

Original Research



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A Real-World, Prospective, Observational Study of Rivaroxaban on Prevention of Stroke and Non-Central Nervous Systemic Embolism in Renally Impaired Korean Patients With Non-Valvular Atrial Fibrillation: XARENAL

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AUTHOR'S SUMMARY

We evaluated the safety profile of rivaroxaban in patients with nonvalvular atrial fibrillation and moderate-to-severe renal impairment in routine clinical practice in Korea. The incidence of major bleeding and fatal bleeding was in the same order of magnitude as in those of other studies, and renal function was not aggravated. Thus, major bleeding rate and renal function change are acceptable following rivaroxaban treatment in routine clinical practice.

ABSTRACT

Background and Objectives: Several real-world studies have been done in patients with nonvalvular atrial fibrillation (NVAF); however, information on its safety profile in patients with renal impairment is limited. XARENAL, a real-world study, aimed to prospectively

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Trial Registration

ClinicalTrials.gov Identifier: [NCT03746301](#)

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Conflict of Interest

The authors have no financial conflicts of interest.

Data Sharing Statement

The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization: Choi KJ, Oh IY; Data curation: Sandmann M; Formal analysis: Sandmann M; Investigation: Choi KJ, Oh IY, Lee CH, Choi EK, Lim HE, Oh YS, Choi JI, Ahn MS, Kim JY, Kim NH, Yoon N; Writing - review & editing: Choi KJ, Oh IY, Lee CH, Choi EK, Lim HE, Oh YS, Choi JI, Ahn MS, Kim JY, Kim NH, Yoon N, Sandmann M.

investigate the safety profile of rivaroxaban in patients with NVAf with renal impairment (creatinine clearance [CrCl], 15–49 mL/min).

Methods: XARENAL is an observational single-arm cohort study in renal impairment NVAf patients. Patients were followed up approximately every 3 months for 1 year or until 30 days following early discontinuation. The primary endpoint was major bleeding events. All adverse events, symptomatic thromboembolic events, treatment duration, and renal function change from baseline were the secondary endpoints.

Results: XARENAL included 888 patients from 29 study sites. Overall, 713 (80.3%) had moderate renal impairment (CrCl, 30–49 mL/min), and 175 (19.7%) had severe renal impairment (CrCl, 15–29 mL/min) with a mean estimated glomerular filtration rate (eGFR) of 45.2 ± 13.0 mL/min/1.73 m². The mean risk scores were 3.3 ± 1.4 and 1.7 ± 0.9 for CHA₂DS₂-VASc score and HAS-BLED score, respectively. An incidence proportion of 5.6% (6.2 events per 100 patient-years) developed major bleeding; however, fatal bleeding occurred in 0.5% (0.5 events per 100 patient-years). The mean change in the eGFR was 2.22 ± 26.47 mL/min/1.73 m² per year.

Conclusions: XARENAL observed no meaningful differences in major bleeding events from other previous findings as well as renal function changes in rivaroxaban-treated NVAf patients with renal impairment, which is considered to be acceptable in clinical practice.

Trial Registration: ClinicalTrials.gov Identifier: [NCT03746301](#)

Keywords: Atrial fibrillation; Rivaroxaban; Renal insufficiency; Safety; Bleeding

INTRODUCTION

Atrial fibrillation (AF) prevalence has increased owing to concomitant diseases and population aging.^{1,2)} In Korea, it has significantly increased from 15.34 to 17.14 per 10,000 person-year between 2008 and 2015.³⁾ Unlike this similarity, Asian patients were reported differently from other ethnic population to have higher stroke-related morbidity and mortality, as well as more frequent bleeding events.⁴⁻⁷⁾

Since approval, nonvitamin K oral anticoagulant (NOAC) has played significant role in primary and secondary stroke prevention in AF patients instead of warfarin, a vitamin K antagonist.⁸⁻¹⁷⁾ However, several evidence found that lower estimated glomerular filtration rate (eGFR) levels increase major bleeding risks in NOAC like warfarin-treated patients with AF, especially in Asian population.^{18,19)} Therefore, anticoagulation strategy decision for Asian AF patients with decreased renal function has been difficult in terms of risk-benefit balance.

