










ORIGINAL ARTICLE

Pooled Analysis of Rivaroxaban therapy for acute venous thromboembolism in FIRST registry, SWIVTER and DRESDEN NOAC registry

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Abstract

Background: The direct factor Xa inhibitor rivaroxaban is approved for the treatment of venous thromboembolism (VTE), based on the results of large phase III trials.

Objectives: To confirm rivaroxaban's effectiveness and safety in routine clinical care of patients with VTE.

Methods: Data were obtained from prospective, noninterventive registries: the FIRST registry (United Kingdom), DRESDEN NOAC registry (Germany), and SWIVTER (Switzerland). Baseline characteristics of these registries and effectiveness and safety outcome rates for the FIRST and DRESDEN NOAC registries were compared.

Results: A total of 1841 rivaroxaban-treated patients with acute VTE (57.9% male, 76.6% deep vein thrombosis [DVT]; 23.4% pulmonary embolism ± DVT; median age, 61 years) were included: 1217 from the FIRST registry, 418 from the DRESDEN NOAC registry, and 206 from SWIVTER. Median time between VTE diagnosis and initiation of rivaroxaban was 1.4 ± 1.81 days (25th–75th percentile 1–1; range, 0–15 days). On-treatment outcome rates for the FIRST and DRESDEN NOAC registries were 0.74 per 100 patient-years (95% confidence interval [CI], 0.35–1.54) versus 0.96 per 100 patient-years (95% CI, 0.46–2.01) for VTE recurrence; 1.16 per 100 patient years (95% CI, 0.64–2.09) versus 2.51 per 100 patient-years (95% CI, 1.58–3.98) for ISTH major bleeding and 1.69 per 100 patient-years (95% CI, 1.21–2.35) versus 1.73 per 100 patient-years (95% CI, 1.27–2.36) for all-cause mortality (intention-to-treat analysis), respectively.

Conclusion: Overall treatment outcomes were consistent with the results of the phase III rivaroxaban trials in VTE treatment, indicating that the use of rivaroxaban offers acceptable treatment results also in routine care. However, we observed significant differences in patient characteristics and management patterns across Switzerland, the

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United Kingdom, and Germany, limiting direct comparisons of unadjusted outcome event rates between registries.

KEYWORDS

anticoagulant, hemorrhage, registries, rivaroxaban, venous thromboembolism

Essentials

- Registries are data collection tools for verifying results from clinical trials in daily routine.
- Thrombosis therapy with rivaroxaban was compared in three registries from the United Kingdom, Switzerland, and Germany.
- Treatment results in registries were comparable to results of clinical trials.
- Differences in methodologies indicate a need for standardization of observational registries.

1 | INTRODUCTION

Compared to vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs) are characterized by a better dose–response relationship and fewer interactions with food or comedications and, therefore, do not require routine monitoring and frequent dose adjustments.¹ Today, DOACs have become the standard anticoagulation therapy for patients with deep vein thrombosis (DVT) and pulmonary embolism (PE). The DOAC rivaroxaban, a direct factor Xa inhibitor, demonstrated noninferior efficacy to VKAs in two large phase III trials, the EINSTEIN DVT and the EINSTEIN PE, leading to approval for venous thromboembolism (VTE) treatment.^{2,3} In a pooled analysis of the two trials, rivaroxaban demonstrated superior safety over VKAs based on an absolute risk reduction for major bleeding of 0.8%, corresponding to a relative risk reduction of 46%.⁴

Current guidelines of the American Society of Hematology, American College of Chest Physicians (ACCP), and the European Society of Cardiology recommend an anticoagulation duration of 3 months in patients with provoked VTE.^{5–7} Extended duration should be considered for patients with a first episode of an unprovoked proximal DVT or PE and low bleeding risk, as well as in patients with persistent risk factors such as ongoing cancer. Anticoagulation treatment of indefinite duration is recommended in patients with a second episode of unprovoked proximal DVT or PE and in those with permanent major risk factors.

However, implementation of guideline recommendations into daily practice is not without challenges, and observational studies such as prospective registries can be used to assess adherence to guidelines. Furthermore, registries can evaluate the external validity of phase III trials in unselected populations treated in routine “real-world” clinical practice.

Several national registries with different designs have been set up, each reporting primarily on rivaroxaban use in VTE^{8–16} and, moreover, on different types of DOACs including rivaroxaban and approved anticoagulation for VTE treatment. However, these observational studies differ considerably in design, patient selection, duration of follow-up, and outcome definitions, limiting generalizability of conclusions. We therefore set out to investigate the methodological

and clinical differences across three prospective regional noninterventional registries: the Follow-up in Rivaroxaban Patients in Setting of Thromboembolism (FIRST) registry in the United Kingdom,^{16,17} the Register for New Oral Anticoagulants (DRESDEN NOAC) registry in Germany^{12,18} and the Swiss Venous Thromboembolism Registry (SWIVTER) in Switzerland.¹³ We assessed the overall effectiveness and safety of acute VTE treatment with rivaroxaban. In addition, we examined differences in VTE treatment patterns and approaches among the United Kingdom, Germany, and Switzerland.

