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ORIGINAL ARTICLE

Rivaroxaban in acute venous thromboembolism: UK prescribing experience

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Abstract

Background: Rivaroxaban was reported as effective as traditional therapies for the acute treatment of venous thromboembolism (VTE) with fewer major bleeding complications in the seminal Einstein program and is now a recommended option for the treatment of VTE around the world.

Objective: To report the safety and efficacy of rivaroxaban in daily care for the management of acute VTE in the United Kingdom.

Patients/Method: The FIRST registry is a UK-only, multicenter, noninterventional, observational VTE study (NCT 02248610). Consecutive patients diagnosed with acute VTE, managed with rivaroxaban, were recruited and followed for up to 5 years. The primary outcomes were treatment-emergent symptomatic objectively diagnosed recurrent VTE, major and clinically relevant nonmajor bleeding (CRNMB), and all-cause mortality.

Results: A total of 1262 participants were recruited between 2014 and 2018. Participants were heterogeneous, with age range 18 to 95 years, weight 35 to 234 kg, and maximum body mass index 64.4 kg/m^2. The median duration of treatment exposure was 135 days (interquartile range [IQR], 84-307) and overall follow-up 497 days (IQR, 175-991). There were seven episodes of symptomatic VTE recurrence, 0.6%, (0.74/100 patient-years; 95% confidence interval [CI], 0.19-1.28). There were 79 of 1239 (6.4%), 8.66 of 100 patient-years (95% CI, 6.90-10.73) first episodes of major or CRNMB, which were most frequently reported by women aged <50 years as abnormal vaginal bleeding.

Conclusions: Rivaroxaban is an effective and safe single drug modality for the treatment of VTE in daily practice in the United Kingdom. Data to determine the optimal anticoagulation therapy for women of childbearing age are needed.

KEYWORDS
anticoagulants, direct-acting oral anticoagulant, pulmonary embolism, rivaroxaban, venous thromboembolism

Essentials

- Safety and efficacy data for rivaroxaban for acute venous thromboembolism in daily practice in the United Kingdom are lacking.
- Our study demonstrates that rivaroxaban is highly effective in a low-risk population.
- The most frequent significant bleeding was abnormal vaginal bleeding in women aged <50 years.
- Data to determine the optimal anticoagulation therapy for women of childbearing age are needed.

1 | INTRODUCTION

For decades, the standard treatment for acute venous thromboembolism (VTE) has been vitamin K antagonists (VKAs), typically warfarin in the United Kingdom. In 2012, there was a significant shift in the treatment of acute VTE with the licensing of rivaroxaban, the first direct oral anticoagulant (DOAC) to become available for the treatment of VTE.[1,2] This promised a much welcomed simpler approach to anticoagulation in comparison to traditional therapies—with a fixed dose, no requirement for bridging therapy and no international normalized ratio (INR) monitoring. In the seminal phase III randomized control trials, rivaroxaban was found to have similar efficacy to traditional therapy, with a lower rate of major bleeding for both deep vein thrombosis (DVT) and pulmonary embolism (PE) indications.[3] However, in the absence of the close monitoring of a clinical trial, there were concerns about how fixed-dose rivaroxaban might perform in daily care in an unselected population and what the long-term outcomes might be.[4,5] Furthermore, the intensive follow-up of the DOAC phase III clinical trials is not typically replicated in routine care, giving rise to concerns around adherence, especially in the first 30 days of treatment when the risk of VTE recurrence is between 0.6% and 5%.[6]

A number of postmarketing observational studies have reported real-world experience of rivaroxaban for the treatment of VTE.[7-11] To date, postmarketing studies have corroborated the efficacy of rivaroxaban for the treatment of acute VTE from the phase III clinical trials, but safety findings are mixed despite the availability of standardized bleeding criteria.[12] Prospective data from clinical practice has reported the proportion of participants having bleeding events as 1.0% to 3.8%, 4.3% to 17.7%, and 9.1% to 45.5%, for major bleeding, clinically relevant nonmajor bleeding (CRNMB), or any bleeding, respectively.[7-11] Further data to understand the true incidence and the determinants of bleeding associated with rivaroxaban are needed.

In the United Kingdom, the management of VTE varies and takes place across a number of clinical settings. Patients with VTE can be managed in primary, secondary, or tertiary care, and are cared for by specialist nurses and pharmacists, as well as physicians. In the hospital setting, the clinical team responsible for patients with VTE could be the emergency department, cardiology, general medicine, or hematology. Further, the number or frequency of follow-up appointments is not mandated and varies across the United Kingdom.

The Follow-up in Rivaroxaban Patients in Setting of Thromboembolism (FIRST) registry opened to recruitment soon after the approval of rivaroxaban. The aim of the FIRST registry was to report on the safety and efficacy of rivaroxaban for the treatment of VTE across the United Kingdom in an unselected population and to describe treatment patterns in daily care.

2 | METHODS

2.1 | Study design and participants

The FIRST registry is a UK-only prospective, noninterventional, investigator-led, multicenter, observational cohort study (NCT02248610).

Patients were eligible for the study if they were aged >18 years, had a symptomatic objective diagnosis of DVT and/or PE confirmed by compression ultrasonography, contrast venography, computed tomographic (CT) venography or magnetic resonance venography for DVT, and ventilation/perfusion scan or CT pulmonary angiography for PE and were to be anticoagulated with rivaroxaban. Patients were recruited from routine clinical practice. This included VTE diagnosed during an unrelated in-patient stay, participants who were hospitalized for part or all of their DVT and/or PE treatment, or those managed exclusively in outpatient clinics or in primary care. Interim heparin therapy for a maximum of 48 hours and/or a single dose of warfarin until definitive diagnostic testing had been completed was permitted. Patients needed to provide written informed consent. Once informed consent had been obtained, participants were followed for up to 5 years.

