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Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial

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Aims	We investigated clinical characteristics and outcomes of patients with significant valvular disease (SVD) 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) trial.
Methods and results	ROCKET AF excluded patients with mitral stenosis or artificial valve prostheses. We used Cox regression to adjust comparisons for potential confounders. Among 14 171 patients, 2003 (14.1%) had SVD; they were older and had more comorbidities than patients without SVD. The rate of stroke or systemic embolism with rivaroxaban vs. warfarin was consistent among patients with SVD [2.01 vs. 2.43%; hazard ratio (HR) 0.83, 95% confidence interval (CI) 0.55−1.27] and without SVD (1.96 vs. 2.22%; HR 0.89, 95% CI 0.75−1.07; interaction $P = 0.76$). However, rates of major and non-major clinically relevant bleeding with rivaroxaban vs. warfarin were higher in patients with SVD (19.8% rivaroxaban vs. 16.8% warfarin; HR 1.25, 95% CI 1.05−1.49) vs. those without (14.2% rivaroxaban vs. 14.1% warfarin; HR 1.01, 95% CI 0.94−1.10; interaction $P = 0.034$), even when controlling for risk factors and potential confounders. In intracranial haemorrhage, there was no interaction between patients with and without SVD where the overall rate was lower among those randomized to rivaroxaban.
Conclusions	Many patients with 'non-valvular atrial fibrillation' have significant valve lesions. Their risk of stroke is similar to that of patients without SVD after controlling for stroke risk factors. Efficacy of rivaroxaban vs. warfarin was similar in patients with and without SVD; however, the observed risk of bleeding was higher with rivaroxaban in patients with SVD but was the same among those without SVD. Atrial fibrillation patients with and without SVD experience the same stroke-preventive benefit of oral anticoagulants.

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Introduction

Recent trials have assessed the efficacy and safety of novel, oral, direct-acting anticoagulants in patients with non-valvular atrial fibrillation (AF).[1–10] There has been some variation in the inclusion and exclusion criteria of these trials (*Table 1*).[1–12] In general, non-valvular AF was considered to be present if there was no mitral stenosis, no heart valve prosthesis, and no valvular disease requiring surgery, whereas only one trial[1,2] also excluded patients with any type of haemodynamically relevant valvular disease. Thus, exclusion criteria of most trials would allow for inclusion of patients with other significant valvular lesions. However, the frequency of including patients in these trials who had significant valvular disease (SVD), but who do not meet these exclusion requirements, has not been reported.

The clinical characteristics and the outcomes of patients with SVD when treated with oral anticoagulants like vitamin K antagonists, especially warfarin or novel factor IIa or Xa inhibitors, are unknown. Therefore, this analysis focuses on AF patients with significant valvular lesions who were not considered to have valvular AF, as defined by haemodynamically significant mitral valve stenosis or prosthetic heart valve (*Table 1*). For this purpose, we retrospectively analysed the data of the large randomized trial 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) that compared warfarin and rivaroxaban, a novel factor Xa inhibitor, in patients with non-valvular AF.[5,6]

Methods

The rationale and design of the ROCKET AF study have been published (ClinicalTrials.gov number, NCT00403767).[5] In brief, ROCKET AF was a multicentre, international, double-blind, double-dummy, randomized trial comparing fixed-dose rivaroxaban with dose-adjusted warfarin for prevention of all stroke (ischaemic or haemorrhagic) or systemic embolism. The study was funded by Johnson & Johnson Pharmaceutical Research & Development (Raritan, NJ, USA) and Bayer HealthCare AG (Leverkusen, Germany). The Duke Clinical Research Institute (Durham, NC, USA) coordinated the trial and performed the statistical analyses for this article independent of the sponsors. An international executive steering committee designed the study and takes responsibility for the accuracy and completeness of the analyses. All appropriate national regulatory authorities and ethics committees at participating centres approved the study.

This analysis included 14 171 of 14 264 patients in the ROCKET AF trial. Due to one site's violations of Good Clinical Practice guidelines that made the data unreliable, 93 patients were excluded from all efficacy analyses before unblinding but were included in the safety analyses.[6]

A total of 2003 patients had SVD. Eleven of these patients were at the site that violated Good Clinical Practice guidelines, and an additional 4 patients were randomized but did not receive study drug. Therefore, 1992 SVD patients were used in the analysis of efficacy endpoints [intention-to-treat (ITT) population], and 1999 SVD patients were used in the analysis of safety endpoints (safety population). None of the patients had undergone transcutaneous aortic valve replacement.