2 | METHODS

2.1 | Subjects

For this project, data from subjects enrolled in either the FIRST registry, the DRESDEN NOAC registry, or SWIVTER were pooled.

The FIRST registry¹⁶ is a United Kingdom–only prospective, noninterventional, investigator-led, multicenter, single-cohort registry. The FIRST registry enrolled patients with acute DVT and/or symptomatic PE confirmed at the site by appropriate diagnostic imaging, which were treated with rivaroxaban. Enrollment, follow-up, and data collection were managed by 22 individual sites locally. The frequency of follow-up visits or patient contact was planned in accordance with the routine clinical practice at each participating site. For all patients, contacts (visits or phone calls) took place at regular intervals that reflect normal clinical practice. When patients were not returning to the hospital, follow-up took place annually by phone call.

The DRESDEN NOAC Registry^{12,18} is an ongoing prospective registry in the administrative district of Dresden (Saxony), Germany, including both patients with atrial fibrillation and VTE. Patients were enrolled by a network of more than 240 physicians from private practices and hospitals and prospectively followed up by phone calls from the central registry office to collect data on the efficacy, safety, and management of DOAC therapy in daily care.

The prospective SWIVTER¹³ enrolled in- and outpatients with VTE from academic and nonacademic primary–tertiary care

hospitals in Switzerland. Inclusion criteria were age 18 years or older and objectively confirmed acute DVT or PE by diagnostic imaging; this included compression ultrasound or venography for DVT, and contrast-enhanced chest computed tomography, ventilation-perfusion scan, or conventional pulmonary angiography for PE, and complete follow-up at 90 days. No exclusion criteria were applied. The diagnosis and management of acute VTE was performed according to the standard of care at each participating hospital.¹⁹

The study synopses for each of the three registries are outlined in Tables S1–S3 in Appendix S1.

All three registries have similar aims but different approaches. They differ in structure and data collection. All three have included a relevant number of patients with VTE treated with rivaroxaban. Participating physicians were not subject to any instructions with regard to the diagnosis and therapy of their patients in all three registries. Each treatment was carried out within clinical routine at the discretion of the physician and according to existing treatment guidelines.

The categorization of the index VTE event as provoked or unprovoked was performed according to ACCP guidelines²⁰:

- VTE provoked by major surgery/major trauma within the past 3 months (a major transient risk factor)
- VTE provoked by a nonsurgical transient risk factor (e.g., estrogen therapy, pregnancy, nonfracture leg injury, flight of greater than 8 h)
- 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)²¹
- Unprovoked VTE

All three registries used different definitions for “active cancer” (Table S4).

2.2 | Objectives

The primary objective was to evaluate the effectiveness and safety of rivaroxaban in acute VTE treatment in a pooled analysis of the FIRST registry, DRESDEN NOAC registry, and SWIVTER.

Although the statistical analysis plan intended to include SWIVTER data in the pooled outcome assessment, this was not possible due to the lack of data granularity with regard to treatment type and duration for specific time points. In SWIVTER, anticoagulant treatment duration was collected only in categories, for example, “less than 3 months, greater than 3 to less than 6 months, greater than 6–12 months, and >12–24 months,” and documentation of treatment type in the database allowed for entry of several anticoagulants per time interval, making censoring or association of outcome events to a specific treatment impossible. Finally, the starting date for rivaroxaban treatment was not specifically collected so that

the exact date was not available for patients switching from initial non-rivaroxaban therapies to rivaroxaban only later. Therefore, the pooled analysis of all three registries was performed only for comparisons of baseline characteristics, and the pooled outcome analysis was restricted to patients enrolled in the FIRST and DRESDEN NOAC registries.

To assess the effectiveness of rivaroxaban therapy in VTE, we evaluated the annualized rate of the recurrent VTE. The main safety outcome was the annualized rate of major bleeding according to the ISTH definition.²² Further safety outcomes were rates of ISTH clinically relevant nonmajor (CRNM) bleeding²³ and all-cause mortality.

The secondary objective was to describe and compare the design and methodology of the registries and differences in VTE treatment patterns and approaches between the United Kingdom and Germany. Furthermore, we compared the baseline characteristics of patients with acute VTE treatment of the FIRST registry, DRESDEN NOAC registry, and SWIVTER.

2.3 | Treatment duration

In the DRESDEN NOAC and FIRST registries, reasons for stopping anticoagulation were collected in detail. Termination of rivaroxaban therapy was classified as “scheduled end of treatment” if the attending physician or site staff regarded rivaroxaban therapy no longer necessary for treatment of the index VTE event. All other treatment discontinuations were classified as “premature stop,” and the reasons for this decision were collected from patients and attending physicians. All patients who did not prematurely stop rivaroxaban treatment were defined as persistent. For patients who switched their anticoagulant treatment, date of discontinuation and duration of rivaroxaban treatment were collected.

