Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Report version and date	v 1.0 27 APR 2021
Study type / Study phase	Observational, Phase IV PASS
EU PAS register number	EUPAS33537
Active substance	Rivaroxaban
Medicinal product	Xarelto (rivaroxaban)
Comparator	Warfarin
Study Initiator and Funder	Bayer AG, 51368 Leverkusen
Research question and objectives	This study aimed to evaluate the incidence of acute and chronic adverse renal outcomes among patients with NVAF in UK primary care. **Primary objective**: to estimate the magnitude of renal decline, incidence of end-stage renal disease (ESRD) and acute kidney injury (AKI) in patients with NVAF treated with rivaroxaban and those treated with a VKA according to the presence of CKD and its severity at the start of OAC therapy in UK primary care. **Secondary objective**: to evaluate the primary objective among specific risk groups reflecting known risk factors for CKD progression: • patients with/without diabetes • patients with/without heart failure
Country(-ies) of study	United Kingdom

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Marketing authorization holder

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1. Abstract

Acronym/Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Report version and date **Author**	v 1.0 27 APR 2021 PPD PPD Spain
Keywords	Acute kidney injury; End-stage renal disease; renal function; chronic kidney disease; oral anticoagulants
Rationale and background	Atrial fibrillation (AF) and chronic kidney disease (CKD) are both common conditions that become more prevalent with advancing age, and they frequently co-exist. Most patients with AF are at high risk of stroke and therefore require preventative therapy with long-term anticoagulation. Patients with both AF and CKD have a further increased risk of thromboembolic events, and they are also at higher risk of bleeding – risks that are higher with progressively declining renal function. For patients with non-valvular AF (NVAF), international guidelines recommend direct oral anticoagulants (DOACs) as the preferred OAC, yet vitamin-K antagonists (VKAs) are still extensively used in clinical practice, including among patients with concomitant CKD. Anticoagulant-related nephropathy (ARN) is a complication associated with the use of anticoagulants that has been reported in recent years, especially in patients on warfarin. Anticoagulant-related nephropathy accelerates the progression of CKD and is a significant risk factor for mortality within the first two months of diagnosis. Previous observational studies among patients with NVAF have shown that use of vitamin K antagonists, such as warfarin, is associated with higher risks of adverse renal outcomes – both long-term (declining renal function) and acute (acute kidney injury) – than rivaroxaban. The rationale for this present study was that further observational evidence demonstrating a differential effect between rivaroxaban and VKAs on adverse renal outcomes in

	patients with NVAF in other settings would help prescribers make more informed benefit–risk decisions regarding choice of anticoagulant therapy for their patients.
Research question and objectives	**Primary objective:** to estimate the magnitude of renal decline, incidence of end-stage renal disease (ESRD) and acute kidney injury (AKI) in patients with NVAF treated with rivaroxaban and those treated with a VKA according to the presence of CKD and its severity at the start of OAC therapy in UK primary care. **Secondary objective**: to evaluate the primary objective among specific risk groups reflecting known risk factors for CKD progression: • patients with/without diabetes • patients with/without heart failure
Study design	Retrospective cohort study using secondary data collection. A new user design was used – patients with NVAF newly initiated on OAC therapy with either rivaroxaban or a VKA were identified and followed up to identify adverse renal outcomes.
Setting	United Kingdom primary care: IQVIA Medical Research Data UK (IMRD-UK) database.
Subjects and study size, including dropouts	The study cohorts included 6903 initiators of rivaroxaban (15 mg, N=1156; 20 mg, N=5747), and 7586 initiators of warfarin.
Variables and data sources	**Exposure:** the first OAC prescribed – either rivaroxaban or warfarin. The main analysis used an intention-to-treat: any change in exposure during follow-up was ignored and we assumed that patients remain on the OAC they initiated for the entire follow-up. **Renal outcomes:** • 100% increase (doubling) of serum creatinine (SCr) from OAC initiation any time during follow-up (confirmed by a subsequent measurement) • ≥20%, ≥30%, ≥40%, and ≥50% increase in SCr from baseline at any point during follow-up (confirmed by a subsequent measurement).

	• ≥20%, ≥30%, ≥40% and ≥50% decline in estimated glomerular filtration rate (eGFR) from baseline at any time during follow-up confirmed by a subsequent measurement • ESRD • Rate of eGFR decline during follow-up • AKI: two case identification methods were used. Method A used coded entries for AKI only, and Method B used recorded SCr values based on a previously reported AKI phenotyping algorithm **Co-variates:** demographics, comorbidities, comedications, health care use, lifestyle variables
Results	**Renal decline and ESRD** After a mean follow-up of 2.5 years, the number of cases with renal outcomes ranged from 3040 for the mildest renal decline endpoint (≥20% decline in eGFR) and 98 for the most severe endpoint (ESRD). The crude incidence rates of renal decline events, i.e. changes in creatinine clearance and eGFR from the baseline, (per 10,000 person-years) were consistently lower among rivaroxaban initiators (ranging from 22.1 for ≥20% decline in eGFR to 983.4 for ESRD depending on the cut-offs) than among warfarin initiators (ranging from 30.5 for ≥20% decline in eGFR to 1050.6 for ESRD). After adjustment for potential confounders, compared with individuals initiating warfarin, those initiating rivaroxaban experienced a reduced risk of renal decline outcomes that ranged from 14% (95% CI: 8%–20%) for ≥20% decline in eGFR to 28% (95% CI: 12%–41%) for ≥50% decline in eGFR. Furthermore, the estimated mean loss in renal function during the study period was 1.82 ml/min/1.73 m^2 per year among warfarin initiators and 1.37 ml/min/1.73 m^2 per year among rivaroxaban initiators (p<0.01). **AKI** The crude incidence rate of AKI using Method A was 88.1 per 10,000 person-years among initiators of rivaroxaban and 69.9 per 10,000 person-years among initiators of warfarin respectively. The corresponding incidence rates for AKI using Method B were 194.4 per 10,000 person-years among initiators of rivaroxaban and 234 per 10,000 person-years.

	After adjusting for confounders, HRs for AKI with rivaroxaban vs. warfarin use were 1.26 (95% CI: 0.99-–1.60) using Method A, and 0.80 (95% CI: 0.69–0.93) using Method B.
Discussion	Our results support the results of previous observational studies that patients with NVAF using rivaroxaban have a significantly reduced risk of renal decline than those using warfarin. Our results also indicate that identifying AKI in the IMRD-UK primary care database is challenging, but when using the most sensitive definition (Method B), rivaroxaban is associated with a significantly reduced risk of AKI when compared with warfarin. Further observational research and evidence from randomized controlled trials would provide the final word regarding this interesting effect of these drugs.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen
Names and affiliations of principal investigators	PPD and PPD PPD PPD , Spain

2. List of abbreviations

AF	atrial fibrillation
AKI	acute kidney injury
ARN	anticoagulant-related nephropathy
BMI	body mass index
PPD	PPD
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DOAC	direct oral anticoaguant
DVT	deep vein thrombosis
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
EU	European Union
HR	hazard ratio
IHD	ischaemic heart disease
INR	international normalized ratio
IR	incidence rate
IS	ischaemic stroke
MI	myocardial infarction
N/A	not applicable
NVAF	non-valvular atrial fibrillation
OAC	oral anticoagulant
PAD	peripheral artery disease
PCP	primary care practitioner
SE	systemic embolism
SCr	serum creatinine
SRC	scientific research committee
THIN	The Health Improvement Network
UK	United Kingdom
US	United States
VKA	vitamin K antagonist

3. Investigators

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5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual Date	Comments
Start of data collection	01 MAR 2020	01 MAR 2020	

End of data collection	30 NOV 2020	30 NOV 2020	
Registration in the EU PAS register	5 MAR 2020	5 MAR 2020	
Final report of study results	27 APR 2021	27 APR 2021	

6. Rationale and background

Atrial fibrillation (AF) and chronic kidney disease (CKD) are both common conditions that become more prevalent with advancing age,(1, 2) and they frequently co-exist.(3) Among 33,024 patients in the GARFIELD AF registry, 27.9% had at least some degree of CKD,(4) while among 9019 patients in the ORBIT AF registry, 38.7% had at least stage 3 CKD.(5) The majority of patients with AF are at high risk of stroke and systemic embolism (SE) and therefore require preventative therapy with long-term anticoagulation. This risk is particularly high in patients with both AF and CKD, and these patients also have a higher risk of bleeding.(6-8) The risk of both thromboembolism and bleeding increases with progressively declining renal function(9) – a factor also highly correlated with age – thus bleeding risk is particularly high among patients with end-stage renal disease (ESRD; stage 5 CKD) on dialysis.(10-12)

For patients with non-valvular AF (NVAF), international guidelines recommend direct oral anticoagulants (DOACs) as the preferred OAC,(1, 13, 14) yet vitamin-K antagonists (VKAs) are still extensively used in clinical practice, including among patients with concomitant CKD. Data from the ORBIT AF registry show that nearly three-quarters (73.9%) of patients with stage III CKD were treated with warfarin (the most commonly used VKA).(5)

Anticoagulant-related nephropathy (ARN) is a complication associated with the use of anticoagulants that has been reported in recent years, especially in patients using warfarin. It is believed that the pathophysiological mechanisms associated with ARN are multifactorial (15). Anticoagulant-related nephropathy accelerates the progression of CKD and is a significant risk factor for mortality within the first 2 months of diagnosis.(16) In addition, a recently published and robustly-designed large-scale observational study(17) demonstrated that among patients with NVAF, warfarin use is associated with higher risks of adverse renal outcomes – both long-term (declining renal function) and acute (acute kidney injury) – than rivaroxaban. A potential pathophysiological explanation to support an observed difference in risks of adverse renal outcomes between these two OACs relates to their differential effect on vitamin K inhibition. Warfarin has been shown to decrease carboxylation of the matrix G1a protein, which is an important vitamin-K-dependent inhibitor of medial and intimal vascular calcification.(18, 19) As vitamin K deficiency is common in patients with CKD, these patients are particular susceptible to vascular calcification.(20)

Since publication of the study by Yao *et al*, three large population-based observational cohort studies (two in the United States, and one in Germany) funded by Bayer have been consistent in showing that among patients with NVAF, rivaroxaban is associated with lower risks of adverse renal outcomes when compared with VKAs.(21-23). Further observational evidence demonstrating a differential effect between rivaroxaban and VKAs on adverse renal outcomes in patients with NVAF in other settings would help prescribers make more informed benefit–risk decisions regarding choice of anticoagulant therapy for their patients. This is an increasingly important issue because the ageing

population means that increasing numbers of people will be living with both AF and CKD in need of anticoagulation. Renal function is expected to be monitored regularly in patients taking anticoagulant therapy and managing these patients in a way that helps to preserve their renal function is essential for the effective prevention of stroke and bleeding.

7. Research question and objectives

This study aimed to evaluate the incidence of acute and chronic adverse renal outcomes among patients with NVAF in UK primary care.

7.1 Primary objective

The primary objective of this study was to estimate the magnitude of renal decline, incidence of end-stage renal disease (ESRD) and acute kidney injury (AKI) in patients with NVAF treated with rivaroxaban and those treated with a VKA according to the presence of CKD and its severity at the start of OAC therapy in UK primary care.

7.2 Secondary objective

The secondary objective in this study was to evaluate the primary objective among specific risk groups reflecting known risk factors for CKD progression:

- patients with/without diabetes
- patients with/without heart failure

8. Amendments and updates

Table 2: Amendments

None.

9. Research methods

9.1 Study design

This was a retrospective cohort study using secondary data collection. A new user design was applied(24) – patients with NVAF newly initiated on OAC therapy with either rivaroxaban or a VKA were identified and followed up to identify adverse renal outcomes.

9.2 Setting

This study was set in UK primary care. In the UK, nearly all residents are registered in a primary care practice that uses a system of electronic health records (EHRs). This study used the IQVIA Medical Research Data-UK (IMRD-UK; formerly known as The Health Improvement Network [THIN]), which is a database of primary care EHRs that is used for research purposes (see **Section 9.5**).

9.3 Subjects

9.3.1 Study population

Inclusion criteria

- aged ≥18 years in the IMRD-UK database
- a first prescription for either rivaroxaban or a VKA (warfarin) (see **Table A1** and **Table A2** for codes) between 01 January 2014 and 31 March 2019. The date of the first rivaroxaban/VKA prescription was the start date (start of follow-up for that patient). Follow-up was extended until 30 September 2019 to ensure that each patient had at least 6 months of potential observation
- a diagnosis of AF (see **Table A3** for codes) recorded any time before start date or within 2 weeks after start date
- registered with their general practice at least 1 year before the start date and have a recorded prescription of any drug at least 1 year before the start date
- registered with a general practice with data considered to be up-to-standard quality
- an eGFR value recorded in the year before OAC initiation.

Exclusion criteria

- a prescription for any OAC (see **Table A4** for codes) before the start date – all first-time rivaroxaban/VKA users were therefore OAC naïve
- a record of heart valve replacement or mitral stenosis (see **Table A5** for codes) any time before the start date or in the 2 weeks after the start date
- a record of deep vein thrombosis, pulmonary embolism, or hip/knee surgery in the 3 months before the start date (because these are all alternative reasons for DOAC initiation; see **Table A6** for codes)
- a record of ESRD (including renal transplant patients) on/before the start date
- initiating rivaroxaban with daily dose other than 15 or 20mg
- initiating more than one OAC on the start date

9.3.2 Study time frame

The study period was from 01 January 2014 to 30 September 2019. To ensure all individuals had at least 6 months potential observation time, entry into the study (date of first rivaroxaban/warfarin prescription) was between 01 January 2014 to 31 March 2019.

