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Drug persistence with rivaroxaban therapy in atrial fibrillation patients—results from the Dresden non-interventional oral anticoagulation registry

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Aims Worldwide, rivaroxaban is increasingly used for stroke prevention in atrial fibrillation (SPAF) but little is known about the rates of or reasons for rivaroxaban discontinuations in daily care. Using data from a prospective, non-interventional oral anticoagulation (NOAC) registry, we analysed rivaroxaban treatment persistence.

Methods and results Persistence with rivaroxaban in SPAF was assessed in an ongoing, prospective, non-interventional registry of >2600 NOAC patients from daily care using the Kaplan–Meier time-to-first-event analysis. Reasons for and management of rivaroxaban discontinuation were assessed. Potential baseline risk factors for treatment discontinuation were evaluated using Cox regression analysis. Between October 2011 and April 2014, 1204 rivaroxaban SPAF patients were enrolled [39.3% switched from vitamin K antagonists (VKAs) and 60.7% newly treated patients]. Of these, 223 patients (18.5%) stopped rivaroxaban during follow-up (median 544 days), which translates into a discontinuation rate of 13.6 (95% CI 11.8–15.4) per 100 patient-years. Most common reasons for treatment discontinuations were bleeding complications (30% of all discontinuations), followed by other side-effects (24.2%) and diagnosis of stable sinus rhythm (9.9%). A history of chronic heart failure (HR 1.43; 95% CI 1.09–1.87; $P = 0.009$) or diabetes (HR 1.39; 95% CI 1.06–1.82; $P = 0.018$) were the only statistically significant baseline risk factors for rivaroxaban discontinuation. After discontinuation of rivaroxaban, patients received antiplatelet therapy (31.8%), VKA (24.2%), another NOAC (18.4%), heparin (9.9%), or nothing (15.7%).

Conclusion Our data indicate that overall persistence with rivaroxaban therapy is high, with a discontinuation rate of ~15% in the first year of treatment and few additional discontinuations thereafter.

Keywords NOAC • Anticoagulants • Atrial fibrillation • Persistence • Rivaroxaban

Introduction

For over more than five decades, vitamin K antagonists (VKAs) had been the standard of long-term anticoagulation in indications such as stroke prevention in atrial fibrillation (SPAF). Although effective, VKA therapy is complicated due to the significant inter-individual variations in metabolism, numerous drug–drug interactions, and the interaction with dietary intake of vitamin K.[1] Therefore, routine monitoring of the anticoagulation intensity is necessary but, despite this, bleeding and other complications are common. As a result, patients often discontinue VKA therapy and discontinuation rates of up to 30% in the first year and up to 50% within 3 years of treatment initiation have been reported.[2,3] In addition to this high rate of VKA discontinuation, up to 40–50% of SPAF patients in daily care do not even start with VKA therapy, mostly due to a fear of complications.[4]

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What's new?

- Our data indicate for the first time that discontinuation rates of rivaroxaban in daily care SPAF patients are around 15% in the first year and very low thereafter.
- Thus, persistence with rivaroxaban in daily care is much higher than that reported for vitamin-K antagonists.

The non-VKA oral anticoagulant (NOAC) rivaroxaban is a selective inhibitor of the activated coagulation Factor X. It has an excellent dose–response relationship, few drug–drug interactions and no drug–food interactions. As a consequence, no routine coagulation monitoring is required and patients can be treated with a fixed dose regimen. In the large phase III trial in SPAF, ROCKET AF, both warfarin and rivaroxaban demonstrated high efficacy and safety,[5] and treatment discontinuation rates were comparable for VKA (22.2%) and rivaroxaban (23.7%). However, the external validity of this finding is questionable, given that strict inclusion and exclusion criteria in Phase III trials may select a trial population that is different from the patient population treated in daily routine and the intensive and highly specialized treatment in trial sites may lead to lower discontinuation rates. On the other hand, the complicated setting of a trial that uses a double-blind, double-dummy design may also have an impact and may actually increase discontinuation. In addition, the double-blind, double-dummy design may have prevented the detection of differences between both treatment arms regarding discontinuation rates. Because continuous anticoagulant treatment is crucial for providing optimal stroke protection in atrial fibrillation (AF), treatment persistence needs to be assessed prospectively in daily care cohorts and risk factors, and the management of rivaroxaban discontinuation needs to be evaluated.

Using data from a large, prospective, multicentre NOAC registry, the following objectives were addressed:

(i) Rates of rivaroxaban discontinuation in daily care SPAF patients.
(ii) Reasons for rivaroxaban discontinuation and following alternative treatments.
(iii) Risk factors for rivaroxaban discontinuation.

