XARENO – Registry

Factor XA – inhibition in RENal patients with non-valvular atrial fibrillation Observational registry

- an observational registry -

Registry Protocol

Version: V2.0

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Medical Coordinator / Registry Chair

Prof. Dr. Reinhold Kreutz

Charité - Universitätsmedizin Berlin
Institute of Clinical Pharmacology and Toxicology
Charitéplatz 1, 10117 Berlin
Germany

Sponsor

GWT-TUD GmbH

Freiberger Str. 33
01067 Dresden
Germany

I. RESPONSIBLE PARTIES

Sponsor

GWT-TUD GmbH	Freiberger Str. 33 01067 Dresden Germany

Medical Coordinator / Registry Chair

Prof. Dr. Reinhold Kreutz	Employee of Charité - Universitätsmedizin Berlin Institute of Clinical Pharmacology and Toxicology Charitéplatz 1, 10117 Berlin Germany
PD Jan Beyer-Westendorf	Employee of Universitätsklinikum Dresden Centre for Vascular Medicine Department of Medicine III Fetscherstraße 74 01307 Dresden Germany

Writing Committee (Steering Committee)

Prof. Dr. Reinhold Kreutz	Charité Berlin
PD Dr. Jan Beyer-Westendorf	Universitätsklinikum Dresden
Prof. Dr. Pontus Persson	Charité Berlin
Dr. Kai Hahn	Nephrologische Praxis, Dortmund
Prof. Dr. Jürgen Flöge	Uniklinikum RWTH Aachen
Prof. Dr. Marianne Gwechenberger	Universität Wien
Prof. Dr. Andreas Luft	Universität Zürich
Prof. Gilbert Deray	Hôpital de la Pitié-Salpêtrière, Paris

Statistics

ClinStat GmbH	ClinStat GmbH, Institute for Clinical Research and Statistics Max-Planck-Str. 22a 50858 Cologne Germany

Registry coordination

Dr. Katja Jersemann	GWT-TUD GmbH Freiberger Str. 33 01067 Dresden

Germany
Phone: +49 351 25933188
FAX: +49 351 25933111
E-Mail: katja.jersemann@gwtonline.de

II. Signatures

We, the undersigned, agree to conduct this observational registry according to the observational plan and to make no additions or changes without the consent of the sponsor. In addition, we agree that the non-interventional registry will be carried out in accordance with the Declaration of Helsinki and with the laws and regulations of the country in which the registry takes place.

Sponsor GWT-TUD GmbH

Frank Schwarz

Dresden, 03.03.2020

place, date

Medical Coordinator / Registry Chair

Prof. Dr. Reinhold Kreutz

Berlin, 3/3/2020

place, date

Registry Chair

PD Dr. Jan Beyer-Westendorf

Dresden, 03-MAR-2020

place, date

Statistics

Dr. Kurtulus Sahin, ClinStat GmbH

Cologne, 4. March 2020

place, date

III. SYNOPSIS

Title	**Factor XA –inhibition in RENal patients with non-valvular atrial fibrillation Observational registry** **XARENO – Registry**
Protocol identifier	**XARENO – Registry**
Sponsor	GWT-TUD GmbH Freiberger Str. 33 01067 Dresden Germany
Medical Coordinator	Prof. Dr. Reinhold Kreutz Charité - Universitätsmedizin Berlin Institute of Clinical Pharmacology and Toxicology Charitéplatz 1 10117 Berlin Germany
Registry Indication	Non-valvular atrial fibrillation (NVAF)
Registry design	Multicentre, prospective, non-interventional and observational registry taking place in Germany, Austria, Switzerland, France, Belgium and Luxembourg.
Research question and objectives	The multicentre registry will collect clinical data from approximately 1600 patients with NVAF and chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) (15-49 mL/min per 1.73 m^2). The overall objective of this registry is to assess CKD progression and safety of anticoagulation strategies in NVAF patients with eGFR 15-49 mL/min per 1.73 m^2 in routine clinical practice.
Specific registry objectives	1. To evaluate CKD progression and safety outcomes in NVAF patients with eGFR 15-49 mL/min per 1.73 m^2 in relation to rivaroxaban and vitamin K antagonist (VKA) treatment as observed in routine clinical practice. 2. To collect data on progression of CKD and safety outcomes in NVAF patients with eGFR 15-49 mL/min per 1.73 m^2 and without anticoagulation therapy (AC) in routine clinical practice.

Primary observational outcomes	1. Progression of CKD:
	- decline in eGFR in mL/min per 1.73 m^2
	
	2. Safety:
	- major bleeding
	- all-cause mortality
	- TIA, stroke or systemic arterial embolism
	- Other major cardiovascular events (MACE)
	    o Myocardial infarction
	    o Acute coronary syndrome/unstable angina
	- symptomatic venous thromboembolic events
	- net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality)

Secondary observational outcomes	- initiation of chronic renal replacement therapy - eGFR < 15 mL/min per 1.73 m^2 (CKD Stage 5 Dialysis and Non-Dialysis) - eGFR decline of ≥ 30% - doubling of serum creatine concentration - acute kidney injury (AKI) events defined as acute kidney injury associated with either hospitalization or emergency department visit, where AKI event is the lead diagnosis - rates, causes and length of hospitalizations - persistence with OAC therapy - reasons for OAC therapy discontinuation
Population	Patients with NVAF and CKD (eGFR 15-49 mL/min per 1.73 m^2)
Treatment and names of medicinal products under investigation	The treatment is carried out at the discretion of the attending physician with rivaroxaban, VKA or no AC.

Inclusion criteria/ Exclusion criteria	Principal inclusion criteria:
	- male and female patients, age ≥ 18 years
	- CKD with eGFR 15 – 49 mL/min per 1.73 m^2
	- documented non-valvular atrial fibrillation (NVAF) with indication for anticoagulation therapy
	- a treatment strategy for the ≥ 3 previous months before enrolment with either:
	  ▪ rivaroxaban or
	  ▪ VKA (OAC cohorts) or
	  ▪ no anticoagulation (no AC cohort)
	received (if applicable) at the earliest in January 2012
	- informed consent
	- availability for follow up
	- life expectancy of ≥6 months
	
	Exclusion criteria:
	- exclusion criteria according to the local product information for the respective anticoagulation treatment
	- planned chronic treatment with other anticoagulants
	- expected renal-replacement therapy within the next 3 months

Time schedule / milestones primary data collection	First patient first visit (FPFV): April 2016 Last patient first visit (LPFV): January 2020 Primary data collection: April 2016 – January 2021
Time schedule extended data collection	Extended data collection I: January 2021 – January 2022 Last patient last visit (LPLV): January 2022 Data base lock (DBL): January 2022 Final registry report: Within 6 months upon DBL Publication: September 2022 Potential extended data collection II: January 2022 – January 2023

Data analysis	- Summary of baseline data (demographic patient characteristics and clinical data)
	    - for continuous variables: mean values, standard deviation or median and interquartile range
	    - for nominal variables: absolute and relative frequency
	- ANOVA with repeated measures for eGFR
	- Survival analysis using Kaplan-Meier estimations
	- Cox-regression-analysis
	- Propensity score matching for event analyses

Financial Support:	Financial support is provided by Bayer AG

IV. TABLE OF CONTENT

V. List of Abbreviations

ANOVA	Analysis of variance
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
ASA	Acetylic salicylic acid
BARC	Bleeding Academic Research Consortium
CBAC	Central Blinded Adjudication Committee
CKD	Chronic kidney disease
CRNM	Clinically relevant non-major bleeding
DVT	Deep vein thrombosis
eCRF	Electronic Case Report Form
FA	Final analysis
FPFV	First patient first visit
FU	Follow up
GFR	Glomerular filtration rate
H	Hour
Hct	Hematocrit
HR	Hazard Ratio
ICF	Informed Consent Form
INR	International Normalized Ratio
ISTH	International Society of Thrombosis and Haemostasis
LMWH	Low-molecular weight heparin
LPFV	Last patient first visit
LPLV	Last patient last visit
MA	Main analysis
No.	Number
NOAC	Novel oral anticoagulants
OAC	Oral anticoagulation
NVAF	Non-valvular atrial fibrillation
PE	Pulmonary embolism
PIL	Patient Identification List
p. o.	Per os
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event

SC	Steering Committee
s.c.	Subcutaneous
SE	Systemic embolism
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient ischemic attack
TTR	Time in therapeutic range
UFH	Unfractionated heparin
UNK	Unknown value
VKA	Vitamin K-antagonist
vs.	Versus
VTE	Venous thromboembolism

VI. LIST OF FIGURES AND TABLES

1. RATIONALE AND BACKGROUND

1.1. Stroke prevention in patients with atrial fibrillation

Atrial fibrillation (AF) affects 1–2% of the general population and 10% of those aged over 75 years (Camm et al., 2012; Hobbs et al., 2015). Stroke risk is increased up to fivefold in patients with AF and AF causes an estimated 25% of all (Hobbs et al., 2015). Strokes in people with AF are more likely to be recurrent, more severe and disabling than in those without AF (Hobbs et al., 2015). Furthermore, mortality 1 year after stroke is nearly doubled in those with AF compared with those without AF (49.5% vs 27.1%); 17% of stroke-associated deaths are attributable to AF and stroke costs the EU an estimated €38 billion per year (Marini et al., 2005; Di Carlo et al., 2009). On the other hand, strokes associated with AF are largely preventable by the use of anticoagulation therapy (Hobbs et al., 2015). Thus, stroke prevention in patients with AF (SPAF) with anticoagulation therapies would reduce morbidity, mortality and economic burden on patients and healthcare systems.

1.2. Treatments used for stroke prevention in AF

The evidence for effective stroke prevention with drugs that inhibit platelets such as ASA in AF is weak (Camm et al., 2012) and associated with a relative risk reduction of about 22% (Hart et al., 2007). Nevertheless, platelet inhibitors exhibit a potential for harm as data indicate that the risk of major bleeding or intracranial haemorrhage (ICH) with ASA is, particularly in the elderly, not significantly different from that of oral anticoagulation (OAC) with vitamin K antagonists (VKA) (Camm et al., 2012). Treatment with VKA, however, leads to much greater benefit with an overall risk reduction of 64% (Hart et al., 2007). Consequently, OAC with VKAs such as warfarin represents the standard of care for SPAF in patients with increased risk for stroke (Camm et al., 2012; Hobbs et al., 2015). However, patients can have an unpredictable and highly variable response to VKAs due to their variable pharmacokinetic profile and potential for interactions with multiple other drugs and vitamin K present in food (Hobbs et al., 2015). This is particularly important in elderly patients, who are more likely to have AF and exhibit more co-morbidities than the general population resulting in complex treatment with multiple medications (Camm et al., 2012; Barnett et al., 2012). Patients treated with VKAs require regular and frequent routine coagulation monitoring (targeting an INR of 2–3) because undertreatment leaves the patient at risk of stroke, while INR levels above this target range increase the risk for bleeding events, including intracranial haemorrhages (Hobbs et al., 2015).

More recently, non-vitamin K oral anticoagulants (NOACs) that inhibit coagulation factors IIa (dabigatran) or Xa (rivaroxaban, apixaban and edoxaban) have been developed as an alternative to VKAs (Camm et al., 2012; Hobbs et al., 2015). NOACs are at least as effective as VKAs at preventing strokes in patients with AF, but have only few food and drug interactions, while routine coagulation monitoring is not required, making them a more convenient choice of therapy (Hobbs et al., 2015). Furthermore, clinical trials have shown that NOACs lead to significantly lower rates of intracranial and fatal bleeds than warfarin (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013).

Nevertheless, both VKAs and NOACs seem to be underused in clinical practice (Camm et al., 2012; January et al., 2014). One systematic review indicated that up to 80% of eligible patients were in fact not receiving OAC therapy for SPAF (Ogilvie et al., 2010). Reported barriers to OAC use include high cost, poor treatment adherence, clinicians' fear of causing bleeding in patients and the presence of co-morbidities (Hobbs et al., 2015; Sen et al., 2014).

1.3. Chronic kidney disease in patients with AF

One common comorbidity in 10-15% of patients with AF is chronic kidney disease (CKD) (Camm et al., 2012), which is in addition to previous staging (Table 1; National Kidney Foundation, 2002) currently defined as a decreased estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2 (Boriani et al., 2015). Previous studies indicated that CKD is common in the elderly, with up to one-third of people over the age of 70 years having moderate-to-end stage renal disease (Coresh et al., 2007). More recently, a population-based analysis of renal function in the elderly in Germany indicated that about 50% of patients 70 years or older exhibit an eGFR value of <60 mL/min per 1.73 m^2 (Schaeffner et al., 2012).

Stage	Description	eGFR (mL/min per 1.73 m^2)
1	Kidney damage with normal or elevated eGFR	≥90
2	Mild	60–89
3	Moderate	30–59
4	Severe	15–29
5	End stage disease, kidney failure	<15

TABLE 1: STAGES OF CHRONIC KIDNEY DISEASE (CKD) AS DEFINED BY THE NATIONAL KIDNEY FOUNDATION 2002

Patients with CKD per se have already an increased risk for cardiovascular events including stroke and also major bleeding events such as intracranial haemorrhage compared with the general population (Kaw et al., 2006). Patients with both AF and CKD are at even higher risk of stroke, bleeding events or mortality than patients with only one of these conditions (Reinecke et al., 2013). For example, in a study of over 100.000 patients with AF, those patients who also had non-end stage CKD were more likely to experience a stroke or systemic embolism than AF patients without CKD (hazard ratio (HR) 1.49; 95°% confidence interval [CI] 1.38 – 1.59; $p < 0.001$) and this risk increases in patients with end stage CKD (HR 1.83; 95 % CI 1.57 – 2.14; $p < 0.001$; Olesen et al., 2012). In addition, the risk for bleeding events was also significantly increased in patients with AF and non-end stage CKD compared to AF patients without CKD (HR 2.24; 95 % CI, 2.10 - 2.38; p < 0.001; Olesen et al., 2012).

It is thus well established that presence of CKD increases the risk of bleeding and scores one point in the HAS-BLED score for predicting major haemorrhages in patients with AF (Pisters et al., 2010). Taken together it is not surprising that further data documented a higher 1-year mortality rate in patients with AF and CKD stage 3 – 5 with 35.6% compared to 20.7% in patients with AF alone (Nelson et al., 2012). Furthermore, patients with AF are at a higher risk of developing incident CKD and vice versa, suggesting that AF and CKD are inter-dependent (Reinecke et al., 2013).

