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Original article

Real-world outcomes of rivaroxaban treatment in patients with nonvalvular atrial fibrillation and worsening renal function

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ABSTRACT

Background: Rivaroxaban is a direct oral anticoagulant administered to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). The Xarelto Post-Authorization Safety and Effectiveness Study in Japanese Patients with Atrial Fibrillation (XAPASS) was a prospective, observational, post-marketing surveillance study that examined the safety and effectiveness of rivaroxaban in routine clinical practice. This sub-analysis of the XAPASS investigated the outcomes of patients with worsening renal function (WRF).

Methods: The XAPASS included 11,308 patients with NVAF who began treatment with rivaroxaban. Of 9578 patients who completed 1-year follow-up, the 7509 patients, for whom the change in creatinine clearance could be assessed, were included in the present analysis. Patients with WRF were those with a decrease in creatinine clearance of $\geq$20% from enrollment to any time point; patients with stable renal function (SRF) were those without such a decrease. Outcomes in patients with WRF versus SRF were compared at 1 year.

Results: We identified 1229 patients with WRF and 6280 patients with SRF. Patients with WRF were older and had higher mean $CHADS_2$ and modified HAS-BLED scores compared to patients with SRF. The incidence rates of any bleeding (hazard ratio: 1.12; 95% confidence interval: 0.88–1.41), major bleeding (1.20; 0.75–1.90), and the composite endpoint stroke/systemic embolism/myocardial infarction (1.06; 0.65–1.71) were similar between the two groups.

Conclusions: No association between WRF and occurrence of any bleeding, major bleeding, and stroke/systemic embolism/myocardial infarction was observed in patients with AF on rivaroxaban treatment during 1-year follow-up in real-world clinical practice. Clinicaltrials.gov: NCT01582737.

Introduction

Atrial fibrillation (AF), one of the most common cardiac arrhythmias, increases the risk of stroke by five-fold [1]. Its prevalence is increasing steadily as the population ages [2]. Warfarin had been the only direct oral anticoagulant available to reduce

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the risk of stroke in patients with nonvalvular AF (NVAF), but nonvitamin K antagonist oral anticoagulants were approved and have become widely adopted in clinical practice per the recommended guidelines [3–6].

Rivaroxaban is a direct factor Xa inhibitor and its safety and efficacy relative to warfarin were examined in two phase III clinical trials. In the ROCKET AF study of 14,264 patients with NVAF at 1178 sites worldwide, rivaroxaban was found to be noninferior to warfarin for the prevention of stroke or systemic embolism [7]. In a similar study, the J-ROCKET AF study, which focused on Japanese patients and Japan-specific rivaroxaban dosages, rivaroxaban was found to be noninferior to warfarin for the principal safety outcome of major and non-major clinically relevant bleeding in patients with AF [8].

Patients with AF and renal disease have risks of both bleeding and thromboembolism [9–12]. A sub-analysis of the ROCKET AF study focused on patients with worsening renal function (WRF) and their outcomes when treated with rivaroxaban versus warfarin [13]. The rates of stroke or systemic embolism (SE) and major or non-major clinically relevant bleeding were similar between patients with stable renal function (SRF) and WRF. Patients with WRF randomized to receive rivaroxaban had lower rates of stroke or SE compared with patients with WRF who received warfarin (1.54 versus 3.25 events per 100 patient-years). There was no difference in major or non-major clinically relevant bleeding between rivaroxaban and warfarin groups.

Although the association between WRF and rivaroxaban treatment outcomes was examined in the phase III clinical trial, it remains unclear in real-world clinical practice. Real-world studies are important because the patient enrollment in clinical trials is restricted and not the same as in a real-world setting. The Xarelto Post-Authorization Safety and Effectiveness Study in Japanese Patients with Atrial Fibrillation (XAPASS) was a nationwide, prospective, single-arm, real-world observational study that examined the safety and effectiveness of rivaroxaban in patients with AF in Japanese real-world clinical practice [14]. The incidence rates of bleeding and thrombolytic events suggest that rivaroxaban is safe and effective for stroke prevention in a real-world setting [15]. The current sub-analysis of the XAPASS 1-year data focused on the safety and effectiveness of rivaroxaban in patients with WRF compared to those with SRF.