Methods

Patients

The Dresden NOAC registry (NCT01588119) has been extensively described elsewhere.[6,7] It is a large, prospective registry of patients treated with a NOAC which are enrolled by a network of over 230 physicians. Patients are followed up by telephone visits at 30 days and quarterly thereafter to collect data on the management of NOAC therapy in daily care.

Data collection and assessment of treatment persistence

In the registry, all patients were asked about the current anticoagulant therapy during every visit. In addition, at 12-month follow-up visits, the drug prescription sheets were obtained from the attending physicians for cross-checks.

For the present analysis, only patients with AF who were enrolled in the rivaroxaban treatment cohort were analysed and treatment persistence with rivaroxaban assessed.

If patients switched from rivaroxaban to any other form of anticoagulant therapy or had discontinued anticoagulation altogether, the reasons for this decision were obtained from patients or attending physicians.

In daily care, temporary interruptions of anticoagulants are common. To differentiate temporary interruption from complete treatment discontinuation, the following scenarios were not regarded as a discontinuation for this analysis:

(i) Discontinuation of rivaroxaban for any reason, but restart within 4 weeks.
(ii) Interruption of rivaroxaban for scheduled major surgery, even if restart occurred later than 4 weeks.

For all discontinuations, reasons for and exact timing of discontinuation and any anticoagulant or antithrombotic therapy prescribed after the discontinuation of rivaroxaban were assessed by consultation with the attending physician and/or review of obtainable treatment documentation.

Statistics

Patient characteristics were compared descriptively for SPAF patients who had a VKA pretreatment and were switched to rivaroxaban before enrolment and SPAF patients newly treated with rivaroxaban.

Data are presented as absolute and relative frequencies, mean and standard deviation, or median with the interquartile range as difference between 25th and 75th percentiles, where appropriate. All *P*-values presented are exploratory in nature; thus, no adjustment of Type I error for multiple testing is conducted. A *P*-value <0.05 was considered to be statistically significant.

Rates of treatment discontinuation were assessed as a Kaplan–Meier time-to-first-event analysis and presented as:

- *Cumulative incidence risk* for drop-out at 1 month, 2, 3, 6, 7, 8, 9, 10, 11, 12, 18, 24 months with confidence limits using the asymptotic method (Greenwood's formula) for standard error estimation.
- Number of events per 100 patient-years with their 95% confidence intervals (CIs) using the following formula:

$$\text{Event rate} = \frac{\text{number of events}}{\text{total time under risk}}.$$

Total time under risk is the sum of all days from inclusion to the registry until the day of first event divided by 100×365 days, and has 100 patient-years as its unit. Corresponding CIs and *P*-values were calculated using the Poisson distribution.

Patients who died withdrew informed consent or did not discontinue rivaroxaban were censored at that specific date or the last date of follow-up contact, but were not counted as discontinuations. In addition to the assessment of total discontinuation rates during follow-up, discontinuation rates for the periods 0–6 months, 6–12 months, and 12–18 months of treatment were evaluated.

Using Cox regression analysis, the influence of patient characteristics on the risk of treatment discontinuation was assessed for the total cohort and for the subgroups of patients switched from VKA to rivaroxaban or newly treated patients initiated on rivaroxaban. The following baseline parameters were included: age in categories, gender (male or female), body mass index (BMI, kg/m^2), arterial hypertension, chronic heart failure, uncontrolled hypertension, diabetes, history of transient ischaemic attack (TIA) or stroke, coronary artery disease, impaired renal function, concomitant non-steroidal anti-inflammatory drugs, concomitant platelet aggregation inhibitor, history of liver disease, $CHADS_2$

score in categories, CHA_2DS_2-VASc score in categories, and HAS-BLED score in categories.

Hazard ratios (HRs) from the Cox model with their corresponding two-sided 95% CIs were calculated. Factors were included in the Cox model with forward selection. The forward selection started with a model including treatment variable only and a factor had to be statistically significant at the 0.15 level before it could be entered into the model.

All statistical analyses were carried out using the software package SAS (SAS Institute, Inc.) version 9.4.

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). All patients provided written informed consent, including a data protection waiver, before enrolment.

