

## Efficacy and Safety of Rivaroxaban Compared With Warfarin Among Elderly Patients With Nonvalvular Atrial Fibrillation in 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)

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**Background**—Nonvalvular atrial fibrillation is common in elderly patients, who face an elevated risk of stroke but difficulty sustaining warfarin treatment. The oral factor Xa inhibitor rivaroxaban was noninferior to warfarin in 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). This prespecified secondary analysis compares outcomes in older and younger patients.

**Methods and Results**—There were 6229 patients (44%) aged  $\geq 75$  years with atrial fibrillation and  $\geq 2$  stroke risk factors randomized to warfarin (target international normalized ratio=2.0–3.0) or rivaroxaban (20 mg daily; 15 mg if creatinine clearance  $< 50$  mL/min), double blind. The primary end point was stroke and systemic embolism by intention to treat. Over 10866 patient-years, older participants had more primary events (2.57% versus 2.05%/100 patient-years;  $P=0.0068$ ) and major bleeding (4.63% versus 2.74%/100 patient-years;  $P<0.0001$ ). Stroke/systemic embolism rates were consistent among older (2.29% rivaroxaban versus 2.85% warfarin per 100 patient-years; hazard ratio=0.80; 95% confidence interval, 0.63–1.02) and younger patients (2.00% versus 2.10%/100 patient-years; hazard ratio=0.95; 95% confidence interval, 0.76–1.19; interaction  $P=0.313$ ), as were major bleeding rates ( $\geq 75$  years: 4.86% rivaroxaban versus 4.40% warfarin per 100 patient-years; hazard ratio=1.11; 95% confidence interval, 0.92–1.34;  $< 75$  years: 2.69% versus 2.79%/100 patient-years; hazard ratio=0.96; 95% confidence interval, 0.78–1.19; interaction  $P=0.336$ ). Hemorrhagic stroke rates were similar in both age groups; there was no interaction between age and rivaroxaban response.

**Conclusions**—Elderly patients had higher stroke and major bleeding rates than younger patients, but the efficacy and safety of rivaroxaban relative to warfarin did not differ with age, supporting rivaroxaban as an alternative for the elderly. (*Circulation*. 2014;130:138-146.)

**Key Words:** aging ■ anticoagulant ■ elderly ■ hemorrhage ■ stroke

The prevalence of atrial fibrillation (AF) increases with age<sup>1</sup> and is a major cause of stroke, disability, and death among the elderly, particularly among older women.<sup>1,2</sup>

Anticoagulation with warfarin reduces the risk of ischemic stroke,<sup>3</sup> and the net benefit of warfarin rises with age.<sup>4</sup> The risk of bleeding during anticoagulant therapy is also

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\*See the online-only Data Supplement for a complete list of ROCKET AF Steering Committee members and investigators.

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amplified by age, thus requiring frequent anticoagulation monitoring. Sensitivity to warfarin, polypharmacy, and comorbidities<sup>5</sup> make it difficult for elderly patients to maintain stable anticoagulation. Consequently, elderly patients are often not prescribed anticoagulation or are unable to sustain warfarin therapy over time, leaving many at high risk of stroke.<sup>6</sup> Novel anticoagulants that specifically inhibit factor IIa or Xa do not require regular monitoring and have few drug and food interactions. These advantages could facilitate more effective stroke prophylaxis across a wider proportion of elderly patients with AF than is generally achieved with warfarin.

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Rivaroxaban, the first oral factor Xa inhibitor approved as an alternative to warfarin for several thromboembolic indications, was noninferior to adjusted-dose warfarin (target international normalized ratio [INR]=2.0–3.0) in 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)<sup>7,8</sup> among patients with nonvalvular AF at moderate to high risk of stroke (mean CHADS<sub>2</sub> score 3.5±0.9 [SD]) and caused less intracranial and fatal bleeding. Because elderly patients with AF bear the highest risk of stroke and greatest susceptibility to adverse drug effects, the balance of risk and benefit is a key therapeutic consideration for older patients. The purpose of this prespecified secondary analysis of the ROCKET AF study was to compare the efficacy (prevention of stroke and systemic embolism) and safety (bleeding) results between warfarin and rivaroxaban in patients aged ≥75 versus <75 years at entry.

### Methods

The rationale, design, and outcomes of the ROCKET AF trial have been described.<sup>7</sup> This international, double-blind, double-dummy, event-driven, parallel-group trial randomized 14 264 patients to treatment with either fixed-dose rivaroxaban or adjusted-dose warfarin to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism over a median treatment duration of 590 days and median follow-up of 707 days.

### Patients

Patients had nonvalvular AF and previous stroke, transient ischemic attack (TIA), or systemic embolism or ≥2 of the following risk factors: heart failure or left ventricular systolic dysfunction (ejection fraction ≤35%), hypertension, age ≥75 years, and diabetes mellitus. Major exclusion criteria were mitral stenosis, prosthetic heart valves, transient or self-limited AF caused by reversible conditions, severe renal insufficiency (calculated creatinine clearance <30 mL/min), active liver disease or serum liver enzyme levels more than twice the upper limit of normal, and conditions associated with increased bleeding risk.

