03 ; 0.21)	0.52 (0.19 ; 1.45)	0.42 (0.14 ; 1.20)
Apixaban	4705.5	10	0.21 (0.1 ; 0.39)	1.17 (0.52 ; 2.64)	1.51 (0.62 ; 3.72)
Edoxaban		<5			
Severe ischemic stroke					
Phenprocoumon	7706.5	22	0.29 (0.18 ; 0.43)	1.0	1.0
Rivaroxaban	5561.7	16	0.29 (0.16 ; 0.47)	1.03 (0.54 ; 1.96)	0.89 (0.46 ; 1.71)
Apixaban	4703.1	17	0.36 (0.21 ; 0.58)	1.24 (0.66 ; 2.34)	1.00 (0.53 ; 1.92)
Edoxaban		<5			
Treatment discontinuation					
Phenprocoumon	9032.2	3620	40.08 (38.78; 41.41)	1.0	1.0
Rivaroxaban	7142.5	1624	22.74 (21.64; 23.87)	0.61 (0.57; 0.65)	0.60 (0.56; 0.63)
Apixaban	5471.2	1301	23.78 (22.50; 25.11)	0.57 (0.53; 0.60)	0.62 (0.57; 0.67)
Edoxaban	580.9	131	22.55 (18.86; 26.76)	0.45 (0.38; 0.54)	0.51 (0.42; 0.62)

Table 8 Additional effectiveness and safety outcomes in NVAF patients with renal impairment, treated with phenprocoumon or low dose NOACs

	Person years at risk	Number of events	Incidence rate % per year (95% CI)	Hazard ratio crude (95% CI)	Hazard ratio adjusted (95% CI)
Ischemic stroke					
Phenprocoumon	7660.8	118	1.54 (1.27 ; 1.84)	1.0	1.0
Rivaroxaban	2327.4	48	2.06 (1.52 ; 2.73)	1.37 (0.98 ; 1.92)	1.19 (0.84 ; 1.68)
Apixaban	2385.5	53	2.22 (1.66 ; 2.91)	1.42 (1.02 ; 1.96)	1.01 (0.71 ; 1.44)
Edoxaban		<5			
Systemic embolism					
Phenprocoumon	7702	14	0.18 (0.1 ; 0.3)	1.0	1.0
Rivaroxaban		<5			
Apixaban	2418.2	8	0.33 (0.14 ; 0.65)	1.81 (0.76 ; 4.33)	1.81 (0.71 ; 4.65)
Edoxaban		<5			

Severe ischemic stroke					
Phenprocoumon	7706.5	22	0.29 (0.18 ; 0.43)	1.0	1.0
Rivaroxaban	2346.8	11	0.47 (0.23 ; 0.84)	1.69 (0.82 ; 3.49)	1.18 (0.56 ; 2.51)
Apixaban	2418.8	8	0.33 (0.14 ; 0.65)	1.14 (0.5 ; 2.56)	0.62 (0.26 ; 1.47)
Edoxaban		<5			
Treatment discontinuation					
Phenprocoumon	9032.2	3620	40.08 (38.78; 41.41)	1.0	1.0
Rivaroxaban	2981.1	657	22.04 (20.39; 23.79)	0.59 (0.54 ; 0.64)	0.52 (0.47 ; 0.56)
Apixaban	2758.2	632	22.91 (21.16; 24.77)	0.54 (0.49 ; 0.58)	0.51 (0.46 ; 0.56)
Edoxaban	243.7	44	18.05 (13.12; 24.23)	0.36 (0.26 ; 0.48)	0.37 (0.27 ; 0.51)

7.2.2 Overall study population and patient subgroups

The study results for the overall population were similar as for patients with renal impairment, including a reduced risk of kidney failure associated with use of rivaroxaban or apixaban (Table 10). Subgroup analyses for the outcomes of IS/SE and ICH did not reveal meaningful differences of effect estimates (Table 11). The lower risk of ICH was observed consistently within subgroups for rivaroxaban and apixaban, while the number of patients with an event was too low to provide estimates for edoxaban.

Table 9 Baseline characteristics of the overall NVAF patients population initiating treatment with phenprocoumon or NOACs

	Phenprocoumon (N=23552)	Apixaban (N=16201)	Rivaroxaban (N=22339)	Edoxaban (N=2828)
Gender				
Female	9868 (41.9%)	7110 (43.9%)	9025 (40.4%)	1131 (40.0%)
Male	13684 (58.1%)	9091 (56.1%)	13314 (59.6%)	1697 (60.0%)
Age in years (Mean±SD)	74.1±9.9	73.6±11.6	70.7±12	72.1±11.4

Table 10 Effectiveness and safety outcomes in NVAF patients (overall population)

	Person years at risk	Number of events	Incidence rate % per year (95% CI)	Hazard ratio crude (95% CI)	Hazard ratio adjusted (95% CI)
Ischemic stroke / systemic embolism					
Phenprocoumon	28601.7	340	1.19 (1.07 ; 1.32)	1.0	1.0
Rivaroxaban	24379.2	271	1.11 (0.98 ; 1.25)	0.93 (0.79 ; 1.09)	0.96 (0.81 ; 1.12)
Apixaban	16497.4	263	1.59 (1.41 ; 1.80)	1.27 (1.08 ; 1.49)	1.03 (0.87 ; 1.21)
Edoxaban	2217.9	27	1.22 (0.80 ; 1.77)	0.84 (0.57 ; 1.25)	0.95 (0.64 ; 1.42)
Ischemic stroke					
Phenprocoumon	28618.2	310	1.08 (0.97 ; 1.21)	1.0	1.0
Rivaroxaban	24390.8	250	1.02 (0.90 ; 1.16)	0.94 (0.80 ; 1.11)	0.96 (0.81 ; 1.14)
Apixaban	16506.1	241	1.46 (1.28 ; 1.66)	1.28 (1.08 ; 1.52)	1.01 (0.85 ; 1.21)
Edoxaban	2219	24	1.08 (0.69 ; 1.61)	0.83 (0.55 ; 1.26)	0.95 (0.62 ; 1.44)

Systemic embolism					
Phenprocoumon	28762.9	31	0.11 (0.07 ; 0.15)	1.0	1.0
Rivaroxaban	24517.1	21	0.09 (0.05 ; 0.13)	0.78 (0.45 ; 1.35)	0.85 (0.49 ; 1.49)
Apixaban	16643.6	23	0.14 (0.09 ; 0.21)	1.18 (0.69 ; 2.02)	1.14 (0.65 ; 1.98)
Edoxaban		<5			
Severe ischemic stroke					
Phenprocoumon	28776.4	40	0.14 (0.10 ; 0.19)	1.0	1.0
Rivaroxaban	24522.8	36	0.15 (0.10 ; 0.20)	1.03 (0.66 ; 1.62)	1.00 (0.63 ; 1.57)
Apixaban	16643.5	34	0.20 (0.14 ; 0.29)	1.39 (0.88 ; 2.20)	1.11 (0.70 ; 1.78)
Edoxaban	2224.4	6	0.27 (0.10 ; 0.59)	1.66 (0.70 ; 3.95)	1.77 (0.74 ; 4.22)
Intracranial hemorrhage					
Phenprocoumon	28736.6	157	0.55 (0.46 ; 0.64)	1.0	1.0
Rivaroxaban	24508.4	76	0.31 (0.24 ; 0.39)	0.56 (0.43 ; 0.74)	0.57 (0.43 ; 0.75)
Apixaban	16645.7	47	0.28 (0.21 ; 0.38)	0.49 (0.36 ; 0.69)	0.43 (0.31 ; 0.60)
Edoxaban		<5			
Fatal bleeding					
Phenprocoumon	28779.6	137	0.48 (0.40 ; 0.56)	1.0	1.0
Rivaroxaban	24528.6	88	0.36 (0.29 ; 0.44)	0.75 (0.58 ; 0.99)	0.78 (0.60 ; 1.03)
Apixaban	16653	48	0.29 (0.21 ; 0.38)	0.58 (0.42 ; 0.80)	0.48 (0.34 ; 0.68)
Edoxaban	2225.1	6	0.27 (0.10; 0.59)	0.49 (0.22 ; 1.12)	0.55 (0.24 ; 1.26)
Kidney failure					
Phenprocoumon	28708.3	150	0.52 (0.44 ; 0.61)	1.0	1.0
Rivaroxaban	24524.8	29	0.12 (0.08 ; 0.17)	0.23 (0.15 ; 0.34)	0.34 (0.23 ; 0.51)
Apixaban	16640	57	0.34 (0.26 ; 0.44)	0.63 (0.47 ; 0.86)	0.67 (0.49 ; 0.92)
Edoxaban		<5			
Acute kidney injury					
Phenprocoumon	28659.4	229	0.80 (0.70 ; 0.91)	1.0	1.0
Rivaroxaban	24484.1	141	0.58 (0.48 ; 0.68)	0.71 (0.58 ; 0.88)	0.81 (0.66 ; 1.00)
Apixaban	16582.8	148	0.89 (0.75 ; 1.05)	1.07 (0.87 ; 1.32)	0.99 (0.80 ; 1.22)
Edoxaban	2222.1	13	0.59 (0.31 ; 1.00)	0.64 (0.37 ; 1.12)	0.74 (0.42 ; 1.29)
Treatment discontinuation					
Phenprocoumon	34187.9	11229	32.84 (32.24; 33.46)	1.0	1.0
Rivaroxaban	31627.1	8527	26.96 (26.39; 27.54)	0.85 (0.83 ; 0.88)	0.82 (0.8 ; 0.85)
Apixaban	19350.8	5343	27.61 (26.88; 28.36)	0.77 (0.75 ; 0.8)	0.86 (0.83 ; 0.9)
Edoxaban	2442.4	669	27.39 (25.35; 29.55)	0.64 (0.59 ; 0.69)	0.77 (0.7 ; 0.84)