1.4. Oral anticoagulation in patients with AF and CKD

Treatment with OACs may not be straightforward in patients with AF and CKD given the higher bleeding risk in patients with CKD and due to changes in the pharmacokinetics of some OACs resulting from impaired renal excretion (Boriani et al., 2015). Renal elimination has, however, no clinically relevant influence on the pharmacokinetics of VKAs (Boriani et al., 2015). Nevertheless, in some countries, i.e. Germany, CKD is listed as a contraindication in the summary of product characteristics for the use of the VKA phenprocoumon (Summary of Product Characteristics – Marcumar, 2015). In contrast, all NOACs are eliminated to some extent by the kidney and monitoring renal function at the start of treatment and during follow up is recommended (Boriani et al., 2015; Heidbuchel et al., 2015). This is of clinical relevance, since NOAC plasma levels are higher in patients with moderate to severe renal impairment, which could lead to a higher rate of bleeding events compared to patients without renal impairment (Boriani et al., 2015; Heidbuchel et al., 2015; Hobbs et al., 2015). The factor Xa inhibitors including rivaroxaban that are currently approved for SPAF in Europe are approved for the treatment in patients with renal impairment including CKD stages 1-4 and are thus not recommended in patients with a creatinine clearance < 15 mL/min (Heidbuchel et al., 2015; Xarelto - Summary of Product Characteristics, 2015). In contrast to the factor Xa inhibitors, the direct thrombin inhibitor dabigatran is contraindicated in Europe in NVAF patients with severe renal impairment, i.e. creatinine clearance < 30 mL/min (Heidbuchel et al., 2015).

To account for the decreased renal elimination of rivaroxaban in renally impaired patients, treatment with the standard dose of 20 mg once daily in SPAF is reduced to 15 mg once daily based on pharmacokinetic modelling of drug exposure in patients with AF and renal impairment (Mueck et al., 2011). Consequently, a reduced dose of 15 mg once daily rivaroxaban has been specifically evaluated for patients with moderate renal impairment (CrCl 30-49 ml/min) within the pivotal ROCKET AF phase III trial comparing rivaroxaban with warfarin in patients with NVAF (Patel et al., 2011; Fox et al., 2011). The data in this subgroup of NVAF patients with moderate renal impairment indicated that despite the higher stroke and bleeding risk observed in these patients the use of the adjusted 15 mg once daily dose in ROCKET AF yielded results consistent with the overall trial in comparison with dose-adjusted warfarin (Fox et al., 2011). Thus, the primary endpoint of stroke or systemic embolism occurred in 2.32 %/year with rivaroxaban 15 mg/OD vs. 2.77 %/year with warfarin [HR 0.84; 95°% CI 0.57 – 1.23] in the per-protocol population. Rates of the principal safety endpoint (major and clinically relevant non-major bleeding: 17.82 vs. 18.28 %/year; p=0.76) and intracranial bleeding (0.71 vs. 0.88 %/year; p=0.54) were similar with rivaroxaban or warfarin. Of interest, however, fatal bleeding (0.28 vs. 0.74 %/year; p=0.047) occurred significantly less often with rivaroxaban.

Overall, clinical data with treatment outcomes of patients with AF and CKD under OAC are still scarce (Boriani et al., 2015). Studies on VKAs are conflicting and warfarin has been observed to increase the risk of stroke in patients with CKD and AF in some studies, and to reduce the risk of stroke in others (Boriani et al., 2015; Reinecke et al., 2013). Apixaban and rivaroxaban appear to reduce stroke risk in patients with AF and moderate renal impairment compared with warfarin; a similar risk reduction has not been demonstrated in patients taking dabigatran (Connolly et al., 2009; Eikelboom et al., 2012; Fox et al., 2011; Hohnloser et al., 2012).

1.5. Influence of VKA treatment on renal function in CKD patients

A potential of VKA to cause or worsen vascular calcification and renal dysfunction has been previously reported in the literature but has not been in the focus of further clinical research due to the lack of alternative drugs for OAC (Asinger and Shroff, 2015). Recently, increased knowledge on the function of extrahepatic vitamin K dependent proteins (VKDPs) provided a mechanistic link between undesired side effects of treatment with VKA in patients with CKD (Brecht et al., 2014). Thus, vascular calcification is one of the recently revealed detrimental effects of VKA in this condition. The discovery that VKDPs are involved in vascular calcification has fostered our mechanistic understanding of this process and has opened novel avenues for diagnosis and treatment (Willems et al., 2014). In a study of 133 patients receiving VKA therapy and 133 matched controls, those patients receiving VKAs developed more calcified coronary plaques than the control group; this increased rate of plaque formation following administration of VKA was also observed in a mouse model of atherosclerosis (Schurgers et al., 2012). Conversely, in the same mouse model, dabigatran and rivaroxaban seemed to inhibit atherosclerotic plaque formation (Preusch et al., 2015; Hara et al., 2015). In this regard a recent analysis from the RE-LY trial reported by Böhm et al. is of interest because it supported the concerns about the detrimental effects of VKA on renal function (Böhm et al., 2015). In this study the authors longitudinally assessed eGFR values among 16,490 NVAF patients assigned to therapy with dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, or adjusted-dose warfarin. After an average follow-up of 30 months, they observed a modest but statistically significant reduction in eGFR in the warfarin group compared with the dabigatran arms indicating a stronger decline in renal function in NVAF patients treated with VKA (Böhm et al., 2015). These results were detected in the overall patient cohort of the RE-LY trial in which overall 63 % of the patients with NVAF had an eGFR>60 mL/min per 1.73 m^2 with an observed mean eGFR of 66 mL/min per 1.73 m^2 at baseline. The difference in eGFR decline between the dabigatran and the VKA groups was apparent after a follow-up of 18 months (Böhm et al., 2015). The results are thus in agreement with previous reports of nephropathy described among patients receiving warfarin therapy and may be related to the detrimental effects of warfarin on renal vascular calcification mediated by the inhibition of VKDPs (Asinger and Shroff, 2015; Willems et al., 2014). Therefore, the important analysis by Böhm et al. highlighted the need for further research on the OAC strategies in NVAF patients with CKD to obtain more data on both the effectiveness and safety including the role of renal function decline in patients with CKD and AF. This notion is also supported by a recent position paper by the European Heart Rhythm Association indicating the need for observational studies and registries to assess occurrence of adverse outcomes and evolution of cardiac and renal functional status in this group of patients (Boriani et al., 2015). While the use of OAC and particularly NOACs in patients with moderate renal impairment (CrCl 30-49 ml/min) is supported by the recent phase III trials comparing NOACs with VKA (Ruff et al., 2014), the rationale for treatment of NVAF patients with more severe renal impairment, i.e. CrCl <30 ml/min), is scarce. In fact, clinicians are less likely to prescribe OAC therapies in this group of patients with CKD on the background of their high risk of bleeding during OAC therapy and the potential negative effects of VKA. Consequently, many patients with advanced CKD and AF may not receive any OAC therapy which may lead to poorer outcomes in this population due to stroke and other major cardiovascular events (Boriani et al., 2015; Reinecke et al., 2013).

2. RESEARCH METHODS

2.1. Design of the registry

This is a prospective registry allowing a structured, non-interventional collection of data. Participating physicians will not be subject to any instructions with regard to the diagnosis and therapy of their patients. All patient treatment is carried out within clinical routine, at the discretion of the physician and according to existing treatment guidelines.

This registry will be carried out as an investigator-initiated, multicentre, prospective, non-interventional and observational registry at 160 sites in Germany, Austria, Switzerland, France, Belgium and Luxembourg.

2.2. Research question

The overall objective of this this registry is to assess CKD progression and safety with regard to different anticoagulation strategies in NVAF patients with eGFR 15-49 mL/min per 1.73 m^2 in routine clinical practice.

The registry will collect clinical data of approximately 1600 patients with CKD (eGFR 15 -49 mL/min per 1.73 m^2) and NVAF receiving rivaroxaban, VKA, or no anticoagulation therapy, who are prospectively followed for a flexible duration with at least 24 months up to 6 years observation. The estimated average observation time per patient is at least 30 months, with the individual observation period for each patient to be continued as long as possible until the defined last visit of any patient in the registry.

During the conduct of the registry, it became apparent that the recruitment of patients was slower than originally planned. Therefore, the extension of the follow-up period seems appropriate. This accounts for slower recruitment and lower overall number of patients (approximately 1600) available for the primary analysis in the two main treatment arms of rivaroxaban and VKA treatment. With the resulting extension of the mean observation time, a more meaningful analysis of renal function loss can be performed in the prospective setting of the XARENO registry. At the same time, the expanded data collection in XARENO continues to support the prospective observation of additional clinical events such as stroke and bleeding in this vulnerable patient population with CKD and atrial fibrillation. The extended data collection is therefore planned for at least one additional year until January 2022 (extended data collection I). After the end of this observation period, an additional one-year extended data collection period until January 2023 may be performed, depending on the overall number of patients still available in the registry (extended data collection II).

2.3. Registry Schedule

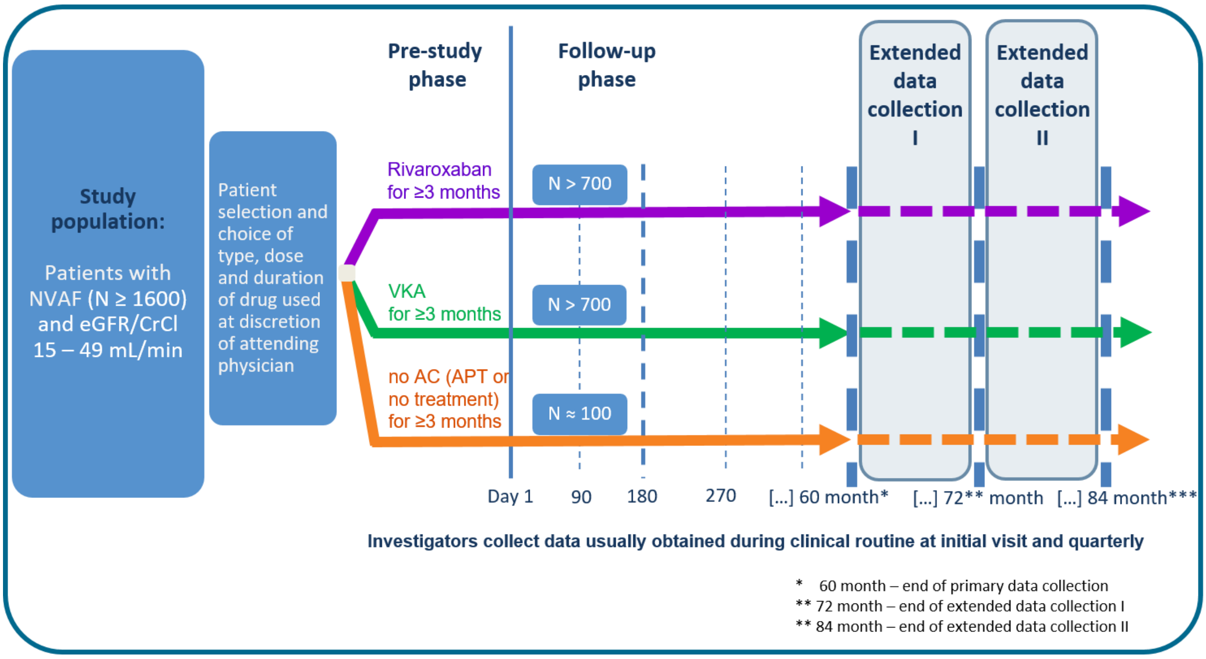


FIGURE 1: REGISTRY FLOW INCLUDING EXTENDED DATA COLLECTION

3. REGISTRY SETTING

3.1. Study population

The plan of the registry is to include at least 1600 patients with CKD and NVAF and rivaroxaban therapy or VKA therapy or no anticoagulation therapy.

The aim is to include at least 700 patients with rivaroxaban therapy and VKA therapy, respectively. Into the exploratory treatment arm of patients receiving no AC therapy about 100 patients will be included.

3.2. Time schedule / milestones of primary data collection

Milestone	Planned date
First patient first visit (FPFV):	April 2016
Last patient first visit (LPFV):	January 2020
Primary data collection:	April 2016 – January 2021

3.3. Time schedule of extended data collection

Milestone	Planned date
Extended data collection I:	January 2021 – January 2022
Last patient last visit (LPLV):	January 2022
Data base lock (DBL):	January 2022
Final registry report:	Within 6 months upon DBL
Publication:	September 2022
Potential extended data collection II:	January 2022 – January 2023

3.4. Objectives of the registry

The overall objective of the present XARENO registry is to gain further insight into the characteristics and management of patients with both NVAF and CKD, as treated in clinical practice. To this end the main objective of the registry is to evaluate CKD progression and safety outcomes in NVAF patients with eGFR 15-49 mL/min per 1.73 m^2 in relation to rivaroxaban and vitamin K antagonist (VKA) treatment as observed in routine clinical practice. A second objective is to collect data on progression of CKD and safety outcomes in NVAF patients with eGFR 15-49 mL/min per 1.73 m^2 and without AC therapy in routine clinical practice. Hence, currently the reasons for avoiding AC in patients with CKD are largely unknown and are probably attributable to the fact that patients with severe renal impairment were excluded from phase III trials (Borani et al., 2015; Heidbuchel et al., 2015) and the anticipated high bleeding risk in CKD patients in response to AC therapy (Friberg et al., 2015). Although, recent retrospective observational registry data obtained in patients with renal failure indicated a clear net-clinical benefit in renal failure patients treated with warfarin as compared to patients with no AC therapy (Friberg et al., 2015). Consequently, it appears important to collect data on patient characteristics as well as on thromboembolic and major bleeding events in patients with CKD and NVAF without AC therapy in this prospective registry.

3.5. Registry outcomes

3.5.1. Primary observational outcomes

- Progression of CKD
- decline in eGFR in mL/min per 1.73 m^2

- Safety
- major bleeding
- all-cause mortality
- TIA, stroke or systemic arterial embolism
- Other major cardiovascular events (MACE)
  - Myocardial infarction
  - Acute coronary syndrome/unstable angina
- symptomatic venous thromboembolic events
- net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality)

3.5.2. Secondary observational outcomes

- initiation of chronic renal replacement therapy
- eGFR < 15 mL/min per 1.73 m^2 (CKD Stage 5 Dialysis and Non-Dialysis)
- eGFR decline of ≥ 30%
- doubling of serum creatine concentration
- acute kidney injury (AKI) events defined as acute kidney injury associated with either hospitalization or emergency department visit, where AKI event is the lead diagnosis
- rates, causes and length of hospitalizations
- persistence with OAC therapy
- reasons for OAC therapy discontinuation

3.6. In- and Exclusion Criteria

3.6.1. Inclusion criteria

- male and female patients, age ≥ 18 years
- CKD with eGFR 15 – 49 mL/min per 1.73 m^2
- documented non-valvular atrial fibrillation (NVAF) with indication for anticoagulation therapy
- a treatment strategy for the ≥ 3 previous months before enrolment with either:
  - rivaroxaban (OAC cohort) **or**
  - VKA (OAC cohort) **or**
  - no anticoagulation (no AC cohort)

  received (if applicable) at the earliest in January 2012
- informed consent
- availability for follow up
- life expectancy of ≥ 6 months

3.6.2. Exclusion criteria

- exclusion criteria according to the local product information for the respective anticoagulation treatment
- planned chronic treatment with further anticoagulants
- expected renal-replacement therapy within the next 3 months

3.6.3. Eligible patients

Patients with documented NVAF and presence of CKD with eGFR values in the range of 15 - 49 mL/min per 1.73 m^2 are in the focus of the XARENO registry.

