Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF

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Summary

Background In ROCKET AF, rivaroxaban was non-inferior to adjusted-dose warfarin in preventing stroke or systemic embolism among patients with atrial fibrillation (AF). We aimed to investigate whether the efficacy and safety of rivaroxaban compared with warfarin is consistent among the subgroups of patients with and without previous stroke or transient ischaemic attack (TIA).

Methods In ROCKET AF, patients with AF who were at increased risk of stroke were randomly assigned (1:1) in a double-blind manner to rivaroxaban 20 mg daily or adjusted dose warfarin (international normalised ratio 2·0–3·0). Patients and investigators were masked to treatment allocation. Between Dec 18, 2006, and June 17, 2009, 14 264 patients from 1178 centres in 45 countries were randomly assigned. The primary endpoint was the composite of stroke or non-CNS systemic embolism. In this substudy we assessed the interaction of the treatment effects of rivaroxaban and warfarin among patients with and without previous stroke or TIA. Efficacy analyses were by intention to treat and safety analyses were done in the on-treatment population. ROCKET AF is registered with ClinicalTrials.gov, number NCT00403767.

Findings 7468 (52%) patients had a previous stroke (n=4907) or TIA (n=2561) and 6796 (48%) had no previous stroke or TIA. The number of events per 100 person-years for the primary endpoint in patients treated with rivaroxaban compared with warfarin was consistent among patients with previous stroke or TIA (2·79% rivaroxaban *vs* 2·96% warfarin; hazard ratio [HR] 0·94, 95% CI 0·77–1·16) and those without (1·44% *vs* 1·88%; 0·77, 0·58–1·01; interaction p=0·23). The number of major and non-major clinically relevant bleeding events per 100 person-years in patients treated with rivaroxaban compared with warfarin was consistent among patients with previous stroke or TIA (13·31% rivaroxaban *vs* 13·87% warfarin; HR 0·96, 95% CI 0·87–1·07) and those without (16·69% *vs* 15·19%; 1·10, 0·99–1·21; interaction p=0·08).

Interpretation There was no evidence that the relative efficacy and safety of rivaroxaban compared with warfarin was different between patients who had a previous stroke or TIA and those who had no previous stroke or TIA. These results support the use of rivaroxaban as an alternative to warfarin for prevention of recurrent as well as initial stroke in patients with AF.

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Introduction

A history of transient ischaemic attack (TIA) or ischaemic stroke is a major risk factor for stroke in patients with non-valvular atrial fibrillation (AF), conferring a 2·5 times increased risk,[1] and is also a risk factor for bleeding with oral anticoagulation.[2] Two randomised trials have examined the benefits and risks of oral anticoagulation with warfarin for secondary stroke prevention in 485 patients with AF and previous stroke or TIA.[3–5] The results were consistent with those in patients without previous stroke or TIA:[6] warfarin reduced recurrent stroke by two-thirds (odds ratio [OR] 0·36, 95% CI 0·22–0·58) and increased major extracranial haemorrhage (4·32, 1·55–12·10) compared with no warfarin.[3–5]

Rivaroxaban, an oral direct factor Xa inhibitor, given at a dose of 20 mg once daily, was non-inferior to adjusted-dose warfarin (target international normalised ratio [INR] 2·0–3·0) in the prevention of stroke and systemic embolism among patients with non-valvular AF who were at moderate-to-high risk of stroke (mean $CHADS_2$ score [a measure of the risk of stroke, in which congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus are each assigned 1 point and previous stroke or TIA is assigned 2 points] 3·5 [SD 0·9]) 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).[7,8] In this prespecified subgroup analysis, we aimed to establish whether the efficacy and safety of rivaroxaban

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compared with warfarin among patients with previous TIA or ischaemic stroke was consistent with results among patients without previous stroke or TIA and the entire study population. Our rationale was that treatment effects might differ between patients with and those without previous stroke or TIA, because the risk of primary efficacy and safety outcomes differs between these groups.[1,2]

Methods

Patients

The design and methods of ROCKET AF have been described.[7,8] Briefly, ROCKET AF was a multinational, randomised, double-blind, double-dummy, event-driven trial that compared fixed-dose rivaroxaban with adjusted-dose warfarin to prevent all stroke (ischaemic or haemorrhagic) or systemic embolism.[7,8]

