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

Victoria Speed MPharm1,2 | Vivian Auyeung PhD2 | Jignesh P. Patel PhD1,2 | Derek Cooper PhD3 | Stephen Miller PhD4 | Lara N. Roberts MD(Res)1 | Raj K. Patel MD1 | Roopen Arya PhD1

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
1 | BACKGROUND

Adherence can be defined as the extent to which patients take medications as prescribed by health care providers. The importance of adherence to anticoagulation therapy has grown in significance in recent years with the advent of short-acting direct oral anticoagu-
lants (DOACs). 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). 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.

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. 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. 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. The level of acceptable adherence >80% (defined by the World Health Organisation) 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.

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. 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. 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. 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. 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. 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. 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) 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. 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
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 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.

aCancer 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, n (%)             | 779 (88.7) | 262 (90.0) | 156 (90.2) | 183 (89.3) | 97 (85.8) |
| Nonadherent, n (%)          | 99 (11.3)  | 29 (10.0) | 17 (9.8) | 22 (10.7) | 16 (14.2) |

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

|                                    | 1 month |                   | 1 year       |                   | 2 years       |
|------------------------------------|---------|-------------------|--------------|-------------------|--------------|
|                                    | Adherent | Nonadherent | P            | Adherent | Nonadherent | P            | Adherent | Nonadherent | 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? n (%) | 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) | .9 | 176 (99.4) | 22 (100.0) | .93 | 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
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 | Adherence | N (%) | ACTS score |
|--------------|---|------------|-----------|-------|------------|
|              |   | Median (IQR) |           |       | Median (IQR) |
| 1 mo         | 878 | Burdens 826 | 56.0 (52.0–59.0) | Adherent 729 (88.3) | 57.0 (53.0–59.0)* |
|              |     | Benefits 828 | 12.0 (10.0–14.0) | Nonadherent 97 (11.7) | 54.0 (50.0–57.0)* |
| 3 mo         | 291 | Burdens 275 | 57.0 (54.5–59.0) | Adherent 247 (89.8) | 57.0 (54.5–59.0) |
|              |     | Benefits 275 | 12.0 (10.0–14.0) | Nonadherent 28 (10.2) | 56.0 (54.1–58.0) |
| 6 mo         | 173 | Burdens 169 | 57.0 (55.0–59.0) | Adherent 152 (89.9) | 57.0 (55.0–59.0) |
|              |     | Benefits 169 | 12.0 (10.0–14.5) | 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) |
|              |     | Benefits 179 | 12.0 (10.0–14.0) | Nonadherent 20 (11.1) | 56.5 (49.0–59.0) |
| 2 y          | 113 | Burdens 103 | 57.0 (55.0–60.0) | Adherent 90 (87.4) | 58.0 (55.0–60.0) |
|              |     | Benefits 105 | 12.0 (10.0–15.0) | Nonadherent 13 (12.6) | 56.0 (55.0–57.0) |

*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

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

Note: Dependent variable, adherent =1.

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

*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). Castellucci reported that older age, female sex, and additional oral medications increased the likelihood of adequate adherence. More recently, Packard and colleagues 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. Unfortunately, the signal from large AF studies is that adherence decreases over time, similar to other medications prescribed for chronic disease. 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. 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. 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. 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. A meta-analysis showed that necessity beliefs and concerns were consistently positively and negatively related to adherence, respectively. 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. 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. 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.

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.

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. 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. 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. 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
DOACs or VKAs should be made with caution. is reported; therefore, comparison or generalization with the other no comparator arm in this study, and only experience for rivaroxaban were insufficient numbers for statistical analysis. Further, there was made to proactively identify those at risk of nonadherence using patient- and system-level approaches.

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* 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  | 1200                                                                     | RCT                       | 12 months            | PE+/−/DVT          | 1149            | Burdens 55.4              | 1149            | Benefits 11.9               |
| EINSTEIN DVT | 737                                                                      | RCT                       | 12 months            | DVT                | 718             | Burdens 55.2              | 718             | Benefits 11.7               |
| XALIA        | 1124                                                                     | Prospective observational Phase VI study | 12 months | PE+/−/DVT          | 458             | Burdens 56.1              | 458             | Benefits 12.1               |
| Hendriks     | 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.

*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.

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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. RKP designed the study, undertook data collection, central event adjudication, and reviewed the manuscript. DC undertook the statistical analysis and reviewed the manuscript.

