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Real-world persistence and adherence to oral anticoagulation for stroke risk reduction in patients with atrial fibrillation

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Aim To assess persistence and adherence to rivaroxaban, dabigatran, and vitamin K antagonist (VKA) treatment in primary care patients with non-valvular atrial fibrillation (AF) newly starting anticoagulant therapy.

Methods and results Prescription data for oral anticoagulants were obtained from 7265 eligible patients from primary care practices across Germany. Persistence with and adherence to anticoagulation were assessed in anticoagulant-naïve patients with AF newly treated with dabigatran, rivaroxaban, or VKA during follow-up periods of at least 180 days, respectively 360 days after the prescription date. Persistence probabilities after 180 days were 66.0% for rivaroxaban, 60.3% for dabigatran, and 58.1% for VKA ($P < 0.001$ for rivaroxaban vs. VKA and $P = 0.008$ for rivaroxaban vs. dabigatran). After 360 days, persistence probabilities were 53.1, 47.3, and 25.5%, respectively ($P < 0.001$ for rivaroxaban and dabigatran vs. VKA). Considering the development over 360 days rivaroxaban demonstrated a better persistence compared with dabigatran ($P = 0.026$). Male gender and the presence of diabetes mellitus were associated with increased persistence, while renal impairment and antiplatelet drug use decreased persistence. High adherence (MPR $\geq$0.80) was observed in 61.4% of rivaroxaban users and in 49.5% of dabigatran users, with means of 0.76 [95% confidence interval (CI) 0.74–0.78] for rivaroxaban and 0.67 (95% CI 0.65–0.69) for dabigatran ($P < 0.001$).

Conclusions Rivaroxaban and dabigatran demonstrated better persistence than VKA at Day 360. Furthermore, rivaroxaban was associated with better persistence and adherence than dabigatran. Further studies are needed to identify factors responsible for this difference and evaluate the impact on outcomes.

Keywords Dabigatran • Oral anticoagulation • Primary care • Real world • Rivaroxaban • Vitamin K antagonist

Introduction

Vitamin K antagonists (VKAs) have been the mainstay of oral anticoagulant (OAC) treatment for several decades and reduce the relative risk of stroke in patients with atrial fibrillation (AF) by ~64%.[1] However, non-VKA oral anticoagulants (NOACs), such as the direct thrombin inhibitor dabigatran and the Factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, are now approved for stroke prevention in patients with AF. Compared with warfarin, these newer agents have all demonstrated at least similar efficacy and safety in stroke prevention.[2] Non-VKA oral anticoagulants also have several potential advantages compared with VKAs, such as fewer drug–drug and food–drug interactions and no requirement for routine coagulation monitoring.[3]

The lack of monitoring, however, may affect patient adherence (proportion of doses taken as prescribed) and treatment persistence (proportion of patients still on initial drug therapy after a fixed time period), which are important in ensuring optimal stroke prevention. Several studies have consistently demonstrated better persistence with rivaroxaban or dabigatran compared with VKAs in the USA.[3–5] However, these results are not necessarily applicable to European patients or healthcare systems. Furthermore, although warfarin is the most commonly used VKA in North America, other VKAs such as acenocoumarol or phenprocoumon are used in some European countries.

The overall objective of the current study was to assess: (1) persistence and adherence to rivaroxaban, dabigatran, and VKA

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What's new?

- In a real-world German healthcare setting, higher therapy persistence was seen with rivaroxaban compared with dabigatran or vitamin K antagonist treatment.
- Patients treated with rivaroxaban demonstrated better adherence than those treated with dabigatran.
- Persistence was positively associated with male gender, statutory health insurance, presence of diabetes mellitus, rivaroxaban treatment, and concomitant cardiovascular drug use.

treatment in primary care patients with non-valvular AF newly in receipt of anticoagulant therapy for stroke prevention and (2) factors associated with treatment persistence.

