Received: 7 May 2021 | Revised: 24 September 2021 | Accepted: 29 September 2021

DOI: 10.1002/rth2.12614

rpth research & practice in thrombosis & haemostasis

ORIGINAL ARTICLE

Adherence to rivaroxaban for the treatment of venous thromboembolism–Results from the FIRST registry

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Funding information
Bayer HealthCare, Grant/Award Number: 17504

Handling Editor: Pantep Angchaisuksiri.

Abstract

Background: Medication nonadherence can result in poor clinical outcomes and significant costs to health care providers. When treating venous thromboembolism (VTE), subtherapeutic anticoagulation may contribute to complications such as recurrent VTE or postthrombotic syndrome.

Objectives: To describe the extent, reasons for, and predictors of nonadherence to rivaroxaban for the treatment of VTE in clinical practice in the United Kingdom reported by participants of the FIRST registry.

Patients/Methods: The FIRST registry was an observational, multicenter registry reporting on the use of rivaroxaban in routine clinical practice. FIRST registry participants completed an adherence screening questionnaire during their treatment and follow-up.

Results: In total, 1028 participants completed 1660 questionnaires over 2 years. One hundred thirteen of 1028 (11%) reported nonadherence at 28 days (interquartile range, 21-45). Reasons given for nonadherence at 1 month were forgetfulness (8.6% vs 74.7%; $P < .001$), carelessness (2.7% vs 27.3%; $P < .001$) or a change in routine (7.4% vs 25.5%; $P < .001$) reported by adherent and nonadherent participants, respectively. Older age (10-year increments) was the strongest predictor of good adherence (adjusted odds ratio, 1.21; 95% confidence interval, 1.06-1.39; 1 = adherent).

Conclusions: Overall adherence to rivaroxaban was high, and most nonadherence was unintentional. Identification of those at risk of nonadherence may reduce the risk of VTE recurrence and long-term complications.

KEYWORDS
anticoagulants, medication adherence, rivaroxaban, venous thromboembolism

Essentials

- Medication nonadherence is prevalent in chronic disease.
- The FIRST registry reports adherence to rivaroxaban for the treatment of VTE in the United Kingdom.
- Overall adherence was good, and nonadherence was mostly unintentional.
- Older age was the strongest predictor of good adherence.

1 | BACKGROUND

Adherence can be defined as the extent to which patients take medications as prescribed by health care providers.[1] The importance of adherence to anticoagulation therapy has grown in significance in recent years with the advent of short-acting direct oral anticoagulants (DOACs).[2,3] Previous research has shown that subtherapeutic anticoagulation may place patients at an increased risk of recurrence of venous thromboembolism (VTE) and long-term complications such as postthrombotic syndrome (PTS).[4-9] Nonadherence has significant costs for health care providers. In Europe, it is estimated that 125 billion euros are spent each year on avoidable hospitalizations, emergency care, and adult outpatient appointments as a result of poor medication adherence.[10,11]

The clinical impact of nonadherence presents a greater risk with DOACs than with vitamin K antagonists (VKAs) due to their shorter half-lives and lack of laboratory monitoring, which results in less contact with health care professionals.[12] For VKAs, the international normalized ratio (INR) and the time in therapeutic range (TTR), a tool used to measure an individual's INR control on a VKA, provide the patient and prescriber with instant feedback on the quality of anticoagulation and can indicate when a patient has been nonadherent.[13-16] In the DOAC era, there is no TTR to guide treating clinicians or patients. In a sense, patients are left to their own devices.

Adherence was not problematic in the landmark VTE trials for rivaroxaban, edoxaban, or apixaban.[17-19] The level of acceptable adherence >80% (defined by the World Health Organisation),[20] was reported as 93.5% in EINSTEIN (pooled results) overall (mean study follow-up 207 ± 95.9 days). This is not surprising in the setting of a phase III clinical trial with frequent intense follow-up and a selected population of highly motivated individuals who have put themselves forward to participate in a clinical trial. It is widely acknowledged that adherence in clinical trials is not replicated in clinical practice, and therefore clinical outcomes comparable with those reported from seminal trials may not be achieved.[21]

In the absence of a routine direct sampling method such as INR monitoring, the measurement of medication adherence for DOACs is challenging both in clinical practice and clinical research. There are a number of different direct and indirect methodologies used in clinical research to report medication adherence, including medication event monitoring systems (electronic pill caps), proportion of days covered (PDC), and self-report, all of which have their advantages and disadvantages.[1,2] Self-report is the most accessible and inexpensive method, by questionnaire or by assessment of the number of doses missed over a defined period.

Rivaroxaban was the first factor Xa inhibitor to be licensed in the United Kingdom in 2012 and is now well established in many centers as first-line treatment for VTE.[22,23] Rivaroxaban is prescribed in primary and secondary care in the United Kingdom, and the frequency and delivery of follow-up varies among centers. To date, adherence data for rivaroxaban has mostly been reported in the setting of stroke prevention with atrial fibrillation (AF). This research has shown that adherence to DOACs decreases over time.[24,25] A US claims database study reported that the percentage of patients with a PDC ≥80% decreased from 73% at 3 months to 55% at 9 months for patients with AF prescribed rivaroxaban.[24] There is a concern that as time passes from an acute VTE event and patients are no longer symptomatic, secondary prevention of VTE becomes analogous to stroke prevention in the setting of AF where adherence is known to be poor.