Detailed inclusion and exclusion criteria have been described.<sup>7,8</sup> Concomitant antithrombotic drugs other than aspirin (≤100 mg/d) or thienopyridine therapy after percutaneous coronary intervention (<2%) were prohibited. Written informed consent was obtained from all patients according to a protocol approved by local review committees governing research involving human subjects.

### Treatment Allocation

Patients were randomized to treatment with either a fixed dose of rivaroxaban (20 mg once daily; 15 mg daily for those with moderately

impaired renal function [creatinine clearance 30–49 mL/min])<sup>9</sup> or adjusted-dose warfarin (target INR=2.0–3.0). The anticoagulants were administered in a double-blind fashion with sham INR monitoring and dose adjustment for patients allocated to rivaroxaban and placebo warfarin. For all patients, warfarin (or placebo) doses were adjusted according to local clinical practice, with INR measurements at least every 4 weeks. Treatment allocation was balanced according to previous stroke or TIA, aspirin therapy at entry, and country, according to an adaptive allocation algorithm.

### End Points and Assessments

Patients were reviewed at 1, 2, and 4 weeks after initiation of randomized treatment and monthly thereafter for detection of primary end points (stroke [ischemic or hemorrhagic] and systemic embolism), TIA, acute myocardial infarction, or bleeding complications. A standardized stroke symptom questionnaire was used to enhance primary event detection. A positive response prompted (1) additional evaluation by local study-affiliated neurologists or stroke specialists blinded to treatment assignment, performed as early after symptom onset as possible, and (2) event diagnosis based on clinical findings and the result of brain computed tomography or magnetic resonance imaging. An independent, blinded, central event adjudication committee reviewed the source data.

### Definitions

Stroke was defined as a sudden focal neurological deficit in the distribution of a single brain artery that persisted beyond 24 hours and was not due to another identifiable cause. An event matching this definition but lasting <24 hours was deemed a TIA. Systemic embolism was defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of another likely mechanism such as atherosclerosis. Myocardial infarction was defined by typical symptoms and cardiac biomarker elevation above the upper limit of normal, new pathological Q waves in at least 2 contiguous ECG leads, or confirmation at autopsy. Bleeding was categorized as major when it was clinically overt and associated with a fatal outcome; a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome) was involved; there was a fall in hemoglobin concentration >2 g/dL; or there was a transfusion of >2 U of whole blood or packed red blood cells. Clinically relevant nonmajor bleeding was overt bleeding that did not meet criteria for major bleeding but entailed medical intervention, unscheduled contact (visit or telephone) with a physician, temporary interruption of study drug (ie, delayed dosing), pain, or impairment of daily activities.

### Statistical Analyses

Baseline demographic and clinical characteristics in patients aged ≥75 and <75 years were summarized by randomized treatment as frequencies and percentages for categorical variables and as medians and quartiles for continuous variables. The distribution of the CHADS<sub>2</sub> score was presented as a categorical variable and summarized as mean and SD. Baseline characteristics were compared between the 2 age groups with the  $\chi^2$  and Wilcoxon tests for categorical and continuous variables, respectively. Efficacy and safety events are presented as rates per 100 patient-years of follow-up. Adjustment of efficacy and safety end points for differences in inclusion criteria related to the age of participants was performed to assess for potential confounding.

For all analyses, *P* values ≤0.05 were considered statistically significant. Hazard ratios (HRs) comparing randomized treatments along with their 95% confidence intervals (CIs) and *P* values were derived from a Cox regression model with treatment as the only covariate. Interactions between the randomized treatment and the age grouping were tested by Cox regression modeling.

Efficacy end points were analyzed in the intention-to-treat population, which included all patients randomized in the trial, excluding those at 1 site (n=93 patients) before unblinding because of violations of good clinical practice that made data unreliable. Safety end points were analyzed in the safety population, which included all patients receiving at least 1 dose of study drug.<sup>8</sup> Statistical analyses were

performed with the use of SAS version 9.2 (SAS Institute, Cary, NC) without correction for multiple testing.

## Results

### Patients

The outcomes of the 14 264 randomized participants during the course of the trial have been described previously.<sup>8</sup> Of the 6229 patients (44%) aged  $\geq 75$  years at entry, the median age was 79 years in both men and women compared with 66 years for younger patients. In the elderly group, 46% were female versus 35% of younger patients, and 42% versus 65%, respectively, had prior stroke, TIA, or systemic embolism. The mean CHADS<sub>2</sub> score was 3.7 for elderly patients versus 3.3 for younger patients. Total patient follow-up was

25 709 patient-years at risk. The median follow-up for elderly patients was 696 days (25th and 75th percentiles, 507 and 873 days) and for younger patients 721 days (25th and 75th percentiles, 533 and 894 days). Patients aged  $\geq 75$  years were treated for a median of 19.4 months (9381 patient-years) and younger patients for a median of 20.2 months (13 071 patient-years).

There was a history of hypertension in 91.1% of older men and 94.7% of older women; the mean systolic blood pressure at entry was 132 mm Hg in older men and 134 mm Hg in older women. Mainly because of a history of coronary artery disease, 34.7% of older men and 34.3% of older women were taking aspirin at randomization. There were no differences between treatment groups with regard to these or other key demographic characteristics.