In general, the recommended dose of rivaroxaban is 20 mg once daily while it is different by renal function based on the ROCKET AF trial, the pivotal study for rivaroxaban, which is 15 mg once daily in patients with moderate (creatinine clearance [CrCl], 30–49 mL/min).¹⁴⁾ For AF patients with severe renal impairment (CrCl, 15–29 mL/min), 15 mg once daily is recommended to be used with caution based on pharmacokinetic and limited clinical data. To see clinical outcome derived from this label recommendation use of rivaroxaban, some real world evidence (RWE) studies of rivaroxaban were conducted.²⁰⁻²³⁾ Particularly, XANAP was a prospective observational single-arm study of nonvalvular atrial fibrillation (NVAf) patients who were prescribed with rivaroxaban (Xarelto®; Bayer AG Pharmaceuticals, Berlin, Germany) under routine treatment conditions for preventing stroke or non-central nervous system (CNS) systemic embolism (SE) in Asian countries.²⁰⁾ However, evaluating the

effectiveness and safety profile in patients with renal impairment in this study was difficult because 48.5% of CrCl data were missing.²⁰⁾ Therefore, this XARENAL study mainly aimed to assess the safety profile of rivaroxaban in patients with NVAF with renal impairment (CrCl, 15–49 mL/min) in routine clinical practice in Korea.

METHODS

Ethical statement

Information on the study's objectives, design, and study population was registered on ClinicalTrial.gov (NCT03746301). This study adhered to the ethical guidelines of the 2013 Declaration of Helsinki, and patients provided written consent to participate by signing an informed consent form before study enrollment. The protocol was approved by independent ethics committees and independent review boards as required (Asan Medical Center IRB approved number: 2018-1358). An independent academic steering committee oversaw the design, execution, and conduct of the study.

Study population and study design

This study was a multicenter prospective observational non-interventional single-arm cohort study in Korea. Adult patients (≥ 19 years old) were eligible if they had a diagnosis of NVAF and moderate-to-severe renal impairment, requiring rivaroxaban for stroke and non-CNS SE prevention per physician's decision. Major exclusion criteria included contraindications for rivaroxaban according to the local label, participating in other interventional studies, having planned treatment with other anticoagulants, or expected renal replacement therapy within the next 3 months. Moderate-to-severe renal impairment was defined as a documented CrCl of 15–49 mL/min within 6 months before study enrollment. Patients were followed up according to routine clinical practice regardless of this study. We collected the data from medical records at baseline visit and approximately every 3 months (months 3, 6, 9, and 12). The observational period was 1 year per patient. If the patient terminates the treatment earlier than planned, patients were followed up until 30 days after the end of rivaroxaban therapy.

The sample size is decided based on the XANAP study, which was the prospective observational study in patients with NVAF who started rivaroxaban across 10 Asia-Pacific countries including South Korea. In the XANAP study, the observed incidence proportion of major bleeding in the renal impaired subgroup was 2.5% among patients receiving 15 mg (or 5 out of 204 patients who experienced a major bleeding). Based on previous studies, the incidence of major bleeding in 1,000 patients with NVAF is assumed to be the same. A sample size of 1,000 patients was therefore considered to be sufficient to estimate the true incidence proportion of major bleeding in renal impaired patients with NVAF in a real-life practice condition by means of the Clopper-Pearson (exact) 95% confidence interval (CI) (width of CI, 2.045 [1.624–3.669]).

Outcomes

The primary endpoint was major bleeding events incidence defined using the International Society on Thrombosis and Hemostasis criteria: overt bleeding associated with a decrease in hemoglobin level of ≥ 2 g/dL, or a transfusion of ≥ 2 units of packed red blood cells or whole blood, or occurrence at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or death. The occurrence of adverse events (AEs), serious adverse events (SAEs), all-cause death, nonmajor

bleeding, symptomatic thromboembolic events, duration of rivaroxaban treatment (days), and renal function change from baseline using an eGFR calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula were the secondary outcomes.