9.3.3 Follow-up and case ascertainment

Patients were followed up from their start date until the occurrence of an adverse renal outcome. Independent follow-ups were undertaken for each renal decline outcome, and for the outcome of AKI (see **Section 9.3.2**) starting from the start date. Patients were censored at:

- First recorded diagnosis of the adverse renal outcome: (Read codes; see **Tables A7 and A8**)
- death
- last date of data collection from the general practice
- end of the study period (30 September 2019).

9.4 Variables

9.4.1 Exposure definition

The exposure of interest was the first OAC prescribed to the patient – either rivaroxaban or warfarin (the starting OAC).

Rivaroxaban tablet strength was derived from the description of the prescribed product and dosing frequency/posology per day was derived from the free text recorded instructions for the prescription. Based on this information we classified individuals according to daily dose using a previously designed algorithm.

We explored exposure to rivaroxaban/warfarin using three different strategies of analysis:

- Intention-to-treat (ITT): any change in exposure during follow-up was ignored and we assumed that patients remained on the OAC they initiated for the entire follow-up.
- On-treatment (OT): patients were censored at the first discontinuation event (i.e. more than 30 days after the end of the last consecutive prescription of the initial drug without a refill).
- As-treated (AT): patients contributed to different exposure categories according to their current exposure irrespective of the drug they initiated. Person-time was classified into the five mutually exclusive exposure categories based on the following exposure definitions:
    - *current use (of either rivaroxaban, warfarin or other OAC):* when the last prescription ended less than 30 days previously)
    - *past use (of either rivaroxaban, warfarin or other OAC): when* the last prescription ended between 30 days and 1 year previously
    - *non-use:* no previous exposure (to either rivaroxaban, warfarin or other OAC) or when the last prescription ended more than a 1 year previously.

  The five mutually-exclusive categories used in the AT analysis were:
    - *warfarin:* current use of warfarin without current/past use of any other OAC)
    - *rivaroxaban:* current use of rivaroxaban without current/past use of any other OAC)
    - *other OAC:* current use of another OAC without current/past use of either rivaroxaban nor warfarin)
    - *no OAC:* non-use of all OAC
    - *multiple:* any other use of OACs.

9.4.2 Outcomes definition

Recorded laboratory test values (serum creatinine [SCr) were used to estimate changes in SCr level and to calculate estimates glomerular filtration rates [eGFR]); additionally diagnostic Read codes (see **Table A7**) and manual review of coded entries in the patient records were used to estimate all adverse renal outcomes defined below.

9.4.2.1 Renal decline

To characterise renal decline, we used available measurements of SCr and eGFR as well as recorded Read diagnostic codes. We defined the baseline SCr and baseline eGFR as the most recent measurement up to (and including) the date of drug initiation. We used different operational cut-off points to define renal decline:

- A 20%, 30%, 40%, or 50% increase in SCr from the baseline value at any point of time during follow-up (confirmed by a subsequent measurement).
- Doubling of serum creatinine (SCr) from initiation (start date) at any point of time during follow-up.

- A 20%, 30%, 40%, or 50% decline of eGFR from the baseline value at any point of time during follow-up (confirmed by a subsequent measurement). These eGFR-based endpoints were assessed because they have been recommended as alternative endpoints in trials of chronic kidney disease progression.
- Incidence of end-stage renal disease: identified by the presence of a Read code in the patient's EHR indicating ESRD, stage 5 CKD, chronic dialysis (defined as dialysis for 30 days or more), or an eGFR value <15ml/min/1.73m^2 during follow-up (confirmed at a subsequent measurement).
- Slope analysis: rate of change in eGFR during the study period. To be included in the eGFR slope analyses at least two post-baseline assessments were required, where the first measurement was less than 120 days after index and the last was more than 180 days after the first post-baseline (reflecting sufficient time for a potential change to occur).

9.4.2.2 Acute kidney injury

We used two different approaches:

- **Method A:** based on a Read code in the patient's EHR indicating AKI (see **Table A8** for the codes) or a code indicating acute dialysis (defined as a presence of a code for dialysis and non-continuation of dialysis after 30 days after the initial dialysis code) along with a record of an outpatient visit to secondary care/ hospitalization. **Method B:** using recorded SCr values based on the Aberdeen AKI phenotyping algorithm developed by Sawhney *et al*, (25) that may be more accurate because it uses all recorded renal function laboratory values during the study period to identify a sudden renal deterioration event based on the following three criteria:
    - **Year:** SCr levels greater than 1.5 times the median of all creatinine values recorded during the previous 8–365 days
    - **Week**: SCr levels greater than 1.5 times the median of all creatinine values recorded during the previous 7 days
    - **Day**: SCr levels more than 26 µmol/L higher than the lowest creatinine within 48 hours.

We used three increasingly stringent AKI case definitions that required the following criteria to be met:

- any of the three criteria (year/week/day); only patients without AKI at baseline were included in this outcome follow-up
- either the week or day criteria
- the day criterion.

9.4.3 Case validation

To validate cases, a random sample of 100 patients experiencing a study outcome had their anonymised EHRs manually reviewed to confirm the renal event.

9.4.4 Covariate definition

To establish patient characteristics at baseline (date of the inclusion into the study), the following variables were extracted/determined from the database on/ever before the start date (for the cohort analysis):

- Demographics (at the start date): age, sex, and Townsend index score of deprivation.(26)
- Lifestyle factors (using the most recently status/values recorded before the start date): smoking status, alcohol intake, body mass index (BMI, calculated using recorded height and weight measurements).
- Renal function was ascertained by using eGFR expressed mL/min/1.73m^2 as using the closest valid serum creatinine value recorded in the year before the start date and applying the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation,(27) but omitting ethnicity because this is not routinely recorded in UK primary care: **eGFR = 141 × min (serum creatinine [SCr] /κ, 1)α × max(SCr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]**, where: SCr is serum creatinine in mg/dL; κ is 0.7 for females and 0.9 for males; α is –0.329 for females and –0.411 for males; min indicates the minimum of SCr /κ or 1, and max indicates the maximum of SCr/κ or 1. Coded clinical entries indicating CKD stage, acute or chronic dialysis will also be used to determine renal function. Patients will be categorised as having no renal impairment or as having renal impairment of a certain stage (i.e. CKD stages 1–5) according to the National Kidney Foundation guidelines: normal renal function (eGFR >50 ml/min/1.73 m^2), mild-to-moderate impairment (eGFR 30–50 ml/min/1.73m^2) and severe impairment (eGFR<30 ml/min/1.73m^2). In situations where the CKD stage based on the calculated eGFR differed from the CKD stage based on Read codes, we used the eGFR value as the measure is believed to be more accurately reflect the true renal function (this is due to the fact that CKD stage coding can be used in an imprecise manner). In few cases when eGFR is directly recorded in the database, we will not use these values.
- Comorbidities and previous clinical events of interest (at the start date or any time before the start date): cardiovascular disease (including myocardial infarction, ischaemic heart disease, ischaemic stroke, haemorrhagic stroke, angina, coronary artery disease, peripheral arterial disease, hypertension), diabetes mellitus, hyperlipidaemia, obesity, major bleeding events, AKI, cancer.
- CHA_2DS_2VASc score for stroke risk: using patients' recorded history of congestive heart failure, hypertension, age, diabetes mellitus and prior stroke/ transient ischaemic attack [TIA].
- Frailty using a frailty index developed for research using primary care databases,(28) based on a wide range of symptoms, signs, diseases, disabilities, abnormal laboratory values and

social circumstances, and categorising patients as fit, mildly frail, moderately frail or severely frail.

- Comedications (prescription in the year before the start date or on the start date) including SGLT2 inhibitors, ACE inhibitors, ARBs and diuretics. Polypharmacy was also evaluated by determining the number of different medications prescribed in the month before (but not including) the start date.
- Healthcare use in the year before the start date and in the year after the start date (number of primary care practitioner [PCP] visits, outpatient visits and hospital admissions).

9.5 Data sources and measurement

The IMRD-UK is a structured de-identified UK database of anonymized primary care EHRs. It holds clinical and prescribing information entered by PCP as part of routine patient care, and covers approximately 6% of the UK population (including practices across England, Wales, Scotland, and Northern Ireland).(29) Medical events (e.g. symptoms, diagnosis, hospital referrals) are entered using Read codes,(30) although there is a free text field for manual data entry. Demographics, lifestyle factors and results of laboratory tests, including those for renal function (e.g. SCr values) are also recorded. Data received from secondary care via email or postal letter are entered into the patient's EHR retrospectively. Prescriptions are entered using multilex codes,(31) and are automatically recorded upon issue. Prescriptions include details on the drug quantity, dose, dosing instructions and the number of days of supply.

Broad ethical approval for the collection of data in IMRD-UK was approved by the PPD in 2003. Ethical approval is not required for individual studies using IMRD-UK but individual study protocols required approval by the Independent Scientific Research Committee for IMRD-UK.

9.6 Bias

All individuals meeting the study inclusion and exclusion criteria were included thereby minimizing selection bias. Sensitivity analyses were conducted to assess other sources of bias, as described in **Section 9.9.4**.

9.7 Study size

All patients enrolled in IMRD-UK and meeting the inclusion criteria were included.

9.8 Data transformation

Data were extracted from IMRD-UK using PPD proprietary tools (Powerfilter, Datacreator, etc.). Information was imported into these datasets into STATA software to prepare the final study datasets (both cohort and case-control datasets) and ran all the analyses.

All research project materials: the study protocol, a copy of Scientific Review Committee approval, computer algorithms, data collections, datasets, STATA programs and the final report and

publications have been kept in one folder cross-shared by the PPD team. Monthly back-ups have been be performed and data are kept in a secure location. All material will be kept for a minimum of 10 years.

9.9 Statistical methods

9.9.1 Main summary measures

The characteristics of patients in the study cohort were described according to the starting OAC. Incidence rates of the study outcomes were calculated by dividing the number of confirmed cases by the total follow-up person-time accrued in each cohort. We estimated 95% confidence intervals (CIs) around those estimates assuming a Poisson distribution. Incidence rates were calculated stratified by age, sex, and CKD status, and for rivaroxaban, also by the dose of the starting prescription (20 mg/day or 15 mg/day).

9.9.2 Main statistical methods

Survival analyses were performed to estimate the time to the occurrence of the study outcomes according to the starting OAC. Cox proportional hazards regression was used to calculate hazard ratios (HRs) with 95% CIs. Crude, age- and sex-adjusted, and fully-adjusted estimates (with adjustment for potential confounders such as patient characteristics, comorbidities and CKD stage at the start date) were obtained. Furthermore, as explained in **Section 9.4.1**, these analyses were undertaken using three different approaches (ITT, OT, and AT). Unless otherwise specified, the main results refer to the ITT analysis.

For the slope analyses, we estimated the eGFR slopes with 95% CIs after OAC initiation in patients starting on rivaroxaban (as an average for the total subcohort) and those starting on warfarin (as an average for the total subcohort). This was performed using a linear mixed regression model where the treatment group (rivaroxaban or warfarin), time (linear), and the interaction between treatment group and time, were included as fixed variables and each initiation was included as a random factor. Covariates at baseline (including comorbidities and comedications as well as frequency of SCr testing) were introduced in the model to obtain estimates adjusted for confounders. Only individuals with at least two SCr measurements (and hence, calculated eGFR values) after treatment initiation were included in this analysis. In an alternative slope analysis, the eGFR slope was estimated by year of follow-up in each of the first five years thereby using only the available follow-up measures recorded during that particular year.

All analyses were performed with Stata 12.1.

9.9.3 Missing values

Given the nature of real-world data, missing data were present in a minority of instances. No data imputation strategies were applied to supplement missing data. Individuals with missing data on certain variables were kept in the analysis and a separate category was created for missing values of that variable.

9.9.4 Sensitivity analyses

Renal decline analyses: In the renal decline analyses (both renal decline events and eGFR slope analyses) we performed a separate analysis comparing initiators of rivaroxaban 20 mg and warfarin with preserved baseline renal function (eGFR >50 mL/min/1.73m^2). Furthermore, the analyses for eGFR slope were repeated across multiple patient subgroups to examine the consistency of the findings such as by estimated frailty index, CHA_2DS_2VASc score, and established atherosclerotic cardiovascular disease.

AKI analyses: In the AKI analysis we performed an alternative analysis in which, for the sake of comparability, the same exclusion criteria were used for the different AKI case ascertainment methods.

9.9.5 Amendments to the statistical analysis plan

The nested case–control analyses were not performed as initially planned. This was because the very comprehensive nature of the cohort analysis that included analysis of multiple cut-off points for outcomes, supported by the manual review of the records, and of which showed consistent results supported the notion that nested case–control analyses would have limited added value.

9.10 Quality control

Standard operating procedures were used to guide the conduct of the study. One researcher prepared the list of codes, tested the computer algorithms to be used and ran statistical analyses after agreement on all phases of analyses with the rest of the team. As one measure of quality control and to minimise data errors, another researcher independently performed several methodological checks including the review of STATA programming and analyses.

10. Results

10.1 Participants

Figure 1 depicts the identification of the study cohorts. The study cohorts comprised 6903 initiators of rivaroxaban (1156 on 15 mg/day; 5747 on 20 mg/day) and 7586 initiators of warfarin.