Methods

Study design

A retrospective database analysis was performed, based on data provided in a validated longitudinal electronic medical records database—IMS® Disease Analyzer.[6] The IMS® Disease Analyzer Germany captures data from a representative compiled sample of 3002 physicians in 2357 unique practices and includes 15.5 million patient records. The current retrospective database analysis was based on data from 1409 office-based primary care physicians (PCPs), which covered ~2.3% of the ~60 800 general practitioner and internists without subspecialty across Germany.[6] Data were collected for patients diagnosed with AF who received either once-daily rivaroxaban (15 or 20 mg), twice-daily dabigatran (110 or 150 mg), or a VKA (in most cases phenprocoumon 3 mg tablets with dose adjustments according to international normalized ratio; INR) between January 2012 and August 2013. Persistence with anticoagulant therapy was evaluated by searching for prescription refill data in the aforementioned database.

Patient population

Patients aged 18 years or older who had been diagnosed with AF no more than 365 days before the date of the first prescription of an OAC (index date) and had no prior exposure to OACs were included in the study. Patient data were required in the database for at least 90 days preceding the index date and for at least 180 days, respectively 360 days after the index date to be included in the study (*Figure 1*).

Patients with valvular AF (ICD-10 codes: I05-I09, I34-I39, O22-O23, and Z95) and patients receiving an OAC for indications other than AF prior to index were excluded. Other reasons for exclusion were prescriptions of off-label dose regimens and no evidence of healthcare contacts throughout the data collection periods pre- and post-index dates (*Figure 1*).

Study analysis

The following patient parameters were assessed: demographics, comorbidities [including congestive heart failure, hypertension, diabetes mellitus, stroke, transient ischaemic attack, thromboembolism, and vascular disease, such as a prior myocardial infarction or the presence of atherosclerotic vascular disease (e.g. peripheral artery disease and aortic or carotid plaques)], stroke risk ($CHADS_2$ score, CHA_2DS_2-VASc score), type of OAC prescribed, concomitant cardiovascular drugs, number of outpatient PCP visits in a defined time period, and, in VKA-treated patients, INR monitoring frequency.

Persistence (or non-persistence) to therapy was analysed from initiation of the index therapy (first prescription date of the initially prescribed therapy) and involved a series of successive prescriptions and refill gaps ≤60 days were allowed. A refill gap of 60 days was chosen as the base case determinant of persistence in accordance with published literature,[4,7] but refill gaps of 30 and 45 days were included in a sensitivity analysis.

- Persistence was defined as a refill within the period covered by the previous prescription or within 60 days after the end of this period. This included patients who may have interrupted treatment but received their following prescription within 60 days.
- Non-persistence was defined as a permanent discontinuation of therapy or a refill later than 60 days after the end of the period covered by the previous prescription.

For non-persistent patients, the start of non-persistence was the last date covered by the last 'persistent' prescription. Therefore, the end date of the previous/last prescription was his/her time to non-persistence.

While rivaroxaban and dabigatran are taken in a fixed daily dosage, VKA is given in INR-adjusted dosages. For the persistence analysis, a mean daily dosage of one tablet (3 mg) phenprocoumon was used, which is in line with the SmPC in Germany. However, sensitivity analyses using 1.5 and 2 tablets/day were also performed.

Adherence was measured indirectly based on the medication possession ratio (MPR) and only determined for patients prescribed either dabigatran or rivaroxaban at the index date. The MPR is calculated as the proportion of days of medication supplied within a defined time period. Overlaps between multiple prescriptions were not double counted. Adherence was classified as low (MPR <0.40), intermediate (MPR 0.40–<0.80), or high (MPR ≥0.80).[8,9] Vitamin K antagonist regimens are individually adapted to maintain the INR in the therapeutic range, which affects refill intervals. Because daily VKA dosages could not be assessed in the current study and MPR could not be calculated, adherence to VKAs was not assessed.

For rivaroxaban, dabigatran, or VKA, factors that may potentially influence persistence were examined. These included age, gender, insurance status, stroke risk ($CHADS_2$ and CHA_2DS_2-VASc scores), history of chronic obstructive pulmonary disease, pre-index co-morbidities, type of OAC used, and use of cardiovascular drugs and antiplatelet drugs during the 180-day post-index period.