**Table 1. Baseline Characteristics of Patients According to Age Category and Treatment Allocation: Intention-to-Treat Population**

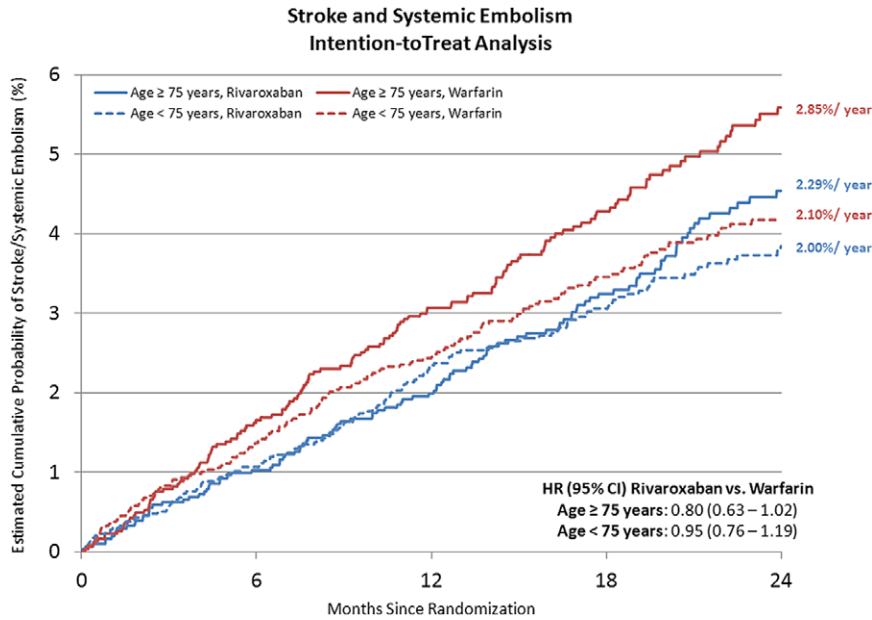
Characteristic	Age $\geq 75$ y			Age $< 75$ y			P Value*
	Overall (n=6229)	Rivaroxaban (n=3120)	Warfarin (n=3109)	Overall (n=8035)	Rivaroxaban (n=4011)	Warfarin (n=4024)	
Age, median (25th, 75th percentiles), y	79 (76, 82)	79 (76, 82)	79 (76, 82)	66 (60, 71)	66 (60, 71)	66 (60, 71)	<0.0001
Female, No. (%)	2878 (46.2)	1446 (46.4)	1432 (46.1)	2782 (34.6)	1384 (34.5)	1398 (34.7)	<0.0001
BMI, median (25th, 75th percentiles), kg/m <sup>2</sup>	27.3 (24.6, 30.5)	27.4 (24.7, 30.7)	27.2 (24.6, 30.4)	29.0 (25.6, 33.1)	29.1 (25.6, 33.3)	29.0 (25.6, 32.7)	<0.0001
BP, median (25th, 75th percentiles), mm Hg							
Systolic	130 (120, 140)	130 (120, 140)	130 (120, 141)	130 (120, 140)	130 (120, 140)	130 (120, 140)	0.0009
Diastolic	80 (70, 84)	80 (70, 84)	80 (70, 85)	80 (72, 88)	80 (73, 88)	80 (72, 87)	<0.0001
Clinical presentation, No. (%)							
Type of AF							0.0856
Persistent	5070 (81.4)	2547 (81.6)	2523 (81.2)	6478 (80.6)	3239 (80.8)	3239 (80.5)	
Paroxysmal	1060 (17.0)	527 (16.9)	533 (17.1)	1454 (18.1)	718 (17.9)	736 (18.3)	
Newly diagnosed/new onset	99 (1.6)	46 (1.5)	53 (1.7)	103 (1.3)	54 (1.4)	49 (1.2)	
Prior aspirin use	2150 (34.5)	1076 (34.5)	1074 (34.5)	3055 (38.0)	1510 (37.7)	1545 (38.4)	<0.0001
Prior VKA use	4111 (66.0)	2055 (65.9)	2056 (66.1)	4793 (59.7)	2388 (59.5)	2405 (59.8)	<0.0001
Clinical risk factors							
CHADS <sub>2</sub> score,† mean (SD)	3.69 (1.01)	3.69 (1.00)	3.69 (1.02)	3.30 (0.84)	3.31 (0.84)	3.29 (0.84)	<0.0001
2, No. (%)	548 (8.8)	275 (8.8)	273 (8.8)	1311 (16.3)	650 (16.2)	661 (16.4)	<0.0001
3, No. (%)	2507 (40.3)	1242 (39.8)	1265 (40.7)	3709 (46.2)	1816 (45.3)	1893 (47.0)	
4, No. (%)	1768 (28.4)	892 (28.6)	876 (28.2)	2323 (28.9)	1200 (29.9)	1123 (27.9)	
5, No. (%)	1123 (18.0)	588 (18.9)	535 (17.2)	690 (8.6)	344 (8.6)	346 (8.6)	
6, No. (%)	282 (4.5)	123 (3.9)	159 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Prior TIA/stroke or systemic embolism, No. (%)	2592 (41.6)	1297 (41.6)	1295 (41.7)	5219 (65.0)	2619 (65.3)	2600 (64.6)	<0.0001
Congestive HF, No. (%)	3650 (58.6)	1839 (58.9)	1811 (58.3)	5258 (65.5)	2628 (65.5)	2630 (65.4)	<0.0001
Hypertension, No. (%)	5777 (92.7)	2877 (92.2)	2900 (93.3)	7133 (88.8)	3559 (88.7)	3574 (88.8)	<0.0001
Diabetes mellitus, No. (%)	2102 (33.8)	1071 (34.3)	1031 (33.2)	3593 (44.7)	1807 (45.1)	1786 (44.4)	<0.0001
Prior MI, No. (%)	1152 (18.5)	543 (17.4)	609 (19.6)	1316 (16.4)	639 (15.9)	677 (16.8)	0.0009
CrCl, median (25th, 75th), mL/min‡	55 (44, 68)	55 (44, 68)	55 (44, 68)	80 (63, 100)	80 (63, 100)	79 (64, 99)	<0.0001
PVD, No. (%)	403 (6.5)	197 (23.5)	206 (24.6)	436 (5.4)	204 (24.3)	232 (27.7)	0.0086
COPD, No. (%)	781 (12.5)	413 (27.6)	368 (24.6)	716 (8.9)	341 (22.8)	375 (25.1)	<0.0001