Results

Cohort characteristics

Between 1 October 2011 and 30 April 2014, 2603 patients were enrolled in the registry. Of these, 1204 (46.3%) received rivaroxaban for SPAF, with 473 (39.3%) switched from VKA pretreatment to rivaroxaban and 731 (60.7%) newly anticoagulated rivaroxaban patients. Regarding most baseline characteristics, these groups were homogeneous (descriptive statistics in *Table 1*). However, higher rates of chronic heart failure (41.9 vs. 34.2%), impaired renal function (16.7 vs. 12.5%) and a larger proportion of patients with a HAS-BLED score of $\geq$2 were observed in the cohort of patients switched from VKA to rivaroxaban. Of note, 32.7% of all patients received a reduced dosage of rivaroxaban (15 mg od instead of 20 mg od), despite the fact that impaired renal function was documented for only 12.5% (*Table 1*). On the other hand, more than 60% of all patients had a HAS-BLED score of $\geq$2 and 12.8% had a HAS-BLED score of $\geq$4 as an indicator of high bleeding risk.

For the cohort of patients with VKA pretreatment, the mean duration of pretreatment was 50 (SD = 60) months.

Of the 473 patients who had a pretreatment with VKA and were switched to rivaroxaban, information about the main reason for switching (as indicated by the enrolling physician, multiple reasons possible) was available for 459 patients (97.0%); these reasons consisted of unstable international normalized ratio (INR) (53.7%), bleeding during VKA treatment (17.3%), frequent falls (12.5%), thromboembolic events during VKA treatment (2.1%), and 'other' (23.9%).

Persistence to rivaroxaban therapy

As of 30 April 2014, follow-up information was available for all 1204 patients (100%). By that date, the median treatment duration with rivaroxaban was 544 days (25th and 75th percentile 444/639 days) for all patients, 548 days (25th and 75th percentile 452/641 days) for patients switched from VKA and 541 days (25th and 75th percentile 371/638 days) for newly treated rivaroxaban patients.

During follow-up, the overall persistence with rivaroxaban therapy was 81.5% (223/1204 patients discontinued rivaroxaban) and similar for patients switched from VKA to rivaroxaban or newly treated rivaroxaban patients (82.0 vs. 81.1%).

In the intention-to-treat analysis, rates of treatment discontinuation per 100 patient-years were assessed as a Kaplan–Meier time-

Table 1 Patient characteristics of 1204 SPAF patients and subgroups of patients with and without VKA pretreatment before rivaroxaban therapy

Baseline parameters	All patients, *N* = 1204	Switch from VKA to rivaroxaban *n* = 473	Newly treated rivaroxaban patients *n* = 731
Rivaroxaban dosage of 20 mg od at baseline, *n* (%)	810 (67.3)	304 (64.3)	506 (69.2)
Male, *n* (%)	631 (52.4)	242 (51.2)	389 (53.2)
Age, years (median; IQR)	75 (70; 81)	75 (71; 80)	75 (70; 82)
Mean BMI ± SD (kg/m^2)	28.7 ± 5.1	28.8 ± 5.3	28.6 ± 5.0
Heart failure, *n* (%)	448 (37.2)	198 (41.9)	250 (34.2)
Arterial hypertension, *n* (%)	999 (83.0)	391 (82.7)	608 (83.2)
Diabetes, *n* (%)	480 (39.9)	202 (42.7)	278 (38.0)
Prior TIA, stroke or systemic embolism, *n* (%)	180 (15.0)	74 (15.6)	106 (14.5)
Coronary artery disease, *n* (%)	265 (22.0)	108 (22.8)	157 (21.5)
Concomitant antiplatelet therapy, *n* (%)	91 (7.6)	22 (4.7)	69 (9.4)
Concomitant NSAID, *n* (%)	123 (10.2)	43 (9.1)	80 (10.9)
Impaired renal function,[a] *n* (%)	151 (12.5)	79 (16.7)	72 (9.8)
$CHADS_2$ ≥2, *n* (%)	876 (72.8)	363 (76.7)	513 (70.2)
CHA_2DS_2-VASc ≥2, *n* (%)	1115 (92.6)	440 (93.0)	675 (92.3)
HAS-BLED ≥2, *n* (%)	750 (62.3)	387 (81.8)	363 (49.7)

BMI, body mass index; GFR, glomerular filtration rate; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; od, once daily; SD, standard deviation; SPAF, stroke prevention in atrial fibrillation; TIA, transient ischaemic attack; VKA, vitamin K antagonist.
[a]Impaired renal function was defined as current or history of GFR <50 mL/min.