Materials and methods

Study design

The XAPASS was a real-world, nationwide, prospective, open-label, single-arm, observational, post-authorization, noninterventional cohort study; its study design has been described in detail elsewhere [14]. The study was approved by the Ministry of Health, Labour, and Welfare in Japan and was carried out in accordance with the standards for Good Post-marketing Study Practice provided by this ministry. The current sub-analysis of the XAPASS examined 1-year outcomes in patients with WRF compared to those with SRF.

Patients

The XAPASS included 11,308 men and women with NVAF from 1419 institutions who were starting rivaroxaban therapy for the prevention of ischemic stroke and SE [14]. The 1-year data included 9578 patients who had completed follow-up for at least 11 months, who discontinued rivaroxaban treatment within 1 year, or who were lost to follow-up within 1 year [15]. Among them, 7509 patients had their creatinine clearance (CrCl) measured at least twice (once at enrollment, and at least once between the day after rivaroxaban treatment initiation and Day 365, or 14 days after treatment discontinuation for patients who discontinued treatment within 1 year). These 7509 patients were included in this sub-analysis. Patients with WRF were defined as those with a CrCl decrease of $\geq$20% of the enrollment measurement, at any time during the 1-year follow-up. Patients with SRF were defined as those without such a decrease. This definition was based on the ROCKET AF sub-analysis [13]. The CrCl was estimated using the Cockcroft-Gault equation.

Treatment

The oral rivaroxaban dosage and treatment duration were at the discretion of the treating physicians. The approved dose in Japan for the prevention of thromboembolic events in NVAF patients is 15 mg once daily (od) (10 mg od for the patients with a CrCl of $<$50 ml/min).

Risk scores

The following stroke risk scores were determined at baseline for patients with WRF versus those with SRF: $CHADS_2$ (congestive heart failure, hypertension, age, diabetes mellitus, stroke) [16] and CHA_2DS_2-VASc [congestive heart failure/left ventricular dysfunction, hypertension, age $\geq$75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, age 65–74 years, sex category] [17]. The modified HAS-BLED bleeding risk score was also determined at baseline and included the following factors: hypertension, abnormal liver/renal function, stroke/TIA history, bleeding predisposition, elderly, and drug/alcohol use. The labile international normalized ratio was excluded from the score [11,15].

Study outcomes

The primary safety outcome was any bleeding. Major bleeding and intracranial hemorrhage were recorded as the components. Major bleeding was defined using the International Society of Thrombosis and Haemostasis criteria [18], whereas non-major bleeding was defined as any bleeding that did not meet those criteria. The primary effectiveness outcome was a composite of stroke (hemorrhagic or ischemic), non-central nervous system (non-CNS) SE, and myocardial infarction (MI). Stroke and ischemic stroke were recorded as individual outcomes. The stroke endpoint did not include TIA. Outcomes were defined previously [14].

Statistical analysis

All statistical analyses were performed using SAS version 9.2 or higher (SAS Institute Inc., Cary, NC, USA). Baseline characteristics were compared between SRF and WRF patients by use of Wilcoxon rank-sum tests for continuous variables and Pearson χ^2 tests for categorical variables. Outcomes during 1 year after the initiation of rivaroxaban treatment were analyzed. Hazard ratios (HRs) were based on COX proportional hazards models. Values for p were calculated by log-rank test. Considering study design of this post-marketing surveillance, p-values less than 5% were considered nominally statistically significant.

Results

Patients

Of 7509 patients included in this sub-analysis, WRF was observed in 1229 patients (16.4%) and 6280 patients (83.6%) had SRF. Characteristics of patients with SRF and those with WRF are compared in Table 1. A higher proportion of patients with WRF

Table 1
Patient characteristics.