Findings from the FIRST registry demonstrated that rivaroxaban was effective for the majority of patients in daily care.[49] However, 7/1262 (0.6%) reported an episode of VTE recurrence. Five out of those seven cases were as a result of nonadherence to anticoagulation therapy. In this analysis we sought to investigate the extent of nonadherence within the FIRST registry, the characteristics of those who were nonadherent, and possible reasons for medication nonadherence.

2 | METHOD

The FIRST registry was a UK-only, multicenter, noninterventional, observational study investigating the long-term complications of VTE for patients treated with rivaroxaban without bridging therapy. The study methodology has previously been reported.[49] The study population for this analysis was the safety population, which included any participant who had received ≥1 dose of rivaroxaban.

An adherence screening tool (AST) was used to quantify and explain reasons for nonadherence (Supporting Information S1) and the Anti-Clot Treatment Scale (ACTS)[26] was used to assess treatment satisfaction with rivaroxaban as a possible reason for nonadherence.

Both questionnaires were provided to patients simultaneously and were completed independently of the local investigator. The questionnaires were administered at 1 month for all participants regardless of treatment duration; end of treatment, typically at 3 or 6 months for those on short-term treatment, or annually for those on long-term treatment.

The AST consisted of 16 questions (Supporting Information S1). Patients were stratified as nonadherent if they self-reported having

missed ≥1 dose of rivaroxaban in the week preceding questionnaire completion. Fourteen questions explore the possible explanations for nonadherence, while the final question explores the worries or concerns of the participant about rivaroxaban treatment.

The ACTS is a 17-item questionnaire validated to measure patient-reported satisfaction with anticoagulation treatment.[26] It comprises a 12-item ACTS burdens subscale and a 3-item ACTS benefits subscale reported using a 5-item Likert scale. The tool includes two global questions regarding overall satisfaction. A high benefits score is indicative of high perceived treatment satisfaction. Convention is to reverse the burdens score for analysis; as such, a high burdens score is indicative of low treatment burdens and therefore greater satisfaction. To account for any missing participant responses, a scale-specific mean imputation method was used. In this study, 9 of 12 items from the burdens subscale and 2 of 3 items from the benefits subscale needed to have been completed for inclusion in the analysis.

2.1 | Statistical analysis

Patient characteristics are reported as descriptive statistics. For quantitative and ordinal data, mean and standard deviation or median and interquartile range (IQR) were calculated as appropriate. For such data, comparison between subgroups was made using a *t* test or Mann-Whitney test. Categorical data were compared between subgroups using the chi-square or Fisher's exact test. Statistical significance was set at $P < .05$. A logistic regression was completed to estimate the effect of patient characteristics and satisfaction on adherence to rivaroxaban treatment, with the results reported as odds ratios with 95% confidence intervals.

2.2 | Ethical approval

Ethical approval was obtained from the West of Scotland Research Ethics Service (14/WS/1120). Each National Health Service (NHS) Trust participating in the study also obtained local research and development approval before opening. All participants provided written informed consent to participate, and confidentiality and anonymity were maintained.

3 | RESULTS

In total, 1262 patients were recruited to the FIRST registry, of which 1239 had received ≥1 dose of rivaroxaban and were eligible for this analysis.

Overall, 1030 of 1239 (83.1%) participants completed at least one AST questionnaire while prescribed rivaroxaban. Since the number of patients that completed the adherence questionnaire declined after 2 years of follow-up, this analysis will focus on those who completed questionnaires up to 2 years after the index VTE event (1028/1239; 83.0%). Participants were less likely to have completed the questionnaire if they were younger; were of Black, Asian, or mixed descent; or had an upper limb or distal lower limb deep vein thrombosis (DVT) as their index event (Supporting Information S2).

Since those on longer-term anticoagulation were likely to complete more questionnaires and therefore had more opportunity to report nonadherence, stratification of the study population was based on the response to the first questionnaire completed. As such, nonadherence was reported by 113 of 1028 (11.0%) participants on their first questionnaire, after a median duration of 28 days (IQR, 21-45) on rivaroxaban after diagnosis.

Considering all questionnaires completed, 155 of 1028 (15.1%) reported nonadherence at least once during their treatment with rivaroxaban.

The characteristics of adherent and nonadherent patients are described in Table 1. Adherent patients were more likely to be older and White. In total, 1660 questionnaires were completed by 1028 participants (1.6 questionnaires per participant). The median duration of rivaroxaban exposure for participants was 168 days (IQR, 89-377). Overall, adherence to rivaroxaban was high, although there was a reduction in the proportion of adherent participants observed 2 years after the initiation of rivaroxaban (Table 2.).