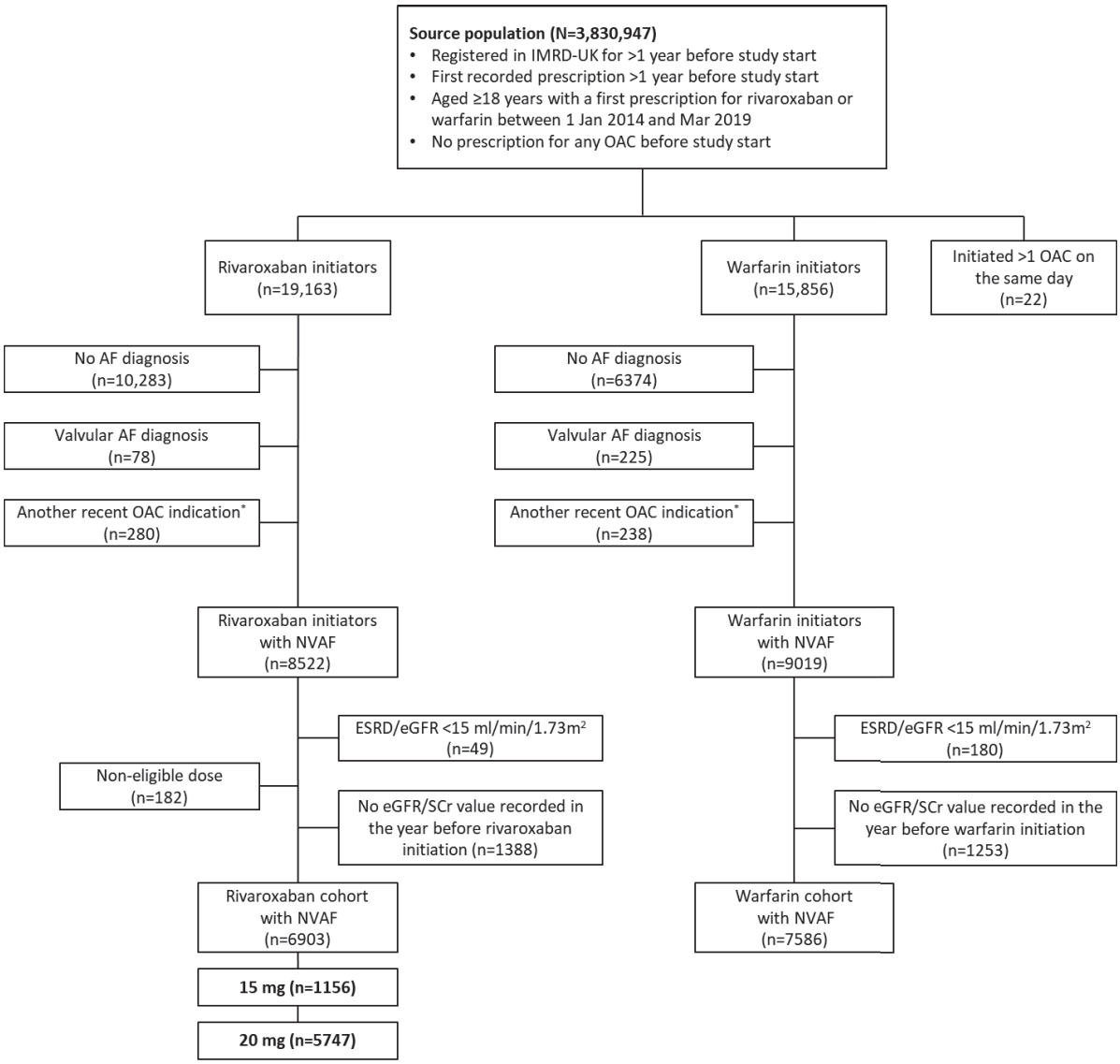

Figure 1. Flowchart depicting the identification of the rivaroxaban and warfarin study cohorts. *Record of VTE a record of deep vein thrombosis, pulmonary embolism, or hip/knee surgery in the 3 months before the start date.

10.2 Descriptive data

The characteristics of these cohorts (by daily dose for rivaroxaban) are shown in **Table 3** (with further details shown in **Table S1**). Mean age was similar for patients in the rivaroxaban 20 mg cohort (73.1 years) and the warfarin cohort (74.3 years); patients in the rivaroxaban 15 mg cohort were older (mean 82.2 years). The same trend was observed for comorbidities and severe frailty,

with similar a prevalence of these in the rivaroxaban 20 mg cohort and in the warfarin cohort, and higher prevalence in the rivaroxaban 15 mg cohort.

Table 3. Baseline characteristics of the study cohorts (all had SCr recorded within the previous year).

	Rivaroxaban cohort (15 mg) N=1156		**Rivaroxaban cohort (20 mg) N=5747**		**Warfarin cohort N=7586**	
	n	**%**	**n**	**%**	**n**	**%**
Age (years)						
18–49	4	0	111	2	104	1
50–59	14	1	462	8	411	5
60–69	64	6	1356	24	1655	22
70–79	281	24	2241	39	3037	40
80–89	573	50	1357	24	2124	28
≥90	220	19	220	4	255	3
Mean (SD)	*82.2 (8.4)*		*73.1 (10.3)*		*74.3 (9.6)*	
Sex						
Male	488	42	3435	60	4258	56
Female	668	58	2312	40	3328	44
eGFR at baseline (mL/min/1.73m^2)						
eGFR >50	510	44	5338	93	6314	83
eGFR 30–50	575	50	393	7	1094	14
eGFR <30	71	6	16	0	178	2
Mean (SD)	51.3 (16.2)		73.4 (54.7)		69.5 (76.6)	
eGFR at baseline (measurements)						
1	16	1	113	2	151	2
2–5	60	5	870	15	1051	14
6–11	177	15	1537	27	1831	24
12–23	419	36	2147	37	2868	38
≥24	484	42	1080	19	1685	22
eGFR follow-up (measurements)						
None	120	10	703	12	783	10
1	93	8	654	11	569	8
2–5	359	31	2268	39	2407	32
6–11	306	26	1385	24	2058	27
12–23	180	16	574	10	1258	17
≥24	98	8	163	3	511	7
Townsend Index						

	Rivaroxaban cohort (15 mg) N=1156		Rivaroxaban cohort (20 mg) N=5747		Warfarin cohort N=7586	
	n	**%**	**n**	**%**	**n**	**%**
Most affluent	207	18	1171	20	1446	19
2nd quintile	215	19	1155	20	1615	21
3rd quintile	208	18	1074	19	1312	17
4th quintile	168	15	802	14	1201	16
Most deprived	103	9	465	8	735	10
Missing	255	22	1080	19	1277	17
Polypharmacy						
0–4	97	8	1066	19	1102	15
5–9	553	48	3149	55	4180	55
≥10	506	44	1532	27	2304	30
Smoking						
Non-smoker	477	41	2395	42	2985	39
Smoker	79	7	469	8	620	8
Ex-smoker	598	52	2877	50	3980	52
Unknown	2	0	6	0	1	0
BMI						
<20	63	5	159	3	197	3
20–24	303	26	1140	20	1498	20
25–29	382	33	2055	36	2688	35
≥30	350	30	2181	38	2961	39
Unknown	58	5	212	4	242	3
PCP visits						
0–4	5	0	45	1	43	1
5–9	53	5	555	10	611	8
10–19	371	32	2480	43	3157	42
≥20	727	63	2667	46	3775	50
Referrals						
0–9	611	53	3428	60	4614	61
10–19	389	34	1832	32	2366	31
≥20	156	13	487	8	606	8
Hospitalisations						
0	531	46	3244	56	4454	59
1	259	22	1317	23	1583	21
≥2	366	32	1186	21	1549	20
Comorbidities						
IHD	399	35	1274	22	2035	27
Cancer	234	20	879	15	1214	16

	Rivaroxaban cohort (15 mg) N=1156		Rivaroxaban cohort (20 mg) N=5747		Warfarin cohort N=7586	
	n	**%**	**n**	**%**	**n**	**%**
Diabetes	319	28	1244	22	1801	24
Heart failure	216	19	591	10	1011	13
AKI (history)	46	4	111	2	129	2
CHA_2DS_2VASc						
0–1	27	2	899	16	845	11
2	78	7	1202	21	1403	18
3	207	18	1421	25	1905	25
4	383	33	1199	21	1793	24
5	257	22	634	11	994	13
≥6	204	18	392	7	646	9
Frailty (eFI)						
Fit	41	4	1079	19	1152	15
Mild frailty	298	26	2499	43	3209	42
Moderate frailty	487	42	1570	27	2315	31
Severe frailty	330	29	599	10	910	12

.

10.3 Outcome data

Outcome data are presented in **Section 10.4** (Main results).

10.4 Main results

10.4.1 Renal decline

10.4.1.1 Incidence rates of renal decline outcomes

The crude incidence rate of renal decline outcomes decreased with increasing outcome severity (see **Table 4**).

Increase in SCr from baseline

The incidence rate of ≥20% increase in SCr from baseline was 1029.8 per 10,000 person-years in the warfarin cohort and 969.2 cases per 10,000 person-years in the rivaroxaban cohort over the entire period of study. Corresponding estimates for ≥100% increase in SCr from baseline (i.e. doubling) were 138.1 per 10,000 person-years (warfarin cohort) and 103.6 cases per 10,000 person-years (rivaroxaban cohort).

Decline in eGFR from baseline

The incidence rate of ≥20% decline in eGFR from baseline was 1050.6 per 10,000 person-years in the warfarin cohort, and 983.4 cases per 10,000 person-years in the rivaroxaban cohort. Corresponding estimates for ≥50% decline in eGFR was 147.1 per 10,000 person-years (warfarin cohort), and 105.9 cases per 10,000 person-years (rivaroxaban cohort).

ESRD

A total of 65 ESRD events were observed in the warfarin cohort, and 33 ESRD events were observed in the rivaroxaban cohort, yielding crude incidence rates of 30.5 per 10,000 person-years and 22.1 cases per 10,000 person-years, respectively. Incidence rates of ESRD increased with age and worse baseline renal function (**Supplementary Table S2a-d** and **Supplementary table S3a-d**).

10.4.1.2 Association between rivaroxaban (vs. warfarin) and risk of renal decline

After adjustment for age, sex, baseline eGFR (both values and number of measurements), Townsend index, polymedication, smoking, body mass index, comorbidity, frailty, and health services use in the year before OAC initiation, the rivaroxaban cohort had a significantly reduced risk of both SCr- and eGFR-based renal decline events compared with the warfarin cohort (ITT analysis). Results in the subsequent tables are shown stratified by rivaroxaban dose (20 mg or 15 mg) due to the substantial differences in their baseline characteristics.

SCr-based events

For ≥20% increase in SCr, a 14% reduction in risk was seen; HR was 0.86 (95% CI: 0.80–0.92), and for ≥100% increase in SCr, a 24% reduction in risk was seen; HR 0.76 (95% CI: 0.62–0.93) (**Table 4**; **Supplementary Table S4**).

The results of the OT analyses were fully consistent with the ITT analyses. For ≥20% increase in SCr, a 11% reduction in risk was seen, HR 0.89 (95% CI: 0.81–0.97), and for ≥100% increase in SCr, a 23% reduction in risk was seen, HR=0.77 (95% CI: 0.59–1.00) (**Supplementary Tables S6 and S7**).

The results of the AT analyses were also consistent with the ITT analyses. For ≥20% increase in SCr, a 12% reduction in risk was seen, HR 0.88 (95% CI: 0.81–0.95), and for ≥100% increase in SCr, a 25% reduction in risk was seen, HR 0.75 (95% CI: 0.60–0.94 (**Supplementary Table S8**).

eGFR-based events

For ≥20% decline in eGFR, a 14% reduction in risk was seen; HR was 0.86 (95% CI: 0.80–0.92), and for ≥50% decline in eGFR, a 28% reduction in risk was seen; HR was 0.72 (95% CI: 0.59–0.88). Of note, this risk reduction was almost exclusively observed among initiators of rivaroxaban 20 mg, as the risk of these events was no different between initiators of rivaroxaban 15 mg and warfarin (**Table 4**; **Supplementary Table S5**). Also, although the reduced risk of renal decline events was slightly more evident among individuals with normal baseline renal function (eGFR >50 mL/min/1.73m^2), there was no evidence of statistical interaction.

The results of the OT analyses were fully consistent with the ITT analyses. For ≥20% decline in eGFR, an 11% reduction in risk was seen, HR 0.89 (95% CI: 0.82–0.97), and for ≥50% decline in eGFR, a 22% reduction in risk was seen, HR=0.78 (95% CI: 0.60–1.00) (**Supplementary Tables S6 and S7**).

The results of the AT analyses were also consistent with the ITT analyses. For ≥20% decline in eGFR, an 11% reduction in risk was seen, HR 0.89 (95% CI: 0.83–0.97), and for ≥50% decline in eGFR, a 27% reduction in risk was seen, HR=0.73 (95% CI: 0.59–0.91) (**Supplementary Table S8**).

ESRD

For ESRD, each analysis indicated a reduced risk among the rivaroxaban cohort vs. the warfarin cohort, although the CIs straddled 1.0. HRs were as follows: ITT analysis, HR 0.93 (95% CI: 0.60–1.43), OT analysis, HR 0.85 (95% CI: 0.49–1.49), and AT analysis, HR 0.79 (95% CI: 0.48–1.28).

Table 4. Renal decline outcomes in the study cohorts by baseline renal function.

