ORIGINAL RESEARCH

Safety and Efficacy of Rivaroxaban in Patients With Cardiac Implantable Electronic Devices: Observations From the ROCKET AF Trial

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***Background*—**Although implantation of cardiac implantable electronic devices (CIEDs) in patients receiving warfarin is well studied, limited data are available on the use of oral factor Xa inhibitors in this setting.

***Methods and Results*—**Using data from 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) (n=14 264), we compared baseline characteristics and clinical outcomes in patients with atrial fibrillation randomized to rivaroxaban versus warfarin who did and did not undergo CIED implantation or revision. In this post-hoc, postrandomization, on-treatment analysis, only the first intervention per patient was analyzed. During a median follow-up of 2.2 years, 453 patients (242 rivaroxaban group; 211 warfarin group) underwent de novo CIED implantation (64.2%) or revision procedures (35.8%). Patients who received CIEDs were older, more likely to be male, and more likely to have past myocardial infarction, but had similar stroke risk compared to patients who did not receive CIEDs. Most patients who received a device had study drug interrupted for the procedure and did not receive bridging anticoagulation. During the 30-day postprocedural period, 11 patients (4.55%) in the rivaroxaban group experienced bleeding complications compared with 15 (7.13%) in the warfarin group. Thromboembolic complications occurred in 3 patients (1.26%) in the rivaroxaban group and 1 (0.48%) in the warfarin group. Event rates were too low for formal hypothesis testing.

***Conclusions*—**Bleeding and thromboembolic events were low in both rivaroxaban- and warfarin-treated patients. Periprocedural use of oral factor Xa inhibitors in CIED implantation requires further study in prospective, randomized trials.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00403767. **(*J Am Heart Assoc*. 2017;6: e004663. DOI: 10.1161/JAHA.116.004663.)**

Key Words: anticoagulation • atrial fibrillation • cardiac resynchronization therapy • factor Xa inhibitor • implantable cardioverter-defibrillator • pacemaker • rivaroxaban • warfarin

Atrial fibrillation (AF) is accompanied by significant morbidity and mortality and often complicates the management of other cardiovascular disorders.[1–5] Many patients with AF benefit from systemic anticoagulation therapy to reduce the risk of stroke.[6–9] Warfarin has been studied in patients who undergo cardiac implantable electronic device (CIED) procedures[10–13]; however, there are limited data on the use and management of non-vitamin-K oral anticoagulants (NOACs) in patients undergoing CIED procedures.

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Observational data suggest that both interrupted and uninterrupted NOAC treatment do not appear to be associated with excess bleeding or embolic complications compared with uninterrupted warfarin during the periprocedural period surrounding CIED implantation or revision.[14–18] However, these studies have included relatively small cohorts, focus mostly on dabigatran, and usually reflect single-center experience. There is much less clinical experience with oral factor Xa inhibitors. Current practice for managing NOACs during the periprocedural period is quite heterogeneous.[19] Given that AF is a common comorbid condition in many patients undergoing CIED surgery and NOAC utilization is increasing, there is a need for more evidence surrounding clinical outcomes of patients treated with NOACs who undergo device implantation or revision.[20]

Methods

The design and results of 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) study have been published previously.[21,22] Briefly, ROCKET AF was a double-blind, double-dummy, international clinical trial that randomized 14 264 patients with nonvalvular AF at moderate-to-high risk for stroke to fixed-dose rivaroxaban or adjusted-dose warfarin (target international normalized ratio [INR], 2.0–3.0) for prevention of stroke and systemic embolism. The study protocol recommended stopping warfarin/placebo 4 days before a planned procedure and rivaroxaban/placebo 2 days before. The point-of-care INR was recommended to be ≤1.5 before proceeding with any invasive procedure. Bridging anticoagulation was allowed, but not mandatory. No specific recommendation was made in the study protocol regarding the time frame for resumption of anticoagulation postprocedure. All decisions regarding the timing of study drug cessation and resumption were ultimately left to the discretion of the managing physician.

Because of the interest in the impact of actual treatment and outcomes, the on-treatment population (patients who received at least 1 dose of study drug and were followed for events while on study drug or within 2 days of last dose) was used for this study (N=14 236).

Definition of Device Procedures

Patients were included in the CIED cohort if they met either of the 2 following criteria: (1) underwent CIED implantation during the study or (2) had a device at the time of randomization and underwent a revision or replacement procedure related to the device (eg, generator replacement, lead revision, upgrade to cardiac resynchronization therapy, etc) during the study. For the purposes of this analysis, CIED refers to pacemakers, implantable cardioverter defibrillators (ICD), and cardiac resynchronization therapy devices. All procedures were at the discretion of the managing physicians.

