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ORIGINAL RESEARCH

Patient-Reported Satisfaction and Study Drug Discontinuation: Post-Hoc Analysis of Findings from ROCKET AF

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ABSTRACT

Introduction: Patient-reported outcomes (PROs) and satisfaction endpoints are increasingly important in clinical trials and may be associated with treatment adherence. In this post hoc substudy from ROCKET AF, we examined whether patient-reported satisfaction was associated with study drug discontinuation. ***Methods***: ROCKET AF (n = 14,264) compared rivaroxaban with warfarin for prevention of stroke and systemic embolism in patients with atrial fibrillation. We analyzed treatment satisfaction scores: the Anti-Clot Treatment Scale (ACTS) and Treatment Satisfaction Questionnaire for Medication version II (TSQM II). We compared satisfaction with study drug between the two treatment arms, and examined the association between satisfaction and patient-driven study drug discontinuation (stopping study drug due to withdrawal of consent, non-compliance, or loss to follow-up).

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Results: A total of 1577 (11%) patients participated in the Patient Satisfaction substudy; 1181 (8.3%) completed both the ACTS and TSQM II 4 weeks after starting study drug. Patients receiving rivaroxaban did not experience significant differences in satisfaction compared with those receiving warfarin. During a median follow-up of 1.6 years, 448 premature study drug discontinuations occurred (213 rivaroxaban group; 235 warfarin group), of which 116 (26%) were patient-driven (52 [24%] rivaroxaban group; 64 [27%] warfarin group). No significant differences were observed between satisfaction level and rates of patient-driven study drug discontinuation.
Conclusions: Study drug satisfaction did not predict rate of study drug discontinuation. No significant difference was observed between satisfaction with warfarin and rivaroxaban, as expected given the double-blind trial design. Although these results are negative, the importance of PRO data will only increase, and these analyses may inform future studies that explore the relationship between drug-satisfaction PROs, adherence, and clinical outcomes.
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Keywords: Anticoagulant; Atrial fibrillation; Drug discontinuation; Patient-reported outcomes; Patient satisfaction endpoints; Rivaroxaban; Warfarin

INTRODUCTION

Patient-reported outcomes (PROs) used in clinical practice and clinical research are health outcomes reported directly by the patient, without interpretation or confirmation from an intermediary, such as a physician, nurse, or study coordinator [1]. In 2004, the National Institutes of Health roadmap for clinical research identified the development of PROs as a key priority, and multiple PRO tools have been created and validated [2–14]. Guidelines have been published recommending best practices for PRO use [15], and there have been calls to comprehensively integrate PROs into cardiovascular clinical trials [16]. PROs have been used to compare patient satisfaction with warfarin versus the direct oral anticoagulants (DOACs), and have found higher satisfaction with DOACs in patients with pulmonary embolism (PE) [17], deep venous thrombosis (DVT) [18], and atrial fibrillation (AF) [19–21]. However, these studies did not examine whether increased satisfaction predicts better medication adherence. Nonadherence precludes treatment efficacy and leads to worse outcomes [22], and in clinical trials, study drug discontinuation can undermine the scientific rigor of the study. The objective of this substudy from 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) [23] was to determine if PROs assessing study drug satisfaction are associated with study drug discontinuation. We hypothesized that patients who were more satisfied with the study drug would be less likely to discontinue the study drug.

METHODS

The design of ROCKET AF (NCT00403767) has been previously described [23]. In brief, ROCKET AF was a phase III, randomized, double-blind, placebo-controlled, multicenter trial of rivaroxaban compared with dose-adjusted warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular AF. A total of 14,264 patients were randomized at 1178 centers in 45 countries. The protocol was approved by ethics committees at participating sites, and all patients provided written informed consent. Patients were included if

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they had moderate-to-high risk for stroke. Patients were randomized to rivaroxaban 20 mg once daily, or 15 mg once daily in patients with a creatinine clearance of 30–49 mL/min, or dose-adjusted warfarin with a target international normalized ratio of 2.0–3.0. It was intended that patients would continue the therapy throughout the duration of the trial, unless discontinuation was clinically indicated, or after meeting a primary endpoint in which case discontinuation was mandated.