Five patients had been randomized despite the presence of a prosthetic valve. The sites were immediately contacted and instructed to discontinue these patients from study drug. These patients were included in the ITT population but not in the safety population. Three of these five patients died before the end of the study in 1 year to about 3 years after enrolment; the other two patients remained alive and were followed until the end of the study.

Patients were randomized to fixed-dose rivaroxaban [20 mg once daily; 15 mg daily for those with moderately impaired renal function (creatinine clearance 30–49 mL/min)] or dose-adjusted warfarin (target international normalized ratio 2.0–3.0), in a double-blind fashion.

Definitions and endpoints

Non-valvular AF was defined[5,6] as the presence of AF and the absence of mitral stenosis or prosthetic heart valves, whereas annuloplasty with or without a prosthetic ring, commissurotomy, and/or valvuloplasty were permitted. In addition, a planned invasive procedure with a potential for uncontrolled bleeding, including major surgery, was an exclusion criterion. Patients with other types of valvular disease could be included in the trial. Specifically, the case report form asked whether there was 'significant valvular disease,' and if so, it asked for 'valve location and abnormality' and 'etiology.' Thus, for the purpose of this study, any type of valvular lesion that did not meet the above exclusion criteria was included in SVD if it was considered to be significant by the recruiting physician(s) in order to reflect clinical practice (external validity).

Additional exclusion criteria were transient or self-limited AF caused by reversible conditions, severe renal insufficiency (creatinine clearance <30 mL/min), active liver disease, or serum enzyme levels >2× the upper limit of normal, conditions associated with increased bleeding risk, and concurrent antithrombotic drugs other than aspirin (≤100 mg/day as monotherapy was allowed).

The primary efficacy endpoint in ROCKET AF was the composite of all stroke (both ischaemic and haemorrhagic) and systemic embolism. Detection of primary endpoints was enhanced by a standardized stroke symptom questionnaire and additional evaluation by local study-affiliated neurologists or stroke specialists blinded to treatment. A full description of the endpoints in ROCKET AF has been published.[5,6] Secondary efficacy endpoints included cardiovascular death; all-cause death; the composite of stroke, systemic embolism, or cardiovascular death; and the composite of stroke, systemic embolism, or all-cause death. The safety endpoint was major or non-major clinically relevant bleeding or intracranial haemorrhage. All suspected primary endpoint events and causes of death were adjudicated by an independent clinical endpoint committee.

Patients were evaluated at a minimum of every 4 weeks throughout the trial for study drug management, ascertainment of adverse events, and surveillance for primary endpoints and other clinical events.

Statistical analysis

We used Cox proportional hazards models to assess the association with the risk of outcomes for (1) patients with SVD vs. patients without SVD and (2) rivaroxaban vs. warfarin within subgroups of patients with and without SVD. All models included a term for the interaction between randomized treatment and SVD as well as covariates identified as predictive

Trial	Exclusion criteria
ROCKET AF[5,6]	Haemodynamically significant mitral valve stenosis. Prosthetic heart valve. Annuloplasty with or without prosthetic ring, commissurotomy, and/or valvuloplasty are permitted. Planned invasive procedure with potential for uncontrolled bleeding, including major surgery
RE-LY[1,2]	History of heart valve disorder (i.e. prosthetic valve or haemodynamically relevant valve disease)
AVERROES[3,4]	Valvular disease requiring surgery. Prosthetic mechanical heart valve. Conditions other than atrial fibrillation that required chronic anticoagulation
ARISTOTLE[7,8]	Moderate or severe mitral stenosis, conditions other than atrial fibrillation that required anticoagulation (e.g. a prosthetic heart valve)
ENGAGE[9,10]	Moderate or severe mitral stenosis, unresected atrial myxoma, or a mechanical heart valve (subjects with bioprosthetic heart valves and/or valve repair could be included)
ACTIVE W and A[11]	Requirement for clopidogrel or for oral anticoagulant (such as prosthetic mechanical heart valve), and mitral stenosis
SPORTIF III[12]	Mitral stenosis or previous valvular heart surgery

Table 2 Type of valvular disease in patients assessed as having significant valvular disease