ORCID

Victoria Speed https://orcid.org/0000-0001-5064-9375
Vivian Auyeung https://orcid.org/0000-0002-6823-9064
Jignesh P. Patel https://orcid.org/0000-0003-4197-8294
Lara N. Roberts https://orcid.org/0000-0003-3871-8491
Roopen Arya https://orcid.org/0000-0001-5630-7990

TWITTER

Victoria Speed @VictoriaSpeed3
Lara N. Roberts @LaraNRoberts1
Raj K. Patel @KingsThrombosis
Roopen Arya @AryaRoopen

REFERENCES

1. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487-497.
2. Abdou JK, Auyeung V, Patel JP, Arya R. Adherence to long-term anticoagulation treatment: what is known and what the future might hold. Br J Haematol. 2016;174(1):30-42.
3. Rodriguez R, Carrier M, Wells P. Non-adherence to new oral anticoagulants: a reason for concern during long-term anticoagulation? J Thromb Haemost. 2013;11(2):390-394.
4. Mearns ES, Kohn CG, Song J, et al. Meta-analysis to assess the quality of international normalized ratio control and associated outcomes in venous thromboembolism patients. Thromb Res. 2014;134(2):310-319.
5. Chitsike R, Rodger M, Kovacs M, et al. Risk of post-thrombotic syndrome after subtherapeutic warfarin anticoagulation for a first unprovoked deep vein thrombosis: results from the REVERSE study. J Thromb Haemost. 2012;10(10):2039-2044.
6. Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. CMAJ. 2008;179(3):235-244.
7. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2008;133(6):1605-1619.
8. Oake N, Fergusson DA, Forster AJ, van Walraven C. Frequency of adverse events in patients with poor anticoagulation: a meta-analysis. CMAJ. 2007;176(11):1589-1594.
9. Van Dongen C, Prandoni P, Frulla M, Marchiori A, Prins M, Hutton B. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. J Thromb Haemost. 2005;3(5):939-942.
10. OECD/European Union. Health at a Glance: Europe 2018: State of Health in the EU Cycle. OECD Publishing; 2018. Available from: 10.1787/health_glance_eur-2018-en
11. Iuga AO, McGuire MJ. Adherence and health care costs. Risk Manag Healthc Policy. 2014;20(7):35-44.
12. Amin A, Marrs JC. Direct oral anticoagulants for the management of thromboembolic disorders: the importance of adherence and persistence in achieving beneficial outcomes. Clin Appl Thromb Hemost. 2016;22(7):605-616.
13. Sevilla-Cazes J, Finkleman BS, Chen J, et al. Association between patient-reported medication adherence and anticoagulation control. Am J Med. 2017;130(9):1092-1098.e2.
14. Erkens PM, ten Cate H, Buller HR, Prins MH. Benchmark for time in therapeutic range in venous thromboembolism: a systematic review and meta-analysis. PLoS One. 2012;7(9):e42269.
15. Kimmel SE, Chen Z, Price M, et al. The influence of patient adherence on anticoagulation control with warfarin: results from the international normalized ratio adherence and genetics (IN-RANGE) study. Arch Intern Med. 2007;167(9):229-235.
16. Rosendaal F, Cannegieter S, Van der Meer F, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993;70(3):236-239.
17. Prins MH, Lensing AW, Bausersch R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J. 2013;11(1):21.
18. Investigators H-VTE. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369(9):1406-1415.
19. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808.
20. World Health Organisation. Adherence to long-term therapies: evidence for action. 2003. Available from: https://www.who.int/chp/knowledge/publications/adherence_full_report.pdf?ua=1.
21. Mendys P, Zullig LL, Burkholder R, Granger BB, Bosworth HB. Medication adherence: process for implementation. Patient Prefer Adherence. 2014;28(8):1025-1034.
22. National Institute of Health and Care Excellence (NICE). Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. Technology appraisal guidance [TA261] 2012.
23. National Institute of Health and Care Excellence (NICE). Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism technology appraisal guidance [TA287] 2013.
24. Brown JD, Shewale AR, Talbert JC. Adherence to rivaroxaban, dabigatran, and apixaban for stroke prevention in incident, treatment-naive nonvalvular atrial fibrillation. J Manag Care Spec Pharm. 2016;22(11):1319-1329.
25. Manzoor BS, Lee TA, Sharp HK, Walton SM, Galanter WL, Nutescu EA. Real-world adherence and persistence with direct oral anticoagulants in adults with atrial fibrillation. Pharmacotherapy. 2017;37(10):1221-1230.