Outcomes

Outcomes of interest were events within 30 days after the CIED procedure. The day of procedure was counted as day 1, and events were included regardless of whether the patients remained on study drug for the entire 30-day observation period. The primary efficacy end point was the occurrence of stroke (ischemic and hemorrhagic) or systemic embolism. Secondary efficacy end points included a composite of stroke, systemic embolism, vascular death, or myocardial infarction (MI); vascular death; and all-cause death. The primary safety end point was major or nonmajor clinically relevant (NMCR) bleeding as defined by the International Society on Thrombosis and Haemostasis.[23] Secondary safety end points included major bleeding, NMCR bleeding, and any transfusion. These outcomes were analyzed for the rivaroxaban versus warfarin groups as well as for continuous versus interrupted oral anticoagulation. For the purposes of this study, “continuous” oral anticoagulation means that no doses of the study drug were held or delayed.

Time in therapeutic range (TTR) was also analyzed for the warfarin group at 30 and 90 days pre- and postprocedure and compared with the TTR for the study as a whole. TTR was calculated as the number of days with an INR between 2.0 and 3.0 (inclusive). INR values for days between measurements were imputed with the Rosendaal method.[24] Patients were included in the 30- and 90-day pre- and postprocedure categories only if they had actual or imputed INR values for at least two thirds of the days in question. For the preprocedure groups, patients were omitted if their procedure occurred too soon after randomization to provide a sufficient number of days of INR values. For postprocedure groups, patients were omitted if they stopped the study drug before the end of the period in question. Exclusions described in this paragraph apply to TTR summaries only.

Statistical Analysis

For description of rates of CIED-related procedures and baseline characteristics of patients who did or did not undergo CIED-related procedures, the cohort of all ROCKET AF patients who received study drug was used. For examination of 30-day postprocedure outcomes, the cohort of patients who underwent CIED-related procedures was used. Only procedures that occurred during the on-treatment period were counted. If a patient underwent more than 1

Table 1. CIED-Related Procedures During the Trial

	All Randomized Patients	Rivaroxaban	Warfarin
New device implant during the study			
N (number of patients without a CIED at baseline)	12 523	6240	6283
Any implant	291 (2%)	152 (2%)	139 (2%)
Pacemaker	235 (2%)	129 (2%)	106 (2%)
ICD	35 (<1%)	17 (<1%)	18 (<1%)
Biventricular pacemaker-defibrillator	21 (<1%)	6 (<1%)	15 (<1%)
Time from randomization to surgery, months	9 (4, 16)	9 (4, 14)	10 (4, 17)
Procedures related to existing device			
N (number of patients with a CIED at baseline)	1713	871	842
Any device-related procedure	162 (9%)	90 (10%)	72 (9%)
Pacemaker—N at baseline	1398	712	686
Procedure	115 (8%)	59 (8%)	56 (8%)
ICD—N at baseline	92	44	48
Procedure	10 (11%)	6 (14%)	4 (8%)
Biventricular pacemaker—N at baseline	223	115	108
Procedure	37 (17%)	25 (22%)	12 (11%)
Time from randomization to procedure, months	9 (5, 16)	10 (5, 18)	8 (5, 15)
Any CIED-related procedure (sum of sections above)			
N (all randomized patients)	14 236	7111	7125
Any CIED-related procedure	453 (3%)	242 (3%)	211 (3%)
Pacemaker	350 (2%)	188 (3%)	162 (2%)
ICD	45 (<1%)	23 (<1%)	22 (<1%)
Biventricular pacemaker-defibrillator	58 (<1%)	31 (<1%)	27 (<1%)
Time from randomization to procedure, months	9 (4, 16)	10 (4, 16)	9 (5, 16)

Time variables are shown as median (25th, 75th percentiles). CIED indicates cardiac implantable electronic device; ICD, implantable cardioverter defibrillator.

CIED-related procedure during the study period, only the first procedure was included in this analysis. Baseline characteristics were summarized as percent (frequency) for categorical variables and as medians with 25th and 75th percentiles for continuous variables, according to the occurrence of a CIED-related procedure and the randomized treatment assignment. For the comparison of patients who underwent CIED procedures versus those with no CIED procedure, continuous variables were compared with Wilcoxon rank-sum tests and categorical variables were compared with Pearson chi-square tests. Within the CIED procedure group, baseline characteristics and events rates for patients in the rivaroxaban arm were compared to those in the warfarin arm. Kaplan–Meier 30-day event rates were generated for outcomes. Because of the low event rates, no hypothesis testing was performed to compare these event rates among groups; these data are presented in a descriptive fashion only, without correction for postrandomization confounders.

The ROCKET AF study was coordinated by the Duke Clinical Research Institute (Durham, NC). The Duke Clinical Research Institute performed all statistical analyses independent of the sponsors of the trial. The study was designed by an international committee that took responsibility for the accuracy and completeness of the analysis. All appropriate national regulatory authorities and institutional ethical review boards approved the study; all patients provided written informed consent. All analyses were conducted using SAS software (version 9.3 or higher; SAS Institute, Inc, Cary, NC).