Prior to inclusion patients should be diagnosed with CKD with a duration of at least 3 months based on eGFR values below 60 mL/min per 1.73 m^2 or presence of markers indicating kidney damage (e.g. albuminuria) or both regardless of the underlying cause.

The therapeutic management of patients is subject to current treatment recommendations and is determined solely by the attending physician.

All patients are registered and recorded by Sponsor according the received therapy. A participation of patients in further studies is permitted.

3.6.4. Eligible sites

To ensure adequate patient numbers per site and high quality of data expert nephrology and cardiology centers or practices as well as hospitals managing patients with CKD and NVAF are eligible for participation. Approximately 200 sites across Germany, Austria, Switzerland, France, Belgium and Luxembourg are planned (with a possible increase to more sites, to achieve country representativeness). The number of patients per site is not limited.

All investigators have to be qualified physicians. Each physician must supply his or her curriculum vitae (updated) for the trial master file (TMF).

The sites must have a pool of suitable patients who can be recruited for the registry.

Also, physicians have to:

- have experience in scope of required indication and medicinal products
- know main features of the respective national drug laws as well as legal and scientific basics of non-interventional studies
- know the registry protocol
- have special experience in the use of NOAC

3.7. Examination program

3.7.1. Treatments to be given

Patients participating in the registry will receive OAC with either rivaroxaban or VKA or no AC therapy at the discretion of the attending physicians according to the local routine care.

Antiplatelet therapy (APT) with, e.g. ASA or Clopidogrel is not considered as AC and may be implemented in patients with OAC therapy at the discretion of the attending physicians. The non-interventional design of the XARENO registry will only record type and dosage of antithrombotic therapy at baseline and during follow-up without providing recommendations for treatment choice, switches or discontinuation of antithrombotic therapy.

To allow for meaningful comparisons between rivaroxaban and VKA, planned prospective treatment with apixaban, dabigatran, edoxaban or any non-approved experimental anticoagulant drug at baseline excludes patients from participation.

3.7.2. Examination and therapy schedule

Patient data will be collected as obtained in clinical practice at baseline and every three months in keeping with the recommendations for follow-up in patients with NVAF and CKD in clinical practice (Heidbuchel et al. 2015; Boriani et al. 2015).

3.7.2.1. Baseline data collection

Informed consent and documentation of baseline characteristics of eligible patients will be obtained by the attending physician and documented in the patient file at visit 1 (day 0). Furthermore, if obtained as part of routine medical care, all inclusion and exclusion criteria, related medical history, relating concomitant medication as well as all events of special interest and documentation of eGFR and CrCl assessment based on serum creatinine measurements will be documented at this visit (see Table 3). For patients receiving VKA, the INR if obtained as part of routine care, will be additionally documented.

3.7.2.2. Quarterly data collection up to month 84 (7 years)

Data for eGFR and CrCl (based on serum creatinine measurements), current anticoagulation therapy, concomitant medications, bleeding events, thromboembolic and cardiovascular events, and all further events of interest will be collected every three months where available and as obtained during routine medical practice. The individual duration for each patient depends on the date of inclusion and is flexible with a planned minimum follow-up duration of 12 months until study end is announced (planned minimum 360 days / planned maximum 84 months). The final data collection will be performed after the last patient reached 12 months of observation as available.

3.7.2.3. Changes in OAC treatment

If a patient changes treatment from Rivaroxaban to VKA or no AC cohort or vice versa, data on follow-up treatment (drug, dose, reason for change, therapy dates, start-/stop date) will be collected where available and the patient will remain in the registry and is further documented. In addition, data on temporary interruptions of rivaroxaban or VKA treatment will be collected where available.

If a patient switches from Rivaroxaban/VKA/no AC cohort to an excluded OAC, data on follow-up treatment will not be collected and the patient will perform an end of study visit. No further documentation is necessary (see also section 5.5).

3.8. Data Collection Procedures

Schedule	Initial visit	Quarterly	Final
Variables			
Informed consent	✓		
inclusion / exclusion criteria	✓		
demographic data	✓		
medical history	✓		
concomitant medication	✓	✓	✓
current anticoagulation		✓	✓
• bleeding complications		✓	✓
• cardiovascular complications		✓	✓
• events of special interest (hospitalisation, start of dialysis, death)	✓	✓	✓
• eGFR, CrCl assessment based on serum creatinine measurements	✓	✓	✓
• INR (for VKA arm)	✓	✓	✓*
• Adverse event documentation		✓	✓

TABLE 2: TABULAR OVERVIEW OF DATA COLLECTION PROCEDURES

* determination of TTR from collected INR values obtained in clinical practice

3.8.1. Data Sources - Information usually obtained during clinical routine and collected where available

3.8.1.1. General information

- Date of collection day (day, month, year)
- Date of informed consent

- Patient demographic data (depending on country regulations)
  - sex
  - date of birth (at least year)
  - race /ethnicity (Asian, Black, Caucasian)
- Vital signs and physical examination
  - weight
  - height at baseline
  - blood pressure
- Lifestyle
  - alcohol use
  - tobacco use
  - drug abuse
- Medical history and baseline findings including risk factors for stroke/non-CNS systemic embolism or bleeding, e.g.:
  - diagnosis of CKD, stage classification (eGFR), causes of CKD (CKD values (eGFR 15 - 49 mL/min per 1.73 m^2) should be available for at least three months (interval of measurements at least 4 weeks)).
  - bleeding diathesis (e.g. gastric ulcer)/history of prior bleedings
  - congestive heart failure
  - hypertension
  - diabetes mellitus
  - prior stroke/TIA/systemic embolism (including date)
  - vascular disease
  - anemia
  - abnormal kidney function
  - abnormal liver function
  - history of unstable INR
  - other individual risk factors
  - other cardiovascular and cerebrovascular disease history
  - other hepatobiliary disease
- Diagnosis of AF
  - date of AF diagnosis
  - type of AF diagnosis (ECG, signs and symptoms, other)
  - type of AF (first diagnosed, paroxysmal, persistent, long-standing persistent, permanent, silent, symptomatic no/yes)
- Laboratory tests (if done within routine practice)
  - serum creatinine concentration (last available value)
  - INR (if patient is/was on VKA) (last available value)
  - haemoglobin (last available value)
  - platelet count
- Oral anticoagulation treatment
  - Rivaroxaban or VKA (start/stop date, dosage)
  - if applicable: prior anticoagulation therapy (e.g. VKA, NOACs, start/stop date(s), dosage)
  - if applicable: reason for discontinuation of prior OAC therapy
- Antiplatelet drugs (start/stop date, dosage)

- Relevant concomitant medications
- AEs (including additional AE forms)

3.8.1.2. Additional data collection

Data - usually obtained at time of hospital discharge and collected where available

- Date of visit/report
- Date of admission and discharge
- Type of AF (first diagnosed, paroxysmal, persistent, long-standing persistent, permanent, silent, symptomatic no/yes)
- Laboratory tests
  - serum creatinine concentration (last available value)
  - INR (if patient is/was on VKA) (last available value)
  - haemoglobin (last available value)
  - platelet count
- Oral anticoagulation treatment
  - Rivaroxaban or VKA (start/stop date, dosage)
  - if applicable: prior anticoagulation therapy (e.g. VKA, NOACs, start/stop date(s), dosage)
  - if applicable: reason for discontinuation of prior OAC therapy
- Antiplatelet drugs (start/stop date, dosage)
- Relevant concomitant medications
- AEs (including additional AE forms)

3.8.2. Previous and concomitant medication

At baseline, information on all concomitant medications will be collected where available. Changes of anticoagulant therapy during the registry will also be collected where available.

In this non-interventional registry, avoidance of prohibited and restricted concomitant medication according to the label and SmPC is in the responsibility of attending physician.

3.8.3. Withdrawal of consent after start of registry

Participants can at any time with and without any statement withdraw from the informed consent. The reasons for patient withdrawal will be recorded in the eCRF and the sponsor has to be informed.

In cases of withdrawal of informed consent, patients are no longer followed, but documented data until withdrawal will be used in finally statistical analysis and publication of registry results.

3.8.4. Premature change or stop of treatment

If treatment with Rivaroxaban/VKA/no AC is being stopped or changed vice versa, patients will continue follow-up until end of the registry to allow collection of data of primary outcome variables.

3.8.5. Premature termination of the registry

The sponsor has the right to terminate the registry prematurely if there are any relevant medical or ethical concerns, or if completing the registry is no longer practicable. If such action is taken, the reasons for terminating the registry must be documented in detail.

The sponsor decides on whether to discontinue the registry in consultation with the steering committee.

4. REGISTRY VARIABLES

4.1. Primary outcome variables

- **Progression of CKD**
  - decline in eGFR in mL/min per 1.73 m^2

- **Safety**
  - major bleeding
  - all-cause mortality
  - TIA, stroke or systemic arterial embolism
  - Other major cardiovascular events (MACE)
    - Myocardial infarction
    - Acute coronary syndrome/unstable angina
  - symptomatic venous thromboembolic events
  - net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality)

4.2. Secondary outcome variables

- initiation of chronic renal replacement therapy
- eGFR < 15 mL/min per 1.73 m^2 (CKD Stage 5 Dialysis and Non-Dialysis)
- eGFR decline of ≥ 30%
- doubling of serum creatine concentration
- acute kidney injury (AKI) events defined as acute kidney injury associated with either hospitalization or emergency department visit, where AKI event is the lead diagnosis
- rates, causes and length of hospitalizations
- persistence with OAC therapy
- reasons for OAC therapy discontinuation

4.3. Adjudication of outcome events

All suspected outcome events will be adjudicated by a central blinded adjudication committee (CBAC).

Event adjudication will be based on all available blinded source data and will be classified into:

- stroke, TIA or systemic embolism
- ACS or myocardial infarction
- Symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE)
- cardiovascular death
- bleeding outcomes will be classified according to ISTH (major bleeding, clinically relevant non-major bleeding, minor bleeding) (Schulman et al., 2005) and according to BARC (BARC type 0 to 5) (Mehran et al, 2011)
- bleeding leading to hospitalization will be additionally assessed

All deaths will be adjudicated by CBAC based on all available blinded source data and classified into:

- cardiovascular death with or without relation to OAC therapy
- fatal bleeding with or without relation to OAC therapy
- any other death

For subjects who switch between OAC therapies or discontinue OAC permanently, the reason for this decision will be collected where available.

5. STATISTICAL METHODS AND SAMPLE SIZE CALCULATION

5.1. Overall rationale for statistical analysis

A direct comparison between groups will be performed only between the OAC therapy groups (rivaroxaban vs. VKA). The statistical analysis and sample size calculation described below applies primarily to these two groups. The aim in the group of patients without AC is to collect data on patient characteristics and to describe the natural course of these patients with CKD and NVAF for the same outcome variables analysed in the two OAC groups.

5.2. Sample size for comparison between OAC groups

The sample size calculation for progression of CKD is based on the mean difference in decline of eGFR rate after 12 months between rivaroxaban and VKA. A difference of at least 1 ml/min after 12 months would be considered a clinically meaningful difference. Data from the RE-LY study comparing treatment with dabigatran and VKA for stroke prevention in NVAF patients implied that a standard deviation of up to 10 ml/min can be assumed

(Böhm et al., 2015). With this information, the total number of patients for a two-sample two-sided t-test of mean differences (expected mean difference of 1.0 ml/min and 1.2 ml/min and an estimated standard deviation of 8 ml/min and 10 ml/min) for a given type I error of α=0.05 is calculated below:

Mean Difference (ml/min)	Std. Dev. (ml/min)	N Total
1.0	10	3142
1.0	8	2012
1.2	10	2184
1.2	8	1398

For an expected mean difference of at least 1 ml/min and a standard deviation below 10 ml/min, a sample size of 1000 patients per treatment arm (i.e. 2000 patients overall) should result in a power of around 80 %. In the worst case of minimal mean difference and maximal standard deviation, the power decreases to 61% and in the best case of maximal mean difference and minimal standard deviation, the power increases to 92 % as shown below in table. With this amendment, the number of rivaroxaban and VKA patients is reduced from 2000 to 1500 patients. The updated power calculations regarding the eGFR are presented in the table below in column "Power with 1500 patients". The power with 1500 patients is about 10 % smaller compared to the power with 2000 patients.

Mean Difference (ml/min)	Std. Dev. (ml/min)	Power with 2000 patients	Power with 1500 patients
1.0	10	0.608	0.490
1.0	8	0.798	0.677
1.2	10	0.765	0.641
1.2	8	0.918	0.827

Assumptions about the eGFR mean differences and standard deviations were based on an earlier publication and included some uncertainty (Böhm et al., 2015). The following table contains some combination of mean differences and SD between treatment groups for eGFR resulting approximately in 80 % power.

Mean Difference (ml/min)	Std. Dev. (ml/min)	Power with 1500 patients
1.2	8	0.827
1.3	9	0.798
1.5	10	0.827

For event variables (e.g. all-cause mortality, MACE and major bleeding) the expected annual event rates depend on baseline risk and event rates between 2 % to 5 % are presumed based on previous studies in NVAF patients (Camm et al., 2015). Due to the reduced number of patients from 2000 to 1500, about 15 to 38 events per treatment arm per year can be expected. On the other side, more events are possible by the prolongation of the study observation period up to 5 years.

Sample size and power calculation were done using SAS 9.4, proc power (SAS Institute, Cary, NC, USA).

5.3. Statistical and analytical plan

Statistical analyses will be descriptive and exploratory only. For continuous parameters summary statistics (Number of observations, mean, standard deviation, minimum, 25 % percentile, median, 75 % percentile, maximum and the interquartile range) will be presented. For categorical variables absolute and relative frequencies will be presented.

All tables will be generated by treatment (Rivaroxaban, VKA or no AC) and total. To get an idea if potentially observed differences in treatment could be of relevance, 95 % confidence intervals of the treatment differences between Rivaroxaban and VKA will be calculated. No interim analysis is planned.

