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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still taking rivaroxaban, 28.2% had a scheduled end of treatment, 7.2% were switched to other anticoagulants, 1.7% had withdrawn their consent and the remaining 3.6% of patients had unplanned complete discontinuation of anticoagulation.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.

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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).

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