Forgetting to take the rivaroxaban and carelessness were consistently reported in a higher proportion in the nonadherent subgroup ($P < .001$; Table 3). Nonadherent participants reported that they were less able to manage a change in their routine with respect to rivaroxaban. This difference was observed at 1 month ($P < .001$) and at 1 year ($P < .05$) but was not observed at 2 years. At 1 and 2 years after the initiation of rivaroxaban, a higher proportion of nonadherent patients reported forgetting to refill their prescription for rivaroxaban ($P < .05$). At 1 year, a higher proportion of nonadherent patients reported not being aware of the long-term benefits of rivaroxaban ($P < .05$), and that they did not have a routine for taking their rivaroxaban ($P < .001$).

The concerns that participants reported regarding rivaroxaban are outlined in Figure 1. Possible side effects and long-term effects of rivaroxaban were the two most frequently reported concerns reported by participants.

3.1 | ACTS Analysis

Treatment satisfaction with rivaroxaban was high. Patient-reported benefits were consistently high, and patient-reported burdens decreased over the study period (Figure 2).

Finally, we sought to assess the relationship between adherence and satisfaction. Table 4 summarizes burdens and benefits scores stratified by adherence at each time point.

There was a significant difference in reported treatment burdens for those who were adherent compared with those who were

TABLE 1 Comparison of participant characteristics between the adherent or nonadherent subgroups

		Adherent n = 915	Nonadherent n = 113	*P*
N				
Sex, n (%)	Female	352 (38.5)	36 (31.9)	.35
	Male	561 (61.3)	77 (68.1)	...
	Transgender	2 (0.2)	0 (0.0)	...
Age, mean (SD)	–	60.1 (14.9)	53.7 (15.8)	<.001
Race, n (%)	White	817 (91.3)	88 (80.7)	.001
	Black	60 (6.7)	13 (11.9)	...
	Asian	16 (1.8)	5 (4.6)	...
	Mixed	2 (0.2)	3 (2.8)	...
	Unknown	20	4	...
Diagnosis, n (%)	Distal DVT	261 (28.5)	30 (26.5)	.35
	Proximal DVT	407 (44.5)	60 (53.1)	...
	PE	211 (23.1)	20 (17.7)	...
	DVT and PE	22 (2.4)	3 (2.7)	...
	Upper limb	14 (1.5)	0 (0.0)	...
Personal history, n (%)	No personal history of VTE	711 (77.9)	80 (70.8)	.14
	1 previous VTE	171 (18.7)	30 (26.5)	...
	>1 previous VTE	31 (3.4)	3 (2.7)	...
	Unknown	2	2	...
Cancer-associated VTE, n (%)[a]	No cancer	888 (97.3)	110 (97.3)	.63
	Cancer	25 (2.7)	3 (2.7)	
Days of rivaroxaban exposure, median (IQR)	–	168 (90-379)	116 (84-352)	.15

Note: Participants were stratified as adherent or nonadherent based on the response from the first questionnaire completed. This approach was adopted since as time elapsed from the index event, those on longer-term anticoagulation were likely to complete more questionnaires and therefore had more opportunity to report nonadherence.

Abbreviations: DVT, deep vein thrombosis; IQR, interquartile range; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

[a]Cancer status was not reported for two participants.

TABLE 2 Number of adherence screening tool questionnaires completed, stratified by adherent or nonadherent at each time point

	Time Questionnaire Completed				
	1 month	3 months	6 months	1 year	2 years
N participants	878	291	173	205	113
Adherent[a], n (%)	779 (88.7)	262 (90.0)	156 (90.2)	183 (89.3)	97 (85.8)
Nonadherent[a], n (%)	99 (11.3)	29 (10.0)	17 (9.8)	22 (10.7)	16 (14.2)

[a]The proportion of adherent and nonadherent participants at each time point are presented. Inferences about the trend of nonadherence for individuals cannot be drawn since questionnaires were not all completed at the same time points by the same participants.

nonadherent after 1 month (Table 4). The responses to the individual ACTS questions were explored at 1 month and compared between those who were adherent and nonadherent at that time point (Supporting Information S3). There were significantly lower scores (higher treatment burdens) for the nonadherent subgroup for a number of questions in the first month, including the possibility of bleeding complications as a result of vigorous activity; avoiding other medications; the hassle of daily and occasional aspects; having difficulty following the treatment regimen; and the perceived extent of worry, frustration, or burden associated with rivaroxaban treatment. At 1 month, 3 months, 6 months, and 1 year after the index event, nonadherent participants were more likely to report greater hassle with the daily aspects of rivaroxaban (eg, remembering to take at the same time each day).

The results of the logistic regression found that older age, White race, having no personal history of VTE, and lower patient-reported treatment burdens were significant predictors of good adherence (Table 5).