Characteristic	SRF group (*N* = 6280)	WRF group (*N* = 1229)	*p*-Value
Age, years	72.9 ± 9.5	75.0 ± 9.6	<0.001
Female sex	2319 (36.9)	536 (43.6)	<0.001
Body weight, kg	61.3 ± 12.5	61.3 ± 15.0	0.157
BMI, kg/m^2	23.8 ± 3.7	24.5 ± 5.0	0.002
SCr, mg/dl	0.9 ± 0.2	0.8 ± 0.3	<0.001
CrCl, ml/min	66.6 ± 24.8	70.9 ± 31.8	0.003
CrCl, ml/min [*n* (%)]			
<15	2 (<0.1)	0	
15 to <30	176 (2.8)	49 (4.0)	
30 to <50	1463 (23.3)	274 (22.3)	
50 to <80	2968 (47.3)	512 (41.7)	
≥80	1671 (26.6)	394 (32.1)	
$CHADS_2$ score, mean ± SD	2.1 ± 1.3	2.5 ± 1.3	<0.001
Score, *n* (%)			
0	547 (8.7)	47 (3.8)	
1	1604 (25.5)	212 (17.2)	
2	1902 (30.3)	393 (32.0)	
3	1211 (19.3)	309 (25.1)	
4	703 (11.2)	171 (13.9)	
5	261 (4.2)	71 (5.8)	
6	52 (0.8)	26 (2.1)	
CHA_2DS_2-VASc score	3.4 ± 1.6	3.9 ± 1.6	<0.001
Score			
0	159 (2.5)	8 (0.7)	
1	605 (9.6)	72 (5.9)	
2	1132 (18.0)	134 (10.9)	
3	1495 (23.8)	288 (23.4)	
4	1410 (22.5)	313 (25.5)	
5	876 (13.9)	234 (19.0)	
6	428 (6.8)	116 (9.4)	
7	154 (2.5)	46 (3.7)	
8	20 (0.3)	17 (1.4)	
9	1 (<0.1)	1 (<0.1)	
Modified HAS-BLED score[a]	1.5 ± 1.0	1.7 ± 1.0	<0.001
Score			
0	800 (12.7)	99 (8.1)	
1	2602 (41.4)	448 (36.5)	
2	1954 (31.1)	429 (34.9)	
3	746 (11.9)	197 (16.0)	
4	158 (2.5)	52 (4.2)	
5	18 (0.3)	4 (0.3)	
6	1 (<0.1)	0	
7	0	0	
8	0	0	
Baseline comorbidities			
Hypertension	4728 (75.3)	989 (80.5)	<0.001
Diabetes mellitus	1441 (22.9)	316 (25.7)	0.036
Prior stroke/TIA	1427 (22.7)	334 (27.2)	<0.001
Congestive heart failure	1472 (23.4)	434 (35.3)	<0.001
Hepatic dysfunction	395 (6.3)	93 (7.6)	0.097
Type of AF			0.904
Paroxysmal	2112 (33.6)	407 (33.1)	
Persistent	2268 (36.1)	452 (36.8)	
Permanent	1567 (25.0)	307 (25.0)	
Other	16 (0.3)	3 (0.2)	
Unknown	317 (5.0)	60 (4.9)	
Concomitant use of antiplatelet(s)			<0.001
No	5282 (84.1)	987 (80.3)	
Yes	975 (15.5)	238 (19.4)	
Aspirin	560 (8.9)	127 (10.3)	0.116

Data are presented as *n* (%) or mean ± standard deviation.
AF, atrial fibrillation; BMI, body mass index; CrCl, creatinine clearance; INR, international normalized ratio; SCr, serum creatinine; SRF, stable renal function; TIA, transient ischemic attack; WRF, worsening renal function.
[a] Maximum score is 8 because of the exclusion of the factor "labile INR" from the HAS-BLED score.

were female ($p < 0.001$). Patients with WRF were older ($p < 0.001$) and had a higher body mass index ($p = 0.002$) than SRF patients. Patients with WRF also had higher $CHADS_2$ and CHA_2DS_2-VASc scores, indicating an increased risk of stroke, and a higher modified HAS-BLED score, indicating an increased risk of major bleeding (all $p < 0.001$).