A subset of patients in ROCKET AF was given two treatment satisfaction questionnaires: The Anti-Clot Treatment Scale (ACTS) and the Treatment Satisfaction Questionnaire for Medication version II (TSQM II). Both scales are validated [24–27] and have been used extensively in previous trials of anticoagulants [17–21, 28]. The subset of patients given the questionnaires was selected at random from pre-selected sites in the USA, Germany, and The Netherlands. Sample size calculation was not performed, as these analyses examining PROs and study-drug discontinuation were not preplanned at the start of ROCKET AF.

The ACTS is a 15-item patient-reported instrument of satisfaction with anticoagulant treatment and is summarized as two scales that represent both negative and positive aspects of anticoagulation treatment: ACTS Burdens (12 items), and ACTS Benefits (3 items). The ACTS is an adaptation of the previously validated Duke Anticoagulation Satisfaction Score [29]. For each item, patient experience with anticoagulation treatment is rated on a five-point Likert scale from "Not at all" to "Extremely." The 12 items of ACTS Burdens are reverse coded (scored 5–1), whereas the three items of ACTS Benefits are coded normally (scored 1–5), so that higher scores indicate greater patient satisfaction. Item scores are summed across domains to give an ACTS Burdens score ranging from 12 to 60 and an ACTS Benefits score ranging from 3 to 15. A patient must have data for all items of a scale for the scale to be calculated. The ACTS was measured at 4, 8, 12, and 24 weeks after randomization.

The TSQM II consists of ten items representing four scales: Effectiveness (2 items), Side Effects (3 items), Convenience (3 items), and Global Satisfaction (2 items). Experiences of treatment satisfaction are rated on five-point and seven-point Likert scales from "Extremely dissatisfied" to "Extremely satisfied," with scale scores being converted to a score between 0 and 100, where higher scores indicate greater satisfaction with treatment. A patient must have data for all items of a scale in order for the scale to be calculated, except for the Side Effects and Convenience scales, for which up to one item each could be missing. The TSQM II was measured at 4 and 24 weeks after randomization.

The current analysis includes data from both questionnaires at 4 and 24 weeks, the time points at which both surveys were carried out. Our primary analysis examines survey responses at 4 weeks, a time point that is far enough into the course of therapy to gauge satisfaction, but potentially early enough to intervene before discontinuation occurs. In addition, we examined longer-term satisfaction using data at 24 weeks. Patients who were randomized and received at least one dose of study drug were included in the analysis if they had complete data for both ACTS and TSQM II at 4 weeks and were still on the assigned study drug at the 4-week visit.

Details about study drug administration were collected rigorously including timing, duration, and reason for interruptions or discontinuation of study drug. Study drug discontinuation was defined as a permanent discontinuation of randomized study drug (i.e., stopping study drug and not starting it again later). Temporary interruptions of study drug, defined as stopping study drug and starting it again later (for example for a surgical procedure), were not included as discontinuation outcomes. These discontinuation definitions were used across all ROCKET AF analyses that considered discontinuation in any way [30]. Discontinuations were classified as patient-driven discontinuation or non-patient-driven discontinuation. Patient-driven discontinuation was defined as stopping study drug due to any of the following reasons: withdrawal of consent, noncompliance, or loss to follow-up. Non-patient-driven discontinuation was defined as discontinuation for any other reason (e.g., adverse event, clinical efficacy endpoint reached, investigator decision, protocol violation).

Baseline characteristics and reasons for discontinuation are summarized using number (percent) for categorical variables and median (25th, 75th percentiles) for continuous variables. Scores for individual scales are summarized using both median (25th, 75th percentiles) and mean (standard deviation). These scale summaries were carried out for both 4-week and 24-week data.