Patients were excluded if follow-up was unlikely or impossible, they were unable to give consent, they had received more than 48 hours of interim heparin therapy before an objective VTE diagnosis, had received more than one dose of warfarin, had an indication for anticoagulation other than VTE (eg, atrial fibrillation), or had any contraindication listed in the summary of product characteristics for rivaroxaban.[13] The study was open to recruitment between November 2014 and November 2018 and ceased follow-up July 2020.

2.2 | Selection of study sites

The FIRST registry was adopted by the National Institute of Health Research (NIHR) clinical research network (CRN) portfolio in the United Kingdom (UK CRN ref: 17766). Using the NIHR CRN, centers expressed interest in participating to the lead site

and sponsor, King's College Hospital, London. Local sites were selected to participate if rivaroxaban was the local treatment of choice for acute VTE. The recruiting centers are listed in the Supporting Information and included a mix of secondary and tertiary care providers.

2.3 | Data collection

Patient data were collected during the initial visit and routine follow-up visits, or by telephone contact, by the team directly responsible for patient care. The investigator collected relevant demographics, clinical characteristics, and medical history from medical records if available, or by interviewing the participant. There were no specified follow-up visits, and follow-up occurred according to routine clinical practice at each local site, anticipated at 3 months, 6 months, and annually thereafter for those on long-term treatment.

Participants with both distal and proximal DVTs as index events were included, and those with involvement of the popliteal vein were categorized as proximal for the purpose of this study. The severity of PE was calculated using both the simplified Pulmonary Embolism Severity Index (sPESI) and the Pulmonary Embolism Severity Index (PESI) score.[14,15] Creatinine clearance (CrCl) was calculated using the Cockcroft Gault equation,[16] and participants were defined as fragile if they were either aged >75 years, <50 kg, or had CrCl < 50 mL/min, as has previously been reported by the EINSTEIN investigators.[3]

The FIRST registry used Progeny Clinical for the electronic case report form. Data were entered locally, and the lead investigating site reviewed the completeness and accuracy of the data collected. A 100% source data verification took place for DVT diagnosis for sites recruiting >15 participants, and all suspected episodes of recurrent VTE were subject to central adjudication. The data were extracted from the study database on August 20, 2020.

2.4 | Outcomes

The primary efficacy outcome was incidence of recurrent VTE. Recurrent VTE was defined as a symptomatic event objectively confirmed by compression ultrasonography, contrast venography, CT venography, or magnetic resonance venography for DVT, and ventilation/perfusion scan, or CT pulmonary angiography for PE.

Major bleeding (MB) and CRNMB were the primary safety outcomes. The site of bleeding was reported as well as the bleed severity as defined by the ISTH.[12,17]

Secondary safety outcomes included all-cause mortality and the rates of nonhemorrhagic stroke/transient ischemic attack and myocardial infarction.

2.5 | Sample size

The target sample size was based on the combined analysis of the EINSTEIN DVT and PE studies that reported the rate of major bleeding and VTE recurrence as 1% and 2.1%, respectively.[3] For the recurrent VTE incident rates, assuming an incidence rate of ≈2.1%, 1500 patients would provide an estimate of this value with 95% CI ± 0.7%. For major bleeding assuming the major bleeding is ≈1%, 1500 patients were required in order to provide an estimate of this value with 95% CI ± 0.5%.

The sample size was reduced by the sponsor to 1250 in light of recruitment challenges in the early stages of the study. A total of 1250 patients would provide an estimate of recurrent VTE incident rates with 95% CI ± 0.8% and for major bleeding of 95% CI ± 0.6%.

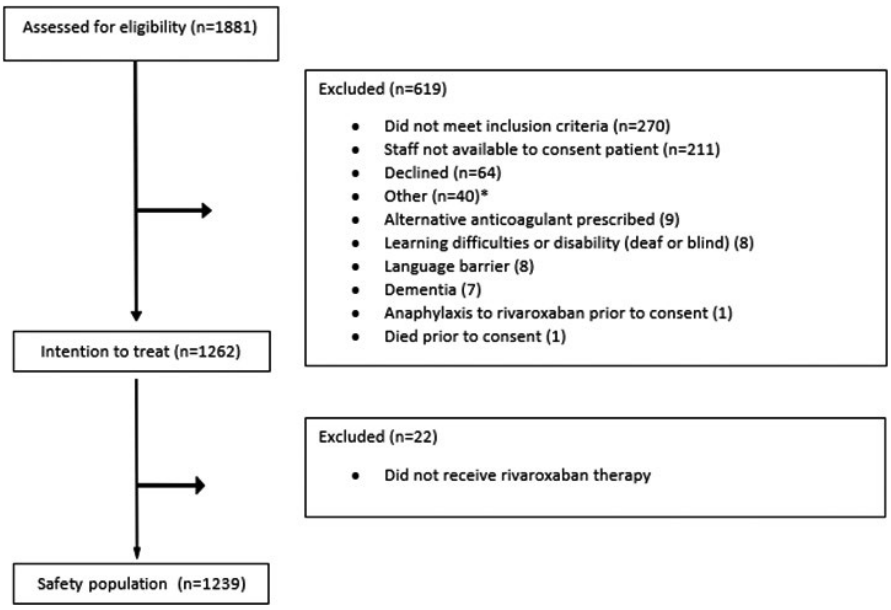

FIGURE 1 Consolidated Standards of Reporting Trials diagram for the FIRST Registry. Screening/eligibility data was gathered by 16 of 22 sites recruiting to FIRST (The six sites that did not contribute this data had 164 participants in total [13%], median 19.5 participants per site recruited [IQR, 6-40]). * See Supporting Information