Characteristic	N (%)
Valve location/abnormality[a]	
Aortic stenosis	215 (11.0%)
Aortic regurgitation	486 (24.8%)
Mitral regurgitation	1756 (89.6%)
Other (without any of preceding)	11 (0.6%)
Etiology[a]	
Rheumatic	62 (3.2%)
Congenital	15 (0.8%)
Calcific/degenerative	791 (40.4%)
Post-infarction and/or ischaemic	253 (12.9%)
Other	307 (15.7%)
Unknown	312 (15.9%)
No data	268 (13.7%)
Prior cardiac valvular procedures	106 (5.3%)
Valvuloplasty	64 (60.4%)
Other cardiac valvular procedure	42 (39.6%)

In 1960 of 2003 patients, detailed information was available. Percentages for valve location/abnormality and etiology calculated among patients with history of significant valvular disease. Percentages for valvular procedures calculated among patients with prior procedure.
[a]A patient could be in more than one category.

of outcomes by modelling in the full ROCKET AF cohort. The efficacy endpoint models used the ITT population and time period to site notification, and they contained the following as covariates: age, sex, body mass index, prior stroke/transient ischaemic attack, vascular disease (myocardial infarction, peripheral artery disease, carotid occlusive disease), chronic heart failure, hypertension, chronic obstructive pulmonary disease, diabetes mellitus, paroxysmal AF, diastolic blood pressure, creatinine clearance (Cockcroft−Gault), heart rate, and abstinence from alcohol use. The safety endpoint model (safety model I) used the safety population and time period while on treatment, defined as on therapy

plus 2 days, and contained the following as covariates: age, sex, prior stroke/transient ischaemic attack, anaemia, prior gastrointestinal bleeding, chronic obstructive pulmonary disease, diastolic blood pressure, creatinine clearance (Cockcroft−Gault), platelets, albumin, and prior aspirin, vitamin K antagonist, or thienopyridine use. In a second step (safety model II), heart failure was added to this model as a covariate on an exploratory basis since it was hypothesized that congestion and hypoperfusion of the gastrointestinal tract and of the liver might increase the propensity to bleeding.

Categorical variables are summarized as percentages (counts), and differences were tested with the Pearson χ^2-test. Continuous variables are summarized as medians (25th, 75th percentiles), and differences were tested with the Wilcoxon rank-sum test. Outcomes are presented as events per 100 patient-years (pt-yrs). Risk relationships are presented as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) derived from the adjusted Cox models. The time to event for each group was assessed using the Kaplan−Meier method. All statistical analyses were performed by the Duke Clinical Research Institute using SAS software (version 9.2, SAS Institute, Cary, NC, USA).

Results

Clinical characteristics of patients with and without significant valvular disease

Among 14 171 patients included in this analysis, 2003 (14.1%) patients had SVD as classified by the investigator. Data from 1992 patients were used for analysis of efficacy endpoints, and data from 1999 patients were used for safety analysis. Table 2 presents information on type of SVD. Mitral regurgitation predominated (89.6%), followed by aortic regurgitation (24.8%), and aortic stenosis (11.0%), exceeding 100% due to cases with more than one type of valvular lesion. The etiology was considered as calcific or degenerative in 40.4% of cases, post-infarction and/or ischaemic in 12.9%, rheumatic in 3.2%, and other, unknown, or having no data in 15.7, 15.9, and 13.7% of cases, respectively. A prior cardiac valvular procedure had been performed in 106 cases (5.3%), which had been a valvuloplasty in 64 of these cases (60.4%) or designated as 'other cardiac valvular procedure' in the remaining 42 cases.

Table 3 Baseline characteristics for all intention-to-treat patients and for patients grouped by the absence or presence of significant valvular disease

