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Venous thromboembolism therapy with rivaroxaban in daily-care patients: Results from the Dresden NOAC registry

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ABSTRACT

The effectiveness and safety of acute venous thromboembolism (VTE) treatment with rivaroxaban, demonstrated in phase-III trials, needs to be confirmed in daily care.
To confirm the positive results of phase-III VTE treatment trials with rivaroxaban in daily care, we used data from the ongoing, prospective, non-interventional *Dresden NOAC Registry*.
For this analysis, only patients with acute VTE who started rivaroxaban within 14 days after diagnosis of VTE and who were enrolled within these 14 days were evaluated with regard to patient characteristics, treatment persistence and clinical outcomes.
Between December 1st 2011 and 30th September 2016, 418 patients with acute VTE and rivaroxaban treatment were enrolled. During rivaroxaban treatment (median rivaroxaban exposure 206d; median follow-up 862d) rates of recurrent VTE and ISTH major bleeding were 1.9% and 3.8%, respectively. At 6 months. 58.3% of patients were still taking rivaroxaban, 28.2% had a scheduled end of treatment, 7.2% were switched to other anticoagulants, 1.7% had withdrawn their consent and the remaining 3.6% of patients had unplanned complete discontinuation of anticoagulation. After permanent discontinuation of rivaroxaban, 20 patients experienced a recurrent VTE (7 pulmonary embolism ± deep vein thrombosis, 13 deep vein thrombosis) with a mean time between last intake of rivaroxaban and VTE recurrence of 374.3 ± 247.6 days (range 28–927 d).
In daily care patients with acute VTE, rivaroxaban demonstrated high effectiveness with acceptable major bleeding rates. Initial dosing was according to label in over 90% of patients and persistence to rivaroxaban therapy was adequate with low rates of unplanned complete discontinuation.

1. Introduction

Although vitamin K antagonists (VKA) have been the standard anticoagulation therapy for patients with venous thromboembolism (VTE) for decades, they are more and more replaced by direct-acting, non-vitamin K antagonist oral anticoagulants (NOAC), which demonstrate a much better dose–response relationship and less interactions with food or co-medications and, therefore, do not require routine monitoring and frequent dose adjustments [1,2]. The NOAC rivaroxaban is a direct factor Xa inhibitor that is approved for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), based on the results of two large phase III trials (EINSTEIN DVT and EINSTEIN PE), in which rivaroxaban demonstrated non-inferior efficacy to VKA [3–5]. Even more important, in a pooled analysis of the EINSTEIN DVT and PE trials rivaroxaban demonstrated superior safety over VKA with an absolute risk reduction for major bleeding of 0.8%, which translated into a relative risk reduction of 46% [5].

However, the external validity of phase III trials needs to be confirmed in daily-care settings, in which patients may have significant co-morbidities and are treated without a strict protocol under less intense surveillance, also because the specific design of phase-III trial protocols can have a major impact on outcomes [6]. Consequently, observational studies are needed to confirm trial findings of rivaroxaban in daily-care settings. Furthermore, such studies should not only evaluate short-term outcomes of VTE treatment but should include a long-term follow up and also evaluate patients who continue oral anticoagulation beyond the initial therapy as well as patients who discontinue anticoagulation therapy for whatever reason.

Using data from an ongoing large multicentric cross-indicational NOAC registry, we prospectively evaluated the management and long-term outcome of patients with VTE treated with rivaroxaban.

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2. Methods

2.1. Patients

The Dresden NOAC Registry (NCT01588119) is a prospective registry in the administrative district of Dresden (Saxony), Germany. In this ongoing project, a network of >230 physicians from private practices and hospitals are enrolling consecutive NOAC recipients treated for VTE or atrial fibrillation. All patients are prospectively followed up by the central registry office. The design and methodology of the Dresden NOAC Registry has been published previously [7–12]. Inclusion criteria include the indication for NOAC therapy for at least 3 months, availability for telephone follow-up and written informed consent for participation in the registry. No exclusion criteria apply. Patients are followed up by telephone interview 30 days after enrolment and quarterly thereafter to collect data on the efficacy, safety, and management of NOAC therapy in daily care. No formal adjudication of the index DVT/PE event was performed, since diagnosis of acute VTE in Germany is predominantly in the hands of vascular or cardiac specialists and objective testing (mainly with ultrasound for suspected DVT and computed tomography pulmonary angiography or V/Q scan for suspected PE) are readily available, the established standard of care and consistently used across Germany, as has been demonstrated by the TULIPA registry [13].

In the Dresden NOAC registry, all suspected outcome events are reviewed by a central adjudication committee. For this analysis, only patients with acute PE and/or acute distal or proximal lower limb DVT who started rivaroxaban within 14 days after diagnosis of VTE and who were enrolled within these 14 days were evaluated with regard to patient characteristics, treatment persistence and clinical outcomes.