Statistics analysis

Continuous variables were expressed as means $\pm$ standard deviations, and categorical variables were expressed as percentages (%). The raw incidence proportion (patients with events/number of treated patients) and incidence rate (number of patients with at least one event divided by the cumulative person time at risk per 100 patient-years) were presented with corresponding 95% CIs. Furthermore, analysis of major bleeding and renal function change according to the CrCl group at baseline (CrCl, 15–29 mL/min [severe]; CrCl, 30–49 mL/min [moderate]; and overall) was performed using Kaplan–Meier estimates. The analysis population of this study was full analysis set (FAS), which included all patients who were indicated as NVAF, had taken at least one dose of rivaroxaban, and had at least one post-baseline information collected. All tests were performed at the 2-sided 5% level, and all statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

Overall, 941 patients were screened from 29 study sites in Korea between December 2018 and July 2021, 924 (98.2%) of whom were included after 17 (1.8%) did not meet the inclusion and exclusion criteria. A total of 912 patients (96.9%) were completed in this study. Ultimately, 888 patients (94.4%) were included in the FAS. The reason for exclusion from the FAS was that no information was collected post-baseline (n=21) and concomitant medication treatment (n=3) (**Figure 1**).

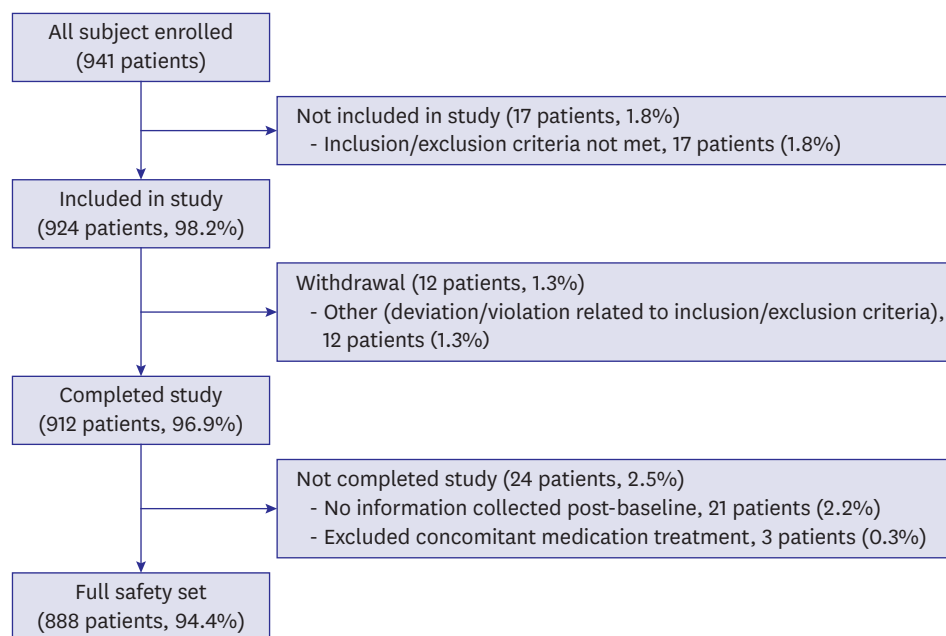


Figure 1. Patient disposition.

Table 1. Baseline characteristics and demographics of patients in XARENAL

Demographics	Rivaroxaban (n=888)
Age (years)	77.8±6.7
Sex (male)	492 (55.4)
Weight (kg)	62.3±10.6
BMI (kg/m ²)	24.3±3.5
Baseline CrCl (mL/min)	37.0±8.5
≥15 and <30	175 (19.7)
≥30 and <50	713 (80.3)
Baseline eGFR (CKD-EPI, mL/min per 1.73 m ²)	45.2±13.0
Dose	
20 mg	3 (0.3)
15 mg	791 (89.1)
10 mg	94 (10.6)
Comorbidities	
Congestive heart failure	234 (26.4)
Hypertension	703 (79.2)
Diabetes mellitus	304 (34.2)
Prior stroke/non-CNS SE/TIA	156 (17.6)
Prior MI	37 (4.2)
AF type	
First diagnosed	64 (7.2)
Paroxysmal	330 (37.2)
Persistent	376 (42.3)
Permanent	118 (13.3)
Medication at baseline	
Antithrombotic agents	122 (13.7)
Betablockers	525 (59.1)
RAS-acting agents	515 (58.0)
Lipid modifying agents	482 (54.3)
Calcium channel blockers	239 (26.9)
Diuretics	520 (58.6)
Vasoprotectives	18 (2.0)
Peripheral vasodilators	23 (2.6)
Antihypertensives	10 (1.1)
CHADS ₂ score	1.7±1.1
CHA ₂ DS ₂ -VASC score	3.3±1.4
HAS-BLED score	1.7±0.9

Values are presented as mean ± standard deviation or number (%).