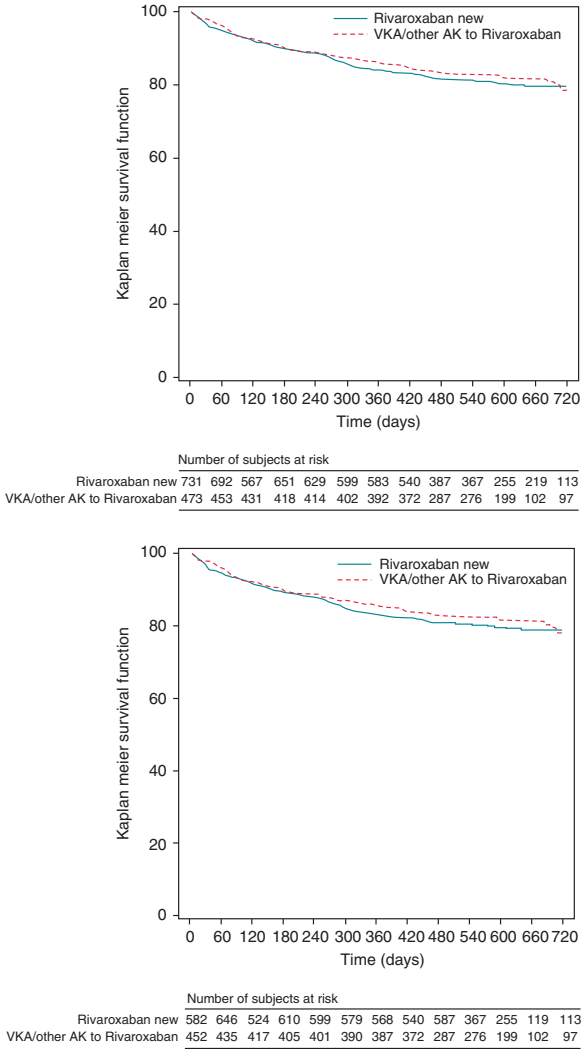

Figure 1 Kaplan–Meier analysis of persistence to rivaroxaban treatment for all patients (top diagram) and for all patients who were observed for at least 12 months (bottom diagram), according to VKA pretreatment.

to-first-event analysis and found to be 13.6(95% CI 11.8–15.4) for all patients and similar for newly treated rivaroxaban patients [14.1(95% CI 11.9–16.7)] and patients switched from VKA to rivaroxaban [12.7(95% CI 10.1–15.7); $P = 0.35$; *Figure 1A*]. This finding did not change if only patients with a completed 12-month follow-up were assessed (*Figure 1B*).

Discontinuation rates were highest in the first 6 months of treatment [9.9%(95% CI 7.7–12.1%) for patients newly treated with rivaroxaban and 10%(95% CI 7.3–12.7%) for patients switched from VKA pretreatment to rivaroxaban] and declined similarly in both subgroups over time [for 6–12 months: 6%(95% CI 5.5–6.4%) and 3.9% (95% CI 3.5–4.4%), respectively; after 12 months: 4.4% (95% CI 3.9–5%) and 7.7%(95% CI 6.0–9.2%), respectively].

Baseline characteristics of persistent patients and patients with rivaroxaban discontinuation are presented in *Table 2*.

Reasons for and management of treatment discontinuation of rivaroxaban therapy

The reasons for discontinuation are presented in *Table 3*. The most common reasons were bleeding complications (67/223 discontinuations; 30.0%) followed by non-bleeding side-effects (54/223; 24.2%), stable sinus rhythm (19/223; 8.5%), and worsening of renal function (18/223; 8.1%). Thromboembolic complications such as stroke (1.8%), TIA (1.3%), or acute coronary syndrome (1.3%) were rarely the reason for rivaroxaban discontinuation. Within the group of 67 bleeding complications, according to the International Society on Thrombosis and Haemostasis bleeding definition, 14 were major and 53 were non-major clinically relevant bleeding events that led to treatment discontinuation. In the group of patients who discontinued rivaroxaban due to bleeding ($n = 67$), concomitant therapy with antiplatelet drugs was present in five cases (7.5%), with NSAIDS in three cases (4.5%) and a combination of both in one case (1.5%).

After discontinuation of rivaroxaban in 223 patients, the following treatment options were chosen by the attending physician: continuation on single antiplatelet therapy (67; 30.0%); continuation on VKA (54; 24.2%), continuation on apixaban (23; 10.3%), continuation on dabigatran (18; 8.1%), continuation on heparin (22; 9.9%), continuation on dual antiplatelet therapy (4; 1.8%), or total discontinuation of any anticoagulant or antithrombotic treatment (35; 15.7%).

Risk factors for discontinuation of rivaroxaban therapy

To evaluate potential risk factors for rivaroxaban discontinuation, a Cox proportional hazard analysis was performed (*Table 4*). A history of chronic heart failure (HR 1.43; 95% CI 1.09–1.87; $P = 0.009$] or diabetes (HR = 1.39; 95% CI 1.06–1.82; $P = 0.018$) were the only statistically significant baseline risk factors for rivaroxaban discontinuation.