Patients were categorized as satisfied or not satisfied in two ways, using 4-week data. For our primary analysis, for each scale, we found the minimum score reflecting satisfaction (e.g., an answer of Satisfied, Very Satisfied, or Extremely Satisfied for all score components; details in the Supplemental Appendix). A patient was then considered satisfied at 4 weeks if their score was equal to or greater than this minimum score (see Supplemental Appendix: Definition of "satisfied vs. "not satisfied" for each scale; minimum score for satisfaction for each subscale was: ACTS Benefits > 12, ACTS Burdens > 42, TSQM Effectiveness > 66.67, Side Effects > 100, TSQM Convenience > 66.7, TSQM Global Satisfaction > 66.7). For our sensitivity analysis, to address any possible subjectivity in our definition for the primary analysis, we used the median of each score distribution as the minimum score cut-off to define satisfaction.

Rates of patient-driven discontinuation after the 4-week survey are summarized for satisfaction groups using events per 100 patient-years and total events. To formally test this relationship, we used Fine and Gray models, which are semi-parametric proportional hazards models that account for competing risks, in this case, non-patient-driven discontinuation. Start time for the models was the time of the 4-week questionnaire. Models were adjusted for the following variables found to be predictive of patient-driven discontinuation in the full ROCKET AF cohort (details of model development are in the Supplemental Appendix): age, sex, race, geographic region, prior stroke or transient ischemic attack, history of depression, prior vitamin K antagonist (VKA) use, and post-randomization occurrence of bleeding or a temporary interruption of study drug for a procedure. Risk relationships are presented as hazard ratios with 95% confidence intervals.

All analyses were conducted using SAS version 9.4 or higher (SAS Institute Inc., Cary, NC).

RESULTS

Of 14,264 patients in ROCKET AF, 1577 participated in the Patient Satisfaction substudy and 1181 remained on study drug at 4 weeks and completed both the ACTS and TSQM II questionnaires 4 weeks after starting the study drug. Of these patients, 572 (48.4%) had been randomized to rivaroxaban, 609 (52.6%) to warfarin. Baseline demographic characteristics were similar in the two groups (Table 1). A total of 855 patients completed both the ACTS and TSQM II at 24 weeks (72% of those who completed both questionnaires at 4 weeks), including 398 (46.5% of those who completed both questionnaires at 24 weeks) randomized to rivaroxaban, and 457 (53.4% of those who completed both questionnaires at 24 weeks) randomized to warfarin.

Patient satisfaction measures at 4 weeks after randomization, overall and by randomized treatment, are presented in Table 2 and Fig. 1. As expected, because of the double-blind design, no differences were observed between the randomized treatment arms in any scales.

In the longer term, satisfaction scores at 24 weeks were similar to those at 4 weeks (Supplemental Table 1 and Supplemental Figure 1), indicating that levels of satisfaction remained consistent over time.

Over a median follow-up of 1.6 years, 448 early permanent study drug discontinuations occurred; 116 (26%) of those were patient-driven (Table 3). Of those, 100 were due to withdrawal of consent and 16 to noncompliance. Among the 332 non-patient-driven discontinuations, 210 were due to adverse events, 52 to reaching a clinical efficacy endpoint, 44 to investigator decision, and 26 to protocol violations. Discontinuation reasons for the entire ROCKET AF cohort are in Supplemental Table 2.

The relationship between satisfaction and discontinuation is presented in Table 4 and Fig. 2. Although on three of the subscales (ACTS Burdens, ACTS Benefits, and TSQM II Effectiveness) there were numerically higher rates of

Table 1 Baseline characteristics for patients participating in the patient satisfaction surveys