Comparisons of persistence with rivaroxaban, dabigatran, or VKA therapy at 180 and 360 days were conducted. For the analyses of adherence to dosing regimens with rivaroxaban or dabigatran and the identification of factors that may potentially influence persistence, the treatment period of 180 days was used.

Statistical analysis

The demographic and clinical characteristics of study patients were described using frequency and percentage distributions for categorical variables, and with descriptive statistics (mean, standard deviation, and median) for continuous and count variables, measured from the patient's index date or based on his/her pre-index period (90 days preceding index date), unless otherwise specified.

The statistical significance of the extent of differences of patient baseline characteristics and of differences in outcomes between treatment groups was assessed using the following measures for independent samples: χ^2 test for categorical measures, and Student's *t*-test for non-normally distributed continuous variables whenever appropriate.

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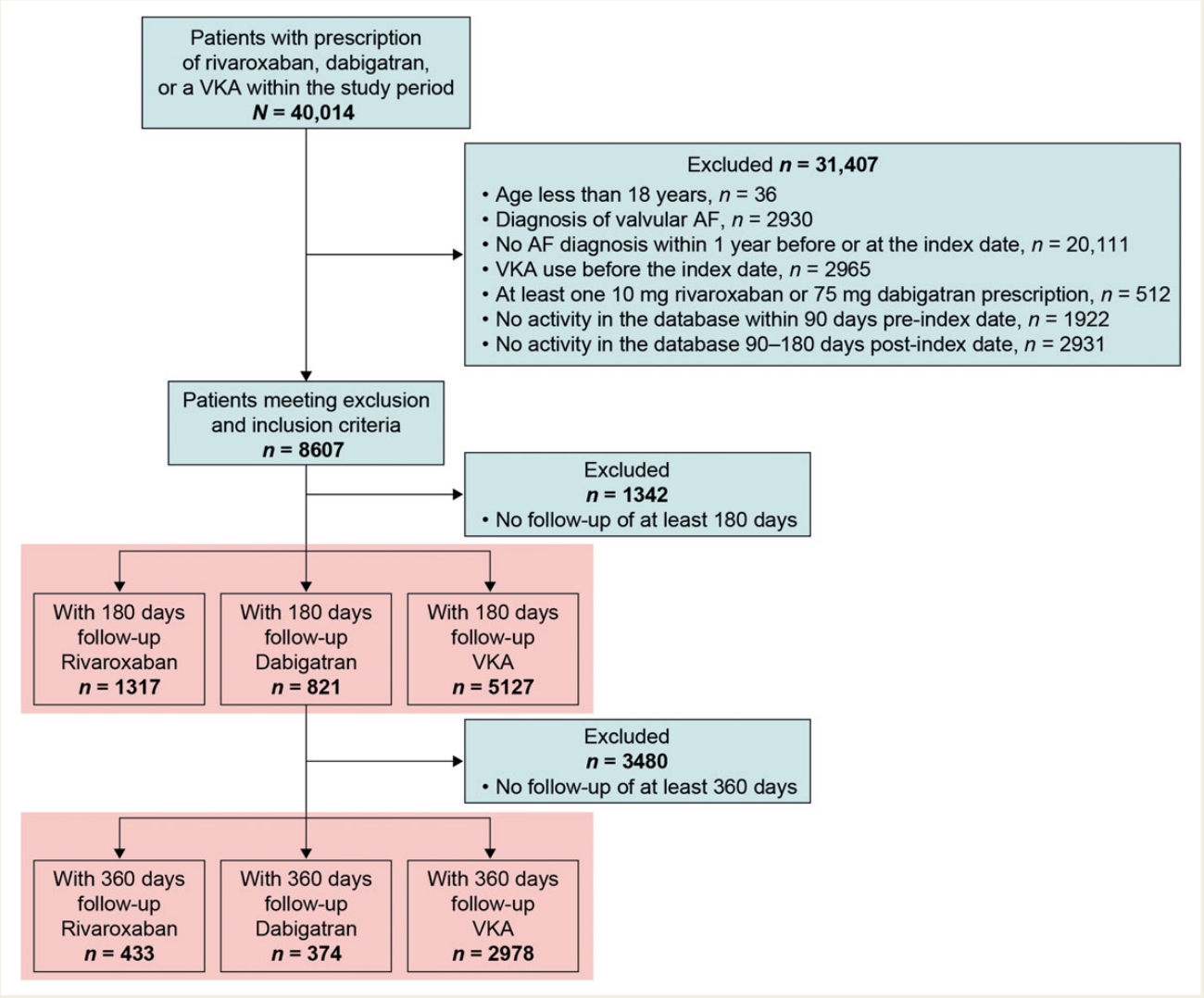