Endpoint	Baseline eGFR	Cohort	Individuals	Person-years	Failures	IR × 10,000	HR[†]	95% CI	P>|z|
SCr ≥20% increase	**ALL**	Warfarin[*]	7586	17,237.2	1775	1029.8	1.00		
		Rivaroxaban	6903	12,505.1	1212	969.2	0.86	(0.80–0.92)	<0.01
		15 mg	1156	1806.1	268	1483.9	1.02	(0.89–1.16)	0.83
		20 mg	5747	10699	944	882.3	0.82	(0.76–0.89)	<0.01
	eGFR >50	Warfarin[*]	6314	14,769.3	1454	984.5	1.00		
		Rivaroxaban	5848	10,754.5	1000	929.8	0.85	(0.79–0.93)	<0.01
		15 mg	510	755.1	130	1721.7	1.12	(0.93–1.34)	0.25
		20 mg	5338	9999.5	870	870.1	0.83	(0.76–0.90)	<0.01
	eGFR 30–50	Warfarin[*]	1094	2214.6	271	1223.7	1.00		
		Rivaroxaban	968	1611.9	201	1247.0	0.92	(0.76–1.11)	0.36
		15 mg	575	949.4	129	1358.8	0.98	(0.79–1.22)	0.84
		20 mg	393	662.5	72	1086.8	0.82	(0.63–1.08)	0.16
	eGFR <30	Warfarin[*]	178	253.3	50	1974.0	1.00		
		Rivaroxaban	87	138.7	11	793.2	0.43	(0.21–0.87)	0.02
		15 mg	71	101.7	9	885.4	0.43	(0.20–0.93)	0.03
		20 mg	16	37	2	540.1	0.43	(0.08–2.17)	0.30
SCr ≥30% increase	**ALL**	Warfarin[*]	7586	18924	1151	608.2	1.00		
		Rivaroxaban	6903	13,587.8	737	542.4	0.83	(0.76–0.92)	<0.01
		15 mg	1156	2009.5	172	855.9	0.95	(0.80–1.13)	0.56
		20 mg	5747	11,578.2	565	488.0	0.80	(0.73–0.89)	<0.01
	eGFR >50	Warfarin[*]	6314	16,214.3	923	569.3	1.00		
		Rivaroxaban	5848	11,700.4	590	504.3	0.82	(0.74–0.91)	<0.01
		15 mg	510	872.9	76	870.7	0.98	(0.77–1.24)	0.85
		20 mg	5338	10,827.5	514	474.7	0.80	(0.72–0.90)	<0.01
	eGFR 30–50	Warfarin[*]	1094	2429.3	187	769.8	1.00		
		Rivaroxaban	968	1740.9	138	792.7	0.96	(0.76–1.20)	0.72
		15 mg	575	1030	88	854.4	1.00	(0.77–1.31)	0.98
		20 mg	393	710.9	50	703.3	0.89	(0.65–1.23)	0.48
	eGFR <30	Warfarin[*]	178	280.4	41	1462.3	1.00		
		Rivaroxaban	87	146.5	9	614.3	0.45	(0.20–1.03)	0.06
		15 mg	71	106.7	8	749.9	0.54	(0.23–1.27)	0.16
		20 mg	16	39.8	1	251.1	0.18	(0.02–1.69)	0.13
SCr ≥40% increase	**ALL**	Warfarin[*]	7586	19,828.7	796	401.4	1.00		
		Rivaroxaban	6903	14,114.8	484	342.9	0.82	(0.73–0.92)	<0.01
		15 mg	1156	2102.7	126	599.2	1.02	(0.84–1.25)	0.81
		20 mg	5747	12,012.1	358	298.0	0.76	(0.67–0.87)	<0.01
	eGFR >50	Warfarin[*]	6314	16,963.9	634	373.7	1.00		
		Rivaroxaban	5848	12,134.1	383	315.6	0.80	(0.70–0.91)	<0.01
		15 mg	510	914.1	56	612.7	1.07	(0.80–1.41)	0.66
		20 mg	5338	11,220.1	327	291.4	0.77	(0.67–0.88)	<0.01
	eGFR 30–50	Warfarin[*]	1094	2568.1	134	521.8	1.00		
		Rivaroxaban	968	1830.2	94	513.6	0.95	(0.72–1.25)	0.70
		15 mg	575	1078	64	593.7	1.06	(0.78–1.45)	0.72
		20 mg	393	752.2	30	398.8	0.78	(0.52–1.17)	0.23
	eGFR <30	Warfarin[*]	178	296.6	28	943.9	1.00		

Endpoint	Baseline eGFR	Cohort	Individuals	Person-years	Failures	IR × 10,000	HR[†]	95% CI	P>|z|
		Rivaroxaban	87	150.5	7	465.2	0.54	(0.19–1.52)	0.24
		15 mg	71	110.7	6	542.2	0.77	(0.26–2.31)	0.64
		20 mg	16	39.8	1	251.1	0.15	(0.01–1.67)	0.12
SCr ≥50% increase	**ALL**	Warfarin[*]	7586	20,345.9	573	281.6	1.00		
		Rivaroxaban	6903	14,414.2	329	228.3	0.79	(0.69–0.91)	<0.01
		15 mg	1156	2162.9	91	420.7	1.07	(0.85–1.36)	0.56
		20 mg	5747	12,251.2	238	194.3	0.72	(0.62–0.84)	<0.01
	eGFR >50	Warfarin[*]	6314	17,388.2	460	264.6	1.00		
		Rivaroxaban	5848	12,374.1	255	206.1	0.75	(0.64–0.88)	<0.01
		15 mg	510	936	40	427.4	1.09	(0.78–1.53)	0.60
		20 mg	5338	11,438.1	215	188.0	0.71	(0.60–0.84)	<0.01
	eGFR 30–50	Warfarin[*]	1094	2644.5	95	359.2	1.00		
		Rivaroxaban	968	1889.1	69	365.3	0.99	(0.72–1.36)	0.94
		15 mg	575	1115.7	47	421.3	1.15	(0.80–1.66)	0.45
		20 mg	393	773.4	22	284.5	0.76	(0.47–1.23)	0.26
	eGFR <30	Warfarin[*]	178	313.2	18	574.7	1.00		
		Rivaroxaban	87	151	5	331.1	1.47	(0.28–7.57)	0.65
		15 mg	71	111.2	4	359.7	1.97	(0.34–11.40)	0.45
		20 mg	16	39.8	1	251.1	0.58	(0.03–12.14)	0.72
SCr ≥100% increase (i.e. doubling)	**ALL**	Warfarin[*]	7586	20,997.3	290	138.1	1.00		
		Rivaroxaban	6903	14,763.1	153	103.6	0.76	(0.62–0.93)	0.01
		15 mg	1156	2240.1	51	227.7	1.26	(0.91–1.74)	0.16
		20 mg	5747	12523	102	81.5	0.64	(0.51–0.80)	<0.01
	eGFR >50	Warfarin[*]	6314	17,925.3	231	128.9	1.00		
		Rivaroxaban	5848	12,663.1	115	90.8	0.71	(0.56–0.89)	<0.01
		15 mg	510	972	24	246.9	1.39	(0.89–2.17)	0.14
		20 mg	5338	11,691.1	91	77.8	0.63	(0.49–0.80)	<0.01
	eGFR 30–50	Warfarin[*]	1094	2742.3	51	186.0	1.00		
		Rivaroxaban	968	1944.6	35	180.0	0.90	(0.58–1.41)	0.64
		15 mg	575	1153.1	24	208.1	1.10	(0.66–1.82)	0.72
		20 mg	393	791.5	11	139.0	0.64	(0.33–1.26)	0.20
	eGFR <30	Warfarin[*]	178	329.7	8	242.6			
		Rivaroxaban	87	155.3	3	193.1			
		15 mg	71	115	3	260.8			
		20 mg	16	40.3	0	0.0			
eGFR ≥20% decline	**ALL**	Warfarin[*]	7586	17200	1807	1050.6	1.00		
		Rivaroxaban	6903	12,537.9	1233	983.4	0.86	(0.80–0.92)	<0.01
		15 mg	1156	1731.3	308	1779.0	1.08	(0.95–1.23)	0.26
		20 mg	5747	10,806.6	925	856.0	0.80	(0.74–0.87)	<0.01
	eGFR >50	Warfarin[*]	6314	14,826.7	1440	971.2	1.00		
		Rivaroxaban	5848	10,858.8	983	905.3	0.85	(0.78–0.92)	<0.01
		15 mg	510	740	140	1891.9	1.21	(1.01–1.45)	0.03
		20 mg	5338	10,118.9	843	833.1	0.81	(0.75–0.89)	<0.01
	eGFR 30–50	Warfarin[*]	1094	2131.4	310	1454.4	1.00		
		Rivaroxaban	968	1549.1	235	1517.0	0.91	(0.76–1.08)	0.29
		15 mg	575	898.4	155	1725.3	1.00	(0.81–1.22)	0.97

Endpoint	Baseline eGFR	Cohort	Individuals	Person-years	Failures	IR × 10,000	HR[†]	95% CI	P>|z|
eGFR ≥30% decline		20 mg	393	650.7	80	1229.5	0.78	(0.61–1.01)	0.06
	eGFR <30	Warfarin[*]	178	241.9	57	2356.5	1.00		
		Rivaroxaban	87	129.9	15	1154.3	0.57	(0.30–1.05)	0.07
		15 mg	71	92.9	13	1399.1	0.62	(0.32–1.19)	0.15
		20 mg	16	37	2	540.1	0.34	(0.07–1.65)	0.18
	ALL	Warfarin[*]	7586	19,358.4	1002	517.6	1.00		
		Rivaroxaban	6903	13,876.7	606	436.7	0.80	(0.73–0.89)	<0.01
		15 mg	1156	2027.4	160	789.2	0.96	(0.80–1.15)	0.67
		20 mg	5747	11,849.3	446	376.4	0.76	(0.68–0.85)	<0.01
	eGFR >50	Warfarin[*]	6314	16,627.9	780	469.1	1.00		
		Rivaroxaban	5848	11,981.6	467	389.8	0.79	(0.70–0.88)	<0.01
		15 mg	510	892.7	68	761.7	1.02	(0.79–1.32)	0.87
		20 mg	5338	11,088.9	399	359.8	0.76	(0.67–0.86)	<0.01
	eGFR 30–50	Warfarin[*]	1094	2453.4	182	741.8	1.00		
		Rivaroxaban	968	1750.4	129	737.0	0.90	(0.72–1.14)	0.40
		15 mg	575	1028	84	817.1	0.97	(0.74–1.27)	0.82
		20 mg	393	722.4	45	622.9	0.81	(0.58–1.13)	0.21
	eGFR <30	Warfarin[*]	178	277.2	40	1443.2	1.00		
		Rivaroxaban	87	144.7	10	690.9	0.52	(0.24–1.14)	0.10
		15 mg	71	106.7	8	749.9	0.56	(0.24–1.30)	0.17
		20 mg	16	38	2	525.7	0.41	(0.07–2.22)	0.30
eGFR ≥40% decline	**ALL**	Warfarin[*]	7586	20,377.3	564	276.8	1.00		
		Rivaroxaban	6903	14,441.2	320	221.6	0.78	(0.68–0.90)	<0.01
		15 mg	1156	2148.4	99	460.8	1.07	(0.85–1.34)	0.58
		20 mg	5747	12,292.8	221	179.8	0.70	(0.60–0.82)	<0.01
	eGFR >50	Warfarin[*]	6314	17,453.8	433	248.1	1.00		
		Rivaroxaban	5848	12,421.5	237	190.8	0.74	(0.63–0.87)	<0.01
		15 mg	510	935.7	41	438.2	1.15	(0.82–1.60)	0.42
		20 mg	5338	11,485.8	196	170.7	0.69	(0.59–0.82)	<0.01
	eGFR 30–50	Warfarin[*]	1094	2617.7	111	424.0	1.00		
		Rivaroxaban	968	1869	76	406.7	0.89	(0.66–1.20)	0.44
		15 mg	575	1101.7	52	472.0	1.00	(0.71–1.41)	1.00
		20 mg	393	767.2	24	312.8	0.72	(0.45–1.13)	0.15
	eGFR <30	Warfarin[*]	178	305.9	20	653.8	1.00		
		Rivaroxaban	87	150.8	7	464.3	1.86	(0.51–6.82)	0.35
		15 mg	71	110.9	6	540.8	2.07	(0.53–8.16)	0.30
		20 mg	16	39.8	1	251.1	1.11	(0.07–18.35)	0.94
eGFR ≥50% decline	**ALL**	Warfarin[*]	7586	20,876.3	307	147.1	1.00		
		Rivaroxaban	6903	14,736.6	156	105.9	0.72	(0.59–0.88)	<0.01
		15 mg	1156	2230.1	52	233.2	1.10	(0.80–1.51)	0.54
		20 mg	5747	12,506.5	104	83.2	0.61	(0.49–0.77)	<0.01
	eGFR >50	Warfarin[*]	6314	17,831.5	244	136.8	1.00		
		Rivaroxaban	5848	12,652.2	111	87.7	0.63	(0.50–0.80)	<0.01
		15 mg	510	970.4	21	216.4	1.07	(0.67–1.70)	0.78
		20 mg	5338	11,681.9	90	77.0	0.58	(0.46–0.74)	<0.01
		Warfarin[*]	1094	2727.5	51	187.0	1.00		

Endpoint	Baseline eGFR	Cohort	Individuals	Person-years	Failures	IR × 10,000	HR†	95% CI	P>|z|
	eGFR 30–50	Rivaroxaban	968	1931.3	41	212.3	1.02	(0.66–1.57)	0.92
		15 mg	575	1146.9	27	235.4	1.07	(0.65–1.75)	0.80
		20 mg	393	784.4	14	178.5	0.95	(0.51–1.75)	0.86
	eGFR <30	Warfarin*	178	317.3	12	378.2			
		Rivaroxaban	87	153.1	4	261.3			
		15 mg	71	112.8	4	354.7			
		20 mg	16	40.3	0	0.0			
ESRD	**ALL**	Warfarin*	7586	21,282.8	65	30.5	1.00		
		Rivaroxaban	6903	14,913.1	33	22.1	0.93	(0.60–1.43)	0.74
		15 mg	1156	2276.3	20	87.9	1.05	(0.62–1.79)	0.85
		20 mg	5747	12,636.8	13	10.3	0.79	(0.42–1.47)	0.45
	eGFR >50	Warfarin*	6314	18,215.6	16	8.8	1.00		
		Rivaroxaban	5848	12,807.1	8	6.3	0.88	(0.36–2.13)	0.78
		15 mg	510	1003	2	19.9	1.97	(0.39–9.93)	0.41
		20 mg	5338	11,804.2	6	5.1	0.76	(0.29–1.99)	0.57
	eGFR 30–50	Warfarin*	1094	2771.8	19	68.6	1.00		
		Rivaroxaban	968	1956.9	18	92.0	1.37	(0.69–2.74)	0.37
		15 mg	575	1164.1	12	103.1	1.32	(0.61–2.87)	0.48
		20 mg	393	792.8	6	75.7	1.48	(0.55–3.93)	0.44
	eGFR <30	Warfarin*	178	295.4	30	1015.4	1.00		
		Rivaroxaban	87	149	7	469.7	0.76	(0.27–2.16)	0.61
		15 mg	71	109.2	6	549.5	0.83	(0.27–2.56)	0.75
		20 mg	16	39.8	1	251.1	0.51	(0.05–5.36)	0.57

*Reference category.