TABLE 3 The results of the adherence screening tool stratified by adherence at 1 month, 1 year, and 2 years

		1 month			1 year			Two years		
		Adherent	Nonadherent		Adherent	Nonadherent		Adherent	Nonadherent	
		779	99	*P*	183	22	*P*	97	16	*P*
Do you ever forget to take your rivaroxaban? n (%)	No	708 (91.4)	25 (25.3)	<.001	156 (87.2)	5 (22.7)	<.001	82 (85.4)	3 (18.8)	<.001
	Yes	67 (8.6)	74 (74.7)		23 (12.8)	17 (77.3)		14 (14.6)	13 (81.2)	
Do you find it difficult to take your rivaroxaban (eg, swallowing your tablet)? n (%)	No	768 (99.2)	98 (99.0)	…	179 (98.9)	22 (100.0)	–	95 (100.0)	16 (100.0)	…
	Yes	6 (0.8)	1 (1.0)		2 (1.1)	0 (0.0)		0 (0.0)	0 (0.0)	
Are you confident that you are taking your rivaroxaban in the correct way? (%)	No	106 (13.7)	10 (10.2)	.42	31 (17.0)	4 (18.2)	…	16 (17.0)	2 (12.5)	.93
	Yes	668 (86.3)	88 (89.8)		151 (83.0)	18 (81.8)		78 (83.0)	14 (87.5)	
When you feel better, do you sometimes stop taking your rivaroxaban? n (%)	No	765 (99.1)	95 (96.9)	.17	179 (98.4)	21 (95.5)	.91	95 (99.0)	15 (93.8)	.66
	Yes	7 (0.9)	3 (3.1)		3 (1.6)	1 (4.5)		1 (1.0)	1 (6.2)	
Do you take your rivaroxaban only when you feel you need to? n (%)	No	761 (98.3)	97 (99.0)	.95	175 (97.2)	21 (95.5)	.50	95 (99.0)	15 (93.8)	.66
	Yes	13 (1.7)	1 (1.0)		5 (2.8)	1 (4.5)		1 (1.0)	1 (6.2)	
Do you know the long-term benefits of taking your rivaroxaban as told to you by your doctor, nurse, or pharmacist? n (%)	No	155 (20.0)	22 (22.2)	.70	25 (13.9)	8 (36.4)	.007	16 (16.8)	2 (13.3)	…
	Yes	620 (80.0)	77 (77.8)		155 (86.1)	14 (63.6)		79 (83.2)	13 (86.7)	
Do you think the rivaroxaban you have been prescribed has been effective in treating your condition? n (%)	No	54 (7.6)	7 (7.7)	…	9 (5.2)	0 (0.0)	.58	3 (3.4)	2 (13.3)	.32
	Yes	657 (92.4)	84 (92.3)		165 (94.8)	22 (100.0)		85 (96.6)	13 (86.7)	
Sometimes if you feel worse when you take your rivaroxaban, do you stop taking it? n (%)	No	764 (98.8)	94 (98.9)	…	176 (99.4)	22 (100.0)	…	93 (100.0)	15 (93.8)	.32
	Yes	9 (1.2)	1 (1.1)		1 (0.6)	0 (0.0)		0 (0.0)	1 (6.2)	
Sometimes do you stop taking your rivaroxaban so your body can take a break from its effects? n (%)	No	767 (99.2)	95 (96.9)	.12	180 (99.4)	21 (95.5)	.52	95 (100.0)	15 (93.8)	.31
	Yes	6 (0.8)	3 (3.1)		1 (0.6)	1 (4.5)		0 (0.0)	1 (6.2)	
Sometimes do you forget to refill your prescription for your rivaroxaban on time? n (%)	No	735 (97.1)	87 (95.6)	.65	167 (92.3)	16 (72.7)	.004	92 (95.8)	12 (75.0)	.01
	Yes	22 (2.9)	4 (4.4)		14 (7.7)	6 (27.3)		4 (4.2)	4 (25.0)	
Do you have a routine to help you take your rivaroxaban regularly? n (%)	No	121 (15.6)	23 (23.2)	.08	25 (13.7)	11 (52.4)	<.001	15 (15.6)	4 (25.0)	.57
	Yes	653 (84.4)	76 (76.8)		157 (86.3)	10 (47.6)		81 (84.4)	12 (75.0)	
When there is a change in your routine, are you confident you can continue to take your rivaroxaban on time? n (%)	No	57 (7.4)	25 (25.5)	<.001	19 (10.4)	7 (31.8)	.005	12 (12.5)	4 (25.0)	.35
	Yes	713 (92.6)	73 (74.5)		163 (89.6)	15 (68.2)		84 (87.5)	12 (75.0)	
Are you careless at times about taking your rivaroxaban? n (%)	No	745 (97.3)	72 (72.7)	<.001	179 (98.4)	15 (71.4)	<.001	90 (94.7)	8 (53.3)	<.001
	Yes	21 (2.7)	27 (27.3)		3 (1.6)	6 (28.6)		5 (5.3)	7 (46.7)	
Do you believe that you need to take your rivaroxaban regularly? n (%)	No	29 (3.8)	5 (5.1)	.72	7 (3.9)	1 (4.5)	…	5 (5.3)	0 (0.0)	.77
	Yes	744 (96.2)	94 (94.9)		172 (96.1)	21 (95.5)		89 (94.7)	16 (100.0)	

4 | DISCUSSION

The FIRST registry reports the largest data set for patient-reported adherence to rivaroxaban in the setting of VTE to date. Real-world adherence data is reported for 1028 participants from the FIRST registry recruited from 22 NHS hospitals in the United Kingdom. Participants were followed up in primary and secondary care or a combination of both representing the heterogeneous nature of VTE treatment and follow-up in the United Kingdom.

