Observational Study/Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Report version and date	V1.0, 10 JAN 2022
IMPACT study number	21456
Study type / Study phase	Observational, Phase IV, PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS36102
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Medicinal product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Product reference	N/A
Procedure number	N/A
Comparator / Reference therapy	Heparins (B01AB) Vitamin-K antagonist, Phenprocoumon (B01AA04)
Study Initiator and Funder	Bayer AG 13353 Berlin, Germany
Research question and objectives	The primary objective of this study was: •To assess the risk of recurrent venous thromboembolic (VTE) events in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon The secondary objective of this study is: •To assess the risk of fatal bleeding in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon Other objectives of this study are:

	•To assess the risk of end stage renal disease (CKD stage 5 or dialysis) in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon •To assess the health care resource consumption in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon To assesses the overall and sector specific costs in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon
Country(-ies) of study	This study was conducted using secondary data from German sick funds.
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Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
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1. Abstract

Acronym/Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Report version and date **Author**	*v* 1.0, 10 JAN 2022
IMPACT study number	21456
Keywords	Venous thromboembolism; rivaroxaban; phenprocoumon; heparin; historical cohort study; effectiveness; safety
Rationale and background	Rivaroxaban, a direct-acting oral anticoagulants (DOAC), is indicated for VTE treatment. No data on the real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon is available.
Research question and objectives	The study aimed to assess the risk of recurrent VTE events, fatal bleeding, and end stage renal disease in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon. In addition, differences in healthcare resource consumption and healthcare costs were investigated.
Study design	This was a non-interventional retrospective cohort study, using data between January 2013 and December 2019.
Setting	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. Patients were followed up from their index date (first anticoagulation dispensing) until the outcome event, discontinuation of the index anticoagulation regimen, death, end of continuous insurance in the SHI or the end of the study period (31 December 2019), whichever came first.
Subjects and study size, including dropouts	Patients had to have a new diagnosis of VTE, and no diagnoses of alternative indications of oral anticoagulant use. The study included a total of 16081 (rivaroxaban) and 6072 (phenprocoumon) patients, which were followed up for at least 12 months.
Variables and data sources	The study was based on German claims data from the InGef (Institute for Applied Healthcare Research Berlin) research database. Main exposure of interest were derived from

	pharmacy dispensations of rivaroxaban, heparin, and phenprocoumon. A large number of pre-defined covariates were extracted to control for potential confounding. Outcomes of interest were hospitalizations for recurrent VTE; fatal bleeding; end stage renal disease; healthcare consumption; and costs.
Results	The risk of recurrent VTE events leading to hospitalization were similar in patients treated with rivaroxaban and phenprocoumon (HR=1.01; 95% CI 0.84-1.21), while the risk of end-stage kidney disease was lower in patients treated with rivaroxaban (HR=0.45; 95% CI 0.30-0.69). The risk of fatal bleeding was not significantly different between treatment groups (HR=1.42; 95% CI 0.74-2.71). Health resource utilization revealed similar service use in both treatment groups. Healthcare costs were also similar in both treatment groups. While patients treated with rivaroxaban had slightly higher overall drug costs per year (cost difference 991.95€; 95% CI 670.31€-1313.59€), the inpatient costs and costs related to kidney diseases were lower than in users of phenprocoumon.
Discussion	Patients treated with rivaroxaban vs. heparin/phenprocumon had similar risks of hospitalization for recurrent VTE or for fatal bleeding, but lower risks of end-stage kidney disease. Health resource utilization and overall healthcare costs were similar in both treatment groups.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen

2. List of abbreviations

ATC	Anatomical Therapeutic Chemical Classification
CKD	Chronic kidney disease
CPN	Central pharmaceutical number
DDD	Defined daily dose
DOAC	Direct-acting oral anticoagulant
DVT	Deep vein thrombosis
EBM	Einheitlichen Bewertungsmaßstab für Ärzte (German ambulatory claims system)
HR	Hazard ratio
ICD-10 GM	International Statistical Classification of Diseases Version 10, German Modification

InGef	Institute for Applied Healthcare Research Berlin
IPTW	Inverse probability of treatment weighting
LMWH	Low molecular weight heparin
OPS	Operationen- und Prozedurenschlüssel (German Procedure Coding System)
pDDD	Personalized defined daily dose
PE	Pulmonary embolism
SHI	Statutory health insurance
VKA	Vitamin-K-antagonist
VTE	Venous thromboembolism

3. Investigators

Role:	Principal Investigator (external)
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Address	InGef – Institute for Applied Health Research Berlin Spittelmarkt 12, 10117 Berlin
E-mail:	PPD

4. Other responsible parties

4.1 Study Team (internal or external)

Role:	OS Conduct Responsible
Name:	PPD
E-mail:	PPD
Role:	OS Safety Lead / PV Country Head
Name:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Statistician
Name:	PPD (Ingef)
Role:	OS Epidemiologist
Name:	PPD
Role:	Qualified Person responsible for Pharmacovigilance (EU QPPV)
Name:	PPD
Role:	MAH contact person
Name:	PPD

Contact details of the responsible parties are available upon request.

5. Milestones

Table 1. Milestones

Milestone	Planned date	Actual Date	Comments
Start of data collection	01 July 2020	31 July 2020	
End of data collection	31 May 2021	30 April 2021	
Registration in the EU PAS register	01 July 2020	30 June 2020	
Final report of study results	31 January 2022	10 January 2022	

6. Rationale and background

Venous thromboembolism (VTE) manifests as deep vein thrombosis (DVT) or pulmonary embolism (PE). It is the third most common cardiovascular disease worldwide. VTE is a common disease with an incidence around 1-2 cases per 1000 patients per year. It is the third most common acute cardiovascular disease. In 10-30% of all cases a DVT leads to a PE which is the major reason for death after hospitalizations. 30% of these individuals will develop a recurrent venous thromboembolism within 10 years of their initial event. Continuing anticoagulation treatment can reduce the risk of recurrent venous thromboembolism but is associated with increased bleeding risk.

Rivaroxaban, a direct-acting oral anticoagulants (DOAC), is indicated for VTE treatment, being increasingly used in routine clinical practice because of the fixed dosing and favorable pharmacological profiles (i.e. no requirement of INR monitoring; reduced rate of major bleeding while being comparable in terms of rates of recurrent VTE). Evidence on risk reduction for recurrent venous thromboembolism and major bleeding events between rivaroxaban and heparin followed by VKA in the real-world setting is still scarce. The American College of Chest Physicians (CHEST) guidelines recommends the use of DOACs over VKAs in patients with venous thromboembolism without an associated cancer diagnosis. Because patients with unprovoked venous thromboembolism are at higher risk of developing recurrent venous thromboembolism than are those with provoked venous thromboembolism, this study aimed to classify patients as having provoked or unprovoked venous thromboembolism at baseline.

7. Research question and objectives

7.1 Primary objective

The primary objective of this study was:

- To assess the risk of recurrent venous thromboembolic (VTE) events in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon

7.2 Secondary objectives

The secondary objective of this study was:

- To assess the risk of fatal bleeding in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon

7.3 Other objectives

Other objectives of this study were:

- To assess the risk of end stage renal disease (CKD stage 5 or dialysis) in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon
- To assess the health care resource consumption in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon
- To assesses the overall and sector specific costs in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon

8. Amendments and updates

None.

9. Research methods

9.1 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 2013 and December 2019.

9.2 Setting

9.2.1 Study population

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.

Treatment of VTE traditionally consists of acute anticoagulation treatment with heparin (mainly low molecular weight heparin; LMWH), followed by maintenance oral anticoagulation with vitamin-K antagonists (in Germany almost exclusively phenprocoumon). Direct acting oral anticoagulants (DOACs) are an alternative to this treatment approach, with some of them, including rivaroxaban, approved for both the acute and maintenance phase of VTE treatment. Treatment of VTE can occur in an ambulatory or an in-hospital setting, depending on severity of the condition, comorbidities, local health system environment etc.

The following patient groups were identified for the aims of this study:

Patient group 1: Initial in-hospital treatment with primary hospital discharge diagnosis of VTE (=Initial in-hospital treatment of VTE without prior ambulatory anticoagulation). These patients developed VTE out of hospital and were hospitalized for VTE.

Patient group 2: Initial in-hospital treatment with secondary hospital discharge diagnosis of VTE (=Initial in-hospital treatment without prior ambulatory anticoagulation). It is assumed that these patients were admitted to hospital for a different reason, and developed VTE during their hospital stay.

Patient group 3: Ambulatory treatment of VTE (Initiation of anticoagulation in ambulatory setting, without hospitalization for VTE within 14 days after treatment initiation). In these patients, treatment for VTE was administered out of hospital.

Patient group 4: Initial ambulatory treatment, followed by in-hospital treatment with primary or secondary hospital discharge diagnosis of VTE within 14 days after treatment initiation. In these patients, initial treatment of VTE occurred in the outpatient setting, but patients were then (e.g. due to worsening or any other reasons) admitted to hospital due to the initial VTE event.

In the main analysis, patients from all four patient groups were analyzed together. Potential differences between these four groups were evaluated in subgroup analyses.

It should be noted that only patients with at least one dispensing of VKA; rivaroxaban for VTE were included in the study, i.e. patients treated with heparins only were not included.

9.2.2 Study time frame

Data from 2013 was used for the assessment of demographic and clinical characteristics, and to identify prevalent users of rivaroxaban and phenprocoumon (Figure 1). The enrollment was from 01 January 2014 to 30 June 2019. Data from 1 July to 31 December 2019 was considered as follow-up only to allow a follow-up of at least 6 months.

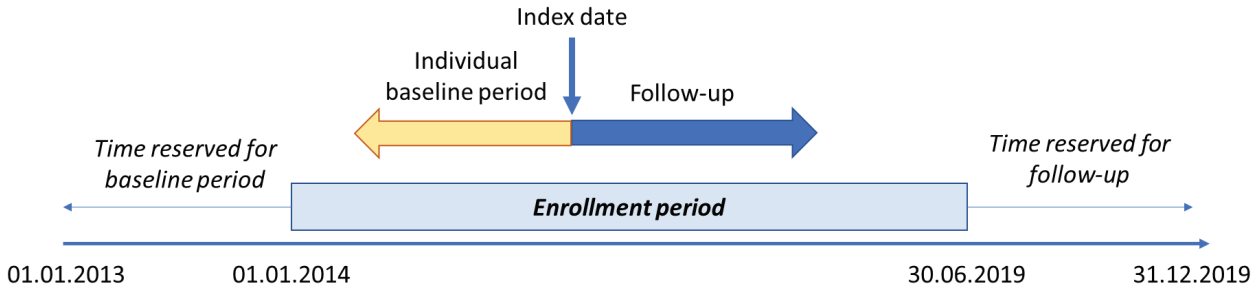

Figure 1. Study periods

9.3 Subjects

Inclusion criteria

All patients had to fulfill all of the following inclusion to be eligible for the study:

- At least one new diagnosis of VTE during the inclusion period:

- Ambulatory diagnosis, coded as verified
- Primary hospital discharge diagnosis
- Secondary hospital discharge diagnosis

The quarter of the first VTE diagnosis in the inclusion period was defined as the *index quarter*. For hospital diagnoses, the date of admission was used to define the index quarter. The use of an index quarter was necessary as ambulatory diagnoses are recorded on quarterly basis only in Germany.

The assignment to patient groups one to four, and the definition of the *index date* was done based on the following algorithm and additional inclusion criteria:

- Patients with only a hospital diagnosis of VTE in the index quarter (i.e. no ambulatory diagnosis): The hospitalization with the first diagnosis of VTE was selected as the *index hospitalization*. Patients with a primary discharge diagnosis of VTE in index hospitalization were assigned to **patient group 1.** Patients with only a secondary discharge diagnosis of VTE in index hospitalization were assigned to **patient group 2**. Patients were included if they had a first ambulatory dispensing of the following anticoagulation regimens within 14 days after hospital discharge:
  - Rivaroxaban
  - Phenprocoumon
  - heparin + phenprocoumon (dispensed on the same day)
  - heparin, followed by a first phenprocoumon dispensing within 14 days

  The date of the first anticoagulation dispensing after hospital discharge was defined as the *index date* of the patient (Figure 2).

- Patients with only an ambulatory diagnosis of VTE in the index quarter (i.e. no in-hospital VTE diagnoses in the index quarter): Patients were included if they had at least one pharmacy dispensing of a new anticoagulation treatment (heparin; phenprocoumon; rivaroxaban) in the index quarter and were assigned to **patient group 3**. The day of the first anticoagulation dispensing was defined as the *index date* (Figure 3). Patients were included if they had a first ambulatory dispensing of the following anticoagulation regimens at the index date:
  - Rivaroxaban
  - Phenprocoumon
  - heparin + phenprocoumon (dispensed on the same day)
  - heparin, followed by a first phenprocoumon dispensing within 14 days
- Patients with both an ambulatory diagnosis of VTE and a hospital diagnosis of VTE in the index quarter:
  - Patients *without* any anticoagulation treatment (heparins; vitamin-K antagonists; rivaroxaban; other DOACs) before the hospitalization with the first diagnosis of VTE were treated like *patients with only a hospital diagnosis of VTE in the index quarter* (see above).

- Patients who *had* a first anticoagulation treatment with heparin; heparin + phenprocoumon; or rivaroxaban within 14 days before the hospitalization with the first diagnosis of VTE were assigned to **patient group 4**. These patients were only included if they additionally had an ambulatory dispensing of the following anticoagulation regimens within 14 days after hospital discharge:
  - Rivaroxaban
  - Phenprocoumon
  - heparin + phenprocoumon (dispensed on the same day)
  - heparin, followed by a first phenprocoumon dispensing within 14 days

  The date of the first anticoagulation dispensing after hospital discharge was defined as the *index date* of the patient (Figure 2). The rationale for defining group 4 is to ensure that the acute treatment phase of the patient (i.e. the time since initiation of the first anticoagulation prior to hospitalization until end of hospitalization) can be distinguished from the person-time at risk of developing the primary outcome of interest.
- Patients who *had* a first anticoagulation treatment dispensing (heparins; vitamin-K antagonists; rivaroxaban; other DOACs) more than 14 days before the hospitalization with the first diagnosis of VTE were treated like *patients with only an ambulatory diagnosis of VTE in the index quarter* (see above).

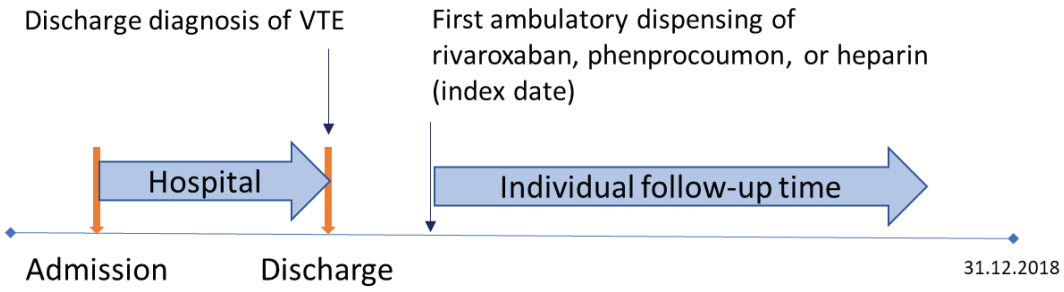

Figure 2. Definition of index date in patients who were hospitalized for VTE (patient groups 1,2, and 4)

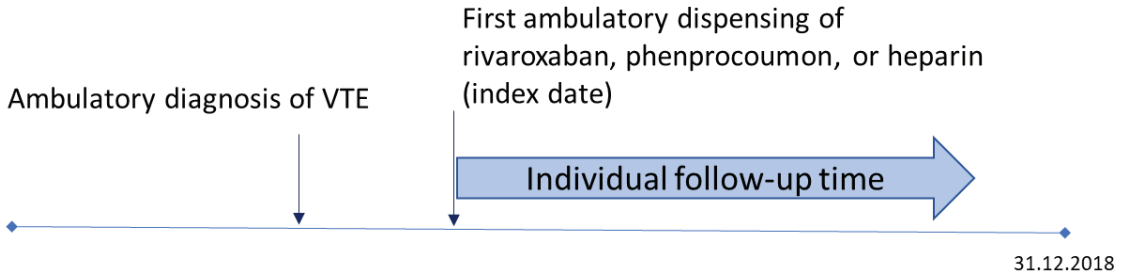

Figure 3. Definition of index date in patients who received ambulatory treatment for VTE (patient group 3)

The 12 months prior to the index date defined the *baseline period* for all included patients. Patients treated with anticoagulation regimens other than defined above (e.g. other DOACs) were not included in the study.

All patients had to fulfill the additional inclusion criteria:

- Continuous enrolment in the baseline period
- ≥ 18 years of age at index date

Exclusion criteria

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

- A verified ambulatory or primary/ secondary hospital discharge diagnosis of VTE in the baseline period
- A verified ambulatory or primary/ secondary hospital discharge diagnosis of atrial fibrillation in the baseline period;
- A pharmacy dispensing of oral anticoagulation, heparin, or fondaparinux in the baseline period
- Individuals with documented cardiac valve surgery in the baseline period;
- A verified ambulatory or primary/ secondary hospital discharge diagnosis indicating pregnancy in the baseline period;
- Any diagnosis indicating that the index VTE is pregnancy-related
- A dispensation of any anticoagulation treatment (heparins; vitamin-K antagonists; rivaroxaban; other DOACs) in the baseline period;
- A verified ambulatory or primary/ secondary hospital discharge diagnosis of end-stage kidney disease or a claim for dialysis in the baseline period;

- Patients assigned to rivaroxaban exposure groups who were initially treated with a dose strength other than 15 mg or 20 mg per tablet.