In accordance with the higher $CHADS_2$ and CHA_2DS_2-VASc scores, a higher proportion of patients with WRF had baseline comorbidities of hypertension ($p < 0.001$), diabetes mellitus ($p = 0.036$), prior stroke/TIA ($p < 0.001$), and congestive heart failure ($p < 0.001$). Furthermore, WRF patients were significantly more likely to use concomitant antiplatelet agents ($p < 0.001$).

Treatment

Of the 4639 patients with SRF and a CrCl of ≥50 ml/min, 3040 (65.5%) patients received a rivaroxaban dosage of 15 mg od, and 1599 (34.5%) received a dosage of 10 mg od (under-dose). Of the 906 patients with WRF and a CrCl of ≥50 ml/min, 498 (55.0%) patients received a rivaroxaban dosage of 15 mg od, and 408 (45.0%) received a dosage of 10 mg od (under-dose).

Of the 1641 patients with SRF and a CrCl of <50 ml/min, 190 (11.6%) received a rivaroxaban dosage of 15 mg od (over-dose), and 1451 (88.4%) received a dosage of 10 mg od. Of the 323 patients with WRF and a CrCl of <50 ml/min, 17 (5.3%) received a rivaroxaban dosage of 15 mg od (over-dose), and 306 (94.7%) received a dosage of 10 mg od.

The mean treatment duration was 316 ± 104 days (median 365 days) in patients with SRF and 316 ± 102 days (median 365 days) in patients with WRF. At the 1-year follow-up with SRF, 4450 (70.9%) continued rivaroxaban treatment, and 703 (11.2%) discontinued rivaroxaban treatment; the remaining 1127 (17.9%) were lost to follow-up (including patient transfer). Of the patients with WRF, 822 (66.9%) continued rivaroxaban treatment, and 160 (13.0%) discontinued rivaroxaban treatment; the remaining 247 (20.1%) were lost to follow-up (including patient transfer).

Safety outcomes

There were no significant differences in any bleeding, major bleeding, or intracranial hemorrhage between the SRF and WRF groups (Table 2 and Fig. 1A and B). There was a significantly higher incidence rate of bleeding with transfusion of ≥2 units of packed red blood cells or whole blood in the WRF group vs. the SRF group (0.5 vs. 0.1 events per 100 patient-years, HR 3.19, 95% CI 1.04–9.74) and the actual numbers of patients who received ≥2 units were 5 (0.4%) and 8 (0.1%), respectively. Patients with WRF also had a higher incidence rate of all-cause mortality (4.2 vs. 1.8 events per 100 patient-years, HR 2.29, 95% CI 1.62–3.24). Adverse events leading to death in patients with SRF and WRF are listed in Online Table 1. Death caused by adverse drug reaction occurred in 18 (0.3%) and 4 (0.3%) patients in SRF and WRF group, respectively (HR 1.14, 95% CI 0.39–3.37).

Effectiveness outcomes

There were no significant differences in the composite stroke/non-CNS SE/MI endpoint (Fig. 1C) or in the stroke or ischemic stroke endpoints between the SRF and WRF groups (Table 2).

The effect of initial CrCl on outcomes

When each safety and effectiveness outcome was dichotomized by CrCl at enrollment (CrCl of ≥50 ml/min. vs. CrCl of <50 ml/min, Table 3), there was no difference in incidence rates for any bleeding, major bleeding, intracranial hemorrhage, stroke/non-CNS SE/MI,

Table 2
Study outcomes.

