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Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment

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Aims Patients with non-valvular atrial fibrillation (AF) and renal insufficiency are at increased risk for ischaemic stroke and bleeding during anticoagulation. Rivaroxaban, an oral, direct factor Xa inhibitor metabolized predominantly by the liver, preserves the benefit of warfarin for stroke prevention while causing fewer intracranial and fatal haemorrhages.

Methods and results We randomized 14 264 patients with AF in a double-blind trial to rivaroxaban 20 mg/day [15 mg/day if creatinine clearance (CrCl) 30–49 mL/min] or dose-adjusted warfarin (target international normalized ratio 2.0–3.0). Compared with patients with CrCl >50 mL/min (mean age 73 years), the 2950 (20.7%) patients with CrCl 30–49 mL/min were older (79 years) and had higher event rates irrespective of study treatment. Among those with CrCl 30–49 mL/min, the primary endpoint of stroke or systemic embolism occurred in 2.32 per 100 patient-years with rivaroxaban 15 mg/day vs. 2.77 per 100 patient-years with warfarin [hazard ratio (HR) 0.84; 95% confidence interval (CI) 0.57–1.23] in the per-protocol population. Intention-to-treat analysis yielded similar results (HR 0.86; 95% CI 0.63–1.17) to the per-protocol results. Rates of the principal safety endpoint (major and clinically relevant non-major bleeding: 17.82 vs. 18.28 per 100 patient-years; $P = 0.76$) and intracranial bleeding (0.71 vs. 0.88 per 100 patient-years; $P = 0.54$) were similar with rivaroxaban or warfarin. Fatal bleeding (0.28 vs. 0.74% per 100 patient-years; $P = 0.047$) occurred less often with rivaroxaban.

Conclusion Patients with AF and moderate renal insufficiency have higher rates of stroke and bleeding than those with normal renal function. There was no evidence of heterogeneity in treatment effect across dosing groups. Dose adjustment in ROCKET-AF yielded results consistent with the overall trial in comparison with dose-adjusted warfarin.

Keywords Prevention • Stroke and systemic embolism • Rivaroxaban • Compared warfarin • Non-valvular atrial fibrillation and moderate renal impairment

While most patients with non-valvular atrial fibrillation (AF) benefit from anticoagulation to prevent ischaemic stroke and systemic embolism, those with renal dysfunction face high risks of both thromboembolism and bleeding during antithrombotic therapy.[1–3] In observational studies, anticoagulant therapy is frequently not administered in patients with AF and renal dysfunction[4,5] based on the concern that bleeding may outweigh the potential benefit. A key question is whether reliable anticoagulation without excessive bleeding risk can be achieved in patients with reduced renal function.

Rivaroxaban is a direct factor Xa inhibitor with predictable pharmacokinetics and a rapid onset and offset of action after oral

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administration; it is metabolized predominantly (approximately two-thirds) by the liver, with approximately one-third excreted unchanged in the urine.[6,7] The Rivaroxaban Once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) compared the oral factor Xa inhibitor rivaroxaban with warfarin for prevention of all stroke and systemic embolism in 14 264 patients with AF.[8] The trial was designed to reflect the comorbidities often seen in clinical practice, and as a result, the risk profile of the randomized population was higher than in other recent trials of patients with AF.[9–11] Rivaroxaban was non-inferior to warfarin, superior to warfarin while patients were receiving randomized treatment, and resulted in similar overall rates of bleeding, but reduced intracranial and fatal bleeding compared with warfarin.[8]

In subjects with moderate renal insufficiency [creatinine clearance (CrCl) 30–49 mL/min at baseline, 20.7% of the trial cohort], the dose of rivaroxaban was reduced from 20 to 15 mg daily based on extensive pharmacodynamic data and pharmacokinetic modelling. This pre-specified secondary analysis assessed the risks and benefits of the lower dose of rivaroxaban compared with warfarin in the high-risk cohort of patients with moderate renal insufficiency. It examined the extent to which the findings were consistent with those seen in patients with preserved renal function and in the trial overall.