For the main analysis, patients were followed from the index date until the first diagnosis of the respective outcome event, discontinuation of the index anticoagulation regimen, death, end of continuous insurance in the SHI or the end of the study period (31 December 2019), whichever came first. A switch to a different anticoagulation regimen (i.e. from rivaroxaban to VKA or another DOAC; or from heparin/phenprocoumon to any DOAC) was also considered as discontinuation of the index anticoagulation regimen.

For the analysis on healthcare resource consumption and costs, patients were followed from the index date until 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 2019), whichever came first. A switch to a different anticoagulation regimen (i.e. from rivaroxaban to VKA or another DOAC; or from heparin/phenprocoumon to any DOAC) was also considered as discontinuation of the index anticoagulation regimen.

9.4 Variables

9.4.1 Exposure definition

As exposure, dispensations of heparin, phenprocoumon and rivaroxaban were assessed. All dispensations were assessed based on the documented dispensation date. Each patient was assigned to one of the two exposure groups based on the index drug: new users of heparin+phenprocoumon, or rivaroxaban.

Exposure time for heparin+phenprocoumon and rivaroxaban started on the index date for analyses of safety outcomes and the day after the index date for analyses of effectiveness outcomes and was 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 dispensation of the index drug was allowed. 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).

For rivaroxaban, the days of supply corresponds to the number of tablets in a dispensed package (assuming daily use of one tablet). For starter packs, the days of supply was calculated based on the recommended tablets per day. For heparin, the days of supply was calculated based on the recommended application regimen for the respective product (e.g. based on the number of syringes to be administered daily). The exposure time calculation for phenprocoumon is, however, not straightforward due to interindividual variation in the number of tablets needed to reach a targeted INR range. To account for the intra- and interpersonal variability of phenprocoumon treatment, a personalized defined daily dose (pDDD) based on the observed phenprocoumon dispensations for each patient in the InGef database was calculated. For this purpose, amount of active ingredient (AAI) dispensed to each patient of the phenprocoumon group was obtained for each dispensation. 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 dispensations received during follow-up ($k \in \{1, K\}$).
- T= number of days between the first and the last dispensation during follow-up

For the sake of simplicity, only dispensations of patients who were solely treated with phenprocoumon during follow-up (i.e. no other OAC used) 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 dispensation 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:

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

For rivaroxaban, heparin and phenprocoumon, stockpiling was assumed, i.e. if a dispensation of the index drug was refilled before the estimated end of supply, the remaining supply of the dispensation was added to following dispensation.

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

Patients were considered as having switched from the index drug to a different anticoagulation regimen, if they received a dispensation of the respective drug during continuous exposure time to the index drug as described above. The date of the first dispensation of a different anticoagulation regimen was defined as the date of treatment switch at which patients were censored.

As a sensitivity to the primary approach of defining the person-time at risk, an intention-to-treat approach was utilized. In this analysis, patients were considered to be exposed to their initial anticoagulation regimen, independently from treatment discontinuation or switching. Person-time was censored at 6 months after the index date in this sensitivity analysis.

9.4.2 Outcomes definition

As the effectiveness outcome, recurrent VTE was analyzed (primary objective), while safety outcomes included fatal bleeding (secondary objective), and end stage renal disease (other objectives).

A recurrent VTE event was defined as a hospitalization with a primary hospital discharge diagnoses for VTE for which the admission date was >14 days after the index date. In a sensitivity analysis, only admissions later than 60 days after the index date were considered to evaluate the impact of potentially including early hospital admissions that actually represent worsening of the index VTE. An additional sensitivity analysis was conducted that combined the occurrence of a VTE hospitalization as defined above with treatment discontinuation. Recurrent VTE events were only counted as new events if there were no ambulatory follow-up dispensation of the OAC where patients were exposed to at time point of event, after the calculated end of exposure time (+30 days gap period).

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.

The definition of end stage renal disease (CKD stage 5 or dialysis) was based on verified ambulatory or hospital discharge diagnoses, and on codes indicating dialysis. The date of the first code indicating end stage renal disease was used to define the event date. For ambulatory diagnoses, the date of the first encounter with the diagnosing physician in the respective quarter was used as the date of the ambulatory diagnosis.

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. Overall costs (from SHI perspective) were defined as sum of hospital costs, ambulatory care costs, drug dispensation costs, and remedies and aids costs. Costs for each of the mentioned healthcare sectors were analyzed as separate outcomes. 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 2018 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%; 2017-2018: 1.7%; 2018-2019: 1.7% (Source: https://data.oecd.org/price/inflation-cpi.htm; inflation for 2018-2019 assumed to be the same as 2017-2018.)

9.4.3 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 be the admission date of the respective hospitalization and for ambulatory diagnoses the date of the first encounter with the diagnosing physician in the respective quarter (as ambulatory diagnoses are available on a quarterly basis only). Data derived from OPS codes and EBM codes 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

- Patient group (1,2,3, or 4) = treatment setting
- Type and localization of VTE index event:
  - PE (I26)
  - DVT lower extremity proximal (I80.1; I80.20)
  - DVT lower extremity localization not specified (I80.2 excluding I80.20; I80.3)
- $CHADS_2$ score
- CHA_2DS_2-VASc score
- modified HAS-BLED score (the 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 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
- Primary or secondary thrombophilia
- Psychosis
- Pulmonary disease
- Rheumatoid arthritis/collagen vascular disease
- Stroke or TIA
- 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

- 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.)

9.4.4 Subpopulations and Subgroups

Subgroups were only build on the basis of conditions already present at index date.

The following subgroups of special interest were defined:

- Age group (<=60 vs. 60+ years)

Age was assessed at the index date.

- Type of index event (DVT only; PE)

The categorization was based on the diagnoses made during the index hospitalization (patient groups 1,2, and 4), or during the index quarter (patient group 3).

- Provoked and unprovoked VTE (Kearon et al. 2016; Journal of Thrombosis and Haemostasis,14: 1480–1483)

All patients were classified based on identified transient and/or persistent risk factors of VTE into the following three categories:

  - VTE provoked by a transient risk factor: Patients who had at least one of the following medical events / conditions in the three months before their indext date:
    - Any surgery associated with hospitalization for at least 3 days
    - Emergency hospitalization for at least 3 days
    - Estrogen therapy
    - Leg injury
    - All patients in patient group 2 (developed VTE in hospital)
  - VTE provoked by a persistent risk factor: Patients who had at least one of the following chronic medical conditions in their baseline period:
    - Cancer (excl. non-melanoma skin cancer)
    - Inflammatory bowel disease
    - Primary or secondary Thrombophilia
  - VTE unprovoked: All patients not classified as having had a provoked VTE were considered as having had unprovoked VTE.

- Treatment setting of index event (patient groups 1, 2, 3, 4)

The analysis was performed for the four patient groups that define the study population, if feasible by sample size. This was limited for patients in patient group 4 (initially treated ambulatory, then in hospital) due to the low number of patients.

- Patients with lung, breast, or prostate cancer

Patients with lung, breast, or prostate cancer were identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses in the baseline period.

- 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.

For the healthcare resource consumption and costs analysis, the same subgroups as described above were analyzed.

9.5 Data sources and measurement

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 >60 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

9.6 Bias

Although the analysis dataset obtained from the InGef database covers more than 6 million insured members of SHIs all over Germany, representativeness for all phenprocoumon and rivaroxaban users in Germany cannot be guaranteed if differences exist for instance by socioeconomic status or region. However, this will not affect the internal validity of the study results as the objectives of the study are related to relative risks rather than absolute risk estimates. It is expected that these relative risk estimates could be extrapolated to all German inhabitants, as it seems unlikely that factors like socioeconomic status or region act as effect modifiers of the relative risks.

As our study did not include a review of individual patient files to confirm the occurrence of individual outcomes, which for data protection reasons is generally not feasible, case validation was not possible and outcome misclassification cannot be ruled out.

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

For the patient group 2 (Initial in-hospital treatment with secondary hospital discharge diagnosis of VTE), it was assumed that these patients were admitted to hospital for a different reason, and developed VTE during their hospital stay. This may not be correct in all cases, e.g. if a historic diagnosis of VTE is recorded, and treatment with rivaroxaban or heparin/VKA is initiated for another indication. However, as patients with identified prior VTE are excluded from the cohort, the probability of such misclassification is considered rather low.

In the analysis of recurrent VTE events, only events treated in hospital were included, as it was not possible to distinguish an ambulatory diagnosis of a recurrent VTE from a historical VTE diagnosis. However, it can be expected that especially rather early events (occurring within the first year after the index date), have a high probability of being treated in a hospital setting. In addition, it is expected that the number of missed events are of a similar magnitude in both treatment groups.

With regard to drug usage, it has to be noted that the dispensation the respective drug does not necessarily imply that the patient actually took the medication. In addition, the estimation of duration of phenprocoumon treatment is limited by the fact that no information on the prescribed daily dose is available and thus have to be indirectly concluded from the treatment pattern (pDDD approach). Therefore, exposure misclassification is generally possible; however, in case of continuous drug dispensations to the same patient the amount of misclassification is expected to be low.

There was no cause-of-death information available for patients who died during their person-time at risk. Fatal bleeding events thus had to be limited those events that led to hospitalization, and in which the patient died within the hospital. This may lead to a number of missed events (i.e. patients who die from bleeding before reaching the hospital), but it is considered that this proportion is probably low. In addition, it is expected that the number of missed events are of a similar magnitude in both treatment groups.

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

9.7 Study size

Based on a feasibility analysis, we estimated a sample size of approximately 13,000 new users of rivaroxaban and 5,000 new users of heparin+phenprocoumon with VTE during the inclusion period. We used the cumulative incidence (incidence proportion) from a pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE studies (Prins MH et al. 2013) to estimate the expected number of recurrent VTE in users of anticoagulation regimens, assuming an average follow-up time of 200 days per person (as reported by Prins ME et al. 2013). The lower and upper 95% confidence intervals were calculated, assuming that the same incidence would be observed as in the pooled

analysis of the RCTs. Precision was defined as the half width of the 95% confidence interval, related to the incidence estimate. Precision for the expected incidence estimates were 12.1% for rivaroxaban, and 18.7% for heparin+phenprocoumon, which was considered sufficient for the aims of this study.

Table 3. Expected precision of the cumulative incidence, assuming an average follow-up of 200 days per patient

Oral anticoagulant	Estimated number of drug users	Assumed cumulative incidence	Assumed number of events	Lower 95%-CI	Upper 95%-CI	Precision
Rivaroxaban	13,000	20.7 per 1,000	269	18.3 per 1,000	23.3 per 1,000	12.1%
heparin+phenprocoumon	5,000	23.0 per 1,000	115	19.0 per 1,000	27.6 per 1,000	18.7%

9.8 Data transformation

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 are person-level, and contain variables as specified in section 9.4.

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

9.9 Statistical methods

9.9.1 Main summary measures

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 recurrent VTE, fatal bleeding, and end stage renal disease 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.

9.9.2 Main statistical methods

Analyses were conducted in line with good statistical practices. There was no a priori hypothesis for this study. Models considered confounding factors to adjust for group differences.

In a first step, Cox proportional hazards regression models were applied in the rivaroxaban group compared to phenprocoumon (reference) to estimate crude and confounder adjusted hazard ratios (HRs) of the above mentioned outcomes with accompanying 95% confidence intervals. Kaplan-Meier cumulative incidence plots were generated to characterize risk of outcome events of interest over time. Patients were censored in case of discontinuation of the index anticoagulation regimen (including switch to a different anticoagulation regimen), death (except outcome fatal bleeding), end of continuous insurance in the SHI or the end of the study period (31 December 2019), whichever came first.

For the analyses of healthcare resource consumption, quasi-Poisson 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 rivaroxaban 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 rivaroxaban and phenprocoumon as the reference category. In addition, the absolute difference in mean costs between rivaroxaban vs. phenprocoumon users per person year was calculated with 95% confidence intervals. Forward selection (significance level of 0.1 to enter the model) was used to select appropriate covariates.

In a second step, stabilized inverse probability of treatment weighting (IPTW) approach based on the propensity score was used to adjust for potential confounding resulting from imbalances in the baseline characteristics of different treatment groups. The objective of IPTW based analysis was to create a weighted sample, for which the distribution of possible confounding variables is approximately the same between comparison groups (Xu et al. 2010; Austin 2011). The propensity score is defined as the patient's probability to receive a treatment under investigation (i.e. phenprocoumon) given a set of known patient's baseline characteristics. Propensity scores were calculated using multiple logistic regression based on all covariates listed in section 9.4.3.

In the analyses IPTW with stabilized weights were used which ensure more robust effect estimates. The stabilized weight is defined as $sw = \frac{P(Z=1)*Z}{e} + \frac{(1-P(Z=1))*(1-Z)}{1-e}$.

In a third step, we additionally conducted a propensity score matched analyses. 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 will be checked in analogy to the description above.

Adjusted COX-regression models were considered as the base case model, while IPTW and PS matching was considered as sensitivity analyses to confirm robustness of results.

While the main time-to-event analysis considered the total exposed person-time after index date (as defined above), risk estimates were additionally estimated for two time periods:

- For the treatment of VTE up to six months: In this analysis, follow-up times was censored at 182 days after index date.

- For the extended treatment of VTE (after six months): In this analysis, only patients who were still at risk at day 183 after the index date were included (Landmark analysis approach). In this analysis, the risk period started at day 183.

9.9.3 Missing values

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

9.9.4 Sensitivity analyses

The following sensitivity analyses were performed for the main COX regression model and the outcomes of recurrent VTE; fatal bleeding; and end stage renal disease:

- As described above, the adjusted COX-regression models were considered as the base case model, while IPTW and PS matching was considered as sensitivity analyses to confirm robustness of results.
- In one sensitivity analysis, we only considered recurrent VTE events that occurred more than 60 days after the index date. This analysis will allow to evaluate the impact of early (re-)hospitalizations and the fact that early hospitalizations may actually represent worsening of the index event, rather than a new VTE.
- To evaluate the impact of longer term follow-up, patients were censored after 180 and 360 days in two sensitivity analyses.
- In an additional sensitivity analysis, follow-up was censored 30 days after the last prescription of rivaroxaban/phenprocoumon to address the uncertainty of duration of exposure especially after the last prescription.
- In one analysis, data were analyzed based on an intention-to-treat approach with censoring after 180 days.
- As one would expect a change in the anticoagulation regimen after recurrent VTE, another sensitivity analysis considered recurrent VTE events if the respective oral anticoagulant is discontinued after the event (i.e. no follow-up dispensations within 3 months after hospital discharge).
- Due to the uncertainty on the actual daily dose of phenprocoumon (and thus the corresponding duration of exposure attributed to a certain number of phenprocoumon tablets), a sensitivity analysis was performed that assumed a daily dose of 3mg for all phenprocoumon users.

In addition, the following sensitivity analyses were conducted for the healthcare resource consumption and cost analyses:

- Censoring of follow-up after 30 days (see above)
- Intention-to-treat approach with a maximum follow-up of 180 days (see above)
- Assumption of a daily dose of 3mg for all phenprocoumon users (see above)

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.

9.9.5 Amendments to the statistical analysis plan

No statistical analysis plan was developed for this project, as all planned analyses were described in the study protocol.

9.10 Quality control

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

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

- As part of the management strategy the InGef documents and implements:
- Quality control processes around reference data.
- Rules for raw data checks for completeness reasonability and volume
- Control processes for production files and outputs.
- Process flow and maintenance processes including standard operating procedures.
- Database metrics including quality and completeness
- Procedures for handling internal inquiries

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

Data acquisition

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

The data is then checked for compliance and completeness:

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

Data-processing checks include:

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

Processed-data checks include:

- Control of individual data-suppliers - total data volume versus expected and previous periods

- Checks for missing data estimations
- Check for aggregated data by analysis unit, e.g. values for surgeries, hospitals, regions

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

As part of the management strategy InGef documents and implements:

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

Indicator Quality Assurance:

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

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

10. Results

10.1 Participants

From a total of N=25034 patients who were treated with rivaroxaban, N=16081 (64.2%) fulfilled all inclusion and exclusion criteria for study inclusion (Figure 4). For the phenprocoumon group, 6072 out of 16699 patients (36.4%) were finally included into the study (Figure 5). The higher proportion of excluded patients in the phenprocoumon group were mainly due to a higher proportion of patients who were already treated with OACs in the baseline period (i.e. prevalent users; rivaroxaban: 15.2%; phenprocoumon: 47.9%).