Figure 1 Study histogram. Red boxes indicate cohorts included in persistence assessments at Days 180 and 360.

The statistical significance of the difference in persistence rates between the treatment groups was tested using the *Z*-test.

Cumulative distribution functions were used to describe the retention distribution of persistence over time. The development of persistence over 360 days was tested using the Wilcoxon test, as appropriate.

The evaluation of factors with a potential influence on treatment persistence was performed using a logistic regression model. One model, utilizing relevant demographic and clinical variables (as indicated in *Table 3*), was run. Variable selection procedures (forward/backward selection) were not applied.

In all formal statistical comparisons, a *P*-value of <0.05 was considered statistically significant. All analyses employed SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Ethics

The IMS® Disease Analyzer contains no personal data but exclusively anonymous information (in accordance with § 3 Abs. 6 'Bundesdatenschutzgesetz'—German Federal Data Protection Act). Since the patient data were anonymized, German regulations do not require approval from an ethics committee for this study.

Results

From a total of 8607 patients available for analysis, 7265 patients (84.4%) fulfilled the inclusion criteria of being followed up for at least 180 days post-index date, and 3785 patients (44.0%) fulfilled the criteria of being followed up for at least 360 days post-index date. Characteristics of the patient population with a minimum of 180 days follow-up and 360 days follow-up are described in *Table 1*. Generally, patient characteristics were similar between groups for each drug and irrespective of whether follow-up data were available at 180 days, 360 days, or not at all.

Persistence at 180 days

The following proportions of therapy-persistent patients at 180 days were found: rivaroxaban 66.0%, dabigatran 60.3%, and VKAs 58.1%. Persistence with rivaroxaban was significantly higher compared with VKAs when tested by the *Z*-test (66.0 vs. 58.1%; $P < 0.001$). Persistence with rivaroxaban was significantly higher compared with dabigatran (66.0 vs. 60.3%; $P = 0.008$) (*Table 2*). Dabigatran also

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Table 1 Patient characteristics by treatment group—180 and 360 days follow-up

	VKA		Dabigatran		Rivaroxaban	
	With 180 days follow-up *n* = 5127	With 360 days follow-up *n* = 2978	With 180 days follow-up *n* = 821	With 360 days follow-up *n* = 374	With 180 days follow-up *n* = 1317	With 360 days follow-up *n* = 433
Age (years)						
Mean (SD)	74.7 (9.8)	74.6 (9.7)	73.9 (10.1)	74.0 (9.8)	74.8 (10.4)	74.3 (10.0)
Sex						
Male, % (*n*)	51.9 (2659)	52.2 (1556)	53.3 (438)	54.8 (205)	49.5 (652)	51.5 (223)
Insurance						
SHI, % (*n*)	94.4 (4841)	94.4 (2810)	86.6 (711)	87.2 (326)	84.4 (1111)[a]	82.9 (359)
Privately insured, % (*n*)	5.6 (286)	5.6 (168)	13.4 (110)	12.8 (48)	15.6 (206)[a]	17.1 (74)
Risk scores						
$CHADS_2$ score, mean (SD)	1.9 (1.1)[a]	1.9 (1.1)	2.0 (1.3)	2.0 (1.2)	2.0 (1.2)	2.0 (1.2)
CHA_2DS_2-VASc score, mean (SD)	4.0 (1.5)[a]	4.0 (1.5)	4.0 (1.6)	3.9 (1.6)	4.1 (1.5)	4.1 (1.5)

SD, standard deviation; SHI, statutory health insurance; VKA, vitamin K antagonist.
[a]Significant differences in characteristics were identified between patients who did or did not have 180-day follow-up.