Variable	All patients (N = 1181)	Rivaroxaban (N = 572)	Warfarin (N = 609)
Randomized to rivaroxaban	572 (48%)		
Age (years)	75 (67, 79)	75 (67, 79)	75 (67, 79)
Female sex	398 (34%)	189 (33%)	209 (34%)
Geographic region			
North America	776 (66%)	373 (65%)	403 (66%)
Western Europe	405 (34%)	199 (35%)	206 (34%)
Type of AF			
Persistent	881 (75%)	423 (74%)	458 (75%)
Paroxysmal	286 (24%)	139 (24%)	147 (24%)
New onset	14 (1%)	10 (2%)	4 (1%)
$CHADS_2$ score, mean (SD)	3.2 (1.0)	3.2 (1.0)	3.2 (1.0)
$CHADS_2$ score			
2	316 (27%)	146 (26%)	170 (28%)
3	471 (40%)	228 (40%)	243 (40%)
4	270 (23%)	137 (24%)	133 (22%)
5	96 (8%)	47 (8%)	49 (8%)
6	28 (2%)	14 (2%)	14 (2%)
Presenting characteristics			
BMI (kg/m^2)	29.8 (26.3, 33.8)	29.9 (26.6, 34.3)	29.8 (26.0, 33.5)
SBP (mmHg)	130 (120, 140)	130 (120, 140)	130 (120, 142)
DBP (mmHg)	78 (70, 85)	78 (70, 85)	78 (70, 85)
Heart rate (bpm)	72 (63, 82)	72 (63, 81)	72 (63, 82)
Creatinine clearance[a] (mL/min)	70 (54, 93)	72 (55, 94)	69 (53, 93)
Baseline comorbidities			
Prior stroke/TIA/embolism	464 (39%)	225 (39%)	239 (39%)
Congestive HF	585 (50%)	286 (50%)	299 (49%)
Prior MI	248 (21%)	122 (21%)	126 (21%)
PAD	84 (7%)	34 (6%)	50 (8%)
Hypertension	1092 (92%)	531 (93%)	561 (92%)
Diabetes	540 (46%)	263 (46%)	277 (45%)
COPD	181 (15%)	94 (16%)	87 (14%)

Table 1 continued

Variable	All patients (N = 1181)	Rivaroxaban (N = 572)	Warfarin (N = 609)
Medications			
Prior VKA use	1020 (86%)	489 (85%)	531 (87%)
Prior chronic aspirin use	324 (27%)	158 (28%)	166 (27%)
ACE inhibitor/ARB at baseline	894 (76%)	444 (78%)	450 (74%)
Beta blocker at baseline	866 (73%)	410 (72%)	456 (75%)
Digitalis at baseline	443 (38%)	207 (36%)	236 (39%)
Diuretic at baseline	749 (63%)	366 (64%)	383 (63%)

Continuous variables are shown as median (25th, 75th percentiles) except where noted, and categorical variables as no. (%)
ACE angiotensin converting enzyme, *AF* atrial fibrillation, *ARB* angiotensin receptor blocker, *BMI* body mass index, *bpm* beats per minute, $CHADS_2$ congestive heart failure, hypertension, age $\geq$ 75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, *COPD* chronic obstructive pulmonary disease, *DBP* diastolic blood pressure, *HF* heart failure, *MI* myocardial infarction, *PAD* peripheral artery disease, *SBP* systolic blood pressure, *SD* standard deviation, *TIA* transient ischemic attack, *VKA* vitamin K antagonist
[a] Calculated using the Cockcroft–Gault equation

Table 2 ACTS and TSQM scores at 4 weeks after randomization, overall and by randomized treatment

Questionnaire/Scale	All patients (N = 1181)	Rivaroxaban (N = 572)	Warfarin (N = 609)	P value
ACTS				
ACTS Burdens	57 (54, 59)	57 (54, 59)	57 (53, 59)	0.20
	55.6 (5.0)	55.9 (4.7)	55.4 (5.2)	
ACTS Benefits	12 (10, 14)	12 (10, 14)	12 (9, 14)	0.54
	11.3 (3.1)	11.4 (3.0)	11.3 (3.2)	
TSQM II				
Effectiveness	67 (67, 83)	67 (67, 83)	67 (67, 83)	0.68
	71.9 (19.1)	72.1 (19.1)	71.6 (19.1)	
Side Effects	100 (92, 100)	100 (92, 100)	100 (92, 100)	0.48
	93.2 (14.9)	92.8 (15.9)	93.6 (13.9)	
Convenience	78 (67, 89)	78 (67, 89)	78 (67, 83)	0.26
	77.2 (14.8)	77.7 (15.3)	76.8 (14.4)	
Global Satisfaction	75 (67, 83)	75 (67, 83)	75 (67, 83)	0.24
	75.4 (16.1)	75.9 (16.4)	74.9 (15.9)	