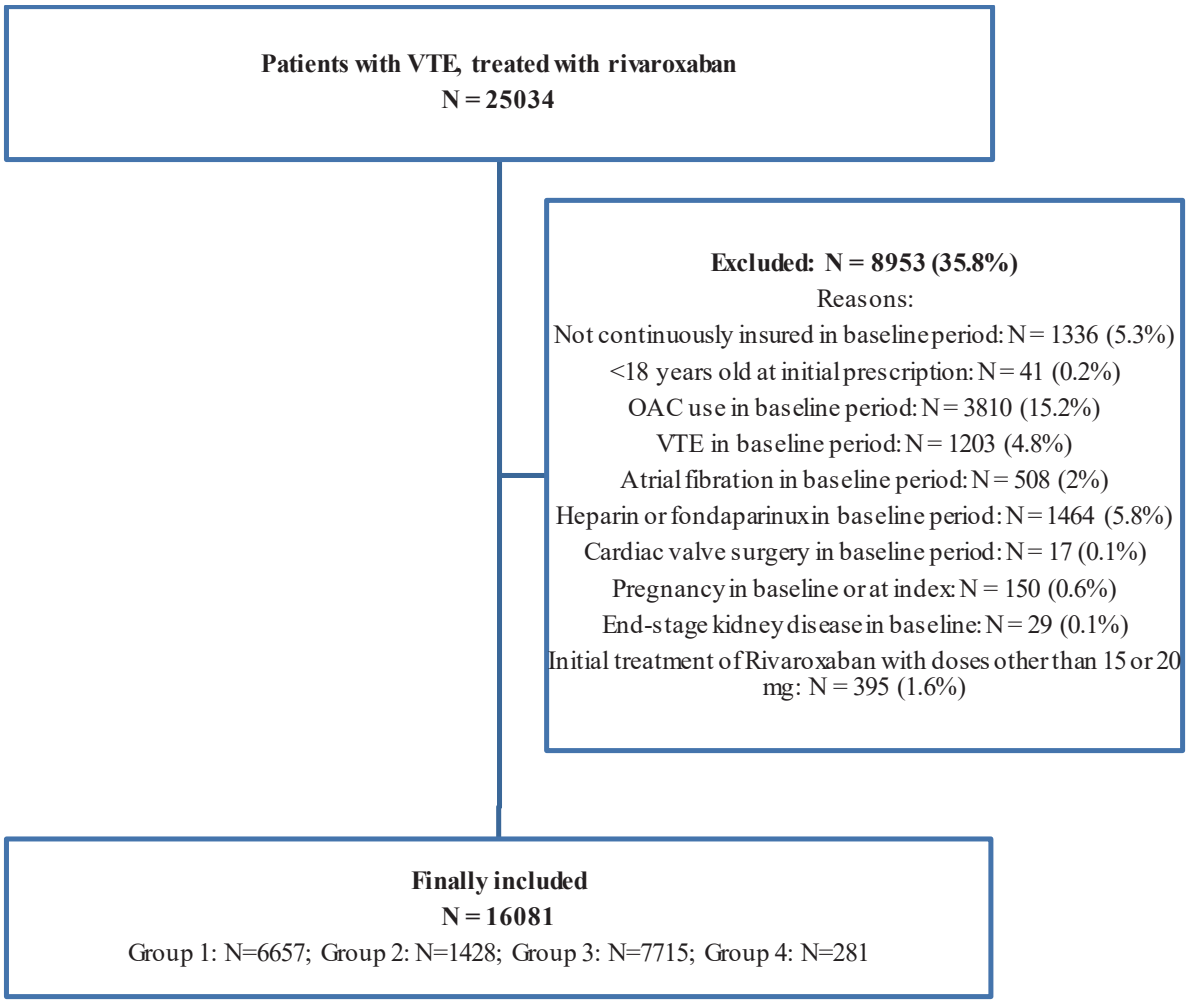

Figure 4. Patient selection rivaroxaban

Source: Statistical Output Tables (Table 1). Group 1 = Initial in-hospital treatment of VTE developed in outpatient setting. Group 2 = Initial in-hospital treatment of VTE developed during a hospital-stay. Group 3 = Ambulatory treatment of VTE. Group 4 = Initial ambulatory treatment of VTE, followed by in-hospital treatment of VTE within 14 days of prior ambulatory treatment initiation.

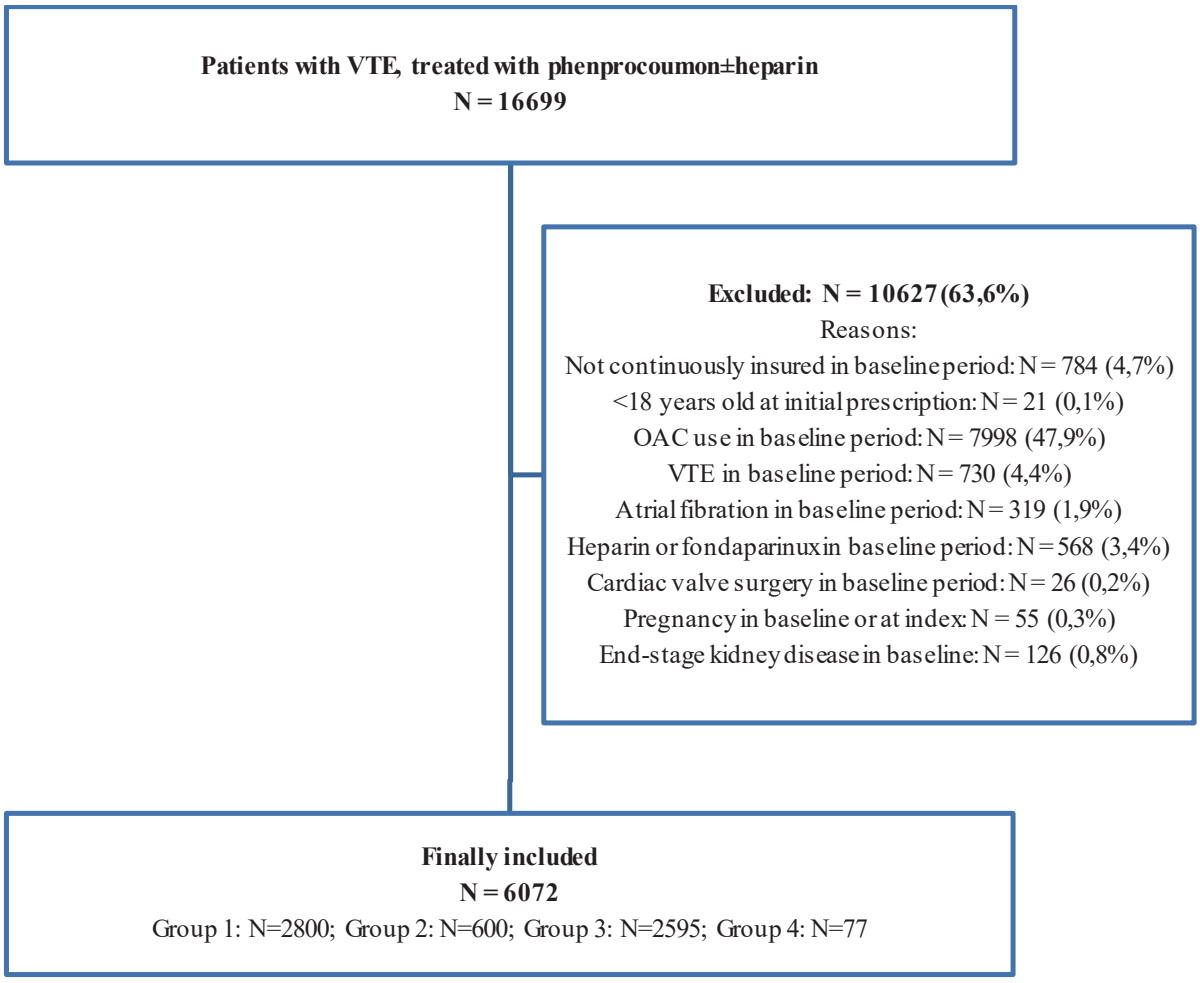

Figure 5. Patient selection phenprocoumon±heparin

Source: Statistical Output Tables (Table 1). Group 1 = Initial in-hospital treatment of VTE developed in outpatient setting. Group 2 = Initial in-hospital treatment of VTE developed during a hospital-stay. Group 3 = Ambulatory treatment of VTE. Group 4 = Initial ambulatory treatment of VTE, followed by in-hospital treatment of VTE within 14 days of prior ambulatory treatment initiation.

10.2 Descriptive data

10.2.1 Baseline characteristics in patients with VTE (unmatched cohorts)

The baseline characteristics of patients with VTE included in this study are reported in Table 4. Most patients had a DVT of the lower extremity without specified localization (rivaroxaban: 65.0%, phenprocoumon: 62.6%), while only in a minority had a diagnosis indicating proximal DVT (12.6% and 14.1%, respectively). Approximately 40% of patients had a diagnosis of PE in both treatment groups. Most patients were initially treated by general practitioners (rivaroxaban: 7771 out of 16081 patients, 48.3%; phenprocoumon: 3187 out of 6072 patients, 52.5%), followed by specialists in internal medicine (rivaroxaban: 3782 out of 16081 patients, 23.5%; phenprocoumon: 1504 out of 6072 patients, 24.8%). All prescribing specialties are included in the Statistical Output Tables / Table 9. Overall, no substantial differences in patient characteristics were evident between patients treated with rivaroxaban vs. those treated with phenprocoumon. Patients treated with phenprocoumon had a slightly higher age; and a slightly higher proportion of patients with comorbidities such as chronical renal disease / renal impairment; ischemic heart disease; diabetes; hyperlipidemia; hypertension; and peripheral vascular disease. The two treatment groups were also rather similar with respect to health resource utilization and health care costs (Table 7) in the baseline period.

Table 4. Baseline characteristics of patients with VTE

	Rivaroxaban (N=16081)	Phenprocoumon (N=6072)	SMD
Sex			
	PPD		0,01
			-0,01
Age (mean±SD)	60,4 ± 16,7	64,2 ± 15,8	0,23
Type of VTE[1]			
With PE	6316 (39,3%)	2430 (40,0%)	-0,02
DVT lower extremity proximal	2032 (12,6%)	859 (14,1%)	-0,04
DVT lower extremity localization not specified	10448 (65,0%)	3800 (62,6%)	0,05
Risk scores (mean±SD)			
CHADS2 Score	1,2 ± 1,3	1,5 ± 1,4	0,21
CHA2DS2-VASc Score	2,2 ± 1,9	2,7 ± 2,0	0,23
HAS-BLED Score	1,8 ± 1,3	2,1 ± 1,3	0,25
Comorbidities[1]			
Acute kidney injury	357 (2,2%)	209 (3,4%)	-0,07
Alcohol abuse	419 (2,6%)	165 (2,7%)	-0,01
Anemia	1197 (7,4%)	600 (9,9%)	-0,09
Aortic plaque	346 (2,2%)	151 (2,5%)	-0,02
Chronic renal disease	830 (5,2%)	735 (12,1%)	-0,25
Coronary heart disease	2078 (12,9%)	1094 (18%)	-0,14
Acute ischemic heart diseases	41 (0,3%)	27 (0,4%)	-0,03

	Rivaroxaban (N=16081)	Phenprocoumon (N=6072)	SMD
Angina pectoris	402 (2,5%)	204 (3,4%)	-0,05
Chronic ischemic heart disease	1833 (11,4%)	1001 (16,5%)	-0,15
Coronary artery bypass graft(s)	177 (1,1%)	140 (2,3%)	-0,09
Myocardial infarction	600 (3,7%)	341 (5,6%)	-0,09
Percutaneous coronary intervention	104 (0,6%)	110 (1,8%)	-0,11
Dementia	926 (5,8%)	325 (5,4%)	0,02
Depression	3817 (23,7%)	1353 (22,3%)	0,03
Diabetes mellitus	2818 (17,5%)	1396 (23%)	-0,14
Drug abuse	1275 (7,9%)	502 (8,3%)	-0,01
Gastric or peptic ulcer disease/diseases of gastrointestinal tract	4915 (30,6%)	2083 (34,3%)	-0,08
Heart failure	2336 (14,5%)	1135 (18,7%)	-0,11
History of major bleeding (hospitalization only)	511 (3,2%)	260 (4,3%)	-0,06
Hospitalized CKD	864 (5,4%)	746 (12,3%)	-0,25
Hyperlipidemia	5492 (34,2%)	2417 (39,8%)	-0,12
Hypertension	8902 (55,4%)	3906 (64,3%)	-0,18
Hypothyroidism	2290 (14,2%)	939 (15,5%)	-0,03
Inflammatory bowel disease	827 (5,1%)	326 (5,4%)	-0,01
Ischemic stroke or transient ischemic attack	740 (4,6%)	323 (5,3%)	-0,03
Latest CKD Stage 1	72 (0,4%)	43 (0,7%)	-0,03
Latest CKD Stage 2	387 (2,4%)	185 (3%)	-0,04
Latest CKD Stage 3	731 (4,5%)	552 (9,1%)	-0,18
Latest CKD Stage 4	72 (0,4%)	156 (2,6%)	-0,17
Latest CKD Stage 5	0 (0%)	0 (0%)	0,00
Latest CKD Stage Unspecified	179 (1,1%)	113 (1,9%)	-0,06
Leg injury	1725 (10,7%)	598 (9,8%)	0,03
Liver disease	1940 (12,1%)	803 (13,2%)	-0,03
Malignant cancer (excl. non-melanoma skin cancer)	2418 (15%)	942 (15,5%)	-0,01
Obesity	3628 (22,6%)	1493 (24,6%)	-0,05
Other cerebrovascular disease	1285 (8%)	570 (9,4%)	-0,05
Other metabolic disorders	1890 (11,8%)	842 (13,9%)	-0,06
Other vascular disease	1259 (7,8%)	685 (11,3%)	-0,12
Peripheral artery disease	1361 (8,5%)	740 (12,2%)	-0,12
Pregnancy	0 (0%)	0 (0%)	0,00
Primary or secondary Thrombophilia	201 (1,2%)	109 (1,8%)	-0,04
Psychosis	504 (3,1%)	169 (2,8%)	0,02
Pulmonary disease	2073 (12,9%)	994 (16,4%)	-0,10
Renal impairment	2242 (13,9%)	1409 (23,2%)	-0,24
Rheumatoid arthritis/collagen vascular disease	2167 (13,5%)	943 (15,5%)	-0,06
Stroke or TIA	794 (4,9%)	353 (5,8%)	-0,04

	Rivaroxaban (N=16081)	Phenprocoumon (N=6072)	SMD
Systemic embolism	148 (0,9%)	114 (1,9%)	-0,08
Tobacco abuse:	380 (2,4%)	154 (2,5%)	-0,01
Volume depletion	801 (5%)	304 (5%)	0,00
Concomitant drugs[1]			
Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers	6304 (39,2%)	2848 (46,9%)	-0,16
Antiarrhythmics	31 (0,2%)	14 (0,2%)	-0,01
Antidepressants	2234 (13,9%)	854 (14,1%)	0,00
Antiplatelets	1228 (7,6%)	636 (10,5%)	-0,10
Antiulcer drugs (except proton-pump inhibitors)	213 (1,3%)	86 (1,4%)	-0,01
Beta blockers	4049 (25,2%)	1978 (32,6%)	-0,16
Calcium channel blockers	2199 (13,7%)	1067 (17,6%)	-0,11
Diabetes drugs (incl. insulin)	1528 (9,5%)	815 (13,4%)	-0,12
Diuretics	2796 (17,4%)	1477 (24,3%)	-0,17
Erythropoietin-simulating agents	17 (0,1%)	20 (0,3%)	-0,05
Estrogens	511 (3,2%)	180 (3%)	0,01
Lipid modifying agents	2541 (15,8%)	1216 (20%)	-0,11
Non-steroidal anti-inflammatory drugs:	6900 (42,9%)	2650 (43,6%)	-0,01
Proton-pump inhibitors	5441 (33,8%)	2162 (35,6%)	-0,04
Surgery (any)	3851 (23,9%)	1607 (26,5%)	-0,06

[1]Overlapping categories. Source: Statistical Output Tables (Table 3; Table 4; Table 5; Table 8)

Table 5. Baseline health resource utilization and costs (EUR) in patients with VTE

	Rivaroxaban (N=16081)	Phenprocoumon (N=6072)	SMD
Health Resource utilization			
Number of hospitalizations	1,2 ± 1,4	1,3 ± 1,4	0,07
Number of hospital days	12,7 ± 26,6	14,6 ± 24,7	0,07
Number of emergency room visits	0,6 ± 0,8	0,6 ± 0,9	0,04
Number of outpatient visits	20,1 ± 16,7	20,9 ± 15,5	0,05
Number of different drugs used	6,4 ± 5,3	7,0 ± 5,4	0,11
Costs			
Overall	7398,29 ± 12093,46	7536,62 ± 9976,97	0,01
Outpatient	966,55 ± 1090,11	944,24 ± 964,39	-0,02
Inpatient	4844,07 ± 9479,65	5152,15 ± 8062,51	0,03
Medication	1153,39 ± 5233,45	1059,63 ± 4187,53	-0,02
Aids and remedies	434,27 ± 1951,07	380,59 ± 921,27	-0,03
Renal Impairment	24,28 ± 761,42	54,93 ± 823,97	0,04

Source: Statistical Output Tables (Table 6; Table 7)

10.2.2 Baseline characteristics after application of propensity scores (IPTW or matching)

The similarity in the unmatched patient populations, as observed in the descriptive analyses of baseline characteristics, was confirmed by a rather large overlap of the two propensity score distributions (Figure 6). After 1:1 matching, the propensity score distribution were even more homogenous (Figure 7). The baseline characteristics (Table 6) and measures of health resource utilization and costs (Table 7) of the two treatment groups were in very good balance after IPTW. The same was observed after propensity score matching (Table 8; Table 9).