Methods

The design and main results of the ROCKET-AF trial have been reported previously.[8,9] In brief, this was a multicentre, randomized, double-blind, double-dummy, event-driven trial comparing fixed-dose rivaroxaban (20 mg daily or 15 mg daily in patients with CrCl 30–49 mL/min at baseline) with adjusted-dose warfarin [target international normalized ratio (INR) 2.0–3.0] for prevention of all stroke (ischaemic or haemorrhagic) or systemic embolism.[9] To maintain blinding, the HemoSense point-of-care device was used to generate real INR or sham values. The doses of warfarin and matching placebo tablets were adjusted based on these values.[12]

Renal function and dose assignment

Patients with a CrCl <30 mL/min were excluded from ROCKET-AF. Creatinine clearance was determined by the Cockcroft–Gault formula.[13] Based upon prior studies, patients with moderate renal insufficiency (CrCl 30–49 mL/min) have maximal serum concentrations of rivaroxaban 25–30% higher than those with preserved renal function.[14,15] Pharmacokinetic models projected that a 25% dose reduction would lead to similar exposure and trough levels in patients with moderate renal insufficiency. The decision about this dose was also informed by analysis of the bleeding risks in the older population with renal dysfunction and associated co-morbidity. Patients were assigned study drug dose based upon CrCl during the screening visit: 20 mg daily or 15 mg daily in patients with CrCl 30–49 mL/min at baseline. There were no dose adjustments post-baseline for changing CrCl. However, patients with CrCl <30 mL/min were required to discontinue study drug.

Study participants

Patients with electrocardiographically documented non-valvular AF at moderate-to-high risk of stroke were recruited at 1178 participating sites in 45 countries. Elevated stroke risk was indicated by a history of stroke, transient ischaemic attack, or systemic embolism or at least two of the following risk factors: heart failure or left ventricular ejection fraction ≤35%, hypertension, age ≥75 years, or diabetes mellitus ($CHADS_2$ score ≥2). Complete inclusion and exclusion criteria have been published. Those with a high risk for bleeding (including prior intra-cerebral bleeding, surgical trauma within 30 days, gastrointestinal bleeding within 6 months) were excluded.[9]

Outcomes

The primary efficacy endpoint was the composite of all stroke (both ischaemic and haemorrhagic) and systemic embolism. Secondary endpoints included the composite of stroke, non-central nervous system systemic embolism, cardiovascular death, and myocardial infarction, and individual components of the composite endpoints. The principal safety endpoint was the composite of major and non-major clinically relevant bleeding events.[16] Bleeding events involving the central nervous system meeting the definition of stroke were adjudicated as haemorrhagic strokes and included in both the primary efficacy and safety endpoints. An independent clinical events committee applied the protocol definitions and adjudicated all suspected stroke, systemic embolism, myocardial infarction, death, and bleeding events contributing to the pre-specified efficacy and safety endpoints.

Statistical analysis

The statistical analysis plan specified testing the efficacy and safety of the randomized comparison in patients with moderate renal dysfunction for consistency with the overall trial results. By design, ROCKET-AF was a non-inferiority trial, and the primary analysis was performed in the per protocol on treatment population.[9] In this pre-specified analysis, rivaroxaban patients are classified as 15 mg or 20 mg based on the first dose of study drug. Event rates by treatment arm and renal dysfunction group are presented as per 100 patient-years (%/year). The homogeneity of treatment effects on the occurrence of the primary efficacy and safety endpoints across subgroups of renal dysfunction status (30–49 mL/min and ≥50 mL/min) was tested with a treatment by renal dysfunction interaction. The interaction term, including randomized treatment and renal dysfunction (treatment*renal impairment), was included as a covariate in all of the Cox models.

Estimates and two-sided 95% confidence intervals (CIs) for the hazard ratio (HR) (rivaroxaban vs. warfarin) within levels of renal dysfunction based on the previous model are presented in the per-protocol, on-treatment population for the efficacy endpoints and in the safety, on-treatment population for the safety endpoints. All statistical analyses were performed with SAS software (version 9.2, SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Of the 14 264 patients randomized with AF, 2950 (20.7%) had moderate renal impairment (CrCl 30–49 mL/min) at enrollment. Those randomized with moderately impaired renal function had a median age of 79, a mean $CHADS_2$ score of 3.7 ± 1, 62% were previously treated with a vitamin K antagonist, and 36% were taking aspirin. As shown in *Table 1*, patients with moderately impaired renal function were older, had higher $CHADS_2$ scores, higher prevalence of heart failure, peripheral vascular disease and prior myocardial infarction. Additionally, compared with those with CrCl >50 mL/min, patients with moderately impaired renal

Table 1 Baseline patient characteristics randomized to rivaroxaban 15 mg or warfarin[a]