2.2. Outcome measures

To assess effectiveness of rivaroxaban therapy in VTE, the annualized rate of the recurrent VTE was evaluated. If, in case of death, PE could not be ruled out in central adjudication this was regarded as a fatal PE and counted as a recurrent VTE event.

The main safety outcome was the annualized rate of major bleeding according to the International Society on Thrombosis and Hemostasis (ISTH) definition [14]. Further safety outcomes were rates of ISTH non-major clinically relevant (NMCR) bleeding, minor bleeding and all-cause mortality.

Outcomes are reported for days 90, 180, 365 and >365.

To put outcome event rates into perspective with available real-world data in the discussion section, a formal literature search was performed on June 15; 2017 using the search terms “rivaroxaban” in combination with “deep vein thrombosis”; “DVT”; “pulmonary embolism”; “PE” and “real world”.

2.3. Treatment discontinuation

In accordance with previously published analyses from atrial fibrillation cohorts, treatment discontinuation was defined as a permanent discontinuation or an unscheduled interruption of rivaroxaban for longer than 4 weeks without the initial plan to restart rivaroxaban [15]. This included patients who were permanently switched to another anticoagulant. In contrast, treatment persistence was defined as the continuation of rivaroxaban therapy over the entire follow-up period, allowing for temporary interruptions. At every visit, any change in anticoagulant therapy was assessed, and the reasons for this decision as well as the future treatment plan were obtained from patients or attending physicians. Missing values were left blank and not replaced by imputation.

2.4. Statistics

Two different analysis sets were defined and evaluated:

a) The overall rate of recurrent VTE was evaluated in the *intention-to-treat analysis*, including all VTE patients who were enrolled in the registry and received rivaroxaban for acute VTE at baseline. 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.
b) Furthermore, rates of recurrent VTE events on treatment and rates of bleeding complications (all, major, and NMCR bleeding) were evaluated in the *on-treatment analysis*. This analysis also included all VTE patients enrolled in the rivaroxaban group at baseline, but only outcome events that occurred during rivaroxaban treatment or within 3 days after last intake of rivaroxaban (in case of temporary interruption or permanent discontinuation of treatment) were included.

The statistical analysis plan of the *Dresden NOAC Registry* specifies the appropriate tests used to evaluate for significant differences for patient characteristics at baseline or outcome event rates during follow-up, which is relevant for all included patients. However, although such analyses were performed for our atrial fibrillation cohorts [12,16,17], no such tests for statistically significant differences were performed for subgroups of VTE patients because of the much smaller sample size of the VTE cohort and it's subgroups (DVT vs. PE; provoked vs. unprovoked VTE). As a consequence, such subgroup analyses are presented in a descriptive manner only and numerical differences were not assessed for statistical significance to avoid type 2 error.

Baseline characteristics 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.

In both the intention-to-treat and the on-treatment analysis set, outcome event rates were calculated using Kaplan–Meier time-to-first-event analysis, with data presented as events per 100 patient-years with their 95% CIs, using the following formula: Event rate = number of events/total time under risk (defined as the sum of all days from inclusion in the registry until the day of the first event divided by 100 × 365 days and 100 patient-years as its unit). Corresponding CIs and *P*-values were calculated using the Poisson distribution.

In addition, the following sensitivity analyses were performed as Kaplan-Meier time-to-first event analyses:

- Recurrent VTE during the acute phase until day 90 for patients who started rivaroxaban within 72 h; 3–7 days or 8–14 d after VTE diagnosis
- Recurrent VTE during the acute phase until day 90 for patients who were treated for provoked by major transient trigger vs. minor transient or persistent trigger vs. unprovoked VTE. Major transient triggers included immobilization or surgery within 4 weeks prior to VTE diagnosis; active cancer; pregnancy. Minor triggers included long-distance travel, acute infectious diseases without immobilization; estrogen use; obesity with BMI >30; smoking; family history of VTE
- Net clinical benefit (defined as recurrent VTE and/or major bleeding and/or all-cause mortality) for patients who had a scheduled end of treatment at 6 months and stopped rivaroxaban between days 150–210 vs. those who were selected to continue rivaroxaban beyond 210 days (which were censored at the day of rivaroxaban discontinuation in case of later treatment cessation)

All statistical analyses were carried out using the IBM® SPSS® Statistics version 19, software package SAS release 9.4 (SAS Institute), and R version 3.1.0 (Comprehensive R Archive Network) with RStudio version 0.98.953.

2.5. Ethics

The study protocol of the Dresden NOAC Registry was approved by the local ethics committee at the Technical University Dresden (AZ EK 349092011) and registered at ClinicalTrials.gov (NCT01588119). The study complies with the principles and requirements of the Declaration of Helsinki. All patients provided written informed consent, including a data protection waiver, before enrolment.