Table 11 Risk of main effectiveness and safety outcomes in patient subgroups of the overall population (adjusted)

	Hazard Ratio (95% CI)		
	Rivaroxaban	Apixaban	Edoxaban
Effectiveness outcome: Ischemic stroke / systemic embolism			
Overall study population	0.96 (0.81; 1.12)	1.03 (0.87; 1.21)	0.95 (0.64; 1.42)
Without renal impairment	0.95 (0.76 ; 1.14)	1.08 (0.88 ; 1.34)	1.19 (0.77 ; 1.83)
With renal impairment	0.95 (0.73 ; 1.24)	0.99 (0.74 ; 1.30)	-[1]

Non-frail	0.94 (0.77 ; 1.15)	0.92 (0.74 ; 1.16)	0.89 (0.53 ; 1.48)
Frail	0.97 (0.74 ; 1.27)	1.13 (0.88 ; 1.46)	0.95 (0.51 ; 1.77)
Age < 80 years	0.96 (0.78 ; 1.18)	1.00 (0.79 ; 1.25)	0.99 (0.59 ; 1.65)
Age 80+ years	0.96 (0.75 ; 1.24)	1.12 (0.87 ; 1.43)	0.83 (0.44 ; 1.54)
Without prior IS/SE/TIA	0.95 (0.78 ; 1.15)	0.99 (0.79 ; 1.23)	0.95 (0.59 ; 1.55)
Prior IS/SE/TIA	1.03 (0.78 ; 1.36)	1.09 (0.84 ; 1.42)	0.91 (0.46 ; 1.81)
Standard dose of NOACs	0.95 (0.80 ; 1.13)	0.96 (0.80 ; 1.15)	0.88 (0.56 ; 1.39)
Reduced dose of NOACs	0.96 (0.76 ; 1.21)	1.06 (0.85 ; 1.33)	0.94 (0.48 ; 1.84)
Without cancer	0.95 (0.80 ; 1.13)	0.96 (0.80 ; 1.15)	0.88 (0.56 ; 1.39)
With cancer	0.91 (0.60 ; 1.37)	1.39 (0.94 ; 2.05)	1.17 (0.50 ; 2.78)
Without diabetes	1.06 (0.86 ; 1.31)	1.04 (0.83 ; 1.30)	1.18 (0.73 ; 1.91)
With diabetes	0.83 (0.65 ; 1.07)	1.03 (0.80 ; 1.32)	0.64 (0.31 ; 1.30)
Safety outcome: intracranial hemorrhage			
Overall study population	0.57 (0.43; 0.74)	0.43 (0.31; 0.60)	-[1]
Without renal impairment	0.54 (0.38 ; 0.75)	0.40 (0.27 ; 0.61)	
With renal impairment	0.62 (0.37 ; 1.01)	0.41 (0.23 ; 0.74)	
Non-frail	0.56 (0.40 ; 0.79)	0.43 (0.28 ; 0.67)	
Frail	0.61 (0.38 ; 1.00)	0.51 (0.30 ; 0.87)	
Age < 80 years	0.51 (0.35 ; 0.74)	0.47 (0.31 ; 0.73)	
Age 80+ years	0.68 (0.44 ; 1.03)	0.37 (0.22 ; 0.62)	
Without prior IS/SE/TIA	0.56 (0.40 ; 0.77)	0.35 (0.23 ; 0.55)	
Prior IS/SE/TIA	0.58 (0.34 ; 0.99)	0.56 (0.33 ; 0.95)	
Standard dose of NOACs	0.59 (0.43 ; 0.81)	0.47 (0.31 ; 0.70)	
Reduced dose of NOACs	0.54 (0.35 ; 0.84)	0.35 (0.21 ; 0.58)	
Without cancer	0.53 (0.39 ; 0.72)	0.39 (0.27 ; 0.57)	
With cancer	0.77 (0.42 ; 1.44)	0.50 (0.24 ; 1.06)	
Without diabetes	0.48 (0.34 ; 0.67)	0.42 (0.28 ; 0.63)	
With diabetes	0.77 (0.49 ; 1.21)	0.41 (0.22 ; 0.74)	

[1]No estimates possible due to low number of patients with events (n<5).

7.2.3 Sensitivity analyses

The observed hazard ratios of effectiveness and safety outcomes were generally robust with respect to the method of analysis used. The results of the propensity score based methods are included in Table 12. Several sensitivity analyses (i.e. consideration of tablet stockpiling; estimation of a personalized daily dose of NOACs/phenprocoumon; assumption of use of one tablet of phenprocoumon per day; and exclusion of patients with an outcome event in the baseline period) were performed to investigate the impact of methodological aspects on the risk estimates of the main effectiveness and safety outcomes. None of these aspects indicated an important influence on the risk estimates of IS/SE or ICH (Table 13).

Table 12 Hazard ratios of effectiveness and safety outcomes vs. phenprocoumon based on different analytical methods (renal impairment population)

	Hazard Ratio (95% CI)			
	Confounder adjusted analysis	IPTW analysis	IPTW analysis trimmed	PS Matching
Ischemic stroke / systemic embolism				
Rivaroxaban	0.95 (0.73;1.24)	1.05 (0.81;1.38)	1.1 (0.84;1.44)	1.17 (0.85;1.6)
Apixaban	0.99 (0.74;1.3)	0.97 (0.74;1.27)	1 (0.76;1.32)	1.18 (0.81;1.72)
Edoxaban	-[1]			
Ischemic stroke				
Rivaroxaban	1.02 (0.77;1.36)	1.08 (0.82;1.42)	1.13 (0.85;1.49)	1.18 (0.85;1.64)
Apixaban	0.98 (0.73;1.3)	0.91 (0.68;1.21)	0.93 (0.69;1.25)	1.09 (0.73;1.61)
Edoxaban	-[1]			
Systemic embolism				
Rivaroxaban	0.42 (0.14;1.2)	0.81 (0.31;2.1)	0.85 (0.32;2.24)	1.01 (0.29;3.49)
Apixaban	1.51 (0.62;3.72)	1.69 (0.73;3.9)	1.89 (0.79;4.52)	3.34 (0.69;16.14)
Edoxaban	-[1]			
Severe ischemic stroke				
Rivaroxaban	0.89 (0.46;1.71)	1.15 (0.61;2.17)	1.11 (0.58;2.11)	1.06 (0.52;2.15)
Apixaban	1 (0.53;1.92)	0.89 (0.46;1.74)	0.93 (0.48;1.81)	1.54 (0.63;3.72)
Edoxaban	-[1]			
Intracranial hemorrhage				
Rivaroxaban	0.62 (0.37;1.01)	0.62 (0.38;1.01)	0.69 (0.42;1.14)	0.59 (0.34;1.02)
Apixaban	0.41 (0.23;0.74)	0.37 (0.2;0.69)	0.38 (0.2;0.71)	0.46 (0.2;1.07)
Edoxaban	-[1]			
Fatal bleeding				
Rivaroxaban	0.63 (0.42;0.95)	0.74 (0.51;1.08)	0.72 (0.49;1.08)	0.71 (0.45;1.1)
Apixaban	0.39 (0.24;0.62)	0.45 (0.29;0.7)	0.47 (0.3;0.74)	0.41 (0.22;0.77)
Edoxaban	-[1]			
Kidney failure				
Rivaroxaban	0.27 (0.16;0.43)	0.28 (0.18;0.42)	0.29 (0.19;0.45)	0.26 (0.15;0.43)

Apixaban	0.43 (0.29;0.63)	0.39 (0.27;0.56)	0.42 (0.29;0.61)	0.51 (0.32;0.81)
Edoxaban	-[1]			
Acute kidney injury				
Rivaroxaban	0.77 (0.58;1.01)	0.77 (0.59;1.00)	0.8 (0.61;1.05)	0.8 (0.59;1.1)
Apixaban	0.9 (0.69;1.17)	0.84 (0.65;1.08)	0.92 (0.71;1.18)	0.79 (0.57;1.11)
Edoxaban	0.86 (0.45;1.65)	1.74 (1.09;2.76)	1.82 (1.14;2.89)	0.98 (0.42;2.31)
Treatment discontinuation				
Rivaroxaban	0.82 (0.78;0.87)	0.84 (0.8;0.89)	0.85 (0.81;0.89)	0.87 (0.82;0.92)
Apixaban	0.77 (0.73;0.82)	0.8 (0.76;0.84)	0.83 (0.79;0.88)	0.83 (0.78;0.9)
Edoxaban	0.61 (0.53;0.7)	0.61 (0.53;0.7)	0.6 (0.52;0.69)	0.64 (0.54;0.76)

[1]No estimates possible due to low number of patients with events (n<5).