Characteristic	CrCl 30–49 mL/min		CrCl ≥50 mL/min	
	Rivaroxaban 15 mg (*n* = 1474)	Warfarin (*n* = 1476)	Rivaroxaban 20 mg (*n* = 5637)	Warfarin (*n* = 5640)
Age, median (25th, 75th), years	79 (75, 82)	79 (75, 83)	71 (63, 76)	71 (63, 76)
Female, *n* (%)	811 (55.0)	825 (55.9)	2008 (35.6)	1999 (35.4)
Body mass index, median (25th, 75th), kg/m^2	25.1 (22.7, 28.0)	25.2 (22.8, 27.9)	29.2 (26.1, 33.0)	28.9 (26.0, 32.7)
Blood pressure, median (25th, 75th), mm Hg				
Systolic	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)
Diastolic	80 (70, 82)	80 (70, 82)	80 (71, 86)	80 (72, 86)
Clinical presentation, *n* (%)				
Type of atrial fibrillation				
Persistent	1211 (82.2)	1231 (83.4)	4560 (80.9)	4516 (80.1)
Paroxysmal	245 (16.6)	215 (14.6)	997 (17.7)	1052 (18.7)
Newly diagnosed/new onset	18 (1.2)	30 (2.0)	80 (1.4)	72 (1.3)
Prior aspirin use, *n* (%)	529 (35.9)	552 (37.4)	2049 (36.4)	2060 (36.5)
Prior vitamin K antagonist use, *n* (%)	924 (62.7)	904 (61.3)	3507 (62.2)	3548 (62.9)
Clinical risk factors				
$CHADS_2$ score[†], mean ± SD	3.68 (1.00)	3.67 (1.01)	3.42 (0.91)	3.41 (0.92)
2, *n* (%)	130 (8.8)	134 (9.1)	793 (14.1)	797 (14.1)
3, *n* (%)	594 (40.3)	595 (40.3)	2453 (43.5)	2555 (45.3)
4, *n* (%)	426 (28.9)	419 (28.4)	1661 (29.5)	1577 (28.0)
5, *n* (%)	267 (18.1)	267 (18.1)	663 (11.8)	612 (10.9)
6, *n* (%)	56 (3.8)	48 (4.0)	67 (1.2)	99 (1.8)
Prior TIA/stroke or systemic embolism, *n* (%)	738 (50.1)	725 (49.1)	3167 (56.2)	3160 (56.0)
Congestive heart failure, *n* (%)	973 (66.0)	964 (65.3)	3484 (61.8)	3468 (61.5)
Hypertension, *n* (%)	1352 (91.7)	1360 (92.1)	5067 (89.9)	5100 (90.4)
Diabetes mellitus, *n* (%)	468 (31.8)	492 (33.3)	2401 (42.6)	2319 (41.1)
Prior myocardial infarction, *n* (%)	276 (18.7)	302 (20.5)	902 (16.0)	977 (17.3)
Creatinine clearance, median (25th, 75th), mL/min[b]	42 (37–46)	42 (37–46)	75 (62–94)	74 (61–92)
Peripheral vascular disease, *n* (%)	107 (7.3)	115 (7.8)	292 (5.2)	322 (5.7)
Chronic obstructive pulmonary disease, *n* (%)	169 (11.3)	177 (11.9)	582 (39.0)	563 (37.8)

SD, standard deviation; TIA, transient ischaemic attack.
[a]The safety analysis population included 14 236 patients; however, 9 patients assigned to warfarin had no creatinine clearance data, leaving 14 227 patients as analysed here.
[b]Using the Cockcroft–Gault formula.[13]
[†]CHADS2 Score: One point assigned for: congestive heart failure, hypertension, age over 75, diabetes; 2 points for prior stroke or transient ischaemic attack.

function had lower body mass indices, less frequent history of stroke or transient ischaemic attack, and were less likely to be diabetic (*Table 1*). Among those patients with CrCl 30–49 mL/min randomized to warfarin, the median time in therapeutic range was 57.7 (25th/75th percentiles: 42.2–69.9. Among those patients with CrCl ≥50 mL/min randomized to warfarin, the median time in therapeutic range was 58.0 (25th/75th percentiles: 43.1–70.8).