A descriptive analysis of baseline characteristics after LPFV is planned.

In addition to the main analysis (MA) using the data until the end of primary data collection at 12 months, a similar analysis will be performed using all data until the end of the extended data collection (final analysis [FA]). Full details of the statistical analysis methods to be used will be described in the Statistical Analysis Plan (SAP).

All statistical analyses will be carried out using the software package SAS release 9.4 (SAS Institute, Cary, NC, USA) or higher.

5.4. Data analysis sets

The intention to treat (ITT) principle as per ICH E9 should be followed as closely as possible. This means that all subjects included in the registry should be analyzed. Deviations from this principle may occur depending on specific requirements for analysis of the various endpoints and will be explained in the respective section below.

5.5. Patients switching anticoagulation-treatment during the observational period

Depending on the endpoint analyzed subjects who switch their treatment during the observational period may be considered only for the time under their initial treatment. For analyses in which multiple treatments per patients are considered the following rules apply:

- duration under initial treatment = Date of enrollment until date of first dose of subsequent treatment

- duration under subsequent treatment = Date of first dose + 90 days until next subsequent treatment or last recorded treatment in the study
- the period of the first 90 days under a subsequent treatment will not be considered for analysis as this period is needed to stabilize the new treatment

These rules will also apply if patients switch treatment more than once during the observational period. If patients switch to an excluded OAC and drop out of the study, treatment stops with the date of the intake of the first dose of the excluded OAC. An end of study visit will be performed at this point of time.

No anticoagulation-treatment is considered a treatment in this context, so these rules also apply to patients who start or stop anticoagulation-treatment during the observational period.

5.6. Analysis of outcome variables

5.6.1. Primary outcome variables

5.6.1.1. Estimated glomerular filtration rate (eGFR)

Primary timepoint for analysis of eGFR is the change from 12 months visit to baseline. It will be analyzed in subjects who have a non-missing baseline eGFR measurement and a non-missing post baseline value at 12 months. Further analysis of eGFR after more than 12 months will be conducted with the data of patients available at those visits.

The eGFR data will be analyzed using an ANOVA with repeated measurements and difference to baseline of eGFR as dependent variable, and treatment (rivaroxaban versus VKA) as a fix factor. For this analysis patients who will switch their treatment during the observational period will only be considered for the time under their initial treatment. Country may be added as cofactor into the model, if corresponding categories are not too small. The final decision on the cofactors used in the model will be made during the final review meeting.

Additionally, for each patient with a baseline value and at least one post baseline value, the available data for eGFR will be modelled in a linear model to obtain an estimated rate of decrease (slope) in eGFR over time for that patient. The estimated decline in eGFR for each patient is then summarized using summary statistics as described above. For this analysis patients who switch their treatment during the observational period will be considered only for the time under their initial treatment. However, for sensitivity analysis this analysis will be repeated with patients who switched their treatment using all available treatment information.

5.6.1.2. Primary safety variables

The primary safety outcome variables will be analyzed in ITT analysis set under initial treatment. Patients that switched treatment will be censored after the interval of their initial treatment.

These variables will be analyzed using survival analysis and Kaplan Meier estimation of time to first event by treatment (rivaroxaban versus VKA).

5.6.2. Event outcome analyses

All outcome events will be included into analyses that occurred throughout the primary data collection period and the extended data collection period, including those occurring at any time after interruption or discontinuation of OAC treatment.

Start day of event analyses is day 1, i.e. inclusion date into the registry for all patients. Censoring date is the minimum of death date or the last contact date and for the rivaroxaban and VKA groups, the stop of OAC treatment date + 2 days. The proportion of events and number of subjects at risk (crude incidences) as well as the 95 % confidence intervals (CIs) of these proportions will be calculated according to the Clopper–Pearson method.

Outcome event rates will also be calculated using Kaplan–Meier time-to-first-event analysis, with data presented as events per 100 patient-years and their 95 % CIs, using the following formula:

- Event rate = number of events / total time under risk (defined as the sum of all days from inclusion in the registry until the day of the first event divided by 100 × 365 days and 100 patient-years as its unit).

Corresponding CIs will be calculated using the Poisson distribution. As a sensitivity analysis of all time-to-first-event analyses, analysis of multiple events will be performed using the counting process approach as extension of the cox model where applicable (Thernau et al., 2000). The counting process model of Andersen-Gill and the conditional model will be used for this analysis. Results of the multiple event analysis will be compared with the results of the time-to-first-event analysis.

5.7. Limitation of study results

All results from statistical tests are exploratory in nature only. No confirmatory conclusions can be drawn from any result.

In a non-randomized registry, differences between treatment groups at baseline may be present.

In this registry, especially, different stages of renal impaired patients may be treated with the same treatment depending on physician/site or country. Other potential factors for confounding might be age, pre-medication and co-morbidities at baseline.

The reduction in power because of the reduced sample size is an additional limitation of the study. In total, N=1537 subjects with informed consent date until end of October 2019 were enrolled into the study (Rivaroxaban: N=759 subjects, VKA: N=687, No anticoagulation: N=91).

If treatment groups should differ at baseline for eGFR the individual slopes of decrease in GFR will be analyzed for differences between the treatment groups.

In case of event analysis, the propensity score matching will be used to reduce bias and minimize the impact of confounding in case of event analysis.

6. DATA MANAGEMENT

The IT infrastructure and data management staff will be supplied by the sponsor. The database will be developed and validated prior to data entry based on standard operating procedures at the sponsor. The data management system is based on commercial trial software (Macro 4.0) and stores the data in a database, storing all changes in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The database is integrated into a general IT infrastructure and safety concept with a firewall and backup system. A regularly backup of all trial data will be performed by InferMed (London). After completion and cleaning of data, the database will be locked, and the data will be exported for statistical analysis.

Sites will enter data online via Internet. Plausibility checks are run during data entry, thereby detecting discrepancies immediately. The Data Management will conduct further checks for completeness and plausibility and will clarify any questions with the sites electronically via trial software. Discrepancies and implausible values will be clarified in writing between the data manager and the site. These electronic queries have to be answered by the sites without unreasonable delay.

6.1. Documentation of records

All data relevant to the registry are immediately documented by the site in the electronic case report form (eCRF) supplied.

6.2. Data collection and documentation

All data collected should be promptly recorded and documented in the eCRF.

The following electronic Case Report Forms should be documented:

- patient registration
- documentation of baseline characteristics (see 3.8.1.1)
- documentation of each course of therapy
- documentation of therapy switch
- documentation of adverse events
- periodic follow-up of patients

For suspected or confirmed outcome events all relevant documents need to be collected by registry personnel using copies of the informed consent.

Event adjudication dossiers need to be prepared and all suspected or confirmed outcome events need to be adjudicated by the central independent adjudication committee (CBAC), using standardized adjudication forms. The finalisation of each event adjudication as well as adjudication result will be documented in an independent registry outcome event database.

7. DATA MONITORING AND QUALITY CONTROL

7.1. Monitoring

The sites will be risk-based monitored to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the subject´s safety and rights as a registry participant are respected, that accurate, valid and complete data are collected, and that the registry is conducted in accordance with the protocol.

The risk-based monitoring of participating sites will be done by central remote monitoring and by data analysis to identify significant data trends (defined data areas, consistency checks and checks of data completeness). Furthermore, data distributions are tested within and between centers. Based on the data analysis the frequency and extend of onsite-monitoring will be planned and carried out.

During onsite monitoring the monitor will verify informed consent documentation and perform source data verification against the subjects’ medical records.

A monitoring visit report will be prepared for each on-site visit describing the progress of the registry and any problems (e.g. refusal to give access to documentation). The monitor has the responsibility to treat all information confidentially and to safeguard the integrity and personal privacy of the participants.

All physicians agree that the monitor will visit pre-selected sites and assure that the monitor will receive appropriate support in their activities at the site, as agreed in separate contracts with each site. The declaration of informed consent includes a statement to the effect that the monitor has the right – while observing the provisions of data protection legislation – to compare the case report forms (eCRFs) with the trial subject’s medical records (physicians notes, laboratory printouts etc.). The physician will secure access for the monitor to all necessary documentation for trial-related monitoring. The aims of the monitoring visits are as follows:

- to check the declarations of informed consent
- to monitor subject´s safety (occurrence and documentation/reporting of AEs and SAEs)
- to check the completeness and accuracy of entries on the eCRFs
- to validate the entries on the eCRFs against those in the source documents (source data verification)
- to evaluate the progress of the registry
- to evaluate compliance with the registry protocol
- to discuss with the physician’s aspects of registry and any deficiencies found

7.2. Audits/Inspections

As part of quality assurance, the sponsor has the right to audit the registry site. The aim of an audit is to verify the validity, accuracy and completeness of data, to establish the credibility of the registry, and to check whether the subject's rights and safety are being maintained. The sponsor may assign these activities to persons otherwise not involved in the registry (auditors). These persons are allowed access to all documentation (especially the protocol, case report forms, trial subjects' medical records, and registry-related correspondence).

The sponsor and all registry site personnel involved will support audits and inspections by the competent authorities at all times and allow access to the necessary original documentation.

All persons conducting audits will keep all subject data and other data confidential.

7.3. Registry file

All registry documents will be provided in English, if not stated otherwise. Each physician will receive a registry file that contains all documents required for the registry:

- registry agreement between sponsor and the physician
- observational plan including synopsis (English, summary in local language)
- Patient Identification List (not to be used outside the site)
- approval letter / notification acknowledgement for registry from the IEC that is applicable for the respective site
- informed consent forms
- sample print-out of the eCRF
- other registry materials

The investigator records the participation of a person at the Patient Identification List (PIL). This list is meant to identify participating persons at a later point of time. The identification list will be a part of the registry folder. The PIL remains in the study site after the observational registry is finished. In addition, participation in the observational registry has to be recorded in the patient's chart (including: patient number, start and end of participation in the observational registry).

During monitoring, the registry folder will be checked for completeness and actuality. After the observational registry is finished or stopped, the registry file has to be stored 15 years.

8. SAFETY – MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

8.1. Definitions of (serious) adverse events, adverse drug reactions and suspected unexpected serious adverse reactions

8.1.1. Adverse event (AE) and Adverse drug reaction (ADR)

An adverse event (AE) is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written IC for participation in the registry. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product (IP).

If laboratory findings reveal abnormal values, if clinically significant, they should be documented as an AE. This is up to the physician's discretion and should be documented in the source documentation.

In the following differentiation between medical history and AEs, the term "condition" may include a diagnosis, abnormal physical examination findings, symptoms, laboratory, or ECG findings.

- Conditions that started before signing of IC and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of IC and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of IC will be documented as adverse events. This includes intercurrent illnesses.

An adverse drug reaction (ADR) is any noxious and unintended response to an investigational medicinal product (IP) related to any dose with at least a reasonably possible causal relationship with the IP.

8.1.2. Serious Adverse Events (SAE) and Serious Adverse Reactions (SADR)

A serious adverse event (SAE) or serious ADR (SADR) is any untoward medical occurrence that at any dose:

1. results in death
2. is life-threatening at the time of the event
3. requires inpatient hospitalization or prolongation of existing hospitalization
4. results in persistent or significant disability/incapacity
5. is a congenital anomaly or birth defect
6. is another serious or important medical event as judged by the investigator

Inpatient hospitalization is defined as any stay in hospital on the part of a trial subject that includes at least one night (midnight to 06:00 am). Admission to hospital as an inpatient planned before the first administration of the medication are not SAEs but must be documented in the proper manner in the trial subject's medical records and eCRF.

If an AE is classified as an SAE, this is documented on a separate SAE sheet in addition to the standard AE documentation.

8.1.3. Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an adverse event the nature or severity of which is not consistent with the product information available for the medication, is regarded as serious, and has at least a possible causal relationship with the medication.

8.2. Reporting of SUSARs

8.2.1. Notification of ethics committee and competent supreme federal authority

Sponsor and physician at all registry sites are responsible for all pharmacovigilance obligations and safety reporting pursuant to the applicable laws and regulations in the country/countries where the study is performed.

For instance, every fatal or life-threatening SUSAR that becomes known in the registry will be reported by the sponsor or PI to the competent supreme federal authority and the ethics committee.

<u>Fatal and life-threatening SUSARs</u>

The competent authority and the ethics committee responsible must be informed by the sponsor of all fatal or life-threatening SUSARs. This must be done without delay, at the latest 7 calendar days after becoming aware of the minimum criteria for reporting. In all cases, attempts must be made to obtain further relevant information which must be supplied to the competent supreme federal authority and the ethics committee within a further 8 days. Furthermore, if a trial subject dies, this information must be passed on to the ethics committee responsible for the region in which the death occurred.

If the information at the time of reporting is incomplete, further information to enable adequate assessment of the case will be requested from the reporter or other available sources.

8.2.2. Informing the physicians

The sponsor will inform physicians of all SUSARs arising from the study including all relevant further information within the periods set by the competent authority.

If new information becomes known that is different from the scientific information given to the physician, all physicians will be informed of this by the sponsor.

8.2.3. Informing the marketing authorisation holder

The sponsor or PI will also inform the marketing authorization holder about all SUSARs including information reported to the competent supreme authority and ethics committee in accordance with contractual agreements.

8.3. Rules for AE and SAE Reporting

- All effectiveness outcome events as mentioned in section 4.1 except death of any cause will be exempted from expedited SAE reporting, but will be documented in the eCRF using the respective outcome event documentation eForm.
- All bleeding events as mentioned in section 4.1 regardless severity and outcome are safety outcomes and will be exempted from SAE reporting, but will be documented in the eCRF using the respective outcome event documentation eForm.
- All hospitalizations have to be documented into the eCRF using the outcome hospitalization eForm. These events have to be evaluated whether being an endpoint (outcome event documentation eCRF, exempted from expedited SAE reporting) or a reportable SAE.
- Hospitalizations, which were planned before inclusion in the registry (e.g. elective or scheduled surgery arranged prior to the start of the study), will not be regarded as AEs. This pertains also to hospitalizations which are ambulant (< 12 hours) or are part of the normal treatment or monitoring of the studied disease and which are not due to a worsening of the disease.
- All other events that fulfill the seriousness criteria have to be recorded on the AE page of the eCRF and have to be reported within 24 hours of the physician's awareness using the provided SAE form.
- Death of any cause has always to be documented as SAE
- All pregnancies in female study subjects or in female partner of a male study subject as well as endpoints of the pregnancies have to be reported within 24 hours of the physician's awareness. For pregnancy reports, the Pregnancy Monitoring Forms are to be used.
- All non-serious AEs will be documented in eCRF but do not require further reporting.
- Of the AEs reported, reportable events (i.e. SUSARs) have to be reported to the competent authorities and to the Independent IECs/IRBs according to legal requirements.