AF = atrial fibrillation; BMI = body mass index; CKD-EPI = chronic kidney disease epidemiology collaboration; CNS = central nervous system; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; RAS = renin-angiotensin system; SE = systemic embolism; TIA = transient ischemic attack.

The patient characteristics are presented in **Table 1**. For the FAS, the mean age was 77.8±6.7 years, and 55.4% of participants were male. The mean of baseline CrCl was 37.0±8.5 mL/min, and the mean of baseline eGFR was 45.2±13.0 mL/min/1.73 m². Renal impairment severity classified on the basis of CrCl was moderate ranged from 30 to 49 mL/min and severe ranged from 15 to 29 mL/min in 80.3% (n=713) and 19.7% (n=175) of participants, respectively. Most patients had hypertension (HTN, n=703, 79.2%), followed by diabetes mellitus (DM, n=304, 34.2%) and congestive heart failure (CHF, n=234, 26.4%). Over half of the patients used beta blocker (n=525, 59.1%), diuretics (n=520, 58.6%), renin-angiotensin system-acting agents (n=515, 58.0%), and lipid modifying agents (n=482, 54.3%). The mean risk scores for CHADS₂, CHA₂DS₂-VASC, and HAS-BLED were 1.7±1.1, 3.3±1.4, and 1.7±0.9, respectively. In the FAS of 888 patients, 7.2% (n=64), 42.3% (n=376), 37.2% (n=330), and 13.3% (n=118) were first diagnosed with NVAf, persistent AF, paroxysmal AF, and permanent AF, respectively. Most patients (n=791, 89.1%) were treated with 15 mg of rivaroxaban once daily, 10.6% (n=94) with 10 mg, and 0.3% (n=3) with 20 mg.

Table 2. Summary of primary and secondary outcome

	Incidence proportion	Incidence rate per 100 patient-years (95% CI)
Primary outcome		
Major bleeding*	50 (5.6)	6.2 (4.6–8.2)
Decrease of hemoglobin of ≥ 2 g/dL	27 (3.0)	3.3 (2.2–4.9)
Transfusion of ≥ 2 units of packed red blood cells or whole blood	32 (3.6)	4.0 (2.7–5.6)
Fatal	4 (0.5)	0.5 (0.1–1.3)
Gastrointestinal major bleeding	19 (2.1)	2.3 (1.4–3.7)
Secondary outcome		
Adverse event	463 (52.1)	-
Serious adverse event	169 (19.0)	-
All-cause death	18 (2.0)	-
Non-major bleeding	93 (10.5)	-
Symptomatic thromboembolic events	12 (1.4)	-
Rivaroxaban persistence (days)	336.0 $\pm$ 111.6	-
eGFR (CKD-EPI) change from baseline (mL/min per 1.73 m ² per year)	2.22 $\pm$ 26.47	-

Values are presented as number (%) or mean $\pm$ standard deviation.

CI = confidence interval; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate.

*Occurrence at a critical site (intracranial, intra-spinal, intraocular, pericardial, intra articular, intra-muscular with compartment syndrome, retroperitoneal) were not collected.

Outcomes

The primary and secondary outcomes are presented in **Table 2**. Overall, 5.6% (n=50) of 888 patients developed major bleeding. The incidence proportion of major bleeding by categories was 3.6% (n=32) with transfusion of ≥ 2 units of packed red blood cells or whole blood, 3.0% (n=27) with a decrease in hemoglobin level of ≥ 2 g/dL, and 2.1% (n=19) with gastrointestinal major bleeding. Fatal bleeding occurred in 4 patients (0.5%). The incidence rate of major bleeding was 6.2 events per 100 patient-years (95% CI, 4.6–8.2); transfusion of ≥ 2 units of packed red blood cells or whole blood, decrease in hemoglobin level of ≥ 2 g/dL, gastrointestinal major bleeding, and fatal bleeding occurred at 4.0 (95% CI, 2.7–5.6), 3.3 (95% CI, 2.2–4.9), 2.3 (95% CI, 1.4–3.7), and 0.5 events per 100 patient-years (95% CI, 0.1–1.3), respectively.