Table 2 Persistence after 180 days (percentage of patients)

	VKA	Rivaroxaban	VKA	Dabigatran	Rivaroxaban	Dabigatran
Number of patients	5127	1317	5127	821	1317	821
Persistent % (*n*), 95% CI	58.1 (2977) (56.7–59.4)	66.0 (869) (63.4–68.5)	58.1 (2977) (56.7–59.4)	60.3 (495) (56.9–63.6)	66.0 (869) (63.4–68.5)	60.3 (495) (56.9–63.6)
95% CI for the difference between proportions	7.9 (5.0–10.8)		2.2 (−1.4 to 5.8)		5.7 (1.5–9.9)	
Z-test	**<0.001**		0.235		**0.008**	

VKA, vitamin K antagonist.
Bold indicates values significant (<0.05).

demonstrated higher persistence compared with VKAs (60.3 vs. 58.1%), but the difference was not statistically significant.

In the 180-day analysis, 64 of 1317 patients (4.9%) restarted rivaroxaban after a gap of more than 60 days (these interrupters were counted as treatment non-persistent in accordance with the pre-specified definition). The respective number for dabigatran was 33 of 821 patients (4.0%).

Factors associated with persistence at 180 days

At Day 180, the following factors were found to be associated with higher persistence to OAC: male gender, statutory health insurance (compared with privately insured), concomitant presence of essential hypertension or diabetes mellitus (diagnosed before the index date), treatment with rivaroxaban, and concomitant use of cardiovascular drugs (*Table 3*). Patients with higher age, renal failure, or concomitant use of antiplatelet drugs had a significantly lower likelihood of persistence over 180 days.

Persistence at 360 days

Baseline characteristics were similar between patients followed up for 360 days and those followed up for a shorter period (*Table 1*). The most frequent co-morbidities identified in these patients prior to the index date were hypertension, vascular disease, and diabetes mellitus, with no real difference between the different treatment groups (see Supplementary material online, *Figure S1*).

At 360 days, persistence with rivaroxaban was significantly higher compared with VKA (53.1 vs. 25.5%; $P < 0.001$) and numerically higher compared with dabigatran (53.1 vs. 47.3%; $P = 0.100$). Dabigatran demonstrated higher persistence compared with VKAs (47.3 vs. 25.5%; $P < 0.001$) (*Table 4*, *Figure 2*). When the development of persistence over 360 days was analysed, the difference between the rivaroxaban and dabigatran groups was also statistically significant ($P = 0.026$).The comparison of rivaroxaban and dabigatran with VKA until Day 360 was not compared with the Wilcoxon test because the respective survival curves crossed (*Figure 2*). The mean time until non-persistence over 360 days follow-up was 253 days for patients receiving rivaroxaban, 228 days for patients receiving dabigatran, and 216 days for patients receiving a VKA.

In the 360-day cohort, 61 of 433 rivaroxaban patients (14.1%) and 42 of 374 dabigatran patients (11.2%) restarted their index OAC after a gap of more than 60 days (these interrupters were counted as treatment non-persistent patients in accordance with the pre-specified definition). Adding these patients, overall treatment continuation after 360 days was 67.2% for rivaroxaban and 58.5% for

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Table 3 Relationship between patient factors and treatment persistence (persistent yes/no after 180 days post-index); results from a logistic regression model