For time-to-event analysis and for calculation of the treatment duration, the following formula was used:

$$\text{Duration in days} = \text{event or stop date of treatment} - \text{start date of rivaroxaban} + 1$$

For follow-up and treatment duration, median with 25th and 75th percentiles were calculated.

2.4 | Statistical Analysis

Statistical analysis was performed for all patients in the FIRST, DRESDEN NOAC, and the SWIVTER registries together as a pooled descriptive and comparative analysis among the respective registries. All patients who were anticoagulated with rivaroxaban for DVT and/or PE and followed up for at least 3 months were included in the analysis.

For comparison among the three registries, the baseline characteristics of each registry are presented as absolute and relative frequencies, mean and standard deviation, or median with interquartile range as difference between 25th and 75th percentile, where

appropriate. Missing values were left blank and not imputed. All *p* values presented are exploratory in nature; thus, no adjustment of type I error for multiple testing was conducted. A *p* value of 0.05 or less was considered to be statistically significant. For categorical variables, the overall *p* value is calculated using a generalized chi-squared test for the comparison among the registries. For continuous variables, the overall *p* value is calculated using a one-way analysis of variance for the comparison among the registries assuming normal distribution. For pairwise comparisons the chi-squared test is used for categorical variables and the unpaired *t* test for continuous variables.

For the outcome event analysis of the FIRST and DRESDEN NOAC registries, two different analysis sets were defined and evaluated:

- The overall rate of recurrent VTE and all-cause mortality rate were evaluated in the intention-to-treat (ITT) analysis. All effectiveness outcome events were included that occurred throughout the follow-up period, including those occurring at any time during or after temporary interruption or discontinuation of rivaroxaban.
- The on-treatment analysis also included all patients with VTE enrolled in the rivaroxaban group at baseline, but only outcome events that occurred during rivaroxaban treatment were included in the calculation of outcome event rates for recurrent VTE events, ISTH major bleeding, and CRNM bleeding.

Outcome event rates for the ITT and the on-treatment analysis set were calculated and performed using Kaplan–Meier estimation for time to first event. In addition, event rates were assessed on the basis of the following two approaches:

- The cumulative incidence risk was estimated at different points in time using the Kaplan–Meier method separately for each registry and overall.
- The incidence rate per 100 subject-years was also determined separately for each registry.

For calculation of event rates per 100 subject-years and their 95% confidence intervals (CIs), the following formula was used:

$$\text{Event rate} = \frac{\text{total number of events of interest}}{\text{total time subjects were under risk}} \\ \left(\frac{\text{defined as the sum of all days from start rivaroxaban treatment until day of first event}}{\text{divided by } 100 \times 365 \text{ days and } 100 \text{ patient-years as its unit}} \right)$$

All statistical analyses were carried out using the software package SAS release 9.4 or higher (SAS Institute Inc.).

2.5 | Ethics

The study protocol of the FIRST registry (NCT02248610), the DRESDEN NOAC registry (NCT01588119), and SWIVTER complied with the principles and requirements of the Declaration of Helsinki.

Written informed consent, including a data protection waiver, was provided or waived by all patients before enrollment, according to local regulations.

3 | RESULTS

3.1 | Patients

Since the start of the respective study period of the three registries (DRESDEN NOAC registry from December 2011 to July 2016; FIRST registry from December 2014 to October 2018; SWIVTER from June 2012 to January 2015) until October 31, 2018, a total of 1841 rivaroxaban-treated patients with acute VTE and completed 3 months of follow-up, including 1217 patients from the FIRST registry, 418 from the DRESDEN NOAC registry, and 206 from SWIVTER were enrolled (Table 1). Of these, 1411 (76.6%), were treated for acute DVT and 430 (23.4%) for PE as the index event. The proportion of DVT only versus PE ± DVT was similar in the three registries: 80.6% versus 19.4% in DRESDEN NOAC registry, 75.1% versus 24.9% in the FIRST registry, and 77.7% versus 22.3% in SWIVTER.

Proportions of unprovoked index VTE were different across registries. In the DRESDEN NOAC registry, 60.8% of patients had an unprovoked index VTE event compared to SWIVTER (66%) and the FIRST registry (71.1%). Overall, 57.9% (*n* = 1066) were male, and two patients (0.1%) were transgender. The FIRST registry and the SWIVTER enrolled more male than female patients (61.9 and 53.9% male, respectively), whereas female patients dominated in the DRESDEN NOAC registry (48.3% male). Overall, median age was 61 years (25th–75th percentile, 48–71 years) with a range from 14 up to 95 years, but age distributions differed considerably among registries: highest median age was observed in the DRESDEN NOAC registry (64 years), followed by the FIRST registry (61 years) and SWIVTER (58 years). The median body mass index (BMI; 25th–75th percentile) was 28.3 kg/m² (25.0–32.2 kg/m²) with a median BMI of 27.4 kg/m² (24.7–30.7 kg/m²) in the DRESDEN NOAC registry and 28.6 kg/m² (25.3–32.8 kg/m²) in the FIRST registry. BMI was not available for 322 patients, including all 206 patients from SWIVTER. Proportions of patients weighing more than 120 kg also varied among the three registries (6.1% of patients in the FIRST registry

versus 2.2% in the DRESDEN NOAC registry vs. 0.5% in SWIVTER).