Table 13 Hazard ratios of main effectiveness and safety outcome vs. phenprocoumon in sensitivity analyses (renal impairment population)

	Hazard Ratio (95% CI)				
	Main analysis	Stockpiling	Personalized daily dose	Assuming use of one tablet of phenproco-umon per day	Exclusion of patients with an outcome event in the baseline period
Ischemic stroke / systemic embolism					
Rivaroxaban	0.95 (0.73 ; 1.24)	0.95 (0.74 ; 1.23)	1.03 (0.79 ; 1.35)	1.00 (0.72 ; 1.38)	0.84 (0.60 ; 1.16)
Apixaban	0.99 (0.74 ; 1.30)	0.98 (0.75 ; 1.27)	1.06 (0.81 ; 1.41)	0.92 (0.66 ; 1.29)	0.93 (0.66 ; 1.3)
Edoxaban	-[1]	0.47 (0.19 ; 1.16)	-[1]	-[1]	-[1]
Intracranial hemorrhage					
Rivaroxaban	0.62 (0.37 ; 1.01)	0.68 (0.44 ; 1.04)	0.67 (0.41 ; 1.10)	0.53 (0.29 ; 0.96)	0.7 (0.42 ; 1.16)
Apixaban	0.41 (0.23 ; 0.74)	0.42 (0.25 ; 0.70)	0.46 (0.26 ; 0.82)	0.42 (0.22 ; 0.80)	0.45 (0.25 ; 0.84)
Edoxaban	-[1]	-[1]	-[1]	-[1]	-[1]

[1]No estimates possible due to low number of patients with events (n<5).

7.3 Healthcare resource utilization and costs

During the baseline period, patients treated with apixaban or rivaroxaban had a higher mean number of hospitalizations than patients treated with phenprocoumon, while it was lower in edoxaban patients (

Table 14). The number of ambulatory physicians contacts were highest with phenprocoumon. Overall baseline costs were highest for apixaban and lowest for edoxaban. These differences were mainly attributable to differences in hospitalization costs.

After treatment initiation, overall indicators of health resource utilization (hospitalizations; EMR visits; hospital days; number of different drugs used) were similar in the different treatment groups in the main as-treated approach that considers actual exposure pattern during follow-up (Table 15). Only the rate ratio of hospital days tended to be slightly higher in patients treated with edoxaban compared to those treated with phenprocoumon. The results of the sensitivity analyses using a modified intention-to-treat approach are reported in Table 16 (follow-up censored after one year) and Table 17 (follow-up censored after two years).

During follow-up, overall HRU costs were higher in patients treated with NOACs compared to phenprocoumon in the main as-treated approach (Table 18). PS matched differences in overall costs ranged between additional 1771€ per year for rivaroxaban and 5493€ per year for edoxaban. Main drivers for these differences were hospital costs and drug prescription costs. Costs associated with renal impairment were lower in patients treated with rivaroxaban or apixaban than in patients treated with phenprocoumon. A similar trend was observed for edoxaban (although not statistically significant). PS matched mean differences remained significantly lower for rivaroxaban (-1164€). The lower costs associated with renal impairment were mainly attributable to lower dialysis-associated costs. The results of the sensitivity analyses using a modified intention-to-treat approach are reported in Table 19 and Table 20.

Table 14 Baseline health resource utilization and costs of NVAF patients with renal impairment, initiating treatment with phenprocoumon or NOACs

HRU / costs in baseline period	Phenprocoumon (N=7289)	Apixaban (N=4750)	Rivaroxaban (N=5121)	Edoxaban (N=682)
Number of hospitalizations (mean+-SD)	1.39±1.33	1.53±1.36	1.46±1.33	1.24±1.23
Number of hospital days (mean+-SD)	15.07±19.55	17.42±22.16	15.26±20.89	12.91±22.08
Number of emergency room visits (mean+-SD)	0.77±0.95	0.96±1	0.85±0.96	0.73±0.88
Number of different medications used (mean+-SD)	10.88±5.61	10.56±5.71	10.31±5.79	10.08±5.59
Number of ambulatory physician contacts (mean+-SD)	17.93±8.63	17.02±8.33	17.35±8.73	17.85±8.75
Overall costs (mean+-SD)	10242.83 ± 12700.89€	11771.68 ± 14047.68€	10974.3 ± 16760.7€	9395.03 ± 12753.3€
Hospital costs (mean+-SD)	7028.21 ± 10689.65€	8408.38 ± 12520.09€	7580.36 ± 13970.14€	6304.12 ± 11488.97€
Ambulatory care costs (mean+-SD)	1188.86 ± 1254.24€	1197.15 ± 889.29€	1188.21 ± 962.66€	1235.23 ± 922.33€

Drug presription costs (mean+-SD)	1436.73 ± 4910.01€	1396.44 ± 3506.93€	1419.83 ± 4331€	1266.03 ± 3316.9€
Remedies and aids costs (mean+-SD)	589.02 ± 1415.56€	769.71 ± 1759.96€	785.91 ± 5906.65€	589.66 ± 1545.95€
Costs associated with renal impairment (mean+-SD)	90.03 ± 1217.27€	74.71 ± 595.02€	50.38 ± 524.4€	62.45 ± 567.69€
Costs associated with dialysis	14.67 ± 886.07€	0 ± 0€	0 ± 0€	0 ± 0€
Costs associated with non-dialysis renal impairment (mean+-SD)	75.35 ± 835.96€	74.71 ± 595.02€	50.38 ± 524.4€	62.45 ± 567.69€

Table 15 Follow-up health resource utilization of NVAF patients with renal impairment, initiating treatment with phenprocoumon or NOACs – Main analysis ("as-treated")

	Phenprocoumon	Rivaroxaban	Apixaban	Edoxaban
Hospitalizations				
EPY	2 (1,9 ; 2,1)	2,1 (2 ; 2,3)	2,2 (2,1 ; 2,4)	2,1 (1,8 ; 2,4)
EPY ratio crude	1	1.04 (0.98 ; 1.09)	1.07 (1.01 ; 1.13)	0.99 (0.88 ; 1.11)
EPY ratio adjusted	1	1.05 (1 ; 1.1)	1 (0.94 ; 1.06)	1.08 (0.96 ; 1.21)
Mean difference crude	0	0.05 (-0.02 ; 0.13)	0.1 (0.02 ; 0.18)	-0.02 (-0.18 ; 0.15)
Mean difference (PS matched)	0	0.08 (-0.01 ; 0.17)	0 (-0.1 ; 0.11)	0.14 (-0.08 ; 0.37)
Emergency room visits				
EPY	1.2 (1.1 ; 1.3)	1.3 (1.2 ; 1.4)	1.4 (1.3 ; 1.5)	1.3 (1.1 ; 1.6)
EPY ratio crude	1	1.01 (0.95 ; 1.09)	1.16 (1.09 ; 1.24)	1.01 (0.87 ; 1.17)
EPY ratio adjusted	1	1 (0.94 ; 1.07)	0.99 (0.92 ; 1.07)	1.09 (0.94 ; 1.27)
Mean difference crude	0	0.01 (-0.04 ; 0.06)	0.13 (0.07 ; 0.19)	0.01 (-0.12 ; 0.13)
Mean difference (PS matched)	0	0.01 (-0.05 ; 0.08)	0.04 (-0.04 ; 0.11)	0.07 (-0.09 ; 0.23)
Hospital days				
EPY	19 (18.1 ; 19.9)	18.2 (17.3 ; 19.3)	20 (18.8 ; 21.2)	20.1 (16.8 ; 23.7)
EPY ratio crude	1	0.96 (0.88 ; 1.03)	1.05 (0.97 ; 1.14)	1.05 (0.88 ; 1.25)
EPY ratio adjusted	1	0.99 (0.91 ; 1.07)	0.96 (0.88 ; 1.05)	1.19 (1 ; 1.43)
Mean difference crude	0	-0.82 (-2.25 ; 0.62)	0.89 (-0.65 ; 2.44)	0.95 (-2.51 ; 4.42)
Mean difference (PS matched)	0	-0.57 (-2.27 ; 1.14)	-0.48 (-2.66 ; 1.7)	3.21 (-1.51 ; 7.93)
Number of different drugs used				
EPY	25 (23.7 ; 26.4)	26.1 (24.8 ; 27.4)	26.4 (25 ; 27.9)	23.9 (20.5 ; 28.4)
EPY ratio crude	1	1.02 (0.99 ; 1.05)	1.06 (1.03 ; 1.09)	0.97 (0.91 ; 1.03)
EPY ratio adjusted	1	1.02 (0.99 ; 1.05)	0.96 (0.93 ; 0.99)	1.01 (0.96 ; 1.07)
Mean difference crude	0	0.42 (-0.13 ; 0.97)	1.09 (0.53 ; 1.65)	-0.61 (-1.67 ; 0.45)
Mean difference (PS matched)	0	0.37 (-0.3 ; 1.05)	-0.61 (-1.42 ; 0.19)	1.04 (-0.28 ; 2.36)