A schematic overview on AE, SAE and outcome reporting is given in figure 2.

The physician must report immediately (within 24 hours of the physician's awareness) to the sponsor all SAEs described above as requiring expedited reporting.

The physician is responsible for continuous monitoring of all SAE reports (whether or not related to study drug) until resolution or until the event is considered chronic and/or stable by the physician and/or other physician who has the responsibility for the subject's medical care. Follow-up SAE reports will be reported according to the same timelines as initial reports, as soon as new significant information becomes available.

Effectiveness and safety outcome events will be reviewed and adjudicated. Safety events (bleedings) are expected events and as such would not generate SUSARs (see SmPC Rivaroxaban).

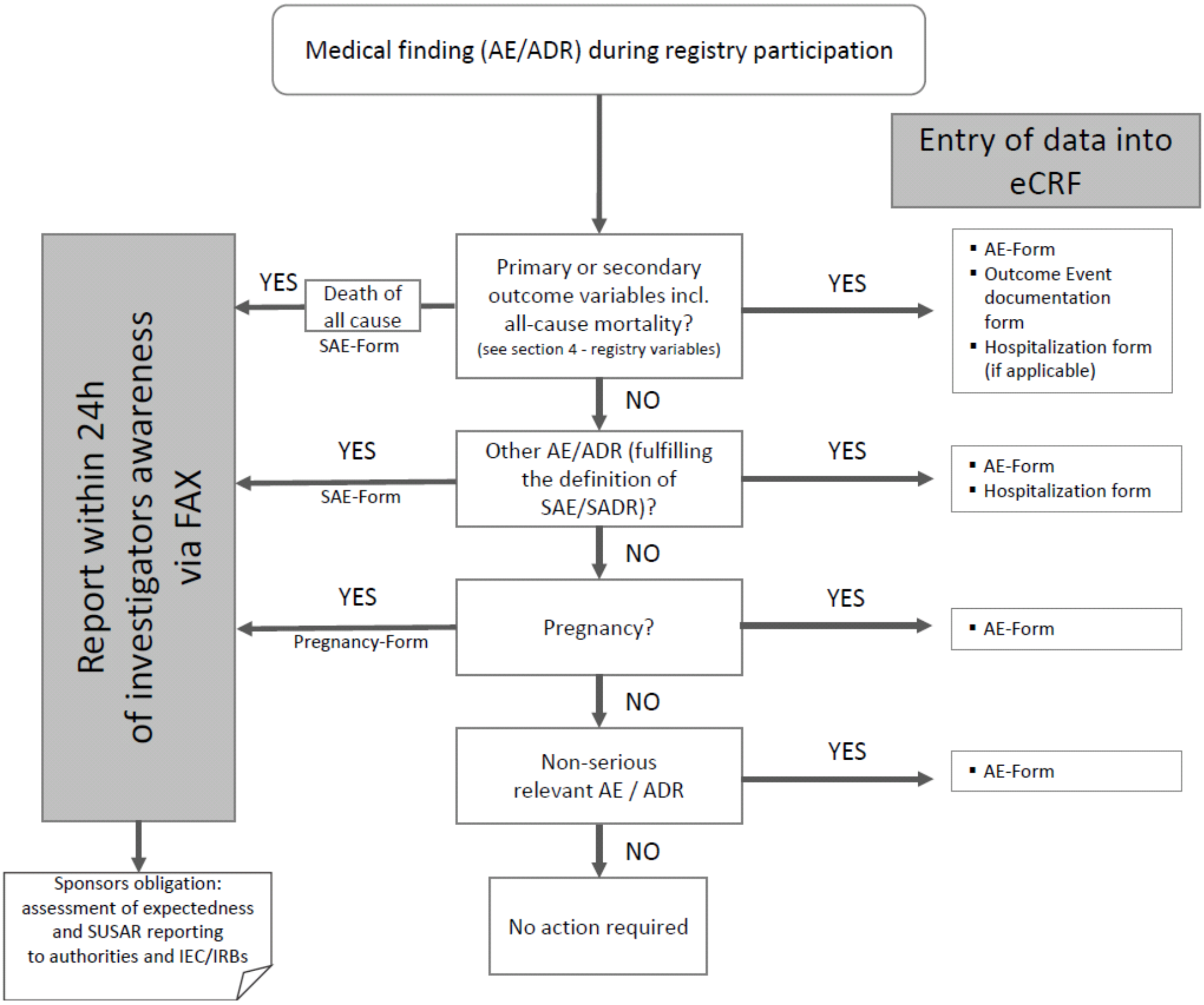


FIGURE 2: REPORTING OF OUTCOME AND (S)AE / (S)ADR

9. PROTECTION OF HUMAN SUBJECTS AND ORGANISATIONAL ASPECTS OF THE REGISTRY

9.1. Patient information and informed consent

All subjects will be informed about the aims of the registry, the informed consent form (ICF) will be provided in the local national language. The ICF and any revision(s) will be presented to the responsible to the ethics committee for consultation. It is the responsibility of the physician in the registry site to obtain a voluntary informed consent from the patient for participation in the registry before any data of a patient will be entered in the eCRF. The informed consent will be given by the patient only after having received an adequate explanation of the objectives and methods of the registry and having a sufficient time for decision. Before signing the ICF, the patient should have the opportunity to ask questions and receive satisfactory answers. All informed consent forms must be signed and personally dated by the patient or by the patient’s legal representative. The patient’s informed consent will be documented in the patient’s medical records.

The sponsor affirms the subject’s right to protection against invasion of privacy. In compliance with the Law of Data Protection, the physician permits representatives’ regulatory authorities to review and/or copy any medical records relevant to the registry in accordance with local laws.

9.2. Data protection

The provisions of data protection legislation will be observed. It is assured by the sponsor that all investigational materials and data will be pseudonymized in accordance with data protection legislation before scientific processing.

Subjects will be informed that their pseudonymized data will be passed on in accordance with provisions for documentation and notification pursuant applicant regulations to the recipients described there. Patients who do not agree that the information may be passed on in this way will not be enrolled into the registry.

9.3. Responsibility of participating physicians

The physician will comply with the confidentiality policy as described in the registry / site-agreement. The physician will comply with the observational plan (which has been notified or approved (if applicable) by the IEC). The physician is responsible for the conduct of all aspects of the observational registry at the registry site and verifies by signature the integrity of all data transmitted to the sponsor respectively the sponsor´s representative.

9.4. Case fee payment

According to the time spent to consent subjects and to document patients’ data, the physician´s registry personnel efforts will be compensated. This payment also includes the honorarium for responding to queries and for monitoring if applicable.

9.5. Ethical and regulatory aspects

The present observational protocol of the registry was developed in accordance with the Declaration of Helsinki in the version of October 2008 (59th General Assembly of the World Medical Association, Seoul, Republic of Korea). This will also apply to any potential future amendments.

For each site, the registry will not be started before consultation of the competent local ethics committee. The observational plan and patient information/ consent forms will be submitted (resubmitted) to the responsible independent ethic committees (IEC) for an evaluation of the submitted documents.

Before the start of the registry, all necessary documentation will be announced to the competent supreme federal authority for notification.

The registry will be listed in the ClinicalTrials.gov database.

9.6. Documentation and archiving

The sponsor is responsible for archiving of the registry documentation. Archived data may be held on electronic record, provided that a backup exists and that hard copies can be obtained, if required.

The physician must ensure that the records and documents pertaining to the conduct of the observational registry and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; documents regarding subject treatment and registry original signed informed consents, etc.]) will be retained by the physician for as long as needed (for at least 15 years or according to local legislation) to comply with national and international regulations. The coordinating physician agrees to adhere to the document/records retention procedures by signing the protocol.

Before the final destruction of the archived registry documents the consent of the sponsor must be obtained.

There is no further obligation for archiving by the participating sites.

9.7. Insurance and liability

As there is no relevant risk due to disease registry (a non-interventional registry) for participating patients, no special insurance is necessary.

9.8. Reports and publications

Statistical analysis and a final statistical report will be carried out by the responsible statistician as soon as possible after completion of the registry.

The sponsor, the financing partners and participating physicians will be informed regarding the progress and status of the XARENO registry by a periodic status report that contains a section on project management (recruitment status, information on legal, technical, administrative issues) and tabular listings of data.

Ethics committee will be informed within 90 days that the non-interventional registry has officially ended.

Within one year of the completion of the registry, the ethics committee will be supplied with a summary of the final report on the non-interventional registry containing the principle results.

Therefore, a final report that summarizes the tables of the analysis and explanatory text will be written. After approval of members of the Steering Committee and the sponsor, a final version will be generated that may be used for regulatory purposes, but also as basis for the publications of the registry.

For all publications data protection for the personal data of the patients as well as of the participating physicians will be maintained.

The Medical coordinator of the registry is responsible for coordination of scientific publications in consultation with the sponsor.

It is planned to publish the results, in mutual agreement with the physicians, in a scientific journal and at international congresses. Publication of the results of the registry as a whole is intended. Any publication will take account of the 'Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors' (ICMJE).

The registry will also be registered in a public register (www.clinicaltrials.gov) in accordance with the recommendations of the ICMJE.

Any published data will observe data protection legislation covering the subject and physicians. Success rates or individual findings at individual trial sites are known only to the sponsor.

9.9. Financing

The financial support will be provided by a research grant by Bayer AG.

10. AMENDMENTS AND UPDATES

10.1. Changes to registry protocol

To ensure that comparable conditions are achieved as far as possible at individual sites and in the interests of a consistent and valid data analysis, changes to the provisions of this registry protocol are not planned. In exceptional cases, however, changes may be made to the trial protocol. Such changes can only be made if agreed by the sponsor, sponsor's representative, the Medical Coordinator and biometrician, and all authors of this registry protocol. Any changes to the procedures must be made in writing and must be documented with reasons and signed by all authors of the original registry protocol.

10.2. Changes from protocol version 1.1 to version 1.6 (Adaptation #1)

Adaptation 1 is dated 24 MAY 2017

10.2.1. Modification 1: Participating countries

Due to slower than expected recruitment, France, Belgium and Luxembourg were added as 3 additional participating countries with additional approximately 100 sites. The number of planned participating sites was therefore extended to 200 sites in 6 countries.

Section affected by this modification:

Section I Responsible parties

Section I Registry design

Section 2 Research Methods

Section 3 Registry Setting

10.2.2. Modification 2: Clarifications

Due to frequently asked questions from the study sites, text passages in various sections were adapted. This included a specification of one of these outcome events (i.e. MACE). In the course of this specification some of the primary observational outcome events formerly classified as safety outcomes were classified as effectiveness outcomes. Additionally one primary observational outcome event was now classified as secondary observational outcome event. Furthermore, the description of eligible patients, the procedure for changes in OAC treatment, premature change or stop of the treatment, and premature termination of the registry was specified. Also the rules for Adverse Event and Serious Adverse Event reporting were clarified and extended. Finally a schematic overview of AE, SAE and outcome event reporting was added.

Section affected by this modification:

Section III Synopsis

Section 3 Registry Setting

Section 4 Registry variables

Section 5 Statistical methods and sample size calculation

Section 8 Safety – Management and reporting of adverse events / adverse reactions

10.2.3. Modification 3: Time schedule:

Since site selection and recruitment was slower than anticipated the time schedule was adjusted.

Section affected by this modification:

Section III Synopsis

Section 3 Registry Setting

10.2.4. Modification 4: Minor editorial/consistency/administrative changes

Section affected by this modification:

Title page: protocol version

Footer: protocol version

Section I Responsible parties: name of responsible person of registry coordination

Section III Synopsis: changed title of financier

Section IV table of content: updated

Section VI List of figures and tables: added

Section 3 Registry Setting: numbering updated

Section 6 Data Management: wording

Section 7 Data monitoring and quality control: time of document archiving

Section 8 Safety – Management and reporting of adverse events / adverse reactions: abbreviations added

Section 9 Protection of human subjects and organizational aspects of the registry: time of document archiving and title of financier

10.2.5. Changes to the protocol text

Section number and title	Previous Text (V1.1)	New Text (V1.6)	Modifi-cation
Title page	Version: ~~V.1.1 25.02.2016~~	Version: V1.6 24.05.2017	4
Footer	Registry protocol_ ~~V1.1 25.02.2016~~	Registry protocol_ V1.6 24.05.2017	4
I. Responsible Parties – Writing Committee (Steering Committee)		Prof. Gilbert Deray Hôpital de la Pitié-Salpêtrière, Paris	1
I. Responsible Parties – Registry coordination	Dr. Katja ~~Reichardt~~ … E-Mail: ~~katja.reichardt@gwtonline.de~~	Dr. Katja Jersemann … E-Mail: katja.jersemann@gwtonline.de	4
III. Synopsis – Registry design	Multicentre, prospective, non-interventional and observational registry taking place in Germany, Austria ~~and~~ Switzerland.	Multicentre, prospective, non-interventional and observational registry taking place in Germany, Austria, Switzerland, France, Belgium and Luxembourg.	1
III. Synopsis – Primary observational outcomes	~~1. Progression of CKD:~~ ~~- decline in eGFR~~ ~~2. Safety:~~ ~~- major bleeding~~ ~~- all-cause mortality~~ ~~- TIA, stroke or systemic arterial embolism~~ ~~- major cardiovascular events (MACE)~~	1. Effectiveness: - Progression of CKD (decline in eGFR in mL/min per 1.73 m^2) - all-cause mortality - TIA, stroke or systemic arterial embolism - Other major cardiovascular events (MACE)	2