TABLE 1 Patient characteristics of those recruited to the FIRST registry

		DVT (N = 956)	PE (N = 306)	Overall (N = 1262)
Sex				
Female, n (%)		351 (36.7)	127 (41.5)	478 (37.9)
Male, n (%)		604 (63.2)	178 (58.2)	782 (62.0)
Transgender, n (%)		1 (0.1)	1 (0.3)	2 (0.2)
Age				
Mean [SD]		58.6 [15.4]	58.8 [16.0]	58.7 [15.5]
Race/Ethnicity				
White, n (%)		828 (88.7)	265 (88.0)	1093 (88.6)
Black, n (%)		73 (7.8)	27 (9.0)	100 (8.1)
Asian, n (%)		26 (2.8)	5 (1.7)	31 (2.5)
Mixed, n (%)		6 (0.6)	4 (1.3)	10 (0.8)
Unknown, n		23	5	28
Diagnosis				
Distal DVT, n (%)		371 (38.8)	–	371 (29.4)
Proximal DVT, n (%)		563 (58.9)	–	563 (44.6)
PE, n (%)		–	277 (90.5)	277 (21.9)
DVT and PE, n (%)		–	29 (9.5)	29 (2.3)
Upper limb, n (%)		22 (2.3)	–	22 (1.7)
Bodyweight (kg)				
Mean (SD)		87.7 (19.5)	87.8 (23.6)	87.7 (20.5)
Bodyweight categorization (kg)				
≤49 kg, n (%)		7 (0.7)	7 (2.3)	14 (1.1)
50–99 kg, n (%)		738 (77.8)	228 (76.3)	966 (77.4)
100–149 kg, n (%)		199 (21.0)	57 (19.1)	256 (20.5)
≥150 kg, n (%)		5 (0.5)	7 (2.3)	12 (1.0)
Unknown, n		7	7	14
Creatinine clearance (mL/min)[a]				
Mean (SD)		106 (40.4)	106 (45.6)	106 (41.7)
Creatinine clearance categorization (mL/min)				
≤29 mL/min, n (%)		4 (0.4)	1 (0.3)	5 (0.4)
30–49 mL/min, n (%)		43 (4.7)	12 (4.1)	55 (4.5)
50–89 mL/min, n (%)		305 (33.1)	107 (36.9)	412 (34.0)
≥90 mL/min, n (%)		569 (61.8)	170 (58.6)	739 (61.0)
Unknown, n (%)		35	16	51
BMI categorization (kg/m^2)				
Underweight, n (%)	<18.5	10 (1.1)	4 (1.4)	14 (1.2)
Normal, n (%)	18.5–25	212 (22.9)	70 (24.3)	282 (23.3)
Overweight, n (%)	25–30	337 (36.5)	102 (35.4)	439 (36.2)
Obese (class I), n (%)	30–35	213 (23.1)	56 (19.4)	269 (22.2)
Obese (class II), n (%)	35–40	102 (11.0)	35 (12.2)	137 (11.3)
Obese (class III), n (%)	>40	50 (5.4)	21 (7.3)	71 (5.9)
Unknown, n		32	18	50
Treatment for suspected VTE before objective diagnosis				
No treatment received before objective diagnosis, n (%)		565 (59.3)	113 (37.4)	678 (54.0)
LMWH (1 dose), n (%)		243 (25.5)	119 (39.4)	362 (28.8)

(Continued)

TABLE 1 (Continued)

	DVT (N = 956)	PE (N = 306)	Overall (N = 1262)
LMWH (2 doses), n (%)	90 (9.4)	59 (19.5)	149 (11.9)
Rivaroxaban, n (%)	53 (5.6)	9 (3.0)	62 (4.9)
Unfractionated heparin, n (%)	1 (0.1)	1 (0.3)	2 (0.2)
Warfarin, n (%)	1 (0.1)	1 (0.3)	2 (0.2)
Unknown, n	3	4	7

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; FIRST, Follow-up in Rivaroxaban Patients in Setting of Thromboembolism; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

[a]Creatinine clearance at baseline calculated using Cockcroft-Gault and total bodyweight.

2.6 | Statistical analysis

The data were divided into two clearly defined data sets for analysis. Efficacy outcomes were reported from the intention-to-treat (ITT) population. The ITT population was defined as any patient who had consented to the study regardless of the duration of rivaroxaban received or if there were a change of treatment regimen. Safety outcomes were reported from the safety population, defined as participants who were recruited to the study who had received ≥1 day of rivaroxaban therapy and included those who temporarily interrupted or permanently discontinued treatment, or switched to an alternative anticoagulant. Bleeding events were reported for participants on rivaroxaban therapy and for up to 48 hours after the last dose. Baseline characteristics are reported as absolute and relative frequencies, mean and standard deviation, or median with interquartile ranges where appropriate. Participants with missing data were not removed from the analysis, and an available case analysis was conducted. All statistical analysis was performed using SPSS Statistics for Windows version 25.0 (IBM, Armonk, NY, USA).

Recurrent VTE and MB/CRNMB rates are reported as a crude incidence and as incidence rates, presented as event per 100 patient-years, with corresponding confidence intervals (CIs). Outcomes were compared between subgroups using the chi-squared/Fisher's exact test or *t* test as appropriate.

To show the differences between groups for time to the bleeding event, Kaplan-Meier plots were developed, and comparisons made between groups using the log-rank test. A Cox proportional hazards model was also performed to investigate factors associated with the safety outcome. Significance was set at $P < .05$.

2.7 | Ethics statement

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

3 | RESULTS

Between December 2014 and November 2018, 1262 patients were recruited to the FIRST registry from 22 NHS trusts. A Consolidated Standards of Reporting Trials diagram is presented in Figure 1.

Patient characteristics stratified by index event and risk factors for VTE are described in Tables 1 and 2, respectively.

The mean age of participants was 58.7 years (standard deviation ± 15.5) and 782 (62.0%) were men. The majority of patients had lower-limb DVTs (n = 934, 74.0%; distal, n = 371, 29.4%; and proximal, n = 563, 44.6%), and 277 (21.9%) had a PE only. Twenty-two patients (1.7%) had an upper-limb thrombosis.