Results

Cohort Characteristics

ROCKET AF enrolled 14 264 patients, of whom 14 236 received at least 1 dose of study drug. At time of enrollment, 1713 (12.0%) patients had a CIED. During a median follow-up

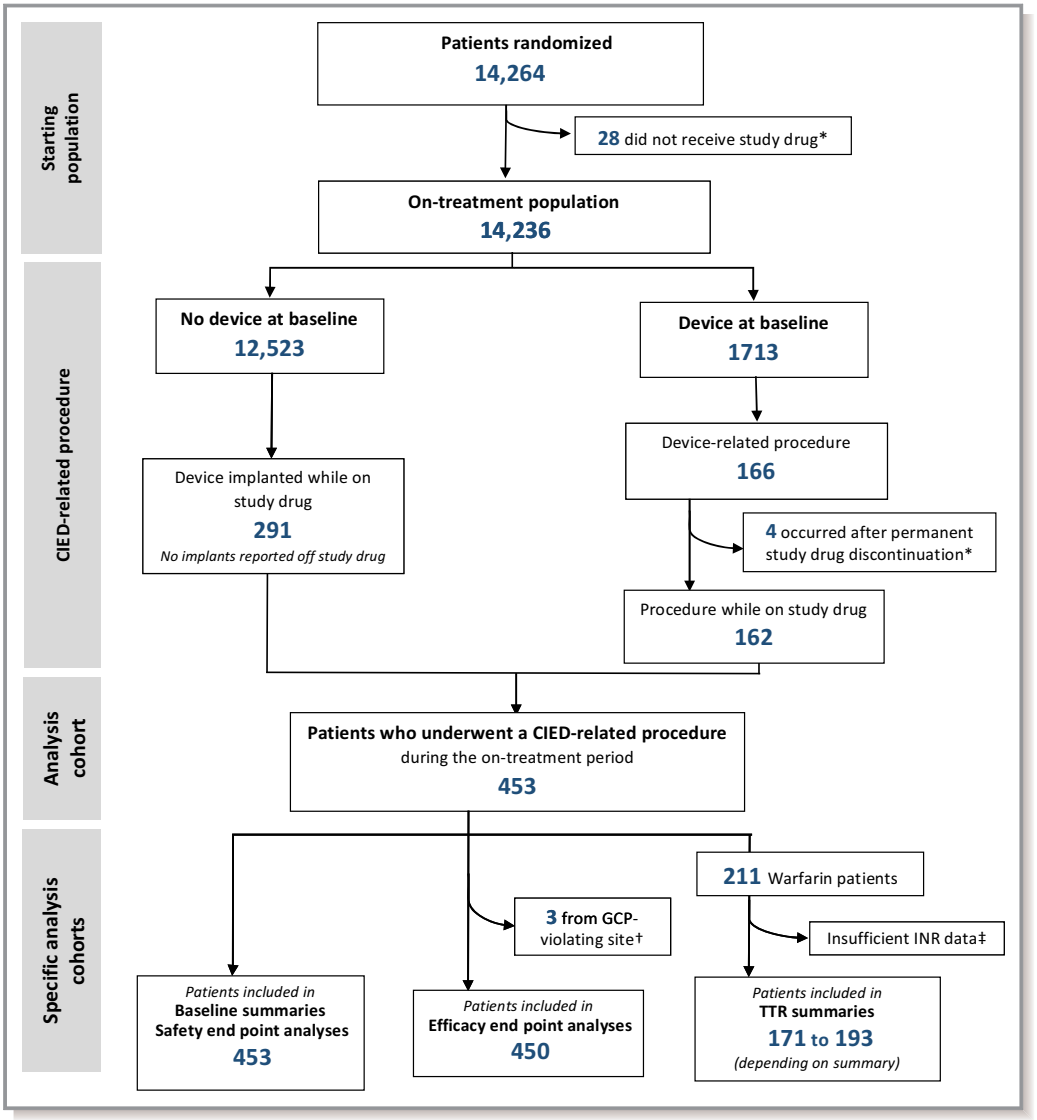

Figure 1. Flow chart depicting all patients who underwent CIED procedures and exclusions from this analysis. *Patients not receiving study drug—at any time or after permanent discontinuation—were followed for efficacy events only. Other events were occasionally, but not systematically, recorded. Thus, 28 patients who never received study drug are omitted from the analysis, because both postimplant device status and safety (bleeding) events are unknown, and 4 patients who underwent a device-related procedure (replacement) after the end of study drug are omitted because (1) it is unlikely they are a complete accounting of device-related procedures during that period and (2) their safety event status is unknown. †Violations in good clinical practice guidelines at 1 site made their efficacy data unreliable; patients from this site are omitted from all efficacy analyses. Safety data were unaffected. ‡Patients were included in the 30 and 90 days pre- and postprocedure TTR summaries only if they had actual or imputed INR values for at least two thirds of the days in question. For the preprocedure groups, patients were omitted if their procedure occurred too soon after randomization to provide a sufficient number of days of INR values. For postprocedure groups, patients were omitted if they stopped the study drug before the end of the period in question. CIED indicates cardiac implantable electronic devices; GCP, Good Clinical Practice; INR, international normalized ratio; TTR, time in therapeutic range.