Predictors	Odds ratio	*P*-value	95% CI	
			Lower limit	Upper limit
Age				
Increasing age (per year)	**0.99**	**<0.001**	0.9804	0.9900
Gender (reference: female)				
Male	**1.11**	**0.029**	1.0109	1.2255
Insurance (reference: privately insured)				
SHI insured	**1.22**	**0.022**	1.0294	1.4449
Relevant co-morbidities (reference: no co-morbidity)				
Congestive heart failure	1.20	0.261	0.8736	1.6460
Essential hypertension	**1.19**	**0.003**	**1.0609**	**1.3375**
Diabetes mellitus	**1.21**	**<0.001**	**1.0944**	**1.3356**
Stroke/TIA	1.04	0.644	0.8911	1.2050
Pulmonary embolism/thromboembolism	1.03	0.784	0.8331	1.2738
Vascular disease	1.03	0.601	0.9274	1.1393
Acute coronary syndrome (incl. myocardial infarction)	1.08	0.390	0.9052	1.2907
Functional dyspepsia	1.10	0.553	0.8037	1.5043
Renal failure	**0.77**	**<0.001**	**0.6704**	**0.8873**
Treatment (reference: VKA)				
Dabigatran	1.09	0.279	0.9339	1.2674
Rivaroxaban	**1.43**	**<0.001**	**1.2602**	**1.6329**
Use of cardiovascular drugs[a] (reference: no)				
Yes	**1.34**	**0.014**	**1.0622**	**1.6899**
Use of antiplatelet drugs[a] (reference: no)				
Yes	**0.75**	**<0.001**	**0.6614**	**0.8537**

Odds ratio assessed persistence with treatment compared with the 'Reference' group: an odds ratio of >1 implied improved persistence and an odds ratio of <1 implied poorer persistence.
$CHADS_2$ score: 0 = low risk; 1 = intermediate risk; 2–6 = high risk.[17]
SHI, statutory health insurance; TIA, transient ischaemic attack; VKA, vitamin K antagonist.
[a]Within 180 days post-index date.
Bold indicates values significant (<0.05).

Table 4 Persistence after 360 days (percentage of patients)

	VKA	Rivaroxaban	VKA	Dabigatran	Rivaroxaban	Dabigatran
Number of patients	2978	433	2978	374	433	374
Persistent % (*n*), 95% CI	25.5 (760) (24–27.1)	53.1 (230) (48.4–57.8)	25.5 (760) (24–27.1)	47.3 (177) (42.3–52.4)	53.1 (230) (48.4–57.8)	47.3 (177) (42.3–52.4)
95% CI for the difference between proportions	27.6 (22.6–32.5)		21.8 (16.6–27.1)		5.8 (−1.1–12.6)	
Z-test	**<0.001**		**<0.0001**		0.100	

VKA, vitamin K antagonist.
Bold indicates values significant (<0.05).

dabigatran therapy. The percentage of treatment interrupters is not provided for VKA because the figure could not be meaningfully interpreted owing to individualized dosing.

Adherence to dosing regimens with rivaroxaban and dabigatran

Patients with a follow-up of at least 180 days showed significantly greater adherence to rivaroxaban during the first 180 days compared with dabigatran prescription. High adherence (MPR ≥0.80%) was observed in 61.4% of rivaroxaban users and in 49.5% of dabigatran users (χ^2 test: $P < 0.001$) after 180 days. Mean MPR was 0.76 [95% confidence interval (CI) 0.74–0.78] for rivaroxaban and 0.67 (95% CI 0.65–0.69) for dabigatran (*Figure 3*). The difference was statistically significant ($P < 0.001$). These results are consistent with the adherence over the entire individual follow-up of rivaroxaban users (mean follow-up 252.1 ± 119.7 days) and

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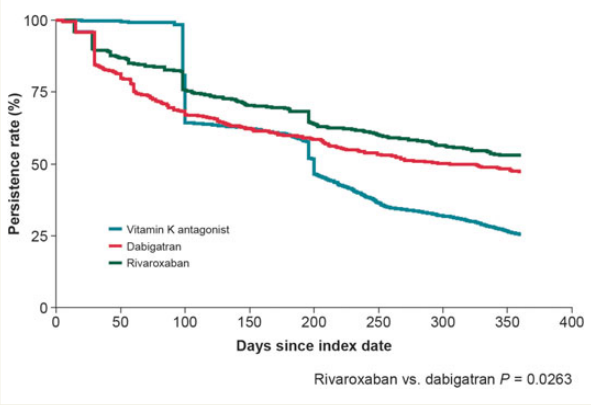

Figure 2 Proportion of persistent patients over 360-day follow-up period. Of note, since the VKA curve crosses the other curves, only rivaroxaban and dabigatran treatments were statistically compared using the Wilcoxon test.