Concomitant diseases at baseline were documented differently in all three registries, with very limited information recorded in the FIRST registry. Overall, 120 patients were reported to have concomitant malignant disease, but information on active cancer versus history of cancer was captured inconsistently. Proportions of patients with malignant disease were 47 (11.2%) for the DRESDEN NOAC registry, 55 (4.5%) for the FIRST registry, and 18 (8.7%) for SWIVTER, respectively. In addition, cutoffs for “impaired renal function” were

TABLE 1 Patient characteristics at baseline in FIRST registry, DRESDEN NOAC registry and SWIVTER

	All patients (n = 1841)	FIRST registry (n = 1217)	DRESDEN NOAC registry (n = 418)	SWIVTER (n = 206)
Index VTE event				
PE, n (%)	430/1841 (23.4)	303/1217 (24.9)	81/418 (19.4)	46/206 (22.3)
DVT, n (%)	1411/1841 (76.6)	914/1217 (75.1)	337/418 (80.6)	160/206 (77.7)
Proximal DVT, n (%)	889/1406 (63.2)	550/914 (60.2)	234/332 (70.5)	105/160 (65.6)
Distal DVT, n (%)	517/1406 (36.8)	364/914 (39.8)	98/332 (29.5)	55/160 (34.4)
Male, n (%)	1066/1841 (57.9)	753/1217 (61.9)	202/418 (48.3)	111/206 (53.9)
Median age, years (25th–75th percentile)	61 (48–71)	61 (48–70)	64 (49–74)	58 (45–70)
Median BMI, kg/m (25th–75th percentile) ²	28.3 (25–32.2)	28.6 (25.3–32.8)	27.4 (24.7–30.7)	Not registered
Mean time between VTE diagnosis and initiation of Rivaroxaban, days ± SD	1.4 ± 1.8	1 ± 0	2.8 ± 3.4	1 ± 0
Unprovoked event VTE, n (%)	1255/1841 (68.2)	865/1217 (71.1)	254/418 (60.8)	136/206 (66.0)
Recurrent VTE event, n (%)	447/1837 (24.3)	275/1213 (22.7)	128/418 (30.6)	44/206 (21.4)
Malignant disease, n (%)	120/1841 (6.5)	55/1217 (4.5)	47/418 (11.2)	18/206 (8.7)
Active cancer, n (%)	61/117 (52.1)	39/52 (75.0)	11/47 (23.4)	11/18 (61.1)
Chronic lung disease, n (%)	13/206 (6.3)	Not registered	Not registered	13/206 (6.3)
Congestive heart failure, n (%)	34/624 (5.4)	Not registered	20/418 (4.8)	14/206 (6.8)
History of stroke, n (%)	23/624 (3.7)	Not registered	16/418 (3.8)	7/206 (3.4)
Renal dysfunction, n (%)	100/1743 (5.7)	CrCl ≤50 ml/min: 5/1119 (4.9)	eGFR ≤50 ml/min: 35/418 (8.4)	eGFR <30 ml/min: 10/206 (4.9)
Hepatic Impairment, n (%)	3/624 (0.5)	Not registered	1/418 (0.2)	2/206 (1)
Diabetes mellitus, n (%)	85/624 (13.6)	Not registered	72/418 (17.2)	13/206 (6.3)
Hypertension, n (%)	280/624 (44.9)	Not registered	230/418 (55)	50/206 (24.3)

Note: In each field, the denominator represents the number of patients with available data.

Abbreviations: BMI, body mass index; CrCl, creatinine clearance; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

set differently: creatinine clearance of 50 ml/min or less in the FIRST registry; estimated glomerular filtration rate (eGFR) of 50 ml/min or less in the DRESDEN NOAC registry, and eGFR less than 30 ml/min in SWIVTER (Table 1).

Comparisons between the DRESDEN NOAC registry and SWIVTER revealed that cardiovascular risk factors were more prevalent in the DRESDEN NOAC registry compared to SWIVTER (diabetes, 17.2% vs. 6.3%; $p = 0.0002$; hypertension, 55% vs. 24.3%; $p < 0.0001$). More details on baseline characteristics are presented in Table 1.

When the available baseline data of all three registries were compared to the exclusion criteria in the respective phase III trials EINSTEIN DVT/PE, we found that a large proportion of the registry patients would not have been eligible to participate in the EINSTEIN trials: 517 had distal DVT, 45 underwent VTE recanalization, 19 had a creatinine clearance less than 30 ml/min, and 6 were younger than 18 years (Table S5). In addition, a relevant proportion had parenteral pretreatment for longer than 36 h.

3.2 | Follow-up

The overall median follow-up was 746 days (25th–75th percentile, 318–1462.5 days), with a median follow-up of 541 days (25th–75th percentile, 185–1075 days) in the FIRST registry and 2074.5 days (25th–75th percentile, 1708–2764 days) in the DRESDEN NOAC registry. Data on exact follow-up duration were not available from SWIVTER.