Non-major bleeding and symptomatic thromboembolic events were observed in 93 (n=10.5%) and 12 (1.4%) patients, respectively. All-cause death including due to major bleeding occurred in 18 patients (2.0%) during the observational period. The mean rivaroxaban treatment persistent duration was 336.0 $\pm$ 111.6 days, and the mean change in eGFR per year was 2.22 $\pm$ 26.47 mL/min/1.73 m². Approximately half of the patients (n=463, 52.1%) experienced AEs, and 19.0% (n=169) were reported as SAEs. Large portions among AEs were found from mediastinal disorders (16.8%) such as dyspnea or cough, gastrointestinal disorder (11.9%) including constipation, cardiac disorders (10.5%) like palpitation, and general condition disorders (9.7%). Among them, drug-related AEs was 11.8% of which the largest portion was found from gastrointestinal disorders (3.8%) including gingival bleeding (0.8%).

Additional outcomes

The detailed baseline characteristics and demographics by CrCl group of 15–29 (severe group, n=175) and 30–49 mL/min (moderate group, n=713) are shown in **Supplementary Table 1**.

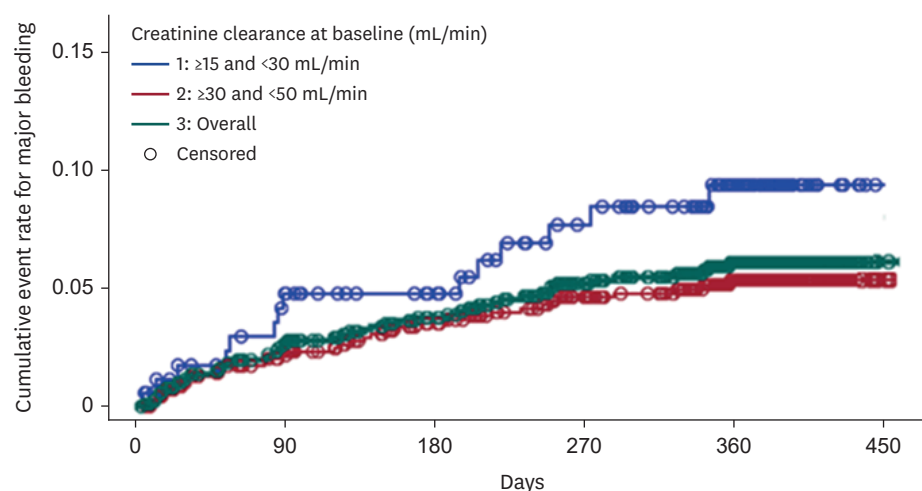
The mean age of participants in the severe and moderate groups was 81.7 $\pm$ 5.7 and 76.9 $\pm$ 6.6 years, respectively, and the proportion of males was 41.7% and 58.8% in the severe and

moderate groups, each. The mean body mass index was 22.8 ± 3.0 and 24.7 ± 3.6 kg/m² in the severe and moderate groups, respectively. The severe group had higher mean risk scores than the moderate group (CHADS₂ score, 2.1 ± 1.1 vs. 1.6 ± 1.1 ; CHA₂DS₂-VASc score, 3.9 ± 1.4 vs. 3.1 ± 1.3 ; and HAS-BLED score, 1.9 ± 0.9 vs. 1.6 ± 0.8 , respectively).

In both the CrCl groups, most patients (81.7% in severe group and 90.9% in moderate group) were treated with 15 mg of rivaroxaban once daily. However, the proportion of patients treated with 10 mg of rivaroxaban was higher in the severe group (17.7%) comparing the moderate group (8.8%). eGFR change from baseline to final visit was evaluated in patients who had data at 12 months or early termination because there were missing data per visit; 106 and 395 patients in the severe and moderate groups, respectively, were included in the analysis (**Supplementary Table 2**).

The incidence proportion of major bleeding was 8.6% (n=15) of 175 and 4.9% (n=35) of 713 patients in the severe and moderate groups, respectively (**Supplementary Table 3**). Fatal bleeding occurred in 0.6% (n=1) and 0.4% (n=3) of the patients in the severe and moderate groups, respectively. The cumulative event rate for major bleeding gradually increased with time on treatment, both in moderate and severe renal impairment; however, it was higher in patients with severe renal impairment (**Figure 2**). The incidence proportion of major bleeding was generally higher in patients with severe renal impairment.