Nonadherence was reported by 113 of 1028 (11%) prescribed rivaroxaban (based on the first questionnaire completed). Older age, White race, no previous personal history of VTE, and lower

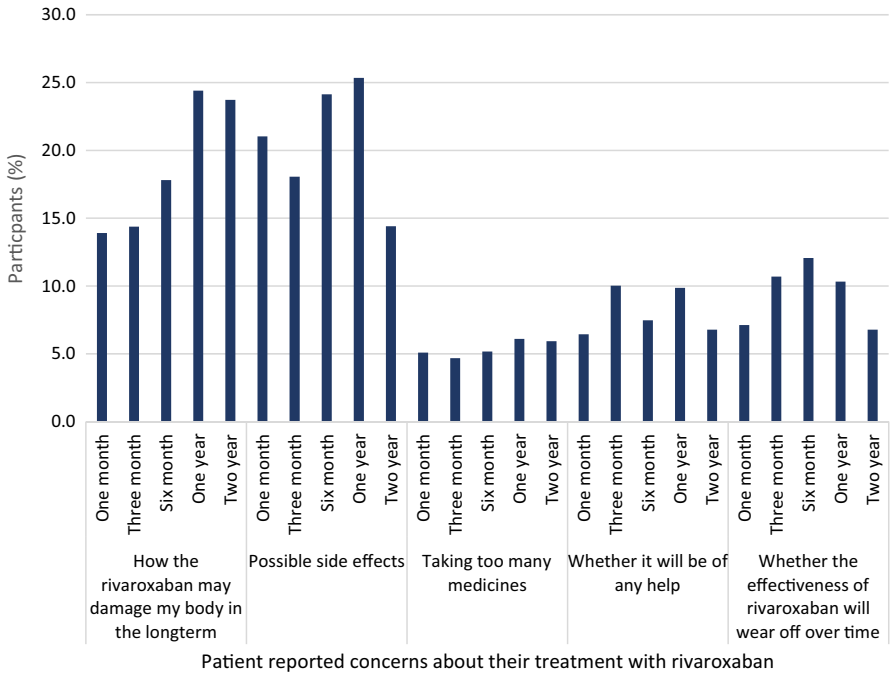

FIGURE 1 Patient-reported concerns about their treatment with rivaroxaban

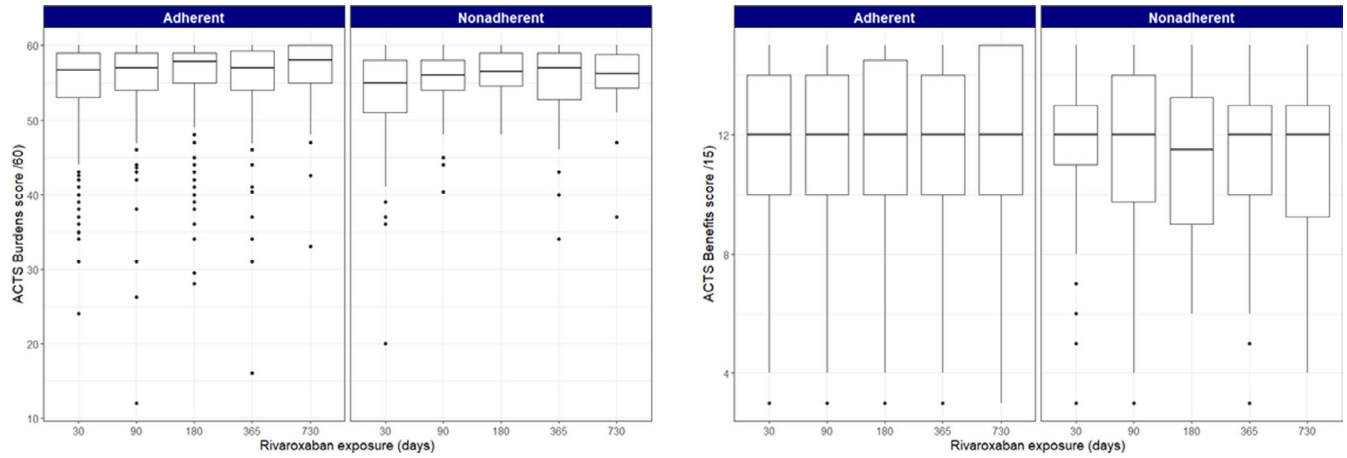

FIGURE 2 The results of the ACTS Burdens and Benefits Scale reported at each time point up to 2 years for adherent and nonadherent participants. ACTS burdens (/60), a higher score represents lower overall patient reported burdens; ACTS benefits (/15), a higher score represents higher overall patient reported benefits

treatment burdens were predictive of good adherence. Treatment satisfaction in the study was high, measured by ACTS burdens and benefits subscales. During the first month, there was an association between higher perceived treatment burdens and nonadherence ($P < .001$).

The proportion of nonadherent participants in this study was only slightly higher than reported in the EINSTEIN program (6.5% nonadherent defined as a PDC <80%).[17] This low level of nonadherence was also reported for edoxaban and apixaban in their phase III studies for VTE.[18,19] It is reassuring that nonadherence in this study from routine clinical practice was only marginally higher than that reported in phase III studies of highly selected participants who underwent intensive follow-up.

To date, adherence research for rivaroxaban in clinical practice for the treatment of VTE has been limited and has involved a variety of methods.