3.3 | VTE treatment

Median time between VTE diagnosis and initiation of rivaroxaban was 1 day (25th–75th percentile, 1–1; range, 0–15 days). The overall median treatment duration was 169 days (25th–75th percentile, 86–390 days), with a median treatment duration of 144 days (25th–75th percentile, 85–337 days) in the FIRST registry and 214 days (25th–75th percentile, 105–640 days) in the DRESDEN NOAC registry. Data on exact duration of rivaroxaban treatment were not available

from SWIVTER. Patients with PE received longer anticoagulant therapy compared to patients with DVT (202 days for PE vs. 122 days for DVT; $p = 0.0007$). Similarly, patients with malignant disease received longer anticoagulant therapy compared to patients without cancer (172.50 days vs. 169 days; $p = 0.18$). However, within the cancer population, treatment durations differed across the registries: In the FIRST registry, patients with malignant diseases had a median rivaroxaban exposure of 89 days compared to 372 days in the DRESDEN NOAC registry ($p = 0.0002$).

3.4 | Clinical outcomes

In the ITT population, 144 of 1635 patients developed a recurrent VTE, which translated into an overall crude incidence of 8.81% (95% CI, 7.48–10.29). Crude incidence rate was numerically higher in the DRESDEN NOAC (14.83% [95% CI, 11.56–18.61]) compared to the FIRST registry (6.74% [95% CI, 5.39–8.29]). Annualized incidence rates for recurrent VTE were 3.49 per 100 patient-years (95% CI, 2.96–4.11), with a nonsignificant trend toward higher rates in the FIRST registry (4.08/100 patient-years [95% CI, 3.28–5.06]) compared to the DRESDEN NOAC registry (2.93/100 patient-years [95% CI, 2.28–3.76]) (Figure 1A; Table S6).

The event rate in the group of patients with DVT as the index event (3.96/100 patient-years [95% CI, 3.33–4.72]) was significantly higher compared to patients with PE as the index event (1.9/100 patient years [95% CI, 1.2–3.02]; $p = 0.004$). For patients with provoked versus unprovoked VTE and proximal versus distal DVT, crude incidences of VTE recurrence are provided in Table S7.

A total of 14 patients developed recurrent VTE during active treatment with rivaroxaban (7 in the DRESDEN NOAC registry and 7 in the FIRST registry). In the on-treatment analysis, this corresponded to a pooled annualized incidence rate of 0.83 per 100 patient-years (95% CI, 0.49–1.40), with comparable incidence rates for the DRESDEN NOAC registry (0.96/100 patient-years [95% CI, 0.46–2.01]) and the FIRST registry (0.74/100 patient-years [95% CI, 0.35–1.54]; Figure 1B).

ISTH major bleeding during active treatment with rivaroxaban was experienced by a total of 29 patients (crude incidence rate, 1.77% [95% CI, 1.19–2.54]). This translated into an annualized incidence rate of 1.74 per 100 patient-years (95% CI, 1.21–2.5). ISTH major bleeding was more frequently reported in the DRESDEN NOAC registry ($n = 18/418$; 4.31%) compared to the FIRST registry ($n = 11/1217$; 0.9%), with corresponding annualized incidence rates of 2.51 per 100 patient-years (95% CI, 1.58–3.98) and 1.16 per 100 patient-years (95% CI, 0.64–2.09), respectively (Figure 2). In both registries, major bleeding was much more frequent in patients with malignant disease (DRESDEN NOAC registry annualized incidence rates, 6.27/100 patient-years [95% CI, 2.82–13.95] vs. FIRST registry, 3.22/100 patient-years [95% CI, 0.45–22.88]) compared to patients without cancer (DRESDEN NOAC registry annualized incidence rates, 1.93/100 patient-years [95% CI, 1.1–3.4] vs. FIRST registry, 1.09/100 patient-years [95% CI, 0.59–2.02]; Figures S1, S2).

CRNM bleeding events occurred in 96 cases in the DRESDEN NOAC registry (22.97% [95% CI, 19.02–27.3]), which translated into an annualized incidence rate of 17.62 per 100 patient-years (95% CI, 14.43–21.53). In comparison, only 68 cases reported CRNM bleeding in the FIRST registry, corresponding to a crude incidence of 5.59% (95% CI, 4.36–7.03) and an annualized incidence rate of 7.42 per 100 patient-years (95% CI, 5.85–9.41; Figure 3).

Overall, 75 patients died, which translated into an all-cause mortality event rate of 1.71 per 100 patient-years (95% CI, 1.36–2.14). Event rates were considerably higher in the DRESDEN NOAC registry (crude incidence rate, 9.57% [95% CI, 6.92–12.80]; 1.73/100 patient-years [95% CI 1.27–2.36]) compared to the FIRST registry (crude incidence rate, 2.88% [95% CI, 2.01–3.98]; 1.69/100 patient-years [95% CI, 1.21–2.35]).