Discussion

To our knowledge, our data are the first available prospective results regarding the persistence respective to the rates of and reasons for rivaroxaban discontinuation in SPAF patients from daily care.

Treatment persistence of rivaroxaban therapy

The protection of patients with AF is related to the efficacy and safety of oral anticoagulation, but also to drug adherence (the patient's reliable daily intake of the recommended drug dosage) and to drug persistence (the continuation of therapy throughout the scheduled treatment period). In daily care, drug persistence to oral anticoagulation is an important topic, given that stroke prevention is important but discontinuation rates were comparatively high in all recent Phase III trials: 23.7% for rivaroxaban and 22.2% for warfarin during a mean exposure time of 590 days in the ROCKET AF trial;[5] 21% for dabigatran and 16% for warfarin at 24 months in the RE-LYtrial;[8] 25.3% for apixaban and 27.5% for warfarin during the total 2-year study period of ARISTOTLE[9] and ~34% for warfarin and edoxaban during a mean duration of exposure of 907 days in the ENGAGE-AF trial.[10] Generally, direct comparisons between these trials should be

Table 2 Patient characteristics of 1204 SPAF patients and subgroups of patients with and without rivaroxaban discontinuation

Baseline parameters	All patients $n = 1204$	Persistent patients, $n = 981$	Rivaroxaban discontinuation $n = 223$
Rivaroxaban dosage of 20 mg od at baseline, *n* (%)	810 (67.3)	681 (69.4)	129 (57.8)
Male, *n* (%)	631 (52.4)	513 (52.3)	118 (52.9)
Age, years (median; IQR)	75 (70; 81)	75 (70; 81)	76 (70; 83)
Mean BMI ± SD (kg/m^2)	28.7 ± 5.1	28.8 ± 5.2	28.0 ± 4.9
Heart failure, *n* (%)	448 (37.2)	347 (35.4)	101 (45.3)
Arterial hypertension, *n* (%)	999 (83.0)	822 (83.8)	177 (79.4)
Diabetes, *n* (%)	480 (39.9)	376 (38.3)	104 (46.6)
Prior TIA, stroke, or systemic embolism, *n* (%)	180 (15.0)	138 (14.1)	42 (18.8)
Coronary artery disease, *n* (%)	265 (22.0)	211 (21.5)	54 (24.2)
Concomitant antiplatelet therapy, *n* (%)	91 (7.6)	71 (7.2)	20 (9.0)
Concomitant NSAID, *n* (%)	123 (10.2)	105 (10.7)	18 (8.1)
Impaired renal function,[a] *n* (%)	151 (12.5)	114 (11.6)	37 (16.6)
$CHADS_2 \geq 2$, *n* (%)	876 (72.8)	699 (71.3)	177 (79.4)
CHA_2DS_2-VASc ≥ 2, *n* (%)	1115 (92.6)	908 (92.6)	207 (92.8)
HAS-BLED ≥ 2, *n* (%)	750 (62.3)	606 (61.8)	144 (64.6)

BMI, body mass index; GFR, glomerular filtration rate; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; od, once daily; SD, standard deviation; SPAF, stroke prevention in atrial fibrillation; TIA, transient ischaemic attack.
[a]Impaired renal function was defined as current or history of GFR <50 mL/min.

avoided, because significant differences existed with regard to study design and patient population. However, the comparator data at least suggest that the more complex double-blind, double-dummy designs of ROCKET AF, ARISTOTLE, and ENGAGE-AF could be responsible for the higher discontinuation rates in all treatment arms compared with the open-label RE-LY trial.

In all of these recent SPAF trials, discontinuation rates were lower than in the SPORTIF V trial,[11] in which, during a 2-year study period, 33% of VKA patients and 37% of ximelagatran patients prematurely stopped their study medication, which indicates that in the recent NOAC trials, more emphasis was placed on achieving high treatment persistence. As a consequence, the external validity of these trials needs to be confirmed in daily care populations.

In our study, rates of rivaroxaban discontinuation per 100 patient-years were 13.6/100 patient-years for the total cohort and similar for newly treated rivaroxaban patients (14.1/100 patient-years) and for patients switched from VKA to rivaroxaban (12.7/100 patient-years). In total, 223 of the 1204 patients stopped taking rivaroxaban (18.4%), with a mean rivaroxaban exposure of the study cohort of 544 days.

Although we accept that it is difficult to compare these daily care results directly with the large Phase III trial results, it is reassuring that the discontinuation rate of rivaroxaban in daily care was found to be lower than that in the respective Phase III trial, which again would indicate that the complexity of double-blind, double-dummy trials increases the risk of premature treatment discontinuation.