Variable	Overall trial population (N = 14 171)	SVD (N = 1992)	No SVD (N = 12 179)	P-value
Age, years	73 (65, 78)	75 (68, 79)	72 (65, 78)	<0.0001
Female	5605 (39.6%)	785 (39.4%)	4820 (39.6%)	0.89
Race				
White	11 786 (83.2%)	1672 (83.9%)	10 114 (83.0%)	<0.0001
Black	180 (1.3%)	20 (1.0%)	160 (1.3%)	
Asian	1786 (12.6%)	273 (13.7%)	1513 (12.4%)	
Other	419 (3.0%)	27 (1.4%)	392 (3.2%)	
Hispanic	2331 (16.4%)	156 (7.8%)	2175 (17.9%)	<0.0001
Region				
Asia/Pacific Islands	2109 (14.9%)	301 (15.1%)	1808 (14.8%)	<0.0001
Eastern Europe	5407 (38.2%)	582 (29.2%)	4825 (39.6%)	
Latin America	1878 (13.3%)	76 (3.8%)	1802 (14.8%)	
North America	2681 (18.9%)	653 (32.8%)	2028 (16.7%)	
Western Europe	2096 (14.8%)	380 (19.1%)	1716 (14.1%)	
Body mass index, kg/m^2	28.2 (25.1, 32.0)	27.7 (24.8, 31.2)	28.3 (25.2, 32.1)	<0.0001
Systolic blood pressure, mm Hg	130 (120, 140)	130 (120, 140)	130 (120, 140)	
Diastolic blood pressure, mm Hg	80 (70, 85)	80 (70, 84)	80 (70, 86)	
Type of atrial fibrillation				
Persistent	11 485 (81.0%)	1653 (83.0%)	9832 (80.7%)	0.049
Paroxysmal	2490 (17.6%)	317 (15.9%)	2173 (17.8%)	
Newly diagnosed or new onset	196 (1.4%)	22 (1.1%)	174 (1.4%)	
Years since AF diagnosis	3 (1, 7)	4 (1, 8)	3 (1, 7)	<0.0001
Prior chronic aspirin use	5184 (36.6%)	690 (34.6%)	4494 (36.9%)	0.052
Prior vitamin K antagonist use	8853 (62.5%)	1444 (72.5%)	7409 (60.8%)	<0.0001
CHADS$_2$ score, mean (SD)	3.5 (0.9)	3.5 (1.0)	3.5 (0.9)	0.98
HAS-BLED score, mean (SD)	2.8 (0.9)	2.8 (1.0)	2.8 (0.9)	0.18
Previous stroke, embolism, or TIA	7767 (54.8%)	961 (48.2%)	6806 (55.9%)	<0.0001
Congestive heart failure	8851 (62.5%)	1402 (70.4%)	7449 (61.2%)	<0.0001
Hypertension	12 824 (90.5%)	1775 (89.1%)	11 049 (90.7%)	0.023
Diabetes mellitus	5647 (39.8%)	798 (40.1%)	4849 (39.8%)	0.84
Previous myocardial infarction	2446 (17.3%)	482 (24.2%)	1964 (16.1%)	<0.0001
Peripheral vascular disease	832 (5.9%)	160 (8.0%)	672 (5.5%)	<0.0001
COPD	1481 (10.5%)	287 (14.4%)	1194 (9.8%)	<0.0001
Previous CABG	1029 (7.3%)	238 (11.9%)	791 (6.5%)	<0.0001
Current smoker	4760 (33.6%)	768 (38.6%)	3992 (32.8%)	<0.0001
Creatinine clearance,[a] mL/min	67 (52, 87)	62 (49, 80)	68 (53, 88)	<0.0001

Patients with significant vascular disease were from the intention-to-treat population that was used for analysis of efficacy outcomes. Continuous variables are shown as median (25th, 75th percentiles). Categorical variables are shown as n (%). P-values are from Wilcoxon rank sum tests for continuous variables and Pearson Chi-square tests for categorical variables. CABG, indicates coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HAS-BLED, score for assessing bleeding risk (**H**ypertension; **A**bnormal renal/liver function; **S**troke history; **B**leeding predisposition; **L**abile international normalized ratio; **E**lderly, age ≥65; **D**rug/alcohol usage); TIA, transient ischaemic attack.
[a]Cockcroft–Gault.

The clinical characteristics of patients in the overall trial population and of patients separated according to the presence or absence of SVD are presented in *Table 3*. Significant valvular disease patients were older than patients without SVD (median 75 vs. 72 years; $P < 0.0001$). There was no difference in sex (female 39.4 vs. 39.6%). There was also no difference in the CHADS$_2$ and

HAS-BLED scores or in the prevalence of diabetes mellitus. Patients with SVD had persistent AF slightly more often but had paroxysmal and newly diagnosed or new-onset AF less often than patients without SVD ($P = 0.049$). The time since AF diagnosis was significantly longer in patients with vs. without SVD (median 4 and 3 years, respectively, $P < 0.0001$). Prior stroke, embolism, or

Table 4 Efficacy and safety outcomes as a function of the absence or presence of significant valvular disease