†Adjusted estimates obtained by using a Cox proportional hazard regression model including the following covariates: age, sex, baseline eGFR (both as categorical and continuous variables), number of previous measurements at baseline, Townsend index, polymedication, smoking, body mass index, health service utilisation in the year before baseline (PCP visits, referrals and hospitalizations), comorbidity (ischemic heart disease, cancer, diabetes, heart failure, and prior acute kidney injury), frailty (eFI), and CHA_2DS_2VASc score.

10.4.1.3 Subgroup analyses

Patients with diabetes at baseline

Results were similar in the subgroup of patients with diabetes as in the main analyses. For ≥20% increase in SCr, a 16% reduction in risk was seen, HR 0.84 (95% CI: 0.74–0.96), and for ≥100% increase in SCr, a 21% reduction in risk was seen, HR 0.79 (95% CI: 0.58–1.06) (**Supplementary Table S9**). For ≥20% decline in eGFR, a 15% reduction in risk was seen, HR 0.85 (95% CI: 0.74–0.96), and for ≥50% decline in eGFR, a 25% reduction in risk was seen, HR=0.75 (95% CI: 0.56–1.01) (**Supplementary Table S10**). For ESRD, there was no difference in the risk of ESRD between the rivaroxaban and warfarin cohorts, HR 1.05 (95% CI: 0.57–1.93).

The results of the OT and AT analyses among patients with diabetes were also compatible with the main analyses (**Supplementary Tables S11–S13**).

Patients with heart failure at baseline

Results were similar in the subgroup of patients with diabetes as in the main analyses. For ≥20% increase in SCr, a 15% reduction in risk was seen, HR 0.85 (95% CI: 0.72–1.01), and for ≥100% increase in SCr, a 27% reduction in risk was seen, HR 0.73 (95% CI: 0.49–1.09). For ≥20% decline in eGFR, a 16% reduction in risk was seen, HR 0.84 (95% CI: 0.71–0.99), and for ≥50% decline in eGFR, a 21% reduction in risk was seen, HR=0.79 (95% CI: 0.60–1.05) (**Supplementary Tables S14–15**).

For ESRD, a reduced risk was seen among the rivaroxaban cohort vs. the warfarin cohort, HR 0.72 (95% CI: 0.29–1.78), although the CI straddled 1.0. The results of the OT and AT analyses among patients with heart failure were compatible with the main analyses (**Supplementary Tables S16-18**).

Further details of the ITT analyses for individual renal decline endpoints can be found in **Supplementary Tables S19–28**.

Slope analysis

A total of 3052 (40.2%) patients in the warfarin cohort, 2228 (38.8%) patients in the rivaroxaban 20 mg cohort, and 515 (44.6%) patients in the rivaroxaban 15 mg cohort were included in the slope analyses (**Figure 2**).

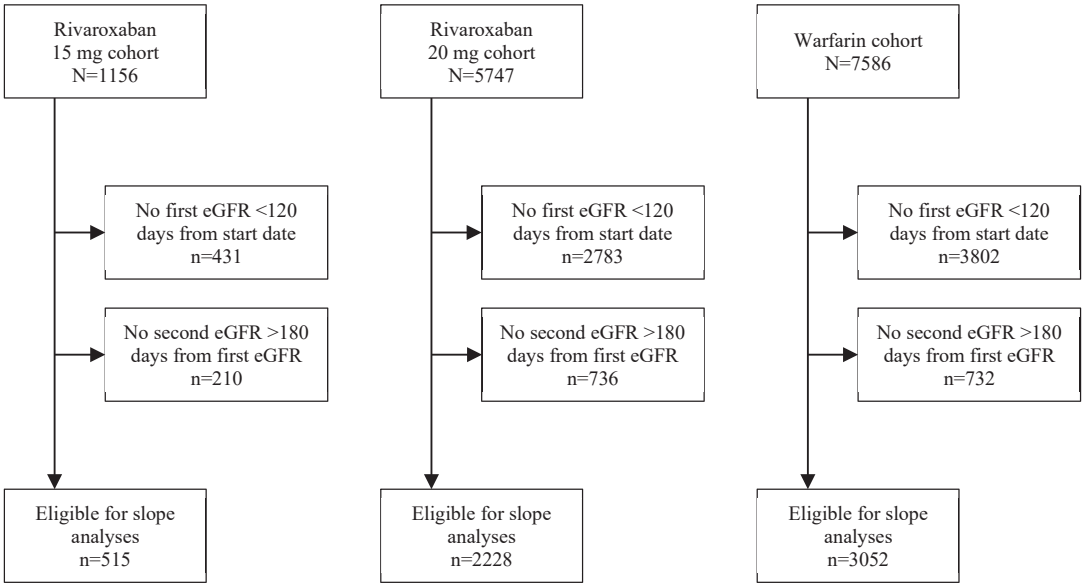

Figure 2. Individuals included in the eGFR slope analyses.

In this analysis, the average number of eGFR measurements per eligible patient during the entire follow-up period was 13.2 (warfarin=14.9; rivaroxaban 15 mg=14.7; rivaroxaban 20 mg=10.5). The average number of eGFR measurements per eligible individual and year of follow-up was 5.6 (warfarin=5.7; rivaroxaban 15 mg=7.4; rivaroxaban 20 mg=5.0).

Estimates for the eGFR slope (i.e. average change in eGFR per year during the study period) were obtained using a mixed model include the following covariates: age, sex, baseline eGFR (both values and number of measurements), Townsend index, polymedication, smoking, body mass index, comorbidity, frailty, and health services use in the year before initiation.

Renal decline was less pronounced among the rivaroxaban cohort (eGFR slope = −1.37 ml/min per 1.73 m^2/yr (95% CI: −1.58 to −1.15) than the warfarin cohort (eGFR slope = −1.82 ml/min per 1.73 m^2/yr, 95% CI: −1.97 to −1.67). Although renal decline appeared to be more pronounced among patients starting on 20 mg rivaroxaban than 15 mg rivaroxaban, this trend disappeared after stratifying by baseline eGFR (**Table 5**; **Figure 3;** **Supplementary Table S29**). The results of the slope analyses among patients with diabetes or heart failure were consistent with those in the main analyses (**Table 5**; **Supplementary Table S30**).

Table 5. eGFR slope (ml/min/1.73 m^2/year; average change in eGFR per year during the study period) in the study cohorts after initiation by baseline renal function and comorbidity.

Population	Cohort/Dose	N	Adjusted analysis[†]		
			eGFR slope (95% CI)	Difference (95% CI)	p-value
All	Warfarin[*]	3052	–1.82 (–1.97 to –1.67)		
	Rivaroxaban	2743	–1.37 (–1.58 to –1.15)	0.45 (0.19 to 0.72)	0.00
	15 mg	515	–0.86 (–1.32 to –0.40)	0.96 (0.48 to 1.44)	0.00
	20 mg	2228	–1.51 (–1.75 to –1.27)	0.31 (0.02 to 0.59)	0.04
eGFR >50	Warfarin[*]	2464	–2.04 (–2.23 to –1.84)		
	Rivaroxaban	2248	–1.64 (–1.92 to –1.37)	0.39 (0.05 to 0.73)	0.03
	15 mg	194	–1.63 (–2.53 to –0.73)	0.40 (–0.52 to 1.32)	0.39
	20 mg	2054	–1.65 (–1.94 to –1.35)	0.39 (0.04 to 0.74)	0.03
eGFR 50–30	Warfarin[*]	487	–0.98 (–1.10 to –0.86)		
	Rivaroxaban	450	–0.38 (–0.55 to –0.22)	0.59 (0.39 to 0.80)	0.00
	15 mg	283	–0.44 (–0.65 to –0.24)	0.53 (0.30 to 0.77)	0.00
	20 mg	167	–0.27 (–0.55 to 0.02)	0.71 (0.40 to 1.02)	0.00
eGFR <30	Warfarin[*]	101	–1.67 (–2.01 to –1.34)		
	Rivaroxaban	45	–0.64 (–1.45 to 0.18)	1.04 (0.16 to 1.92)	0.02
	15 mg	38	–1.14 (–2.03 to –0.24)	0.53 (–0.42 to 1.49)	0.27
	20 mg	7	1.71 (–0.33 to 3.75)	3.38 (1.32 to 5.44)	0.00
No diabetes	Warfarin[*]	2122	–1.54 (–1.77 to –1.31)		
	Rivaroxaban	1973	–1.24 (–1.55 to –0.92)	0.31 (–0.09 to 0.70)	0.13
	15 mg	354	–0.69 (–1.38 to 0.00)	0.85 (0.13 to 1.58)	0.02
	20 mg	1619	–1.38 (–1.74 to –1.03)	0.16 (–0.27 to 0.58)	0.47
Diabetes	Warfarin[*]	930	–2.30 (–2.42 to –2.19)		
	Rivaroxaban	770	–1.66 (–1.84 to –1.48)	0.64 (0.43 to 0.85)	0.00
	15 mg	161	–1.19 (–1.56 to –0.83)	1.11 (0.73 to 1.49)	0.00
	20 mg	609	–1.81 (–2.01 to –1.60)	0.49 (0.26 to 0.73)	0.00
No heart failure	Warfarin[*]	2530	–1.67 (–1.86 to –1.48)		
	Rivaroxaban	2338	–1.30 (–1.56 to –1.03)	0.37 (0.05 to 0.70)	0.02
	15 mg	410	–0.91 (–1.50 to –0.31)	0.76 (0.13 to 1.39)	0.02
	20 mg	1928	–1.39 (–1.68 to –1.10)	0.28 (–0.07 to 0.63)	0.12
Heart failure	Warfarin[*]	522	–2.43 (–2.58 to –2.28)		
	Rivaroxaban	405	–1.67 (–1.89 to –1.45)	0.76 (0.49 to 1.03)	0.00
	15 mg	105	–0.72 (–1.11 to –0.33)	1.71 (1.30 to 2.13)	0.00
	20 mg	300	–2.15 (–2.42 to –1.87)	0.28 (–0.03 to 0.60)	0.08

[*]Reference category.

[†]Adjusted estimates obtained by using a Cox proportional hazard regression model including the following covariates: age, sex, baseline eGFR (both as categorical and continuous variables), number of previous measurements at baseline, Townsend index, polymedication, smoking, body mass index, health service utilisation in the year before baseline (PCP visits, referrals and hospitalizations), comorbidity (ischemic heart disease, cancer, diabetes, heart failure, and prior acute kidney injury), frailty (eFI), and CHA_2DS_2VASc score.

CI, confidence interval; eGFR, estimated glomerular filtration rate; PCP, primary care practitioner

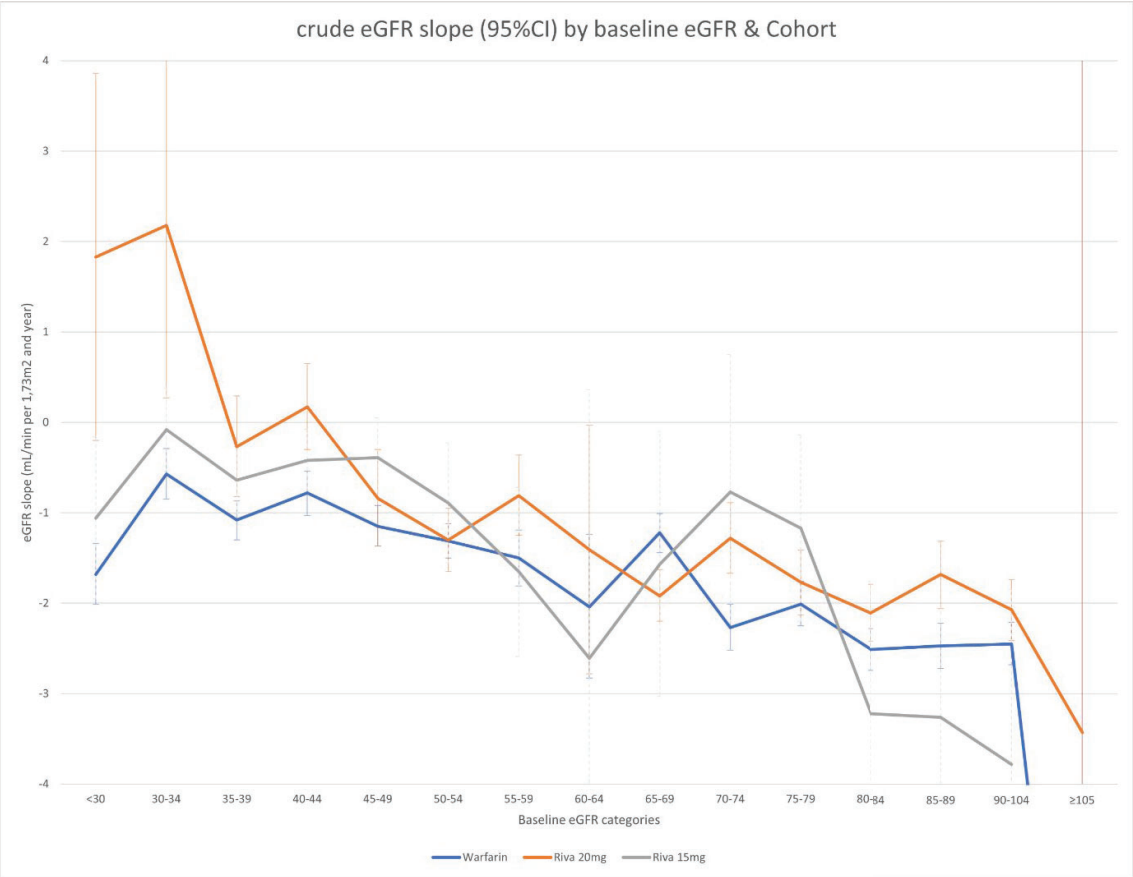

Figure 3. Crude eGFR slope in the study cohorts by baseline renal function.