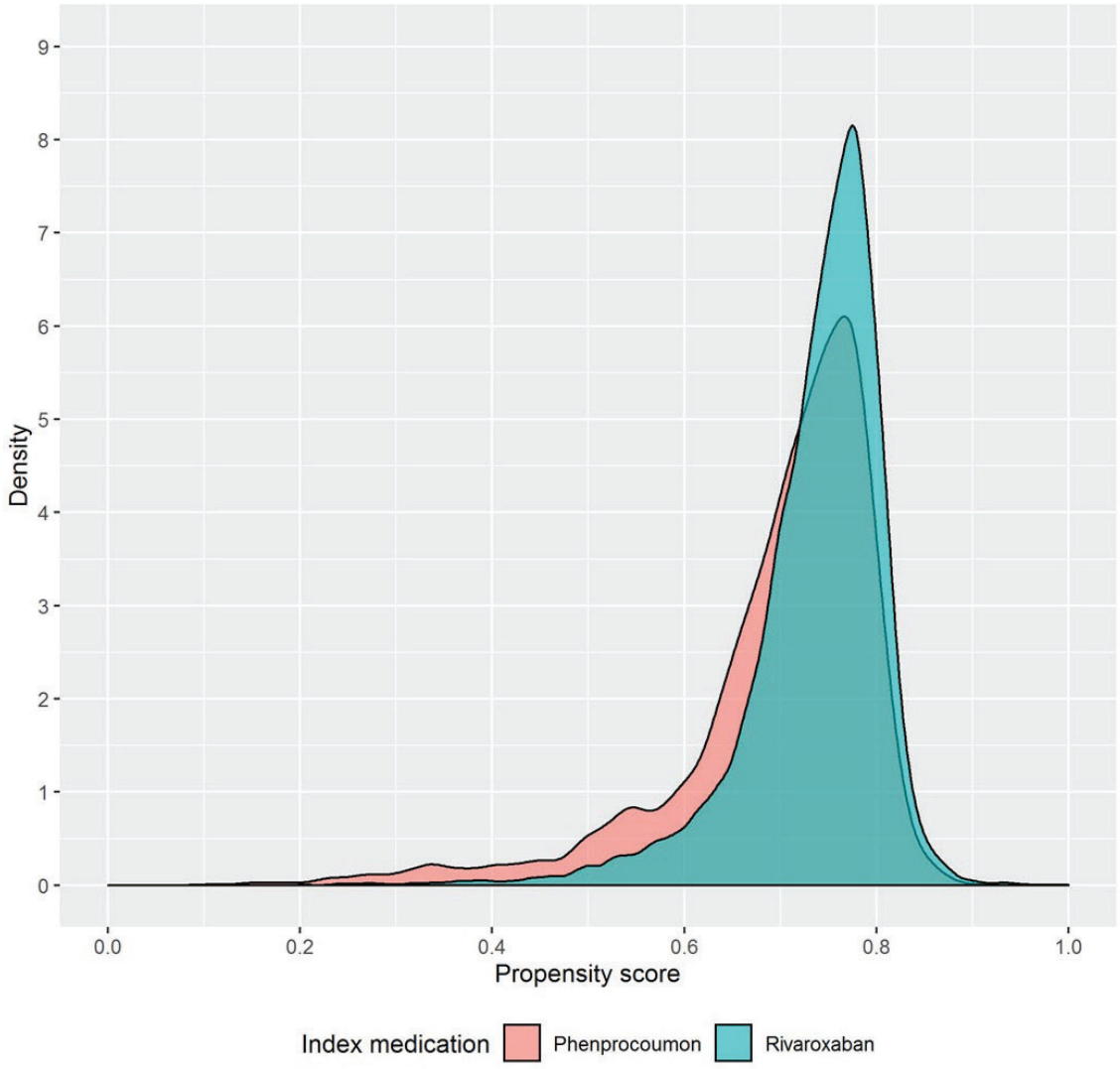

Figure 6. Distribution of propensity scores in unmatched cohorts

Source: Statistical Output Tables (Table 2).

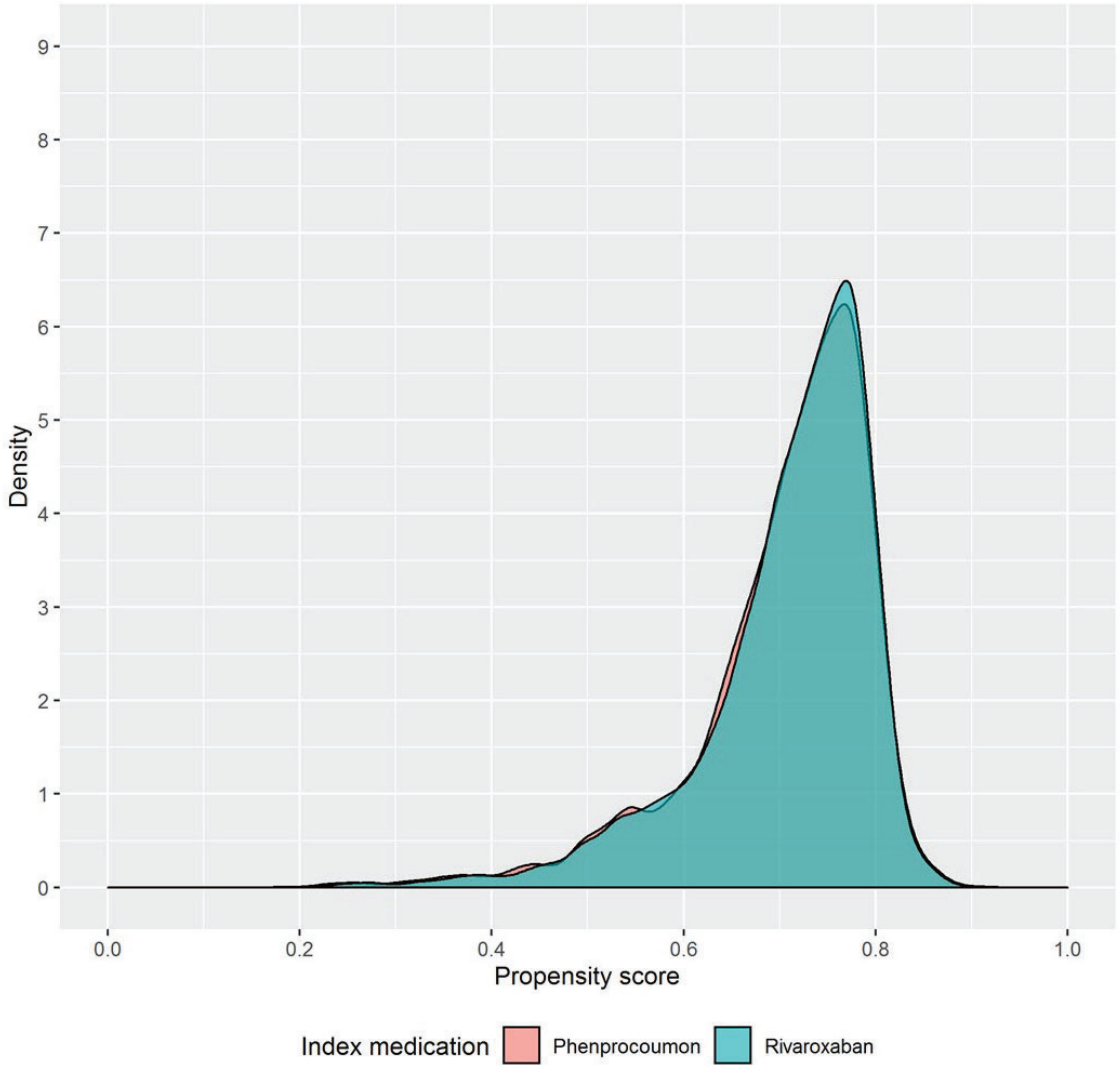

Figure 7. Distribution of propensity scores after propensity score matching

Source: Statistical Output Tables (Table 2).

Table 6. Baseline characteristics of patients with VTE (after IPTW)

	Rivaroxaban (N=16081)[a)]	Phenprocoumon (N=6072)[a)]	SMD
Sex			
	PPD		0,00
			0,00
Age (mean±SD)	61,4 ± 16,6	61,6 ± 16,2	-0,01

	Rivaroxaban (N=16081)[a)]	Phenprocoumon (N=6072)[a)]	SMD
Type of VTE			
With PE	6345 (39,5%)	2367 (39,2%)	0,01
DVT lower extremity proximal	2088 (13%)	782 (13%)	0,00
DVT lower extremity localization not specified	10343 (64,4%)	3898 (64,5%)	0,00
Risk scores (mean±SD)			
CHADS2 Score	1,3 ± 1,3	1,3 ± 1,3	0,00
CHA2DS2-VASc Score	2,4 ± 1,9	2,4 ± 1,9	0,00
HAS-BLED Score	1,9 ± 1,3	1,9 ± 1,3	0,00
Comorbidities			
Acute kidney injury	407 (2,5%)	154 (2,6%)	0,00
Alcohol abuse	423 (2,6%)	162 (2,7%)	0,00
Anemia	1296 (8,1%)	500 (8,3%)	-0,01
Aortic plaque	363 (2,3%)	136 (2,2%)	0,00
Chronic renal disease	1113 (6,9%)	432 (7,1%)	-0,01
Coronary heart disease	2290 (14,3%)	861 (14,3%)	0,00
Acute ischemic heart diseases	49 (0,3%)	19 (0,3%)	0,00
Angina pectoris	437 (2,7%)	163 (2,7%)	0,00
Chronic ischemic heart disease	2041 (12,7%)	773 (12,8%)	0,00
Coronary artery bypass graft(s)	223 (1,4%)	86 (1,4%)	0,00
Myocardial infarction	680 (4,2%)	255 (4,2%)	0,00
Percutaneous coronary intervention	149 (0,9%)	60 (1%)	-0,01
Dementia	914 (5,7%)	332 (5,5%)	0,01
Depression	3756 (23,4%)	1410 (23,4%)	0,00
Diabetes mellitus	3050 (19%)	1150 (19%)	0,00
Drug abuse	1293 (8,1%)	498 (8,2%)	-0,01
Gastric or peptic ulcer disease/diseases of gastrointestinal tract	5069 (31,6%)	1921 (31,8%)	-0,01
Heart failure	2507 (15,6%)	937 (15,5%)	0,00
History of major bleeding (hospitalization only)	560 (3,5%)	208 (3,4%)	0,00
Hospitalized CKD	1136 (7,1%)	441 (7,3%)	-0,01
Hyperlipidemia	5721 (35,6%)	2154 (35,7%)	0,00
Hypertension	9270 (57,7%)	3484 (57,7%)	0,00
Hypothyroidism	2330 (14,5%)	875 (14,5%)	0,00
Inflammatory bowel disease	836 (5,2%)	320 (5,3%)	0,00
Ischemic stroke or transient ischemic attack	775 (4,8%)	291 (4,8%)	0,00
Latest CKD Stage 1	83 (0,5%)	31 (0,5%)	0,00
Latest CKD Stage 2	416 (2,6%)	152 (2,5%)	0,00
Latest CKD Stage 3	932 (5,8%)	351 (5,8%)	0,00
Latest CKD Stage 4	147 (0,9%)	63 (1%)	-0,01
Latest CKD Stage 5	0 (0%)	0 (0%)	0,00
Latest CKD Stage Unspecified	209 (1,3%)	80 (1,3%)	0,00

	Rivaroxaban (N=16081)[a)]	Phenprocoumon (N=6072)[a)]	SMD
Leg injury	1692 (10,5%)	635 (10,5%)	0,00
Liver disease	1982 (12,3%)	738 (12,2%)	0,00
Malignant cancer (excl. non-melanoma skin cancer)	2434 (15,2%)	910 (15,1%)	0,00
Obesity	3709 (23,1%)	1398 (23,2%)	0,00
Other cerebrovascular disease	1345 (8,4%)	501 (8,3%)	0,00
Other metabolic disorders	1983 (12,4%)	749 (12,4%)	0,00
Other vascular disease	1407 (8,8%)	532 (8,8%)	0,00
Peripheral artery disease	1515 (9,4%)	573 (9,5%)	0,00
Pregnancy	0 (0%)	0 (0%)	0,00
Primary or secondary Thrombophilia	221 (1,4%)	87 (1,4%)	0,00
Psychosis	489 (3%)	181 (3%)	0,00
Pulmonary disease	2213 (13,8%)	848 (14%)	-0,01
Renal impairment	2622 (16,3%)	992 (16,4%)	0,00
Rheumatoid arthritis/collagen vascular disease	2258 (14,1%)	852 (14,1%)	0,00
Stroke or TIA	832 (5,2%)	316 (5,2%)	0,00
Systemic embolism	191 (1,2%)	77 (1,3%)	-0,01
Tobacco abuse:	386 (2,4%)	148 (2,5%)	0,00
Volume depletion	806 (5%)	302 (5%)	0,00
Concomitant drugs			
Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers	6627 (41,3%)	2490 (41,2%)	0,00
Antiarrhythmics	31 (0,2%)	12 (0,2%)	0,00
Antidepressants	2243 (14%)	859 (14,2%)	-0,01
Antiplatelets	1356 (8,4%)	518 (8,6%)	0,00
Antiulcer drugs (except proton-pump inhibitors)	220 (1,4%)	84 (1,4%)	0,00
Beta blockers	4343 (27,1%)	1645 (27,2%)	0,00
Calcium channel blockers	2355 (14,7%)	889 (14,7%)	0,00
Diabetes drugs (incl. insulin)	1693 (10,5%)	646 (10,7%)	0,00
Diuretics	3073 (19,1%)	1163 (19,3%)	0,00
Erythropoietin-simulating agents	24 (0,1%)	11 (0,2%)	-0,01
Estrogens	505 (3,1%)	191 (3,2%)	0,00
Lipid modifying agents	2721 (16,9%)	1022 (16,9%)	0,00
Non-steroidal anti-inflammatory drugs:	6911 (43%)	2592 (42,9%)	0,00
Proton-pump inhibitors	5524 (34,4%)	2079 (34,4%)	0,00
Surgery (any)	3956 (24,6%)	1502 (24,9%)	-0,01

[a)]Weighted numbers in categories may not sum up to total N due to rounding. IPTW=Inverse-Probability-of-Treatment-Weighting. Source: Statistical Output Tables (Table 3; Table 4; Table 5; Table 8)

Table 7. Baseline health resource utilization and costs in patients with VTE (after IPTW)

	Rivaroxaban (N=16081)	Phenprocoumon (N=6072)	SMD
Health Resource utilization			
Number of hospitalizations	1,2 ± 1,5	1,2 ± 1,4	-0,01
Number of hospital days	13,3 ± 27,5	13,6 ± 23,6	-0,01
Number of emergency room visits	0,6 ± 0,8	0,6 ± 0,9	0,00
Number of outpatient visits	20,3 ± 16,8	20,4 ± 15,8	-0,01
Number of different drugs used	6,6 ± 5,3	6,6 ± 5,3	0,00
Costs			
Overall	7460,12€ ± 11706,27€	7382,47€ ± 10555,97€	0,01
Outpatient	963,35€ ± 1057,06€	959,67€ ± 1092,51€	0,00
Inpatient	4935,62€ ± 9211,47€	4892,87€ ± 8187,87€	0,00
Medication	1139,94€ ± 5072,04€	1152,52€ ± 4914,21€	0,00
Aids and remedies	421,21€ ± 1742,18€	377,4€ ± 955,24€	0,03
Renal Impairment	31,33€ ± 928,63€	32,37€ ± 602,49€	0,00

IPTW=Inverse-Probability-of-Treatment-Weighting. Source: Statistical Output Tables (Table 6; Table 7)

Table 8. Baseline characteristics of patients with VTE (after matching)

	Rivaroxaban (N=5956)	Phenprocoumon (N=5956)	SMD
Sex			
	PPD		0,00
			0,00
Age (mean±SD)	63,6 ± 16,3	63,9 ± 15,7	0,02
Type of VTE			
With PE	2388 (40,1%)	2362 (39,7%)	0,01
DVT lower extremity proximal	801 (13,4%)	841 (14,1%)	-0,02
DVT lower extremity localization not specified	3783 (63,5%)	3750 (63%)	0,01
Risk scores (mean±SD)			
CHADS2 Score	1,5 ± 1,3	1,5 ± 1,3	0,00
CHA2DS2-VASc Score	2,6 ± 1,9	2,6 ± 1,9	0,00
HAS-BLED Score	2,1 ± 1,3	2,1 ± 1,3	0,01
Comorbidities			
Acute kidney injury	173 (2,9%)	183 (3,1%)	-0,01
Alcohol abuse	154 (2,6%)	160 (2,7%)	-0,01
Anemia	577 (9,7%)	554 (9,3%)	0,01
Aortic plaque	153 (2,6%)	146 (2,5%)	0,01
Chronic renal disease	608 (10,2%)	626 (10,5%)	-0,01
Coronary heart disease	1052 (17,7%)	1029 (17,3%)	0,01
Acute ischemic heart diseases	18 (0,3%)	23 (0,4%)	-0,01