26. Cano S, Lamping DL, Bamber L, Smith S. The Anti-Clot Treatment Scale (ACTS) in clinical trials: cross-cultural validation in
venous thromboembolism patients. Health Qual Life Outcomes. 2012;10(1):1-11.
27. Keita I, Aubin-Augier I, Lalanne C, et al. Assessment of quality of life, satisfaction with anticoagulation therapy, and adherence to treatment in patients receiving long-course vitamin K antagonists or direct oral anticoagulants for venous thromboembolism. Patient Prefer Adherence. 2017;25(11):1625-1634.
28. Morisky DE. Predictive validity of a medication adherence measure for hypertension control. J Clin Hypertens. 2008;10:348-354.
29. Castellucci LA, Shaw J, Van Der Salm K, et al. Self-reported adherence to anticoagulation and its determinants using the Morisky medication adherence scale. Thromb Res. 2015;136(4):727-731.
30. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24(1):67-74.
31. Packard A, Delate T, Martinez K, Clark NP. Adherence to and persistence with direct oral anticoagulant therapy among patients with new onset venous thromboembolism receiving extended anticoagulant therapy and followed by a centralized anticoagulation service. Thromb Res. 2020;193:40-44. doi:10.1016/j.thromres.2020.05.036
32. Yao X, Abraham NS, Alexander GC, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. J Am Heart Assoc. 2016;5(2):e003074.
33. Martinez C, Katholing A, Wallenhorst C, Freedman SB. Therapy persistence in newly diagnosed non-valvular atrial fibrillation treated with warfarin or NOAC. Thromb Res. 2016;115(01):31-39.
34. McHorney CA, Peterson ED, Laliberté F, et al. Comparison of adherence to rivaroxaban versus apixaban among patients with atrial fibrillation. Clin Ther. 2016;38(11):2477-2488.
35. Coleman CI, Tangirala M, Evers T. Medication adherence to rivaroxaban and dabigatran for stroke prevention in patients with non-valvular atrial fibrillation in the United States. Int J Cardiol. 2016;1(212):171-173.
36. DiMatteo MR. Variations in patients’ adherence to medical recommendations: a quantitative review of 50 years of research. Med Care. 2004;42(3):200-209.
37. Horne R, Weinman J. Patients’ beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res. 1999;47(6):555-567.
38. Horne R, Weinman J, Barber N, et al. Concordance, Adherence and Compliance in Medicine Taking. NCCSDO; 2005;2005: 40-46.
39. Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients’ adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the necessity-concerns framework. PLoS One. 2013;8(12):e80633.
40. Bartoli-Abdou JK, Patel JP, Crawshaw J, et al. Exploration of adherence and patient experiences with DOACs one year after switching from vitamin-K antagonists-insights from the switching study. Thromb Res. 2018;162:62-68.
41. Toorop MM, van Rein N, Nierman MC, et al. Self-reported therapy adherence and predictors for nonadherence in patients who switched from vitamin K antagonists to direct oral anticoagulants. Res Pract Thromb Haemost. 2020;4(4):586-593.
42. Kearon C, Aki EA, Ornelas J, Blaias A, Jimenez D, Bounaumaux H. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149(2):315-352. doi:10.1016/j.chest.2015.11.026
43. NICE N. Venous thromboembolic diseases: Diagnosis, management and thrombophilia testing [NG158], 2020. Available from: https://www.nice.org.uk/guidance/ng158
44. Hendrikse T, McGregor S, Rakesh S, Robinson J, Ho KM, Baker R. Patient satisfaction after conversion from warfarin to direct oral anticoagulants for patients on extended duration of anticoagulation for venous thromboembolism-The SWAN study. PLoS One. 2020;15(6):e0234048.
45. Prins MH, Bamber L, Cano SJ, et al. Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of pulmonary embolism; results from the EINSTEIN PE trial. Thromb Res. 2015;135(2):281-288.
46. Einstein Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499-2510.
47. Cano S, Mantovani L, Folkers K, et al. Patient-reported treatment experience with oral rivaroxaban: results from the noninterventional XALIA study of deep-vein thrombosis. TH Open. 2018;2(2):e139-e146.
48. Khan F, Rahman A, Carrier M, et al. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. BMJ. 2019;24(366):j3463.
49. Speed V, Patel JP, Cooper D, Miller S, Roberts LN, Patel RK, Arya R. Rivaroxaban in acute venous thromboembolism: UK prescribing experience. Res Pract Thromb Haemost. 2021; 5(7). doi:10.1002/rth2.12607

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