Outcomes	SRF group		WRF group		HR (95% CI), WRF vs. SRF group	*p*-Value
	Incidence proportion, *n* (%)	Incidence rate, event per 100 patient-years (95% CI)	Incidence proportion, *n* (%)	Incidence rate, event per 100 patient-years (95% CI)		
Safety outcomes	(*N* = 6280)		(*N* = 1229)			
Any bleeding	389 (6.2)	7.2 (6.5–7.9)	85 (6.9)	8.1 (6.4–9.8)	1.12 (0.88–1.41)	0.350
Major bleeding	94 (1.5)	1.7 (1.4–2.0)	22 (1.8)	2.0 (1.2–2.9)	1.20 (0.75–1.90)	0.447
Fatal	11 (0.2)	0.2 (0.1–0.3)	1 (0.1)	0.1 (0.0–0.3)	0.47 (0.06–3.61)	0.454
Critical organ bleeding	49 (0.8)	0.9 (0.6–1.1)	8 (0.7)	0.7 (0.2–1.2)	0.84 (0.40–1.76)	0.636
Intracranial hemorrhage	45 (0.7)	0.8 (0.6–1.0)	7 (0.6)	0.6 (0.2–1.1)	0.80 (0.36–1.76)	0.573
Hemoglobin decrease ≥2 g/dl	32 (0.5)	0.6 (0.4–0.8)	8 (0.7)	0.7 (0.2–1.2)	1.28 (0.59–2.78)	0.532
Transfusion of ≥2 units of packed RBC or whole blood	8 (0.1)	0.1 (0.0–0.2)	5 (0.4)	0.5 (0.1–0.9)	3.19 (1.04–9.74)	0.032
All-cause mortality	103 (1.6)	1.8 (1.5–2.2)	46 (3.7)	4.2 (3.0–5.5)	2.29 (1.62–3.24)	<0.001
Effectiveness outcomes	(*N* = 6260)		(*N* = 1223)			
Stroke/non-CNS SE/MI	97 (1.5)	1.8 (1.4–2.1)	20 (1.6)	1.9 (1.0–2.7)	1.06 (0.65–1.71)	0.824
Stroke	92 (1.5)	1.7 (1.3–2.0)	15 (1.2)	1.4 (0.7–2.1)	0.83 (0.48–1.44)	0.515
Ischemic stroke	62 (1.0)	1.1 (0.8–1.4)	12 (1.0)	1.1 (0.5–1.7)	0.99 (0.53–1.84)	0.977

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; non-CNS SE, non-central nervous system systemic embolism; RBC, red blood cells; SRF, stable renal function; WRF, worsening renal function.