In France, a descriptive observational study from Keita and colleagues reported nonadherence using the Morisky MMAS-8 scale.[27,28] Investigators observed only *moderate adherence* for both DOACs (rivaroxaban, 47/50; 94%) and VKAs for the treatment of acute VTE. In Canada, Castellucci and colleagues report nonadherence to DOAC therapy using the Morisky 4-item tool across all indications in a single center cross-sectional study. In total, 349 of 500 (69.8%) were anticoagulated for the treatment or secondary prevention of VTE. In total, 99 of 126 (78.6%) participants were prescribed rivaroxaban, of which 59.6% reported adequate adherence (median

TABLE 4 Results of the ACTS burdens and benefits scores stratified by patients who were found to be adherent or nonadherent at each time point

ACTS subscale	N	ACTS score Median (IQR)	Adherence	N (%)	ACTS score Median (IQR)
1 mo	878				
Burdens	826	56.0 (52.0–59.0)	Adherent	729 (88.3)	57.0 (53.0–59.0)*
			Nonadherent	97 (11.7)	54.0 (50.0–57.0)*
Benefits	828	12.0 (10.0–14.0)	Adherent	732 (88.4)	12.0 (10.0–14.0)
			Nonadherent	96 (11.6)	12.0 (11.0–13.0)
3 mo	291				
Burdens	275	57.0 (54.5–59.0)	Adherent	247 (89.8)	57.0 (54.5–59.0)
			Nonadherent	28 (10.2)	56.0 (54.1–58.0)
Benefits	275	12.0 (10.0–14.0)	Adherent	249 (90.5)	12.0 (10.0–15.0)
			Nonadherent	26 (9.5)	12.0 (9.0–14.0)
6 mo	173				
Burdens	169	57.0 (55.0–59.0)	Adherent	152 (89.9)	57.0 (55.0–59.0)
			Nonadherent	17 (10.1)	56.0 (54.5–57.3)
Benefits	169	12.0 (10.0–14.5)	Adherent	152 (89.9)	12.0 (10.0–14.0)
			Nonadherent	17 (10.1)	10.0 (8.5–15.0)
1 y	205				
Burdens	180	57.0 (53.6–59.0)	Adherent	160 (88.9)	57.0 (54.0–59.0)
			Nonadherent	20 (11.1)	56.5 (49.0–59.0)
Benefits	179	12.0 (10.0–14.0	Adherent	159 (88.8)	12.0 (10.0–14.0)
			Nonadherent	20 (11.2)	12.0 (9.3–12.8)
2 y	113				
Burdens	103	57.0 (55.0–60.0)	Adherent	90 (87.4)	58.0 (55.0–60.0)
			Nonadherent	13 (12.6)	56.0 (55.0–57.0)
Benefits	105	12.0 (10.0–15.0)	Adherent	92 (87.6)	12.5 (10.0–15.0)
			Nonadherent	13 (12.4)	12.0 (9.0–13.0)

Abbreviation: ACTS, Anti-Clot Treatment Scale.

*$P < .001$ (Mann-Whitney test to compare distribution of adherent and nonadherent participants).

TABLE 5 Logistic regression results reporting predictors of adherence to rivaroxaban treatment

		Adherent	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Sex	Male	561/638 (87.9)		
	Female	352/388 (90.7)	1.34 (0.88-2.04)	
Age (per 10-y increment)			1.29 (1.14-1.46)	1.21 (1.06-1.39)
DVT or PE	DVT	682/772 (88.3)		
	PE	233/256 (91.0)	1.34 (0.83-2.16)	
Personal history of VTE	No history	706/786 (89.8)		
	History	200/233 (85.8)	0.69 (0.44-1.06)	0.63 (0.40-1.00)
White race	Non-White	83/104 (79.8)		
	White	817/905 (90.3)	2.34 (1.39-3.98)	1.82 (1.03-3.21)
ACTS benefits (increment of 1)			0.99 (0.92-1.06)	
ACTS burdens (increment of 1)			1.06 (1.03-1.09)	1.04 (1.01-1.08)

Note: Dependent variable, adherent =1.

Abbreviations: ACTS, Anti-Clot Treatment Scale; PE, pulmonary embolism; VTE, venous thromboembolism.

[a]Participants were stratified as adherent or nonadherent based on the response from the first questionnaire completed. This approach was adopted since as time elapsed from the index event, those on longer-term anticoagulation were likely to complete more questionnaires and therefore had more opportunity to report nonadherence.

duration of therapy, 24 months).[29,30] Castellucci[29] reported that older age, female sex, and additional oral medications increased the likelihood of adequate adherence. More recently, Packard and colleagues[31] reported adherence and persistence to DOACs (n = 305; dabigatran, 191, 62.6%; rivaroxaban, 100, 32.8%; apixaban, 14, 4.6%) for patients prescribed long-term treatment for VTE from a clinical pharmacy service in Colorado. They observed an increase in recurrent VTE in patients with a PDC <80% and identified the determinants of nonadherence as younger age, being a Medicare recipient, and hypertension. They report persistence to DOAC therapy at 12 months to be just 41.3% overall, which is a concern for those recommended long-term anticoagulation, although the proportion prescribed rivaroxaban in this study was low.