Using a study design different to ours, the group of Laliberté and co-workers recently compared real-world rivaroxaban and warfarin SPAF treatment in a retrospective matched-cohort study using data from US patients newly initiated on rivaroxaban or warfarin from May 2011 through July 2012.[12] In this study, treatment persistence for rivaroxaban was found to be 81.5% at 6 months, which was significantly higher than the persistence of warfarin patients (68.3%). However, besides limitations from the study design, another relevant limitation of this work was the short follow-up period, which, on average, was only 83 days for rivaroxaban patients and 113 days for warfarin patients. Furthermore, more than 2% of all patients had prescriptions of other anticoagulants during the observational period but the reasons for this could not be evaluated. Despite these limitations, the low discontinuation rate of rivaroxaban found by Laliberté and co-workers is in line with our findings. Although our data do not allow for a comparison with a VKA cohort, we confirmed high treatment persistence with rivaroxaban in daily care in a prospective cohort study. In addition to this, our study provides data derived at patient level over a much longer observational period, as well as detailed data on the reasons for and the management of rivaroxaban discontinuation, which add significantly to the current knowledge.

Even more importantly, the persistence rates for rivaroxaban reported by Laliberté *et al.* and confirmed in our study are substantially higher than those reported for VKA in daily care settings. Gallagher *et al.*[2] reported retrospectively collected data on VKA prescriptions in a large UK cohort. In this study, warfarin persistence was 70% at 12 months and approximately 60% at 24 months. Similarly, Hylek *et al.*[3] reported a discontinuation rate of 26% within the first year of treatment for patients ≥ 80 years and identified safety concerns as the predominant reason for treatment discontinuation (81%), which was especially relevant in patients with a $CHADS_2$ score ≥ 3.

In addition, Fang *et al.* reported a VKA discontinuation rate of 26.3% at 12 month and 31.3% at 24 months for newly treated AF patients in the ATRIA study.[13] Low $CHADS_2$ score, poor INR control, and age <65 years were found to be independent risk factors for treatment discontinuation, whereas history of stroke, heart failure, and diabetes significantly reduced the risk of VKA

Table 3 Centrally adjudicated reasons for rivaroxaban discontinuation

Reasons for rivaroxaban discontinuation	*n* (%) of all 223 discontinuations
Bleeding complications	67 (30.0)
Mucosal	23 (10.3)
Gastrointestinal	16 (7.2)
Bruising	9 (4.0)
Haematuria	6 (2.7)
Haemoptysis	5 (2.2)
Other	8 (3.6)
Suspected non-bleeding side effects	54 (24.2)
Vertigo/nausea/fatigue	17 (7.6)
Pruritus	8 (3.6)
Dyspepsia	6 (2.7)
Hair loss	4 (1.8)
Eczema	3 (1.3)
Diarrhoea	2 (0.9)
Elevated liver enzymes	2 (0.9)
Other	16 (7.2)
Stable sinus rhythm or LAA occlusion	22 (9.9)
Worsening renal function	18 (8.1)
Patient decision	9 (4.0)
New contraindication for rivaroxaban	5 (2.2)
Anaemia (without overt bleeding)	4 (1.8)
Costs	4 (1.8)
Non-compliance	4 (1.8)
Stroke	4 (1.8)
ACS	3 (1.3)
LAA thrombus	3 (1.3)
TIA	3 (1.3)
Frequent falls	2 (0.9)
Palliative situation	2 (0.9)
Other	15 (6.7)

ACS, acute coronary syndrome; LAA, left atrial appendage; TIA, transient ischaemic attack.

discontinuation. However, it is important to note that 263 patients hospitalized for bleeding complications were excluded from the risk factor assessment, because authors expected relevant bleeding to be a dominant reason for discontinuation. Also, Gomes *et al.* demonstrated a similarly high rate of VKA discontinuation in a large cohort of >120 000 SPAF patients newly started on warfarin. Of these patients, 31.8% discontinued VKA within the first year and 43.2% discontinued within the first 2 years of treatment.[14] Based on these studies, it is reasonable to conclude that ~25–30% of all patients started on VKA are likely to discontinue their treatment within the first year of treatment. Compared with this, our findings clearly indicate better treatment persistence for rivaroxaban.