Eligible patients had electrocardiographically documented AF and increased risk of stroke defined as a history of stroke, TIA, or systemic embolism, or at least two of the following risk factors: heart failure or left ventricular ejection fraction 35% or lower, hypertension, age 75 years or older, or diabetes mellitus. Exclusion criteria consisted of TIA within 3 days, acute stroke within 14 days, or severe disabling stroke (modified Rankin score 4–5, inclusive) within 3 months of randomisation; severe valvular heart disease; high risk of bleeding; creatinine clearance less than 30 mL/min; known significant liver disease or alanine transaminase greater than three times the upper limit of normal; the need for more than 100 mg aspirin daily; and recent or planned treatment with a strong inhibitor or inducer of cytochrome P450 3A4. Patients with previous stroke or TIA were identified from their clinical history and confirmed by the enrolling physician; there was no adjudication or requirement for clinical or imaging records. Patients provided written informed consent and were enrolled into ROCKET AF according to a protocol approved by appropriate national regulatory authorities and ethics committees at the participating centres.

	Without previous stroke or TIA		With previous stroke or TIA		p value*
	Rivaroxaban (n=3377)	Warfarin (n=3419)	Rivaroxaban (n=3754)	Warfarin (n=3714)	
Age (years)	75 (68–79)	75 (67–79)	71 (64–76)	71 (64–77)	<0·0001
Women	1348 (40%)	1382 (40%)	1482 (39%)	1448 (39%)	0·25
Body mass index (kg/m²)	29·0 (25·6–33·2)	28·8 (25·7–32·8)	27·7 (24·8–31·2)	27·5 (24·5–31·0)	<0·0001
Systolic blood pressure (mm Hg)	130 (120–140)	130 (120–140)	130 (120–140)	130 (120–140)	0·08
Diastolic blood pressure (mm Hg)	80 (70–85)	80 (70–85)	80 (71–86)	80 (72–85)	<0·0001
Creatinine clearance (mL/min/1·73 m²)	65 (50–86)	65 (50–86)	69 (54–88)	68 (53–86)	<0·0001
Atrial fibrillation type					
Persistent	2792 (83%)	2832 (83%)	2994 (80%)	2930 (79%)	<0·0001
Paroxysmal	542 (16%)	535 (16%)	703 (19%)	734 (20%)	..
Newly diagnosed	43 (1%)	52 (2%)	57 (2%)	50 (1%)	..
$CHADS_2$ score	3 (3–3)	3 (3–3)	4 (3–5)	4 (3–5)	<0·0001
Previous treatment					
Aspirin	1177 (35%)	1220 (36%)	1409 (38%)	1399 (38%)	0·0039
Vitamin K antagonists	2221 (66%)	2254 (66%)	2222 (59%)	2207 (59%)	<0·0001
Clinical risk factors					
Hypertension	3252 (96%)	3315 (97%)	3184 (85%)	3159 (85%)	<0·0001
Congestive heart failure	2562 (76%)	2561 (75%)	1905 (51%)	1880 (51%)	<0·0001
Diabetes	1956 (58%)	1933 (57%)	922 (25%)	884 (24%)	<0·0001
Myocardial infarction	646 (19%)	691 (20%)	536 (14%)	595 (16%)	<0·0001
Peripheral arterial disease	217 (6%)	244 (7%)	184 (5%)	194 (5%)	<0·0001
Chronic obstructive pulmonary disease	425 (13%)	427 (12%)	329 (9%)	316 (9%)	<0·0001

Data are median (IQR) or number (%). Analyses were done with the Wilcoxon rank sum test. TIA=transient ischaemic attack. *For comparison between patients with and without previous stroke or TIA.

Table: **Demographics and baseline clinical characteristics**

Randomisation and masking

Randomisation was done by a central 24-h, computerised, automated voice-response system. Patients were randomly assigned (1:1) to receive double-blind, fixed-dose rivaroxaban (20 mg daily; 15 mg daily in patients with creatinine clearance 30–49 mL/min) or adjusted-dose warfarin (target INR 2·5, range 2·0–3·0). Patients in each group also received a placebo tablet to maintain masking. Patients and investigators were masked to treatment allocation. An independent clinical events committee who were masked to the treatment allocations applied the protocol endpoint definitions and adjudicated all stroke, non-CNS systemic embolism, myocardial infarction, death, and bleeding events.

Procedures

The primary efficacy endpoint was the composite of adjudicated stroke (both ischaemic and haemorrhagic) and non-CNS systemic embolism. Stroke was defined as a sudden, focal neurological deficit of presumed cerebrovascular cause that was neither reversible within 24 h nor due to another readily identified cause, such as tumour, trauma, or seizure. An event matching this definition but lasting less than 24 h was classed as a TIA. Brain imaging to distinguish haemorrhagic from ischaemic stroke was encouraged but not required. The functional severity of stroke was classified at hospital discharge by site investigators according to the modified Rankin scale.[9] The clinical diagnosis of stroke after randomisation and the pathological subtype of stroke identified by brain imaging or autopsy were adjudicated by the clinical events committee of experts.