EPY = Events per person year. PS = propensity score. All estimates are presented with 95% confidence intervals in brackets.

Table 16 Follow-up health resource utilization of NVAF patients with renal impairment, initiating treatment with phenprocoumon or NOACs – Sensitivity analysis (modified intention-to-treat approach; follow-up censored one year after index date)

	Phenprocoumon	Rivaroxaban	Apixaban	Edoxaban
Hospitalizations				
EPY	1.8 (1.7 ; 1.9)	1.9 (1.7 ; 2)	2 (1.8 ; 2.1)	1.7 (1.5 ; 2)
EPY ratio crude	1	1.02 (0.97 ; 1.08)	1.07 (1.01 ; 1.12)	0.83 (0.74 ; 0.94)
EPY ratio adjusted	1	1.08 (1.03 ; 1.14)	1.14 (1.08 ; 1.21)	0.96 (0.85 ; 1.08)
Mean difference crude	0	0.04 (-0.04 ; 0.11)	0.1 (0.02 ; 0.18)	-0.25 (-0.39 ; -0.1)
Mean difference (PS matched)	0	0.13 (0.04 ; 0.21)	0.16 (0.06 ; 0.26)	-0.15 (-0.36 ; 0.06)
Emergency room visits				
EPY	1.1 (1 ; 1.2)	1.1 (1 ; 1.2)	1.3 (1.2 ; 1.4)	1.1 (0.9 ; 1.4)
EPY ratio crude	1	1.03 (0.96 ; 1.1)	1.18 (1.11 ; 1.26)	0.87 (0.74 ; 1.01)
EPY ratio adjusted	1	1.08 (1.01 ; 1.15)	1.17 (1.09 ; 1.26)	0.99 (0.85 ; 1.16)
Mean difference crude	0	0.02 (-0.03 ; 0.08)	0.14 (0.09 ; 0.2)	-0.11 (-0.21 ; 0)
Mean difference (PS matched)	0	0.06 (0 ; 0.12)	0.15 (0.07 ; 0.22)	-0.08 (-0.23 ; 0.07)
Hospital days				
EPY	17.8 (16.9 ; 18.6)	16 (15.1 ; 17)	17.9 (16.9 ; 19)	16.6 (13.7 ; 19.7)
EPY ratio crude	1	0.91 (0.84 ; 0.99)	1.02 (0.93 ; 1.1)	0.85 (0.71 ; 1.02)
EPY ratio adjusted	1	0.97 (0.89 ; 1.05)	1.02 (0.93 ; 1.13)	0.96 (0.8 ; 1.16)
Mean difference crude	0	-1.59 (-2.95 ; -0.24)	0.27 (-1.2 ; 1.74)	-2.61 (-5.4 ; 0.17)
Mean difference (PS matched)	0	-0.7 (-2.29 ; 0.88)	0.05 (-1.9 ; 2)	-1.27 (-5.41 ; 2.87)
Number of different drugs used				
EPY	17.8 (17 ; 18.8)	18.9 (17.9 ; 20.1)	21 (19.8 ; 22.5)	18.6 (15.8 ; 22.8)
EPY ratio crude	1	0.97 (0.95 ; 0.99)	1.06 (1.04 ; 1.09)	0.93 (0.89 ; 0.97)
EPY ratio adjusted	1	0.99 (0.97 ; 1.01)	1.04 (1.01 ; 1.06)	0.99 (0.95 ; 1.03)
Mean difference crude	0	-0.49 (-0.81 ; -0.16)	0.9 (0.56 ; 1.25)	-1.02 (-1.66 ; -0.38)

Mean difference (PS matched)	0	-0.05 (-0.45 ; 0.34)	0.62 (0.14 ; 1.09)	-0.2 (-1.07 ; 0.67)

EPY = Events per person year. PS = propensity score. All estimates are presented with 95% confidence intervals in brackets.

Table 17 Follow-up health resource utilization of NVAF patients with renal impairment, initiating treatment with phenprocoumon or NOACs – Sensitivity analysis (modified intention-to-treat approach; follow-up censored two years after index date)

	Phenprocoumon	Rivaroxaban	Apixaban	Edoxaban
Hospitalizations				
EPY	1.8 (1.7 ; 1.9)	1.8 (1.7 ; 1.9)	2 (1.8 ; 2.1)	1.7 (1.4 ; 2)
EPY ratio crude	1	1.05 (0.99 ; 1.11)	1.25 (1.18 ; 1.32)	1.17 (1.03 ; 1.33)
EPY ratio adjusted	1	1.08 (1.02 ; 1.14)	1.14 (1.07 ; 1.22)	1.3 (1.15 ; 1.48)
Mean difference crude	0	0.04 (-0.01 ; 0.09)	0.22 (0.16 ; 0.28)	0.15 (0.02 ; 0.28)
Mean difference (PS matched)	0	0.07 (0.01 ; 0.13)	0.11 (0.04 ; 0.18)	0.2 (0.04 ; 0.36)
Emergency room visits				
EPY	1.1 (1 ; 1.2)	1.1 (1 ; 1.2)	1.3 (1.2 ; 1.4)	1.1 (0.9 ; 1.3)
EPY ratio crude	1	1.05 (0.98 ; 1.13)	1.39 (1.29 ; 1.49)	1.21 (1.03 ; 1.42)
EPY ratio adjusted	1	1.07 (1 ; 1.15)	1.17 (1.08 ; 1.26)	1.34 (1.14 ; 1.57)
Mean difference crude	0	0.03 (-0.01 ; 0.06)	0.18 (0.14 ; 0.23)	0.1 (0.01 ; 0.19)
Mean difference (PS matched)	0	0.03 (-0.01 ; 0.07)	0.1 (0.05 ; 0.15)	0.11 (0 ; 0.22)
Hospital days				
EPY	18.2 (17.4 ; 19)	16.1 (15.2 ; 17)	18 (17 ; 19.1)	16.5 (13.8 ; 19.4)
EPY ratio crude	1	0.92 (0.85 ; 1.01)	1.13 (1.04 ; 1.24)	1.07 (0.89 ; 1.3)
EPY ratio adjusted	1	0.97 (0.89 ; 1.05)	1.01 (0.91 ; 1.11)	1.23 (1.02 ; 1.5)
Mean difference crude	0	-0.96 (-2.01 ; 0.09)	1.71 (0.51 ; 2.92)	0.96 (-1.67 ; 3.58)
Mean difference (PS matched)	0	-0.69 (-1.92 ; 0.55)	0 (-1.58 ; 1.59)	2.18 (-1.3 ; 5.66)
Number of different drugs used				
EPY	14.5 (13.7 ; 15.4)	15.9 (15 ; 17)	18.8 (17.6 ; 20.3)	17.5 (14.6 ; 21.8)
EPY ratio crude	1	1.01 (0.98 ; 1.04)	1.29 (1.25 ; 1.33)	1.29 (1.22 ; 1.37)
EPY ratio adjusted	1	1 (0.97 ; 1.02)	1.05 (1.02 ; 1.08)	1.34 (1.27 ; 1.41)

Mean difference crude	0	0.11 (-0.15 ; 0.38)	2.67 (2.36 ; 2.99)	2.69 (2.02 ; 3.36)
Mean difference (PS matched)	0	0 (-0.32 ; 0.33)	0.66 (0.24 ; 1.08)	3.18 (2.41 ; 3.95)

EPY = Events per person year. PS = propensity score. All estimates are presented with 95% confidence intervals in brackets.