Interestingly, Hylek, Fang, and Gomes[3,13,14] consistently demonstrated a decline of discontinuation rates after an initial 'peak' in the first 6–12 months. Our data for rivaroxaban confirm these findings and demonstrate a higher discontinuation rate in the first 6 months of treatment (~10%), declining to ~5% thereafter, which was similar for newly treated patients and patients with VKA pretreatment. However, both in the initial 12 months and thereafter, the discontinuation rate of rivaroxaban was found to be considerably lower than that reported for VKA.[3,13,14]

In contrast to these poor persistence data, Nieuwlaat reported better persistence to VKA in the large prospective Euro Heart Survey that assessed treatment patterns of AF patients across Europe between 2003 and 2004.[15] In this study, only 16% of patients discontinued oral anticoagulation in the first treatment year. However, it should be noted that this study also included patients on stable VKA therapy. Furthermore, a large proportion of patients in this study were in the groups of 'first detected AF' or 'paroxysmal AF' and up to 45% of patients in these groups discontinued treatment. Interestingly, 'cured AF' or 'chronic sinus rhythm' were the most common reasons for treatment discontinuation in this study and in their discussion, the authors stressed the fact that 'cured AF' and 'chronic sinus rhythm' are an 'unreliable diagnosis' due to the high incidence of asymptomatic attacks and lack of adequate non-invasive monitoring tools. As a consequence, the authors assumed that the low oral anticoagulant application rate and frequent stopping of oral anticoagulation in patients with first detected AF contributed to their high mortality rate.[15]

In our discontinuation cohort, 'stable sinus rhythm' was reported for 19 patients as the main reason to stop rivaroxaban, which accounted for 8.5% of all rivaroxaban discontinuations.

Reasons for and management of rivaroxaban treatment discontinuation

In our study, the occurrence of bleeding complications was the most common reason for rivaroxaban discontinuation. It is, therefore, not surprising that only 52% of all patients with discontinuations were switched to other anticoagulants and that anticoagulant or antithrombotic treatment was completely discontinued in 15.7%. However, the largest proportion of patients was switched to antiplatelet therapy (31.8%), which still seems to be considered as a treatment alternative for SPAF patients not eligible for oral anticoagulation. Our data indicate that the results of the AVERROES trial[16] and recent guideline recommendations[17] against aspirin use in SPAF are still not implemented in daily care. In the AVERROES trial, apixaban demonstrated superior stroke prevention, which outweighs the risk of major bleeding compared with antiplatelet therapy in patients seen as not eligible for VKA therapy. As a consequence of this trial, such patients should receive either oral anticoagulation with a NOAC (probably with reduced dosage) or nothing at all. Our finding of frequent switches to antiplatelet therapy after rivaroxaban discontinuation in daily care clearly demonstrates a field for further research and education to improve future oral anticoagulant management.

Risk factors for discontinuation of rivaroxaban therapy

In our analysis, the only risk factors of statistical significance were a history of chronic heart failure or diabetes at baseline with a HR of 1.4, respectively, which are also established risk factors for VKA discontinuation.[3,13] Interestingly, neither age nor history of TIA/stroke or impaired renal function were independent risk factors for treatment discontinuation. Although this may be surprising, we believe

Table 4 Cox proportional hazard model of potential risk factors for rivaroxaban discontinuation

Baseline variable	HR (95% CI)	No discontinuation vs. discontinuation (%)	*P*-value
VKA pretreatment (yes vs. no)	0.85 (0.65–1.12)	No: 18.9% Yes: 18.0%	0.25
BMI (normal vs. underweight)	0.74 (0.55–0.99)	Normal: 21.8% Underweight: 20.0%	0.04
Heart failure (yes vs. no)	1.41 (1.08–1.85)	No: 16.1% Yes: 22.5%	0.01
Arterial hypertension (yes vs. no)	0.73 (0.52–1.01)	No: 22.4% Yes: 17.7%	0.06
Diabetes (yes vs. no)	1.35 (1.03–1.77)	No: 16.4% Yes: 21.7%	0.03
Prior TIA, stroke or systemic embolism (yes vs. no)	1.34 (0.95–1.87)	No: 17.7% Yes: 23.3%	0.09
Renal dysfunction (yes vs. no)	1.32 (0.92–1.90)	No: 17.7% Yes: 24.5%	0.13

BMI, body mass index; CI, confidence interval; TIA, transient ischaemic attack; VKA, vitamin K antagonist