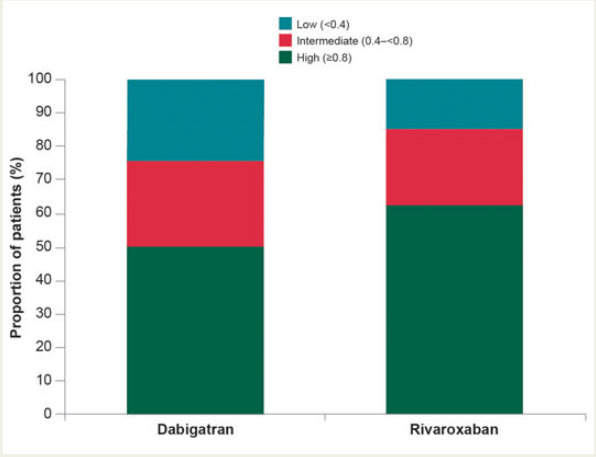

Figure 3 Adherence to dabigatran and rivaroxaban, quantified by MPR.

dabigatran users (mean follow-up 300.6 ± 140.5 days). High adherence (MPR ≥0.80%) was observed in 62.6% of rivaroxaban users and in 47.6% of dabigatran users (χ^2 test: $P < 0.001$). Mean MPR was significantly higher for rivaroxaban compared with dabigatran (0.75; 95% CI 0.73–0.76 vs. 0.64; 95% CI 0.62–0.66; $P < 0.001$).

Discussion

Persistence to prescribed medication is known to be essential for a successful therapeutic outcome and is acknowledged to be important in the treatment of chronic illnesses.[10] The current study is one of the first to evaluate adherence and persistence of different OAC therapies in a 'real-world' German primary care setting, examining data for >7000 patients diagnosed with AF. Our data indicated that treatment persistence was significantly higher in patients treated with NOACs (53% for rivaroxaban and 47% for dabigatran) compared with those taking a VKA (26%; primarily phenprocoumon, which is the dominant VKA in Germany). We also found treatment persistence with rivaroxaban to be significantly higher than that with dabigatran.

There are several factors that may lead to differences in persistence and adherence between treatments in routine practice. Vitamin K antagonist therapy involves regular INR monitoring and dose adjustments.[11] In addition, VKA therapy is influenced by numerous interactions with drugs and foods (e.g. foods rich in vitamin K).[3] Since NOACs do not require routine monitoring and do not have food–drug interactions and fewer drug–drug interactions, our findings of improved persistence with both dabigatran and rivaroxaban treatments over VKA may be explained by the improved convenience of these modern therapies.

Furthermore, our data indicate that rivaroxaban demonstrated significantly higher adherence and a clinically relevant trend towards higher persistence compared with dabigatran. One possible explanation could be the difference in dosing regimens, because rivaroxaban is given once daily, whereas dabigatran is given twice daily.[12] Once-daily regimens are generally preferred by patients taking lifelong medications.[13] Differences in adherence and persistence between rivaroxaban and dabigatran may also be related to their side-effect profiles, because clinical trials and NOAC registries[14–16] indicated a clinically relevant dyspepsia rate for dabigatran (>11% of all patients in RE-LY), which was not seen with VKA or rivaroxaban.

It should be noted that, even in the group of treatment-non-persistent patients (which included patients with drug interruptions of >60 days), a considerable number of patients (14% of patients receiving rivaroxaban and 11% of patients receiving dabigatran) restarted index therapy again within the follow-up period. This is a strong indicator that long interruptions to NOAC treatment in these cases were most likely caused by intercurrent medical conditions (hospitalizations, surgery, temporary organ dysfunction) rather than drug side effects or non-adherence (both of which would have most likely resulted in total discontinuation or switching to VKAs or other anticoagulants). If these cases were added to the group of treatment-persistent patients, >67% of patients with AF newly treated with rivaroxaban and >58% of those treated with dabigatran continued their initially prescribed treatment after 360 days.