4 | DISCUSSION

In this project, we aimed to pool data from three different VTE registries, collecting data on rivaroxaban treatments in Germany, the United Kingdom, and Switzerland.

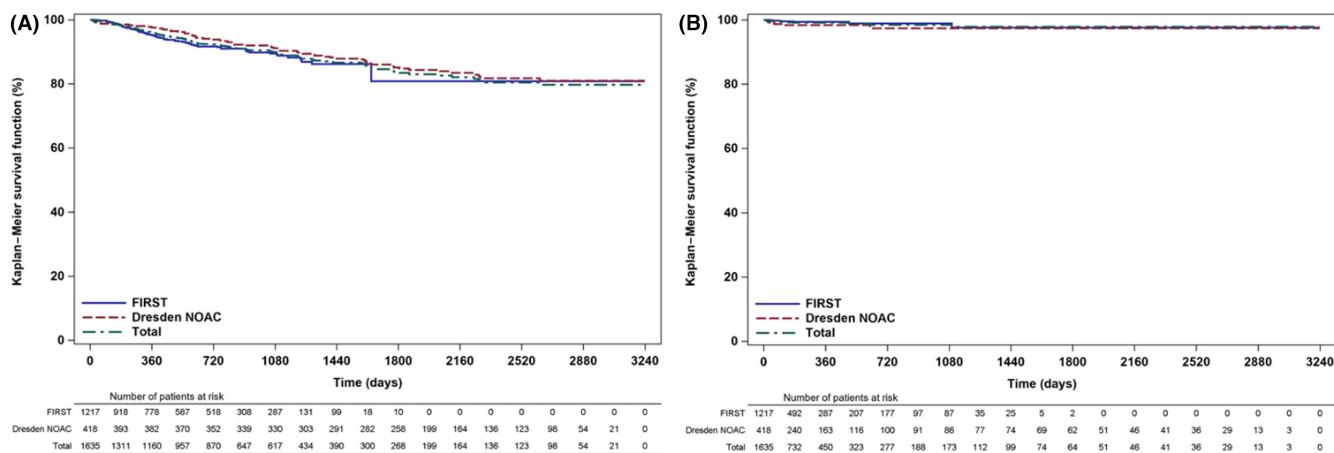


FIGURE 1 Kaplan–Meier event-free survival curves for recurrent VTE in the DRESDEN NOAC and FIRST registries. (A) Intention-to-treat analysis; (B) on-treatment analysis

FIGURE 2 On-treatment Kaplan-Meier event-free survival curves for ISTH major bleeding in the DRESDEN NOAC and FIRST registries

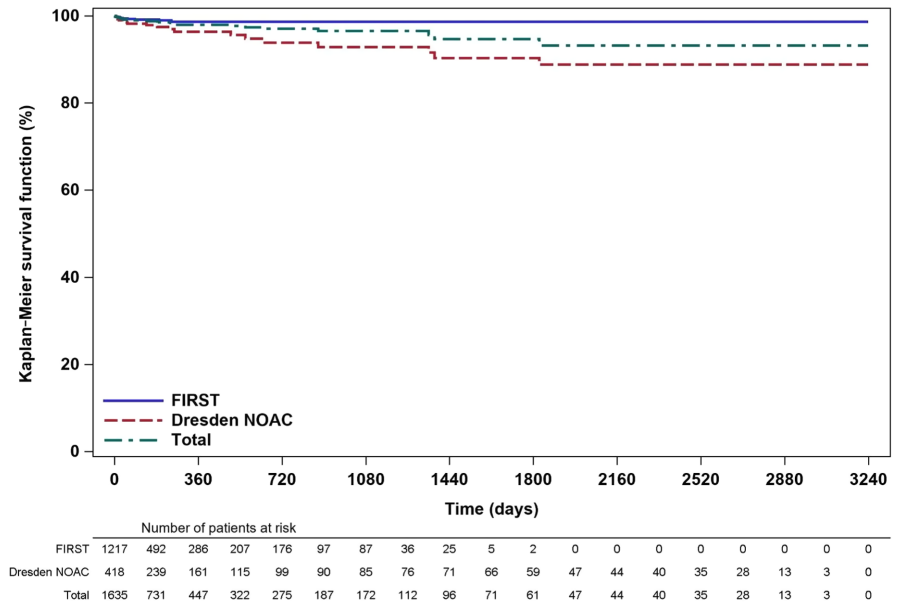
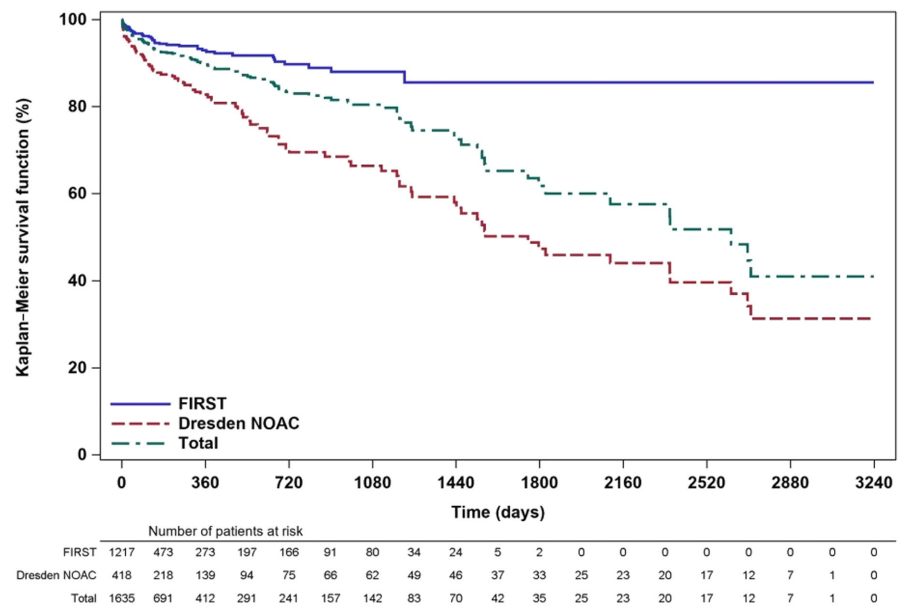