Efficacy outcomes

The primary efficacy analysis for ROCKET-AF showed that stroke or systemic embolism occurred in 429 patients, 188 on rivaroxaban (1.71% per year), and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI 0.66–0.96; $P < 0.001$ for non-inferiority). In those with moderate renal dysfunction (CrCl 30–49 mL/min), rates of stroke and systemic embolism (the principal efficacy analysis) were higher, regardless of treatment received, than for patients with CrCl >50 mL/min (*Table 2*). For the randomized comparison in the per-protocol population, there were 2.32 per primary outcome events (stroke or systemic embolism) per 100 patient-years with rivaroxaban 15 mg/day compared with 2.77 per 100 patient-years with dose-adjusted warfarin (HR 0.84; 95% CI 0.57–1.23). These findings were consistent with those seen in patients with CrCl >50 mL/min (1.57 per 100 patient-years and 2.00 per 100 patient-years) (*Table 2*, *Figure 1*). As shown in *Figure 2*, these relationships were similar in the intention-to-treat analysis (ITT). By ITT, the primary event rate was 2.95 per 100 patient-years with rivaroxaban 15 mg/day compared with 3.44 per 100 patient-years with dose-adjusted warfarin (HR 0.86; 95 % CI 0.63–1.17).

Table 2 Primary trial endpoint: stroke and non-CNS embolism in the per protocol population

Clinical endpoint	CrCl 30–49 mL/min			CrCl ≥50 mL/min			*P*-value for interaction
	Rivaroxaban 15 mg (*n* = 1474)[a]	Warfarin (*n* = 1476)[a]	Hazard ratio (95% CI), rivaroxaban vs. warfarin	Rivaroxaban 20 mg (*n* = 5637)[a]	Warfarin (*n* = 5640)[a]	Hazard ratio (95% CI), rivaroxaban vs. warfarin	
Principal efficacy endpoint (stroke and systemic embolism)	2.32	2.77	0.84 (0.57–1.23)	1.57	2.00	0.78 (0.63–0.98)	0.76
Stroke, systemic embolism, vascular death	4.64	4.83	0.96 (0.73–1.27)	2.76	3.32	0.83 (0.70–0.98)	0.38
Stoke, systemic embolism, MI, vascular death	5.58	6.54	0.85 (0.67–1.09)	3.55	4.16	0.85 (0.73–0.99)	0.98
Stroke							
Ischaemic	1.98	1.78	1.11 (0.71–1.73)	1.20	1.34	0.90 (0.69–1.16)	0.41
Haemorrhagic	0.29	0.52	0.56 (0.21–1.51)	0.26	0.42	0.62 (0.37–1.03)	0.88
Undetermined	0.05	0.09	0.51 (0.05–5.67)	0.07	0.10	0.68 (0.24–1.90)	0.84

[a]Event rates per 100 patient-years of follow-up.

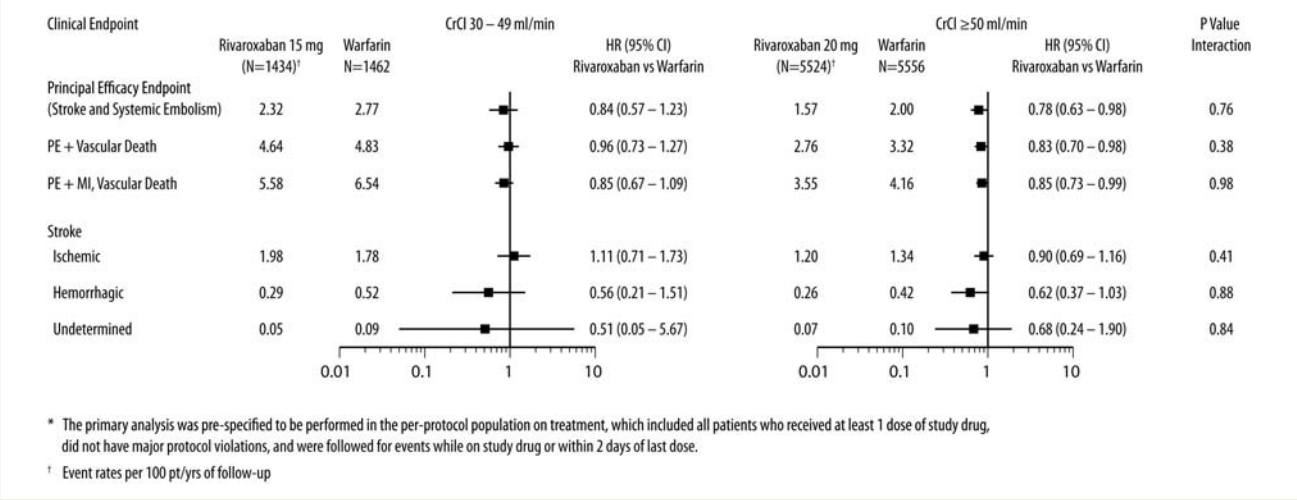

Figure 1 Efficacy events in the per-protocol (on-treatment) population.