of 2.2 years, 453 patients had a CIED-related procedure (3.2% of the total cohort). Of the 453 CIED procedures, 242 were in the rivaroxaban arm and 211 were in the warfarin arm (Table 1). There were a total of 291 (64.2%) de novo CIEDs; 235 were pacemaker implants, 35 were ICDs, and 21 were biventricular pacemaker or biventricular ICD implants. The remaining 162 (35.8%) patients underwent procedures related to existing devices. The majority of these were related to pre-existing pacemakers (115). There were smaller numbers of procedures on pre-existing ICDs (10) and biventricular devices

Table 2. Baseline Characteristics for Patients Who Do Versus Do Not Undergo CIED-Related Procedure

Variable	CIED-Related Procedure (N=453)	No CIED-Related Procedure (N=13 783)	*P* Value*
Randomized to rivaroxaban	242 (53%)	6869 (50%)	0.13
Age, y	75 (69, 79)	73 (65, 78)	<0.0001
Female	147 (32%)	5498 (40%)	0.0014
Race			<0.0001
White	422 (93%)	11 436 (83%)	
Black	6 (1%)	173 (1%)	
Asian	16 (4%)	1765 (13%)	
Other	9 (2%)	409 (3%)	
Geographical region			<0.0001
North America	193 (43%)	2480 (18%)	
Western Europe	73 (16%)	2016 (15%)	
Eastern Europe	117 (26%)	5376 (39%)	
Latin America	45 (10%)	1832 (13%)	
Asia/Pacific	25 (6%)	2079 (15%)	
Type of AF			0.12
Persistent	352 (78%)	11 173 (81%)	
Paroxysmal	96 (21%)	2415 (18%)	
New onset	5 (1%)	195 (1%)	
Time since AF diagnosis, y	4.9 (1.4, 9.2)	3.2 (0.9, 7.1)	<0.0001
$CHADS_2$ score, mean (SD)	3.5 (1.0)	3.5 (0.9)	0.50
$CHADS_2$ score			
1	0 (0)	3 (<1%)	
2	65 (14%)	1790 (13%)	
3	184 (41%)	6019 (44%)	
4	125 (28%)	3960 (29%)	
5	67 (15%)	1742 (13%)	
6	12 (3%)	269 (2%)	
Presenting characteristics			
BMI, kg/m^2	28.8 (25.8, 32.4)	28.1 (25.1, 32.0)	0.0090
Systolic blood pressure, mm Hg	130 (120, 140)	130 (120, 140)	0.0041
Diastolic blood pressure, mm Hg	79 (70, 82)	80 (70, 85)	<0.0001
Heart rate, beats/min	70 (62, 80)	76 (68, 86)	<0.0001
Creatinine clearance,† mL/min	66 (51, 86)	67 (52, 87)	0.34
CIED at time of randomization‡			0.0003
Pacemaker	115 (25%)	1283 (9%)	
ICD	10 (2%)	82 (1%)	
Biventricular pacemaker	37 (8%)	186 (1%)	
Baseline comorbidities			
Past stroke/TIA/embolism	206 (45%)	7588 (55%)	<0.0001
Peripheral artery disease	38 (8%)	798 (6%)	0.021
Carotid occlusive disease	25 (6%)	566 (4%)	0.14
Hypertension	418 (92%)	12 469 (90%)	0.20
Diabetes mellitus	204 (45%)	5479 (40%)	0.024
Past MI	120 (26%)	2340 (17%)	<0.0001
Congestive heart failure	305 (67%)	8589 (62%)	0.030
COPD	61 (13%)	1432 (10%)	0.036
Medications			
Past VKA use	347 (77%)	8542 (62%)	<0.0001
Past chronic ASA use	155 (34%)	5039 (37%)	0.31
ACE-inhibitor/ARB at baseline	345 (76%)	10 238 (74%)	0.37
Beta-blocker at baseline	308 (68%)	8942 (65%)	0.17
Digitalis at baseline	136 (30%)	5332 (39%)	0.0002
Diuretic at baseline	312 (69%)	8178 (59%)	<0.0001

Data presented as n (%) or median (25th, 75th percentile), except where noted. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; TIA, transient ischemic attack; VKA, vitamin K antagonist.