AF indicates atrial fibrillation; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; HF, heart failure; MI, myocardial infarction; PVD, peripheral vascular disease; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

\*P value comparing patients  $\geq 75$  vs  $< 75$  y (randomized treatment combined).

†There were 3 patients with CHADS<sub>2</sub> scores of 1: 1 in the rivaroxaban arm and 2 in the warfarin arm.

‡Using the Cockcroft-Gault formula.



**Figure 1.** Cumulative proportion of patients in each age group experiencing primary end points over 24 months. CI indicates confidence interval; and HR, hazard ratio.

### Compliance With Randomized Therapy

Among older patients, 59.4% of patients on warfarin and 59.3% of patients on rivaroxaban completed the trial taking their assigned treatment compared with 69.9% and 68.7% in younger patients. Details of patient withdrawal and time in the therapeutic range of 2.0 to 3.0 during warfarin treatment have been reported.<sup>10</sup> During clinical follow-up, INR measurements were slightly more frequent for elderly than for younger patients (average interval, 26 versus 26.4 days;  $P=0.0018$ ). Among elderly patients assigned to warfarin, the mean INR was  $2.44\pm 0.86$  (SD) across all measurements during the course of the study versus  $2.40\pm 0.89$  (SD) for younger patients. The mean time within the therapeutic range for individual patients was  $56.9\pm 21.6\%$  for those aged  $\geq 75$  years

(58.4% in men and 55.1% in women) versus  $53.9\pm 20.9\%$  among younger patients. Supratherapeutic (INR  $\geq 3.2$ ) and subtherapeutic (INR  $\leq 1.8$ ) anticoagulation occurred during 11.6% and 19.2%, respectively, of the follow-up duration in elderly patients taking warfarin, and excessive anticoagulation (INR  $\geq 5.0$ ) occurred 1.3% of the time. Correspondingly, in younger patients, anticoagulation was subtherapeutic, supratherapeutic, and excessive 11.2%, 21.9%, and 1.0% of the time, respectively.

### Treatment Efficacy

The intention-to-treat population comprised 14 171 patients. Clinical characteristics of all patients by age are summarized in Table 1. Figure 1 shows the cumulative proportion of patients in the intention-to-treat population in each age group

**Table 2. Efficacy, Safety End Points, and Score by Decade of Age at Entry**

Event	Age Group				
	<55 y (n=786)	55–64 y (n=2508)	65–74 y (n=4741)	75–84 y (n=5566)	$\geq 85$ y (n=663)
Primary efficacy end point (stroke/systemic embolism)	Rate* (Events)	Rate* (Events)	Rate* (Events)	Rate* (Events)	Rate* (Events)
Stroke, systemic embolism, vascular death	1.49 (21)	1.90 (87)	2.21 (188)	2.56 (251)	2.61 (28)
Stroke, systemic embolism, MI, vascular death	3.70 (52)	3.55 (162)	4.35 (369)	5.33 (522)	7.07 (76)
Primary safety end point†	4.44 (62)	4.16 (189)	5.12 (431)	6.19 (601)	7.97 (85)
Major bleeding	8.10 (97)	10.70 (404)	13.42 (916)	18.16 (1328)	23.77 (179)
Intracranial bleeding	1.17 (15)	2.50 (103)	3.14 (236)	4.39 (367)	6.97 (60)
Scores, mean (SD)	0.15 (2)	0.67 (28)	0.51 (39)	0.69 (59)	1.25 (11)
CHADS <sub>2</sub>	3.19 (0.85)	3.29 (0.84)	3.32 (0.84)	3.70 (1.01)	3.66 (0.99)
CHA <sub>2</sub> DS <sub>2</sub> -VASc	3.55 (1.02)	3.77 (1.06)	4.93 (1.08)	5.38 (1.22)	5.42 (1.20)
HAS-BLED	2.05 (0.95)	2.10 (0.87)	3.06 (0.90)	2.94 (0.81)	2.90 (0.79)

MI indicates myocardial infarction.