Similarly, the mean change in eGFR from baseline to final visit was 4.1 ± 21.4 and 1.7 ± 27.7 in patients with severe and moderate renal impairments, respectively (**Supplementary Table 3**). The median of annualized eGFR change from baseline to final visit was similar in patients with severe and moderate renal impairments (**Supplementary Figure 1**).



Number of patients at risk						
1	175	156	140	120	86	5
2	713	664	626	580	431	47
3	888	820	766	700	517	52

At-risk subject counts were calculated as at start of timepoint.

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Figure 2. Kaplan-Meier plot according to the occurrence of major bleeding by baseline creatinine clearance group.

DISCUSSION

XARENAL is the first prospective observational study to evaluate the safety profile of rivaroxaban in NVAF patients with moderate-to-severe renal impairment in clinical practice in Korea. Other previous global prospective observational studies to assess the safety profile of rivaroxaban in routine clinical practice such as XANTUS program including XANTUS study in European region and XANAP study in Asia-Pacific region, and XaMINA in Korea and Taiwan had limited portion of patients with renal impairment, which was around 10%.²⁰⁻²³⁾ As shown in **Table 3**, the demographics of XARENAL were different from the others indicating XARENAL study patients had older age, lower weight, and majority prescribed dose of 15 mg (78.7%). Other distinct difference was that XARENAL study patients had higher co-morbidities such as CHF, HTN, and DM, with relatively low proportion of patients with prior stroke/non-CNS SE/transient ischemic attack as 17.6% (19.0%, 33.0%, 47.0% in XANTUS, XANAP, and XANAP KR, respectively). Additionally, slightly lower stroke risk in XARENAL study was found by mean CHADS₂ and CHA₂DS₂-VASc scores with 1.7 and 3.3, respectively (2 and 3.4 in XANTUS, 2.3 and 3.7 in XANAP, and 2.5 and 3.8 in XANAP KR, respectively). The thromboembolic event occurrence per 100 patient-years were similarly shown in trend as 1.4 in XARENAL, 1.8 in XANTUS, 2.6 in XANAP, and 2 in XANAP KR. On the other hand, the major bleeding incidence rate was much higher in XARENAL study patients as 6.2% compared to 2.1% in XANTUS, 1.5% in XANAP, and 1.1% in XANAP KR. However, fatal bleeding occurrence was similar across the studies, which was 0.5 events per 100 patient-years in XARENAL and <1 event in 100 patients per year in the others. This implied renal impairment condition might increase bleeding tendency on rivaroxaban intake, especially in severe renal impairment group (moderate renal impairment, 4.9%; severe renal impairment, 8.6%) (**Supplementary Table 3**), but the bleeding would not be fatal

Table 3. Baseline characteristics and major outcomes from other real-world studies

	XANTUS (n=6,784)	XANAP (n=2,273)	XANAP KR (n=844)	XaMINA (n=1,094)	XARENAL (n=888)
Baseline characteristics					
Mean age (years)	71.5	70.5	70.1	70.1	77.8
Mean weight (kg)	83	66.1	65.6	66.7	62.3
CrCl <50 mL/min (%)	9.4	16.3	13.1	13.9	100
Dose (first initial dose, %)					
20 mg	78.7	49.8	58.8	44.7	0.3
15 mg	20.8	73.5	35	44.6	89.1
10 mg	0.5*	5.9	6.2	10.7*	10.6
Co-morbidities (%)					
CHF	19	20	15.2	16.1	26.4
HTN	75	74	70.3	72.9	79.2
DM	20	27	25.8	26.8	34.2
Prior stroke/non-CNS SE/TIA	19	33	47	4.3	17.6
Mean CHADS ₂ score	2	2.3	2.5	1.6	1.7
Mean CHA ₂ DS ₂ -VASc score	3.4	3.7	3.8	2.9	3.3
Major outcomes (events/100 patient-years)					
Major bleeding	2.1	1.5	1.1	2.1	6.2
Fatal	0.2	0.2	0.3	0.1	0.5
Thromboembolic events (stroke, non-CNS SE, TIA, and MI)	1.8	2.6	2	0.9	1.4
Stroke	0.7	1.7	1.6	0.5	0.9
MI	0.4	0.5	0.3	0.3	0.2
Death (events/100 patient-years)	1.9	2	1.6	0.8	2.2

CHF = congestive heart failure; CNS = central nervous system; CrCl = creatinine clearance; DM = diabetes mellitus; HTN = hypertension; MI = myocardial infarction; SE = systemic embolism; TIA = transient ischemic attack.