Figure 4 (**Supplementary Table S31**) depicts the alternative slope analysis, where the crude eGFR slope (obtained with a mixed model with no covariates) was estimated by year of follow-up in each of the first five years. Note that while, by definition, among all individuals contributed to the estimation of the eGFR in the first year, only those that remained available for follow-up and had available measurements contributed to the subsequent years.

In an additional analysis that estimating the eGFR slope by year of follow-up among individuals with preserved renal function at baseline (eGFR>50 ml/min per 1.73 m^2), the results were similar (**Supplementary Table S32**).

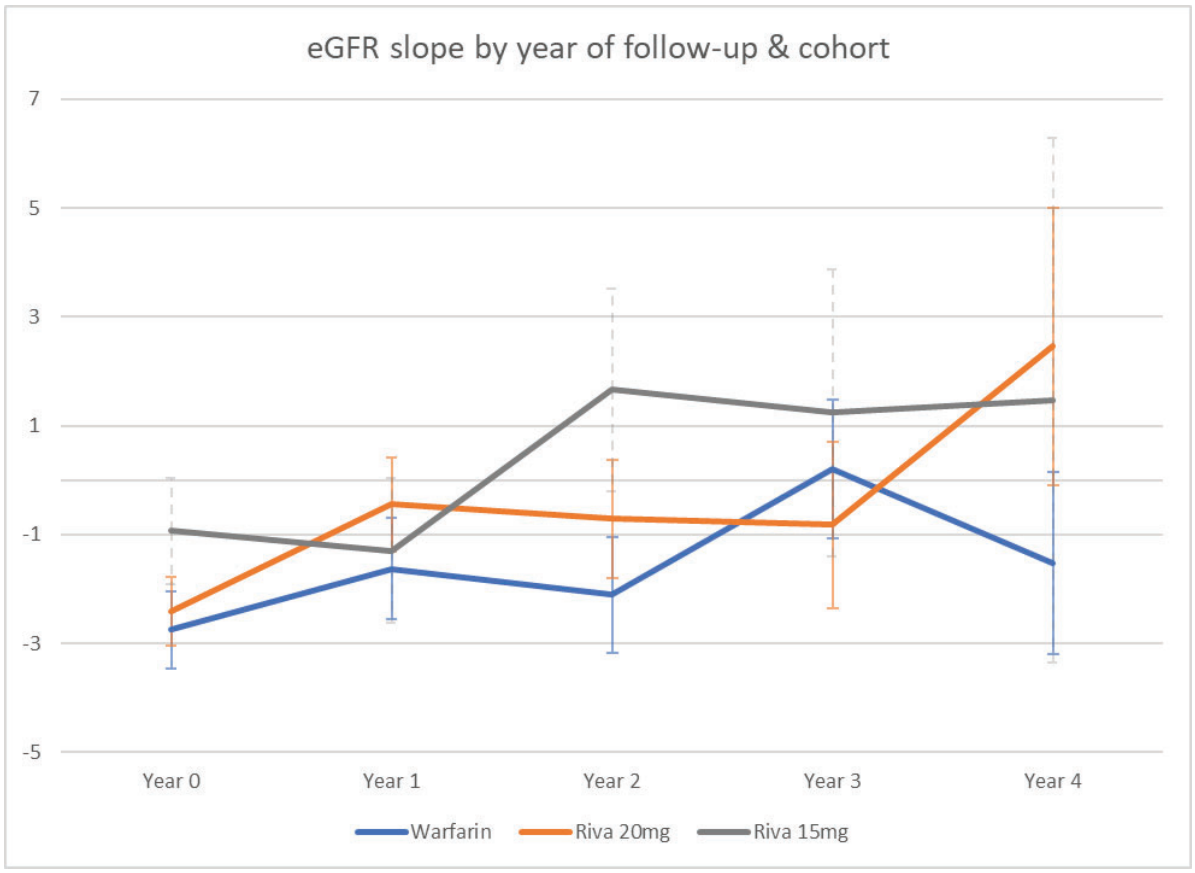

Figure 4. Crude eGFR slope in the study cohorts by year of follow-up.

10.4.2 Acute kidney injury

A total of 274 cases of AKI were identified during the study period using Method A. The corresponding incidence rates were 69.9 per 10,000 person-years in the warfarin cohort and 88.1 cases per 10,000 person-years in the rivaroxaban cohort (**Table 6**).

Crude incidence rates of AKI using cases identified using Method B (Aberdeen algorithm) were as follows:

- using the less stringent case definition (individuals meeting any of the three Aberdeen criteria: year, week or day): 234.5 per 10,000 person-years in the warfarin cohort and 194.4 cases per 10,000 person-years in the rivaroxaban cohort
- using the most stringent case definition (day criterion only): 18.4 per 10,000 person-years in the warfarin cohort and 7.8 cases per 10,000 person-years in the rivaroxaban cohort.

Only 104 AKI cases identified in Method A (38.0%) were also considered AKI cases in Method B (any criteria).

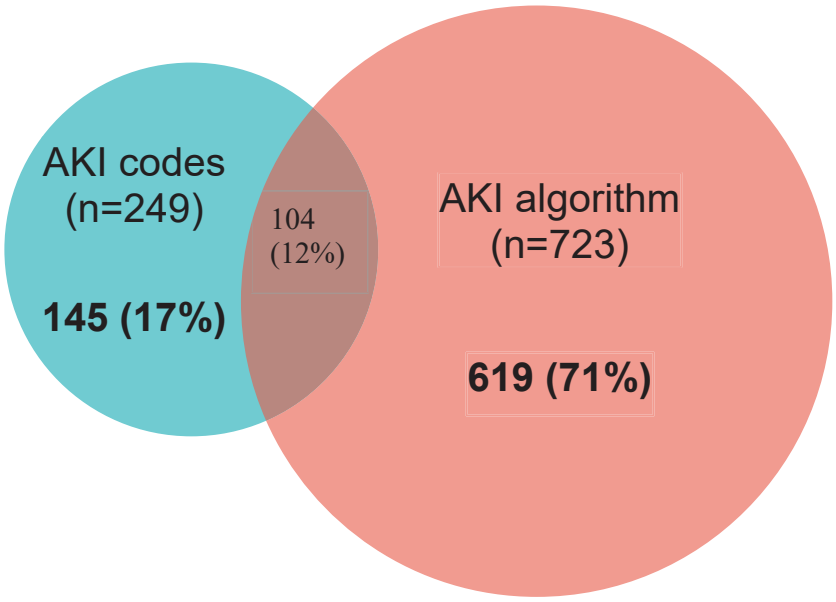

Figure 5. AKI cases identified using Method A and Method B (Of 868 events identified by the two methods, only 104 (12%) were identified by both methods).

In the multivariable adjusted Cox regression analyses, patients in the rivaroxaban cohort had a borderline significant increased risk of AKI when using Method A; HR 1.26 (95% CI: 0.99–1.60). This was explained mostly by an increased risk of AKI in patients starting on 15 mg rivaroxaban, HR 1.94 (95% CI: 1.37–2.73). In contrast, when using Method B, patients in the rivaroxaban cohort had a significantly reduced risk of AKI (Method B), with the reduction greatest when using the most stringent case definition: HR 0.80 (95% CI: 0.69–0.93) for the least stringent case definition, and HR 0.43 (95% CI: 0.21–0.88) for the most stringent case definition.

The results of the OT and AT analyses were compatible with the main analyses (**Supplementary Tables 4-8**). Using Method A, HRs were 1.28 (95% CI: 0.93–1.75) in the OT analysis, and HR 1.22 (95% CI: 0.93–1.59) in the AT analysis. Using Method B, HRs ranged from 0.76 (95% CI: 0.63–0.92) to 0.31 (95% CI: 0.12–0.84) in the OT analysis, and from 0.77 (95% CI: 0.65–0.92) to 0.29 (95% CI: 0.12–0.70) in the AT analysis.

Estimates obtained for patients with diabetes or heart failure did not deviate much from the main ITT analyses. For patients with diabetes, using Method A, the HR was 1.42 (95% CI: 0.94-2.13), and using Method B (any), HR was 0.69 (95% CI: 0.53–0.89). For patients with heart failure, using Method A, the HR was 0.78 (95% CI: 0.45–1.35), and using Method B (any), the HR was 0.88 (95% CI: 0.64–1.20) (**Supplementary Tables S9-18**). Further details of the ITT analyses for the different AKI endpoints can be found in **Supplementary Tables S33-36**.

Table 6. Risk of acute kidney disease in the study cohorts by baseline renal function.

Endpoint	Baseline eGFR	Cohort	Individuals	Person-years	Failures	IR × 10,000	HR†	95% CI	P>|z|
AKI (Method A)	ALL	Warfarin*	7457	20,891.6	146	69.9	1.00		
		Rivaroxaban	6746	14,528.8	128	88.1	1.26	(0.99–1.60)	0.06
		15 mg	1110	2154.3	53	246.0	1.94	(1.37–2.73)	<0.01
		20 mg	5636	12,374.6	75	60.6	1.01	(0.76–1.35)	0.93
	eGFR >50	Warfarin*	6237	17,906.3	98	54.7	1.00		
		Rivaroxaban	5733	12,523.1	83	66.3	1.22	(0.90–1.64)	0.20
		15 mg	495	950.6	20	210.4	2.75	(1.64–4.61)	<0.01
		20 mg	5238	11,572.5	63	54.4	1.04	(0.75–1.44)	0.81
	eGFR 30–50	Warfarin*	1060	2680.6	41	153.0	1.00		
		Rivaroxaban	931	1861.1	41	220.3	1.35	(0.85–2.14)	0.20
		15 mg	548	1097	29	264.4	1.45	(0.87–2.41)	0.15
		20 mg	383	764.1	12	157.0	1.17	(0.60–2.29)	0.65
	eGFR <30	Warfarin*	160	304.7	7	229.8	1.00		
		Rivaroxaban	82	144.7	4	276.4	8.00	(0.29–221.75)	0.22
		15 mg	67	106.7	4	374.9	258.69	(0.93–72,234.05)	0.05
		20 mg	15	38	0	0.0	0.00		1.00
AKI (Method B any)	ALL	Warfarin*	7129	19,492.2	457	234.5	1.00		
		Rivaroxaban	6436	13,686.8	266	194.4	0.80	(0.69–0.93)	<0.01
		15 mg	1000	1915.5	67	349.8	0.89	(0.68–1.17)	0.41
		20 mg	5436	11,771.2	199	169.1	0.77	(0.65–0.92)	<0.01
	eGFR >50	Warfarin*	6043	16,946.4	349	205.9	1.00		
		Rivaroxaban	5547	11,963.1	208	173.9	0.80	(0.67–0.95)	0.01
		15 mg	471	898.7	31	345.0	0.99	(0.68–1.46)	0.98
		20 mg	5076	11,064.5	177	160.0	0.77	(0.64–0.93)	0.01
	eGFR 30–50	Warfarin*	961	2347.6	89	379.1	1.00		
		Rivaroxaban	829	1614	54	334.6	0.87	(0.61–1.24)	0.44
		15 mg	481	939.7	33	351.2	0.90	(0.59–1.36)	0.61
		20 mg	348	674.3	21	311.4	0.83	(0.51–1.36)	0.46
	eGFR <30	Warfarin*	125	198.2	19	958.6	1.00		
		Rivaroxaban	60	109.6	4	364.9	0.02	(0.00–0.40)	0.01
		15 mg	48	77.1	3	388.9	0.00	(0.00–0.13)	<0.01
		20 mg	12	32.5	1	308.0	1.10	(0.02–71.85)	0.96
AKI (Method B Week/Day)	ALL	Warfarin*	7129	20,134.2	60	29.8	1.00		
		Rivaroxaban	6436	14,029.4	21	15.0	0.52	(0.31–0.87)	0.01
		15 mg	1000	1992.7	8	40.2	0.68	(0.31–1.53)	0.36
		20 mg	5436	12,036.8	13	10.8	0.46	(0.25–0.85)	0.01
	eGFR >50	Warfarin*	6043	17,455.3	38	21.8	1.00		
		Rivaroxaban	5547	12,236.7	15	12.3	0.56	(0.30–1.06)	0.07
		15 mg	471	939.8	2	21.3	0.44	(0.08–2.52)	0.36
		20 mg	5076	11297	13	11.5	0.58	(0.30–1.11)	0.10
	eGFR 30–50	Warfarin*	961	2466.1	16	64.9	1.00		
		Rivaroxaban	829	1679.2	6	35.7	0.38	(0.13–1.09)	0.07
		15 mg	481	973.4	6	61.6	0.82	(0.28–2.41)	0.71
		20 mg	348	705.8	0	0.0	0.00		
	eGFR <30	Warfarin*	125	212.7	6	282.1			
		Rivaroxaban	60	113.5	0	0.0			
		15 mg	48	79.5	0	0.0			

Endpoint	Baseline eGFR	Cohort	Individuals	Person-years	Failures	IR × 10,000	HR†	95% CI	P>|z|
		20 mg	12	34	0	0.0			
AKI (Method B Day only)	ALL	Warfarin*	7129	20,159	37	18.4	1.00		
		Rivaroxaban	6436	14,041.6	11	7.8	0.43	(0.21–0.88)	0.02
		15 mg	1000	1997.9	4	20.0	0.46	(0.13–1.55)	0.21
		20 mg	5436	12,043.7	7	5.8	0.42	(0.18–0.96)	0.04
	eGFR >50	Warfarin*	6043	17478	19	10.9	1.00		
		Rivaroxaban	5547	12,243.7	9	7.4	0.74	(0.31–1.75)	0.49
		15 mg	471	939.8	2	21.3	0.84	(0.10–6.73)	0.87
		20 mg	5076	11,303.9	7	6.2	0.72	(0.29–1.79)	0.48
	eGFR 30–50	Warfarin*	961	2468.3	12	48.6	1.00		
		Rivaroxaban	829	1684.5	2	11.9	0.18	(0.04–0.86)	0.03
		15 mg	481	978.6	2	20.4	0.33	(0.07–1.62)	0.17
		20 mg	348	705.8	0	0.0	0.00		
	eGFR <30	Warfarin*	125	212.7	6	282.1			
		Rivaroxaban	60	113.5	0	0.0			
		15 mg	48	79.5	0	0.0			
		20 mg	12	34	0	0.0			

*Reference category.
†Adjusted estimates obtained by using a Cox proportional hazard regression model including the following covariates: age, sex, baseline eGFR (both as categorical and continuous variables), number of previous measurements at baseline, Townsend index, polymedication, smoking, body mass index, health service utilisation in the year before baseline (PCP visits, referrals and hospitalizations), comorbidity (ischemic heart disease, cancer, diabetes, and heart failure), frailty (eFI), and CHA_2DS_2VASc score.