\*Rate per 100 patient-years of follow-up.

†International Society on Thrombosis and Haemostasis major or clinically relevant nonmajor bleeding.

**Table 3. Efficacy End Points According to Age Category and Treatment Allocation: Intention-to-Treat Population**

Clinical End Point	Age $\geq 75$ y			Age $< 75$ y			Interaction P-Value
	Rivaroxaban (n=3082)*	Warfarin (n=3082)*	HR (95% CI) Rivaroxaban vs Warfarin	Rivaroxaban (n=3999)*	Warfarin (n=4008)*	HR (95% CI) Rivaroxaban vs Warfarin	
Principal efficacy end point (stroke and systemic embolism)	2.29	2.85	0.80 (0.63–1.02)	2.00	2.10	0.95 (0.76–1.19)	0.3131
Stroke, systemic embolism, vascular death	5.27	5.74	0.92 (0.78–1.087)	3.94	4.12	0.95 (0.81–1.12)	0.7441
Stroke, systemic embolism, MI, vascular death	6.07	6.68	0.91 (0.78–1.06)	4.61	4.89	0.94 (0.81–1.09)	0.7493
Stroke							
Ischemic	1.71	1.95	0.88 (0.67–1.16)	1.55	1.40	1.10 (0.84–1.44)	0.2448
Hemorrhagic	0.34	0.49	0.70 (0.39–1.25)	0.19	0.41	0.47 (0.25–0.89)	0.3651
Undetermined	0.09	0.16	0.55 (0.19–1.65)	0.19	0.12	1.56 (0.68–3.61)	0.1388

CI indicates confidence interval; HR, hazard ratio; and MI, myocardial infarction.

\*Event rates per 100 patient-years of follow-up.

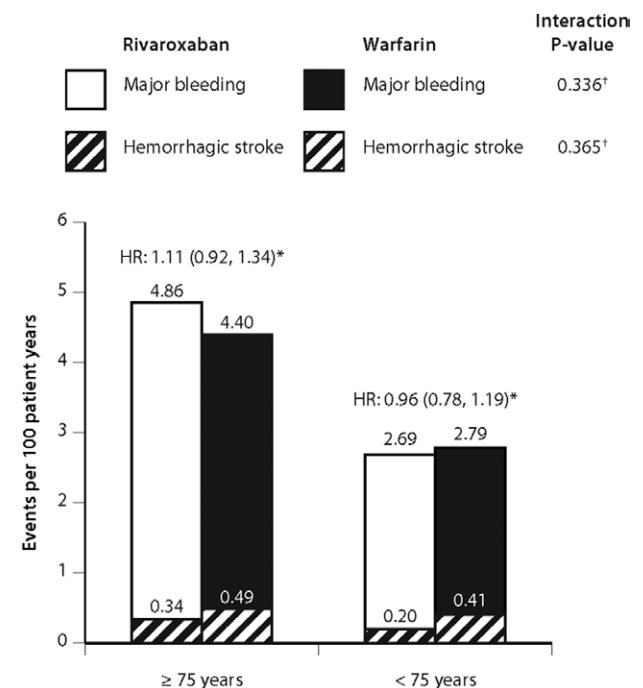
experiencing primary end points over 24 months, and Table 2 shows the event rates in relation to conventional stroke and bleeding risk scores in the population categorized according to age by decade. During 10866 patient-years of exposure, 279 stroke or systemic embolism events occurred among patients aged  $\geq 75$  years. Stroke and systemic embolism were more common in patients aged  $\geq 75$  years than in those aged  $< 75$  years (2.57 versus 2.05 per 100 patient-years;  $P=0.0068$ ). In older patients, the primary event rate was 2.29 (95% CI, 1.92–2.73) per 100 patient-years with rivaroxaban compared with 2.85 (95% CI, 2.43–3.34) per 100 patient-years with warfarin (HR=0.80; 95% CI, 0.63–1.02). In younger patients, the primary event rate was 2.00 (95% CI, 1.69–2.35) per 100 patient-years with rivaroxaban compared with 2.10 (95% CI, 1.79–2.46) per 100 patient-years with warfarin (HR=0.95; 95% CI, 0.76–1.19). There was no significant interaction of treatment efficacy with age for the primary end point ( $P=0.3131$ ).