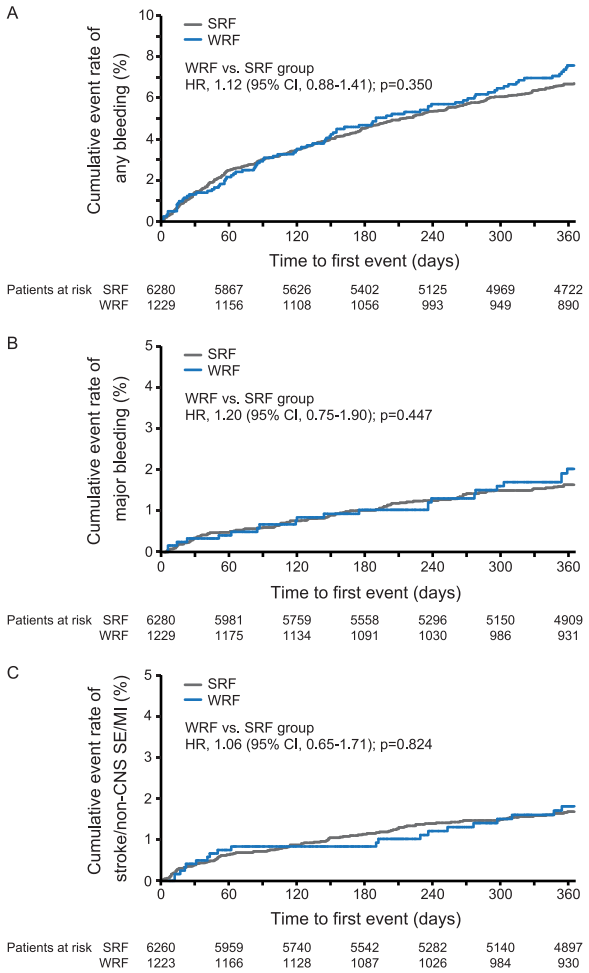


Fig. 1. Cumulative rates of (A) any bleeding, (B) major bleeding, and (C) stroke/non-CNS SE/MI in patients with WRF vs. SRF. MI, myocardial infarction; non-CNS SE, non-central nervous system systemic embolism; SRF, stable renal function; WRF, worsening renal function.

stroke, or ischemic stroke between patients with SRF and those with WRF.

Discussion

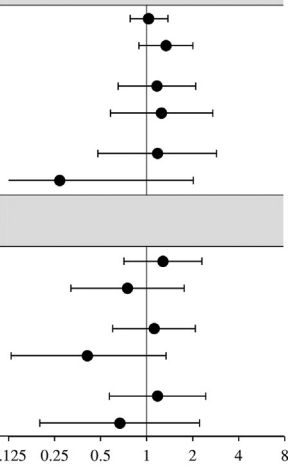
This sub-analysis of the XAPASS focused on the outcomes of patients with both AF and WRF at 1 year after rivaroxaban treatment initiation. Of 7509 patients included in this sub-analysis, 16.4% had WRF. No differences were found in the incidence rates of any bleeding, major bleeding, or stroke/non-CNS SE/MI in patients with WRF compared to those with SRF.

Patients with WRF had higher risks of both stroke and bleeding than did patients with SRF, as shown by their higher $CHADS_2$, CHA_2DS_2-VASc, and modified HAS-BLED scores. This trend was similar in the phase III ROCKET AF sub-analysis, that also examined the effect of WRF on clinical outcome of NVAF patients taking rivaroxaban and warfarin [13]. Although the patient characteristics in the ROCKET AF sub-analysis were generally similar between patients with SRF and WRF, the mean $CHADS_2$ score was slightly higher in patients with WRF compared to patients with SRF (3.5 ± 0.9 vs. 3.4 ± 0.9, $p = 0.0016$). When comparing these two studies, the mean $CHADS_2$ scores were higher in the ROCKET AF sub-analysis (3.5 ± 0.9 for WRF and 3.4 ± 0.9 for SRF) than the respective scores in the current study (2.5 ± 1.3 and 2.1 ± 1.3, respectively). The patients in the ROCKET AF sub-analysis had higher percentages of hypertension, diabetes mellitus, and congestive heart failure, all of which contributed to a higher $CHADS_2$ score. These results could reflect differences in the study design and populations. Patients within the ROCKET AF sub-analysis were a global population in a randomized, controlled trial, whereas the current XAPASS sub-analysis included patients in a Japanese real-world setting.

In the current sub-analysis, despite their higher risk scores of bleeding and stroke compared to patients with SRF, patients with WRF had similar incidence rates of any bleeding, major bleeding, and stroke/non-CNS SE/MI as patients with SRF (Table 2, Fig. 1). Compared to the present study, the ROCKET AF sub-analysis was of longer treatment duration (median 1.6 years vs. 1 year) and included patients with a higher $CHADS_2$ score but had similar

Table 3
Study outcomes according to CrCl at enrollment.