that this could be an indicator of the broad safety window of rivaroxaban in patients with complex co-morbidities, which would be in contrast to VKA therapy, which has a narrow therapeutic window. So far, the data on the influence of age on the quality of VKA treatment are conflicting[18,19] and, as such, no clear correlation could be shown. However, Hylek *et al.* found safety concerns to be the predominant reason for VKA discontinuation in elderly patients (37% of discontinuations in the age group <80 years and 81% of discontinuations in the age group >80 years). In contrast, history of stroke and renal impairment have been shown to correlate to poor INR control in VKA patients[18,20–22] and, therefore, increase the risk of thromboembolic or bleeding complications in VKA patients. In contrast to VKA, rivaroxaban has a more predictable dose–response relationship and routine coagulation monitoring with regular dose adjustments is not necessary. It seems reasonable to expect that, as a consequence, these risk factors are less relevant for persistence to NOAC than for the persistence to or discontinuation of VKA therapy. However, our data do not fully support this consideration. On the one hand, the overall persistence to rivaroxaban was much better than that reported for VKA and thromboembolic complications rarely caused treatment discontinuation, which are indicators that the pharmacological profile of rivaroxaban including a predictable dose–response relationship indeed reduces the effect of factors that increased the risk of VKA discontinuation. On the other hand, it seems that bleeding was also the most frequent reason for rivaroxaban discontinuation (30.0% of all). Although most of these bleeding events were non-major bleeding, one can conclude that attending physicians in daily care seem to view such events as a reason to discontinue anticoagulant therapy totally, which, in our perspective, demonstrates another field for further research and education.

Limitations

There are several limitations to our study. First of all, the design of our registry introduces the possibility of a selection bias, because local physicians within the network are not instructed as to which of their patients should receive NOAC or VKA therapy. As a result, one could assume that physicians are more likely to switch patients to NOAC therapy if they had to discontinue VKA therapy due to complications or risk factors for adverse events during VKA therapy, and, therefore, our cohort might reflect a selection of patients at high risk also for rivaroxaban discontinuation. On the other hand, one may also argue that clinicians could reserve a newly approved anticoagulant for only the healthiest of their patients, perceived to be at the lowest risk of treatment complications. We cannot completely rule out either selection bias. However, demographic characteristics, co-morbidities, and the large number of patients switched from VKA to NOAC due to unstable INR or bleeding events during VKA indicate that our study cohort reflects a moderate- to high-risk population. Either way, our results indicate that for our specific cohort, the overall rate of treatment discontinuation is $\sim$18% in the first year and, thus, lower than the discontinuation rates reported for VKA in daily care.[2,3,13]

Unfortunately, we do not have information regarding the quality of INR control for patients switched from VKA to rivaroxaban. At baseline, in >50% of these patients, 'unstable INR' was the reason for transition provided by the enrolling physician, which, in lack of a time-in-therapeutic range (TTR) seems a subjective assessment. However, the concept of 'TTR' is mainly used for scientific purposes and physicians in daily care rarely estimate TTR values but commonly use more subjective assessments such as 'stable or unstable INR' for their treatment decisions. Since our study is a reflection of what is being done in daily care practices, we believe that the use of a subjective assessment of INR stability is sufficient to explain the treatment decisions done by the attending physicians, even in the absence of TTR values. However, we want to point out that every effort should be made to improve TTR in patients with long-term VKA treatment. The calculation of TTR is simple and specific software is available for this to enable physicians to control and improve quality of care. Information on the reasons for discontinuation

might not be complete because they only include patient contact and information derived from the attending physician or hospital discharge letters.

The lack of a direct comparator group (such as VKA-treated patients) could be regarded as a limitation. However, several large VKA cohort studies in daily care exist and the rates of VKA treatment discontinuation are well established,[2,3,13] which allows for reliable indirect comparisons. As stated above, the design of our registry as well as the risk of selection bias during patient enrolment in the practice of the attending physicians would have limited a direct comparison with a VKA group significantly.

Finally, it could be argued that our quarterly phone calls to the patient were 'interventions' that contributed to the comparatively high rates of treatment persistence. If this is really the case, it would be a favourable effect in real life: if a simple short contact with the patient once in a quarter is sufficient to achieve high treatment persistence with rivaroxaban, this would be easy to perform, given that rivaroxaban prescriptions usually contain 98 tablets and, therefore, the patient has to come back for the next prescription every 3 months. Consequently, we recommend using this situation for a short physician contact to remind the patient of the risks associated with AF and the importance of a regular drug intake, as well as to perform a short assessment of problems or potential side-effects.

Despite all of these potential limitations, the size of our cohort of 1204 SPAF patients treated with rivaroxaban and the prospective evaluation of more than 220 treatment discontinuations in unselected daily care patients is a significant strength of our study. Additionally, the use of a central adjudication process that evaluated reasons for and management of treatment discontinuation contributes to the strength and clinical impact of our data.

Conclusion

According to the current literature, our study is the first to evaluate rates, reasons for, and management of rivaroxaban discontinuation in unselected SPAF patients from daily care. Our data indicate that overall persistence with rivaroxaban therapy is high with a discontinuation rate of ~15% in the first year of treatment and few additional discontinuations thereafter.

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