	- ~~symptomatic venous thromboembolic events~~ - ~~net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality)~~	○ Myocardial infarction ○ Acute coronary syndrome/unstable angina - symptomatic venous thromboembolic events 2. Safety: - major bleeding	
III. Synopsis – Secondary observational outcomes		- net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality)	2
III. Synopsis – Inclusion criteria/ exclusion criteria	- non-valvular atrial fibrillation (NVAF) with indication for anticoagulation therapy	- documented non-valvular atrial fibrillation (NVAF) with indication for anticoagulation therapy	2
III. Synopsis – Time schedule/ milestones primary data collection	First patient first visit (FPFV): February ~~2016~~ Last patient first visit (LPFV): December ~~2017~~ Last patient last visit (LPLV): December ~~2018~~ Data base lock: ~~May 2019~~ Final registry report: within 6 months upon LPLV Publication: ~~December 2019~~	First patient first visit (FPFV): April 2016 Last patient first visit (LPFV): December 2018 Last patient last visit (LPLV): December 2019 Data base lock: March 2020 First registry report: within 6 months upon LPLV Publication: September 2020	3
III. Synopsis – financial support	Financial support is provided by Bayer ~~Pharma~~ AG	Financial support is provided by Bayer AG	4
IV. Table of content		updated	4
VI. List of figures and tables	none	VII. LIST OF FIGURES AND TABLES Figure 1: Flowchart XARENO Registry 20 Figure 2: Reporting of outcome and (S)AE / (S)ADR 42 Table 1: Stages of chronic kidney disease (CKD) as defined by the National Kidney Foundation 2002 16 Table 2: Tabular Overview of Data Collection Procedures 26	4
2.1. Design of the registry	This registry will be carried out as an investigator-initiated, multicentre, prospective, non-interventional and observational registry at approximately ~~100~~ sites in Germany, Austria ~~and~~ Switzerland.	This registry will be carried out as an investigator-initiated, multicentre, prospective, non-interventional and observational registry at approximately 200 sites in Germany, Austria, Switzerland, France, Belgium and Luxembourg	1
3.2. Time schedule / milestones of primary data collection	First patient first visit (FPFV): February ~~2016~~ Last patient first visit (LPFV): December ~~2017~~ Last patient last visit (LPLV): December ~~2018~~ Data base lock: ~~May 2019~~ Final registry report: within 6 months upon LPLV Publication: ~~December 2019~~	First patient first visit (FPFV): April 2016 Last patient first visit (LPFV): December 2018 Last patient last visit (LPLV): December 2019 Data base lock: March 2020 First registry report: within 6 months upon LPLV Publication: September 2020	3
3.4.1. Primary	~~1. Progression of CKD:~~	1. Effectiveness:	2

observational outcomes	- ~~decline in eGFR~~ 2. Safety: - major bleeding - ~~all-cause mortality~~ - ~~TIA, stroke or systemic arterial embolism~~ - ~~major cardiovascular events (MACE)~~ - ~~symptomatic venous thromboembolic events~~ - ~~net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality)~~	- Progression of CKD (decline in eGFR in mL/min per 1.73 m^2) - all-cause mortality - TIA, stroke or systemic arterial embolism - Other major cardiovascular events (MACE) o Myocardial infarction o Acute coronary syndrome/unstable angina - symptomatic venous thromboembolic events 2. Safety: - major bleeding	
3.4.2. Secondary observational outcomes		- net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality)	2
3.5.1. In- and exclusion criteria	- non-valvular atrial fibrillation (NVAF) with indication for anticoagulation therapy	- documented non-valvular atrial fibrillation (NVAF) with indication for anticoagulation therapy	2
3.5.3. Eligible patients	Patients with NVAF and CKD (eGFR 15 - 49 mL/min per 1.73 m^2) are in the focus of the XARENO registry. … All patients are registered and recorded by Sponsor according the received therapy.	Patients with documented NVAF and presence of CKD with eGFR values in the range of 15 - 49 mL/min per 1.73 m^2 are in the focus of the XARENO registry. Prior to inclusion patients should be diagnosed with CKD with a duration of at least 3 months based on eGFR values below 60 mL/min per 1.73 m^2 or presence of markers indicating kidney damage (e.g. albuminuria) or both regardless of the underlying cause. … All patients are registered and recorded by Sponsor according the received therapy. A participation of patients in further studies is permitted.	2
3.5.4. Eligible sites	Approximately ~~100~~ sites across Germany, Austria ~~and~~ Switzerland are planned (with a possible increase to more sites, to achieve country representativeness).	Approximately 200 sites across Germany, Austria, Switzerland, France, Belgium and Luxembourg are planned (with a possible increase to more sites, to achieve country representativeness).	1
3.6.2.2. Quarterly data collection up to day 720 (2 years)	The final data collection will be performed after 12 months as available.	The individual duration for each patient depends on the date of inclusion and is flexible with a planned minimum follow-up duration of 12 months until study end is announced (planned minimum 360 days / planned maximum 720 days). The final data collection will be performed after the last patient reached 12 months of observation as available.	2
3.6.2.3. Changes in OAC treatment	If a patient ~~withdraws from registry because of~~ change of treatment, data on follow-up treatment (drug, dose, reason for change, therapy dates, start-/stop date) will be collected where available. In addition, data on temporary interruptions	If a patient changes treatment from Rivaroxaban to VKA or no AC cohort or vice versa, data on follow-up treatment (drug, dose, reason for change, therapy dates, start-/stop date) will be collected where available and the patient will remain in the	2

	of rivaroxaban or VKA treatment will be collected where available.	register and is further documented. In addition, data on temporary interruptions of rivaroxaban or VKA treatment will be collected where available. If a patient switches from Rivaroxaban /VKA/no AC cohort to an excluded OAC, data on follow-up treatment will not be collected and the patient will perform an end of study visit. No further documentation is necessary (see also section 5.5).	
3.7.1.1. General Information	▪ Patient demographic data ▪ Medical history and baseline findings including risk factors for stroke/non CNS systemic embolism or bleeding, e.g.: - diagnosis of CKD, stage classification (eGFR), causes of CKD ▪ Concomitant medications: ~~- CYP3A4 and p-glycoprotein inhibitors / inducers, NSAIDs, and others~~	▪ Patient demographic data (depending on country regulations) ▪ Medical history and baseline findings including risk factors for stroke/non CNS systemic embolism or bleeding, e.g.: - diagnosis of CKD, stage classification (eGFR), causes of CKD (CKD values (eGFR 15 - 49 mL/min per 1.73 m^2) should be available for at least three months (interval of measurements at least 4 weeks)). ▪ Relevant concomitant medications	1+ 2
3.7.1.2. Additional data collection	▪ Concomitant medications: ~~- CYP3A4 and p-glycoprotein inhibitors / inducers, NSAIDs, and others~~	▪ Relevant concomitant medications	2
3.7.3. Withdrawal of consent after start of registry	3.7.3. Withdrawal of ~~patient~~ after start of registry Participants can at any time ~~at~~ and without any statement withdraw from the informed consent. The reasons for patient withdrawal will be recorded in the eCRF and the sponsor has to be informed. ~~If OAC treatment is being stopped, patients will be asked to continue follow-up until end of the registry to allow collection of data on vascular or bleeding events.~~	3.7.3. Withdrawal of consent after start of registry Participants can at any time with and without any statement withdraw from the informed consent. The reasons for patient withdrawal will be recorded in the eCRF and the sponsor has to be informed.	2 + 4
3.7.4. Premature change or stop of treatment		3.7.4. Premature change or stop of treatment If treatment with Rivaroxaban/VKA/no AC is being stopped or changed vice versa, patients will continue follow-up until end of the registry to allow collection of data on effectiveness or bleeding events.	2
3.7.5. Premature termination of the registry	3.7.4. Premature termination of the registry	3.7.5. Premature termination of the registry	4
4.1. Primary outcome variables	~~1. Progression of CKD:~~ ~~- decline in eGFR~~	1. Effectiveness: - Progression of CKD (decline in eGFR in	2

	2. Safety:
	- major bleeding
	- ~~all-cause mortality~~
	- ~~TIA, stroke or systemic arterial embolism~~
	- ~~major cardiovascular events (MACE)~~
	- ~~symptomatic venous thromboembolic events~~
	- ~~net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality)~~
		mL/min per 1.73 m^2)
		- all-cause mortality
		- TIA, stroke or systemic arterial embolism
		- Other major cardiovascular events (MACE)
		  o Myocardial infarction
		  o Acute coronary syndrome/unstable angina
		- symptomatic venous thromboembolic events
		
		2. Safety:
		- major bleeding	

4.2. Secondary outcome variables		- net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality)	2
5.5. Patients switching anticoagulation treatment during the observational period	If patients switch to excluded OAC and drop out of the study, ~~the date under~~ treatment stops with the date of first dose of the excluded OAC.	If patients switch to an excluded OAC and drop out of the study, the date under treatment stops with the date of the intake of the first dose of the excluded OAC. An end of study visit will be performed at this point of time.	2
5.6.1.2. Primary effectiveness and safety outcomes	5.6.1.2. Primary safety outcomes The primary safety outcome variables will be analyzed in ITT analysis set under initial treatment. Patients that switched treatment will be censored after the interval of their initial treatment. These variables will be analyzed using survival analysis and Kaplan Meier estimation of time to first event by treatment (rivaroxaban versus VKA).	5.6.1.2. Primary effectiveness and safety outcomes The primary effectiveness and safety outcome variables will be analyzed in ITT analysis set under initial treatment. Patients that switched treatment will be censored after the interval of their initial treatment. These variables will be analyzed using survival analysis and Kaplan Meier estimation of time to first event by treatment (rivaroxaban versus VKA).	2
6.2. Data collection and documentation	All data collected should be promptly recorded and documented in the CRF.	All data collected should be promptly recorded and documented in the eCRF.	4
7.3. Registry file	…the registry file has to be stored ~~10~~ years.	…the registry file has to be stored 15 years.	4
8.1.1. Adverse event (AE) and Adverse drug reaction (ADR)	8.1.1. Adverse event and Adverse drug reaction	8.1.1. Adverse event (AE) and Adverse drug reaction (ADR)	4
8.1.2. Serious Adverse Events (SAE) and Serious Adverse Reactions (SADR)	8.1.2. Serious Adverse Events and Serious Adverse Reactions	8.1.2. Serious Adverse Events (SAE) and Serious Adverse Reactions (SADR)	4
8.3. Rules for AE and SAE reporting	▪ ~~Primary or secondary~~ effectiveness ~~endpoints~~ will be exempted from expedited SAE reporting but will be documented in the eCRF. ▪ All bleeding events regardless severity and outcome are safety ~~endpoints~~ and will be exempted from SAE reporting. …	▪ All effectiveness outcome events as mentioned in section 4.1 except death of any cause will be exempted from expedited SAE reporting, but will be documented in the eCRF using the respective outcome event documentation eForm. ▪ All bleeding events as mentioned in section 4.1 regardless severity and	2

<table>
<tr><td></td><td>▪ All other events that fulfill the seriousness criteria have to be recorded on the AE page of the eCRF and have to be reported within 24 hours of the physician’s awareness.

The physician must report immediately (within 24 hours of the physician’s awareness) to the sponsor all SAEs described above as requiring expedited reporting.
…
~~Efficacy~~ and safety ~~endpoints~~ will be reviewed and adjudicated. Safety events (bleeding) are expected events and as such would not generate SUSARs (see SmPC Rivaroxaban).</td><td>outcome are safety outcomes and will be exempted from SAE reporting, but will be documented in the eCRF using the respective outcome event documentation eForm.
▪ All hospitalizations have to be documented into the eCRF using the outcome hospitalization eForm. These events have to be evaluated whether being an endpoint (outcome event documentation eCRF, exempted from expedited SAE reporting) or a reportable SAE.
…
▪ All other events that fulfill the seriousness criteria have to be recorded on the AE page of the eCRF and have to be reported within 24 hours of the physician’s awareness using the provided SAE form.
▪ Death of any cause has always to be documented as SAE.

A schematic overview on AE, SAE and outcome reporting is given in figure 2.

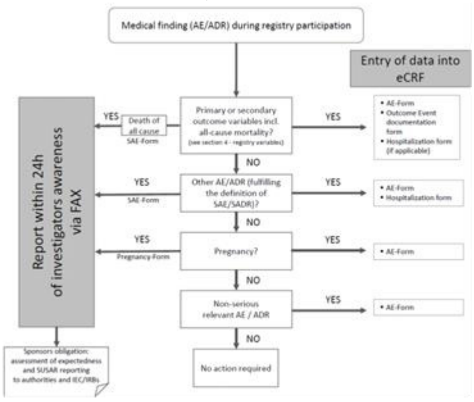
The physician must report immediately (within 24 hours of the physician’s awareness) to the sponsor all SAEs described above as requiring expedited reporting.
…
Effectiveness and safety outcome events will be reviewed and adjudicated. Safety events (bleedings) are expected events and as such would not generate SUSARs (see SmPC Rivaroxaban).


FIGURE 2: REPORTING OF OUTCOME AND (S)AE / (S)ADR</td><td></td></tr>
<tr><td>9.6. Documentation and archiving</td><td>…will be retained by the physician for as long as needed (for at least ~~10~~ years or according to local legislation) to comply with national and international</td><td>…will be retained by the physician for as long as needed (for at least 15 years or according to local legislation) to comply with national and international regulations.</td><td>4</td></tr>
</table>

	regulations.		
9.9. Financing	The financial support will be provided by a research grant by Bayer ~~Pharma~~ AG.	The financial support will be provided by a research grant by Bayer AG.	4

10.3. Changes from protocol version 1.6 to version 2.0 (Amendment #1)

Amendment 1 is dated 28 FEB 2020

10.3.1. Modification 1: Patient number, follow-up time and timelines

Patient number, follow-up time and anticipated timelines were adapted due to a slower than planned recruitment. The executive committee of XARENO decided to stop recruitment on 12th January 2020 thus before reaching the planned patient number of 2500 patients (1000 each in VKA and rivaroxaban arm and 500 in no anticoagulation arm), as this registry generates important and missing data in the medical care of patients with non-valvular atrial fibrillation and chronic kidney disease.

<u>Sections affected by this modification:</u>

- Title page
- Section III Synopsis
- Section V List of Abbreviations
- Section 2 Research methods
- Section 3 Registry Settings
- Section 5 Statistical Methods and sample size calculation
- Section VII References

10.3.2. Modification 2: Observational outcomes

The structure of primary observational outcomes was changed and one secondary observational outcome was reclassified as primary observational outcome.

In protocol Version 1.6 from 24 May 2017 the primary observational outcomes were re-ordered in the course of further specification of the outcome MACE. Thus, outcomes including the events TIA, stroke or systemic embolism events, other major cardiovascular events (MACE) and symptomatic venous thromboembolic events, that are well-established efficacy outcomes in randomized controlled trials, were grouped together with the progression of CKD and assigned to primary-observational effectiveness outcomes. However, in real-world post-marketing observational studies such as XARENO the latter parameters are generally considered as safety outcomes. In the new current protocol version V2.0 from 24 February 2020 this change was corrected and the original assignment of these parameters to primary observational safety outcomes was restored. Furthermore, three renal secondary observational outcomes were added for specification due to an important publication of a retrospective cohort analysis in 2017 (Yao et al., 2017).