The PESI and sPESI were completed by 191 of 306 and 220 of 306 index events of PE ± DVT, respectively. Participants were found to be low risk in 154 of 191 (80.6%) and 151 of 220 (68.6%) according to the PESI and sPESI, respectively. Over half of study participants received either no bridging therapy with low-molecular-weight heparin (LMWH) or were started on rivaroxaban pending a definitive diagnosis of VTE with rivaroxaban (n = 741, 58.7%). The total follow-up was 497 days (interquartile range [IQR], 175-991), and the median duration of exposure on rivaroxaban was 135 days (IQR, 84-307).

3.1 | Treatment patterns

Rivaroxaban was prescribed according to the recommended dose of 15 mg twice daily at initiation in 98.8% of participants. It was prescribed for 3 weeks in the majority of patients, with 83.5% switching to the maintenance dose at 21 days ± 2 days. While the frequency of unlicensed initiation doses was low, doses ranged from 10 mg once daily to 25 mg twice daily. The standard maintenance dose of 20 mg once daily was prescribed in 97.2% of participants, with 21 participants (1.7%) receiving 15 mg once daily as the maintenance dose. Five participants switched to LMWH before the scheduled dose change, three due to investigations for malignancy, one stroke, and one rash.

Two hundred twenty patients (17.4%) were admitted to the hospital for management of their index VTE event; 122 (55.5%) of those participants had had a PE. The median stay was 2 days (IQR, 1-3 days).

TABLE 2 VTE risk factors reported in the FIRST registry

VTE risk factor	N = 1262 n (%)
Personal history of VTE	
No personal history of VTE	974 (77.5)
One previous VTE event	241 (19.2)
>1 previous VTE event	42 (3.3)
Unknown	5
Family history of VTE	
No family history	1052 (84.1)
Family history	199 (15.9)
Unknown	11
Line-associated VTE	
Not applicable	1236 (98.6)
Line related	18 (1.4)
Unknown	8
Recent surgery	
No surgery within 12 weeks	1117 (88.9)
<4 weeks	59 (4.7)
4-8 weeks	58 (4.6)
8-12 weeks	22 (1.8)
Unknown	6
Recent medical illness requiring hospitalization	
No medical illness within 12 weeks	1199 (95.8)
<4 weeks	34 (2.7)
4-8 weeks	17 (1.4)
8-12 weeks	2 (0.2)
Unknown	10
Cancer[a]	
No cancer	1216 (96.8)
Active cancer	17 (1.4)
Palliative care	1 (0.1)
Cancer treated within 6 months	7 (0.6)
Cancer diagnosed after index VTE within 6 months	10 (0.8)
Cancer diagnosed after index VTE after 6 months	5 (0.4)
Unknown	6
Pregnancy	
Not pregnant in the last 6 weeks	389 (98.7)
Miscarriage (<6 weeks)	1 (0.3)
Postpartum (<6 weeks)	4 (1.0)
Unknown	84
Contraception	
No contraception	402 (87.0)
Combined oral contraceptive	41 (8.9)
Contraceptive patch	3 (0.6)
Progesterone-only oral contraceptive	14 (3.0)
Transdermal implant	2 (0.4)
Unknown	16
HRT	
No HRT	465 (96.9)
Oral HRT containing estrogen	10 (2.1)
Transdermal estrogen	4 (0.8)
Local estrogen application	1 (0.2)
Immobilization (paralysis, paresis, or plaster cast)	
No immobilization	1165 (93.4)
<4 weeks	56 (4.5)
4-8 weeks	16 (1.3)
8-12 weeks	10 (0.8)
Unknown	15
Smoking	
Never	670 (54.0)
Current	202 (16.3)
Ex-smoker	368 (29.7)
Unknown	22
IVDU	
Never	1205 (98.8)
Current	2 (0.2)
Ex-IVDU	13 (1.1)
Unknown	42
Recent long-distance travel[b]	
No travel	1094 (86.7)
Recent long-distance travel	168 (13.3)
Known thrombophilia[a]	22 (1.7)
Provoking factors[c]	
Unprovoked	971 (76.9)
Cancer-associated thrombosis[a]	35 (2.8)
Nonsurgical risk factor	147 (11.6)
Surgical risk factor	109 (8.6)

Abbreviations: FIRST, Follow-up in Rivaroxaban Patients in Setting of Thromboembolism; HRT, hormone replacement therapy; IVDU, intravenous drug user; VTE, venous thromboembolism.

[a]Further detail in Supporting Information.

[b]Long distance travel was defined for the purpose of this study as travel over 4 hours up to 8 weeks before the index event. Long-distance travel was not considered a provoking factor for this analysis.

[c]Provoking factors were categorized according to the American College of Chest Physicians guidance.[18] A major transient risk factor, VTE provoked by major surgery/major trauma within past 3 months; nonsurgical transient risk factor (eg, estrogen therapy, pregnancy, immobilization); cancer-associated VTE (defined as cancer diagnosed within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment had been administered within the previous 6 months; or hematologic cancer that was not in complete remission).

Half of the participants in the safety population completed rivaroxaban as planned (625/1239, 50.4%) at a median 98 days (IQR, 85-175 days). Eight participants permanently discontinued

TABLE 3 Efficacy and safety results

	Events on or off rivaroxaban	Events while prescribed rivaroxaban
Efficacy outcomes		
Intention to treat	N = 1262	
Recurrent VTE, n (%)	85 (6.7)	7 (0.6)
Treatment failure, n (%)	…	2 (0.2)
Nonadherence, n (%)	…	5 (0.4)
Safety outcomes		
Safety population	N = 1239	
Bleeding		
Major bleeding, n (%)	…	11 (0.9)
Clinically relevant nonmajor bleeding, n (%)	…	68 (5.5)
Myocardial infarction, n (%)	8 (0.6)	6 (0.5)
CVA or TIA, n (%)	6 (0.5)	3 (0.2)
Death	37[a] (3.0)	7 (0.6)
Cancer-related death, n (%)	13 (1.0)	2 (0.2)
Not VTE or anticoagulation related death, n (%)	13 (1.0)	4 (0.3)
Cause unknown, n (%)	11 (0.9)	1 (0.1)

Abbreviations: CVA, cerebrovascular accident; TIA, transient ischemic attack; VTE, venous thromboembolism.