Relative treatment efficacy with rivaroxaban and warfarin is shown in Table 3. Prevention of ischemic stroke (1.71 [1.30–2.10] per 100 patient-years with rivaroxaban versus 1.95 [1.61–2.36] with warfarin) among older patients (HR=0.88; 95% CI, 0.67–1.16) was comparable to that in younger patients (1.55 [1.29–1.86] per 100 patient-years with rivaroxaban versus 1.40 [1.15–1.70] with warfarin; HR=1.10 [95% CI, 0.84–1.44]; interaction  $P=0.2448$ ). Stroke and systemic embolism occurred at a rate of 2.31 (1.96–2.74) in older men and 2.87 (2.43–3.38) in older women per 100 patient-years (Figure 1). The primary event rate in elderly men assigned to rivaroxaban was 2.07 (1.61–2.66) per 100 patient-years versus 2.56 (2.04–3.21) with warfarin (HR=0.81; 95% CI, 0.58–1.14;  $P=0.2234$ ) and in elderly women was 2.54 (1.99–3.25) per 100 patient-years with rivaroxaban versus 3.19 (2.56–3.98) with warfarin (HR=0.80; 95% CI, 0.57–1.11;  $P=0.1761$ ).

### Hemorrhagic Stroke and Bleeding Events

Rates of major bleeding were higher among older patients (4.63 [4.21–5.09] per 100 patient-years) than in younger

patients (2.74 [2.47–3.04];  $P<0.0001$ ). There were no significant differences, however, in rates of major bleeding among patients on rivaroxaban compared with those on warfarin in either age group (Figure 2), and the relative risk of bleeding in the 2 treatment groups was comparable among older and younger patients (Table 4; interaction  $P=0.336$ ). Older patients randomized to rivaroxaban had higher rates of the combined end point of major or clinically relevant nonmajor bleeding, however, than those assigned to warfarin, whereas there was no difference by treatment in rates of bleeding among younger patients (interaction  $P=0.009$ ). This interaction was restricted to extracranial bleeding and driven primarily by



**Figure 2.** Rates of major bleeding and hemorrhagic stroke based on patient age at entry. \*Hazard ratio (HR) for rivaroxaban vs warfarin for major bleeding. †P values for interaction.

**Table 4. Bleeding Events According to Age Category and Treatment Allocation**

Clinical End Point	Age ≥75 y			Age <75 y			Interaction <i>P</i> Value
	Rivaroxaban (n=3111)*	Warfarin (n=3104)*	HR (95% CI) Rivaroxaban vs Warfarin	Rivaroxaban (n=4000)*	Warfarin (n=4021)*	HR (95% CI) Rivaroxaban vs Warfarin	
Primary safety end point	19.83	17.55	1.13 (1.02–1.25)	11.58	12.43	0.93 (0.84–1.04)	0.0090
Major bleeding	4.86	4.40	1.11 (0.92–1.34)	2.69	2.79	0.96 (0.78–1.19)	0.3357
Hemoglobin drop	3.85	2.98	1.29 (1.03–1.61)	1.99	1.75	1.14 (0.88–1.46)	0.4522
Transfusion	2.28	1.86	1.23 (0.93–1.64)	1.19	0.94	1.27 (0.91–1.77)	0.8978
Clinical organ	1.07	1.42	0.75 (0.52–1.08)	0.63	1.00	0.63 (0.43–0.93)	0.5281
Fatal bleeding	0.28	0.61	0.45 (0.23–0.87)	0.22	0.39	0.55 (0.29–1.05)	0.6839
Intracranial hemorrhage	0.66	0.83	0.80 (0.50–1.28)	0.37	0.68	0.54 (0.33–0.89)	0.2654

CI indicates confidence interval; and HR, hazard ratio.

\*Event rates per 100 patient-years of follow-up.

gastrointestinal bleeding, which was more frequent among elderly patients in the rivaroxaban group than in the warfarin group.

Rates of hemorrhagic stroke were similar in elderly and younger patients and consistent with the overall trial results; there was no significant interaction between patient age and the relative safety of rivaroxaban compared with warfarin (interaction  $P=0.2654$ ). Additional safety data are presented in Tables 4 and 5, and the relative risks of selected efficacy and safety outcomes according to randomized treatment are shown in Figure 3.

Adjustment of the main efficacy and safety end points for the inclusion criteria and based on all variables that were significantly different between patients in the 2 age strata

(Table 1; ie, all variables except the pattern of AF) revealed only small differences that were not clinically meaningful.

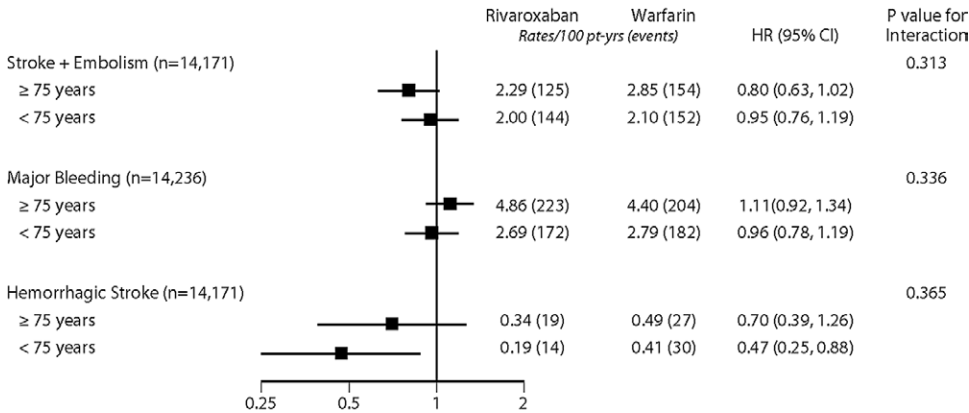
## Discussion

In this prespecified secondary analysis of patients with nonvalvular AF randomized in the ROCKET AF trial, the absolute rates of stroke and systemic embolism and major bleeding were higher among elderly patients compared with younger patients, and the relative effects of the oral factor Xa inhibitor rivaroxaban, administered once daily in a fixed dose without coagulation monitoring, compared with adjusted-dose warfarin were consistent among elderly and younger patients for prevention of stroke and systemic embolism and with respect to the risk of major bleeding. With 6215 elderly