	SVD events/100 pt-yrs (total events)	No SVD events/100 pt-yrs (total events)	HR (95% CI) SVD vs. no SVD	P-value
Efficacy outcomes (ITT population) n = 1992				
Stroke or SE	2.23 (88)	2.09 (487)	1.07 (0.85–1.35)	0.58
Stroke, SE, or vascular death	5.20 (199)	4.31 (982)	1.09 (0.93–1.27)	0.28
Stroke, SE, vascular death, or MI	6.36 (240)	4.99 (1128)	1.14 (0.99–1.31)	0.072
Stroke	1.92 (76)	1.96 (458)	0.98 (0.77–1.26)	0.89
Systemic embolism	0.32 (13)	0.14 (34)	2.02 (1.00–4.08)	0.049
MI	1.51 (60)	0.90 (212)	1.32 (0.98–1.78)	0.065
All-cause death	5.54 (212)	4.39 (1002)	1.09 (0.93–1.26)	0.29
Safety outcomes (safety on-treatment population) n = 1999				
Major or NMCR bleeding	18.24 (493)	14.16 (2431)	1.14 (1.03–1.25)	0.011
Major bleeding	5.11 (156)	3.27 (625)	1.32 (1.10–1.57)	0.0027
GI bleeding	44%	40%		n.s.
ICH	0.80 (25)	0.59 (114)	1.35 (0.87–2.09)	0.18
Composite endpoint: stroke/major bleeding	7.06 (211)	5.25 (982)	1.22 (1.05, 1.42)	0.0099

HR estimates are based on multivariable analysis (see Methods).
CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial haemorrhage: NMCR, non-major clinically relevant; MI, myocardial infarction; pt-yrs, patient-years; SE, systemic embolism; SVD, significant vascular disease.

transient ischaemic attack was less prevalent in SVD patients (48.2 vs. 55.9%, $P < 0.0001$). Significant valvular disease patients also more often had previously received vitamin K antagonists (72.5 vs. 60.8%, $P < 0.0001$) and more often had congestive heart failure (70.4 vs. 61.2%, $P < 0.0001$), prior myocardial infarction (24.2 vs. 16.1%, $P < 0.0001$), peripheral vascular disease (8.0 vs. 5.5%, $P < 0.0001$), chronic obstructive pulmonary disease (14.4 vs. 9.8%, $P < 0.0001$), reduced creatinine clearance (62 vs. 68 mL/min, $P < 0.0001$), and previous coronary artery bypass surgery (11.9 vs. 6.5%, $P < 0.0001$). Significant valvular disease was relatively more frequent in North America and Eastern Europe, and was less frequent in Western Europe and Latin America. There was no substantial difference in race, although the comparison did reach statistical significance ($P < 0.0001$), driven largely by a slight shift between Asian and 'other' groups. There were fewer patients of Hispanic origin in the SVD group vs. the no-SVD group (7.8 vs. 17.9%, $P < 0.0001$).

Efficacy and safety endpoints in patients with and without significant valvular disease

Event rates for efficacy and safety outcomes according to the SVD status are shown in *Table 4*. Although stroke or systemic embolism (*Figure 1*) or other combined secondary endpoints were slightly more frequent in patients with SVD than in those without, these differences were not significant after multivariable adjustments, except for systemic embolism, which occurred more often in SVD patients (0.32 vs. 0.14 events per 100 pt-yrs; $P = 0.049$). Major or non-major clinically relevant bleeding and major bleeding alone occurred significantly more frequently in patients with SVD. The composite endpoint of stroke and major bleeding was significantly ($P = 0.0099$)

Figure 1 Unadjusted primary combined outcome parameters of stroke or systemic embolism in patients without (no SVD) and with (SVD) significant valvular disease.

more frequent in patients with than in those without SVD [adjusted HR 1.22 (1.05, 1.42); *Table 4*].

Efficacy and safety of rivaroxaban vs. warfarin in patients with and without significant valvular disease

The rate of stroke or systemic embolism in patients treated with rivaroxaban compared with warfarin was consistent among patients with SVD (2.01% rivaroxaban vs. 2.43% warfarin; HR 0.83, 95% CI