*Continuous variables are compared with Wilcoxon rank-sum test and categorical variables with Pearson chi-square tests.

†Creatinine clearance calculated using the Cockcroft–Gault equation.

‡For CIED type at baseline, percentages are among all patients in group; *P* value is for difference in type among patients who have a device.

Table 3. Baseline Characteristics by Randomized Treatment Among Patients Who Undergo CIED-Related Procedure

Variable	Rivaroxaban (N=242)	Warfarin (N=211)
Age, y	75 (69, 78)	75 (68, 80)
Female	75 (31%)	72 (34%)
Race		
White	222 (92%)	200 (95%)
Black	3 (1%)	3 (1%)
Asian	11 (5%)	5 (2%)
Other	6 (2%)	3 (1%)
Geographical region		
North America	106 (44%)	87 (41%)
Western Europe	39 (16%)	34 (16%)
Eastern Europe	55 (23%)	62 (29%)
Latin America	25 (10%)	20 (9%)
Asia/Pacific	17 (7%)	8 (4%)
Type of AF		
Persistent	191 (79%)	161 (76%)
Paroxysmal	50 (21%)	46 (22%)
New onset	1 (<1%)	4 (2%)
Time since AF diagnosis, y	5.1 (2.0, 9.6)	4.6 (1.0, 8.3)
$CHADS_2$ score, mean (SD)	3.4 (1.0)	3.6 (1.0)
$CHADS_2$ score		
2	40 (17%)	25 (12%)
3	100 (41%)	84 (40%)
4	65 (27%)	60 (28%)
5	32 (13%)	35 (17%)
6	5 (2%)	7 (3%)
Presenting characteristics		
BMI, kg/m^2	28.7 (25.4, 32.8)	29.0 (26.3, 32.4)
Systolic blood pressure, mm Hg	130 (120, 140)	130 (118, 140)
Diastolic blood pressure, mm Hg	78 (70, 82)	79 (70, 82)
Heart rate, beats/min	70 (63, 80)	70 (61, 77)
Creatinine clearance,* mL/min	68 (51, 91)	65 (50, 84)
Baseline comorbidities		
Past stroke/TIA/embolism	111 (46%)	95 (45%)
Peripheral artery disease	19 (8%)	19 (9%)
Carotid occlusive disease	14 (6%)	11 (5%)
Hypertension	219 (90%)	199 (94%)
Diabetes mellitus	101 (42%)	103 (49%)
Past MI	62 (26%)	58 (27%)
Congestive heart failure	155 (64%)	150 (71%)
COPD	38 (16%)	23 (11%)
Medications		
Past VKA use	186 (77%)	161 (76%)
Past chronic ASA use	84 (35%)	71 (34%)
ACE-inhibitor/ARB at baseline	181 (75%)	164 (78%)
Beta-blocker at baseline	160 (66%)	148 (70%)
Digitalis at baseline	75 (31%)	61 (29%)
Diuretic at baseline	162 (67%)	150 (71%)

Data presented as n (%) or median (25th, 75th percentile), except where noted. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; TIA, transient ischemic attack; VKA, vitamin K antagonist.

*Creatinine clearance calculated using the Cockcroft–Gault equation.

(37). Four device-related procedures that occurred after permanent discontinuation of the study drug were excluded from this analysis (Figure 1). No other CIED implantation or CIED-related procedure was excluded from our analysis.

Patients who underwent CIED-related procedures were, on average, older, more often male and white, and more likely to have past MI, but had similar CHA_2DS_2-VASc scores compared to those who did not undergo CIED-related procedures (Table 2). The rate of CIED procedures was highest among patients randomized in North America (7.2%) or Western Europe (3.5%), with lower rates in Eastern Europe (2.1%), Latin America (2.4%), and Asia/Pacific (1.2%). Baseline characteristics of those undergoing CIED-related procedures were similar regardless of treatment assignment (Table 3).

Management of Anticoagulation During the Periprocedural Period

The majority of patients (341 [75%]) had study drug interrupted for the procedure; however, 112 (25%) patients who underwent procedures did not interrupt study drug. The number of patients undergoing CIED procedures on uninterrupted anticoagulation was similar in the warfarin (57) and rivaroxaban (55) groups. Most patients in whom oral anticoagulation was interrupted for the procedure (299 [66%]) did not receive bridging anticoagulation with a parenteral agent (Figure 2). A small number (42) were treated with bridging anticoagulation, usually low-molecular-weight heparin. As expected based on protocol guidance, patients in the warfarin group were off oral anticoagulation longer, with the study drug stopped at a