FIGURE 3 On-treatment Kaplan-Meier event-free survival curves for ISTH nonmajor clinically relevant bleeding in the DRESDEN NOAC and FIRST registries



At first glance, methodologies (prospective data collection in consecutive patients treated with rivaroxaban for acute VTE) and some of the baseline characteristics were strikingly similar among the three registries: 75%–80% DVT, with two thirds proximal DVT; median age, 58–64 years; median BMI, 27–28 kg/m². However, some baseline characteristics showed pronounced differences (unprovoked VTE much more frequent in the UK registry compared to the Swiss data set; highest rate of recurrent VTE and of malignant disease in the German registry but lowest rate of “active cancer” in this data set). In addition, cutoffs for “impaired renal function” and definitions of “active cancer” were not similar, and data on concomitant diseases were collected differently among the three registries. Finally, the comparison of treatment durations and clinical outcomes revealed differences among the three registries that limited comparison, especially with the Swiss data set.

The first major finding of our analysis therefore is that comparisons across different registries suffer from relevant limitations, whereas generalizability of single registries may also be limited. As a consequence, data collection in prospective registries should be better standardized and should define detailed methodologies.²⁴ Checklists and guidance documents such as Strengthening the Reporting of Observational Studies in Epidemiology²⁵ are an important step toward such standardization but are often applied to the reporting of research results only and not necessarily in the planning phase of observational studies.

Although we conclude from the differences in baseline characteristics that postbaseline comparisons among the three registries need to be handled with caution, we did observe interesting management patterns across the registries. Probably the most striking difference was related to the median rivaroxaban treatment

duration, which overall was 169 days but considerably shorter in UK patients in the FIRST registry (144 days) compared to German patients from the DRESDEN NOAC registry (214 days). This finding cannot be explained by a higher proportion of patients at high risk for VTE recurrence for whom guidelines recommend extended therapy. In fact, the proportion of patients with an unprovoked index VTE event was somewhat lower in the DRESDEN NOAC registry (61%) compared to the FIRST registry (71%). The most likely explanation for the shorter rivaroxaban treatment in the FIRST registry could be that 40% of patients in the FIRST registry had distal DVT (approximately 80% of those unprovoked) and therefore stopped treatment after 3–6 months. In addition, the DRESDEN NOAC registry applied a much longer follow-up (up to 5 years), enhancing the rivaroxaban exposure with long-term treatments.

Finally, in the pooled outcome analysis of the DRESDEN NOAC registry and FIRST registry, we found that during active rivaroxaban therapy the overall rate of VTE recurrence was as low as 0.86% and affected only 14 of 1635 patients undergoing follow-up. Even in the absence of a comparator arm, it seems reasonable to conclude that this finding across two prospective observational registries performed in two different Western European countries confirms the high efficacy of rivaroxaban seen in the EINSTEIN phase III trials. This confirmation is especially important, since patients in the DRESDEN NOAC registry and FIRST registry were not selected by predefined inclusion and exclusion criteria and tended to be slightly older (mean age, 59 years) than patients in the EINSTEIN trials (mean age, 57 years).⁴

Some of the patients with malignancy were enrolled into one of the three registries before trial evidence or guidelines supported the use of rivaroxaban for the management of cancer-associated thrombosis (CAT). Accordingly, confounding among the patients treated with a DOAC for CAT has to be considered. Unfortunately, within our methodology and the available data, we are unable to speculate on the impact of such a confounder, and also because the definitions of “active cancer” were not consistent among the registries.