Sections affected by this modification:

- Section III Synopsis
- Section 3 Registry settings
- Section 4 Registry variables

10.3.3. Modification 3: Minor editorial/consistency/clarification/administrative changes

Sections affected by this modification:

- Title page: adress change for sponsor
- Footer: protocol version and protocol date
- Section I Responsible parties: adress change for sponsor and responsible for registry coordination, updated information about medical coordinator / registry chair
- Section II Signatures: signature of sponsor´s responsible person, medical coordinator / registry chair, addition of signature by statistics
- Section III Synopsis: adress change for sponsor
- Section IV Table of contents: updated page number
- Section V List of abbreviation: correction of one abbreviation
- Section VI List of figures and tables: updated page numbers
- Section 3 Registry setting: updated numbering
- Section 5 Statistical methods: term clarification and spelling
- Section 6 Data management: updated section reference

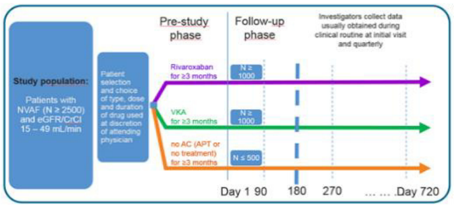
10.3.4. Changes to the protocol text

In this section, all sections affected by the amendment are shown in sequence following the previous protocol version. Administrative and minor editorial changes are not shown. Deletions to the protocol text are crossed out; additions are underlined.

Section number and title	Previous Text (V1.6)	New Text (V2.0)	Modi-fication
Title page	Version: ~~V1.6 24.05.2017~~	Version: V2.0 28.02.2020	3

Title page - Sponsor address	~~Blasewitzer Straße 43~~ ~~01307~~ Dresden Germany	Freiberger Str. 33 01607 Dresden Germany	3
Footer	Registry protocol_~~V1.6 24.05.2017~~	Registry protocol_V2.0 28.02.2020	3
I. Responsible Parties – Sponsor address	~~Blasewitzer Straße 43~~ ~~01307~~ Dresden Germany	Freiberger Str. 33 01607 Dresden Germany	3
I. Responsible Parties – Medical Coordinator / Registry Chair	Prof. Dr. Reinhold Kreutz Charité - Universitätsmedizin Berlin Institute of Clinical Pharmacology and Toxicology Charitéplatz 1, 10117 Berlin Germany PD Jan Beyer-Westendorf ~~Study site of GWT~~ Universitätsklinikum Dresden Centre for Vascular Medicine Department of Medicine III Fetscherstraße 74 01307 Dresden Germany	Prof. Dr. Reinhold Kreutz Employee of Charité - Universitätsmedizin Berlin Institute of Clinical Pharmacology and Toxicology Charitéplatz 1, 10117 Berlin Germany PD Jan Beyer-Westendorf Employee of Universitätsklinikum Dresden Centre for Vascular Medicine Department of Medicine III Fetscherstraße 74 01307 Dresden Germany	3
I. Responsible Parties – Registry coordination	GWT-TUD GmbH ~~Blasewitzer Straße 43~~ ~~01307~~ Dresden Germany	GWT-TUD GmbH Freiberger Str. 33 01067 Dresden Germany	3
II. Signatures – Sponsor	**Sponsor** ~~Claus-Peter Held, GWT-TUD GmbH~~ **Medical Coordinator / Registry Chair** Prof. Dr. Reinhold Kreutz~~, Charité Berlin~~ PD Dr. Jan Beyer-Westendorf~~, GWT -TUD GmbH~~	**Sponsor GWT-TUD GmbH** Frank Schwarz **Medical Coordinator / Registry Chair** Prof. Dr. Reinhold Kreutz PD Dr. Jan Beyer-Westendorf **Statistics** Dr. Kurtulus Sahin, ClinStat GmbH place, date	3
III. Synopsis – Sponsor	GWT-TUD GmbH ~~Blasewitzer Straße 43~~ ~~01307~~ Dresden Germany	GWT-TUD GmbH Freiberger Str. 33 01067 Dresden Germany	3
III. Synopsis - Research question and objectives	The multicentre registry will collect clinical data from ~~2500~~ patients with NVAF and chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) (15-49 mL/min per 1.73 m^2).	The multicentre registry will collect clinical data from approximately 1600 patients with NVAF and chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) (15-49 mL/min per 1.73 m^2).	1
III Synopsis – Primary observational outcomes	1. ~~Effectiveness:~~ - ~~Progression of CKD (~~decline in eGFR in mL/min per 1.73 m^2~~)~~ - ~~all-cause mortality~~ - ~~TIA, stroke or systemic arterial~~	1. Progression of CKD: - decline in eGFR in mL/min per 1.73 m^2 2. Safety: - major bleeding	2

	~~embolism~~ ~~- Other major cardiovascular events (MACE)~~ ~~o Myocardial infarction~~ ~~o Acute coronary syndrome/unstable angina~~ ~~- symptomatic venous thromboembolic events~~ 2. Safety: - major bleeding	- all-cause mortality - TIA, stroke or systemic arterial embolism - Other major cardiovascular events (MACE) o Myocardial infarction o Acute coronary syndrome/unstable angina - symptomatic venous thromboembolic events - net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality)	
III. Synopsis - Secondary observational outcomes	- initiation of chronic renal replacement therapy - eGFR < 15 mL/min per 1.73 m^2 (CKD Stage 5 Dialysis and Non-Dialysis) - rates, causes and length of hospitalizations - persistence with OAC therapy - reasons for OAC therapy discontinuation ~~- net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality~~	- initiation of chronic renal replacement therapy - eGFR < 15 mL/min per 1.73 m^2 (CKD Stage 5 Dialysis and Non-Dialysis) - eGFR decline of ≥ 30% - doubling of serum creatine concentration - acute kidney injury (AKI) events defined as acute kidney injury associated with either hospitalization or emergency department visit, where AKI event is the lead diagnosis - rates, causes and length of hospitalizations - persistence with OAC therapy - reasons for OAC therapy discontinuation	2
III. Synopsis	Time schedule / milestones	Time schedule / milestones primary data collection	1
III. Synopsis – Time schedule/ milestones primary data collection	First patient first visit (FPFV): April 2016 Last patient first visit (LPFV): ~~December 2018~~ ~~Last patient last visit (LPLV): December 2019~~ ~~Data base lock: March 2020~~ ~~Final registry report: within 6 months upon LPLV~~ ~~Publication: September 2020~~	First patient first visit (FPFV): April 2016 Last patient first visit (LPFV): January 2020 Primary data collection: April 2016 – January 2021	1
III. Synopsis - Time schedule extended data collection	none	Time schedule extended data collection Extended data collection I: January 2021 – January 2022 Last patient last visit (LPLV): January 2022 Data base lock (DBL): January 2022 Final registry report: Within 6 months upon DBL Publication: September 2022 Potential extended data collection II: January 2022 – January 2023	1
IV. Table of content	IV. Table of content~~s~~	IV. Table of content updated	3
V. List of	AN~~C~~OVA Analysis of covariance	ANOVA Analysis of variance	3

Abbreviations			
V. List of Abbreviations	none	FA Final analysis FPFV First patient first visit LPFV Last patient first visit LPLV Last patient last visit MA Main analysis	1
VI. List of Figures and tables		updated	3
2.1. Design of the registry	This registry will be carried out as an investigator-initiated, multicentre, prospective, non-interventional and observational registry at ~~approximately 200~~ sites in Germany, Austria, Switzerland, France, Belgium and Luxembourg.	This registry will be carried out as an investigator-initiated, multicentre, prospective, non-interventional and observational registry at 160 sites in Germany, Austria, Switzerland, France, Belgium and Luxembourg	3
2.2. Research question	The overall objective of this this registry is to assess CKD progression and safety with regard to anticoagulation strategies in NVAF patients with eGFR 15-49 mL/min per 1.73 m2 in routine clinical practice. The registry will collect clinical data of approximately ~~2500~~ patients with CKD (eGFR 15 -49 mL/min per 1.73 m2) and NVAF receiving rivaroxaban, ~~OAC with~~ VKA, or no ~~AC~~ therapy, who are prospectively followed for a flexible duration with at least ~~for 12~~ months ~~(for the last enrolled patient) and with an estimated mean of 18 months for the whole registry cohort (Figure 1).~~  ~~FIGURE 1: FLOWCHART XARENO REGISTRY~~	The overall objective of this this registry is to assess CKD progression and safety with regard to different anticoagulation strategies in NVAF patients with eGFR 15-49 mL/min per 1.73 m2 in routine clinical practice. The registry will collect clinical data of approximately 1600 patients with CKD (eGFR 15 -49 mL/min per 1.73 m2) and NVAF receiving rivaroxaban, VKA, or no anticoagulation therapy, who are prospectively followed for a flexible duration with at least 24 months up to 6 years observation. The estimated average observation time per patient is at least 30 months, with the individual observation period for each patient to be continued as long as possible until the defined last visit of any patient in the registry. During the conduct of the registry, it became apparent that the recruitment of patients was slower than originally planned. Therefore, the extension of the follow-up period seems appropriate. This accounts for slower recruitment and lower overall number of patients (approximately 1600) available for the primary analysis in the two main treatment arms of rivaroxaban and VKA treatment. With the resulting extension of the mean observation time, a more meaningful analysis of renal function loss can be performed in the prospective setting of the XARENO registry. At the same time, the expanded data collection in XARENO continues to support the prospective observation of additional clinical events such as stroke and bleeding in this vulnerable patient group with CKD and atrial fibrillation. The extended data collection is therefore	1

		planned for at least one additional year until January 2022 (extended data collection I). After the end of this observation period, an additional one- year extended data collection period until January 2023 may be performed, depending on the overall number of patients still available in the registry (extended data collection II).	
2.3. Registry Schedule	none	FIGURE 1: REGISTRY FLOW INCLUDING EXTENDED DATA COLLECTION	1
3.1. Study population	~~It is planned~~ to include at least ~~1000~~ patients with rivaroxaban therapy ~~and~~ VKA therapy~~, respectively. Into the group of CKD and NVAF patients with no AC therapy, the aim is to include a maximum of 500 patients. Enrolment can be prolonged beyond 2500 patients until 1000 rivaroxaban patients are enrolled~~.	The plan of the registry is to include at least 1600 patients with CKD and NVAF and rivaroxaban therapy or VKA therapy or no anticoagulation therapy. The aim is to include at least 700 patients with rivaroxaban therapy and VKA therapy, respectively. Into the exploratory treatment arm of patients receiving no AC therapy about 100 patients will be included.	1
3.2. Time schedule / milestones of primary data collection	**3.2 Time schedule / milestones** Milestone Planned date First patient first visit (FPFV): April 2016 Last patient first visit (LPFV): ~~December 2018~~ ~~Last patient last visit (LPLV): December 2019~~ ~~Data base lock: March 2020~~ ~~Final registry report: within 6 months upon LPLV~~ ~~Publication: September 2020~~	**3.2. Time schedule / milestones of primary data collection** Milestone Planned date First patient first visit (FPFV): April 2016 Last patient first visit (LPFV): January 2020 Primary data collection: April 2016 – January 2021	1
3.3. Time schedule of extended data collection	none	Milestone Planned date Extended data collection I: January 2021 – January 2022 Last patient last visit (LPLV): January 2022 Data base lock (DBL): January 2022 Final registry report: Within 6 months upon DBL Publication: September 2022 Potential extended data collection II: January 2022 – January 2023	1
Numbering of sections changed from section 3.4. Objectives of the registry up to 3.8.5. Premature termination of the registry	**~~3.3~~ Objectives of the registry** up to **~~3.7.5~~ Premature termination of the registry**	**3.4 Objectives of the registry** up to **3.8.5 Premature termination of the registry**	3
3.5.1. Primary observational outcomes	• ~~Effectiveness~~: - ~~Progression of CKD (~~decline in eGFR in mL/min per 1.73 m^2~~)~~ ~~- all-cause mortality~~ ~~- TIA, stroke or systemic arterial embolism~~	• Progression of CKD: - decline in eGFR in mL/min per 1.73 m^2 • Safety: - major bleeding - all-cause mortality	2

	- ~~Other major cardiovascular events (MACE)~~ o ~~Myocardial infarction~~ o ~~Acute coronary syndrome/unstable angina~~ - ~~symptomatic venous thromboembolic events~~ ● Safety: major bleeding	- TIA, stroke or systemic arterial embolism - Other major cardiovascular events (MACE) o Myocardial infarction o Acute coronary syndrome/unstable angina - symptomatic venous thromboembolic events - net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality)	
3.5.2. Secondary observational outcomes	- initiation of chronic renal replacement therapy - eGFR < 15 mL/min per 1.73 m^2 (CKD Stage 5 Dialysis and Non-Dialysis) - rates, causes and length of hospitalizations - persistence with OAC therapy - reasons for OAC therapy discontinuation - ~~net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality~~	- initiation of chronic renal replacement therapy - eGFR < 15 mL/min per 1.73 m^2 (CKD Stage 5 Dialysis and Non-Dialysis) - eGFR decline of ≥ 30% - doubling of serum creatine concentration - acute kidney injury (AKI) events defined as acute kidney injury associated with either hospitalization or emergency department visit, where AKI event is the lead diagnosis - rates, causes and length of hospitalizations - persistence with OAC therapy - reasons for OAC therapy discontinuation	2
3.7.2.2. Quarterly data collection up to month 84 (7 years)	**3.6.2.2. Quarterly data collection up to ~~day 720~~ (~~2~~ years)** Data for eGFR and CrCl (based on serum creatinine measurements), current anticoagulation therapy, concomitant medications, bleeding events, thromboembolic and cardiovascular events, and all further events of interest will be collected every three months where available and as obtained during routine medical practice. The individual duration for each patient depends on the date of inclusion and is flexible with a planned minimum follow-up duration of 12 months until study end is announced (planned minimum 360 days / planned maximum ~~720 days~~). The final data collection will be performed after the last patient reached 12 months of observation as available.	**3.7.2.2. Quarterly data collection up to month 84 (7 years)** Data for eGFR and CrCl (based on serum creatinine measurements), current anticoagulation therapy, concomitant medications, bleeding events, thromboembolic and cardiovascular events, and all further events of interest will be collected every three months where available and as obtained during routine medical practice. The individual duration for each patient depends on the date of inclusion and is flexible with a planned minimum follow-up duration of 12 months until study end is announced (planned minimum 360 days / planned maximum 84 months). The final data collection will be performed after the last patient reached 12 months of observation as available.	1
3.8.4. Premature change or stop of treatment	If treatment with Rivaroxaban/VKA/no AC is being stopped or changed vice versa, patients will continue follow-up until end of the registry to allow collection of data ~~on effectiveness or bleeding events~~.	If treatment with Rivaroxaban/VKA/no AC is being stopped or changed vice versa, patients will continue follow-up until end of the registry to allow collection of data of primary outcome variables.	
4.1. Primary outcome	● ~~Effectiveness~~: - ~~Progression of CKD (~~decline in eGFR	● Progression of CKD: - decline in eGFR in mL/min per 1.73 m^2	