	Rivaroxaban (N=5956)	Phenprocoumon (N=5956)	SMD
Angina pectoris	178 (3%)	188 (3,2%)	-0,01
Chronic ischemic heart disease	959 (16,1%)	940 (15,8%)	0,01
Coronary artery bypass graft(s)	116 (1,9%)	122 (2%)	-0,01
Myocardial infarction	306 (5,1%)	311 (5,2%)	0,00
Percutaneous coronary intervention	85 (1,4%)	89 (1,5%)	-0,01
Dementia	325 (5,5%)	311 (5,2%)	0,01
Depression	1345 (22,6%)	1320 (22,2%)	0,01
Diabetes mellitus	1323 (22,2%)	1341 (22,5%)	-0,01
Drug abuse	495 (8,3%)	495 (8,3%)	0,00
Gastric or peptic ulcer disease/diseases of gastrointestinal tract	2027 (34%)	2026 (34%)	0,00
Heart failure	1088 (18,3%)	1068 (17,9%)	0,01
History of major bleeding (hospitalization only)	240 (4%)	249 (4,2%)	-0,01
Hospitalized CKD	603 (10,1%)	640 (10,7%)	-0,02
Hyperlipidemia	2350 (39,5%)	2335 (39,2%)	0,01
Hypertension	3784 (63,5%)	3795 (63,7%)	0,00
Hypothyroidism	920 (15,4%)	906 (15,2%)	0,01
Inflammatory bowel disease	329 (5,5%)	320 (5,4%)	0,01
Ischemic stroke or transient ischemic attack	301 (5,1%)	307 (5,2%)	0,00
Latest CKD Stage 1	44 (0,7%)	43 (0,7%)	0,00
Latest CKD Stage 2	178 (3%)	183 (3,1%)	0,00
Latest CKD Stage 3	521 (8,7%)	527 (8,8%)	0,00
Latest CKD Stage 4	68 (1,1%)	74 (1,2%)	-0,01
Latest CKD Stage 5	0 (0%)	0 (0%)	0,00
Latest CKD Stage Unspecified	108 (1,8%)	111 (1,9%)	0,00
Leg injury	572 (9,6%)	587 (9,9%)	-0,01
Liver disease	795 (13,3%)	786 (13,2%)	0,00
Malignant cancer (excl. non-melanoma skin cancer)	882 (14,8%)	913 (15,3%)	-0,01
Obesity	1432 (24%)	1454 (24,4%)	-0,01
Other cerebrovascular disease	552 (9,3%)	542 (9,1%)	0,01
Other metabolic disorders	797 (13,4%)	795 (13,3%)	0,00
Other vascular disease	634 (10,6%)	640 (10,7%)	0,00
Peripheral artery disease	702 (11,8%)	700 (11,8%)	0,00
Pregnancy	0 (0%)	0 (0%)	0,00
Primary or secondary Thrombophilia	106 (1,8%)	105 (1,8%)	0,00
Psychosis	164 (2,8%)	166 (2,8%)	0,00
Pulmonary disease	947 (15,9%)	954 (16%)	0,00
Renal impairment	1296 (21,8%)	1297 (21,8%)	0,00
Rheumatoid arthritis/collagen vascular disease	923 (15,5%)	912 (15,3%)	0,01
Stroke or TIA	325 (5,5%)	336 (5,6%)	-0,01

	Rivaroxaban (N=5956)	Phenprocoumon (N=5956)	SMD
Systemic embolism	98 (1,6%)	109 (1,8%)	-0,01
Tobacco abuse:	154 (2,6%)	152 (2,6%)	0,00
Volume depletion	301 (5,1%)	297 (5%)	0,00
Concomitant drugs			
Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers	2739 (46%)	2754 (46,2%)	-0,01
Antiarrhythmics	16 (0,3%)	12 (0,2%)	0,01
Antidepressants	843 (14,2%)	834 (14%)	0,00
Antiplatelets	614 (10,3%)	600 (10,1%)	0,01
Antiulcer drugs (except proton-pump inhibitors)	88 (1,5%)	81 (1,4%)	0,01
Beta blockers	1896 (31,8%)	1893 (31,8%)	0,00
Calcium channel blockers	1045 (17,5%)	1009 (16,9%)	0,02
Diabetes drugs (incl. insulin)	770 (12,9%)	778 (13,1%)	0,00
Diuretics	1380 (23,2%)	1386 (23,3%)	0,00
Erythropoietin-simulating agents	10 (0,2%)	10 (0,2%)	0,00
Estrogens	165 (2,8%)	177 (3%)	-0,01
Lipid modifying agents	1166 (19,6%)	1147 (19,3%)	0,01
Non-steroidal anti-inflammatory drugs:	2577 (43,3%)	2602 (43,7%)	-0,01
Proton-pump inhibitors	2083 (35%)	2101 (35,3%)	-0,01
Surgery (any)	1530 (25,7%)	1567 (26,3%)	-0,01

Source: Statistical Output Tables (Table 3; Table 4; Table 5; Table 8)

Table 9. Baseline health resource utilization and costs in patients with VTE (after matching)

	Rivaroxaban (N=5956)	Phenprocoumon (N=5956)	SMD
Health Resource utilization			
Number of hospitalizations	1,3 ± 1,5	1,3 ± 1,4	0,00
Number of hospital days	14,2 ± 28,9	14,4 ± 24,4	0,01
Number of emergency room visits	0,6 ± 0,8	0,6 ± 0,8	0,00
Number of outpatient visits	20,7 ± 17,3	20,8 ± 15,4	0,01
Number of different drugs used	6,9 ± 5,3	6,9 ± 5,3	0,00
Costs			
Overall	7382,47€ ± 10555,97€	7443,15€ ± 9968,52€	0,00
Outpatient	959,67€ ± 1092,51€	939,51€ ± 968,22€	-0,01
Inpatient	4892,87€ ± 8187,87€	5076,09€ ± 8035,06€	0,00
Medication	1152,52€ ± 4914,21€	1052,98€ ± 4221,11€	-0,01
Aids and remedies	377,4€ ± 955,24€	374,57€ ± 914,35€	0,00
Renal Impairment	32,37€ ± 602,49€	46,44€ ± 697,98€	0,00

Source: Statistical Output Tables (Table 6; Table 7)

10.2.3 Exposure and follow-up times

Patients treated with phenprocoumon had higher mean total follow-up times (defined as the time from index date to 31-Dec-2019) than those treated with rivaroxaban (1539 vs. 1174 days). This was due to the fact that the majority of patients treated with phenprocoumon entered the cohort early (i.e. in calendar years 2014 and 2015), while at later time periods, more patients initiated treatment with rivaroxaban. Exposed follow-up times were thus also higher in patients treated with phenprocoumon (464 days vs. 313 days). More patients treated with phenprocoumon than with rivaroxaban switched to another oral anticoagulant after the index date (16.6% vs. 8.7%). A higher proportion of patients treated with phenprocoumon had only one prescription of an oral anticoagulant, i.e. their index prescription (33.6% vs. 21.3%). In the rivaroxaban group, a switch to 10mg dose was identified in 1087 patients (6.8%). Median time to switch was 330 days (mean 490.8 days) in these patients.

Phenprocoumon was almost exclusively dispensed in 3 mg tablet strength (99.97% of all dispensations), while for rivaroxaban, the dispensing were for 15 mg strength in 61.1%, for 20 mg in 16.7% and for a combined 15 mg / 20 mg package in 19.0% (the remaining were combinations of different packages). Median number of tablets per package were 100 for phenprocoumon, and 42 for rivaroxaban. Further Details on exposure times, number of prescriptions during follow-up, etc. are included in the Statistical Output Tables (Tables 10, 11, and 12) and in the Statistical Output Tables Supplement 1 (Tables 2 and 3).

10.3 Outcome data

A total of 382 recurrent VTE events were observed in patients treated with rivaroxaban, corresponding to a crude incidence rate of 2.97 (95% CI 2.68 to 3.29) per 100 patient years. In users of phenprocoumon, 167 events were identified, with an incidence rate of 2.29 (95% CI 1.95 to 2.66) per 100 patient years. The crude incidence rates of end-stage kidney disease were 0.29 (95% CI 0.21-0.40) for rivaroxaban, and 0.93 (95% CI 0.72-1.17) for phenprocoumon. Hospitalizations with fatal bleeding events occurred in 38 out of 16081 patients treated with rivaroxaban (0.2%), and 13 out of 6072 patients treated with phenprocoumon (0.2%), resulting in incidence rates of 0.28 (95% CI 0.20 to 0.38) and 0.17 (95% CI 0.09-0.29), respectively.

10.4 Main results

10.4.1 Clinical outcomes

The risk of recurrent VTE events leading to hospitalization were similar in patients treated with rivaroxaban and phenprocoumon, while the risk of end-stage kidney disease was lower in patients treated with rivaroxaban (Table 10). No statistically significant differences were observed for hospitalizations with fatal bleedings or the bleeding subtypes gastrointestinal or intracranial, but the confidence intervals were broad due to the rather low number of events in both treatment groups.

Table 10. Risk of main effectiveness and safety outcomes in VTE patients treated with rivaroxaban or phenprocoumon

	Rivaroxaban (N=16081)	Phenprocoumon (N=6072)	HR unadjusted	HR adjusted
Recurrent VTE event (min. 14 days from index)	382 (2,4%)	167 (2,8%)	1,08 (0,90; 1,30)	1,01 (0,84; 1,21)
End-stage kidney disease	40 (0,2%)	71 (1,2%)	0,31 (0,21; 0,45)	0,45 (0,30; 0,69)

Hospitalizations with fatal bleeding	38 (0,2%)	13 (0,2%)	1,48 (0,78; 2,80)	1,42 (0,74; 2,71)
Hospitalizations with fatal bleeding - (Gastrointestinal)	12 (0,1%)	5 (0,1%)	1,30 (0,45; 3,75)	1,46 (0,50 4,25)
Hospitalizations with fatal bleeding - (Other / unspecified)	8 (0,0%)	-	-	-
Hospitalizations with fatal bleeding - (Intracranial)	15 (0,1%)	6 (0,1%)	1,22 (0,47; 3,16)	1,21 (0,47; 3,15)

Source: Statistical Output Tables (Table 13). Hazard ratios were estimated by COX regression models.

10.4.2 Healthcare resource utilization and costs

Measures of health resource utilization revealed similar service use in both treatment groups (Table 11). Only the hospitalizations and number of different medications used were slightly higher in the rivaroxaban group.

Overall healthcare costs were similar in both treatment groups (Table 12). While patients treated with rivaroxaban had slightly higher overall drug costs, inpatient costs and costs related to kidney diseases were lower.

Table 11. Health resource utilization in VTE patients treated with rivaroxaban or phenprocoumon

	Numbers per patient year (rate)		Rate Ratio adjusted
	Rivaroxaban (N=16081)	Phenprocoumon (N=6072)	
Days in hospital	11,9 (11,9; 12,0)	10,6 (10,5; 10,7)	1,05 (0,98; 1,13)
Hospitalizations	0,8 (0,8; 0,9)	0,8 (0,8; 0,8)	1,06 (1,01; 1,11)
Emergency Admissions	0,4 (0,4; 0,4)	0,4 (0,4; 0,4)	1,01 (0,94; 1,08)
Number of different medications	6,7 (6,7; 6,8)	6,3 (6,2; 6,3)	1,08 (1,05; 1,11)

Source: Statistical Output Tables (Table 14). Adjusted rate ratios were estimated by multivariate Poisson regression.

Table 12. Healthcare costs (EUR) in VTE patients treated with rivaroxaban or phenprocoumon

	Costs per patient year[a)]		Cost ratio adjusted	Mean cost difference
	Rivaroxaban (N=16081)	Phenprocoumon (N=6072)		
Ambulatory	1391,48	1280,56	1,05 (1,00; 1,10)	122,94 (6,42; 239,47)
Drugs	3321,73	1860,89	1,46 (1,34; 1,58)	991,95 (670,31; 1.313,59)
Inpatient	3743,45	3418,18	0,88 (0,77; 1,00)	-657,49 (-1.240,60; -74,39)
Aids and Remedies	838,09	642,09	1,02 (0,91; 1,14)	57,62 (-57,20; 172,44)
Kidney-Related	106,67	299,43	0,35 (0,16; 0,72)	-275,70 (-508,44; -42,95)
Overall	9294,75	7201,72	1,05 (1,00; 1,10)	515,02 (-242,05; 1.272,09)

[a)]Unadjusted. Source: Statistical Output Tables (Table 15). Adjusted cost ratios were estimated by multivariate generalized gamma regression models. Mean cost differences were estimated by multivariate linear regression models.

10.5 Other analyses

10.5.1 Clinical outcomes: sensitivity analyses

A number of sensitivity analyses were planned and performed. In the main analyses, adjusted COX regression models were used to control for confounding factors. In addition, propensity score based approaches (IPTW and matching) were utilized to evaluate the robustness of the results. The propensity score based methods revealed similar hazard ratios as in the main analysis, confirming robustness of the findings (Table 13).

Table 13. Adjusted hazard ratios of main effectiveness and safety outcomes in VTE patients treated with rivaroxaban or phenprocoumon, using different methodological approaches to control for confounding

	Multivariate adjusted	IPTW	PS matched
Recurrent VTE event[a)]	1,01 (0,84; 1,21)	1,03 (0,86; 1,24)	0,88 (0,69; 1,11)
End-stage kidney disease	0,45 (0,30; 0,69)	0,46 (0,30; 0,70)	0,38 (0,22; 0,66)
Hospitalizations with fatal bleeding	1,42 (0,74; 2,71)	1,55 (0,79; 3,05)	1,18 (0,54; 2,56)

[a)]Minimum 14 days from index. Source: Statistical Output Tables (Table 13). Hazard ratios were estimated by COX regression models.

For the primary outcome of recurrent VTE events leading to hospitalization, only events occurring 14 days or later after the index date were considered to separate a recurrence from the worsening of

the index event. In a sensitivity analysis, this time was extended to 60 days, resulting in a hazard ratio that's similar to the main analysis (HR=1.09; 95% CI 0.89 to 1.35).

A number of additional sensitivity analyses for the endpoints of recurrent VTE events were performed, which results are summarized in Figure 8. The sensitivity analyses indicated that the results were generally stable, but were changed when requiring no further dispensation of the index drug after the recurrent VTE event to define an event. If this additional requirement was introduced, the effects estimates were lower, indicating a lower risk with rivaroxaban than with phenprocoumon (Figure 8). The sensitivity analyses that were performed for the endpoints fatal bleeding and end-stage kidney disease revealed robustness of the main analyses (Figure 9).

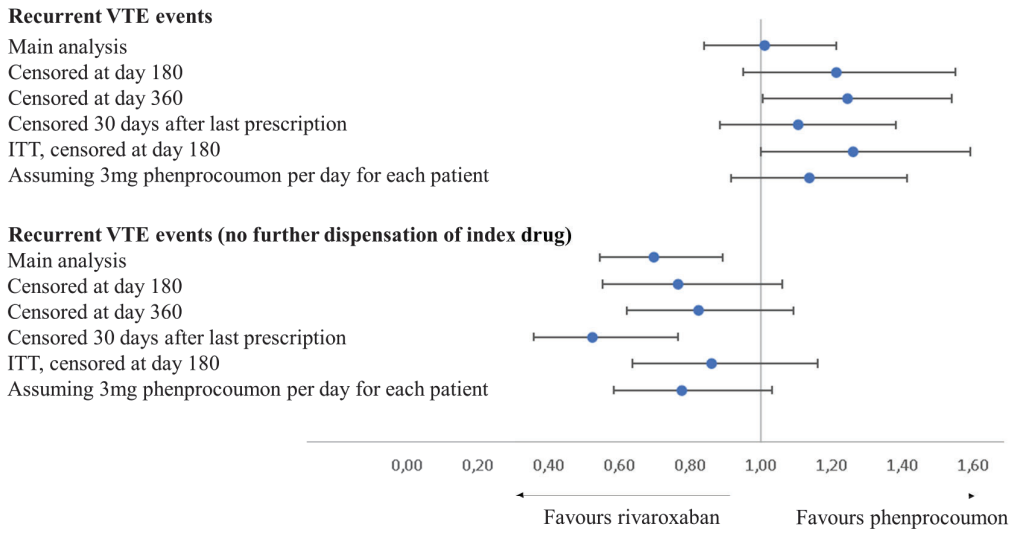

Figure 8. Sensitivity analyses for recurrent VTE events

Source: Statistical Output Tables (Table 13). Displayed are adjusted hazard ratios from multivariate COX regression models, including 95% confidence intervals.

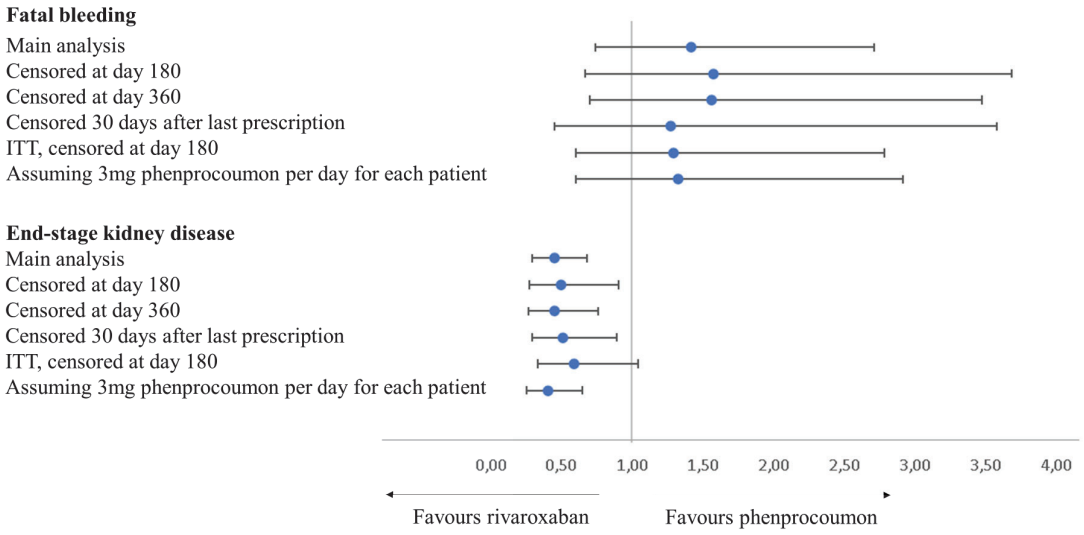

Figure 9. Sensitivity analyses for hospitalization with fatal bleeding and end-stage kidney disease

Source: Statistical Output Tables (Table 13). Displayed are adjusted hazard ratios from multivariate COX regression models, including 95% confidence intervals.