3. Results

Between December 1st 2011 and 30th September 2016, a total of 878 patients receiving rivaroxaban for VTE treatment were enrolled. Of these, 418 patients were treated for acute lower limb DVT and/or PE, started rivaroxaban and were enrolled into the registry within 14 days after VTE diagnosis (Fig. 1). These patients constituted the study cohort for the present analysis and, of these, 337 (80.6%) were enrolled with isolated DVT without confirmed PE and 81 (19.4%) patients had an objectively confirmed PE with or without DVT. Overall, 48.3% were male and mean age was 60.8 ± 17.2 years. Details on patient characteristics and index VTE are presented in Table 1. Mean time between VTE diagnosis and initiation of rivaroxaban was 1.8 ± 3.4 days (median 0 d; IQR 0–2 d) and numerically longer for PE vs. DVT (mean 3.7 ± 3.7 days vs. 1.4 ± 3.1 days). At baseline, rivaroxaban doses consisted of 15 mg BID in 92.3%, 20 mg OD in 4.3%, 15 mg OD in 3.1% and 10 mg OD in 0.2% of patients. Reasons for not using 2 × 15 mg rivaroxaban BID were pre-treatment with therapeutic parenteral anticoagulants for ≥7 days in 18 cases, comorbidities (e.g. bleeding history, renal impairment) in 4 cases and not reported in the remaining 10 cases.

During follow-up (FU) (mean 911 ± 483 d; median 862 d; IQR 470–1356 d), the mean rivaroxaban exposure was 403 ± 440 days (median 206 d IQR 105–449 d). During this time, a total of 32 patients (7.7%) experienced a recurrent VTE, which translated into a recurrence rate of 3.2/100 pr. years (95% CI 2.2–4.5) for the intention-to-treat population.

During active treatment with rivaroxaban, 8/418 patients (1.9%) experienced a recurrent VTE, which translated into a recurrence rate of 1.8/100 pt. years (95% CI 0.8–3.5) for the on-treatment population. VTE recurrence rates were highest during the first 90 days of therapy (Table 2; Fig. S1).

A total of 190 patients (45.5%; 73.5/100 pt. years; 95% CI 63.4–84.7) reported any bleeding events during rivaroxaban exposure. ISTH major bleeding occurred in 16 cases (3.8%; 3.5/100 pt. years; 95% CI 2.0–5.7), including one fatal intracranial bleeding. Furthermore, NMCR bleeding events occurred in 74 cases (17.7%; 18.8/100 pt. years; 95% CI 14.8–23.6).

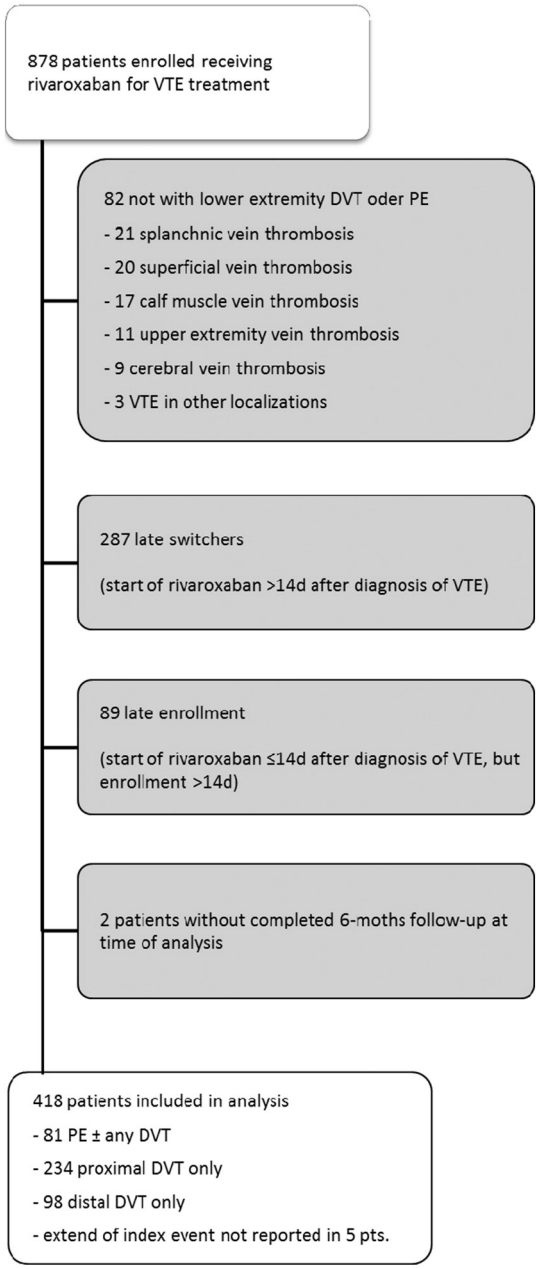

Figure 1. Flowchart of study cohort.

