2 Synopsis

Date of Report	06 Jan 2023
Title of the study	Factor XA-inhibition in RENal patients with non-valvular atrial fibrillation Observational registry
NCT number	NCT02663076
Sponsor	GWT-TUD GmbH Medical Consulting Freiberger Strasse 33 01067 Dresden, Germany
Phase	IV
Study objectives	The overall objective of this registry was to assess chronic kidney disease (CKD) progression and safety of anticoagulation strategies in non-valvular atrial fibrillation (NVAF) patients with an estimated glomerular filtration rate (eGFR) of 15-49 mL/min per 1.73 m^2 in routine clinical practice.
Treatment and names of medicinal products under investigation	The treatment was carried out at the discretion of the attending physician with rivaroxaban, vitamin K antagonists (VKA) or no anticoagulation therapy.
Indication	Non-valvular atrial fibrillation (NVAF)
Diagnosis and main criteria for inclusion	Patients with NVAF and CKD <u>Principal inclusion criteria:</u> - Male and female patients, age ≥ 18 years - CKD with eGFR 15 – 49 mL/min per 1.73 m^2 - Documented NVAF with indication for anticoagulation therapy - A treatment strategy for the ≥ 3 previous months before enrolment with either: ▪ rivaroxaban or ▪ VKA (oral anticoagulation [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 <u>Exclusion criteria:</u> - 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
Study design	Multicenter, prospective, non-interventional and observational registry taking place in Germany, Austria, Switzerland, France and Belgium.
Methodology	Patient data were 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.

Medical Coordinator / Registry Chair	Prof. Dr. Reinhold Kreutz Charité - Universitätsmedizin Berlin Institute of Clinical Pharmacology and Toxicology Charitéplatz 1 10117 Berlin, Germany
Study centers and investigators	For a full list of study centers and investigators please refer to Appendix 16.1.3
Study period	First patient first visit (FPFV) 05 Apr 2016 Last patient last visit (LPLV) 20 Jan 2022 Database lock (DBL) 04 Apr 2022
Early termination	Not applicable
Number of patients	Planned: approximately 1600 Analyzed: 1544 (764 in the rivaroxaban group, 691 in the VKA group and 89 had no AC medication at baseline)
Criteria for evaluation	**Primary outcomes:** 1. Progression of CKD assessed as decline in eGFR 2. Safety: - Major bleeding - All-cause mortality - Transient ischemic attack (TIA), stroke or systemic arterial embolism - Other major cardiovascular events (MACE) o Myocardial infarction o Acute coronary syndrome/unstable angina - Symptomatic venous thromboembolic events (VTE) - Net clinical benefit (stroke and other thromboembolic events, major bleeding, and all-cause mortality) **Secondary 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 AKI 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
Statistical methods	All statistical analyses followed the procedures specified in the Registry Protocol (Version 2.0, dated 28 Feb 2020) and the Statistical Analysis Plan (Version 1.0, dated 01 Nov 2020) and its Amendments (Amendment I dated 08 Jan 2021 and Amendment II dated 09 Mar 2021). Data analysis: - Summary of baseline data (demographic patient characteristics and clinical data) - Analysis of covariance (ANCOVA) with repeated measures for eGFR

	- Survival analysis using Kaplan-Meier estimations - Cox-regression-analysis - Propensity score matching for reduction of confounding A direct comparison between groups was performed only between the OAC therapy groups rivaroxaban vs. VKA. The aim in the group of patients without AC was to collect data on patient characteristics and to describe the natural course of these patients with CKD and NVAF for the same outcome variables analyzed in the two OAC groups. Statistical analyses were of a descriptive and exploratory nature only. A confirmatory statistical analysis was neither intended nor performed. Reported p-values must be interpreted in an exploratory sense only. Statistical significance refers to a two-sided type I error type of 5%. Thus, no adjustment for the type I error level was made. For continuous variables summary statistics (number of observations, mean, standard deviation [STD], minimum, 25% percentile Q1, median, 75% percentile Q3, maximum and the interquartile range) are presented. For categorical variables, absolute and relative frequencies are presented. All descriptive tables were generated by treatment (rivaroxaban, VKA or no AC) and total, if possible. An additional analysis was performed by Craig I. Coleman (University of Connecticut) using estimated propensity scores to weight patients for analysis using an overlap weighting approach to allow for all eligible patients to be included in the analysis. The results are reported under separate cover.
Substantial protocol changes	The study was conducted according to the Registry Protocol Version 1.1 dated 25 Feb 2016 and the following amendments: • Version 1.6 dated 24 May 2017 • Version 1.7 dated 21 Feb 2018 (French version) • Version 2.0 dated 28 Feb 2020
Publications	Kreutz R, Deray G, Floege J, et al. Abstract 13927: Advanced Age and Preferential Use of Vitamin K Antagonists in Severe Renal Impairment: First Results of the XARENO Registry in Patients With Non-valvular Atrial Fibrillation and Non-dialysis Dependent Advanced Chronic Kidney Disease. *Circulation* 2020;142:A13927. Kreutz R, Deray G, Floege J, et al. Rationale and design of XARENO: XA inhibition in RENal patients with non-valvular atrial fibrillation. Observational registry. *Kardiol Pol.* 2021;79(11):1265-1267. Kreutz R, Deray G, Floege J, et al. A real-word, prospective observational study to compare rivaroxaban versus vitamin K antagonist treatment in patients with non-valvular atrial fibrillation and advanced chronic kidney disease. *J Am Coll Cardiol*. 2022, 79(9 suppl):201. https://doi.org/10.1016/S0735-1097(22)01192-5
Financing	Financial support was provided by Bayer AG