0.55–1.27) and without SVD (1.96% rivaroxaban vs. 2.22% warfarin; HR 0.89, 95% CI 0.75–1.07; interaction *P* = 0.76) (*Figure 2* and *Table 5*). However, the rates of major and non-major clinically relevant bleeding in patients with SVD were higher among those treated with rivaroxaban compared with warfarin (19.8% rivaroxaban vs. 16.8% warfarin; HR 1.25, 95% CI 1.05–1.49), whereas there was no difference among those without SVD (14.2 vs. 14.1%; HR
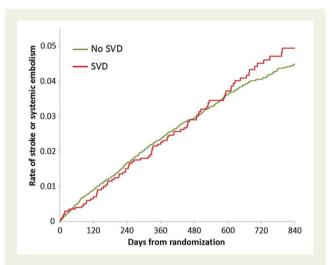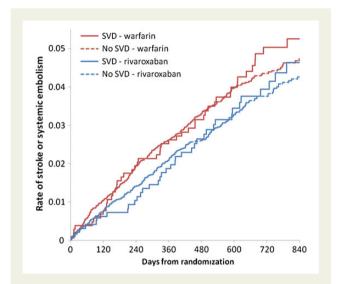

Figure 2 Unadjusted primary combined outcome parameters of stroke or systemic embolism in patients with and without significant valvular disease (SVD) randomized to either rivaroxaban or warfarin.

1.01, 95% CI 0.94–1.10; interaction *P* = 0.034). There was no difference in HRs whether heart failure was included in the safety model or not (Supplementary material online), and there was also no difference in the new use of any antiplatelet drugs or the duration of aspirin use during follow-up (Supplementary material online). Median time in therapeutic range of INR values (TTR) was not significantly different in warfarin patients with and without SVD (60.8 vs. 57.4). The rate of intracranial haemorrhage was lower with rivaroxaban than with warfarin among those without SVD but was about the same among those with SVD. This difference in interaction of SVD and treatment did not achieve statistical significance (*P* = 0.084), however.

Discussion

Large, multicentre randomized trials[1–10] have recently established the efficacy and safety of novel direct-acting oral anticoagulants for the prevention of stroke and systemic embolism in patients with non-valvular AF. In these trials, non-valvular AF was defined as the absence of (rheumatic) mitral stenosis and prosthetic heart valves (*Table 1*), but haemodynamically relevant valve disease was also generally excluded.[1] However, uncertainty and even confusion exists among physicians as to whether patients with other types of SVD and AF paradoxically fall under the category of non-valvular AF and may be treated by novel anticoagulants. Based on the inclusion and exclusion criteria used in ROCKET AF, a large fraction of included patients had SVD.

Definition of non-valvular atrial fibrillation

The American College of Cardiology/American Heart Association/European Society of Cardiology 2006 guidelines stated that 'The term "non-valvular AF" is restricted to cases in which the rhythm

Table 5 Efficacy (intention-to-treat population) and safety (on-treatment population) outcomes in patients with and without significant valvular disease in patients randomized to rivaroxaban and warfarin

	SVD			No SVD			*P*-value for interaction of SVD and treatment
	Rivaroxaban events/100 pt-yrs (total events)	Warfarin events/100 pt-yrs (total events)	Rivaroxaban vs. Warfarin HR (95% CI)	Rivaroxaban events/100 pt-yrs (total events)	Warfarin events/100 pt-yrs (total events)	Rivaroxaban vs. Warfarin HR (95% CI)	
Efficacy outcomes							
Stroke or SE	2.01 (38)	2.43 (50)	0.83 (0.55–1.27)	1.96 (231)	2.22 (256)	0.89 (0.75–1.07)	0.76
Stroke, SE, or vascular death	5.14 (94)	5.26 (105)	0.99 (0.75–1.31)	4.16 (478)	4.47 (504)	0.94 (0.83–1.06)	0.72
Stroke, SE, vascular death, or MI	6.09 (110)	6.62 (130)	0.94 (0.73–1.21)	4.81 (549)	5.17 (579)	0.94 (0.83–1.05)	0.98
All-cause death	5.48 (100)	5.60 (112)	0.98 (0.75–1.29)	4.19 (482)	4.60 (520)	0.91 (0.80–1.03)	0.60
Safety outcomes							
Major or NMCR bleeding	19.81 (253)	16.83 (240)	1.25 (1.05–1.49)	14.19 (1222)	14.14 (1209)	1.01 (0.94–1.10)	0.034
Major bleeding	6.14 (88)	4.20 (68)	1.56 (1.14–2.14)	3.22 (307)	3.33 (318)	0.98 (0.84–1.15)	0.010
ICH	0.88 (13)	0.73 (12)	1.27 (0.58–2.79)	0.43 (42)	0.74 (72)	0.59 (0.40–0.86)	0.084