Table 18 Follow-up health care costs of NVAF patients with renal impairment, initiating treatment with phenprocoumon or NOACs – Main analysis ("as-treated")

	Phenprocoumon	Rivaroxaban	Apixaban	Edoxaban
Overall costs				
CPY	15170€ (14392.6€ ; 16055.3€)	17318.2€ (16364.4€ ; 18320.7€)	17928.9€ (16760.6€ ; 19207.8€)	18171.1€ (15281.5€ ; 21154€)
CPY ratio crude	1	1.14 (1.09 ; 1.19)	1.18 (1.13 ; 1.23)	1.2 (1.09 ; 1.32)
CPY ratio adjusted	1	1.21 (1.16 ; 1.26)	1.16 (1.11 ; 1.22)	1.43 (1.3 ; 1.57)
Mean difference crude	0 €	2145.39€ (1455.43€ ; 2835.35€)	2758.22€ (2031.18€ ; 3485.27€)	3001.88€ (1301.81€ ; 4701.95€)
Mean difference (PS matched)	0 €	1771.72€ (962.88€ ; 2580.56€)	1948.36€ (926.67€ ; 2970.06€)	5493.83€ (3525.1€ ; 7462.55€)
Hospital costs				
CPY	10574.4€ (9881.3€ ; 11383.3€)	11188.8€ (10229.7€ ; 12115.2€)	12122.9€ (11033.5€ ; 13442.7€)	13036.6€ (10280.6€ ; 16321.8€)
CPY ratio crude	1	1.06 (0.99 ; 1.13)	1.15 (1.07 ; 1.23)	1.23 (1.06 ; 1.44)
CPY ratio adjusted	1	1.13 (1.06 ; 1.21)	1.13 (1.04 ; 1.22)	1.48 (1.27 ; 1.73)
Mean difference crude	0 €	614.37€ (-114.54€ ; 1343.29€)	1548.39€ (767.5€ ; 2329.27€)	2462.44€ (495.31€ ; 4429.58€)
Mean difference (PS matched)	0 €	636.8€ (-231.58€ ; 1505.19€)	1304.01€ (187.27€ ; 2420.76€)	4959.41€ (2693.7€ ; 7225.12€)
Ambulatory costs				
CPY	1393.5€ (1341.8€ ; 1451.2€)	1326.4€ (1270€ ; 1387.5€)	1298€ (1242.4€ ; 1372€)	1198.4€ (1094.8€ ; 1332€)
CPY ratio crude	1	0.95 (0.92 ; 0.98)	0.93 (0.9 ; 0.96)	0.86 (0.8 ; 0.92)
CPY ratio adjusted	1	0.97 (0.94 ; 1)	0.95 (0.92 ; 0.99)	0.9 (0.85 ; 0.96)
Mean difference crude	0 €	-67.03€ (-108.34€ ; -25.72€)	-95.48€ (-136.43€ ; -54.53€)	-194.96€ (-276.11€ ; -113.82€)
Mean difference (PS matched)	0 €	-27.5€ (-76.83€ ; 21.82€)	-80.84€ (-137.21€ ; -24.47€)	-160.37€ (-271.44€ ; -49.29€)

Drug prescription costs				
CPY	2333.1€ (2177.1€ ; 2498.7€)	3642.5€ (3477.7€ ; 3826.6€)	3271.9€ (3126.1€ ; 3432€)	3019.7€ (2696.9€ ; 3400.8€)
CPY ratio crude	1	1.56 (1.51 ; 1.62)	1.4 (1.35 ; 1.46)	1.29 (1.19 ; 1.41)
CPY ratio adjusted	1	1.82 (1.77 ; 1.88)	1.55 (1.49 ; 1.6)	1.75 (1.63 ; 1.88)
Mean difference crude	0 €	1309.47€ (1194.89€ ; 1424.05€)	939.13€ (830.68€ ; 1047.59€)	685.67€ (429.86€ ; 941.49€)
Mean difference (PS matched)	0 €	1122.16€ (986.06€ ; 1258.25€)	627.61€ (484.58€ ; 770.63€)	684.59€ (396.13€ ; 973.05€)
Remedies and aids costs				
CPY	869€ (818.4€ ; 921€)	1160.5€ (975.7€ ; 1478.5€)	1236.1€ (1158.5€ ; 1327.5€)	916.3€ (771.2€ ; 1082.5€)
CPY ratio crude	1	1.34 (1.25 ; 1.43)	1.42 (1.34 ; 1.51)	1.05 (0.91 ; 1.22)
CPY ratio adjusted	1	1.05 (0.99 ; 1.12)	1.09 (1.02 ; 1.17)	1.01 (0.88 ; 1.15)
Mean difference crude	0 €	291.45€ (222.42€ ; 360.48€)	367.05€ (298.16€ ; 435.95€)	47.31€ (-82.82€ ; 177.45€)
Mean difference (PS matched)	0 €	42.88€ (-30.6€ ; 116.36€)	98.46€ (5.15€ ; 191.78€)	9.1€ (-162.94€ ; 181.15€)
Costs associated with renal impairment				
CPY	2251.4€ (1765€ ; 2835.3€)	1106.2€ (647.3€ ; 1659.2€)	1430.3€ (914.5€ ; 2068.4€)	2023.7€ (459€ ; 4000.9€)
CPY ratio crude	1	0.49 (0.34 ; 0.7)	0.63 (0.45 ; 0.89)	0.9 (0.43 ; 1.87)
CPY ratio adjusted	1	0.42 (0.28 ; 0.62)	0.51 (0.33 ; 0.79)	0.55 (0.25 ; 1.2)
Mean difference crude	0 €	-1147.54€ (-1689.16€ ; -605.92€)	-823.37€ (-1406.62€ ; -240.13€)	-229.81€ (-1725.01€ ; 1265.39€)
Mean difference (PS matched)	0 €	-1164.42€ (-1844€ ; -484.84€)	-73.39€ (-927.54€ ; 780.76€)	86.54€ (-1872.18€ ; 2045.27€)
Costs associated with dialysis				
CPY	1925.4€ (1423.7€ ; 2550.9€)	824.7€ (416.4€ ; 1284.7€)	1005€ (524.7€ ; 1599.7€)	1755.4€ (268.7€ ; 3765.3€)
CPY ratio crude	1	0.43 (0.26 ; 0.7)	0.52 (0.33 ; 0.81)	0.91 (0.35 ; 2.4)
CPY ratio adjusted	1	0.4 (0.24 ; 0.67)	0.49 (0.28 ; 0.84)	0.78 (0.27 ; 2.22)
Mean difference crude	0 €	-1102.48€ (-1661.25€ ; -543.72€)	-922.68€ (-1502.6€ ; -342.76€)	-172.35€ (-1883.8€ ; 1539.09€)
Mean difference (PS matched)	0 €	-1134.43€ (-1816.77€ ; -452.1€)	-40.69€ (-860.68€ ; 779.31€)	77.13€ (-2069.43€ ; 2223.69€)
Costs associated with non-dialysis renal impairment				
CPY	326.8€ (233.1€ ; 438.5€)	283.3€ (144.7€ ; 458€)	425€ (257.4€ ; 638.5€)	268.3€ (57.8€ ; 554.4€)
CPY ratio crude	1	0.41 (0.21 ; 0.8)	0.95 (0.51 ; 1.78)	1.53 (0.39 ; 5.93)

CPY ratio adjusted	1	0.53 (0.26 ; 1.09)	0.47 (0.22 ; 1.03)	1.67 (0.38 ; 7.42)
Mean difference crude	0 €	-18.41€ (-30.63€ ; -6.19€)	-1.5€ (-20.38€ ; 17.38€)	16.44€ (-47.31€ ; 80.19€)
Mean difference (PS matched)	0 €	-10.93€ (-23.05€ ; 1.18€)	24.4€ (-2.57€ ; 51.37€)	21.43€ (-49.46€ ; 92.33€)

CPY= Costs per person year. PS = propensity score. All estimates are presented with 95% confidence intervals in brackets.