Non-CNS systemic embolism was defined as abrupt vascular insufficiency associated with clinical or radiographic evidence of arterial occlusion in the absence of another likely mechanism (eg, atherosclerosis, trauma,

or arterial catheterisation). In the presence of atherosclerotic peripheral arterial disease, angiographic demonstration of abrupt arterial occlusion in the absence of intrinsic vascular pathology was needed for a diagnosis of lower extremity arterial embolism.

The principal safety endpoint was a composite of major and non-major clinically relevant bleeding events. Major bleeding was defined as clinically overt bleeding associated with fatality or involving a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), a decrease in haemoglobin concentrations of at least 2 g/dL, or transfusion of at least 2 units of whole blood or packed red blood cells. All CNS bleeding events that met the definition of acute stroke were included as haemorrhagic strokes in the primary endpoint analysis and counted both as efficacy and safety events. Non-major clinically relevant bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but that needed medical intervention, unscheduled (visit or telephone) contact with a physician, or temporary interruption of the study drug (ie, delayed dosing), or that caused pain or impairment of daily activity. Other overt bleeding that did not meet the criteria for major or non-major clinically relevant bleeding was classed as minor.

Statistical analysis

ROCKET AF was a non-inferiority trial and the primary analysis was done in the per-protocol, on-treatment population.[7] In this prespecified secondary analysis, estimates and two-sided 95% CIs for the hazard ratio (HR; rivaroxaban *vs* warfarin) for patients with and without previous stroke or TIA are presented in the intention-to-treat population for efficacy endpoints and in the safety on-treatment population for safety endpoints.

We used Cox proportional hazards regression models with treatment, stroke history, and the treatment by stroke history interaction as covariates to test for interaction between the differential effects of rivaroxaban and warfarin on stroke or non-CNS systemic embolism (primary events) among patients with and without previous TIA or stroke. The proportional hazards assumption was tested by the methods of Lin and colleagues.[10] The time to event for each group was assessed by the Kaplan–Meier method. Secondary aims were to test treatment by stroke history interactions for other predefined efficacy and safety endpoints.

Differences in features of patients with and without a previous stroke or TIA (regardless of treatment) were tested with Wilcoxon rank sum tests and χ^2 tests. HRs were assessed by Cox regression analysis with stroke history as the sole covariate. All statistical analyses were done with SAS (version 9.2).

ROCKET AF is registered with ClinicalTrials.gov, number NCT00403767.

Role of the funding source

Johnson and Johnson Pharmaceutical Research and Development and Bayer HealthCare sponsored the ROCKET AF trial. The Duke Clinical Research Institute coordinated the trial, managed the database, and undertook the primary analysis independent of the sponsors. The sponsors funded these analyses, reviewed and commented on the manuscript, and two sponsor employees are coauthors. The trial investigators had full access to all the data in the study and the members of the trial executive committee and writing committee, listed as authors, had final responsibility for the decision to submit for publication.

Results

Between Dec 18, 2006, and June 17, 2009, 14 264 patients from 1178 centres in 45 countries were randomly assigned to treatment in ROCKET AF. 7468 (52%) had experienced a stroke or TIA before study entry (2561 TIA and 4907 ischaemic or haemorrhagic stroke, stroke of unknown type, or both stroke and TIA) and 6796 (48%) had no previous stroke or TIA. The median time from previous stroke or TIA to randomisation was 551 days (IQR 126–1702).

Among all patients with a previous stroke or TIA, 3754 were allocated to receive rivaroxaban and 3714 to receive warfarin. The table shows the baseline demographic and clinical characteristics of patients with and without previous stroke or TIA.