Clinical outcomes	CrCl at enrollment, ml/min	Incidence rate, event per 100 patient-years (95% CI) SRF group	WRF group	HR (95% CI), WRF vs. SRF group	*p*-value
Safety outcomes	**≥50 <50**	**(N=4639) (N=1641)**	**(N=906) (N=323)**		
Any bleeding	≥50	6.8 (6.0-7.6)	7.0 (5.2-8.9)	1.03 (0.78-1.38)	0.825
	<50	8.4 (6.8-9.9)	11.3 (7.2-15.4)	1.34 (0.89-2.01)	0.164
Major bleeding	≥50	1.5 (1.1-1.8)	1.7 (0.8-2.6)	1.17 (0.65-2.09)	0.597
	<50	2.4 (1.6-3.2)	3.0 (0.9-5.1)	1.25 (0.58-2.71)	0.568
Intracranial hemorrhage	≥50	0.6 (0.4-0.9)	0.7 (0.1-1.3)	1.18 (0.48-2.86)	0.718
	<50	1.4 (0.8-2.0)	0.4 (0.0-1.1)	0.27 (0.04-2.02)	0.171
Effectiveness outcomes	**≥50 <50**	**(N=4624) (N=1636)**	**(N=901) (N=322)**		
Stroke/non-CNS SE/MI	≥50	1.3 (1.0-1.7)	1.7 (0.8-2.6)	1.28 (0.71-2.30)	0.409
	<50	3.0 (2.1-3.9)	2.3 (0.5-4.1)	0.75 (0.32-1.76)	0.507
Stroke	≥50	1.3 (1.0-1.7)	1.5 (0.6-2.3)	1.12 (0.60-2.08)	0.731
	<50	2.7 (1.8-3.6)	1.1 (0.0-2.4)	0.41 (0.13-1.34)	0.130
Ischemic stroke	≥50	0.9 (0.6-1.2)	1.1 (0.4-1.8)	1.18 (0.57-2.44)	0.653
	<50	1.7 (1.0-2.4)	1.1 (0.0-2.4)	0.67 (0.20-2.22)	0.506



CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; MI, myocardial infarction; non-CNS SE, non-central nervous system systemic embolism; SRF, stable renal function; WRF, worsening renal function.

results. The incidence rates of major bleeding, stroke/SE (composite endpoint) and MI in the ROCKET AF sub-analysis were similar between patients with WRF and those with SRF, which supports the results of the current sub-analysis [13]. On the other hand, the sub-analysis of ARISTOTLE reported that WRF was associated with higher risks of stroke/SE and major bleeding, which differs from results in the current sub-analysis and ROCKET AF sub-analysis. This might be explained by the older age and cardiovascular comorbidities observed in the WRF patients and different definition of WRF (an annual decrease in eGFR of more than 20%) in the sub-analysis of ARISTOTLE [19]. The previous studies have reported that renal dysfunction was associated with higher risk of bleeding and thromboembolism [9,12]. Indeed, the current analysis showed that the incidence rates of any bleeding, major bleeding, and stroke/non-CNS SE/MI were relatively higher in patients with baseline CrCl of <50 ml/min compared to those with baseline CrCl of ≥50 ml/min in both SRF and WRF groups (Table 3). In addition, patients with WRF had a higher incidence rate of all-cause mortality than patients with SRF, although most of the deaths were not associated with anticoagulation and significant difference was not observed in the incidence rate of death caused by adverse drug reaction between patients with SRF and those with WRF. These results imply that periodic evaluation of renal function and treatment regimen is important for individual patients, and such careful follow-up might contribute to the similar incidence rates of bleeding and thromboembolism between patients with SRF and those with WRF in the current analysis. Altogether, our data suggest that rivaroxaban could be a treatment option for patients for whom future decline of renal function is predicted. In this sub-analysis, treatment duration and dosage of rivaroxaban was at the discretion of the treating physicians. There was no difference in treatment duration between the 2 groups (SRF: 316 ± 104 days; WRF: 316 ± 102 days), however, patients with WRF tended to receive lower dosages of rivaroxaban than those with SRF. Of patients with a CrCl of ≥50 ml/min, 65.5% of those with SRF received 15 mg od, the dosage approved for patients with this CrCl level in Japan, versus only 55.0% of those with WRF. The treating physicians may have been intentionally conservative with their dosing in patients with WRF since these patients had higher risk scores or comorbidities at enrollment. Even with comparatively lower doses of rivaroxaban, patients with WRF had similar outcomes as patients with SRF.