Table 19 Follow-up health care costs of NVAF patients with renal impairment, initiating treatment with phenprocoumon or NOACs – Sensitivity analysis (modified intention-to-treat approach; follow-up censored one year after index date)

	Phenprocoumon	Rivaroxaban	Apixaban	Edoxaban
Overall costs				
CPY	14409.6€ (13670.1€ ; 15185.7€)	15262.2€ (14386.6€ ; 16202.7€)	16286.5€ (15113.8€ ; 17505.9€)	15722.1€ (13417.8€ ; 18806.4€)
CPY ratio crude	1	1.06 (1.02 ; 1.1)	1.13 (1.08 ; 1.18)	1.09 (0.99 ; 1.2)
CPY ratio adjusted	1	1.14 (1.1 ; 1.19)	1.1 (1.05 ; 1.15)	1.29 (1.18 ; 1.41)
Mean difference crude	0 €	852.51€ (242.75€ ; 1462.27€)	1876.15€ (1221.63€ ; 2530.66€)	1315.01€ (-133.32€ ; 2763.35€)
Mean difference (PS matched)	0 €	666.41€ (-49.07€ ; 1381.89€)	875.12€ (-17.24€ ; 1767.48€)	3550.87€ (1830.3€ ; 5271.45€)
Hospital costs				
CPY	10199€ (9511.7€ ; 10995.2€)	9703.4€ (8926.8€ ; 10591.3€)	10818€ (9804.5€ ; 11987.2€)	10769.8€ (8447.3€ ; 13435.5€)
CPY ratio crude	1	0.95 (0.89 ; 1.01)	1.06 (0.99 ; 1.13)	1.06 (0.91 ; 1.22)
CPY ratio adjusted	1	1.04 (0.98 ; 1.11)	1.02 (0.94 ; 1.1)	1.29 (1.12 ; 1.49)
Mean difference crude	0 €	-495.54€ (-1123.67€ ; 132.58€)	619.11€ (-71.17€ ; 1309.39€)	570.85€ (-994.29€ ; 2136€)
Mean difference (PS matched)	0 €	-383.06€ (-1134.83€ ; 368.71€)	-90.05€ (-1055.39€ ; 875.28€)	2980.17€ (1113.91€ ; 4846.44€)
Ambulatory costs				
CPY	1392.2€ (1344.6€ ; 1444.1€)	1269.3€ (1237.3€ ; 1302.8€)	1282.6€ (1245.4€ ; 1325.2€)	1221.9€ (1120.5€ ; 1342.6€)

CPY ratio crude	1	0.91 (0.89 ; 0.94)	0.92 (0.9 ; 0.95)	0.88 (0.83 ; 0.93)
CPY ratio adjusted	1	0.95 (0.93 ; 0.97)	0.94 (0.92 ; 0.97)	0.91 (0.86 ; 0.96)
Mean difference crude	0 €	-122.95€ (-157.43€ ; -88.48€)	-109.63€ (-145.65€ ; -73.62€)	-170.28€ (-242.85€ ; -97.7€)
Mean difference (PS matched)	0 €	-89.1€ (-130.04€ ; -48.17€)	-59.38€ (-108.66€ ; -10.11€)	-89.96€ (-186.73€ ; 6.8€)
Drug prescription costs				
CPY	1978.9€ (1863€ ; 2123.5€)	3191.6€ (3024.9€ ; 3372.8€)	3002.8€ (2858.5€ ; 3148.3€)	2781.5€ (2448.6€ ; 3167€)
CPY ratio crude	1	1.61 (1.56 ; 1.67)	1.52 (1.47 ; 1.57)	1.41 (1.3 ; 1.52)
CPY ratio adjusted	1	1.92 (1.86 ; 1.97)	1.77 (1.71 ; 1.83)	1.91 (1.8 ; 2.04)
Mean difference crude	0 €	1213.64€ (1118.44€ ; 1308.84€)	1023.77€ (931.23€ ; 1116.3€)	802.67€ (583.88€ ; 1021.47€)
Mean difference (PS matched)	0 €	1094.27€ (981.84€ ; 1206.7€)	915.1€ (801.11€ ; 1029.09€)	694.35€ (437.73€ ; 950.96€)
Remedies and aids costs				
CPY	839.5€ (794.6€ ; 884.3€)	1097.9€ (935.1€ ; 1347.4€)	1183.2€ (1105.3€ ; 1263.4€)	948.8€ (807.3€ ; 1121.7€)
CPY ratio crude	1	1.31 (1.23 ; 1.39)	1.41 (1.33 ; 1.5)	1.13 (0.99 ; 1.29)
CPY ratio adjusted	1	1.03 (0.99 ; 1.07)	1.04 (0.98 ; 1.11)	1.07 (0.95 ; 1.21)
Mean difference crude	0 €	258.39€ (197.03€ ; 319.75€)	343.64€ (280.59€ ; 406.69€)	109.25€ (-17.89€ ; 236.39€)
Mean difference (PS matched)	0 €	44.27€ (-20.45€ ; 108.99€)	109.61€ (25.9€ ; 193.31€)	-34.21€ (-212.26€ ; 143.84€)
Costs associated with renal impairment				
CPY	2217.2€ (1755.6€ ; 2819.9€)	1174.9€ (664.9€ ; 1769.8€)	1553.7€ (996.3€ ; 2175.8€)	1756.8€ (385.2€ ; 3680.3€)
CPY ratio crude	1	0.53 (0.37 ; 0.75)	0.7 (0.5 ; 0.97)	0.79 (0.4 ; 1.56)
CPY ratio adjusted	1	0.46 (0.31 ; 0.68)	0.64 (0.42 ; 0.98)	0.48 (0.23 ; 1)
Mean difference crude	0 €	-1044.52€ (-1583.53€ ; -505.51€)	-665.9€ (-1251.22€ ; -80.58€)	-462.7€ (-1681.07€ ; 755.67€)
Mean difference (PS matched)	0 €	-1029.11€ (-1710.51€ ; -347.71€)	95.49€ (-744.24€ ; 935.22€)	-1.8€ (-1715.75€ ; 1712.16€)

Costs associated with dialysis				
CPY	1903.8€ (1433.5€ ; 2488.6€)	868.2€ (457.6€ ; 1339€)	1197.3€ (714.7€ ; 1785.8€)	1548.5€ (255€ ; 3495.2€)
CPY ratio crude	1	0.46 (0.29 ; 0.72)	0.63 (0.41 ; 0.95)	0.81 (0.3 ; 2.16)
CPY ratio adjusted	1	0.55 (0.33 ; 0.92)	0.69 (0.42 ; 1.14)	0.96 (0.34 ; 2.72)
Mean difference crude	0 €	-1038€ (-1586.9€ ; -489.1€)	-708.85€ (-1307.24€ ; -110.47€)	-357.94€ (-1894.29€ ; 1178.4€)
Mean difference (PS matched)	0 €	-1049.15€ (-1727.02€ ; -371.28€)	205.3€ (-615.75€ ; 1026.35€)	53.64€ (-1929.16€ ; 2036.44€)
Costs associated with non-dialysis renal impairment				
CPY	313.3€ (226€ ; 429.2€)	307.7€ (147.4€ ; 516.9€)	356.2€ (213.1€ ; 556.5€)	208.3€ (71.2€ ; 427.1€)
CPY ratio crude	1	0.46 (0.29 ; 0.72)	0.63 (0.41 ; 0.95)	0.81 (0.3 ; 2.16)
CPY ratio adjusted	1	0.55 (0.33 ; 0.92)	0.69 (0.42 ; 1.14)	0.96 (0.34 ; 2.72)
Mean difference crude	0 €	-1038€ (-1586.9€ ; -489.1€)	-708.85€ (-1307.24€ ; -110.47€)	-357.94€ (-1894.29€ ; 1178.4€)
Mean difference (PS matched)	0 €	-1049.15€ (-1727.02€ ; -371.28€)	205.3€ (-615.75€ ; 1026.35€)	53.64€ (-1929.16€ ; 2036.44€)

CPY= Costs per person year. PS = propensity score. All estimates are presented with 95% confidence intervals in brackets.

Table 20 Follow-up health care costs of NVAF patients with renal impairment, initiating treatment with phenprocoumon or NOACs – Sensitivity analysis (modified intention-to-treat approach; follow-up censored two years after index date)

	Phenprocoumon	Rivaroxaban	Apixaban	Edoxaban
Overall costs				
CPY	14791.6€ (14067.7€ ; 15651.9€)	15225.2€ (14359.8€ ; 16077.9€)	16312€ (15243.2€ ; 17523.9€)	15451.6€ (12971.2€ ; 18189.2€)
CPY ratio crude	1	1.03 (0.99 ; 1.07)	1.1 (1.06 ; 1.15)	1.04 (0.96 ; 1.14)
CPY ratio adjusted	1	1.1 (1.06 ; 1.14)	1.08 (1.04 ; 1.13)	1.22 (1.12 ; 1.33)