As shown in *Table 2*, the individual and composite secondary efficacy endpoints were consistent in those with moderately impaired renal function and those with CrCl >50 mL/min ($P > 0.4$ for all interactions). For each of these randomized comparisons, there was no evidence that the treatment effect was different in the impaired renal function subgroup compared with the overall trial.

Safety outcomes

The principal safety endpoint (major and clinically relevant non-major bleeding) occurred more frequently in those with renal insufficiency than in those without, regardless of randomized treatment assignment. However, there was no excess bleeding on rivaroxaban compared with warfarin (*Table 3*, *Figure 3*). There was no excess in the principal safety endpoint (HR 0.98; 95% CI 0.84–1.14) or in the individual bleeding outcomes in those treated with rivaroxaban 15 mg/day compared with dose-adjusted warfarin (*Table 3*). Furthermore, in those with moderate renal insufficiency, critical organ bleeding (HR 0.55; 95% CI 0.30–1.00) and fatal bleeding (HR 0.39; 95% CI 0.15–0.99) were less frequent with rivaroxaban. The lower rate of fatal bleeding was consistent with the findings in those with preserved renal function (HR 0.55; 95% CI 0.32–0.93) (*Table 3*).

Bleeding events were also examined by site of haemorrhage as defined in *Table 4*. In patients with moderate renal insufficiency, rivaroxaban-treated patients had more frequent gastrointestinal bleeding (4.1 vs. 2.6%; $P = 0.02$). While limited by smaller sample size, there were no significant differences in other bleeding sites between rivaroxaban 15 mg and dose-adjusted warfarin. Haemorrhagic stroke was less frequent

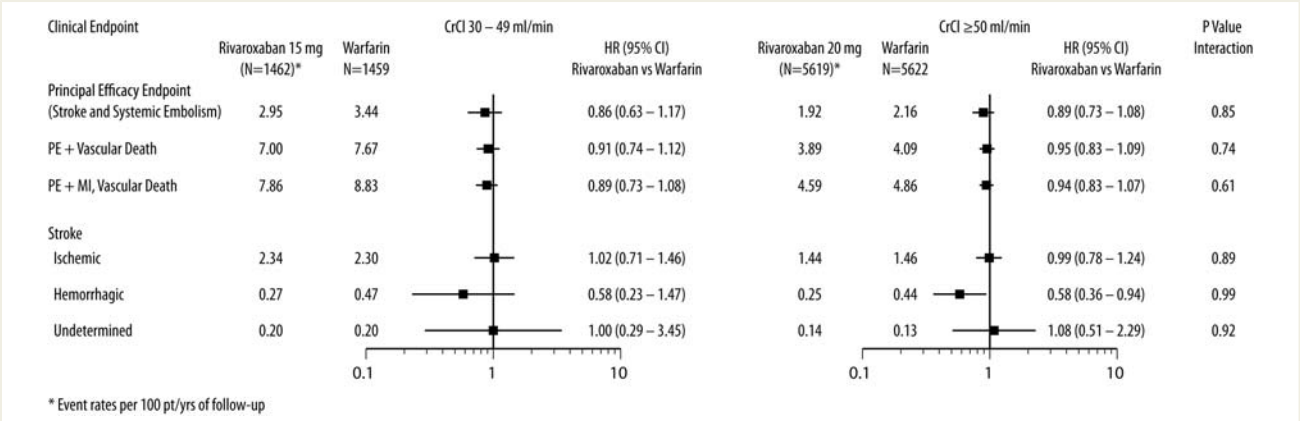

Figure 2 Efficacy endpoints according to the intention to treat.