10.5.2 Clinical outcomes: subgroup analyses

The numbers and percentages of patients in pre-defined subgroups are reported in Table 14.

Table 14. Number and percentage of patients in subgroups.

Subgroup	Rivaroxaban		Phenprocoumon	
	N	%	n	%
Age				
PPD				
Type of DVT				
Patients with PE at index	6.316	39,28	2.430	40,02
Patients with DVT only at index	9.765	60,72	3.642	59,98
Provoked type				
Provoked VTE, persistent	3.268	20,32	1.299	21,39
Provoked VTE, transient	2.740	17,04	1.077	17,74
Provoked VTE	5.176	32,19	2.058	33,89
Unprovoked VTE	10.905	67,81	4.014	66,11
Patient groups (inclusion)[a)]				
Patient group 1	6.657	41,40	2.800	46,11
Patient group 2	1.428	8,88	600	9,88
Patient group 3	7.715	47,98	2.595	42,74
Other subgroups				
Patients with lung, breast, or prostate cancer	1.103	6,86	414	6,82
Patients with CKD	830	5,16	735	12,10

[a)] Patient group 4 is not further analyzed as a subgroup due to the low number of patients (N=281 and N=77, respectively).

Subgroup analyses for recurrent VTE events revealed an influence of age on risk estimates, with a higher hazard ratios for patients =<59 years of age than in those 60 years and older (Figure 10). However, the increase in risk for younger patients was sensitive to some methodological aspects of the study: If outcome events were restricted to those without further dispensing of the index drug, there was no increase in risk with patients 59 years or younger (HR=1,01; 95% CI 0,67 to 1,50). Patients with chronic kidney disease had lower risks of recurrent VTE events if they were treated with rivaroxaban. No substantial impact of the other subgroup characteristics were observed.

For the outcome of hospitalizations with fatal bleeding, the subgroup analyses were limited by the low number of events in the subgroups and are thus not displayed here in detail.

For end-stage renal failure, the analyses revealed that the lower risk associated with rivaroxaban was consistent over the different subgroups analyzed (Figure 11).

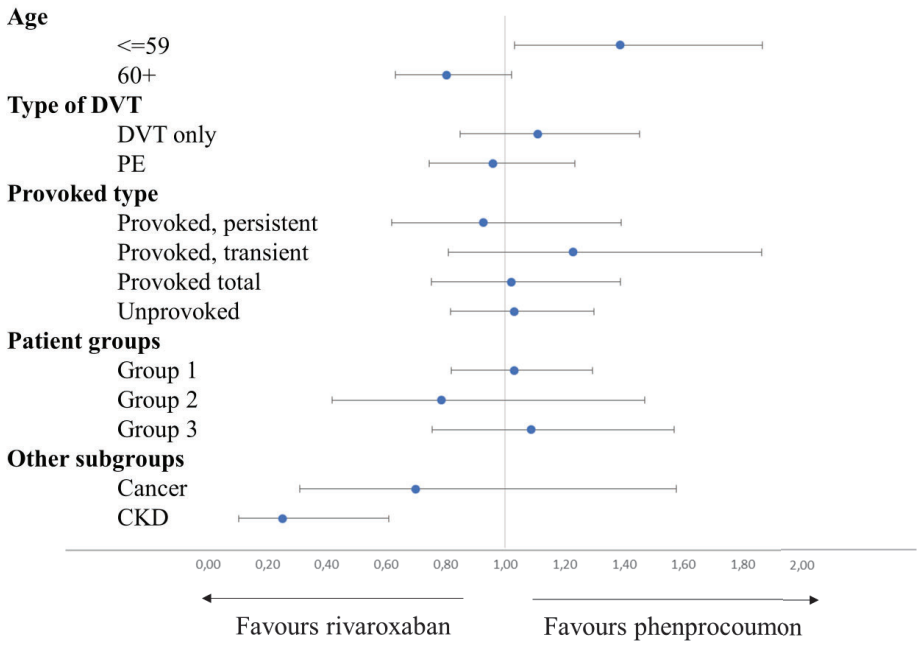

Figure 10. Subgroup analyses for recurrent VTE events

Source: Statistical Output Tables (Table 17). Displayed are adjusted hazard ratios from multivariate COX regression models, including 95% confidence intervals.

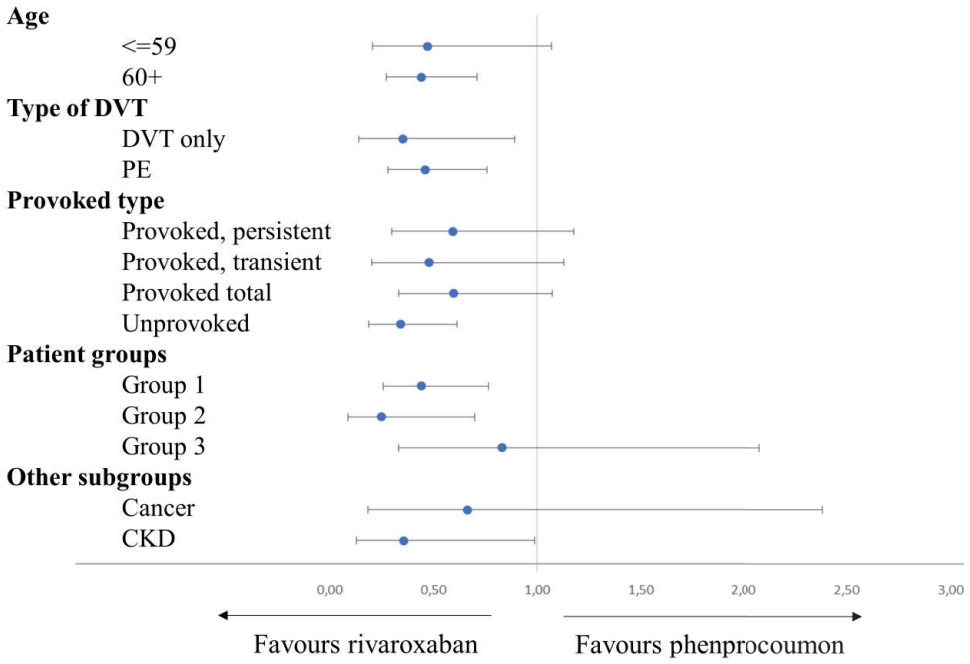

Figure 11. Subgroup analyses for end-stage renal failure

Source: Statistical Output Tables (Table 17). Displayed are adjusted hazard ratios from multivariate COX regression models, including 95% confidence intervals.

10.5.3 Healthcare resource utilization and costs: sensitivity analyses

As for the clinical outcomes, alternative methodological approaches to consider confounding were performed to evaluate robustness of findings for healthcare resource utilization and cost outcomes. The propensity score based approaches revealed similar results to multivariate adjusted models, and thus confirmed robustness of the main analyses (Table 15).

Table 15. Adjusted rate ratios and cost ratios using different methodological approaches to control for confounding

	Multivariate adjusted	IPTW	PS matched
Healthcare resource utilization			
Days in hospital	1,05 (0,98; 1,13)	1,06 (0,99; 1,13)	1,04 (0,96; 1,13)
Hospitalizations	1,06 (1,01; 1,11)	1,06 (1,01; 1,11)	1,06 (0,99; 1,12)
Emergency Admissions	1,01 (0,94; 1,08)	1,01 (0,94; 1,08)	1,00 (0,91; 1,09)
Number of different medications	1,08 (1,05; 1,11)	1,09 (1,06; 1,12)	1,10 (1,07; 1,14)
Costs			
Ambulatory	1,05 (1,00; 1,10)	1,03 (0,99; 1,08)	0,99 (0,95; 1,04)
Drugs	1,46 (1,34; 1,58)	1,48 (1,36; 1,60)	1,45 (1,30; 1,61)
Inpatient	0,88 (0,77; 1,00)	0,90 (0,79; 1,02)	0,93 (0,80; 1,09)
Aids and Remedies	1,02 (0,91; 1,14)	1,00 (0,89; 1,11)	1,00 (0,89; 1,12)
Kidney-Related	0,35 (0,16; 0,72)	0,48 (0,21; 0,99)	0,55 (0,17; 1,78)
Overall	1,07 (1,00; 1,15)	1,08 (1,01; 1,16)	1,08 (0,99; 1,17)

Source: Statistical Output Tables (Table 14; Table 15). Estimates are rate ratios for healthcare resource utilization, and cost ratios for healthcare costs (rivaroxaban vs. phenprocoumon). Numbers in brackets represent 95% confidence intervals.

Additional sensitivity analyses were performed and revealed overall similar results for healthcare resource utilization (Figure 12) and costs (Figure 13). The sensitivity analysis that censored patients 30 days after their last prescription revealed slightly higher estimates than the main analyses for hospitalization and emergency admission rates.

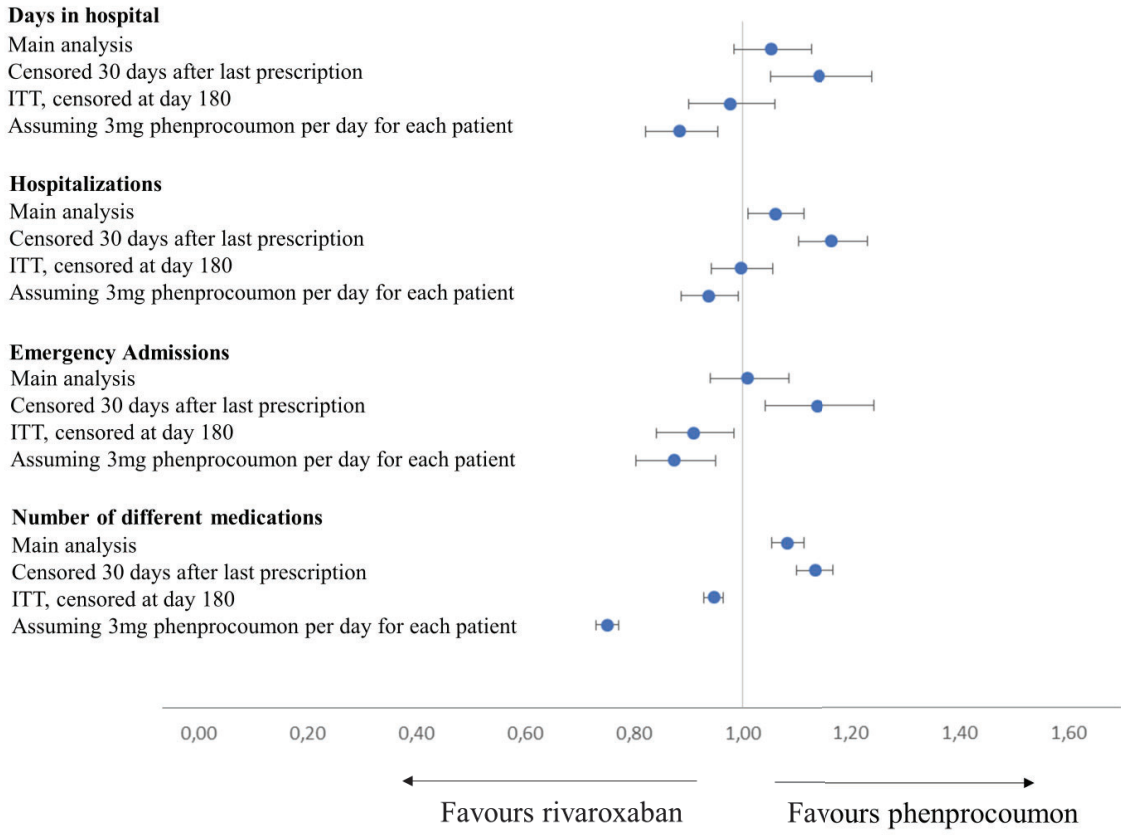

Figure 12. Sensitivity analyses for healthcare resource utilization

Source: Statistical Output Tables (Table 14). Displayed are adjusted rate ratios from multivariate Poiosson regression models, including 95% confidence intervals.

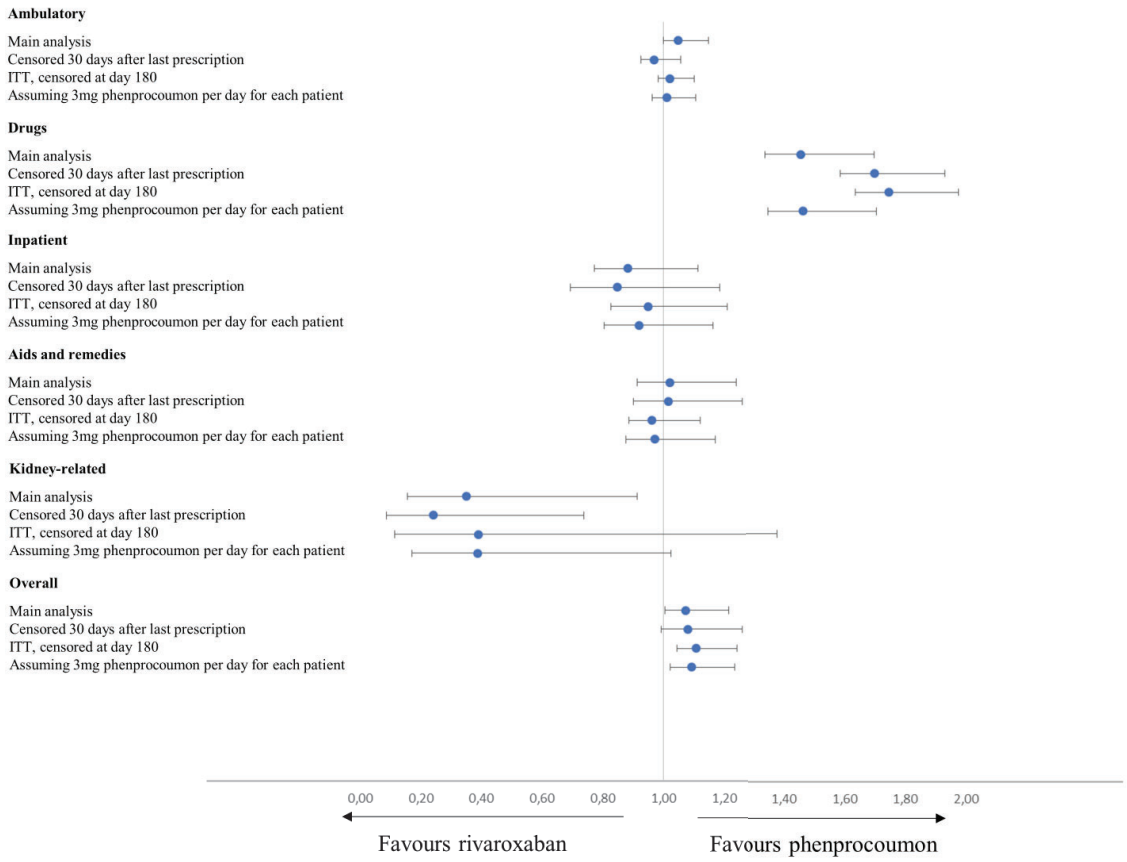

Figure 13. Sensitivity analyses for healthcare costs

Source: Statistical Output Tables (Table 15). Displayed are adjusted cost ratios from multivariate generalized gamma regression models, including 95% confidence intervals.

10.5.4 Healthcare resource utilization and costs: subgroup analyses

Subgroup analyses for measures of healthcare utilization are presented in Figure 14 to Figure 17 and indicate only small differences of treatment effects between subgroups. Healthcare costs were in general also not substantially affected by subgroup characteristics (Figure 18 to Figure 23).

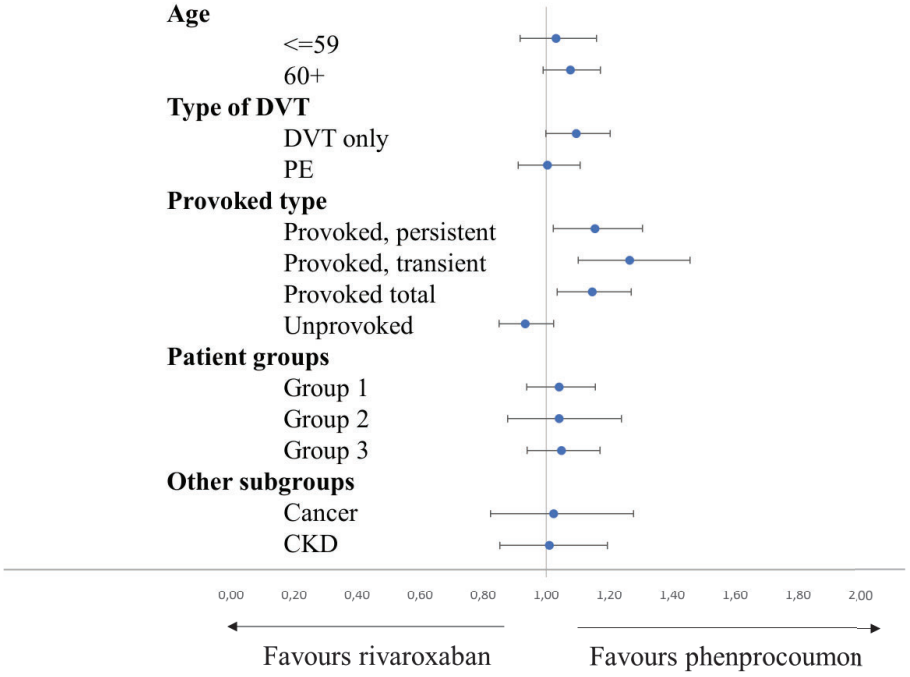

Figure 14. Subgroup analyses for healthcare resource utilization / days in hospital

Source: Statistical Output Tables (Table 18). Displayed are adjusted rate ratios from multivariate Poisson regression models, including 95% confidence intervals.