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See Online for appendix

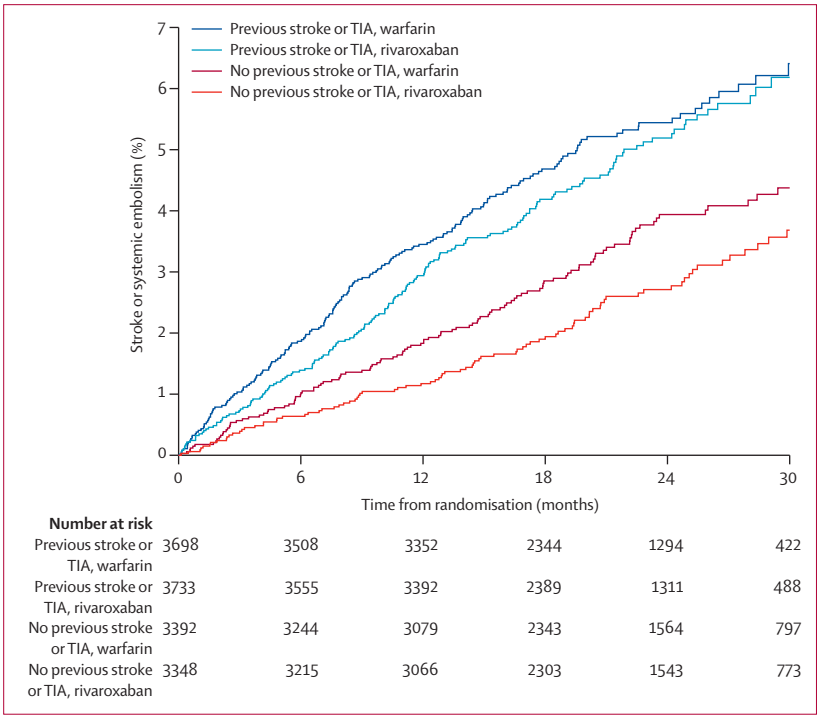

Figure 1: **Kaplan-Meier survival curve showing time to the primary outcome**
TIA=transient ischaemic attack.

The median exposure to study drug was 584 days (IQR 510–845) in patients with previous stroke or TIA and 613 days (392–840) for patients with no previous stroke or TIA. The median duration of follow-up was 676 days (510–845) for patients with previous stroke or TIA and 745 days (530–937) for those without. Among the 12 507 patients who started treatment and who remained free of primary endpoint events and survived throughout the study, 10 457 (84%) completed the first year of treatment (warfarin and no previous stroke, 2454 [83%] of 2951; rivaroxaban and no previous stroke, 2404 [81%] of 2957; warfarin and previous stroke, 2795 [85%] of 3280; rivaroxaban and previous stroke, 2804 [84%] of 3319; p<0·0001 for comparison of groups with previous stroke or TIA *vs* those without). Complete follow-up for vital status was achieved in 14 232 (99·8%) of 14 264 patients; 16 patients with and 16 patients without previous stroke or TIA were lost to follow-up. Among patients with previous stroke or TIA who were assigned to warfarin, the median proportion of time in the therapeutic INR range (including periods after initiation and temporary discontinuation of therapy) was 57·1% (range 42·6–70·1), compared with 58·6% (43·6–71·0) for patients without previous stroke or TIA (p=0·041).

	Events per 100 patient-years (number of events)		HR (95% CI)	p value*
	Rivaroxaban	Warfarin		
Stroke or systemic embolism				
No previous stroke or TIA	1·44 (90)	1·88 (119)	0·77 (0·58–1·01)	0·23
Previous stroke or TIA	2·79 (179)	2·96 (187)	0·94 (0·77–1·16)	
Any stroke				
No previous stroke or TIA	1·31 (82)	1·72 (109)	0·76 (0·57–1·01)	0·16
Previous stroke or TIA	2·66 (171)	2·71 (172)	0·98 (0·79–1·21)	
Haemorrhagic stroke				
No previous stroke or TIA	0·17 (11)	0·42 (27)	0·41 (0·20–0·83)	0·21
Previous stroke or TIA	0·34 (22)	0·46 (30)	0·73 (0·42–1·26)	
Ischaemic or unknown stroke				
No previous stroke or TIA	1·13 (71)	1·29 (82)	0·88 (0·64–1·21)	0·41
Previous stroke or TIA	2·34 (151)	2·27 (144)	1·03 (0·82–1·30)	
Non-disabling stroke (MRS 0–2)				
No previous stroke or TIA	0·67 (42)	0·61 (39)	1·09 (0·71–1·69)	0·97
Previous stroke or TIA	1·13 (73)	1·05 (67)	1·08 (0·77–1·50)	
Disabling or fatal stroke (MRS 3–6)				
No previous stroke or TIA	0·59 (37)	1·00 (64)	0·58 (0·39–0·88)	0·07
Previous stroke or TIA	1·41 (92)	1·53 (98)	0·93 (0·70–1·23)	
Disabling stroke (MRS 3–5)				
No previous stroke or TIA	0·25 (16)	0·39 (25)	0·65 (0·35–1·21)	0·40
Previous stroke or TIA	0·71 (46)	0·79 (51)	0·89 (0·60–1·33)	
Fatal stroke (MRS 6)				
No previous stroke or TIA	0·33 (21)	0·61 (39)	0·54 (0·32–0·93)	0·09
Previous stroke or TIA	0·70 (46)	0·73 (47)	0·97 (0·64–1·45)	
Non-CNS systemic embolism				
No previous stroke or TIA	0·14 (9)	0·16 (10)	0·91 (0·37–2·24)	0·56
Previous stroke or TIA	0·17 (11)	0·26 (17)	0·64 (0·30–1·36)	
Myocardial infarction				
No previous stroke or TIA	1·04 (65)	1·34 (85)	0·77 (0·56–1·07)	0·12
Previous stroke or TIA	1·00 (65)	0·89 (57)	1·13 (0·79–1·61)	
Death from any cause				
No previous stroke or TIA	4·65 (294)	5·28 (338)	0·88 (0·75–1·03)	0·41
Previous stroke or TIA	4·40 (288)	4·54 (294)	0·97 (0·82–1·14)	
Vascular death				
No previous stroke or TIA	2·89 (183)	3·23 (207)	0·89 (0·73–1·09)	0·53
Previous stroke or TIA	2·93 (192)	3·00 (194)	0·98 (0·80–1·19)	
Non-vascular death				
No previous stroke or TIA	1·28 (81)	1·37 (88)	0·93 (0·69–1·26)	0·91
Previous stroke or TIA	1·02 (67)	1·07 (69)	0·96 (0·68–1·34)	