Table 3 Bleeding rates by treatment group rivaroxaban vs. warfarin

Clinical endpoint	CrCl 30–49 mL/min			CrCl ≥50 mL/min			*P*-value for interaction
	Rivaroxaban 15 mg (*n* = 1474)[a]	Warfarin (*n* = 1476)[a]	Hazard ratio (95% CI), rivaroxaban vs. warfarin	Rivaroxaban 20 mg (*n* = 5637)[a]	Warfarin (*n* = 5640)[a]	Hazard ratio (95% CI), rivaroxaban vs. warfarin	
Primary safety endpoint	17.82	18.28	0.98 (0.84–1.14)	14.24	13.67	1.04 (0.96–1.13)	0.4496
Major bleeding	4.49	4.70	0.95 (0.72–1.26)	3.39	3.17	1.07 (0.91–1.26)	0.4800
Hb drop	3.76	3.28	1.14 (0.83–1.58)	2.54	2.03	1.25 (1.03–1.52)	0.6456
Transfusion	2.34	2.00	1.17 (0.77–1.76)	1.49	1.16	1.28 (0.99–1.65)	0.7066
Clinical organ	0.76	1.39	0.55 (0.30–1.00)	0.83	1.13	0.74 (0.55–0.99)	0.3866
Fatal bleeding	0.28	0.74	0.39 (0.15–0.99)	0.23	0.43	0.55 (0.32–0.93)	0.5302
Intracranial haemorrhage	0.71	0.88	0.81 (0.41–1.60)	0.44	0.71	0.62 (0.42–0.92)	0.5065

[a]Event rates per 100 patient-years of follow-up.

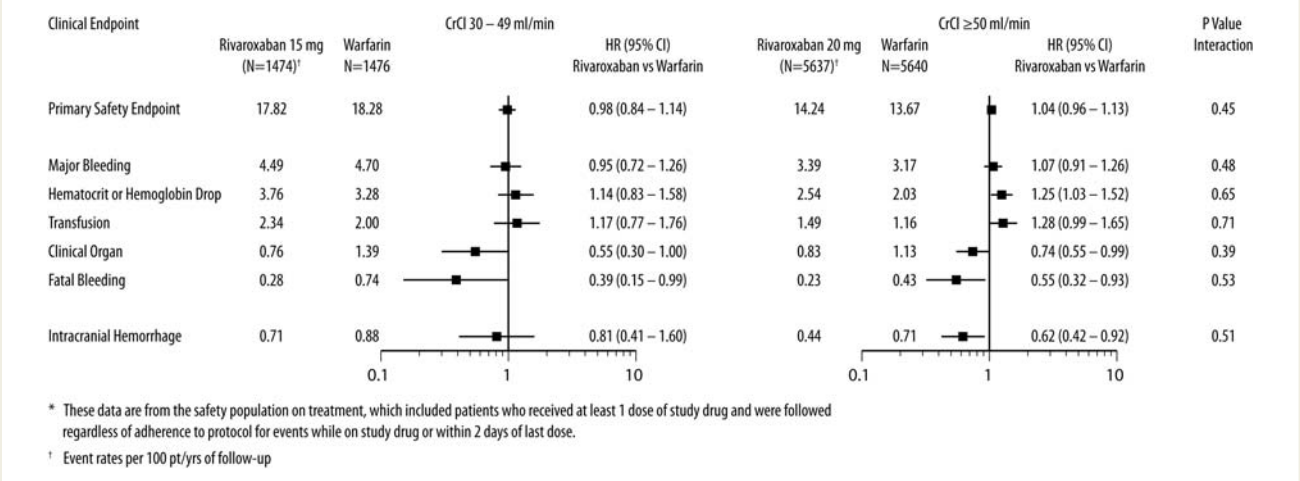

Figure 3 Safety endpoints.

Table 4 Bleeding sites

	CrCl 30–49 mL/min		CrCl ≥50 mL/min	
	Rivaroxaban 15 mg (*n* = 1474)	Warfarin (*n* = 1476)	Rivaroxaban 20 mg (*n* = 5637)	Warfarin (*n* = 5640)
Major bleeding, *n* (%)	Event rates per 100 patient-years of follow-up	Event rates per 100 patient-years of follow-up	Event rates per 100 patient-years of follow-up	Event rates per 100 patient-years of follow-up
Gastrointestinal (upper, lower, and rectal)	2.88	1.77	1.79	1.12
Intracranial	0.71	0.88	0.44	0.71
Intraparenchymal	0.43	0.55	0.31	0.48
Non-traumatic	0.38	0.51	0.28	0.47
Traumatic	0.05	0.05	0.03	0.01
Intraventricular	0.19	0.28	0.10	0.26
Subdural hematoma	0.28	0.46	0.09	0.19
Subarachnoid	0.14	0.28	0.04	0.09
Epidural hematoma	0.00	0.00	0.00	0.01
Macroscopic haematuria	0.05	0.18	0.28	0.19
Bleeding associated with non-cardiac surgery	0.24	0.42	0.15	0.19
Intraocular/retinal	0.05	0.18	0.18	0.22
Intra-articular	0.00	0.23	0.18	0.17
Epistaxis	0.19	0.09	0.10	0.13

with rivaroxaban than with warfarin for those with CrCl >50 mL/min (HR 0.58; 95% CI 0.36–0.94), and the finding in those with moderate renal insufficiency was consistent (HR 0.58; 95% CI 0.23–1.47) (*Figure 2*).