[a]One patient was lost to follow up and therefore the cause of death and whether they were prescribed rivaroxaban at the time of death is unknown.

TABLE 4 Bleeding outcomes, location, and severity

	Major bleeding n = 11 n (%)	CRNMB n = 79 n (%)	Minor bleeding n = 62 n (%)	All bleeds[a] n = 157 n (%)
Abnormal vaginal bleeding	6 (54.5)	23 (30.3)	11 (18.6)	40 (27.4)
Epistaxis	…	9 (11.8)	14 (23.7)	23 (15.8)
Rectal	…	13 (17.1)	6 (10.2)	19 (13.0)
Macroscopic hematuria	2 (18.2)	12 (15.8)	3 (5.1)	17 (11.6)
Gingival	…	3 (3.9)	8 (13.6)	11 (7.5)
Skin	…	2 (2.6)	8 (13.6)	10 (6.8)
Hemoptysis	…	8 (10.5)	1 (1.7)	9 (6.2)
Hematoma	…	2 (2.6)	4 (6.8)	6 (4.1)
Upper gastrointestinal	2 (18.2)	1 (1.3)	–	3 (2.1)
Puncture site	…	…	2 (3.4)	2 (1.4)
Subconjunctival	…	1 (1.3)	1 (1.7)	2 (1.4)
Other urogenital	…	1 (1.3)	1 (1.7)	2 (1.4)
Intramuscular (without compartment syndrome)	…	1 (1.3)	–	1 (0.7)
Intra-abdominal	1 (9.1)	…	…	1 (0.7)
Data not available	…	3	3	11

Abbreviation: CRNMB, clinically relevant nonmajor bleeding.

[a]There are five patients for whom the severity of bleed was not reported.

TABLE 5 Results univariate and multivariate Cox regression for CRNMB or MB

Variable	Category	Proportion of CRNMB or MB (%)	Unadjusted HR (95% CI)	(After taking account of sex and age group) Adjusted HR[c] (95% CI)
Sex	Male	35/768 (4.6)		
	Female	43/469 (9.2)	2.15 (1.37-3.36)	
Age <50 y	No	50/885 (5.6)		
	Yes	29/354 (8.2)	1.91 (1.20-3.04)	
Weight <50 kg	No	77/1213 (6.3)		
	Yes	2/13 (15.4)	2.32 (0.57-9.45)	1.63 (0.39-6.72)
CrCl <50 mL/min	No	71/1132 (6.3)		
	Yes	6/57 (10.5)	1.65 (0.72-3.79)	1.63 (0.69-3.87)
Preexisting anemia[a]	No	60/1022 (5.9)		
	Yes	16/170 (9.4)	1.86 (1.07-3.23)	1.86 (1.06-3.26)
Cancer[b]	No	76/1200 (6.3)		
	Yes	3/34 (8.8)	1.96 (0.62-6.22)	2.04 (0.64-6.52)
Alcohol intake (moderate or heavy)	No	62/888 (7.0)		
	Yes	15/256 (5.9)	0.79 (0.45-1.39)	0.96 (0.54-1.71)
Concomitant antiplatelets	No	73/1164 (6.3)		
	Yes	6/75 (8.0)	1.29 (0.56-2.97)	1.63 (0.70-3.79)
Concomitant NSAID	No	77/1193 (6.5)		
	Yes	2/46 (4.3)	0.61 (0.15-2.47)	0.62 (0.15-2.55)
Fragile[c]	No	64/1027 (6.2)		
	Yes	15/212 (7.1)	1.04 (0.60-1.84)	1.08 (0.58-2.00)

Abbreviations: CrCl, creatinine clearance; CRNMB, clinically relevant nonmajor bleeding; HR, hazard ratio; MB, major bleeding; NSAID, nonsteroidal anti-inflammatory drug.

1 = Dependent variable was a MB/CRNMB event.

[a]Baseline anaemia defined as <120 g/L in female participants, and <130 g/L in male participants.

[b]Cancer-associated VTE (defined as cancer diagnosed within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment had been administered within the previous 6 months; or hematologic cancer that was not in complete remission).

[c]Fragile (participants with any one of the following characteristics; age >75, weight <50 kg, CrCl <50 mL/min)

anticoagulation therapy after experiencing an adverse effect on rivaroxaban, and 2 of 8 discontinued before completing 3 months of anticoagulation. In total, 121 of 1262 (9.6%) patients switched from rivaroxaban to an alternative agent; the reasons for switching are described later.

Long-term treatment with rivaroxaban was recommended in 324 of 1262 (25.7%) of cases. Thirty-five participants (2.8%) had a rivaroxaban dose reduction to 10 mg once daily for secondary VTE prevention.

Thirty participants (2.4%) did not have a treatment plan recorded, and 72 of 1262 (5.7%) had no follow up data reported.

3.2 | Clinical outcomes

There were seven episodes of VTE recurrence while participants were prescribed rivaroxaban (0.6%, 0.74/100 patient-years; 95% CI, 0.19-1.28; Table 3). Five were associated with nonadherence, and two were considered treatment failures. The treatment failures were objectively diagnosed, symptomatic events following uninterrupted rivaroxaban therapy. Both episodes resulted in participants changing to an alternative anticoagulant: LMWH/warfarin and apixaban. Of note, all episodes of recurrence occurred in men with lower-limb DVTs (six proximal and one distal). Five of the seven events were unprovoked. There were no episodes of recurrence in participants with cancer and one episode of recurrence in a participant weighing 135 kg (associated with nonadherence) as previously reported.[19] There were 78 of 1262 episodes of VTE recurrence (6.2%) that occurred when the participants were no longer prescribed rivaroxaban.