Data are based on multivariable analysis (see Methods). The overall ICH-adjusted hazard ratio (95% confidence interval) were 0.67 (0.47–0.93) *P* = 0.02.[6]
CI, confidence interval; HR, hazard ratio; ICH, intracranial haemorrhage: NMCR, non-major clinically relevant; MI, myocardial infarction; pt-yrs, patient-years; SE, systemic embolism; SVD, significant vascular disease.

disturbance occurs in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.'[13] Similarly, the recent update of the European Society of Cardiology guidelines continue to divide AF into 'valvular' or 'non-valvular' categories. 'Valvular AF' was used to imply that AF is related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.[13,14] The pinpointing of rheumatic mitral stenosis and prosthetic heart valves as separate entities is based on the generally accepted higher risk of thromboembolic stroke in these patients.[15]

Prevalence of valvular heart disease in clinical practice: results from clinical registries

Several recent registries have shown that patients with valvular disease are relatively prevalent in clinical practice.[16–21] However, the prevalence of rheumatic valve disease varied between 2 and 4.3% of patients included in such registries.[17,19] Non-rheumatic valve disease was reported in 19–48%[16,17] or even 81%, if minor degrees of mitral regurgitation were also considered (Bosch R, Cardio Centrum Ludwigsburg-Bietigheim, Ludwigsburg, Germany; Personal communication; 1 July 2013, referring to ref.[19]).

Although these registries show some variability, the generally high prevalence of patients with any type of valvular disease in clinical practice underlines the need for a better understanding of the benefits and risks of treating patients with SVD with a novel anticoagulant like rivaroxaban. To our knowledge, there has not been a fully published analysis of patients with SVD among the population traditionally designated as 'non-valvular.' Several observations suggest that the incidence and localization of thrombus formation in patients with 'rheumatic' AF (i.e. in mitral stenosis) may be different from that in non-valvular AF. Among patients with rheumatic AF, about half of thrombi were found in the left atrial appendage and the rest in its cavity, whereas in non-valvular AF, thrombi were predominantly found in the left atrial appendage.[22] This difference in location of thrombi may influence outcomes and efficacy of anticoagulant therapy.

Clinical characteristics and outcomes of patients with and without significant valvular disease in ROCKET AF

The ROCKET AF protocol was designed and conducted specifically to ensure that patients in the trial were similar to those in the clinical trials upon which the non-inferiority margin was based.

Apart from patients with haemodynamically significant mitral valve stenosis, prosthetic heart valves, or planned invasive procedures with potential for uncontrolled bleeding, including major surgery (Table 1), SVD of other types occurred in 14% of patients in ROCKET AF (Table 2), most frequently mitral (89.6%) or aortic regurgitation (24.8%), and aortic stenosis (11.0%).

Mitral regurgitation of rheumatic origin has become a relatively rare entity since mitral regurgitation nowadays is mostly due to (i) the presence of coronary artery disease and its complications or (ii) left ventricular dysfunction due to other causes. This is consistent with the higher prevalence of heart failure and prior myocardial infarction observed in patients with mitral regurgitation in ROCKET

AF and substantiates the observation that SVD patients were more prevalent in North America and Eastern Europe (Table 3).

The major finding in this *post hoc* analysis was that after adjusting for differences in baseline prognostic factors, participants with SVD shared an incidence of thromboembolic ischaemic events and mortality that was similar to that of participants without SVD. In line with identical $CHADS_2$ scores, the rates of stroke were similar among patients with and without SVD. However, the rate of systemic embolism was twice as high in SVD patients and reached marginal statistical significance ($P = 0.049$). All other efficacy outcomes were not significantly different, although they also tended to be numerically higher in SVD patients. The differences in the rates of systemic embolism may reflect the play of chance.

We observed a significantly higher prevalence of major or non-major clinically relevant bleeding, and of major bleeding alone after multivariable adjustment, which included (among other factors) prior aspirin, vitamin K antagonist, or thienopyridine use, and renal function. There were no significant differences between patients with and without SVD with regard to gastrointestinal bleeding. The HAS-BLED[23,24] score as a measure of the risk of bleeding did not differ between patients with and without SVD.