Adverse events according to randomized treatment were similar in those with CrCl 30–49 mL/min compared with those with CrCl >50 mL/min (*Table 5*). In those with CrCl 30–49 mL/min, the adverse event rates were similar between those randomized to rivaroxaban and warfarin.

Discussion

Among patients with AF, renal dysfunction is common and progressively increases with older age.[17] As reflected in the ROCKET-AF trial, such patients also demonstrate complex co-morbidity, including congestive heart failure, prior hypertension, and diabetes. ROCKET-AF differs from a number of prior trials in AF, both in design (double-blind vs. open-label) and in the risk profile of the included patients (ROCKET-AF mean $CHADS_2$ score = 3.5 vs. RE-LY mean $CHADS_2$ score = 2.1). Due to differences in both study design and the selected population, caution must be exercised when comparing across trials.[18] Consistent with prior observations, this study demonstrates that those with renal dysfunction are at increased risk for stroke and embolic events and, irrespective of anticoagulant administered, they are also at increased risk for bleeding events. For the randomized comparison of rivaroxaban vs. warfarin, the findings in the patients with moderate renal dysfunction were consistent with the overall trial. Specifically, the reduced dose of rivaroxaban preserved the treatment effect of warfarin without increasing bleeding and with fewer fatal bleeds.

Rivaroxaban 15 mg dose selection in moderate renal insufficiency

A single dose of rivaroxaban inhibits thrombin generation for 24 h and prolongs the pro-thrombin time in a dose-dependent manner.[6,19] In prior studies of prophylaxis of venous thromboembolism, once-daily and twice-daily regimens differed only in rivaroxaban trough concentrations, not total exposure as measured by the area under the curve.[20,21] In post-operative deep vein thrombosis prevention studies, once-daily dosing led to similar efficacy as twice-daily dosing with less bleeding.[22,23] Accordingly, ROCKET-AF employed once-daily dosing of rivaroxaban. While rivaroxaban is predominantly metabolized by the liver, approximately one-third is cleared renally.[24] In patients with moderate renal insufficiency (CrCl 30–49 mL/min), there is a moderate but relevant effect on rivaroxaban exposure; maximal serum concentrations are 25–30% higher[14] and pharmacokinetic models projected that a 25% dose reduction would lead to similar exposure and trough levels in patients with moderate renal insufficiency. Additionally, the higher intrinsic risk of bleeding in patients with moderate renal impairment combined with the comorbidities of an elderly AF population also favoured a lower dose. Therefore, based upon the aggregate data, patients in ROCKET-AF with moderate renal insufficiency were treated with a 25% dose reduction (15 mg daily).[9] Major and clinically relevant non-major bleeding occurred more frequently in those with renal insufficiency than in those without, regardless of randomized treatment assignment,

Table 5 Adverse events according to renal function and randomized treatment

Adverse event[b], *n* (%)	CrCl 30–49 mL/min		CrCl ≥50 mL/min	
	Rivaroxaban 15 mg (*n* = 1474)	Warfarin (*n* = 1476)	Rivaroxaban 20 mg (*n* = 5637)	Warfarin (*n* = 5640)
Total patients with treatment-emergent adverse events[a]	1248 (84.7)	1281 (86.8)	4543 (80.6)	4520 (80.1)
Epistaxis	150 (10.2)	121 (8.2)	571 (10.1)	488 (8.7)
Peripheral oedema	115 (7.8)	120 (8.1)	320 (5.7)	324 (5.7)
Dizziness	110 (7.5)	118 (8.0)	323 (5.7)	330 (5.9)
Nasopharyngitis	76 (5.2)	84 (5.7)	345 (6.1)	369 (6.5)
Cardiac failure	104 (7.1)	120 (8.1)	293 (5.2)	299 (5.3)
Bronchitis	94 (6.4)	90 (6.1)	302 (5.4)	326 (5.8)
Dyspnoea	83 (5.6)	102 (6.9)	297 (5.3)	292 (5.2)
Diarrhoea	84 (5.7)	96 (6.5)	295 (5.2)	300 (5.3)
Cough	81 (5.5)	74 (5.0)	262 (4.6)	279 (4.9)
Back pain	58 (3.9)	74 (5.0)	280 (5.0)	272 (4.8)
Upper respiratory tract infection	62 (4.2)	70 (4.7)	274 (4.9)	255 (4.5)
Headache	68 (4.6)	70 (4.7)	256 (4.5)	291 (5.2)
Arthralgia	73 (5.0)	69 (4.7)	228 (4.0)	262 (4.6)
Haematuria	47 (3.2)	58 (3.9)	249 (4.4)	183 (3.2)
Urinary tract infection	72 (4.9)	105 (7.1)	221 (3.9)	216 (3.8)