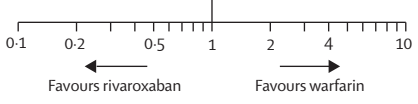

Figure 2: **Intention-to-treat analyses of efficacy outcome events**
Analyses were done with the Cox proportional hazards multiple regression model. HR=hazard ratio. TIA=transient ischaemic attack. MRS=modified Rankin scale.
*For the interaction of treatment (rivaroxaban or warfarin) and history of previous stroke or TIA (yes or no).

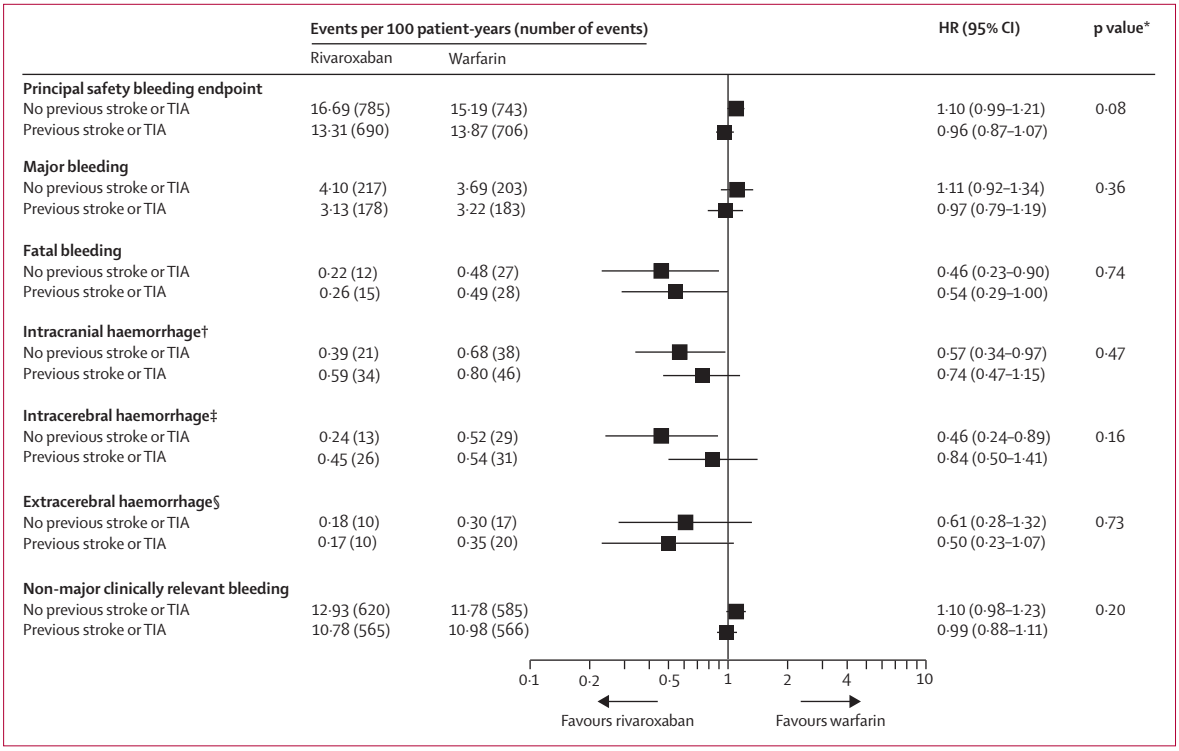

***Figure 3*: On-treatment analyses of safety outcome events**
Analyses were done with the Cox proportional hazards multiple regression model. HR=hazard ratio. TIA=transient ischaemic attack. *For the interaction of treatment (rivaroxaban or warfarin) and history of previous stroke or TIA (yes or no). †17 intracranial haemorrhages were considered both intracerebral and extracerebral. ‡Includes intraparenchymal and intraventricular haemorrhage. One intraparenchymal haemorrhage that occurred with extracerebral haematoma was classified as traumatic. §Includes subarachnoid haemorrhage, subdural haematoma, and epidural haematoma.

The number of stroke or non-CNS systemic embolism events per 100 person-years of all randomised patients, regardless of treatment exposure, was significantly higher among patients with (2·87%) than without (1·66%) previous stroke or TIA (HR 1·70, 95% CI 1·44–2·02; p<0·0001; figure 1). The efficacy of rivaroxaban compared with warfarin was consistent among patients with previous stroke or TIA (HR 0·94, 95% CI 0·77–1·16) and those without (0·77, 0·58–1·01; interaction p=0·23; figure 2). The efficacy results were also consistent in the safety on-treatment population (appendix).

In terms of safety, the overall number of adverse events per 100 person-years was similar in both treatment groups and in patients with and without a previous stroke or TIA. On-treatment analysis of the composite of major and non-major clinically relevant bleeding events revealed a similar number of events per 100 person-years among patients with previous stroke or TIA who were treated with rivaroxaban and those treated with warfarin (HR 0·96, 95% CI 0·87–1·07; figure 3). The effect of rivaroxaban compared with warfarin on this safety outcome was consistent with findings in patients who had no previous stroke or TIA (HR 1·10, 95% CI 0·99–1·21; interaction p=0·08; figure 3).