The question arises as to whether the adjusted differences in extra-cranial bleeding events are a play of chance, are a true biological effect, or may reflect hitherto unidentified residual confounding effects (e.g. differences in practice patterns). Since patients with SVD more frequently had vascular disease, deviations from baseline concomitant drug therapy, especially antiplatelet drugs, during the course of the trial would be a possible explanation. However, there was no difference in the new use of antiplatelet drugs in those who were not on any one drug at baseline, or of the duration of aspirin use in all patients or in those on rivaroxaban or warfarin, nor in the presence of heart failure (as hypothesized above; Supplementary material online). Although a higher proportion of patients in the SVD group had been on vitamin K antagonism therapy, which beforehand could have influenced the outcomes in the SVD group in favour of warfarin, prior vitamin K antagonist use was adjusted for in the analysis and, thus, is improbable as an explanation. Overall, the clinical importance of these *post hoc* observations requires further study.

Efficacy and safety of rivaroxaban vs. warfarin in patients with and without significant valvular disease

While the above observations are based on patients with and without SVD independent of treatment allocation to either warfarin or rivaroxaban, the question arises as to whether any differences might exist with regard to the outcomes on either drug. The results of our present analyses show that the effects of warfarin and rivaroxaban on thromboembolic and ischaemic cardiovascular outcomes did not differ among AF patients with and without SVD. With regard to bleeding, a statistically significant quantitative interaction was observed between treatment and SVD, with HRs for major or non-major clinically relevant bleeding combined and major bleeding alone that were higher with rivaroxaban than with warfarin in patients with (1.25 and 1.56, respectively, with 95% CIs above 1.0) and without SVD (1.1 and 0.98, respectively). Whether this effect is

real or simply the result of multiple *post hoc* reviews of the data is debatable.

Is non-valvular atrial fibrillation a misnomer?

The generally accepted term 'non-valvular AF' is misleading since the ROCKET AF trial, as well as other trials (*Table 1*), has allowed the inclusion of patients who, although not having mitral stenosis or artificial heart valves or valve repair, could have other types of valvular heart disease. In ROCKET AF, these valvular lesions were considered by the recruiting investigator and his or her team as significant. As long as there is no agreed-upon new term, 'non-valvular AF' will continued to be used, but one should always stress that this does not exclude patients with other types of valvular heart disease from therapy with novel anticoagulants like rivaroxaban.

Limitations

The protocol did not include precise quantification of valve disease. However, the term 'significant' valvular lesion implied that the physician did not consider it as less than moderate. On the other hand, it could also not be of such haemodynamic significance that cardiac surgery would be necessary in the foreseeable future since this was an exclusion criterion. Thus, the majority of patient can be suspected to have had moderate valve disease.

Some baseline characteristics of patients with SVD differed significantly from those of patients without SVD. Thus, despite statistical adjustments, substantial bias might remain, and, therefore, results should be regarded as hypothesis generating. Finally, the number of events in the group of patients with SVD, especially intracranial bleeding, was particularly low, which may indicate that these differences may have occurred by chance.

Conclusions

In the ROCKET AF trial, every seventh patient had SVD. This proportion is probably a low estimate of the prevalence of SVD in clinical practice.[16–21] Importantly, AF patients with SVD experienced the same stroke-prevention benefit from oral anticoagulants as did AF patients without SVD. The quantitative interaction in bleeding rates that were higher with rivaroxaban than with warfarin in patients with SVD requires special attention and careful use of rivaroxaban in these patients. Therefore, SVD patients, except for those with haemodynamically significant mitral valve stenosis or prosthetic heart valves, represent an important part of the spectrum of non-valvular AF to which the results of trials of oral anticoagulants apply, at least as far as the use of rivaroxaban is concerned.

The type of patients included in this trial corresponds to the definition of non-valvular atrial fibrillation as was just re-emphasized in the very recent AHA/ACC/HRS guidelines.[25] Since these patients are encompassed in the prescription labels of the drug regulatory authorities, it is important for the physician to know that there might be some differences between patients with and without SVD, even if patients meet the criteria for non-valvular AF.

Previous presentation

These data were partly presented at the Scientific Sessions of the American College of Cardiology 2013: G. Breithardt *et al.* Characteristics and Outcomes of Patients with Atrial Fibrillation and Significant Valvular Lesions: Experience from the ROCKET AF Trial. *J Am College Cardiol* 2013;61:Supplement, E282; G. Breithardt *et al.* Outcomes of Patients with Atrial Fibrillation and Significant Valvular Lesions: Comparison of the Effects of Rivaroxaban and Warfarin in the ROCKET AF Trial. *J Am College Cardiol* 2013;61:Supplement, E339.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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