Based on safety population.
[a]Events that started on or after the first dose of study medication and up to 2 days after the last dose of study medication.
[b]Fifteen most frequent treatment-emergent adverse events based on the rivaroxaban group.

but there was no excess bleeding with rivaroxaban compared with warfarin. There was no excess in the individual bleeding outcomes in those treated with rivaroxaban 15 mg/day compared with dose-adjusted warfarin, and critical organ bleeding (HR 0.55; 95% CI 0.30–1.00) and fatal bleeding (HR 0.39; 95% CI 0.15–0.99) were less frequent with rivaroxaban. The lower rate of fatal bleeding was consistent with the findings in those with preserved renal function. Clearance of rivaroxaban (mean terminal elimination half-life up to 9 h) is more rapid than for wafarin and standard medical and surgical measures are recommended, if necessary, to control bleeding (as set out in the protocol of the study).[8] No additional measures were required among the patients in the ROCKET AF trial to control bleeding. The study protocol specified that bleeding may be managed (after attention to other potential causes of bleeding, including concomitant therapies) by infusion of fresh frozen plasma and, if necessary, factor concentrates.[8] Although bleeding is not more frequent than with warfarin, the treatment of bleeding due to rivaroxaban merits additional study.

Implications of the findings

Irrespective of geographic location, observational studies reveal that older patients with AF and those with renal dysfunction are under-treated with anticoagulants.[5,25,26] Concerns about bleeding and falls among frail patients with AF have often led to the decision not to treat with anticoagulants, despite the known risks of stroke and embolism. In the US-based NABOR program, almost half of the patients at high risk for stroke were not treated with an anticoagulant, and a similar proportion of moderate-risk patients were untreated.[27] Previous studies have shown that bleeding increases with $CHADS_2$ score (19.5 major bleeds per 100 patient-years for $CHADS_2$ of 3; 23.5 per 100 patient-years for $CHADS_2$ of 4: compared with 7.2 per 100 patient-years overall).[28] Similarly, in this US-based study, managing warfarin anticoagulation was more challenging in those with congestive heart failure.[28,29] Previous randomized trials of anticoagulants in AF have focused on lower-risk patients ($CHADS_2$ median of approximately 2) than those randomized in the ROCKET-AF trial ($CHADS_2$ median >3) and seen in unselected clinical practice.[10,11,30] Those with moderate renal insufficiency have higher $CHADS_2$ values than patients without renal dysfunction (*Table 1*), hence the importance of testing the randomized comparison of rivaroxaban and warfarin in a population that included a substantial cohort with moderate renal insufficiency (one in five study patients). This study has shown that it is possible to anticoagulate patients with moderate renal dysfunction, without excessive bleeding.

The strengths of this study are that the double-blind, randomized comparison was conducted in a wide range of countries and different health care systems. This is relevant to the translation of trial evidence into clinical practice. Although those with moderate renal insufficiency are a substantial cohort within the ROCKET-AF trial, this analysis was not powered to demonstrate non-inferiority or superiority for the comparison of rivaroxaban vs. warfarin. Nevertheless, the findings show consistency between the subgroup with renal dysfunction and those without renal dysfunction.

Conclusion

Patients with AF and moderate renal impairment respond favourably to a reduced dose of rivaroxaban (15 mg once daily)

compared with warfarin and in a fashion similar to those with preserved renal function given 20 mg of rivaroxaban daily. Although we were unable to demonstrate non-inferiority or superiority for the comparison of rivaroxaban vs. warfarin in patients with moderate renal insufficiency (CrCl 30–49 mL/min), the absence of heterogeneity between overall results and this subgroup suggests that the dose adjustment of rivaroxaban in patients with moderate renal insufficiency yields results consistent with the overall trial. Rivaroxaban preserved the benefit of warfarin in preventing stroke and systemic embolus, and produced lower rates while on treatment. Bleeding rates with the reduced dose of rivaroxaban were similar to those on warfarin therapy, and there were fewer fatal bleeds with rivaroxaban.

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