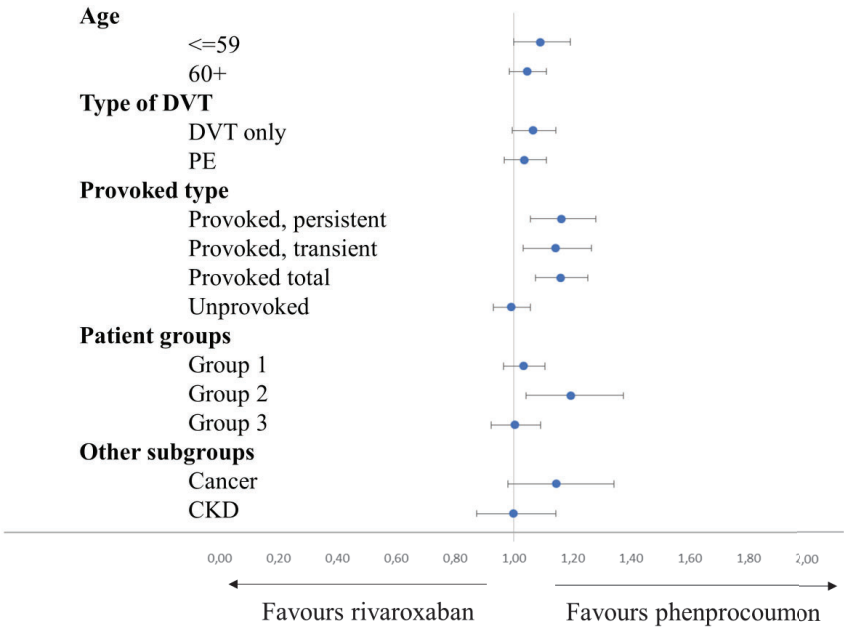

Figure 15. Subgroup analyses for healthcare resource utilization / hospitalizations

Source: Statistical Output Tables (Table 18). Displayed are adjusted rate ratios from multivariate Poisson regression models, including 95% confidence intervals.

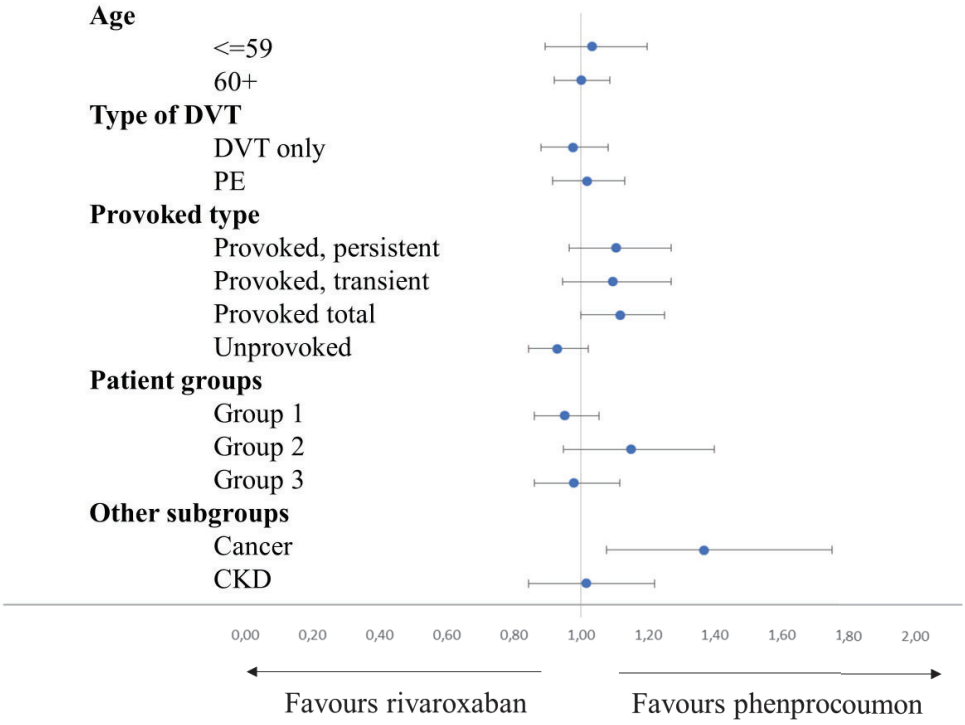

Figure 16. Subgroup analyses for healthcare resource utilization / emergency admissions

Source: Statistical Output Tables (Table 18). Displayed are adjusted rate ratios from multivariate Poisson regression models, including 95% confidence intervals.

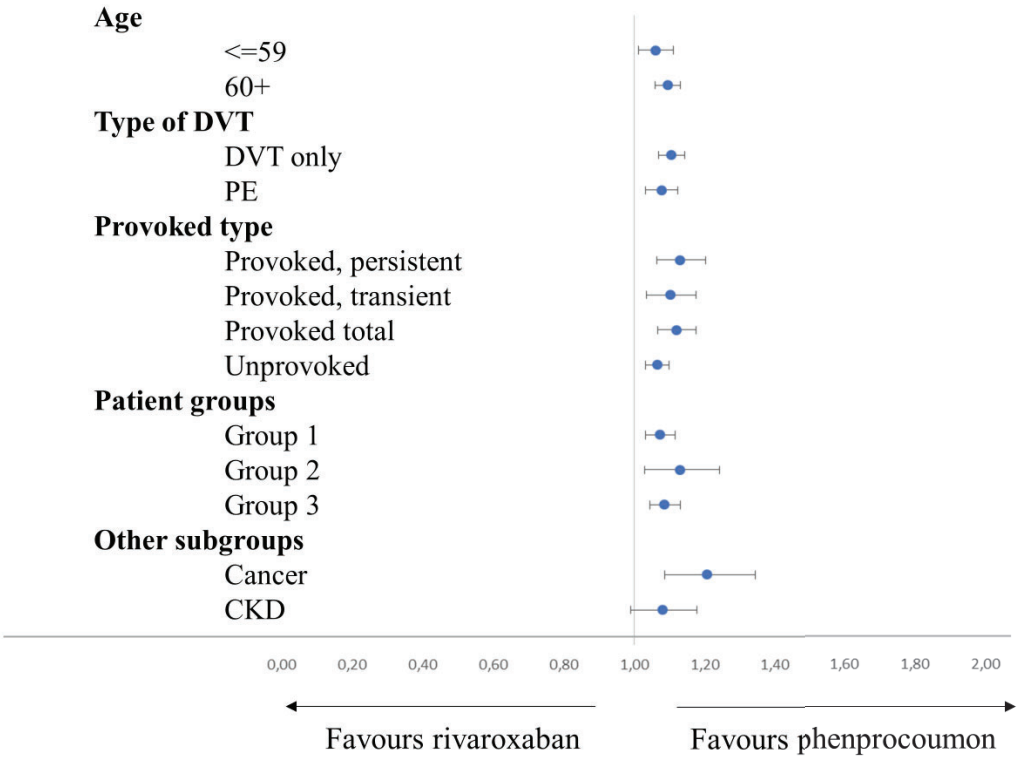

Figure 17. Subgroup analyses for healthcare resource utilization / number of different drugs used

Source: Statistical Output Tables (Table 18). Displayed are adjusted rate ratios from multivariate Poisson regression models, including 95% confidence intervals.

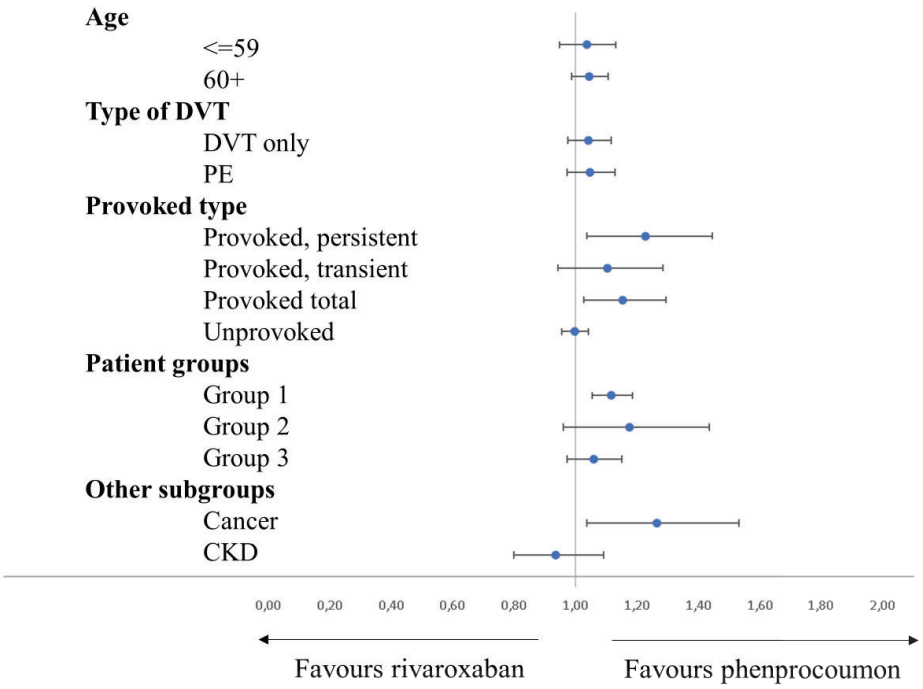

Figure 18. Subgroup analyses for ambulatory healthcare costs

Source: Statistical Output Tables (Table 19). Displayed are adjusted cost ratios from multivariate generalized gamma regression models, including 95% confidence intervals.

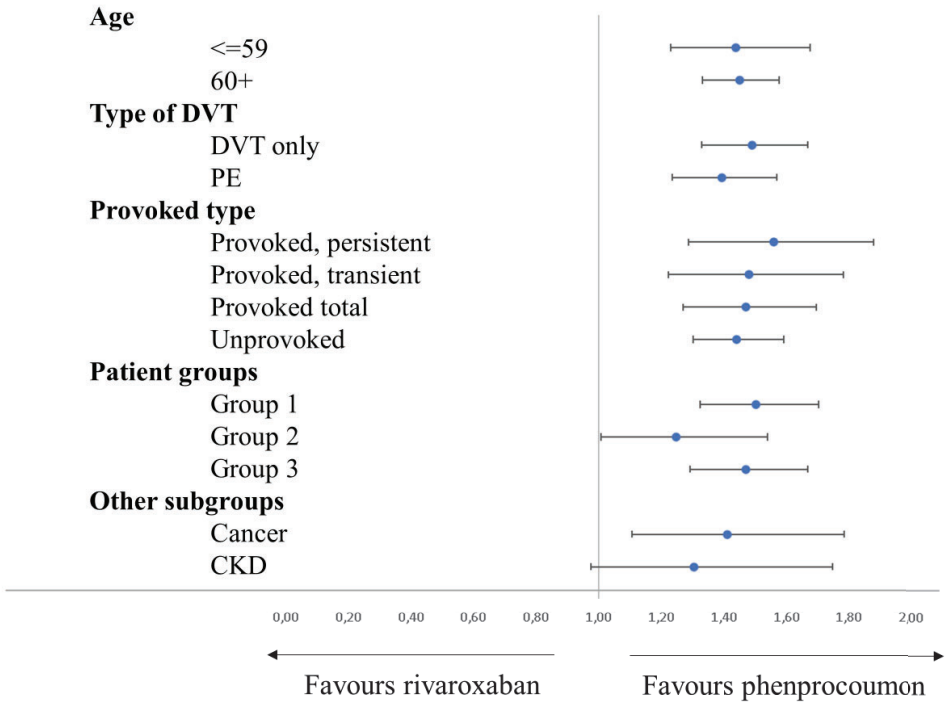

Figure 19. Subgroup analyses for drug costs

Source: Statistical Output Tables (Table 19). Displayed are adjusted cost ratios from multivariate generalized gamma regression models, including 95% confidence intervals.

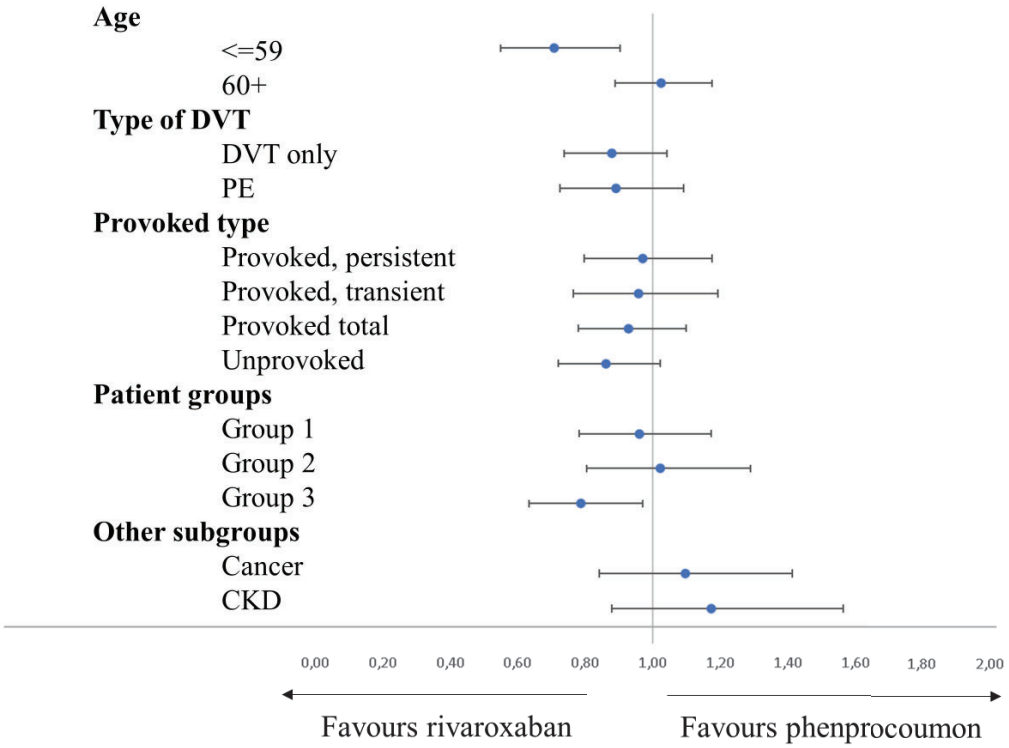

Figure 20. Subgroup analyses for hospitalization costs

Source: Statistical Output Tables (Table 19). Displayed are adjusted cost ratios from multivariate generalized gamma regression models, including 95% confidence intervals.

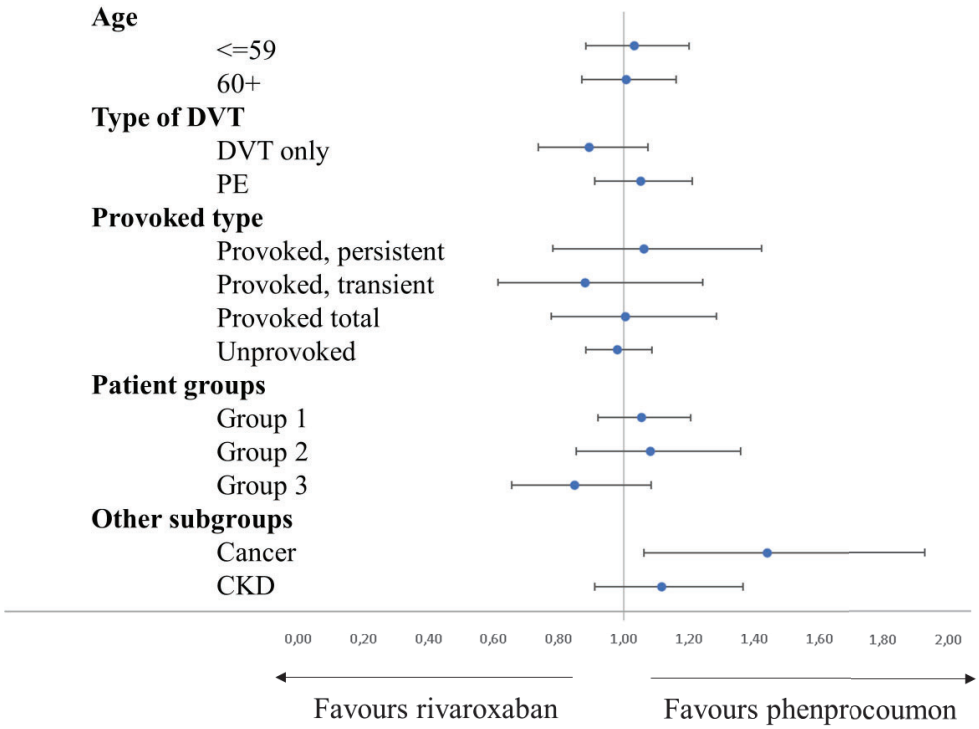

Figure 21. Subgroup analyses for aids and remedies costs

Source: Statistical Output Tables (Table 19). Displayed are adjusted cost ratios from multivariate generalized gamma regression models, including 95% confidence intervals.