<table>
<tr>
<td>variables</td>
<td>in mL/min per 1.73 m^2~~)~~
~~- all-cause mortality~~
~~- TIA, stroke or systemic arterial embolism~~
~~- Other major cardiovascular events (MACE)~~
~~o Myocardial infarction~~
~~o Acute coronary syndrome/unstable angina~~
~~- symptomatic venous thromboembolic events~~

● Safety:
- major bleeding</td>
<td>● Safety:
- major bleeding
- all-cause mortality
- TIA, stroke or systemic arterial embolism
- Other major cardiovascular events (MACE)
o Myocardial infarction
o Acute coronary syndrome/unstable angina
- symptomatic venous thromboembolic events
- net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality)</td>
<td></td>
</tr>
<tr>
<td>4.2. Secondary outcome variables</td>
<td>- initiation of chronic renal replacement therapy
- eGFR < 15 mL/min per 1.73 m^2 (CKD Stage 5 Dialysis and Non-Dialysis)
- rates, causes and length of hospitalizations
- persistence with OAC therapy
- reasons for OAC therapy discontinuation
- ~~net-clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality~~)</td>
<td>- initiation of chronic renal replacement therapy
- eGFR < 15 mL/min per 1.73 m^2 (CKD Stage 5 Dialysis and Non-Dialysis)
- eGFR decline of ≥ 30%
- doubling of serum creatine concentration
- acute kidney injury (AKI) events defined as acute kidney injury associated with either hospitalization or emergency department visit, where AKI event is the lead diagnosis
- rates, causes and length of hospitalizations
- persistence with OAC therapy
- reasons for OAC therapy discontinuation</td>
<td>2</td>
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<tr>
<td>5.2. Sample size for comparison between OAC groups</td>
<td>For an expected mean difference of at least 1 ml/min and a standard deviation below 10 ml/min, a sample size of 1000 patients per treatment arm (i.e. 2000 patients overall) should result in a power of around 80 %. In the worst case of minimal mean difference and maximal standard deviation, the power decreases to 61% and in the best case of maximal mean difference and minimal standard deviation, the power increases to 92 % as shown below in table

<table>
<tr><th>Mean Difference (ml/min)</th><th>Std. Dev. (ml/min)</th><th>Power</th></tr>
<tr><td>1.0</td><td>10</td><td>0.608</td></tr>
<tr><td>1.0</td><td>8</td><td>0.798</td></tr>
<tr><td>1.2</td><td>10</td><td>0.765</td></tr>
<tr><td>1.2</td><td>8</td><td>0.918</td></tr>
</table>
For ~~primary safety outcome~~ variables (e.g. ~~stroke~~ and major bleeding) the expected annual event rates depend on baseline risk and event rates between 2 % to 5 % are ~~expected~~ based on previous studies in NVAF patients (Camm</td>
<td>For an expected mean difference of at least 1 ml/min and a standard deviation below 10 ml/min, a sample size of 1000 patients per treatment arm (i.e. 2000 patients overall) should result in a power of around 80 %. In the worst case of minimal mean difference and maximal standard deviation, the power decreases to 61% and in the best case of maximal mean difference and minimal standard deviation, the power increases to 92 % as shown below in table. With this amendment, the number of rivaroxaban and VKA patients is reduced from 2000 to 1500 patients. The updated power calculations regarding the eGFR are presented in the table below in column "Power with 1500 patients". The power with 1500 patients is about 10 % smaller compared to the power with 2000 patients.
<table>
<tr><th>Mean Difference (ml/min)</th><th>Std. Dev. (ml/min)</th><th>Power with 2000 patients</th><th>Power with 1500 patients</th></tr>
<tr><td>1.0</td><td>10</td><td>0.608</td><td>0.490</td></tr>
<tr><td>1.0</td><td>8</td><td>0.798</td><td>0.677</td></tr>
<tr><td>1.2</td><td>10</td><td>0.765</td><td>0.641</td></tr>
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<td>1</td>
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<table>
<tr><td></td><td>et al., 2015). ~~Therefore, with the calculated number of 2000 patients, 20 to 50 events per treatment arm can be expected.~~</td><td><table><tr><td>1.2</td><td>8</td><td>0.918</td><td>0.827</td></tr></table>Assumptions about the eGFR mean differences and standard deviations were based on an earlier publication and included some uncertainty (Böhm et al., 2015). The following table contains some combination of mean differences and SD between treatment groups for eGFR resulting approximately in 80 % power.<table><tr><th>Mean Difference (ml/min)</th><th>Std. Dev. (ml/min)</th><th>Power with 1500 patients</th></tr><tr><td>1.2</td><td>8</td><td>0.827</td></tr><tr><td>1.3</td><td>9</td><td>0.798</td></tr><tr><td>1.5</td><td>10</td><td>0.827</td></tr></table>For event variables (e.g. all-cause mortality, MACE and major bleeding) the expected annual event rates depend on baseline risk and event rates between 2 % to 5 % are presumed based on previous studies in NVAF patients (Camm et al., 2015). Due to the reduced number of patients from 2000 to 1500, about 15 to 38 events per treatment arm per year can be expected. On the other side, more events are possible by the prolongation of the study observation period up to 5 years.</td><td></td></tr>
<tr><td>5.3. Statistical and analytical plan</td><td>Statistical analyses will be descriptive and exploratory only. For continuous parameters summary statistics (Number of observations, mean, standard deviation, minimum, 25 % percentile, median, 75 % percentile, maximum and the interquartile range) will be presented. For categorical variables absolute and relative frequencies will be presented.
All tables will be generated by treatment (Rivaroxaban, VKA or no AC) and total. To get an idea if potentially observed differences in treatment could be of relevance, 95 % confidence intervals of the treatment differences between Rivaroxaban and VKA will be calculated. No interim analysis is planned.
Full details of the statistical analysis methods to be used will be described in the Statistical Analysis Plan (SAP).</td><td>Statistical analyses will be descriptive and exploratory only. For continuous parameters summary statistics (Number of observations, mean, standard deviation, minimum, 25 % percentile, median, 75 % percentile, maximum and the interquartile range) will be presented. For categorical variables absolute and relative frequencies will be presented.
All tables will be generated by treatment (Rivaroxaban, VKA or no AC) and total. To get an idea if potentially observed differences in treatment could be of relevance, 95 % confidence intervals of the treatment differences between Rivaroxaban and VKA will be calculated. No interim analysis is planned.
A descriptive analysis of baseline characteristics after LPFV is planned.
In addition to the main analysis (MA) using the data until the end of primary data collection at 12 months, a similar analysis will be performed using all data until the end of the extended data collection (final analysis [FA]). Full details of the statistical analysis methods to be used will be described in the Statistical Analysis Plan (SAP).</td><td>1</td></tr>
<tr><td>5.6.1.1. Estimated glomerular</td><td>Primary timepoint for analysis of eGFR is the change from 12 months visit to baseline. It will be analyzed in subjects</td><td>Primary timepoint for analysis of eGFR is the change from 12 months visit to baseline. It will be analyzed in subjects who</td><td>3</td></tr>
</table>

filtration rate (eGFR)	who have a non-missing baseline eGFR measurement and a non-missing post baseline value at 12 months. Further analysis of eGFR after more than 12 months will be conducted with the data of patients available at those visits. The eGFR data will be analyzed using an AN~~C~~OVA with repeated measurements and difference to baseline of eGFR as dependent variable, and treatment (rivaroxaban versus VKA) as a fix factor. For this analysis patients who will switch their treatment during the observational period will only be considered for the time under their initial treatment. Country may be added as cofactor into the model, if corresponding categories are not too small. The final decision on the cofactors used in the model will be made during the final review meeting.	have a non-missing baseline eGFR measurement and a non-missing post baseline value at 12 months. Further analysis of eGFR after more than 12 months will be conducted with the data of patients available at those visits. The eGFR data will be analyzed using an ANOVA with repeated measurements and difference to baseline of eGFR as dependent variable, and treatment (rivaroxaban versus VKA) as a fix factor. For this analysis patients who will switch their treatment during the observational period will only be considered for the time under their initial treatment. Country may be added as cofactor into the model, if corresponding categories are not too small. The final decision on the cofactors used in the model will be made during the final review meeting.	
5.6.1.2. Primary safety variables	**5.6.1.2. Primary ~~effectiveness and~~ safety ~~outcomes~~** The primary ~~effectiveness and~~ safety outcome variables will be analyzed in ITT analysis set under initial treatment. Patients that switched treatment will be censored after the interval of their initial treatment. These variables will be analyzed using survival analysis and Kaplan Meier estimation of time to first event by treatment (rivaroxaban versus VKA).	**5.6.1.2. Primary safety <u>variables</u>** The primary safety outcome variables will be analyzed in ITT analysis set under initial treatment. Patients that switched treatment will be censored after the interval of their initial treatment. These variables will be analyzed using survival analysis and Kaplan Meier estimation of time to first event by treatment (rivaroxaban versus VKA).	2
5.6.2. Analysis of secondary outcome variables	~~All secondary outcomes except hospitalizations and reasons for OAC therapy discontinuation will also be analyzed using survival analysis and Kaplan Meier estimations of time to first event. For this analysis, patients switching treatment will be considered with all available information.~~	<u>none</u>	2
5.6.2. Event outcome analyses	**5.6.~~3~~. Event outcome analyses** All outcome events will be included into ~~analysis~~ that occurred throughout the follow-up period, including those occurring at any time after interruption or discontinuation of OAC treatment. Start day of event ~~analysis~~ is day 1, i.e. inclusion date into the registry for all patients. Censoring date is the minimum of death date or the last contact date and for the rivaroxaban and VKA groups, the stop of OAC treatment date + 2 days. The proportion of events and number of subjects at risk (crude incidences), the 95 % confidence intervals (CIs) of these proportions will be calculated according	**5.6.<u>2</u>. Event outcome analyses** All outcome events will be included into <u>analyses</u> that occurred throughout the <u>primary data collection</u> period <u>and the extended data collection period</u>, including those occurring at any time after interruption or discontinuation of OAC treatment. Start day of event <u>analyses</u> is day 1, i.e. inclusion date into the registry for all patients. Censoring date is the minimum of death date or the last contact date and for the rivaroxaban and VKA groups, the stop of OAC treatment date + 2 days. The proportion of events and number of subjects at risk (crude incidences) <u>as well as</u>	1 + 3

	to the Clopper–Pearson method. Outcome event rates will also be calculated using Kaplan–Meier time-to-first-event analysis, with data presented as events per 100 patient-years and their 95 % CIs, using the following formula: ▪ Event rate = number of events / total time under risk (defined as the sum of all days from inclusion in the registry until the day of the first event divided by 100 × 365 days and 100 patient-years as its unit). Corresponding CIs will be calculated using the Poisson distribution. As a sensitivity analysis of all ~~time to first event~~ analyses, analysis of multiple events will be performed using the counting process approach as extension of the cox model where applicable (Thernau et al., 2000). The counting process model of Andersen-Gill and the conditional model will be used for this analysis. Results of the multiple event analysis will be compared with the results of the ~~time to first event~~ analysis.	the 95 % confidence intervals (CIs) of these proportions will be calculated according to the Clopper–Pearson method. Outcome event rates will also be calculated using Kaplan–Meier time-to-first-event analysis, with data presented as events per 100 patient-years and their 95 % CIs, using the following formula: ▪ Event rate = number of events / total time under risk (defined as the sum of all days from inclusion in the registry until the day of the first event divided by 100 × 365 days and 100 patient-years as its unit). Corresponding CIs will be calculated using the Poisson distribution. As a sensitivity analysis of all time-to-first-event analyses, analysis of multiple events will be performed using the counting process approach as extension of the cox model where applicable (Thernau et al., 2000). The counting process model of Andersen-Gill and the conditional model will be used for this analysis. Results of the multiple event analysis will be compared with the results of the time-to-first-event analysis.	
5.7. Limitation of study results	All results from statistical tests are exploratory in nature only. No confirmatory conclusions can be drawn from any result. In a non-randomized registry, differences between treatment groups at baseline may be present. In this ~~register~~, especially, different stages of renal impaired patients may be treated with the same treatment depending on physician/site or country. Other potential factors for confounding might be age, pre-medication and co-morbidities at baseline. If treatment groups should differ at baseline for eGFR the individual slopes of decrease in GFR will be analyzed for differences between the treatment groups. In case of event analysis, the propensity score matching will be used to reduce bias and minimize the impact of confounding in case of event analysis.	All results from statistical tests are exploratory in nature only. No confirmatory conclusions can be drawn from any result. In a non-randomized registry, differences between treatment groups at baseline may be present. In this registry, especially, different stages of renal impaired patients may be treated with the same treatment depending on physician/site or country. Other potential factors for confounding might be age, pre-medication and co-morbidities at baseline. The reduction in power because of the reduced sample size is an additional limitation of the study. In total, N=1537 subjects with informed consent date until end of October 2019 were enrolled into the study (Rivaroxaban: N=759 subjects, VKA: N=687, No anticoagulation: N=91). If treatment groups should differ at baseline for eGFR the individual slopes of decrease in GFR will be analyzed for differences between the treatment groups. In case of event analysis, the propensity score matching will be used to reduce bias and minimize the impact of confounding in case of event analysis.	1
6.2. Data collection and documentation	All data collected should be promptly recorded and documented in the eCRF. The following electronic Case Report	All data collected should be promptly recorded and documented in the eCRF. The following electronic Case Report Forms	3

	Forms should be documented: ▪ patient registration ▪ documentation of baseline characteristics (see ~~3.7.1.1~~) ▪ documentation of each course of therapy ▪ documentation of therapy switch ▪ documentation of adverse events ▪ periodic follow-up of patients	should be documented: ▪ patient registration ▪ documentation of baseline characteristics (see 3.8.1.1) ▪ documentation of each course of therapy ▪ documentation of therapy switch ▪ documentation of adverse events ▪ periodic follow-up of patients	
7.2. Audits /Inspections	The sponsor and all registry site personnel involved support audit~~ers~~s and inspections by the competent authorities at all times and allow access to the necessary original documentation.	The sponsor and all registry site personnel involved will support audits and inspections by the competent authorities at all times and allow access to the necessary original documentation.	3
VII. References	none	**Posch** F, Ay C, Stöger H, Kreutz R, Beyer-Westendorf J. Exposure to vitamin k antagonists and kidney function decline in patients with atrial fibrillation and chronic kidney disease. Research and Practice in Thrombosis and Haemostasis. 2019 Mar 5;3(2):207-216. **Yao X**, Tangri N, Gersh BJ, Sangaralinghham LR, Shah ND, Noseworthy PA. Renal outcomes in anticoagulated patients with atrial fibrillation. J Am Coll Cardiol. 2017;70(21):2621-32.	1+2

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