Because of its single-arm, open-label, observational design, the XAPASS had several limitations as described previously [14,15]. First, selection bias could exist because of its open-label design. Second, since the XAPASS had no comparative arm, the outcomes could not be compared between patients treated with rivaroxaban and those treated with other anticoagulants. Third, the loss of patients to follow-up might have led to an underestimation of the event rates. Fourth, the CrCl measurement was performed at the discretion of the treating physicians. Due to the lack of adequate CrCl data, 2069 of the 9578 patients who completed the 1-year follow-up could not be included in this sub-analysis. Fifth, this sub-analysis did not examine the timing of occurrence of events and CrCl decrease. Sixth, the differences in patient characteristics (e.g. age, stroke/bleeding risk scores, baseline CrCl, and other confounding factors) between patients with SRF and WRF might have influenced the current results. Finally, this sub-analysis was based on the 1-year follow-up data with the maximum treatment duration of 365 days; therefore, the results might differ with a longer treatment duration.

Conclusion

No association between WRF and occurrence of any bleeding, major bleeding, and stroke/non-CNS SE/MI was observed during the 1-year follow-up of the XAPASS. Although periodic monitoring of renal function is important for the safety of patients undergoing anticoagulation therapy, the current sub-analysis suggests that rivaroxaban could be a treatment option for patients for whom future decline of renal function is predicted.

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Conflicts of interest

JN received research grant from Nihon Medi-Physics and was a member of advisory board for Bayer Yakuhin, Ltd. TI received research grant from Daiichi Sankyo, Bristol-Myers Squibb, Medtronic Japan, St. Jude Medical, and Bayer Yakuhin, Ltd. and honoraria from Daiichi Sankyo, Ono Pharma, Bayer Yakuhin, Ltd., Bristol-Myers Squibb, and Pfizer and was a member of the advisory board for Bayer Yakuhin, Ltd. and Bristol-Myers Squibb. SO was a member of the advisory board for Bayer Yakuhin, Ltd. TK received research grant from Bayer Yakuhin, Ltd. and was a member of the advisory board for Bayer Yakuhin, Ltd. KM received honoraria from Bayer Yakuhin, Ltd., Otsuka Pharmaceutical, Boehringer-Ingelheim, AstraZeneca, Pfizer, Mitsubishi Tanabe Pharma Cooperation, Japan Stryker, Kowa, Nihon Medi-Physics Co., BMS, Sawai Pharmaceutical Co., Sumitomo Dainippon Pharma Co., Ltd, Dai-ichi Sankyo, Asteras Pharma, and Nippon Chemiphar and was a member of the advisory board for CSL Behring, Medico's Hirata, and Bayer Yakuhin, Ltd. SM received research grant from Takeda Pharma, CSL Behring, Meiji Seika Pharma, MSD, Astellas Pharma, Eisai, Otsuka Pharma, Carl Zeiss Meditec, Philips Electronics Japan, Sanofi, Siemens Healthcare, Daiichi Sankyo, Mitsubishi-Tanabe Pharma, Chugai Pharma, Nihon Medi-Physics, Pfizer, Bristol-Myers Squibb, Brainlab, Mizuho, and Medtronic and was a member of the advisory board for Bayer Yakuhin, Ltd. YM received research grants from Bayer Yakuhin, Ltd., Daiichi Sankyo, and Boehringer-Ingelheim and honoraria from Bayer Yakuhin, Ltd., Daiichi Sankyo, Boehringer-Ingelheim, and Bristol-Myers Squibb and was a member of the advisory board for Bayer Yakuhin, Ltd. MT, YK, YO, TS, SS, and SY are employees of Bayer Yakuhin, Ltd.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.06.003.

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