Mean difference crude	0 €	432.01€ (-163.1€ ; 1027.11€)	1519.69€ (880.51€ ; 2158.87€)	657.79€ (-712.61€ ; 2028.18€)
Mean difference (PS matched)	0 €	448.26€ (-251.95€ ; 1148.47€)	676.51€ (-204.98€ ; 1558.01€)	2994.16€ (1320.61€ ; 4667.71€)
Hospital costs				
CPY	10410.5€ (9660.7€ ; 11139€)	9703.2€ (8869.7€ ; 10547.1€)	10905.1€ (9805.6€ ; 12100.4€)	10518.7€ (8143.3€ ; 13032.6€)
CPY ratio crude	1	0.93 (0.88 ; 0.99)	1.05 (0.99 ; 1.11)	1.01 (0.88 ; 1.17)
CPY ratio adjusted	1	1.02 (0.96 ; 1.08)	1.01 (0.94 ; 1.08)	1.23 (1.07 ; 1.42)
Mean difference crude	0 €	-707.39€ (-1284.04€ ; -130.74€)	494.51€ (-149.53€ ; 1138.55€)	108.17€ (-1389.95€ ; 1606.29€)
Mean difference (PS matched)	0 €	-459.44€ (-1150.19€ ; 231.3€)	-176.44€ (-1078.51€ ; 725.62€)	2460.37€ (709.39€ ; 4211.36€)
Ambulatory costs				
CPY	1461.1€ (1405.9€ ; 1521.9€)	1251.5€ (1220€ ; 1285.5€)	1273€ (1231.7€ ; 1319.7€)	1193.5€ (1097.1€ ; 1305.3€)
CPY ratio crude	1	0.86 (0.83 ; 0.88)	0.87 (0.85 ; 0.9)	0.82 (0.77 ; 0.87)
CPY ratio adjusted	1	0.91 (0.89 ; 0.93)	0.93 (0.91 ; 0.96)	0.86 (0.81 ; 0.9)
Mean difference crude	0 €	-209.64€ (-244.93€ ; -174.36€)	-188.12€ (-225.47€ ; -150.77€)	-267.66€ (-341.28€ ; -194.04€)
Mean difference (PS matched)	0 €	-140.72€ (-181.77€ ; -99.67€)	-64.75€ (-114.33€ ; -15.17€)	-169.51€ (-269.08€ ; -69.94€)
Drug prescription costs				
CPY	2046€ (1925.9€ ; 2176.3€)	3154.5€ (2988.1€ ; 3323.4€)	2950.2€ (2822.3€ ; 3096.6€)	2786.4€ (2456.1€ ; 3131.6€)
CPY ratio crude	1	1.54 (1.49 ; 1.6)	1.44 (1.39 ; 1.49)	1.36 (1.26 ; 1.48)
CPY ratio adjusted	1	1.78 (1.73 ; 1.83)	1.64 (1.59 ; 1.69)	1.84 (1.73 ; 1.96)
Mean difference crude	0 €	1108.35€ (1012.84€ ; 1203.87€)	903.95€ (811.88€ ; 996.03€)	740.46€ (521.7€ ; 959.21€)
Mean difference (PS matched)	0 €	1013.23€ (900.48€ ; 1125.98€)	803.85€ (690.58€ ; 917.12€)	723.41€ (471.19€ ; 975.63€)

Remedies and aids costs				
CPY	873.9€ (833.4€ ; 916.3€)	1116.1€ (951.9€ ; 1403.1€)	1183.7€ (1109.3€ ; 1260.4€)	953€ (817.5€ ; 1100.4€)
CPY ratio crude	1	1.28 (1.21 ; 1.35)	1.35 (1.28 ; 1.43)	1.09 (0.96 ; 1.24)
CPY ratio adjusted	1	1.02 (0.97 ; 1.08)	1.04 (0.98 ; 1.1)	1.04 (0.92 ; 1.17)
Mean difference crude	0 €	242.18€ (183.63€ ; 300.73€)	309.75€ (249.35€ ; 370.15€)	79.04€ (-44.59€ ; 202.67€)
Mean difference (PS matched)	0 €	34.72€ (-26.95€ ; 96.38€)	113.23€ (33.44€ ; 193.01€)	-20.36€ (-188.2€ ; 147.49€)
Costs associated with renal impairment				
CPY	2699.7€ (2174.6€ ; 3349€)	1355.4€ (859.8€ ; 1972.7€)	1745.6€ (1182.8€ ; 2370.9€)	1704.8€ (427€ ; 3686.2€)
CPY ratio crude	1	0.5 (0.37 ; 0.68)	0.65 (0.48 ; 0.86)	0.63 (0.33 ; 1.19)
CPY ratio adjusted	1	0.46 (0.33 ; 0.63)	0.68 (0.47 ; 0.97)	0.4 (0.2 ; 0.79)
Mean difference crude	0 €	-1346.89€ (-1891.33€ ; -802.45€)	-956.81€ (-1550.63€ ; -362.98€)	-998.07€ (-2134.08€ ; 137.93€)
Mean difference (PS matched)	0 €	-1177.16€ (-1863.12€ ; -491.2€)	41.24€ (-791.21€ ; 873.69€)	-450.19€ (-2121.25€ ; 1220.87€)
Costs associated with dialysis				
CPY	2376.9€ (1898.1€ ; 2939.5€)	1041.8€ (627.1€ ; 1534.2€)	1367€ (834.7€ ; 1984.3€)	1506.3€ (228.7€ ; 3212.5€)
CPY ratio crude	1	0.44 (0.3 ; 0.64)	0.57 (0.4 ; 0.82)	0.63 (0.27 ; 1.49)
CPY ratio adjusted	1	0.46 (0.31 ; 0.7)	0.69 (0.45 ; 1.04)	0.46 (0.18 ; 1.16)
Mean difference crude	0 €	-1337.32€ (-1894.09€ ; -780.56€)	-1012.34€ (-1616.28€ ; -408.4€)	-872.79€ (-2207.26€ ; 461.69€)
Mean difference (PS matched)	0 €	-1212.06€ (-1900.82€ ; -523.31€)	116.25€ (-701.34€ ; 933.84€)	-389.64€ (-2296.02€ ; 1516.74€)
Costs associated with non-dialysis renal impairment				
CPY	322.7€ (230.5€ ; 440.5€)	315.5€ (154.2€ ; 534.7€)	378.4€ (227.1€ ; 584.6€)	198.4€ (77.5€ ; 381.9€)
CPY ratio crude	1	0.44 (0.3 ; 0.64)	0.57 (0.4 ; 0.82)	0.63 (0.27 ; 1.49)

CPY ratio adjusted	1	0.46 (0.31 ; 0.7)	0.69 (0.45 ; 1.04)	0.46 (0.18 ; 1.16)
Mean difference crude	0 €	-1337.32€ (-1894.09€ ; -780.56€)	-1012.34€ (-1616.28€ ; -408.4€)	-872.79€ (-2207.26€ ; 461.69€)
Mean difference (PS matched)	0 €	-1212.06€ (-1900.82€ ; -523.31€)	116.25€ (-701.34€ ; 933.84€)	-389.64€ (-2296.02€ ; 1516.74€)

CPY= Costs per person year. PS = propensity score. All estimates are presented with 95% confidence intervals in brackets.

8. Discussion

In this observational study of patients with NVAF and renal impairment, rivaroxaban and apixaban were similar to phenprocoumon with respect to clinical effectiveness, but were associated with lower risks of important safety outcomes such as intracranial hemorrhage occurred or fatal bleeding. The risk of kidney failure was significantly reduced in users of rivaroxaban and apixaban, compared to phenprocoumon use, being more pronounced for rivaroxaban. Similar effects were observed for acute kidney injury, even though not reaching statistical significance. The results in the overall study population (i.e. patients with and without renal impairment included) were similar to those observed in the renal impairment population.

Effectiveness

Risks of IS/SE in patients with NVAF and renal impairment were similar in users of rivaroxaban and apixaban, compared to users of phenprocoumon. For edoxaban, results were only available for the overall population, and also indicated comparable effectiveness. This finding is in line with the results of phase III RCTs of the respective individual NOACs. For rivaroxaban, a subgroup analysis of patients with a creatinine clearance of 30 to 49 mL/min included in the ROCKET AF trial (Patel et al. 2011) revealed a hazard ratio of 0.84 (95% CI 0.57-1.23) in the per-protocol population (Fox et al. 2011). In the phase III RCTs of apixaban (Granger et al. 2011; Hohnloser et al. 2012) and edoxaban (Giugliano et al. 2013; Bohula et al. 2016), the primary endpoint consisted of a composite of stroke/SE, but included ischemic as well as hemorrhagic strokes. A subgroup analysis of patients with renal impairment included in the ARISTOTLE trial (Hohnloser et al. 2012) is thus difficult to interpret, as it focuses on the primary endpoint that includes measures of effectiveness (IS/SE) and safety (hemorrhagic stroke). A subgroup analysis of the ENGAGE AF-TIMI 48 study (Bohula et al. 2016) reported results for IS/SE and showed similar efficacy for patients with moderate renal dysfunction treated with edoxaban versus warfarin (HR=0.93; 95% CI 0.67-1.30). It needs to be noted that patients with severe renal dysfunction were excluded in the phase III RCTs of factor Xa NOACs, while they were included in this observational study. Even though no stratified analyses for patients with stage 4 CKD were possible, the study findings confirm the external validity of the RCT subgroup analyses on chronic kidney disease (Fox et al. 2011; Hohnloser et al. 2012).