*Indicated as other dose.

mostly. Apart from the post-hoc analysis of renal impairment population from ROCKET-AF trial, a retrospective observational chronic kidney disease (CKD) cohort study supported this finding with reported occurrence of 84.1% non-fatal bleeding event in non-end-stage CKD.²⁴⁾²⁵⁾ Similar finding was presented from the GLORIA-AF study with clinical outcome in dabigatran treated patients stratified by CrCl, though there were limited data to compare this results with other NOACs or warfarin.²⁶⁾

The overall mean change in annualized eGFR from baseline to final visit was 2.22 mL/min/1.73 m² in XARENAL (**Table 2**). From exploratory analysis for renal function specification, patients with severe renal impairment experienced an increase of 4.1 mL/min/1.73 m², and patients with moderate renal impairment had an increase of 1.7 mL/min/1.73 m² (**Supplementary Table 3, Supplementary Figure 1**). This change was similar to a previous retrospective study that evaluated the renal outcome of anticoagulants in patients with AF in Thailand (the eGFR change was 4.63 mL/min/1.73 m² in NOAC-treated patients).²⁷⁾ Moreover, the decline in annualized eGFR in adults with more advanced CKD ranged from -1.92 to -4.12 mL/min/1.73 m² according to the NICE guideline 2021 for CKD management.²⁸⁾ The renal function change was <5 mL/min/1.73 m² for 1 year in XARENAL, indicating no clinically significant changes in renal function. This result reassured that rivaroxaban does not act as a renal function aggravating factor. Nonetheless, we should be more cautious to monitor renal function in patients with CKD, as clinical guidelines recommend reassessing renal function at a minimum interval of 10 months if the CrCl is <60 mL/min.²⁹⁾ But, this study revealed the current situation of low rate of renal function laboratory test per follow-up visit, even in the population with severe renal impairment (CrCl, 15–29 mL/min) (**Supplementary Table 2**).

Overall findings from this study will help demonstrate the safety profile and effectiveness of rivaroxaban in the population with renal impairment, allowing its more comprehensive use in stroke and SE prevention in NVAf. Especially for the CrCl 15–29 patients, this data may be additional clinical evidence for use beside existing RWE data.²⁰⁻²³⁾ Because this indication of range was excluded from ROCKET AF and got approved based on limited clinical data and a pharmacokinetic model analysis of phase II study population.¹⁴⁾³⁰⁾

However, there are some limitations which should be noted. Firstly, selection or reporting bias (Hawthorne effect) could exist owing to observational study inheritance. Secondly, missing and incomplete data during follow-up visits were not avoidable despite efforts were made to collect as complete data as possible and provide instructions to investigators. Thirdly, there were differences in eGFR and CrCl estimates because of the lack of body weight in several patients. Lastly, interpretation for subgroup analysis for severe and moderate renal impairment comparison should be cautious due to its exploratory nature in statistics. Additional study with well-designed is needed in the future.

XARENAL is the first real-world study in prospective manner to evaluate the safety profile of rivaroxaban in patients with NVAf and moderate-to-severe renal impairment in Korea. Although the bleeding incidence was higher than other RWE studies, rivaroxaban in patients with NVAf with moderate-to-severe renal impairment ranging from 15 to 49 mL/min was found to be generally well tolerated with favorable benefit-risk balance. Therefore, XARENAL is meaningful in contributing to the wealth of data needed in clinical practice.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline characteristics and demographics by CrCl groups

Supplementary Table 2

Sample size for estimated glomerular filtration rate per visit and baseline CrCl groups

Supplementary Table 3

Summary of primary outcome and renal function change by CrCl group

Supplementary Figure 1

Annualized estimated glomerular filtration rate change from baseline to final visit.

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