The number of major bleeding events per 100 person-years among patients who received at least one dose of study drug was significantly lower among those with previous stroke or TIA (n=361, 3·18%) than in those without previous stroke or TIA (n=420, 3·89%; HR 0·81, 95% CI 0·70–0·93; p=0·0037), but the safety of rivaroxaban compared with warfarin with respect to major bleeding showed no interaction among patients with previous stroke or TIA (HR 0·97, 95% CI 0·79–1·19) and those without (1·11, 0·92–1·34; interaction p=0·36; figure 3). Figure 3 shows that the effect of rivaroxaban compared with warfarin on intracerebral haemorrhage was consistent among patients with previous stroke or TIA (HR 0·84, 95% CI 0·50–1·41) and those without (HR 0·46, 95% CI 0·24–0·89; interaction p=0·16). The effect of rivaroxaban compared with warfarin on all efficacy (figure 2) and safety (figure 3) outcomes was consistent among patients with and those without previous stroke or TIA.

Discussion

In ROCKET AF, rivaroxaban was non-inferior to warfarin for prevention of stroke or systemic embolism in patients with non-valvular AF who were at risk of thromboembolism. There was also no significant between-group difference in the risk of major bleeding.[8] In this subgroup analysis of ROCKET AF, we noted that patients with previous stroke or TIA had higher rates of stroke and non-CNS systemic embolism but lower rates of major

Panel: **Research in context**

Systematic review

We searched PubMed with the terms "rivaroxaban", "warfarin", "atrial fibrillation", "stroke", and "clinical trial" for reports published before February 2012. 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)[7,8] was the only published report of the final results of a clinical trial that compared rivaroxaban with warfarin in patients with atrial fibrillation (AF).