A first treatment-emergent bleeding event (all severities) was reported by 129 of 1239 (10.4%) of participants in the safety population. Overall, there were 157 episodes of bleeding reported, as some participants reported more than one episode (Table 4).

There were 11 of 1239 (0.9%) and 68 of 1239 (5.5%) first episodes of MB and CRNMB, respectively, with no fatal bleeds reported. The incidence rate of CRNMB or MB was 8.66 of 100 patient-years (95% CI, 6.90-10.73). Bleeding of any severity was most frequently reported as abnormal vaginal bleeding in 40 of 157 (25.5%) and in 26 of 79 (32.9%) of episodes categorized as CRNMB or MB. The second

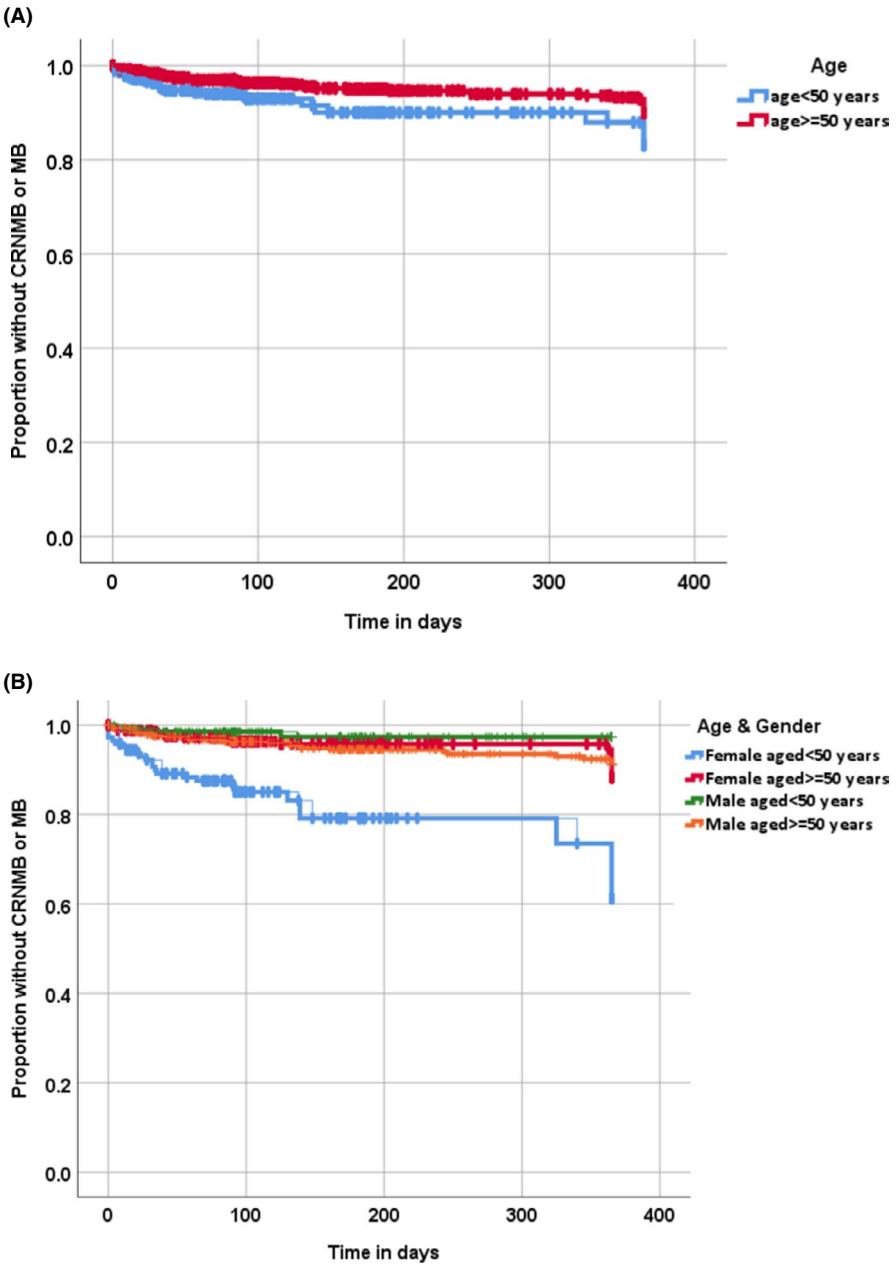

FIGURE 2 Kaplan-Meier curve for clinically relevant major or nonmajor bleeding stratified by age <50/≥50 and sex (A) stratified by age alone and (B) stratified by age and sex. CRNMB, clinically relevant nonmajor bleeding; MB, major bleeding

most frequently reported site of CRNMB or MB was hematuria (14/79, 17.7%), which most frequently occurred in male participants.

The rate of CRNMB or MB was dependent on age *and* sex (Table 5. and Figure 2). The rate of bleeding in female participants aged <50 years (n = 25) was 38.88/100 patient-years (95% CI, 25.68-56.47), and ≥50 years (n = 18), 7.14/100 patient-years (95% CI, 4.36-11.06). The relative risk of CRNMB or MB in female participants aged <50 years compared with >50 years was 5.44 (95% CI, 2.97-9.97).