Summary and conclusions

Study subjects

From 1626 patients that were enrolled in this registry (i.e. patients that signed informed consent) 1544 were eligible to be included in the observation phase. Of these 1544 eligible patients 764 were included in the rivaroxaban treatment group, 691 in the VKA treatment group and 89 had no AC medication at baseline.

In the intention-to-treat (ITT) analysis set patients were of similar high age with the highest age in the no AC treatment group: rivaroxaban 77.70 ± 7.35 (79) years (Mean ± STD (Median)), VKA 78.45 ± 7.55 (79) years, no AC 80.60 ± 9.17 (83) years. In all three groups the proportion of males was higher than the proportion of females: count and proportion of males was 415 (54.3%) in the rivaroxaban treatment group, 397 (57.5%) in the VKA treatment group and 50 (56.2%) in the no AC treatment group. The vast majority of patients (>98%) was white.

Evaluation of different risk scores for baseline characteristics revealed that patients in the rivaroxaban treatment group were healthier than patients in the VKA treatment group and propensity score matching (PSM) did not completely remove this imbalance.

Evaluation of efficacy endpoints

Primary endpoint

The primary analysis of progression of CKD concerned the change from baseline to month 12 in eGFR and was conducted in the PSM analysis set. An ANCOVA for the change from baseline with treatment group as factor and baseline eGFR as covariate yielded the following results: The least squares mean (LSMean) of the change in eGFR was (LSMean [95% CI]) 0.89 [-0.18, 1.96] mL/min/1.73 m² in the rivaroxaban treatment group and -0.11 [-1.16, 0.94] mL/min/1.73 m² in the VKA treatment group with a difference (rivaroxaban - VKA) of 0.99 [-0.51, 2.49] mL/min/1.73 m² (*p*-value: 0.1935). Although the result is not statistically significant it shows a tendency in favor of rivaroxaban. This result is supported by the corresponding analysis in the ITT analysis set which showed an LSMean change from baseline of 0.72 [-0.13, 1.57] mL/min/1.73 m² in the rivaroxaban treatment group and -0.01 [-0.92, 0.89] mL/min/1.73 m² in the VKA treatment group with a difference of 0.73 [-0.54, 2.00] mL/min/1.73 m² (*p*-value: 0.2571).

Sensitivity analyses performed in the PSM and ITT analysis set using a repeated measurement model for the eGFR change at months 3, 6, 9 and 12 with treatment and time as factor, a treatment*time interaction term and baseline eGFR as covariate showed a statistically significant difference between the rivaroxaban and VKA treatment groups for the month 9 analysis visit (*p*-value: 0.0233). The results in the ITT analysis set were similar but without a statistically significant difference.

Primary safety outcomes

With regard to the primary safety outcomes, in the PSM analysis set there was no evidence of a significant difference between the rivaroxaban and the VKA treatment group. For all-cause mortality and net clinical benefit (at least for the event rates per 100 patient years), a statistically significant difference was observed in the ITT analysis set, this difference, however, can be attributed to the fact that patients in the rivaroxaban treatment group were generally healthier than patients in the VKA treatment group.