For each scale, the top entry is median (25th, 75th percentiles) score and the bottom entry is mean (SD)
ACTS Anti-Clot Treatment Scale, *TSQM II* Treatment Satisfaction Questionnaire for Medication version II

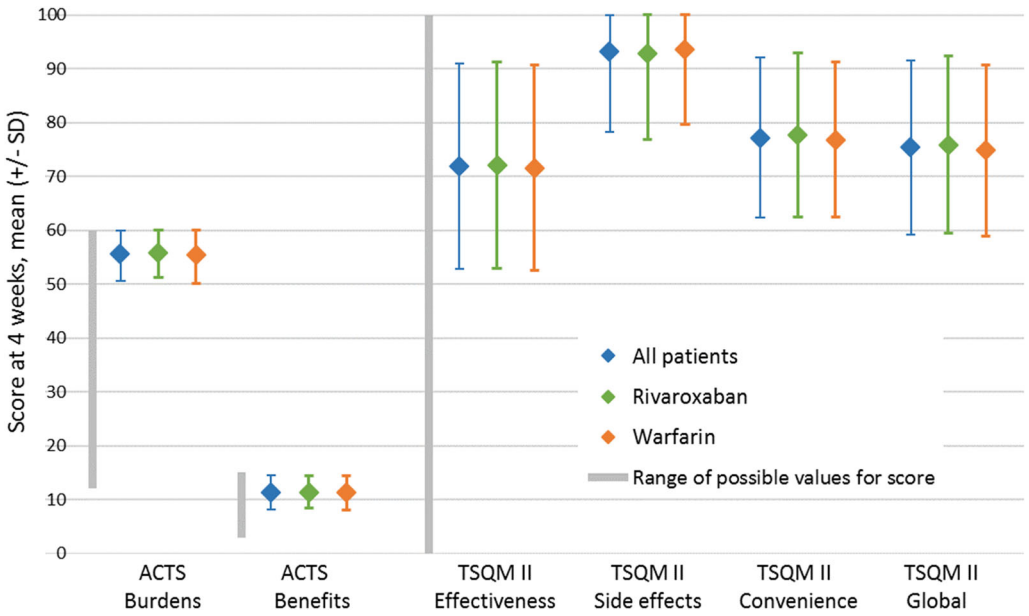

Fig. 1 Scales of patient satisfaction for the entire analysis cohort and by randomized treatment at 4 weeks after randomization

Table 3 Reasons for early permanent study drug discontinuation in the analysis cohort

	All patients (*N* = 1181)	**Rivaroxaban (*N* = 572)**	**Warfarin (*N* = 609)**
Discontinued study drug early	448 (37.9%)	213 (37.2%)	235 (38.6%)
Reason for discontinuation (% among discontinuing patients)			
Patient-driven discontinuation	116 (25.9%)	52 (24.4%)	64 (27.2%)
Consent withdrawn	100 (22.3%)	46 (21.6%)	54 (23.0%)
Noncompliant with study medication	16 (3.6%)	6 (2.8%)	10 (4.3%)
Lost to follow-up	0	0	0
Non-patient-driven discontinuation	332 (74.1%)	161 (75.6%)	171 (72.8%)
Adverse event	210 (46.9%)	109 (51.2%)	101 (43.0%)
Clinical efficacy endpoint reached	52 (11.6%)	24 (11.3%)	28 (11.9%)
Investigator decision	44 (9.8%)	19 (8.9%)	25 (10.6%)
Protocol violation	26 (5.8%)	9 (4.2%)	17 (7.2%)

Data presented as no. (%)

discontinuations in the less satisfied group, there were no statistically significant differences in discontinuation rates between the more and the less satisfied groups for any of the six satisfaction subscales. The results of our sensitivity analysis (which compared patients who were above versus below median satisfaction) are displayed in Supplemental Table 3. In this analysis, too, there were no statistically

Table 4 Association of patient satisfaction scales at 4 weeks with subsequent early study drug discontinuation