During rivaroxaban treatment, rates for recurrent VTE were numerically higher in patients with DVT as an index event (2.1/100 pt. years; 95% CI 0.6–3.8) compared to PE as an index event (0.9/100 pt. years; 95% CI 0.02–4.9) but rates of major bleeding were comparable (3.5/100 pt. years [95% CI 1.8–6.1] vs. 3.5/100 pt. years [95% CI 0.9–8.9]). Effectiveness and safety profiles were consistent across relevant subgroups (Table S1 and Figs. S2 and S3).

During follow-up, 20 patients died (1.9/100 pt. years; 95% CI 1.2–3.0), of which 9 deaths occurred during or within 3 days after last intake of rivaroxaban (1.9/100 pt. years; 95% CI 0.9–3.7). Most common causes of death were fatal cardiovascular event ($n = 8$; including 2 cases of confirmed fatal PE and 3 cases of sudden cardiac death which were ruled as PE, although all three patients had severe cardiac disease), terminal malignant disease ($n = 5$), sepsis/infection ($n = 3$), age related death ($n = 2$), fatal bleeding ($n = 1$) and other causes (n = 1).

At 6 months (FU completed in 415 pts.), 411 patients were still alive. Of these, 58.3% were still taking rivaroxaban, 28.2% had a scheduled end of treatment, 7.2% were switched to other anticoagulants, 1.7% had withdrawn their consent and the remaining 3.6% of patients had unplanned complete discontinuation of anticoagulation. At 12 months (FU completed in 386 pts.), 380 patients were still alive. Of these, 38.2% of patients were still taking rivaroxaban. The remaining patients had a scheduled end of treatment (45.3%), were switched to other anticoagulants (8.7%), had withdrawn consent (1.8%) or had an unplanned complete discontinuation at 12 months (6.1%).

In the subgroup of 299 patients who permanently discontinued rivaroxaban for any reason and at any time, 20 patients experienced a recurrent VTE (7 PE ± DVT, 13 DVT), which translated into a recurrence rate of 3.6/100 pt. years (95% CI 2.2–5.6). Mean time between last intake of rivaroxaban and VTE recurrence was 374.3 ± 247.6 days (range 28–927 d). Interestingly, 18/20 patients who developed recurrent VTE after oral anticoagulation (OAC) discontinuation had a scheduled end of anticoagulant treatment as the reason for discontinuation and 6 of them were switched to low-dose aspirin, whereas the remaining 12 patients did not receive any antithrombotic therapy. The 19th patient was scheduled to receive long-term OAC but rivaroxaban was stopped due to frequent falls. This patient was switched to low-dose aspirin, which did not prevent VTE recurrence. The 20th patient was scheduled to receive long-term OAC but rivaroxaban was stopped by the family physician for unknown reasons. This patient received no further antithrombotic therapy until the recurrent VTE event.

Despite discontinuation of oral anticoagulation in 299 patients, major bleeding still occurred in 3 patients (1.0%; Table S2), which translated into an anticoagulation-unrelated major bleeding rate of 0.5/100 pt. years (95% CI 0.1–1.5). Fig. S4 demonstrates the impact on the physicians' choice at 6 months to either discontinue rivaroxaban electively (between days 150–210) or to continue beyond 6 months. During

Table 1
Patient characteristics at baseline.

	All $n = 418$	DVT $n = 337$	PE ± DVT $n = 81$
Male, n (%)	202/418 (48.3)	156/337 (46.3)	46/81 (56.8)
Mean age (SD)	60.8 ± 17.2	61.0 ± 17.3	60.1 ± 16.8
Number of concomitant drugs, mean (SD)	3.1 ± 2.9	3.0 ± 2.9	3.7 ± 3.2
Mean time between VTE diagnosis and initiation of rivaroxaban (SD)	1.8 ± 3.4	1.4 ± 3.1	3.7 ± 3.7
Unprovoked event VTE, n (%)	91/418 (21.8)	78/337 (23.1)	13/81 (16.0)
Event VTE provoked by minor persistent or transient triggers, n (%)	193/418 (46.2)	151/337 (44.8)	42/81 (51.9)
Event VTE provoked by major transient triggers, n (%)	134/418 (32.1)	108/337 (32.0)	26/81 (32.1)
Recurrent event VTE, n (%)	128/418 (30.6)	105/337 (31.2)	23/81 (28.4)
Proximal vs. distal DVT, n (%) (extend of index event not reported in 5 pts.)	234/418 (56) 98/418 (23.4)	234/337 (69.4) 98/337 (29.1)	n.a.
Confirmed thrombophilia, n (%)	27/418 (6.5)	22/337 (6.5)	5/81 (6.2)
Malignant disease, n (%)	47/418 (11.2)	34/337 (10.1)	13/81 (16.0)
- Active cancer, n (%)	11/418 (2.6)	7/337 (2.1)	4/81 (4.9)
Glomerular filtration rate (GFR) < 50 ml/min, n (%)	35/418 (8.4)	32/337 (9.5)	3/81 (3.7)
- GFR 30–50 ml/min, n (%)	31/418 (7.4)	28/337 (8.3)	3/81 (3.7)
- GFR < 30 ml/min, n (%)	4/418 (1.0)	4/337 (1.2)	0
Thrombolytic therapy before enrolment	12/418 (2.9)	3/337 (0.9)	9/81 (11.1)