Interpretation

ROCKET AF showed that, in patients with AF, rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism, and there was no significant between-group difference in the risk of major bleeding. In the subgroup analysis reported here, we noted no evidence that the efficacy and safety of rivaroxaban compared with warfarin was different between participants with a history of previous stroke or transient ischaemic attack (TIA) and participants without a history of previous stroke or TIA. Hence, the more reliable results of ROCKET AF in the overall trial population can be applied to patients with AF and previous stroke or TIA. This analysis also showed that patients with AF who had previous stroke or TIA have higher absolute rates of stroke or systemic embolism and lower rates of major bleeding than those without previous stroke or TIA; therefore, the absolute benefits of anticoagulation among individuals with AF might be greater for secondary stroke prevention than primary stroke prevention.

bleeding on anticoagulant therapy than those without previous stroke or TIA (panel). After testing for interaction, we also noted that the treatment effects of rivaroxaban and warfarin in patients with previous stroke or TIA were consistent with those in patients without previous stroke or TIA and with the overall trial population. The more reliable results of the overall trial population can thus be generalised to patients with AF and previous stroke or TIA. Therefore, rivaroxaban is an alternative to warfarin for the prevention of recurrent stroke as well as initial stroke, particularly given the lower rates of intracranial and fatal bleeding with rivaroxaban than with warfarin.[8]

The strengths of this subgroup analysis are that it was prespecified, the potential heterogeneity of treatment effect related to history of stroke or TIA is plausible, the treatment groups are similar in terms of important prognostic factors, all subgroup analyses undertaken were reported, the analysis incorporated appropriate statistical tests of interaction, and we interpreted the results cautiously on the premise that even prespecified subgroup analyses are intrinsically limited.[11,12] The main limitation of this analysis is that it involved a subgroup of the overall trial population and the false positive rates for subgroup treatment effect interaction when no true interaction exists have been estimated at 5% per subgroup.[11,12] All tests for interaction among subgroups in this study were negative at the $p<0·05$ level, reducing the potential for false positive assessment. However, one or more of the tests for interaction among subgroups might have been falsely negative ($p>0·05$) because of the small number of outcome events in each subgroup and therefore limited statistical power to minimise random error among the estimates of event rates. Another potential limitation is that the qualifying history of previous stroke or TIA was not adjudicated, so some patients with a reported history of stroke or TIA might have been incorrectly included in this subgroup. Furthermore, some patients without reported history of stroke or TIA might have had a history of unrecognised stroke or TIA. Errors in the assessment of previous stroke or TIA might have introduced some misclassification bias, which might have led to underestimation or overestimation of the HRs.

The finding of a higher rate of stroke or systemic embolism per 100 patient-years among patients treated with warfarin who had previous stroke or TIA (2·87%) than among those without previous stroke or TIA (1·66%; figure 2), is consistent with findings from other studies[13] and highlights the significance of previous stroke or TIA as a major risk factor for stroke in patients with AF. However, only 59% of 7468 patients with a history of stroke or TIA who were enrolled in ROCKET AF were receiving anticoagulant medication before enrolment (38% were taking aspirin; table). After randomisation, patients with previous stroke or TIA who were assigned to warfarin had an INR in the therapeutic range just over half the time, on average, suggesting that high-risk patients are often managed suboptimally in clinical practice as well as in the context of a clinical trial, which suggests that there is a widespread deficiency in care.[14,15] The number of recurrent stroke events per 100 person-years among patients with previous stroke or TIA who were assigned warfarin in ROCKET AF was lower than reported in the European Atrial Fibrillation Trial (EAFT) and the Studio Italiano Fibrillazione Atrial (SIFA) study (4·0% per year)[3,4] but similar to that among such patients in the Randomised Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial (2·8% per year)[13] and the Stroke Prevention using an Oral Thrombin Inhibitor in atrial fibrillation (SPORTIF) III and V trials (3·3% per year).[16] The lower stroke rates observed recently might suggest improved identification and management of associated risk factors such as hypertension, improved anticoagulation control, differences in trial populations, or other factors.

The lower number of major bleeding events among patients with previous stroke or TIA compared with those without in this subgroup analysis contrasts with other studies that reported previous stroke as a risk factor for bleeding during anticoagulation therapy.[2,13] This difference could be due to random (chance) or systematic error (patient selection bias), because patients without previous

stroke or TIA who were enrolled in ROCKET AF had a higher prevalence of risk factors for bleeding (advanced age and greater prevalence of hypertension and diabetes) than those with previous stroke or TIA. Performance bias seems less likely, since the time for which anticoagulation INR was in the therapeutic range on warfarin was not significantly lower among patients with than in those without previous stroke or TIA.