**Table 5. Bleeding Sites According to Age Category and Treatment Allocation**

	Age ≥75 y			Age <75 y		
	Rivaroxaban (n=3111)*	Warfarin (n=3104)*	<i>P</i> Value	Rivaroxaban (n=4000)*	Warfarin (n=4021)*	<i>P</i> Value
Gastrointestinal (upper, lower, and rectal)	2.81	1.66	0.0002	1.41	0.94	0.0136
Intracranial	0.66	0.83	0.3531	0.37	0.68	0.0156
Intraparenchymal	0.41	0.49	0.5565	0.28	0.50	0.0441
Nontraumatic	0.34	0.47	0.3437	0.26	0.48	0.0402
Traumatic	0.06	0.02	0.3348	0.02	0.02	0.9947
Intraventricular	0.19	0.36	0.1288	0.06	0.20	0.0422
Subdural hematoma	0.23	0.32	0.4347	0.05	0.18	0.0343
Subarachnoid	0.11	0.19	0.2972	0.03	0.08	0.2836
Epidural hematoma	0.00	0.02	...	0.00	0.00	...
Macroscopic hematuria	0.32	0.19	0.2213	0.17	0.18	0.8687
Bleeding associated with noncardiac surgery	0.26	0.36	0.3575	0.11	0.14	0.6408
Intraocular/retinal	0.17	0.25	0.3811	0.14	0.18	0.5432
Intra-articular	0.21	0.28	0.5495	0.09	0.12	0.6094
Epistaxis	0.11	0.23	0.2292	0.11	0.05	0.2100

\*Event rates per 100 patient-years of follow-up.



**Figure 3.** Relative risks of major clinical outcome events with rivaroxaban vs warfarin in older and younger patients. CI indicates confidence interval; and HR, hazard ratio.

patients observed over 9381 patient-years of exposure, the ROCKET AF trial provides the largest prospective experience involving high-risk elderly patients with AF using oral anticoagulation.

Elderly patients are a particularly high-risk group for stroke in AF but also face the highest risk of adverse drug events. Indeed, even though the risk requirements for enrollment resulted in a higher prevalence of other stroke risk factors (such as prior stroke or TIA) in younger patients, the elderly participants in this trial exhibited higher absolute rates of stroke and systemic embolism and higher rates of bleeding. Rates of hemorrhagic stroke, however, were similar to those in younger patients. The relative effects of rivaroxaban and warfarin were consistent among elderly and younger patients for both treatment efficacy and safety. Anticoagulation with rivaroxaban was as effective as warfarin in reducing stroke and systemic embolism in older patients and was associated with less intracranial bleeding.

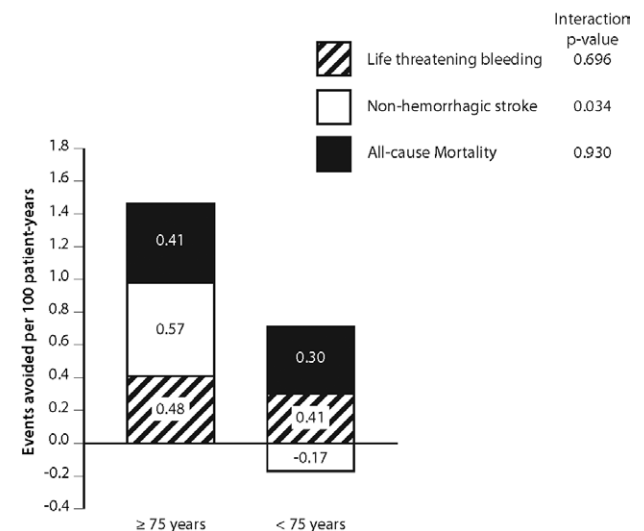
The efficacy of warfarin treatment in the large, international ROCKET AF trial was achieved with close monitoring of the INR. We found no difference between younger and older patients in time spent in the therapeutic range. Older patients developed more major and clinically relevant nonmajor bleeding events than younger patients, and rivaroxaban was associated with a higher risk of this combined bleeding end point in elderly patients compared with patients randomized to warfarin, mainly as a result of more frequent nonmajor bleeding. Rates of major bleeding were not significantly different between the rivaroxaban and warfarin groups. In younger patients on rivaroxaban, the lower risk of major and clinically relevant nonmajor bleeding was not statistically significant compared with patients on warfarin.