Questionnaire/Scale	Cut-off[a]	Not satisfied[b]	Satisfied[b]	HR (95% CI)[c] Not satisfied vs. satisfied	*P* value[c]
ACTS					
Burdens					
N	42	29	1152		
Events/100 pt-years (total events)		6.89 (4)	5.41 (112)	1.44 (0.44–3.46)	0.50
Benefits					
N	12	462	719		
Events/100 pt-years (total events)		6.02 (51)	5.07 (65)	1.18 (0.81–1.71)	0.38
TSQM II					
Effectiveness					
N	67	195	986		
Events/100 pt-years (total events)		7.00 (23)	5.16 (93)	1.23 (0.76–1.91)	0.38
Side Effects					
N	100	326	855		
Events/100 pt-years (total events)		5.55 (31)	5.41 (85)	0.99 (0.64–1.48)	0.95
Convenience					
N	67	98	1083		
Events/100 pt-years (total events)		4.61 (8)	5.52 (108)	0.77 (0.34–1.48)	0.48
Global Satisfaction					
N	67	149	1032		
Events/100 pt-years (total events)		5.32 (14)	5.47 (102)	0.95 (0.52–1.61)	0.86

ACTS Anti-Clot Treatment Scale, *CI* confidence interval, *HR* hazard ratio, *TSQM II* Treatment Satisfaction Questionnaire for Medication version II

[a] Satisfaction is defined as a score at or above the cut-off

[b] Groups are defined using "satisfied" or "not satisfied" survey answers (primary analysis; see Methods)

[c] Hazard ratio and *P* value for discontinuation are from adjusted model

significant differences in discontinuation rates between more and less satisfied patients.

DISCUSSION

In this substudy of anticoagulation-related quality of life from the ROCKET AF trial, patients with AF who were randomly assigned in a double-blind fashion to rivaroxaban or warfarin reported no difference in satisfaction with study drug at 4 versus 24 weeks after enrollment. As expected given the double-blind trial design, similar satisfaction between patients randomized to rivaroxaban versus warfarin was observed. However, in contrast to our hypothesis, we found no association between anticoagulation satisfaction and patient-driven study drug discontinuation.