In conclusion, after testing for interaction, the efficacy and safety of rivaroxaban and warfarin for prevention of stroke and non-CNS systemic embolism and avoidance of major and non-major clinically relevant bleeding among patients who had previous stroke or TIA were consistent with findings in the entire ROCKET AF population. The subgroup analyses were not powered to detect whether the effects varied by subgroup, but the overlapping HRs suggest that the effects of rivaroxaban and warfarin are probably consistent when the drugs are used for either primary or secondary stroke prevention. The results support the use of rivaroxaban as an alternative to warfarin for prevention of recurrent as well as initial stroke in patients with AF. Individuals receiving rivaroxaban should be informed not to discontinue it before talking with their health-care professional. We make this recommendation because at the end of ROCKET AF, when patients were transitioned from study drug to vitamin K antagonists such as warfarin, the median time to reach therapeutic INR was longer (13 days) for those previously assigned rivaroxaban than those previously assigned warfarin (3 days). Additionally, the number of primary events (stroke or systemic embolism) during the first month after termination of randomised treatment was significantly greater among patients transitioning from rivaroxaban than from warfarin (22 rivaroxaban *vs* 7 warfarin; p=0·008).[8]

Contributors

This subgroup analysis was implemented under the direction of WH. GJH wrote the first version of the manuscript. WH, GJH, RCB, JFP, GB, JLH, KWM, MRP, CCN, DES, RMC, and KAAF were members of the trial executive committee and assisted with manuscript revision. JLM, AC, H-CD, GAD, AM, BN, RR, and LW also assisted with manuscript revision. SRS did the statistical analyses.

Conflicts of interest

GJH has received honoraria for serving on trial executive committees for Johnson and Johnson, Bayer, and Sanofi-Aventis; and on trial adjudication committees and an advisory board for Boehringer Ingelheim. MRP has received honoraria for serving on executive committees for Johnson and Johnson and Bayer, has received consulting fees from Ortho McNeil Janssen and Bayer HealthCare, and has served on an advisory board for Genzyme. RCB has received research support from Bayer and Johnson and Johnson. GB has received honoraria for serving on a steering committee for Johnson and Johnson and Bayer and has received fees for serving on advisory boards for Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Sanofi-Aventis. AC has received honoraria as a member of a steering committee for Johnson and Johnson and Bayer, and for participation in clinical trials, contributions to advisory boards, or oral presentations from Sanofi-Aventis, Bristol-Myers Squibb, Solvay, Abbott, and Pfizer. H-CD has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, CoAxia, D-Pharm, EV3, Fresenius, GlaxoSmithKline, Janssen Cilag, Knoll, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Sankyo, Schering-Plough, Servier, Solvay, Thrombogenics, Wyeth, and Yamaguchi; and H-CD's institution has received financial support for research projects from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis, and Talecris. GAD has acted on an advisory board for Boehringer Ingelheim. JLH has received honoraria for serving on a steering committee for Johnson and Johnson and Bayer and fees for advisory activities for Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. KWM has received grant support from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Johnson and Johnson, Merck, Momenta Pharmaceuticals, Novartis, Portola, Pozen, Regado Biotechnologies, Sanofi-Aventis, Schering-Plough (now Merck), and The Medicines Company; and consulting fees from AstraZeneca, Johnson and Johnson, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Ortho/McNeill, Pfizer, Polymedix, Sanofi-Aventis, and Schering-Plough (now Merck). J-LM has received honoraria for serving on a steering committee for Johnson and Johnson and Bayer and fees for serving on advisory boards for Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer. BN has received consultancy payments from Bayer, payment for lectures from Allergan and Bayer, and royalties for a book published by Karolinska University Press. BN's institution has received honoraria for consultancy from Syngis, Servier, Bayer, PhotoThera, and Boehringer Ingelheim. CCN is an employee of Johnson and Johnson Pharmaceutical Research and Development (Raritan, NJ, USA) and owns stock in Johnson and Johnson. JFP is a former employee of Bayer HealthCare. ROR has received honoraria as a member of a steering committee from Johnson and Johnson and Bayer and for participating in clinical trials, contributions to advisory boards, or oral presentations from Bayer, Boehringer Ingelheim, Servier, Lundbeck, and Schering. DES has received honoraria for serving on advisory boards or payments for consulting, or both from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Johnson and Johnson, Pfizer, and Sanofi. LW has received honoraria as a member of a steering committee for Johnson and Johnson and Bayer, and for participation in clinical trials, contributions to advisory boards, or oral presentations from Sanofi-Aventis, Bristol-Myers Squibb, Boehringer Ingelheim, and Pfizer. RMC has received consulting fees and research funding from Johnson and Johnson; all other industry interactions are listed at www.dcri.org. KAAF has received grants and honoraria from Bayer, Lilly, Boehringer Ingelheim, Sanofi-Aventis, and GlaxoSmithKline. WH has received honoraria for serving on an executive committee for Johnson and Johnson and Bayer and advisory board fees from Boehringer Ingelheim. SRS and AM declare that they have no conflicts of interest.

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