In a post hoc analysis of bleeding events in relation to age in a randomized trial of 2 doses of the oral direct thrombin inhibitor dabigatran etexilate, there was a significant interaction between treatment and age for major bleeding, such that the lower dose (110 mg twice daily) was associated with a rate of major bleeding similar to that with warfarin, whereas the higher dose (150 mg twice daily) was associated with a greater risk of major bleeding compared with warfarin among those aged ≥75 years.<sup>11</sup> This interaction between treatment and age was evident for extracranial bleeding but not for intracranial bleeding,

was lower with both doses of dabigatran compared with warfarin, irrespective of patient age. Differences in the enrolled patient populations, treatment blinding, and other characteristics require the use of caution in drawing inferences based on comparisons.

Although there is no universally accepted method of calculating the net clinical benefit of antithrombotic therapy, one approach is based on avoidance of ischemic stroke, severe (life-threatening) bleeding, including intracranial hemorrhage, and all-cause mortality. When considered in this way, the benefit of rivaroxaban compared with warfarin is more pronounced in elderly patients than in younger patients, mainly as a result of prevention of nonhemorrhagic stroke (Figure 4).

Management of warfarin therapy in clinical practice is challenging and often suboptimal even in well-organized centers.<sup>12,13</sup> The low rate of major bleeding events in randomized trials does not always reflect the incidence in clinical practice,<sup>6</sup> related to subject selection, the intensity of monitoring, and follow-up or other factors. The number of major bleeding episodes in this study may have been too small to detect a significant difference in subgroups. Previous studies



**Figure 4.** Net clinical benefit of rivaroxaban compared with warfarin in older and younger patients.

found INR values  $\geq 5.0$  to be an independent risk factor for warfarin-associated bleeding,<sup>14</sup> and INR values  $\geq 3.5$  are associated with an increased risk of cerebral hemorrhage in older patients.<sup>15,16</sup> In our study, excessive anticoagulation (INR  $\geq 5$ ) occurred 1.3% of the time in patients on warfarin treatment, and INR values  $\geq 3.2$  occurred 11.6% of the time. The risk of major bleeding with warfarin may be higher in clinical practice, where the INR is often less carefully monitored.<sup>17</sup>

In addition to the limitations inherent in any secondary analysis of clinical trial data, the duration of the ROCKET AF trial may have been too short to expose potential adverse events of treatment over a longer period. Eligibility required relatively high stroke risk based on CHADS<sub>2</sub> scores, and most patients had previous stroke or TIA, heart failure, or diabetes mellitus. Adverse events were more common among the elderly patients, including bleeding, but these did not differ significantly by treatment with rivaroxaban versus warfarin. There is no proven reversal strategy for rivaroxaban or for any of the direct factor Xa inhibitors or dabigatran, although anticoagulation with these agents is associated with lower rates of intracranial bleeding than with the use of warfarin in both older and younger patients.

The main clinical implication of this study is that in elderly patients with nonvalvular AF at high risk of stroke, factor Xa inhibition with rivaroxaban is as effective as adjusted-dose anticoagulation with warfarin. Although rivaroxaban caused more clinically relevant nonmajor bleeding, it carried less risk of intracranial bleeding, a particular concern in the elderly. Simplifying anticoagulation management in the elderly is a substantial advantage. The availability of rivaroxaban and other factor Xa inhibitors<sup>18,19</sup> may allow anticoagulation of a higher proportion of high-risk elderly patients with AF, offering protection against stroke.

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### CLINICAL PERSPECTIVE

Atrial fibrillation is common among the elderly, who face high rates of disabling ischemic stroke if untreated but risk bleeding during anticoagulation with warfarin. The vitamin K antagonists require routine blood test monitoring of anticoagulation intensity, making it difficult for many elderly patients to sustain prophylaxis. The first oral factor Xa inhibitor, rivaroxaban, given once daily, proved noninferior to adjusted-dose warfarin (target international normalized ratio=2–3) for prevention of stroke and systemic embolism (primary events) in the double-blind 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) of >14 000 patients (mean CHADS<sub>2</sub> score=3.5), with comparable rates of major and clinically relevant non-major bleeding and significantly lower rates of cerebral hemorrhage. This prespecified secondary analysis compares outcomes in 6229 patients aged ≥75 years with younger patients. The older participants had higher rates of primary events (2.57 versus 2.05%/100 patient-years;  $P=0.0068$ ) and major bleeding (4.63 versus 2.74%/100 patient-years;  $P<0.0001$ ), but the relative risks of stroke during treatment with rivaroxaban versus warfarin were consistent among older and younger patients (hazard ratio=0.80 versus 0.95; interaction  $P=0.313$ ), as were risks of major bleeding (hazard ratio=1.11 versus 0.96; interaction  $P=0.336$ ); hemorrhagic stroke rates were lower with rivaroxaban, as seen in younger patients. There was no interaction between age and response to rivaroxaban. Whereas the elderly patients with atrial fibrillation exhibited higher rates of stroke and major bleeding than younger patients, the relative efficacy and safety of rivaroxaban compared with warfarin did not differ with age. These results support use of rivaroxaban as an alternative to warfarin in elderly patients with atrial fibrillation.

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