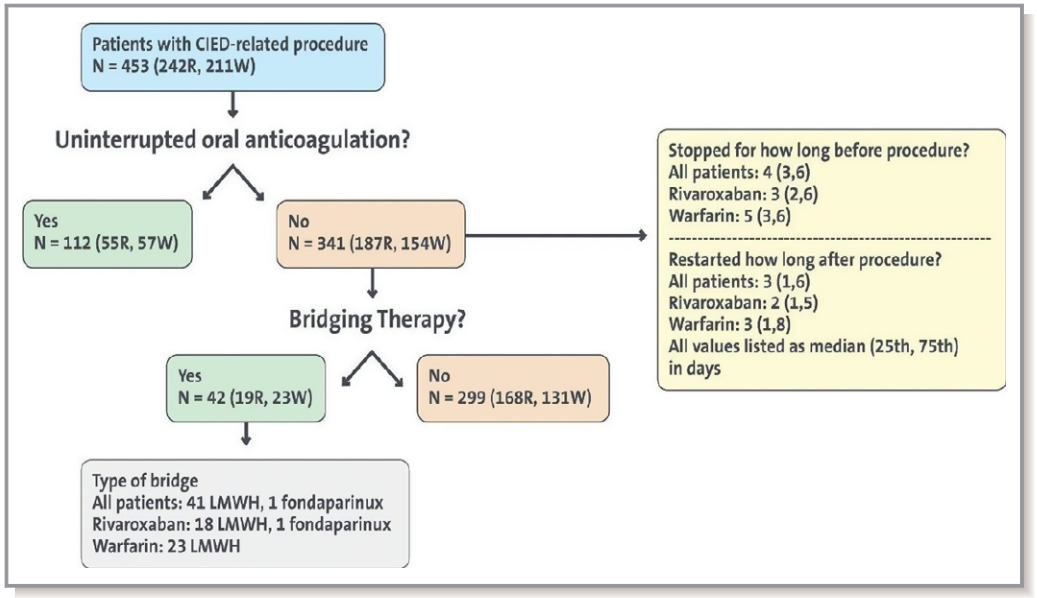

Figure 2. Study drug interruption and bridging therapy at the time of CIED-related procedure. CIED indicates cardiac implantable electronic devices; LMWH, low-molecular-weight heparin; R, rivaroxaban; W, warfarin.

median of 5 (25th, 75th percentiles: 3, 6) days before and resumed at a median of 3 (1, 8) days after the procedure, compared to a median of 3 (2, 6) days before and 2 (1, 5) days after in the rivaroxaban group (Figure 2).

Time in Therapeutic Range

TTR for warfarin was calculated for 30 and 90 days pre- and postprocedure (Table 4). TTR was markedly lower in the 30 days postprocedure versus 30 days preprocedure (43% vs 60%). The median TTR in the overall ROCKET AF trial was 58%,[25] which is comparable with the TTR for the 30 days preprocedure. Beyond the 90-day postprocedure period, the TTR was comparable with that of the study overall (60%).

30-Day Postprocedure Outcomes

Adverse events during the postprocedural period were rare in both rivaroxaban- and warfarin-treated patients (Table 5).

Table 4. TTR for Warfarin Patients Who Undergo CIED-Related Surgery

Time Period	N	TTR, %*
30 days preprocedure	193	60 (23, 100)
30 days postprocedure	171	43 (23, 73)
90 days preprocedure	185	58 (37, 78)
90 days postprocedure	173	60 (39, 75)

TTR indicates time in therapeutic range.
*Median (25th, 75th).

There were numerically more bleeding events in the warfarin- versus rivaroxaban-treated patients (15 [7.13%] vs 11 [4.55%]) and, specifically, more pocket hematomas (6 [2.86%] vs 1 [0.41%]). There were numerically more strokes/systemic embolic events in the rivaroxaban group versus the warfarin group (3 [1.26%] vs 1 [0.48%]) and also more site infections (3 [1.26%] vs 1 [0.49%]). Event rates were too low for any formal hypothesis testing.

Incidence of stroke/systemic embolism (1.79% vs 0.59%) and major/NMCR bleeding (6.28% vs 5.57%) were low among patients who continued the study drug periprocedurally and in those in whom the study drug was interrupted (Table 6). Stroke/systemic embolism occurred in 0 patients who received bridging anticoagulation versus 2 (0.68%) who did not receive bridging. Major/NMCR bleeding occurred in 2 patients (4.82%) in the bridging group versus 17 (5.69%) in the nonbridging group. However, the bridged group was very small (42 patients), and patients with higher CHA_2DS_2-VASc scores were more likely to have bridging anticoagulation with low-weight-molecular heparin (Table 7).