In an alternative analysis with identical exclusion criteria for both Method A and Method B (i.e. individuals with either an AKI read code recorded or any of the Aberdeen criteria met before start date were excluded), the total number of AKI cases (*Method A*) dropped to 249, and incidence rates were to 67.9 per 10,000, and 81.2 cases per 10,000 in the rivaroxaban cohort (**Supplementary Table S37**). In the fully adjusted model (ITT), the HR for AKI was 1.20 (95% CI: 0.93–1.55). Estimates for AKI using Method B remained the same as in the main because this was already the exclusion in place for this method.

10.5 Other analyses

A separate analysis focused on patients with NVAF and preserved renal function (eGFR >50 mL/min/1.73m^2) because this subcohort was most comparable to the warfarin cohort in terms of demographics and clinical characteristics, including baseline renal function,. From the total of 11,652 patients, 5338 in the rivaroxaban 20 mg cohort (mean age 72.6 year, SD 10.2; 61% male) and 6314 in the warfarin cohort (mean age 73.2 years, SD 9.5; 58% male) were identified. The distribution of other baseline characteristics were very similar between treatment groups (**Table 7**).

10.5.1 SCr doubling, ≥30% decline in eGFR, and ESRD

After a mean follow-up of 2.5 years, the number of incident cases within the two cohorts was: doubling sCr (n=322), ≥30% decline in eGFR (n=1179), and ESRD (n=22). Incidence rates by study cohort are shown in **Table 8**.

After adjusting for age, sex, baseline renal function and comorbidity, we found strong evidence for a significantly reduced risk of SCr doubling and a ≥30% decline in eGFR with use of rivaroxaban vs. warfarin, HR 0.63 (95% CI: 0.49–0.81) for SCr doubling, and HR 0.76 (95% CI: 0.67–0.86) for ≥30% decline in eGFR. Evidence for a reduced risk of ESRD with use of rivaroxaban vs. warfarin was weaker, HR 0.77 (95% CI: 0.29–2.04) (**Table 8**). Similar results were observed among patients with diabetes or heart failure (**Table 9** and **Table 10**).

Rate of eGFR decline (slope analysis)

A total of 2054 patients on rivaroxaban and 2464 on warfarin were included in the slope analysis. After adjustment for confounders, there was strong evidence that the rate of eGFR decline was significantly slower in the rivaroxaban cohort than the warfarin cohort. The mean decline in renal function over the study period was –2.03 ml/min/1.73 m^2 per year in the warfarin cohort (95% CI: –2.23 to –1.84), and 1.65 ml/min/1.73 m^2 in the rivaroxaban cohort (95% CI: –1.94 to –1.35), a difference of 0.39 (95% CI: 0.04–0.74; p=0.03) (**Table 11**). The slower rate of renal decline in the rivaroxaban cohort was observed over most of the first 5 years of follow-up (**Figure 6**, **Table 12**).

Table 7. Baseline characteristics of patients with preserved renal function.

	Rivaroxaban 20 mg (N=5338) n (%)	**Warfarin (N=6314) n (%)**
Age (years)		
18–49	111 (2)	103 (2)
50–59	455 (9)	403 (6)
60–69	1330 (25)	1541 (24)
70–79	2097 (39)	2594 (41)
80–89	1174 (22)	1522 (24)
≥90	171 (3)	151 (2)
Mean (SD)	72.6 (10.2)	73.2 (9.5)
Sex		
Male	3253 (61)	3644 (58)
Female	2085 (39)	2670 (42)
Mean eGFR (SD) at baseline	75.7 (56.1)	75.5 (82.6)
Townsend index		
Most affluent	1100 (21)	1223 (19)
2nd quintile	1082 (20)	1365 (22)
3rd quintile	995 (19)	1082 (17)
4th quintile	741 (14)	991 (16)
Most deprived	430 (8)	593 (9)
Missing	990 (19)	1060 (17)
Smoking		
Non-smoker	2210 (41)	2477 (39)
Smoker	444 (8)	548 (9)
Ex-smoker	2678 (50)	3288 (52)
Missing	6 (0)	1 (0)
Body mass index		
<20	148 (3)	158 (3)
20–24	1053 (20)	1247 (20)
25–29	1914 (36)	2236 (35)
≥30	2029 (38)	2468 (39)
Missing	194 (4)	205 (3)
PCP visits		
0–4	44 (1)	41 (1)
5–9	535 (10)	552 (9)
10–19	2330 (44)	2759 (44)
≥20	2429 (46)	2962 (47)
Hospitalisations		
0	3041 (57)	3776 (60)

	Rivaroxaban 20 mg (N=5338) n (%)	**Warfarin (N=6314) n (%)**
1	1224 (23)	1296 (21)
≥2	1073 (20)	1242 (20)
Ischemic heart disease	1142 (21)	1612 (26)
Cancer	801 (15)	986 (16)
Diabetes	1118 (21)	1362 (22)
Heart failure	519 (10)	710 (11)
CHA_2DS_2VASc		
0–1	894 (17)	825 (13)
2	1166 (22)	1324 (21)
3	1343 (25)	1630 (26)
4	1062 (20)	1415 (22)
5	544 (10)	716 (11)
≥6	329 (6)	404 (6)
Frailty (eFI)		
Fit	1066 (20)	1122 (18)
Mild frailty	2381 (45)	2848 (45)
Moderate frailty	1401 (26)	1776 (28)
Severe frailty	490 (9)	568 (9)
ALL	5338 (100)	6314 (100)

Table 8. HRs (95% CI) for risk of renal decline among users of rivaroxaban 20 mg vs. warfarin.

Endpoint	**Cohort**	**Individuals**	**Person-years**	**Events**	**IR × 10,000**	**Fully-adjusted estimates[†]**		
						HR	**95% CI**	**P>|z|**
sCr 100% increase	Warfarin[*]	6314	17,925.3	231	128.9	1.00		
	Rivaroxaban	5338	11,691.1	91	77.8	0.63	(0.49–0.81)	0.00
eGFR 30% decline	Warfarin[*]	6314	16,627.9	780	469.1	1.00		
	Rivaroxaban	5338	11,088.9	399	359.8	0.76	(0.67–0.86)	0.00
ESRD	Warfarin[*]	6314	18,215.6	16	8.8	1.00		
	Rivaroxaban	5338	11,804.2	6	5.1	0.77	(0.29–2.04)	0.60

[*]Baseline category. [†]Estimates obtained using a Cox proportional hazards regression model with age, sex, baseline eGFR (both as categorical and continuous variables), number of previous measurements at baseline, Townsend index, polymedication, smoking, body mass index, health service utilisation in the year before baseline (PCP visits, referrals and hospitalizations), comorbidity (ischemic heart disease, cancer, diabetes, heart failure, and prior acute kidney injury), frailty (eFI) and CHA_2DS_2VASc score as covariates.

Table 9. Risk of renal decline among rivaroxaban 20 mg vs. warfarin initiators with heart failure.

Endpoint	Cohort	Individuals	Person-years	Events	IR × 10,000	Fully-adjusted estimates[†]		
						HR	95% CI	P>|z|
sCr 100% increase	Warfarin[*]	710	1822.0	61	334.8	1.00		
	Rivaroxaban	519	1087.1	22	202.4	0.55	(0.33–0.92)	0.02
eGFR 30% decline	Warfarin[*]	710	1515.8	181	1194.1	1.00		
	Rivaroxaban	519	946.7	86	908.4	0.77	(0.59–1.00)	0.05
ESRD	Warfarin[*]	710	1909.0	5	26.2	1.00		
	Rivaroxaban	519	1116.3	1	9.0	0.18	(0.00–7.27)	0.37

[*]Baseline category. [†]Estimates obtained using a Cox proportional hazards regression model with age, sex, baseline eGFR (both as categorical and continuous variables), number of previous measurements at baseline, Townsend index, polymedication, smoking, body mass index, health service utilisation in the year before baseline (PCP visits, referrals and hospitalizations), comorbidity (ischemic heart disease, cancer, diabetes, heart failure, and prior acute kidney injury), frailty (eFI) and CHA_2DS_2VASc score as covariates.

Table 10. Risk of renal decline among rivaroxaban 20 mg vs. warfarin initiators with diabetes.

Endpoint	Cohort	Individuals	Person-years	Events	IR × 10,000	Fully-adjusted estimates[†]		
						HR	95% CI	P>|z|
sCr 100% increase	Warfarin[*]	1362	3719.7	97	260.8	1.00		
	Rivaroxaban	1118	2402.3	43	179.0	0.69	(0.48–1.00)	0.05
eGFR 30% decline	Warfarin[*]	1362	3313.9	265	799.7	1.00		
	Rivaroxaban	1118	2179.2	148	679.2	0.83	(0.67–1.02)	0.08
ESRD	Warfarin[*]	1362	3842.8	7	18.2	1.00		
	Rivaroxaban	1118	2447.2	3	12.3	0.87	(0.17–4.33)	0.86

[*]Baseline category. [†]Estimates obtained using a Cox proportional hazards regression model with age, sex, baseline eGFR (both as categorical and continuous variables), number of previous measurements at baseline, Townsend index, polymedication, smoking, body mass index, health service utilisation in the year before baseline (PCP visits, referrals and hospitalizations), comorbidity (ischemic heart disease, cancer, diabetes, heart failure, and prior acute kidney injury), frailty (eFI) and CHA_2DS_2VASc score as covariates.

Table 11. Average eGFR slope (ml/min/1.73 m^2/year) in rivaroxaban 20 mg vs. warfarin initiators during entire follow-up.

Cohort/Dose	N	Adjusted analysis[†]		
		eGFR slope (95% CI)	Difference (95% CI)	p-value
Warfarin[*]	2464	–2.03 (–2.23 to –1.84)		
Rivaroxaban	2054	–1.65 (–1.94 to –1.35)	0.39 (0.04 to 0.74)	0.03

[*]Reference category for test of difference. [†]eGFR slopes (change in mL/min/1.73m^2/year) are estimated using linear mixed regression models, where the treatment group, time of eGFR measurement, and the interaction between treatment group and time are included as fixed factors and each individual will be included as a random factor (i.e. random intercept model). In order to obtain adjusted estimates the following variables were included as additional fixed factors in the linear mixed model: age, sex, baseline eGFR (categorical variable), Townsend index, polymedication, smoking, body mass index, health service utilisation in the year before baseline (PCP visits, referrals and hospitalizations), comorbidity (ischemic heart disease, cancer, diabetes, heart failure, and prior acute kidney injury), frailty (eFI) and CHA_2DS_2VASc score.

Table 12. eGFR slope (ml/min/1.73 m^2/year) in rivaroxaban 20 mg vs. warfarin initiators by year during the first five years of follow-up.