Table 2
Outcome event rates according to treatment phase and treatment continuation.

n = 418	Events at 90 days		Events at 180 days		Events at 365 days		Events >365 days	
	ITT	On treatment	ITT	On treatment	ITT	On treatment	ITT	On treatment
Recurrent VTE; n (%)	5 (1.2)	5 (1.2)	3 (0.7)	1 (0.2)	4 (1.0)	0	20 (4.8)	2 (0.5)
Fatal VTE; n (%)	0	0	2 (0.5)	0	0	0	3 (0.7)	1 (0.2)
Major bleeding; n (%)	8 (1.9)	7 (1.7)	1 (0.2)	1 (0.2)	5 (1.2)	4 (1.0)	6 (1.4)	4 (1.0)
Fatal bleeding; n (%)	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Mortality; n (%)	5 (1.2)	3 (0.7)	3 (0.7)	0	2 (0.5)	2 (0.5)	10 (2.4)	4 (1.0)

ITT = intention- to-treat population, which includes all outcome events during follow-up, irrespective of anticoagulation status; VTE = venous thromboembolism.

the follow-up period, the Kaplan-Meier curves for the combined endpoint of recurrent VTE, major bleeding and all-cause mortality overlapped until day 720 but separated due to slightly higher event rates in the discontinuation arm, although this observation as based on small numbers only. Of note, due to the small cohort size, no adjustment for differences in baseline characteristics, VTE or bleeding risk factors was performed.

4. Discussion

In a large cohort of patients treated with rivaroxaban for acute VTE in daily care, we confirmed the effectiveness and safety of rivaroxaban seen in phase III studies. In the EINSTEIN phase III trials which did not report annualized rates, absolute rates of recurrent VTE and ISTH major bleeding were 2.1% and 1.0% respectively for patients treated for 3–12 months [3,4]. In our study, recurrent VTE occurred in 1.9% of patients (1.8/100 pt. years) and ISTH major bleeding in 3.8% of patients (3.5/100 pt. years). The higher event rates seen in our study may partly be explained by the fact that no exclusion criteria were applied, whereas phase-III trials restrict enrolment of patients at unacceptably high risk for complications by defining explicit inclusion and exclusion criteria. Furthermore, mean age of our cohort (60.8 years) was higher than that in the EINSTEIN trials (mean 57.0 years) [5]. Finally, the majority of patients in the EINSTEIN studies were treated for only 6 months and, therefore, neither our crude bleeding incidences nor our annualized bleeding event rates, derived from a cohort with considerably longer treatment duration, can be directly compared to the EINSTEIN data. Other important observations in our study were the low rate of unscheduled premature discontinuation (3.6% at 6 months) as well as the clear trend towards prolonged treatment, since nearly 60% of patients were treated for longer than 6 months, which is in line with the large proportion of unprovoked or recurrent VTE in our cohort and, thus, in line with current guideline recommendations.

Our data are not the first real-life data for VTE treatment with rivaroxaban. Prospective registries such as XALIA [18] and RIETE [19], retrospective registries such as SWIVTER [20] as well as retrospective claim database analyses [21–23] have recently reported effectiveness and safety data for rivaroxaban in VTE treatment (Table 3). However, all of these analyses have only reported short-term outcomes with follow-up durations of 90–180 days only, with the exception of XALIA, which reported follow-up of 239 days [18]. Furthermore, Table 3 demonstrates the results of our systematic literature search on real-world evidence for VTE treatment with rivaroxaban. It highlights that previously reported real-world studies on VTE treatment with rivaroxaban often lacked important information (such as rivaroxaban dosing, treatment persistence, outcome after rivaroxaban discontinuation, proportion of provoked VTE, PE patients or patients with cancer), allowed for late switches to rivaroxaban [20], did not include VTE patients diagnosed in an outpatient setting [20–22,24] or did not use central outcome event adjudication [19–23]. In contrast, our study provides a comprehensive set of data that covers most of these limitations of previous reports.

Despite the differences in patient characteristics and outcome assessments, our data are very much in line with most of the outcome data in previous real-world studies in which VTE recurrence ranged between 1.2 and 3.0% (1.9% in our study). Similarly, our findings were in line with the previously reported major bleeding rates, which ranged between 0.2 and 2.4% in short-term follow up (3.8% in our study for 911d of follow-up). Taken together, all real-world studies on rivaroxaban VTE treatment reported so far used very different methodologies, somewhat different populations and outcome event definitions with or without central event adjudications but still confirmed consistently the benefits of rivaroxaban seen in the EINSTEIN trial program [3,4].