It is not surprising that the overall rate of VTE recurrence in the ITT analysis of our cohort (8.8%; $n = 144/1635$) exceeded the ITT event rate reported in the EINSTEIN phase III trials (2.1% for patients treated for 3–12 months). First, most of the observed events occurred after discontinuation of rivaroxaban therapy, and such events would not have been counted in EINSTEIN phase III trials, where patients were censored after stopping rivaroxaban. Second, although the three registries included a large proportion of patients with distal DVT, ITT event rates were only slightly lower than for patients with proximal DVT. Although recurrent VTE was rarely observed during active rivaroxaban therapy, the guideline-recommended short treatment of distal DVT (maximum, 3 months) and the high rate of VTE recurrence after treatment discontinuation contributed a relevant number of recurrent VTE events to the presented data set. Third, it should also be taken into account that the rate of recurrent VTE events in the ITT population in the EINSTEIN trials refers to a maximum follow-up period of 12 months. In our cohort, only 36.8% ($n = 53/144$) of recurrent VTE events occurred

within the first 360 days after enrollment. Therefore, the considerably longer follow-up period in our cohort is an important reason for the higher rate of recurrent VTE events in the ITT population.

Similar considerations apply to the safety signals in our pooled analysis. During rivaroxaban treatment, 29 of 1635 (1.77%) patients in the DRESDEN NOAC registry and FIRST registry reported major bleeding complications. In addition, CRNM bleeding events were reported in our cohort during rivaroxaban treatment, with a crude incidence of 10.03%. In the EINSTEIN phase III trials, absolute rates of ISTH major bleeding events of 1.0% and absolute rates of CRNM bleeding events of 8.6% were reported for patients treated for 3–12 months. In our cohort, 24.1% ($n = 7/29$) of ISTH major bleeding events and 31.1% ($n = 51/164$) CRNM bleeding events occurred after the first 360 days after study inclusion. Again, the significantly longer follow-up period in our cohort could be an important reason for a numerically higher rate of ISTH major and CRNM bleeding events during active treatment with rivaroxaban. Therefore, we conclude that, even in the absence of a comparator arm, our findings confirm the generalizability of safety findings in the large EINSTEIN phase III program.

5 | LIMITATIONS

The results of our work should be interpreted in the context of their limitations. First of all, our study cohort evaluating clinical outcomes consisted of a total of 1841 patients. However, 1217 patients from the FIRST registry and only 418 patients from the DRESDEN NOAC registry were included in the outcome analyses. Outcome data could not be derived from SWIVTER. Thus, treatment effects in our pooled analysis are strongly driven by UK patients from the FIRST registry. In addition, the potential for selection bias cannot be avoided in noninterventional registries, where local physicians are not instructed which type or dosage of treatment patients should receive. In addition, data on race/ethnicity were not available for the DRESDEN NOAC registry and SWIVTER. Therefore, our results may not be generalizable to other settings or cohorts, especially since selection patterns may vary across regional or cultural settings.

Assessment of potential outcome events is based predominantly on patient contacts and patient-derived information. Although all suspected outcome events were adjudicated on the basis of available source documents, it is possible that some events were not reported or were misclassified. Outcome analyses were also not adjusted for competing risks. However, in the DRESDEN NOAC registry and FIRST registry, overall mortality was low (1.71/100 patient-years) and consistent between both registries (1.73 and 1.69/100 patient-years, respectively). As such, death as the most important competing risk was not considered relevant here.

Another limitation is the lack of a direct randomized comparator group. Nevertheless, over the past decade, many large observational studies of VTE treatment with other anticoagulants (VKA, parenteral drugs, DOACs other than rivaroxaban) have been published, enabling the reader to reflect on potential differences in treatment

patterns and outcomes, although indirect comparison in observational research face severe potential for confounding.

Despite all these limitations, the large size of our total cohort of 1841 patients with VTE treated with rivaroxaban and the prospective evaluation of patients from three different registries in three different countries are important strengths of our work. In addition, the long follow-up duration and the central adjudication of suspected outcome events in all three registries are important features to support the generalizability of the EINSTEIN trials.

6 | CONCLUSION

In different prospective observational registries, we found that recurrent VTE and major bleeding are rare events during active rivaroxaban therapy in VTE treatment, which supports the findings from the large EINSTEIN trials. However, our data also indicate significant differences in patient characteristics, management patterns, and outcome data collection across Switzerland, the United Kingdom, and Germany, limiting direct comparisons of unadjusted outcome event rates among registries.

AUTHOR CONTRIBUTIONS

JBW, RA, RP, NK, and DS designed the study and wrote the protocol. SM, LT, LR, JP, and VS collected the data, and KS performed analyses. JBW, SM, and LT wrote the first draft of the manuscript. All authors reviewed and revised the manuscript and approved the submission.

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LR has received speaker fees and travel grant from Bayer, and investigator-initiated research grant and travel grant from Sanofi. RP 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. JP has received an investigator-initiated research grant from Bayer. VS has received speaker fees from Bayer. NK reports grants from Concept Medical, Bard, and Bayer; and personal fees from Bayer, Bard, Medtronic, Boston Scientific, BTG, and Pfizer, outside the submitted work. DS reports employment by Sanofi-Aventis (Suisse) SA, outside the submitted work. JB-W has received honoraria and research support

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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