The largest amount of adherence data for rivaroxaban in clinical practice lies with the AF population, who are recommended long-term anticoagulation. There are both positive and negative signals from rivaroxaban use in this cohort. In general, persistence and adherence to the DOACs appears greater than for VKAs.[32,33] Unfortunately, the signal from large AF studies is that adherence decreases over time, similar to other medications prescribed for chronic disease.[33-35] In chronic disease, nonadherence can be as high as 50% and is more problematic in those who are asymptomatic or have a low disease burden, which is typical of a patient requiring long-term secondary VTE prevention.[36] The experience of nonadherence to DOACs in AF raises concern about the optimal use of the DOACs for long-term secondary VTE prevention.

Medication nonadherence can be categorized as intentional or unintentional.[37] In the FIRST registry, nonadherent participants report predominantly unintentional nonadherence. Unintentional nonadherence occurs when a patient's intention to take their medication is thwarted, such as forgetting to take it, or other competing attentions such as work or family life, or a change in routine.[38] Therefore, at an individual patient level, a conversation about how rivaroxaban is going to fit in with daily life and a discussion about anticipated barriers may help the patient to develop a good medicine-taking routine.

Necessity beliefs and concerns about medication are determinants of adherence.[37] A meta-analysis showed that necessity beliefs and concerns were consistently positively and negatively related to adherence, respectively.[39] Those with VTE have been reported to have high necessity but low concerns, as described previously in qualitative research from our group. A thematic analysis of semi-structured interviews demonstrated that patients with VTE prioritized their antithrombotic therapy, relying on it to treat and prevent further thrombosis. This was in comparison with the patients with AF, who reported their antithrombotic therapy to be no more important than most of their other medications.[40] Given this motivation, it is unlikely that patients intentionally omit doses unless advised to do so. Data from this study support the finding that nonadherence to rivaroxaban is predominantly unintentional.

Despite nonadherence being mainly unintentional, further research is required to identify those at risk of nonadherence and to develop effective interventions at a system level (such as unclaimed prescriptions) and at an individual patient level (interventions directly targeting a patient's medication taking behavior or concerns) to optimize DOAC therapy and reduce the risk of VTE recurrence. In the Netherlands, a large study of 1399 participants who had switched from warfarin to a DOAC completed a postal survey to report their persistence and adherence to their new anticoagulant. The indication for anticoagulation was mixed in the study. Adherence was assessed using a pragmatic approach rather than a validated tool. Participants were asked whether they occasionally forgot to take their oral anticoagulant as prescribed. In total, 14% of participants reported nonadherence. The Dutch study highlighted two important modifiable factors—the frequency of dose and consultation frequency—as predictors of nonadherence.[41] For VTE, the National Institute of Health and Care Excellence and the American College of Chest Physician recommend an annual review, which may identify those who are not taking their rivaroxaban as prescribed.[42,43]

In our study, we report the specific worries and concerns of participants at each time point. The most frequently reported concerns at each time point were possible side effects and any long-term effects that rivaroxaban might have. Addressing these concerns at initiation or at follow-up review could help to maintain good adherence, as higher medication concerns have been observed to have a negative impact on medication adherence.[39]

Treatment satisfaction for rivaroxaban in the FIRST registry was high. The burdens and benefits subscale scores were comparable with previous studies for rivaroxaban for the treatment of VTE (Table 6). Existing data are predominantly from the clinical trial setting, with the exception of Hendriks and colleagues in Australia.[44] Greater patient-reported treatment burdens were found to be predictive of nonadherence showing the important relationship of patient satisfaction and medication adherence.

In this study, the rate of VTE recurrence was low, at just 0.6% (7/1262) and reported adherence good. However, following a first unprovoked VTE, the risk of recurrence after 3 months of anticoagulation would be expected to be up to 10% at 1 year, increasing up to 25% at 5 years if anticoagulation was discontinued.[48] Similarly, the development of PTS was significantly associated with subtherapeutic anticoagulation (defined as an INR <2, >20% of the time) in a multinational multicenter study of 349 participants with a first unprovoked proximal DVT.[5] The impact of nonadherence on the incidence and severity of PTS with the DOACs has not yet been reported, but experience with VKAs should be borne in mind. While omitting a single dose of rivaroxaban may not signify a significant interruption to anticoagulation, frequent or persistent omission may place patients at risk of recurrence and long-term complications of VTE. Indeed, temporary discontinuation of anticoagulation was reported in five of seven episodes of recurrent VTE in this study.