Discussion

In a clinical trial of more than 14 000 patients with nonvalvular AF and a relatively high prevalence of advanced cardiovascular disease randomly assigned to receive rivaroxaban or warfarin, 453 underwent CIED-related procedures (242 rivaroxaban group, 211 warfarin group). In this analysis, there were 2 major findings. First, there was substantial variation in the management of oral anticoagulation during the

Table 5. Events in the 30 Days Following CIED-Related Procedure, by Randomized Treatment

	All Patients	Rivaroxaban	Warfarin
Efficacy end points			
N	450*	239	211
Stroke/systemic embolism	4 (0.89%)	3 (1.26%)	1 (0.48%)
Stroke/systemic embolism/vascular death/MI	7 (1.56%)	3 (1.26%)	4 (1.90%)
All-cause death	2 (0.44%)	1 (0.42%)	1 (0.47%)
Vascular death	1 (0.22%)	0 (0)	1 (0.47%)
Safety end points			
N	453	242	211
Major or NMCR bleeding	26 (5.75%)	11 (4.55%)	15 (7.13%)
Major bleeding	5 (1.11%)	3 (1.24%)	2 (0.95%)
NMCR bleeding	21 (4.64%)	8 (3.31%)	13 (6.18%)
Transfusion	2 (0.44%)	1 (0.41%)	1 (0.47%)
Hematoma at surgical site†	7 (1.56%)	1 (0.41%)	6 (2.86%)
Infection at surgical site	4 (0.90%)	3 (1.26%)	1 (0.49%)

Thirty-day Kaplan–Meier rates are shown, with total number of events. CIED indicates cardiac implantable electronic device; MI, myocardial infarction; NMCR, nonmajor clinically relevant.

*Efficacy events were excluded for patients from a single good clinical practice-violating site, so the N for efficacy end points is slightly smaller than the N for safety end points.

†Six of the 7 hematomas (the 1 in rivaroxaban patients and 5 of the 6 in warfarin patients) were adjudicated as NMCR.

periprocedural period for CIED implantations and revisions. Second, the incidence of stroke or systemic embolism and bleeding events in the 30 days following the procedure was low in both the rivaroxaban and warfarin groups.

There was substantial heterogeneity in the management of oral anticoagulation around the CIED procedures. The study protocol recommended stopping warfarin/placebo 4 days before and rivaroxaban/placebo 2 days before a planned procedure. On average, both drugs were held for longer preprocedure than recommended, but with considerable variability. There was also considerable variability in the time frame for resuming oral anticoagulation. There is not enough evidence currently available to make a firm recommendation on the optimal time frame for stopping rivaroxaban before a procedure, but the current recommendation to stop rivaroxaban 2 days in advance of a planned procedure seems reasonable until stronger evidence is available.

Adverse events were uncommon in all groups during the 30 days postprocedure. Rates of stroke/systemic embolism and bleeding complications were low in the rivaroxaban and warfarin groups and comparable with other reports of invasive procedures in patients maintained on oral anticoagulation, aside from a slightly higher than expected rate of periprocedural thromboembolic complications in the rivaroxaban group. Other analyses[11,26–29] have consistently reported periprocedural stroke/systemic embolization rates in the 0.3% to 0.7% range. This is consistent with the stroke rate in the warfarin group in this analysis (0.48%). The stroke rate in the rivaroxaban group was slightly higher (1.26%); however, this may be an artifact of the small numbers in this study; there were only 4 total thromboembolic events in our cohort. Two previous ROCKET AF analyses looking at permanent discontinuations of the study drug[27] and therapeutic interruptions from any cause[28] reported stroke/systemic embolism rates in the 0.3% to 0.7% range, which suggests that the higher stroke rate in the rivaroxaban group here may be a statistical anomaly attributable to small sample size. It seems unlikely that there is an increased stroke risk with interrupted rivaroxaban, but ideally this should be examined prospectively.

There were numerically fewer major or NMCR bleeds in patients treated with rivaroxaban compared with warfarin (11 vs 15). It is unclear whether the increased lability in INR during the immediate postprocedural period has any impact on event rates given the low event rates. These data argue against a major increase in bleeding risk with factor Xa inhibitors, but the relative bleeding risks of warfarin versus rivaroxaban in CIED procedures should be assessed in a prospective trial.

Although there were too few patients treated with bridging anticoagulation in ROCKET AF to comment on this strategy, the recent BRIDGE trial[29] found that unbridged warfarin was noninferior when compared with bridging with low-molecular-weight heparin in a population of patients mostly at low-to-moderate vascular risk. There are currently no comparable data regarding NOACs and bridging with low-molecular-weight heparin. The shorter half-life of the NOACs compared with warfarin makes bridging anticoagulation less of a concern given that patients are not subtherapeutic on their anticoagulation for as long. Currently, there does not seem to be a compelling rationale for bridging patients on rivaroxaban; however, this is based largely on inference from the warfarin data. Ideally, this would be investigated in a prospective manner.