Only few large observational studies including patients with renal impairment, and comparing factor Xa NOACs with vitamin-K antagonists are available. One study (Siontis et al. 2018) compared apixaban with warfarin and found no differences in terms of IS/SE risk (HR= 0.88; 95% CI 0.69–1.12). Another study that used the same data source as the RELOADED study and compared rivaroxaban with phenprocoumon (Bonnemeier et al. 2019) reported a lower risk of ischemic stroke in patients treated with rivaroxaban (HR=0.72; 95% CI 0.55–0.94). Observational studies that included a composite endpoint of IS/SE in unselected patient populations (i.e. patients with and without renal impairment included) showed similar or reduced risks for users of NOACs, compared to warfarin. For rivaroxaban, some studies indicated a lower risk (Chan et al. 2016; Chan et al. 2019; Larsen et al. 2016), while others did not indicate a difference between treatments (Maura et al. 2015; Nielsen et al. 2017). Similarly, results for apixaban differed also among observational studies: While one study reported a decreased risk (Chan et al. 2019), others did report no difference (Larsen et al. 2016) or even a trend towards a higher risk (Nielsen et al. 2017). One study that investigated the risk associated with edoxaban indicated a reduced risk (Chan et al. 2019). To our knowledge, no previous observational study has reported the composite outcome IS/SE for the comparison vs. phenprocoumon instead of warfarin.

Bleeding

The RELOADED study indicated a decreased risk of ICH associated with rivaroxaban or apixaban use, compared to phenprocoumon, both in the renal impairment population and the overall study population. In the subgroup of patients with moderate renal impairment included in the ROCKET AF trial (Fox et al. 2011), intracranial bleeding was not significantly different between treatment groups rivaroxaban and warfarin (HR=0.81; 95% CI 0.41-1.60). The subgroup analysis of the phase III apixaban RCT (Hohnloser et al. 2012) reported results for the primary safety endpoint (major bleeding) only. An observational study (Siontis et al. 2018) reported a hazard ratio of 0.79 (95% CI 0.49–1.26) for the risk of intracranial bleeding with apixaban vs. warfarin. For the comparison of rivaroxaban vs. phenprocoumon, a hazard ratio of 0.66 (95% CI 0.38–1.14) was reported by another observational study involving patients with renal impairment (Bonnemeier et al. 2019).

More data are available for unselected patient populations (i.e. patients with and without renal impairment included). In the ROCKET AF study (Patel et al. 2011), the risk of ICH was significantly lower in patients randomized to rivaroxaban (HR= 0.67; 95% CI 0.47;0.93). This finding was replicated in several observational studies using warfarin as the comparison group (Chan et al. 2016; Larsen et al. 2016; Norby et al. 2017; Yao et al. 2016). Some studies did not show a difference between treatments, possibly due to low statistical power (Halvorsen et al. 2016; Laliberte et al. 2014; Martinez et al. 2019; Staerk et al. 2017). Two studies that included phenprocoumon as the reference group also showed significantly lower risks in users of rivaroxaban (Hohnloser et al. 2018; Bonnemeier et al. 2019). For apixaban, the ARISTOTLE trial (Granger et al. 2011) showed a reduced risk of ICH in comparison to warfarin (HR=0.42; 95% CI 0.30;0.58). This was also found in observational studies comparing apixaban versus warfarin (Halvorsen et al. 2016; Staerk et al. 2017; Yao et al. 2016) or phenprocoumon (Hohnloser et al. 2018). One study did not show a difference in comparison to warfarin (Larsen et al. 2016). From the RELOADED study, no conclusions on the risk of ICH in users of edoxaban were possible due to the low number of patients with events. The phase III RCT indicated a smaller risk than with warfarin (Giugliano et al. 2013), like the other Factor Xa NOACs.

All phase III RCTs indicated lower risks of fatal bleeding in patients randomized to factor Xa NOACs compared to warfarin (Patel et al. 2011; Granger et al. 2011; Giugliano et al. 2013). Hardly any data on this important safety outcome is available from observational studies so far. The RELOADED study thus adds important new data on this endpoint and indicates lower event rates for users of factor Xa NOACs in comparison to phenprocoumon.

Renal outcomes

A recent systematic review and meta-analysis of RCTs and observational studies indicated a significantly lower risk of renal impairment in AF patients treated with rivaroxaban or apixaban (Zhang et al. 2019). The estimates for edoxaban were numerically lower, but not statistically significant, possibly due to low statistical power. The occurrence of warfarin-related nephropathy has been discussed as a potential mechanism of acute kidney injury in warfarin treated patients. Case series indicated that this may be attributable to glomerular hemorrhage and renal tubular obstruction by red-blood cell casts (Brodsky SV et al. 2009). RELOADED is the first study reporting on renal outcomes in patients treated with NOACs compared to phenprocoumon, both for patient with pre-existing renal damage and for the overall patient population. The risk of kidney failure in patients were significantly reduced in patients treated with rivaroxaban or apixaban, and the risk of acute kidney injury numerically lower for users of rivaroxaban or edoxaban. This was observed in both study populations of the study, i.e. in those with renal impairment and in the unselected overall study population.

Treatment discontinuation

The main analysis (i.e. without considering drug stockpiling to estimate time to discontinuation) was identified as leading to an unfair methodological advantage for phenprocoumon: Phenprocoumon is often prescribed in larger package size than the NOACs, and this causes a lower probability of identifying a gap in the treatment period than for NOACs. This could, at least in part, be addressed by considering stockpiling in case the patient collects the follow-up prescription before the previous package is used completely. The stockpiling analyses were thus considered to be more appropriate for the evaluation of treatment discontinuation, and showed lower rates of treatment discontinuation in users of NOACs compared to users of phenprocoumon.

Healthcare resource utilization and costs

Although summary HRU measures such as hospitalization rates; EMR visits; in-hospital days; or number of different drugs used did not indicate differences between treatment groups, overall HRU costs were higher in patients treated with NOACs than in those treated with phenprocoumon. The differences were mainly attributable to differences in hospitalization costs and drug costs. Interestingly, costs associated with renal impairment were lower in patients treated with rivaroxaban or apixaban. This is in correspondence with the observed lower rates of risk of kidney failure.

Strengths and limitations

The RELOADED study utilized data from a large German health insurance claims database. It is one of the few observational studies so far that focused on patients with renal impairment, but also reported results for the overall patient population. As no individual patient consent was necessary

due to the anonymized nature of the data, no selection bias due response/non-response could occur. The study focused on factor Xa NOACs including the newer drug edoxaban, for which data is rather scarce. RELOADED included outcomes that were rarely investigated so far, e.g. fatal bleeding or renal outcomes. Due to the almost exclusive use of phenprocoumon instead of warfarin, it was possible to use this drug as the vitamin-K-antagonist reference category and add data to the rather low number of observational studies that included phenprocoumon. The observed results were robust in several sensitivity analyses. In addition, different approached of analysis (i.e. adjustement vs. PS-based methods) resulted in consistent results.

Some limitations of the study need to be considered. In the RELOADED study, several pre-defined potential confounders were evaluated for inclusion into the multivariate or PS models. However, residual confounding is always a concern in observational research and can thus also not be excluded for this study. For edoxaban, some analyses were limited by the low number of included patients with events. No data on laboratory values were available. This may be of special relevance for phenprocoumon and the International Normalized Ratio (INR), as patients with too low or high values might be under increased risks of thromboembolic events or bleeding, respectively. In addition, it is not straightforward to estimate the exposure time for phenprocoumon due to variation in daily doses. As an approximation, data on the median number of tablets taken was derived from a real-world survey. In addition, sensitivity analyses were included that used different methods to estimate the person time exposed to phenprocoumon, revealing similar results as the main analysis. A validation of outcomes as in RCTs was not possible, which may have resulted in a reduced power to discriminate treatments with respect to outcome rates.

9. Other information

NA

10. Conclusion

In this observational study of patients with NVAF and renal impairment, factor Xa NOACs were similar to phenprocoumon with respect to measures of clinical effectiveness (i.e. IS/SE combined or separately; severe IS). Rivaroxaban and apixaban were associated with lower risks of ICH and kidney failure. The results were similar in the overall patient population and in important patient subgroups, and not affected by methodological aspects or the general approach of analysis (adjustment vs. propensity-score based methods). The observed lower risks of kidney failure associated with rivaroxaban and apixaban support previous studies indicating favourable risk profiles compared to vitamin K antagonists. It is of clinical relevance that this finding was evident in patients with pre-existing renal impairment, as well as the unselected overall NVAF patient population.

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Appendices

Annex 1 OS Protocol

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Annex 2 OS Statistical Analysis Plan

N/A

Annex 3 Publication(s) or manuscript(s)

N/A

Annex 4 Tables, Listings and Figures

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