Figure 2 shows the time to event analysis for CRNMB or MB stratified by age (Figure 2A) and age and sex (Figure 2B) up to 1 year. Figure 2A illustrates that the risk of CRNMB or MB is higher for participants aged <50 years compared with ≥50 years, and Figure 2B illustrates that this is predominantly seen in women aged <50 years. The Cox proportional hazards model found that there were no factors statistically significantly associated with bleeding for those aged ≥50 years or those aged <50 years and male. For those women aged <50 years, those with anemia at baseline had a greater probability of presenting with CRNMB or MB (hazard ratio [HR], 5.01; 95% CI, 2.24-11.23; $P < .001$).

To further describe the relationship between age and sex and the rate of CRNMB or MB, Kaplan-Meier plots were developed describing the time to first bleeding event (CRNMB or MB) stratified by sex for four different age categories. Figure S1A reports the time to CRNMB or MB in participants aged <50 years. Younger female participants experienced significantly more bleeding complications than did male patients of the same age ($P < .001$). Between the ages of 50 and 60 years, no sex difference was observed (Figure S1B), and then over 60 years, more male participants report CRNMB or MB, although not statistically significantly (Figure S1C). Over age

TABLE 6 Summary of safety and efficacy data for rivaroxaban

Study	N	PE ± DVT, %	Mean age, y	Unprovoked, %	Mean length of follow-up, d
FIRST registry (current study)	1262	24	59	76.9	607
EINSTEIN PE[27]	2419	100	57.9	64.7	365
EINSTEIN DVT[28]	1731	0.7	55.8	60.9	365
Xalia and Xalia LEA[7]	3904	16	58	65	225
HOT-PE[21]	519	100	57	...	90
Dresden[9]	418	19	61	22	911
Remote V[10]	308	90	62	83	180
ROSE[29]	1532	33	63	–	84

Abbreviations: CRNMB, clinically relevant nonmajor bleeding; DVT, deep vein thrombosis; HOT-PE, The Home Treatment of Pulmonary Embolism (HoT-PE) study; PE, pulmonary embolism; ROSE, Rivaroxaban Observational Safety Evaluation; VTE, venous thromboembolism; XALIA, XArelto for Long-term and Initial Anticoagulation in venous thromboembolism; XALIA-LEA - XArelto for Long-term and Initial Anticoagulation in venous thromboembolism in Latin America, Europe, Middle East, and Africa (EMEA), and Asia.

70 years, more women appeared to experience more bleeding, although this did not reach statistical significance (Figure S1D).

The rate of CRNMB or MB was comparable in fragile/nonfragile participants (fragile patients were those <50 kg or CrCl < 50 mL/min or age >75 years, as previously defined in the EINSTEIN program[3]), those with/without active cancer, and those at/not at extremes of bodyweight, although the number of participants weighing <50 kg and with cancer were low (Supporting Information). A first episode of minor bleeding (self-limiting bleeding) was reported by 47 of 1239 (3.8%) participants. The most frequently reported sites of nuisance bleeding were vaginal bleeding, gingival bleeding, and epistaxis.

3.3 | Switching treatment

In total, 121 of 1262 (9.5%) patients switched from rivaroxaban to an alternative anticoagulant; 81 of 121 (66.9%) switched due to patient-reported adverse effects while prescribed rivaroxaban (Supporting Information), 40 of 81 (49.4%) switched to apixaban, and 18 of 81 (22.2%) to LMWH. The most frequently reported adverse effect(s) prompting a switch from rivaroxaban to an alternative agent was a bleeding-related complication in 26 of 81 (32.1%). Of note, 47 of 81 (58.0%) switches were due to patient-reported non–bleeding-related adverse effects (Supporting Information).

Other clinical reasons for switching included a new diagnosis of malignancy, diagnosis of antiphospholipid syndrome, and patient or clinician preference.

4 | DISCUSSION

We report the results of a large multicenter registry for patients prescribed rivaroxaban for the treatment of acute VTE in routine clinical practice. Routine clinical practice was heterogeneous; rivaroxaban was prescribed by emergency departments, thrombosis teams, and cardiologists as well as general practitioners in primary care. The 1262 participants exemplify an unselected real-world population with bodyweight ranging from 35 to 234 kg, age range 18 to 95 years, and a creatinine clearance ranging from 21 to 367 mL/min, the majority of whom were managed with the same fixed dose of rivaroxaban.

The FIRST registry demonstrates that rivaroxaban is a safe and effective, single-modality treatment for acute VTE that most patients tolerate well; with a low rate of VTE recurrence and major bleeding. VTE recurrence and major bleeding rates were comparable with EINSTEIN and Xarelto for Long-Term and Initial Anticoagulation in Venous Thromboembolism (XALIA) (Table 6).[3,20] Rates of VTE recurrence and bleeding reported from real-world data is varied. Differences are most likely due to the variation in study methodologies, such as data capture and the frequency of study follow-up. The FIRST registry results were comparable with those of the Home Treatment of Pulmonary Embolism (HOT-PE) study, which reported safety and efficacy data for rivaroxaban for low-risk PE (VTE recurrence 0.6% and 0.6%, respectively).[21] The inclusion criteria for FIRST, such that patients may have only had up to 48 hours of bridging therapy before diagnosis, may have limited the numbers of more unstable patients or those with greater thrombus burden, rendering the FIRST population a lower-risk study population.