In addition to available real-world data for VTE treatment with rivaroxaban, our study includes long periods on and off rivaroxaban treatment and relevant subgroups analyses such as PE vs. DVT, or provoked vs. unprovoked VTE. Our data indicate that a large proportion of patients is currently treated for longer than 3–6 months (up to 40% were still taking rivaroxaban at 12 months), that rates of recurrent VTE and major bleeding in long-term treatment are low (compared to the moderately higher rates in the first 3 months) and that the risk of VTE recurrence is high after discontinuation of rivaroxaban even in patients perceived to be candidates for scheduled discontinuation, while these patients still have a residual risk of major bleeding complications after treatment discontinuation.

Although our net clinical benefit analyses of patients with and without treatment need to be interpreted with great caution, the finding is at least hypothesis generating. Since it can be assumed that patients at higher risk for recurrence were selected to continue with rivaroxaban (which also introduced a treatment-related bleeding risk), the net clinical benefit in these patients was similar to those who were perceived to be at low risk for VTE recurrence and were selected to discontinue oral anticoagulation. This latter group demonstrated a relevant risk for VTE recurrence and also some anticoagulation-unrelated major bleeding events occurred. The recently published EINSTEIN CHOICE trial addressed this common clinical problem in long-term VTE care and indicated that low-dose rivaroxaban (10 mg/d) has the potential to offer a long-term treatment with a favourable benefit/risk profile [25]. This would be particularly desirable for those patients in whom full-dose rivaroxaban is prematurely discontinued in spite of an unprovoked presentation or for cases in whom VTE was associated with persistent risk factors but may also impact the decision for or against treatment continuation in some patients previously regarded as candidates for scheduled discontinuation. However, the use of 10 mg rivaroxaban for long-term VTE treatment is currently not licensed and, after approval, its effectiveness and safety will also need to be confirmed in real-world cohorts.

5. Limitations

There are several limitations to our study, which have been discussed in detail in our previous publications [9,11,16,26].

5.1. Sample size and potential for selection bias

Our cohort consisted of 418 patients, and our sample size as well as the small number of outcome events may have been too small to detect statistically significant signals, which is especially true for our subgroup analyses. The design of our registry introduces the possibility of a

Table 3
Available real-word data on the effectiveness and safety of VTE treatment with rivaroxaban.

Study	Study design	Central event adjudication	Data on rivaroxaban persistence	Data on rivaroxaban dosing	Outcome data after stopping rivaroxaban	Rivaroxaban initiation in acute phase	Sample size rivaroxaban cohort	In- and out-patients	Mean age	Pro-portion of PE	Unprovoked VTE	cancer	Duration of follow-up	VTE recurrence during rivaroxaban-ban treatment	Major bleeding during rivaroxaban-ban treatment
Present study	Prospective single cohort registry	Yes	Yes	Yes	Yes	Yes	418	Both	60.8 y	19%	22%	11%	911 d	1.9% (1.8/100 pt. years)	ISTH: 3.8% (3.5/100 pt. years)
XALIA [18]	Prospective cohort registry	Yes	Yes	Yes	Ø	Yes	2619	Both	59 y	8%	65%	6%	239 d	1.4%	ISTH: 0.7%
SWIVTER [20]	Retrospective registry (only pts. with available 90 d FU were included)	Ø	Ø	Ø	Ø	Acute and late starters	417	Inpatient only	56 y	38%	Unk	10%	90 d	1.2%	ISTH: 0.5%
RIETE [19]	Prospective cohort registry	Ø	Ø	Yes	Ø	Yes	1591	Both	58 y	53%	42%	7%	360 d	Not specifically reported	Not specifically reported
REMOTEV [24]	Prospective cohort registry	Yes	Yes	Ø	Ø	Yes	308	Inpatient only	62 y	90%	83%	15%	180 d	2.4%	ISTH: 1.1%
Coleman et al. [21]	Retrospective claim database analysis	Ø	Ø	Ø	Ø	Yes	3466	Inpatient only	Unk	100%	Unk	Unk	90 d	1.7% ad-mission for recurrent VTE	0.2% ad-mission for bleeding
Sindet-Pedersen et al. [23]	Retrospective claim database analysis	Ø	Ø	Ø	Ø	Yes	5411 (2161 excluded from propensity score matching)	Inpatient and out-patient clinic	Median: 66 y	Unk	Unk	Unk	180 d; Starting 7 days post discharge only	3.0%	Pre-defined ICD-10 codes: 2.3%
Larsen et al. [22]	Retrospective claim database analysis	Ø	Ø	Ø	Ø	Yes	1751	Inpatient only	62.6 y	Unk	100%	Unk	180d	9.8/100 pt. years	Pre-defined ICD-10 codes: 2.4/100 pt. years

selection bias, because local physicians within the network are not instructed on which of their patients should receive which type or dosage of oral anticoagulant therapy.