Cohort	Year of follow-up	eGFR slope	*p*-value	LL	UL
Warfarin	Year 1	–3.12	0.00	–4.01	–2.23
	Year 2	–1.92	0.00	–3.07	–0.76
	Year 3	–2.11	0.00	–3.42	–0.81
	Year 4	0.88	0.27	–0.67	2.42
	Year 5	–1.78	0.09	–3.80	0.25
Rivaroxaban 20mg	Year 1	–2.39	0.00	–3.05	–1.72
	Year 2	–0.23	0.63	–1.14	0.69
	Year 3	–0.52	0.38	–1.67	0.64
	Year 4	–1.41	0.09	–3.02	0.21
	Year 5	2.65	0.05	–0.04	5.33

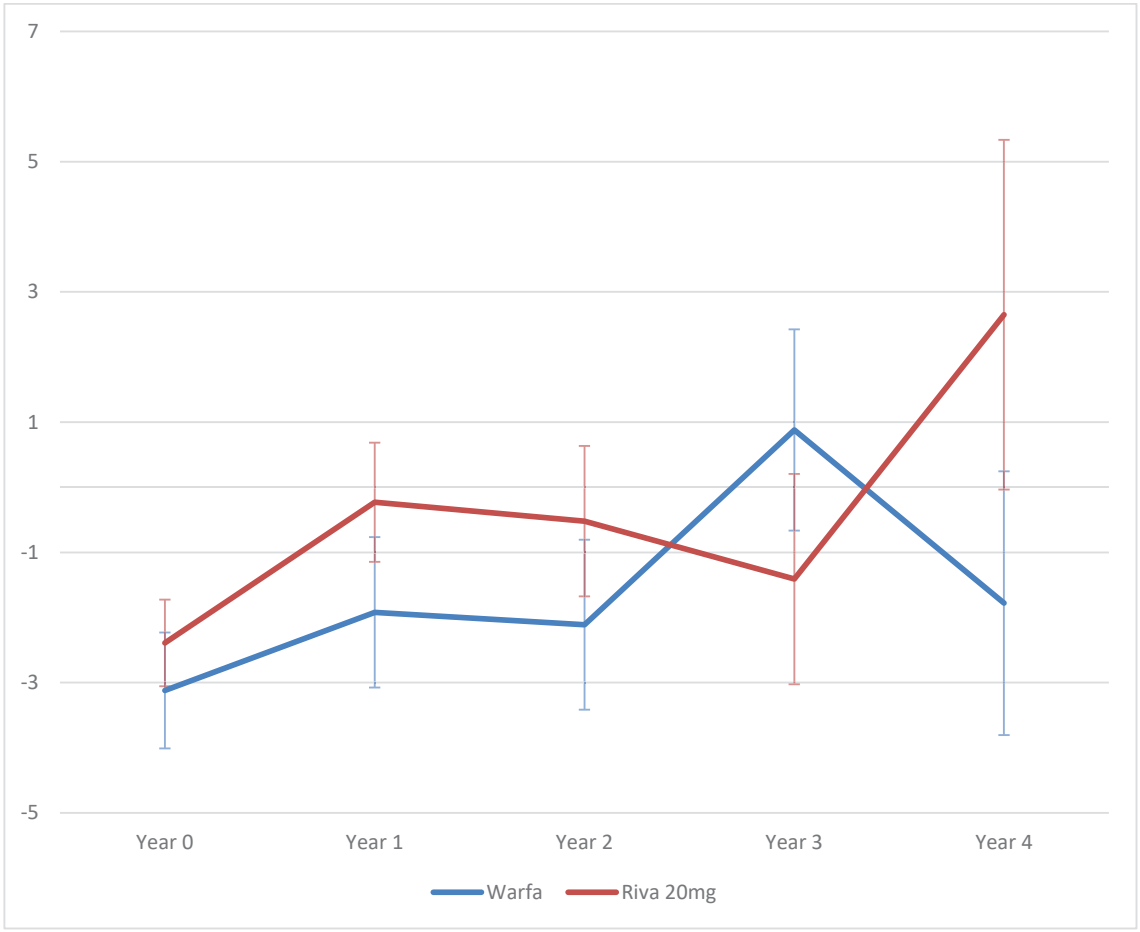

Figure 6. eGFR slope (ml/min per 1.73 m^2 per year) in rivaroxaban 20 mg vs. warfarin initiators by year up during the first five years of follow-up.

10.6 Safety data (Adverse events/adverse reactions)

Not applicable.

11. Discussion

11.1 Key results

In this study of patients with NVAF, there was clear evidence that users of rivaroxaban 20 mg had a significantly reduced risk of renal decline compared with users of warfarin, including a 24% reduced risk of SCr doubling and a 28% reduced risk of ≥50% decline in eGFR. The magnitude of the observed risk reductions seemed to increase with the severity of the renal decline outcome, and consistent findings were seen among patients with diabetes or heart failure. In addition, the rate of renal decline during the first five years of drug use was significantly slower for users of rivaroxaban 20 mg vs. warfarin. For ESRD, the point estimate was indicative of a potential benefit effect of rivaroxaban, yet statistical power was limited to be able to detect a significant difference between exposure groups.

These findings for renal decline are consistent with those from previous claims database studies in the United States(17, 21, 32, 33) and Germany,(34) especially with those from Yao and colleagues.(17) Stronger evidence for a beneficial effect of rivaroxaban over VKAs on progression to ESRD/Stage 5 CKD, has been reported by others.(21) (34) Using the Marketscan database in the US, Coleman *et al*(21) reported a significant 18% reduction in progression to stage 5 CKD/dialysis for rivaroxaban vs. warfarin, while in Germany, Bonnemeier *et al*(34) found rivaroxaban to be associated with a significant 66% reduction in ESRD when compared with phenprocoumon. Also using Marketscan, Vaitsiakhovich and colleagues (32) reported a 47% reduction for rivaroxaban vs. warfarin in patients with stage 3 or 4 CKD at baseline, as well as in those with type 2 diabetes, consistent with findings from another Marketscan study restricted to patients with diabetes.(33) However, while Pastori *et al*(35) reported a lower rate of eGRF worsening when comparing DOACs as a class and VKAs, this effect was partially lost in patients with diabetes.

Our study also found that after adjusting for confounders, the risk of AKI was higher in users of rivaroxaban (vs. warfarin) when using case identification Method A, and a 20% significantly lower risk for AKI when using case identification Method B. In the claims database study by Yao *et al*, that used linked hospitalisation data (including both primary and secondary diagnoses), the incidence rate of AKI was 687 per 10,000 person-years, which is much higher than the rates of 88.1 cases per 10,000 person-years (Method A) and 194.4 per 10,000 person-years (Method B) found in this present study. However, in their adjusted ITT analysis, Yao *et al*. reported a 24% decreased risk of AKI among rivaroxaban vs. warfarin users, which is in line with the 20% decreased seen in our study using Method B. The lack of overlap between the two AKI case identification methods in our study (only one third of cases identified by Method A were also considered to be cases according to Method B), indicated that the two case identification strategies were capturing different things. Although speculative, but it could be explained by the doctors coding AKI less rigorously compared to recording lab values as clinical decisions are guided by the latter.

Daily dose of rivaroxaban (20 mg/15 mg) on renal decline outcomes

In this study, there was a lower crude incidence rate of virtually all renal decline study outcomes among rivaroxaban initiators than among warfarin initiators. However, while lower incidence rates were seen in patients on rivaroxaban 20 mg (vs. warfarin), higher rates were seen in patients on rivaroxaban 15 mg. While the characteristics of individuals initiating warfarin were similar to individuals initiating rivaroxaban 20 mg, both were different to those of individuals initiating

rivaroxaban 15 mg, who were, on average, older, more frail, more likely to be female, and with worse baseline renal function which reflects rivaroxaban labeling instructions on the dose adjustment. These differences should be considered when attempting comparisons with rivaroxaban 15 mg, which may be challenging as this study did not aim to evaluate appropriateness of prescribing 15 mg rivaroxaban, and obtaining a comparable group of warfarin users (i.e. with same baseline risk) would be difficult.

Comparison of incidence rates in ANTENNA with those from Yao et al

The incidence rate of renal outcomes in ANTENNA were consistently lower than those in the study by Yao *et al*, e.g. the incidence rate of ≥30% decline in eGFR among patients on rivaroxaban in ANTENNA was 463.7 per 10,000 person-years compared with 1463 per 10,000 person-years in Yao *et al*. A similar difference was seen in the incidence rate of ESRD among patients on rivaroxaban; 22.1 per 10,000 person-years in ANTENNA compared with 64 per 10,000 person-years in Yao *et al*. A smaller, yet still substantial, difference was seen in the incidence rate of doubling of SCr among users of rivaroxaban, 103.8 per 10,000 person-years in ANTENNA compared with 140 cases per 10,000 person-years in Yao *et al*. Although both studies used a similar new user cohort design, and were performed in large databases, differences in the methods are likely responsible for these large difference in incidence rates. The case definition of renal decline events in ANTENNA required a subsequent confirmatory measurement to ensure that a chronic progressive renal deterioration was captured rather than a transient extreme measurement. The only renal decline outcome that did not require this confirmatory measurement was doubling of SCr levels. While incidence rates of ≥30% decline and ESRD were roughly three times larger in the US study than in ANTENNA, the incidence rate of SCr doubling was also only 40% higher. Also, in the US study, only patients with both baseline and follow-up measurements were included in the analyses. In contrast, in ANTENNA, at least one baseline measurement (i.e. anytime from one year before to the date of drug initiation) was required, but there were no exclusion/inclusion criteria after the date of drug initiation (an advisable criterion to avoid introducing biases). This is important because between 10% and 12% of patients in the ANTENNA study cohorts did not have any follow-up measurements and therefore were not able to contribute to the numerator while contributing to the denominator. These individuals were removed from the US study, thus, even though our estimates are lower, we believe they are more reliable. Notwithstanding this, the magnitude of the difference in adverse renal events difference rivaroxaban and warfarin cohorts in Yao *et al* was similar to that shown in our study.

11.2 Limitations

- Some non-differential misclassification may have occurred between outcome groups, biasing risk estimates towards the null. This may have resulted from when patients discontinued or switched OAC during follow-up. However, the latter is likely minimal as shown from the ‘on-treatment’ and ‘as-treated’ sensitivity analyses where results were consistent with the main findings.
- Potential for misclassification of exposure (in particular, estimation of the end of supply) to a warfarin due to complex dosing and variable package size with multiple strengths of tablets prescribed concomitantly. Additionally, we did not evaluate international normalised ratio

levels in the warfarin cohort, thus were unable to take into account potential overdosing that could lead to renal damage in these patients, which could have led to residual confounding.

- Non-differential outcome misclassification may have occurred from unrecorded/incorrect laboratory measurements or coding errors. Detection bias is possible if laboratory investigations were more common among one exposure group, potentially favouring the drug associated with fewer investigations due to the lower likelihood of renal event diagnosis.
- Residual confounding from unknown or unmeasurable confounders.

11.3 Interpretation

In this population-based study of patients with NVAF, we found clear evidence that users of rivaroxaban 20 mg had a significantly reduced risk of renal decline compared with users of warfarin, with a 24% reduction in SCr doubling and 28% reduced risk of ≥50% decline in eGFR. Consistent findings were seen among patients with diabetes or heart failure. The rate of renal decline during the first five years of drug use was significantly slower for users of rivaroxaban 20 mg vs. warfarin. Similarly, although our study had limited power to detect a significant difference in ESRD between exposure groups, the point estimate was indicative of a potential benefit effect of rivaroxaban. We also found evidence of a significant decrease in risk of AKI among users of rivaroxaban 20 mg vs. warfarin when using a stringent and potentially more reliable AKI case definition.

Of note is that the decline in renal function over time was seen progressive throughout follow-up. This is clinically meaningful given the life-long nature of OAC therapy in patients with AF and also that the decline may partly be related to age-related physiological decline as well as OAC therapy itself. This underscores the importance of continuous monitoring renal function in this patient population as OAC dose adjustment may be required with time.

11.4 Generalizability

The IMRD-UK is considered representative of the general UK population thus the results from this study can be considered as generalizable to UK as a whole.

In addition, individuals without laboratory eGFR measurements recorded in the year before OAC initiation were excluded in this study. These excluded patients were more likely to have preserved renal function than those remaining in the study. However, the proportion of individuals excluded was below 17% among rivaroxaban initiators and below 14% among warfarin initiators. This suggests that the study cohorts were relatively representative of the population of NVAF patients who initiate OAC therapy.

12. Other information

None.

13. Conclusion

The results of this study provide strong evidence that patients with NVAF and preserved renal function using rivaroxaban have a significantly reduced risk and rate of renal decline and AKI compared with those using warfarin. Further evidence to support a causal association from RCTs and well-designed observational studies in other settings would help prescribers make more informed benefit–risk decisions regarding choice of long-term OAC therapy for their patients.

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Appendices

Annex 1. List of stand-alone documents

List of multilex codes for drugs READ codes for clinical conditions

Annex 2 Additional information

Supplementary Material

Annex 3 Signature Pages

Signature Page - Study Conduct Responsible

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Report version and date	v 1.0 27 APR 2021
IMPACT study number	21347
Study type / Study phase	Observational, Phase IV PASS
EU PAS register number	EUPAS33537
Medicinal product	Xarelto (rivaroxaban)
Comparator	Warfarin
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 5/6/2021, _____ PPD _____

Signature Page - Study Epidemiologist

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Report version and date	v 1.0 27 APR 2021
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EU PAS register number	EUPAS33537
Medicinal product	Xarelto (rivaroxaban)
Comparator	Warfarin
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 5/6/2021, PPD

Signature Page - Study Safety Lead

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Report version and date	v 1.0 27 APR 2021
IMPACT study number	21347
Study type / Study phase	Observational, Phase IV PASS
EU PAS register number	EUPAS33537
Medicinal product	Xarelto (rivaroxaban)
Comparator	Warfarin
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 5/11/2021, _____ PPD _____

Signature Page - Study Medical Expert

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Report version and date	v 1.0 27 APR 2021
IMPACT study number	21347
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EU PAS register number	EUPAS33537
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Print Name: PPD

Date, Signature: 5/9/2021, PPD

Signature Page - MAH Contact Person (Regulatory Affairs)

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Report version and date	v 1.0 27 APR 2021
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Print Name: PPD

Date, Signature: 5/18/2021, PPD

Signature Page - OS Data Science Representative

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Report version and date	v 1.0 27 APR 2021
IMPACT study number	21347
Study type / Study phase	Observational, Phase IV PASS
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Comparator	Warfarin
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

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Print Name: PPD

Date, Signature: 5/7/2021, PPD

Signature Page - Study Statistician – External (PPD)

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Report version and date	v 1.0 27 APR 2021
IMPACT study number	21347
Study type / Study phase	Observational, Phase IV PASS
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Comparator	Warfarin
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

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Print Name: PPD

Date, Signature: 5/6/2021, PPD

Signature Page – Principal Investigator

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Report version and date	v 1.0 27 APR 2021
IMPACT study number	21347
Study type / Study phase	Observational, Phase IV PASS
EU PAS register number	EUPAS33537
Medicinal product	Xarelto (rivaroxaban)
Comparator	Warfarin
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

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Print Name: PPD

Date, Signature: 5/6/2021, PPD