VTE recurrence, %	Any bleed, %	CRNMB, %	Major bleeding, %	Switched, %
0.6	10.4	6.4 8.66/100 patient-years (95% CI, 6.90-10.73)	0.9 1.16/100 patient-years (95% CI, 0.61-2.02)	9.5
2.1	…	9.5	1.1	…
2.1	…	7.3	0.8	…
1.4	10.1	–	1.0 1.74/100 patient-years (95% CI, 1.24-2.38)	…
0.6	…	6.0	1.2	…
1.9	45.5	17.7 18.8/100 patient-years (95% CI, 14.8-23.6)	3.8 3.5/100 patient-years (95% CI, 2.0-5.7)	7.2
2.4	…	4.3	1.1	6.2
–	–	4.9 27.6/100 patient-years (95% CI, 21.7-34.6)	1.5 8.3/100 patient-years (95% CI, 5.3-12.5)	–

The subgroup most likely to experience a first MB or CRNMB event were women aged <50 years. This was most frequently reported as abnormal vaginal bleeding, typically heavy menstrual bleeding. A post hoc analysis of the premenopausal women in the EINSTEIN program reported that the risk of any abnormal uterine bleeding or abnormal uterine bleeding requiring transfusion was higher for the participants on rivaroxaban compared with traditional anticoagulant therapies (HR, 2.13; 95% CI, 1.57-2.89).[22] This has also been reported by a number of other studies from clinical practice as well as by the XALIA investigators.[7,23-25] The reporting of abnormal vaginal bleeding in anticoagulation studies is challenging, assessment is often subjective and based on personal experience, and definitions of abnormal vaginal bleeding may not capture this outcome in women.[26] Importantly, unless specifically asked about their menstrual cycle, many women may not report a problem.

A bleeding signal, although not statistically significant, was observed for older male participants (aged 61-70 years) experiencing more CRNMB or MB than female participants of the same age. This most frequently manifested as macroscopic hematuria. Importantly, hematuria on initiation of any anticoagulant can be associated with an underlying genitourinary malignancy, and thus warrants further timely investigation.[30,31]

Due to the short half-life of the DOACs, patients with suboptimal adherence to rivaroxaban may be at greater risk of recurrence; indeed, the majority of recurrent VTE reported in this study were related to nonadherence. In Canada, Castellucci et al[32] reported that 40% of patients prescribed rivaroxaban were nonadherent. Older age, being female, and the use of other oral medications were factors that positively influenced adherence to rivaroxaban. In this study, the majority of patients with recurrent VTE attributed to nonadherence were young male patients in keeping with the Canadian findings.

One in 10 patients in the FIRST registry switched to an alternative anticoagulant. The most frequently reported reason for switching was an adverse event. One in five participants who experienced bleeding switched to an alternative agent. Adverse events affecting the central nervous system (most commonly headaches and lightheadedness) were reported by 4% of the study population, and approximately a quarter of those participants switched to an alternative agent. A high frequency of switching was also reported by investigators in Germany and France.[9,10] With traditional therapies, frequent INR checks in the very acute stages of VTE management mean that patients have more regular interaction and reassurance from their medical team compared with the DOACs. In the Netherlands, a postal survey of patients switching from VKAs to DOACs reported that, among other factors, less frequent clinical review was associated with nonadherence. More frequent reviews may help to identify patients with adverse effects earlier to optimize adherence and tolerance of anticoagulation therapy.[33]

There are a number of limitations that should be considered. While the FIRST registry endeavored to capture rivaroxaban prescribing in routine practice, there were some patients from important vulnerable subgroups that were not recruited (Figure 1). This phenomenon has been reported in the setting of phase III clinical trials, which describe the selected populations that often participate in clinical research.[34,35] Second, given the registry design, there is a risk of underreporting of primary outcomes and missing data. There also may have been selection bias, since treatment was determined by the patient and care provider rather than the registry

protocol.[36,37] There were six centers that did not provide data on participants who were approached but found ineligible to participate in the study. To the best of our knowledge, participants were approached in a consecutive manner in sites using rivaroxaban as their first-line treatment for acute VTE. Given the exclusion criteria for FIRST in which patients could have received only up to 48 hours of LMWH (or an alternative anticoagulant) before their definitive diagnosis, patients with more severe index events (eg, those who may have been hemodynamically unstable, had a large thrombus burden, or had undergone thrombolysis) may not have been included. There were 371 of 1262 (29.4%) participants with isolated distal DVTs as index events and 22 of 1262 (1.7%) upper-limb DVT index events; this should be borne in mind when comparing the rate of VTE recurrence in this study with data from EINSTEIN and other studies in which the rate of recurrence is reported for participants with proximal lower-limb DVTs.

In 2021, rivaroxaban is widely prescribed for the treatment of acute VTE in the UK.[38] It is recommended by the National Institute of Health and Care Excellence over traditional anticoagulant therapies[39] and is prescribed in subgroups, which in the early days of DOAC prescribing had invoked concern. Rivaroxaban is increasingly prescribed in very obese patients (>120 kg or >40 kg/m^2), and data from the FIRST registry has contributed to the growing body of evidence in this population.[19,40,41] Safety and efficacy data for fragile patients was favorable in the phase III program,[3] and real-world data from the Computerized Registry of Patients With Venous Thromboembolism (RIETE) registry supported these data showing that the DOACs (rivaroxaban and apixaban) had comparable composite safety and efficacy outcomes as traditional anticoagulant therapies in this population.[42] Further, in the setting of cancer-associated thrombosis, rivaroxaban can now be considered as an alternative to LMWH with the exception of genitourinary or gastrointestinal cancer primaries.[43,44]

In summary, the results of the FIRST registry demonstrate that rivaroxaban is a highly effective single-modality treatment for acute VTE. For the majority, it is safe at a fixed dose, with comparable rates of bleeding as observed in the licensing studies. Clinicians should approach rivaroxaban with care in women of childbearing age due to a high frequency of abnormal vaginal bleeding. Clinicians should ensure that women know that there are other options if they cannot tolerate rivaroxaban. Patients may benefit from review soon after initiation of a DOAC to assess tolerability and reinforce the need for good adherence.

5 | CONCLUSION

In the United Kingdom, rivaroxaban prescribed for the treatment of VTE is highly effective. Data from the FIRST registry highlight important areas for further research including use of DOACs in women of childbearing age, and use after thrombolysis or in patients with high thrombus burden. Data for the other DOACs from clinical practice are awaited, especially in subgroups of interest such as those at the extremes of bodyweight.

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

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.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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