5.2. Lack of randomized comparator

The lack of a direct randomized comparator group needs to be regarded as a limitation. However, many large observational VTE treatment studies exist from the VKA era [27] and data on VKA complications and VKA treatment discontinuation are well established [28]. In addition, large claim database analyses have attempted to compare VTE treatment of rivaroxaban with VKA [21,22] using propensity score matching. Although this is certainly an important and valid statistical approach it should be noted that matching will not completely rule out residual confounding, also, because a relevant proportion of patients are often not eligible for matching.

Despite these potential limitations, in comparison to existing real-world data on rivaroxaban VTE treatment, the long follow-up duration, the prospective data collection at patient level in daily-care patients, and the central adjudication of effectiveness and safety outcomes are significant advantages of our study.

6. Conclusion

In daily care, rivaroxaban treatment for acute VTE is effective and acceptably safe. We found initial rivaroxaban dosing to be in accordance with label in over 90% of patients and, at 6 and 12 months, persistence to rivaroxaban therapy was high with low rates of unplanned complete discontinuation. Fatal VTE and fatal bleeding are rare events during rivaroxaban therapy and all-cause mortality is mostly related to underlying diseases, age or acute conditions. Treatment discontinuation resulted in a relevant increase in VTE recurrence, of which >40% manifested as PE. In contrast, major bleeding rates declined after discontinuation but with 1%/year remained at a clinically relevant level, probably due to co-morbidities. Consequently, the concept of low-dose rivaroxaban in secondary VTE prevention needs further evaluation.

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Conflict of interest

J.B.-W. has received honoraria and research support from Bayer HealthCare, Boehringer Ingelheim, Daiichi Sankyo, Pfizer and Portola. S.M. has received honoraria from Bayer HealthCare and Daiichi Sankyo. None of the other authors declared a conflict of interest with regard to the NOAC registry or this manuscript.

Authors' contributions

J.B.-W. has designed this analysis. L.T. has written the first draft of the manuscript. L.K., S.M. and J.H. have collected the data. K.S. and L.T. has performed the statistical analyses and drafted the figures. All authors have provided significant contributions to the written presentation, have critically reviewed and approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2017.10.097.

References

[1] C. Kearon, E.A. Akl, J. Ornelas, A. Blaivas, D. Jimenez, H. Bounameaux, et al., Antithrombotic therapy for vte disease: chest guideline and expert panel report, Chest 149 (2) (2016) 315–352.
[2] H. Heidbuchel, P. Verhamme, M. Alings, M. Antz, W. Hacke, J. Oldgren, et al., European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation, Europace 15 (5) (2013) 625–651.
[3] Einstein-Investigators, R. Bauersachs, S.D. Berkowitz, B. Brenner, H.R. Buller, H. Decousus, et al., Oral rivaroxaban for symptomatic venous thromboembolism, N. Engl. J. Med. 363 (26) (2010) 2499–2510.
[4] Einstein-PE-Investigators, H.R. Buller, M.H. Prins, A.W. Lensin, H. Decousus, B.F. Jacobson, et al., Oral rivaroxaban for the treatment of symptomatic pulmonary embolism, N. Engl. J. Med. 366 (14) (2012) 1287–1297.
[5] M.H. Prins, A.W. Lensing, R. Bauersachs, B. van Bellen, H. Bounameaux, T.A. Brighton, 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. 11 (1) (2013) 21.
[6] J. Beyer-Westendorf, A.W. Lensing, R. Arya, H. Bounameaux, A.T. Cohen, P.S. Wells, et al., Choosing wisely: the impact of patient selection on efficacy and safety outcomes in the EINSTEIN-DVT/PE and AMPLIFY trials, Thromb. Res. 149 (2017) 29–37.
[7] J. Beyer-Westendorf, V. Gelbricht, K. Forster, F. Ebertz, C. Kohler, S. Werth, et al., Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry, Eur. Heart J. 35 (28) (2014) 1888–1896.
[8] J. Beyer-Westendorf, V. Gelbricht, K. Forster, F. Ebertz, D. Rollig, T. Schreier, et al., Safety of switching from vitamin-K antagonists to dabigatran or rivaroxaban in daily care - results from the Dresden NOAC registry, Br. J. Clin. Pharmacol. 78 (4) (2014) 908–917.
[9] J. Beyer-Westendorf, K. Forster, S. Pannach, F. Ebertz, V. Gelbricht, C. Thieme, et al., Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry, Blood 124 (6) (2014) 955–962.
[10] J. Beyer-Westendorf, F. Ebertz, K. Forster, V. Gelbricht, F. Michalski, C. Kohler, et al., Effectiveness and safety of dabigatran therapy in daily-care patients with atrial fibrillation. Results from the Dresden NOAC registry, Thromb. Haemost. 113 (6) (2015).
[11] F. Michalski, L. Tittl, S. Werth, U. Hansel, S. Pannach, K. Sahin, et al., Selection, management, and outcome of vitamin K antagonist-treated patients with atrial fibrillation not switched to novel oral anticoagulants. Results from the Dresden NOAC registry, Thromb. Haemost. 114 (5) (2015) 1076–1084.
[12] J. Hecker, S. Marten, L. Keller, S. Helmert, F. Michalski, S. Werth, et al., Effectiveness and safety of rivaroxaban therapy in daily-care patients with atrial fibrillation. Results from the Dresden NOAC registry, Thromb. Haemost. 115 (5) (2016) 939–949.
[13] S.M. Schellong, H. Gerlach, V. Hach-Wunderle, E. Rabe, H. Riess, H. Carnarius, et al., Diagnosis of deep-vein thrombosis: adherence to guidelines and outcomes in real-world health care, Thromb. Haemost. 102 (6) (2009) 1234–1240.
[14] S. Schulman, C. Kearon, Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients, J. Thromb. Haemost. 3 (4) (2005) 692–694.
[15] J. Beyer-Westendorf, K. Forster, F. Ebertz, V. Gelbricht, T. Schreier, M. Gobelt, et al., Drug persistence with rivaroxaban therapy in atrial fibrillation patients-results from the Dresden non-interventional oral anticoagulation registry, Europace 14 (4) (2015) 530–538.
[16] J. Beyer-Westendorf, F. Ebertz, K. Forster, V. Gelbricht, F. Michalski, C. Kohler, et al., Effectiveness and safety of dabigatran therapy in daily-care patients with atrial fibrillation. Results from the Dresden NOAC registry, Thromb. Haemost. 113 (6) (2015) 1247–1257.
[17] S. Helmert, S. Marten, H. Mizera, A. Reitter, K. Sahin, L. Tittl, et al., Effectiveness and safety of apixaban therapy in daily-care patients with atrial fibrillation: results from the Dresden NOAC Registry, J. Thromb. Thrombolysis 44 (2) (2017) 169–178.
[18] W. Ageno, L.G. Mantovani, S. Haas, R. Kreutz, D. Monje, J. Schneider, et al., Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study, Lancet Haematol. 3 (1) (2016) e12–21.
[19] J. Trujillo-Santos, P. Di Micco, F. Dentali, J. Douketis, J.A. Diaz-Peromingo, M.J. Nunez, et al., Real-life treatment of venous thromboembolism with direct oral anticoagulants: the influence of recommended dosing and regimens, Thromb. Haemost. 117 (2) (2017) 382–389.
[20] N. Kucher, D. Aujesky, J.H. Beer, L. Mazzolai, T. Baldi, M. Banyai, et al., Rivaroxaban for the treatment of venous thromboembolism. The SWIss venous ThromboEmbolism registry (SWIVTER), Thromb. Haemost. 116 (3) (2016) 472–479.