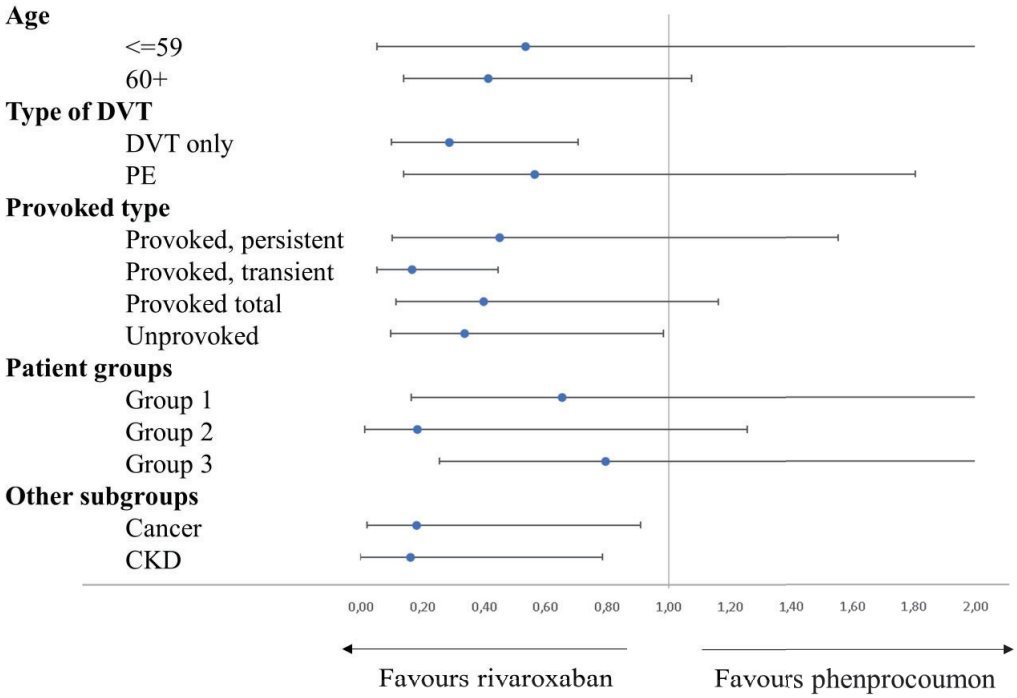

Figure 22. Subgroup analyses for kidney-related healthcare costs

Source: Statistical Output Tables (Table 19). Displayed are adjusted cost ratios from multivariate generalized gamma regression models, including 95% confidence intervals.

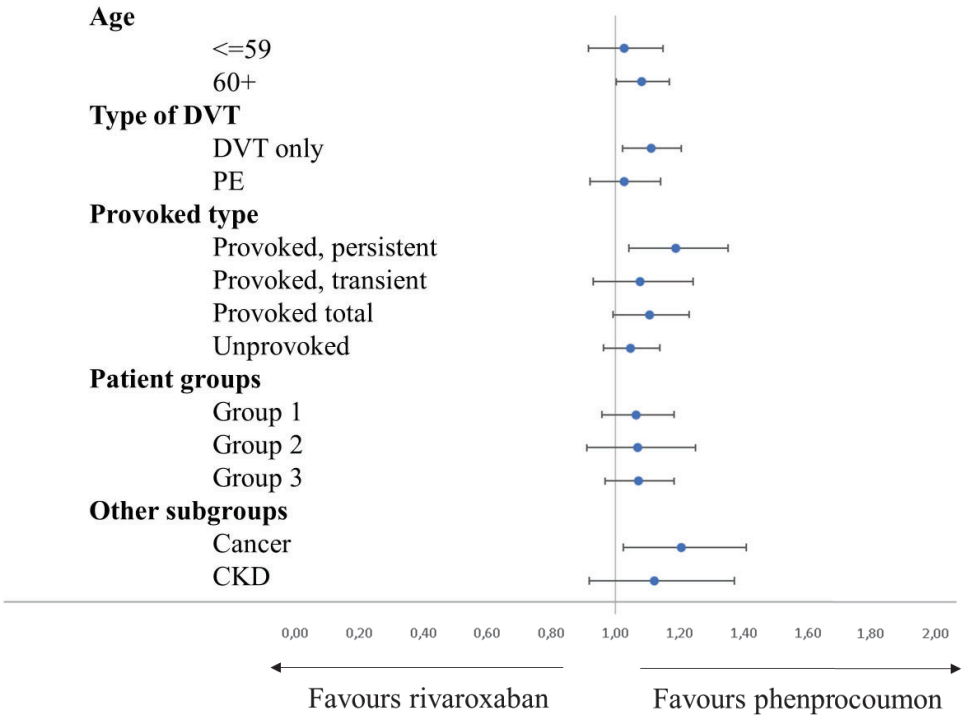

Figure 23. Subgroup analyses for overall healthcare costs

Source: Statistical Output Tables (Table 19). Displayed are adjusted cost ratios from multivariate generalized gamma regression models, including 95% confidence intervals.

10.6 Safety data (Adverse events/adverse reactions)

Not applicable, as the study was based on secondary use of claims data.

11. Discussion

11.1 Key results

In this observational study, patients with VTE who were treated with rivaroxaban (N=16081) were compared with patients treated with phenprocoumon (N=6072; with or without preceding heparin therapy). Overall, no substantial baseline differences in patient characteristics were evident between these two patient groups.

In the adjusted analyses, the risk of recurrent VTE events leading to hospitalization was similar in patients treated with rivaroxaban and phenprocoumon, while the risk of end-stage kidney disease was lower in patients treated with rivaroxaban. No statistically significant differences were observed for hospitalizations with fatal bleedings or the fatal bleeding subtypes gastrointestinal or intracranial, but the confidence intervals were broad due to the rather low number of events in both treatment groups. Results derived from alternative statistical methods to consider confounding (propensity score based approaches) revealed similar results. A number of sensitivity analyses were conducted, and indicated that the hazard ratio of recurrent VTE events in users of rivaroxaban was lower than in users of phenprocoumon, if no further dispensation of the index drug was required as an additional criterion to define recurrent VTE events (based on the expectation that a new VTE event would lead to a change in the OAC treatment regimen). Other methodological aspects (e.g. censoring at 180 or 360 days after index date; intention-to-treat approach) had only small impact on the hazard ratios of recurrent VTE events. Sensitivity analyses for the outcomes fatal bleeding and end-stage kidney disease did not indicate an important impact of any of the methodological aspects explored.

Measures of health resource utilization revealed similar health service use per patient year in both treatment groups, with only the days-in-hospital being slightly lower in the rivaroxaban group. Healthcare costs were also similar in both treatment groups. While patients treated with rivaroxaban had slightly higher overall drug costs, the inpatient costs and costs related to kidney diseases were lower than in users of phenprocoumon.

Subgroup analyses for recurrent VTE events revealed an influence of age on risk estimates, with a higher hazard ratios for patients >=59 years of age than in those 60 years and older, however, these results were not robust to sensitivity analyeses. Patients with chronic kidney disease had lower risks of recurrent VTE events if they were treated with rivaroxaban. No substantial impact of the other subgroup characteristics were observed. For the outcome of hospitalizations with fatal bleeding, the subgroup analyses were limited by the low number of events in the subgroups and are thus not displayed here in detail. For end-stage renal failure, the analyses revealed that the lower risk associated with rivaroxaban was consistent over the different subgroups analyzed. Subgroup analyses for measures of healthcare utilization indicate only small differences of treatment effects between subgroups. Healthcare costs were in general also not substantially affected by subgroup characteristics.

11.2 Limitations

A number of limitations of this observational study have to be considered when interpreting the results:

- The identification of the index VTE events in this study was challenging, due to the different treatment scenarios (outpatient vs. inpatient vs. outpatient/inpatient combined). It is thus uncertain if some index VTE events have been missed, if the patients did not fulfil the predefined inclusion and exclusion criteria. It can be expected, however, that a similar effect would occur in both treatment groups, so that any bias in the comparative analyses should be low.
- The assessment of the person time exposed was based on drug dispensations from pharmacies, i.e. with the assumption that all tablets dispensed were actually taken by the patient. In addition, the estimation of the person time exposed after each dispensation was based on assumptions on

the number of tablets and/or the daily dose. As a consequence, there is some uncertainty on the actually exposed person time, especially after the last dispensation. This is especially the case for phenprocoumon, which was often prescribed in large package sizes and is dosed in an individualized fashion (based on INR values). We thus estimated personalized DDDs for patients treated with phenprocoumon, and included sensitivity analyses to investigate the impact of this aspect (censoring 30 days after the last prescription; assumption of 3mg phenprocoumon per day for each patient). It was, however, not possible to consider changes in phenprocoumon treatment pattern over time, e.g. due to developing instable INR during follow-up.

- The substantial differences in median package sizes between phenprocoumon and rivaroxaban; the differences in drug price (with different potential for stockpiling); the difference in switching pattern (which occurred almost twice as often in phenprocoumon users); and the inability to consider changes in INR stability over time may have biased risk estimates. Especially the large package sizes (with longer estimated exposure time) may have led to including actually unexposed person time for phenprocumon users (as the actual time point of stopping phenprocoumon is unknown).
- In the analysis of recurrent VTE events, only events treated in hospital were included, as it is not possible to distinguish an ambulatory diagnosis of a recurrent VTE from a historical VTE diagnosis. However, it can be expected that especially rather early events (occurring within the first year after the index date), will have a high probability of being treated in a hospital setting. In addition, it is expected that the number of missed events will be of a similar magnitude in both treatment groups.
- For the endpoint of recurrent VTE events, the requirement of "no further dispensation of the index drug" resulted in lower hazard ratios than those observed in the main analyses. This indicates that methodological aspects may have impacted the findings for this outcome, and that actual hazard ratios may be lower than those observed in the main analyses.
- There is no cause-of-death information available for patients who died during their person-time at risk. Fatal bleeding events were thus limited to those events that led to hospitalization, and in which the patient died within the hospital. This may have led to a number of missed events (i.e. patients who die from bleeding before reaching the hospital), but it is considered that this proportion is probably low. In addition, it is expected that the number of missed events would be of a similar magnitude in both treatment groups.
- Unmeasured or residual confounding may have affected the study results because several factors associated with the study outcomes cannot be measured adequately in claims data, e.g. laboratory values, physical activity, smoking. laboratory values and over the counter medications such as aspirin.

11.3 Interpretation

In this study, the risk of recurrent VTE events leading to hospitalization was similar in patients treated with rivaroxaban and phenprocoumon in the main analysis. In the pooled, randomized EINSTEIN studies (i.e. patients with VTE and PE combined as in this study), the pooled risk of recurrent VTE did also not differ between rivaroxaban and warfarin with a hazard ratio of 0.89 (95% CI 0.66 to 1.19) (Prins et al. 2013). The effect estimate was lower in patients with DVT (HR=0.68; 95% CI 0.44 to 1.04; EINSTEIN Investigators 2012) than in patients with PE (EINSTEIN–PE Investigators 2012). Most observational studies revealed that rivaroxaban was associated with a

lower risk of recurrent VTE events compared to warfarin (Coleman 2017b; Coleman et al. 2018a; Coleman et al. 2018b; Coleman et al. 2018c; Larsen et al. 2017). Two studies involving African Americans indicated that the risks were similar in both patient groups (Costa et al. 2020a; Costa et al. 2020b). In the current study, effect estimates were lower if "no further dispensation of the index drug" was required as an additional criterion to identify cases of recurrent VTE. This indicates some level of uncertainty around the effect estimates in the main analyses, and that actual treatment effects might be lower.

No increase in risk was evident for fatal bleeding events. These events were rare in the EINSTEIN studies, but major bleeding risk was lower with rivaroxaban than with warfarin in the pooled analysis (HR=0.54; 95% CI 0.37 to 0.79) (Prins et al. 2013). While some observational studies confirmed these findings (Coleman et al. 2017b; Coleman et al. 2018a; Coleman et al. 2018b), others did not find a statistically significant superiority of rivaroxaban (Costa et al. 2020a; Costa et al. 2020b; Coleman et al. 2018c; Costa et al. 2021; Larsen et al. 2017).

In this study, healthcare costs were similar in both treatment groups. While patients treated with rivaroxaban had slightly higher overall drug costs, the inpatient costs and costs related to kidney diseases were lower than in users of phenprocoumon. This is similar to the findings from Spyropoulos et al. 2019. They reported that total healthcare costs (including pharmacy costs) were similar ($43,034 vs $44,565), while average total medical costs PPPY were $2829 lower with rivaroxaban versus warfarin ($34,824 vs $37,653), which was mainly driven by lower hospitalization costs. Kohn et al. 2017 reported that rivaroxaban use was associated with decreased treatment costs during the index hospital stay. Coleman et al. 2017a reported higher pharmacy costs, but lower inpatient healthcare utilization costs, similar to the findings in our study. In their study, however, also outpatient healthcare utilization costs were lower, resulting in lower total per patient VTE treatment costs.

11.4 Generalizability

Although the analysis dataset obtained from the InGef database covers more than 6 million insured members of SHIs all over Germany, representativeness for all phenprocoumon and rivaroxaban users in Germany cannot be guaranteed if differences exist for instance by socioeconomic status or region. However, it is unlikely that this has affected internal validity of the study results, as the objectives of the study were mainly related to relative rather than absolute risk estimates.

12. Other information

None.

13. Conclusion

Patients with VTE who were treated with rivaroxaban had similar risks of hospitalization for recurrent VTE as patients treated with phenprocoumon. There were also no differences in the risks of fatal bleeding, but the confidence intervals for these analyses were broad. The risk of developing end-stage kidney disease was lower in patients treated with rivaroxaban. Health resource utilization was similar in both treatment groups. While patients treated with rivaroxaban had slightly higher overall drug costs, the inpatient costs and costs related to kidney diseases were lower than in users of phenprocoumon.

14. References

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Appendices

Annex 1: List of stand-alone documents

Table 16: List of stand-alone documents

Document Name	Final version and date (if available)*
Statistical Output Tables (20211118_Outcomes.xlsx)	18 NOV 2021
Statistical Output Tables Supplement 1	26 JAN 2021

20211118_Outcomes.xlsx

Statistical Output Tables Suppl 1.xlsx

Annex 2 Additional information

Not applicable

Annex 3 Signature Pages

Signature Page – OS Conduct Responsible

Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Report version and date	V1.0, 10 JAN 2022
IMPACT study number	21456
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS36102
Medicinal product / Active substance / Medical Device / Combination Product	*BAY 59-7939; 1912, Rivaroxaban, Xarelto®*
Comparator / Reference therapy	Heparins (B01AB) Vitamin-K antagonist, Phenprocoumon (B01AA04)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 1/17/2022, PPD

Signature Page – OS Safety Lead

Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Report version and date	V1.0, 10 JAN 2022
IMPACT study number	21456
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
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Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 1/17/2022, PPD

Signature Page – EP Epidemiologist

Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Report version and date	V1.0, 10 JAN 2022
IMPACT study number	21456
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS36102
Medicinal product / Active substance / Medical Device / Combination Product	*BAY 59-7939; 1912, Rivaroxaban, Xarelto®*
Comparator / Reference therapy	Heparins (B01AB) Vitamin-K antagonist, Phenprocoumon (B01AA04)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 1/17/2022, PPD

Signature Page – OS Medical Expert

Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Report version and date	V1.0, 10 JAN 2022
IMPACT study number	21456
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS36102
Medicinal product / Active substance / Medical Device / Combination Product	*BAY 59-7939; 1912, Rivaroxaban, Xarelto®*
Comparator / Reference therapy	Heparins (B01AB) Vitamin-K antagonist, Phenprocoumon (B01AA04)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 1/17/2022, _____ PPD _____

Signature Page – OS Medical Expert

Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Report version and date	V1.0, 10 JAN 2022
IMPACT study number	21456
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS36102
Medicinal product / Active substance / Medical Device / Combination Product	*BAY 59-7939; 1912, Rivaroxaban, Xarelto®*
Comparator / Reference therapy	Heparins (B01AB) Vitamin-K antagonist, Phenprocoumon (B01AA04)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 1/23/2022, PPD

Signature Page – EP Statistician

Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Report version and date	V1.0, 10 JAN 2022
IMPACT study number	21456
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS36102
Medicinal product / Active substance / Medical Device / Combination Product	*BAY 59-7939; 1912, Rivaroxaban, Xarelto®*
Comparator / Reference therapy	Heparins (B01AB) Vitamin-K antagonist, Phenprocoumon (B01AA04)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature:_____, PPD

1/24/2022

Signature Page – Principal Investigator (External)

Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Report version and date	V1.0, 10 JAN 2022
IMPACT study number	21456
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS36102
Medicinal product / Active substance / Medical Device / Combination Product	*BAY 59-7939; 1912, Rivaroxaban, Xarelto®*
Comparator / Reference therapy	Heparins (B01AB) Vitamin-K antagonist, Phenprocoumon (B01AA04)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 1/24/2022, PPD