Performing CIED procedures in patients on therapeutic warfarin is supported by the most robust evidence base and is the standard of care,[10–13,29] but there is limited evidence regarding procedures on continuous NOACs. Although this strategy has limited clinical experience, continuous rivaroxaban was used in 55 patients in ROCKET AF with few adverse consequences and low event rates. These data do not suggest a major increased risk with continuous rivaroxaban, but given the differences between the continuous and interrupted oral anticoagulant groups, this should be viewed as hypothesis generating. The results of Strategy of Continued Versus Interrupted Novel Oral Anti-coagulant at Time of Device

Table 6. Events in the 30 Days Following CIED-Related Procedure, by Study Drug Status and Bridging Therapy

	On Study Drug	Off Study Drug	Bridging Therapy	No Bridging Therapy
Efficacy end points				
N	112	338	42	296
Stroke/systemic embolism	2 (1.79%)	2 (0.59%)	0 (0)	2 (0.68%)
Stroke/systemic embolism/vascular death/MI	3 (2.68%)	4 (1.18%)	0 (0)	4 (1.35%)
All-cause death	1 (0.89%)	1 (0.30%)	1 (2.38%)	0 (0)
Vascular death	1 (0.89%)	0 (0)	0 (0)	0 (0)
Safety end points				
N	112	341	42	299
Major or NMCR bleeding	7 (6.28%)	19 (5.57%)	2 (4.82%)	17 (5.69%)
Major bleeding	1 (0.90%)	4 (1.17%)	0 (0)	4 (1.34%)
NMCR bleeding	6 (5.38%)	15 (4.40%)	2 (4.82%)	13 (4.35%)
Transfusion	1 (0.90%)	1 (0.29%)	0 (0)	1 (0.33%)
Hematoma at surgical site	3 (2.74%)	4 (1.18%)	0 (0)	4 (1.34%)
Infection at surgical site	1 (0.92%)	3 (0.89%)	0 (0)	3 (1.02%)

Thirty-day Kaplan–Meier rates are shown, with total number of events. CIED indicates cardiac implantable electronic device; MI, myocardial infarction; NMCR, nonmajor clinically relevant.

Surgery in Patients With Moderate to High Risk of Arterial Thromboembolic Events (BRUISE CONTROL-2),[30] an upcoming open-label trial that will randomize patients with nonvalvular AF requiring a CIED procedure to continued or interrupted NOAC, will offer additional insight into this strategy. Performing CIED procedures on uninterrupted NOACs may turn out to be the superior strategy; however, at present there is insufficient evidence to support routine use of uninterrupted NOACs during CIED procedures.

There are several limitations to this study. First, this was a post-hoc analysis with no adjustment for postrandomization confounders. If randomization to rivaroxaban versus warfarin changed the odds of needing a CIED, that would skew the results. Second, there was no specified time frame for resuming anticoagulation after a procedure, and the specified time frame for stopping before the procedure was not consistently followed. Third, patients likely to need a CIED may have had it implanted before enrollment in the trial, which would affect the generalizability to all CIED patients. Finally, and most important, the fairly small numbers of CIED-related procedures and the low rates of adverse events limit the power to detect a potentially significant difference in event rates.

Table 7. Rates of Periprocedural Anticoagulation by CHA_2DS_2-VASc Score

CHA_2DS_2-Vasc Score	N	Any Anticoagulation During Procedure	Uninterrupted Study Drug	Off Study Drug With Bridging Therapy
All patients in cohort				
2 to 4	174	52 (30%)	42 (24%)	10 (6%)
≥5	279	102 (37%)	70 (25%)	32 (11%)
Patients with persistent AF				
2 to 4	138	37 (27%)	30 (22%)	7 (5%)
≥5	214	78 (36%)	53 (25%)	25 (12%)

AF indicates atrial fibrillation.

Conclusions

Patients in ROCKET AF who underwent CIED implantation or revision while on rivaroxaban had low rates of stroke and bleeding. Although current evidence is too limited to make evidence-based recommendations, an interrupted and unbridged rivaroxaban strategy appears reasonable for patients maintained on rivaroxaban who require a CIED procedure. This was the strategy used in the majority of CIED procedures in the ROCKET AF trial and was associated with a low rate of adverse events. It is too early to say whether a continuous rivaroxaban strategy might be superior to interrupted rivaroxaban; that approach will have to be further evaluated in future prospective studies. These results do not suggest a safety difference between warfarin and rivaroxaban; however, they should be viewed as hypothesis generating. There are still many questions regarding the optimal strategy for managing factor Xa inhibitors around planned procedures. These questions should be studied in future prospective trials of factor Xa inhibitors in patients undergoing cardiac device

placement, with more-defined rules for whether to use bridging anticoagulation and how long to hold the drug before/after the procedure.

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