[21] C.I. Coleman, G.J. Fermann, E.R. Weeda, P.S. Wells, V. Ashton, C. Crivera, et al., Is rivaroxaban associated with shorter hospital stays and reduced costs versus parenteral bridging to warfarin among patients with pulmonary embolism? Clinical and Applied Thrombosis/Hemostasis : Official Journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 23 (7) (2017) 830–837.
[22] T.B. Larsen, F. Skjoth, J.N. Kjaeldgaard, G.Y.H. Lip, P.B. Nielsen, M. Sogaard, Effectiveness and safety of rivaroxaban and warfarin in patients with unprovoked venous thromboembolism: a propensity-matched nationwide cohort study, Lancet Haematol. 4 (5) (2017) e237–e244.
[23] C. Sindet-Pedersen, J. Langtved Pallisgaard, L. Staerk, T.A. Gerds, E.L. Fosbol, C. Torp-Pedersen, et al., Comparative safety and effectiveness of rivaroxaban versus VKAs in patients with venous thromboembolism. A Danish nationwide registry-based study, Thromb. Haemost. 117 (6) (2017) 1182–1191.
[24] S. Gaertner, E.M. Cordeanu, S. Nouri, A.M. Faller, A.S. Frantz, C. Mirea, et al., Rivaroxaban versus standard anticoagulation for symptomatic venous thromboembolism (REMOTEV observational study): analysis of 6-month outcomes, Int. J. Cardiol. 226 (2017) 103–109.
[25] J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, et al., Rivaroxaban or aspirin for extended treatment of venous thromboembolism, N. Engl. J. Med. 376 (13) (2017) 1211–1222.
[26] J. Beyer-Westendorf, K. Forster, F. Ebertz, V. Gelbricht, T. Schreier, M. Gobelt, et al., Drug persistence with rivaroxaban therapy in atrial fibrillation patients-results from the Dresden non-interventional oral anticoagulation registry, Europace 17 (4) (2015) 530–538.
[27] V.J. Willey, M.F. Bullano, O. Hauch, M. Reynolds, G. Wygant, L. Hoffman, et al., Management patterns and outcomes of patients with venous thromboembolism in the usual community practice setting, Clin. Ther. 26 (7) (2004) 1149–1159.
[28] L.A. Linkins, P.T. Choi, J.D. Douketis, Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis, Ann. Intern. Med. 139 (11) (2003) 893–900.