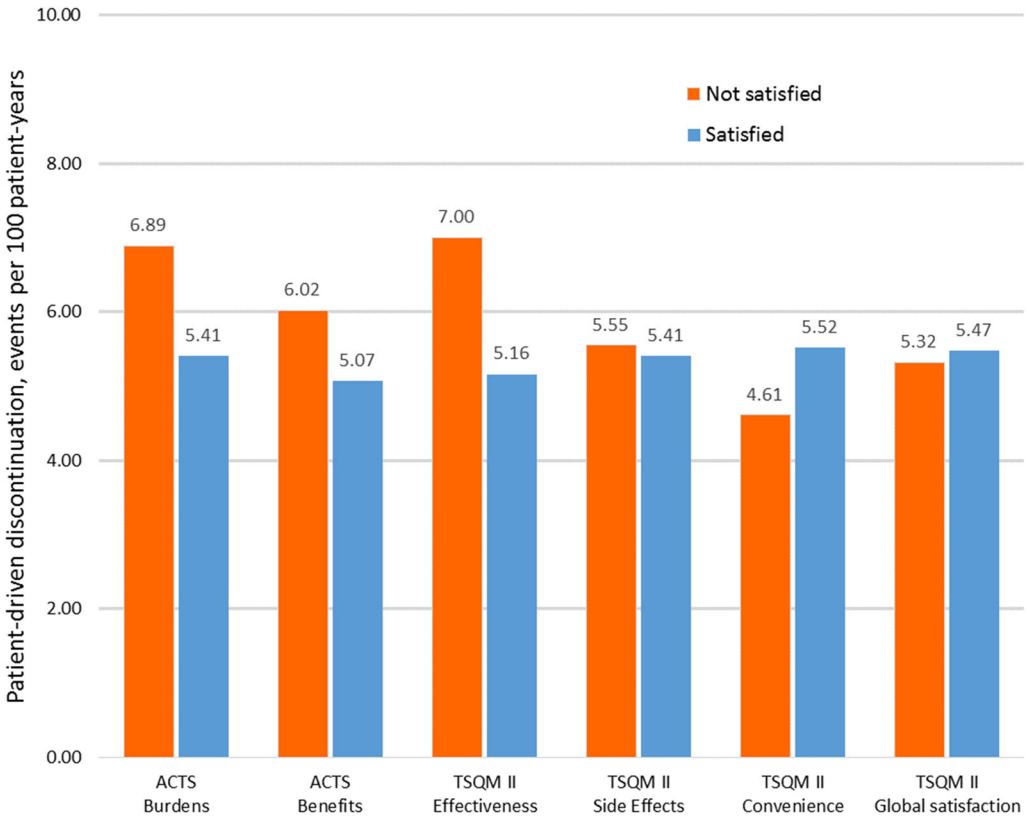

Fig. 2 Patient-driven discontinuation rate (events/100 patient-years) by satisfaction levels at 4 weeks (primary analysis)

As patient-centered care assumes a more prominent role in treatment guidelines, the need to systematically integrate PROs in cardiovascular research has been emphasized [2, 15, 16]. These results build on previous studies of patient satisfaction with anticoagulation. Earlier work has shown that some patients have lower perceived quality of life with warfarin [31, 32], validated PROs measuring satisfaction with warfarin and the DOACs [24–27], and suggested that patients have higher satisfaction with rivaroxaban versus warfarin across a number of indications [17–21]. Furthermore, studies have demonstrated low rates of drug adherence, both in clinical trials and in practice [33–38]. This study builds on these two lines of research by examining whether PROs measuring satisfaction predict anticoagulant nonadherence.

Although we did not find any significant relationship between study drug satisfaction and discontinuation, we did observe some nonsignificant associations. Higher satisfaction on ACTS Burdens, ACTS Benefits, and TSQM II Effectiveness were all nonsignificantly associated with lower discontinuation. This association for the TSQM II Effectiveness subscale was the largest and was present in both our primary and secondary analyses. This may suggest that patients would be willing to tolerate side effects and inconvenience as long as they believe that a drug is effective. Alternatively, it is possible that these previously validated anticoagulation satisfaction scales may not be as powerful predictors in AF as they are in thromboembolic disease. This observation may generate the hypothesis that patients who have already had DVT report higher satisfaction with anticoagulants, and more generally that efficacy is perceived as higher when a drug is used for secondary versus primary prevention. Further studies exploring this hypothesis and the impact of PROs and drug discontinuation

should be studied in open-label trials with larger sample sizes.

Participants assigned to rivaroxaban and warfarin had similar satisfaction at 4 weeks and 24 weeks in this analysis likely because of the double-blind study design that included sophisticated sham INR testing in the rivaroxaban group. These results support that the blinding of the participants was preserved with this approach [23]. Other studies of comparative satisfaction used conditions more similar to actual use, involving blood draws with warfarin but not with rivaroxaban [17, 18]. The similar satisfaction with warfarin and rivaroxaban on every satisfaction subscale suggests that the difference in satisfaction seen in other studies may be attributable to the increased monitoring with warfarin, rather than differences in drug side effects or other non-monitoring-related drug effects.

This study has several limitations. First, only a subset of trial participants from North America and Western Europe participated in the substudy, limiting the generalizability and statistical power. Second, there were a relatively small number of discontinuation events, further reducing statistical power. Third, given the small sample and few endpoint events it was not possible to evaluate the relationships between satisfaction, adherence, and other clinical outcomes.

CONCLUSIONS

In conclusion, in this substudy from ROCKET AF, no statistically significant association between self-reported study drug satisfaction and patient-driven study drug discontinuation was observed. As expected in a double-blind trial, no significant difference between satisfaction between the rivaroxaban group and the warfarin group was observed. Although these results were negative, the importance of PRO data, even in the context of blinded randomized controlled trials, will undoubtedly continue to increase. ROCKET AF successfully collected PRO data in a large clinical trial, and these results may provide important lessons for future clinical trials that collect and monitor PROs to ascertain satisfaction, and explore the relation of PROs to adherence and other clinical outcomes.

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Compliance with Ethics Guidelines. The protocol was approved by ethics committees at participating sites, and all patients provided written informed consent.

Data Availability. The data sets generated during and/or analyzed during the current study are not publically available. Please contact the corresponding author for further inquiries.

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