4.1 | Limitations

Our findings should be considered in the context of their limitations. First, older White patients were more likely to complete the

TABLE 6 Results of the ACTS questionnaire in comparison with other published results

Study	Study participants completing ACTS questionnaire prescribed rivaroxaban N	Study design	Duration of follow up	Indication	Rivaroxaban[a] N	ACTS subscale scores (/60)		VKA/ LMWH N (%)	ACTS subscale scores (/15)	
FIRST Registry	1028	Prospective registry	24 months	PE+/−DVT	1003	Burdens	54.9	…	…	
					1001	Benefits	11.6			
EINSTEIN PE[45]	1200	RCT	12 months	PE+/−DVT	1149	Burdens	55.4	1134	Burdens	51.9
					1149	Benefits	11.9		Benefits	11.4
EINSTEIN DVT[46]	737	RCT	12 months	DVT	718	Burdens	55.2	700	Burdens	52.6
					718	Benefits	11.7		Benefits	11.5
XALIA[47]	1124	Prospective observational Phase VI study	12 months	PE+/−DVT	458	Burdens	56.1	434	Burdens	53.7
					450	Benefits	12.1	430	Benefits	11.9
Hendriks[44]	86	Retrospective cohort study	Not known	Secondary VTE prevention	86	Burdens	57	–	–	
					86	Benefits	13			

Note: ACTS burdens (/60), a higher score represents lower overall patient reported burdens; ACTS benefits (/15), a higher score represents higher overall patient reported benefits.

Abbreviations: DVT, deep vein thrombosis, LMWH; low-molecular-weight heparin; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a]Not all participants in each study completed the burdens and the benefits subscale. For example, 1003 of 1028 participants completed the burdens subscale in the FIRST registry and 1001 of 1028 completed the benefits subscale.

questionnaire, and therefore results may not be generalizable to all ages and ethnicities. Further, participating centers in the FIRST registry were likely to have a special interest in thrombosis and, as such, have more developed follow-up pathways. Using patient self-reported adherence over a period of time relies on patient recall, which may be diminished in older patients. In spite of this, this was a pragmatic and realistic approach that is often used in clinic to establish medicine-taking behavior. Similarly, patient-reported adherence can be overreported, as patients may not want to admit missing tablets. Local study sites were advised that the participants should complete questionnaires independently, so that their responses were not biased by the presence of the study team. While there were 63 questionnaires completed at >3 years after the index event, there were insufficient numbers for statistical analysis. Further, there was no comparator arm in this study, and only experience for rivaroxaban is reported; therefore, comparison or generalization with the other DOACs or VKAs should be made with caution.

5 | CONCLUSIONS

In summary, the FIRST registry reports the largest experience of real-world patient-reported adherence for rivaroxaban for the treatment of VTE to date. For the vast majority, adherence to rivaroxaban remained good, and the rate of VTE recurrence was low. Reassuringly, adherence in the FIRST registry was only marginally lower than that reported in the seminal studies. Efforts should be made to proactively identify those at risk of nonadherence using patient- and system-level approaches.

ACKNOWLEDGMENTS

The FIRST registry was funded by an investigator-initiated research grant from Bayer PLC. The FIRST registry principal investigators were Basildon and Thurrock University Hospitals NHS Foundation Trust – K. Thomas; Basingstoke and North Hampshire Hospital – T. Everington; Bournemouth Hospitals NHS Foundation Trust – J. Mainwaring; Royal Devon and Exeter NHS Foundation Trust – A. Sharp and A. Renouf; The Dudley Group NHS Foundation Trust – S. Jenkins; Epsom and St. Helier University Hospitals – S. Mutgi and C. De Lord; St. Georges University Hospitals NHS Foundation Trust – J. Uprichard; The Hillingdon Hospitals NHS Foundation Trust – M. Pasha; Heartlands Hospital – C. Kartsios; King's College Hospital – R. Arya; University Hospitals of Leicester – B. Myers; University Hospital Lewisham – K. Thanigaikumar; United Lincolnshire Hospitals–B. Myers; Maidstone and Tunbridge Wells NHS Trust – C. Wykes; Newcastle upon Tyne Hospitals NHS Foundation Trust – T. Biss; Poole Hospital NHS Foundation Trust – C. Prescott; Portsmouth Hospitals NHS Foundation Trust – A. Chauhan; Barking, Havering and Redbridge University Hospital–K. Saja; Salisbury NHS Foundation Trust – T. Everington and J. Cullis. The authors thank all physicians, certified research nurses, and hospitals that supported the FIRST registry and all participants from across the United Kingdom for their contribution to the study.

RELATIONSHIP DISCLOSURE

LNR has received speaker fees and travel grant from Bayer, and investigator-initiated research grant and travel grant from Sanofi. RA reports grants from Bayer; personal fees from Bayer, Medtronic, and Sanofi; and nonfinancial support from Bayer and Sanofi. JPP and VA have received an investigator-initiated research grant from Bayer. DC, SM, RKP, and VS have no conflicts of interest.

AUTHOR CONTRIBUTIONS

RA is the chief investigator and designed the study, undertook data collection, undertook central event adjudication, and reviewed the manuscript. RKP designed the study, undertook data collection, undertook central event adjudication, and reviewed the manuscript. JPP designed the study, undertook central adjudication, and reviewed the manuscript. LNR undertook data collection and reviewed the manuscript. VS undertook data collection, central adjudication and wrote the manuscript. DC undertook the statistical analysis and reviewed the manuscript. SM supported the electronic database and reviewed the manuscript. VA designed the study, undertook data analysis, and reviewed the manuscript.

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How to cite this article: Speed V, Auyeung V, Patel JP, et al. Adherence to rivaroxaban for the treatment of venous thromboembolism–Results from the FIRST registry. *Res Pract Thromb Haemost*. 2021;5:e12614. doi:10.1002/rth2.12614