Table 1: Overview of primary safety outcomes (PSM analysis set)

Outcome	Category	Statistics	Rivaroxaban (N=400)	VKA (N=400)
Major bleeding	Event	N (%)	19 (4.8)	20 (5.0)
	No event	N (%)	381 (95.3)	380 (95.0)
All-cause mortality	Event	N (%)	56 (14.0)	59 (14.8)
	No event	N (%)	344 (86.0)	341 (85.3)
TIA, stroke or systemic arterial embolism	Event	N (%)	9 (2.3)	11 (2.8)
	No event	N (%)	391 (97.8)	389 (97.3)
Other major cardiovascular events (MACE)	Event	N (%)	3 (0.8)	5 (1.3)
	No event	N (%)	397 (99.3)	395 (98.8)
Symptomatic venous thromboembolic events	Event	N (%)	3 (0.8)	-
	No event	N (%)	397 (99.3)	400 (100)
Net clinical benefit	Event	N (%)	78 (19.5)	77 (19.3)
	No event	N (%)	322 (80.5)	323 (80.8)

Secondary endpoints

With regard to the secondary renal outcomes there was a significant difference between the rivaroxaban and VKA treatment group in the PSM analysis set namely regarding initiation of chronic renal replacement therapy and development of CKD stage 5 (non-dialysis and dialysis). Also, for rates and lengths of hospitalizations for any cause, there was a statistically significant difference in favor of rivaroxaban in the PSM analysis set. These results were supported by the corresponding results in the ITT analysis set. For all events associated with bleeding no evidence of a statistical difference between rivaroxaban and VKA treatment was shown in either analysis set.

Table 2: Overview of secondary event outcomes (PSM analysis set)

Outcome	Category	Statistics	Rivaroxaban (N=400)	VKA (N=400)
Initiation of chronic renal replacement therapy	Event	N (%)	3 (0.8)	12 (3.0)
	No event	N (%)	397 (99.3)	388 (97.0)
Persistence with OAC therapy	Event	N (%)	224 (56.0)	252 (63.0)
	No event	N (%)	176 (44.0)	148 (37.0)
CKD stage 5 - all events	Event	N (%)	18 (4.5)	40 (10.0)
	No event	N (%)	382 (95.5)	360 (90.0)
Acute kidney injury (AKI)	Event	N (%)	9 (2.3)	11 (2.8)
	No event	N (%)	391 (97.8)	389 (97.3)

Evaluation of safety endpoints

Overall, the safety profile was similar for the rivaroxaban and VKA treatment groups with slightly but - with the exception of cardiac failure which was more frequently observed in the VKA treatment group - not strikingly higher incidences in the VKA treatment group for most categories (reflecting again the fact that patients in the rivaroxaban treatment group were generally healthier at baseline than patients in the VKA treatment group).

Table 3: Summary of adverse events (Safety analysis set)

Category	Rivaroxaban (N=764)		VKA (N=691)		No AC (N=89)		Total (N=1544)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Any AE	454 (59.4)	1471	425 (61.5)	1573	62 (69.7)	181	941 (60.9)	3225
Any SAE	342 (44.8)	736	334 (48.3)	803	51 (57.3)	101	727 (47.1)	1640
Any AE related to AC medication	71 (9.3)	104	77 (11.1)	123	1 (1.1)	1	149 (9.7)	228
Any AE leading to treatment discontinuation	16 (2.1)	17	21 (3.0)	21	--	--	37 (2.4)	38
Any fatal AE	104 (13.6)	115	130 (18.8)	161	27 (30.3)	29	261 (16.9)	305

VKA vitamin K antagonist; AC anticoagulation; AE adverse event; SAE serious adverse event

Table 4: Summary of adverse events reported in at least 2% of patients by preferred term (Safety analysis set)

Category	Rivaroxaban (N=764)		VKA (N=691)		No AC (N=89)		Total (N=1544)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Cardiac failure	76 (9.9)	110	105 (15.2)	142	8 (9.0)	11	189 (12.2)	263
Dyspnea	32 (4.2)	34	36 (5.2)	43	4 (4.5)	4	72 (4.7)	81
Acute kidney injury	28 (3.7)	32	36 (5.2)	45	5 (5.6)	5	69 (4.5)	82
Unspecified death	24 (3.1)	24	26 (3.8)	26	5 (5.6)	5	55 (3.6)	55
Anemia	24 (3.1)	29	25 (3.6)	31	5 (5.6)	6	54 (3.5)	66
Urinary tract infection	26 (3.4)	30	24 (3.5)	28	1 (1.1)	1	51 (3.3)	59
Pneumonia	19 (2.5)	21	25 (3.6)	27	2 (2.2)	3	46 (3.0)	51
Fall	20 (2.6)	20	22 (3.2)	35	2 (2.2)	3	44 (2.8)	58
Edema peripheral	16 (2.1)	17	26 (3.8)	27	2 (2.2)	2	44 (2.8)	46
Epistaxis	23 (3.0)	31	13 (1.9)	16	0	0	36 (2.3)	47
Atrial fibrillation	20 (2.6)	30	14 (2.0)	23	1 (1.1)	1	35 (2.3)	54