Our regression model identified a number of factors associated with improved respective decreased treatment persistence. Patients with pre-existing diabetes mellitus or taking cardiovascular drugs, for instance, were more likely to persist. This may be related to increased understanding in these patients of the importance of persistence and adherence with prescribed regimens. If so, better education for patients may encourage persistence. In contrast, older patients and those with renal failure or concomitant use of antiplatelet drugs had a significantly lower likelihood of persistence, which may be related to treatment complications such as bleeding. However, it is important to point out that these findings should not be over-interpreted since they were derived from a single regression model only used on retrospectively collected database entries.

Although persistence with NOACs seems to be consistently better than persistence with VKAs,[3–5,17,18] absolute values for persistence vary considerably between different studies. This is primarily related to differences in patient population and study methodologies. For example, persistence levels based on prescription data

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(such as the IMS Disease Analyzer) tend to be lower compared with persistence levels based on pharmacy databases, which typically include selected populations with high adherence.[19] Furthermore, persistence and adherence assessments in prospective registries that involve direct patient contacts are usually higher than those reported from database analysis. For instance, the overall persistence with rivaroxaban treatment in the prospective Dresden NOAC Registry was 81.5% over a median of 541 days.[14] Similarly, a persistence rate of 80% was found for rivaroxaban at 1 year in the observational XANTUS study.[20]

Despite methodological differences, our results of higher treatment persistence with NOACs are in line with the findings of other studies that used different methodological approaches. In the USA, a comparison between dabigatran and warfarin including inpatient, outpatient, and pharmacy claims data was performed to measure persistence in newly diagnosed patients with AF, who were naïve to OAC treatment.[4] Treatment persistence was found to be significantly greater for patients receiving dabigatran than for patients receiving warfarin, both at 180 days (71.8 vs. 53.3%) and at 360 days (63.3 vs. 38.8%) after treatment initiation.[4] Treatment persistence with rivaroxaban has also been compared with that of warfarin in a recent study of US claims data of inpatients and outpatients.[3] Patients receiving rivaroxaban had a significantly higher rate of treatment persistence compared with those receiving warfarin over a 1-year period (hazard ratio 0.63, 95% CI 0.59–0.68). A similar trend was demonstrated by Laliberté *et al.*[5,17]

In the Dresden NOAC Registry, persistence to dabigatran persistence was ~70% at 12 months,[16] and lower than the 81.5% reported for rivaroxaban in the same setting. A recent large US claims database analysis also found that patients receiving rivaroxaban were more likely to be persistent to therapy than patients on dabigatran.[7] Therefore, the difference in persistence with rivaroxaban and dabigatran found in the present study is a consistent finding.

Limitations

The database utilized in this study, the IMS Disease Analyzer, acquires prescription data from PCPs rather than actual dispensed drugs. Therefore, a limitation of this study was that it did not take into account primary non-adherence of patients who do not collect drugs from the initial prescription, which, according to an analysis of a US population, may be as common as 28.3% of electronic prescriptions for new medications given at community-based practices.[19] A systematic review found that the most common reasons for non-fulfilment of prescriptions were perceived concerns about the medications, lack of perceived medication need, and medication affordability issues.[21] An additional limitation was that the current study contained information for PCP prescribing but not for hospital-based or specialist prescriptions.

Primary care physician prescriptions from practices not linked to the IMS Disease Analyzer were not captured in the study data and, in addition, patients who may have moved from a PCP in the IMS network to an external PCP would be classified as treatment non-persistent. Vitamin K antagonist adherence could not be calculated because of dynamic dosing.[3,5] Such dosing also meant that the level of treatment persistence attributable to VKAs may have been underestimated in the current study. The dynamic dosing of VKA is likely to have caused the steep decline for VKA at 90-day intervals in *Figure 2*, being an artefact caused by the fact that phenprocoumon dosing in the German real-world scenario varies between 0.5 and 2–3 tablets once daily, while our calculation was based on an average dose of 1 tablet per day. Consequently, given that the VKA package most commonly prescribed contains 90 or 100 pills per package, the assumption of an average intake of 1 tablet per day results in a pronounced decline at 90-day intervals and a somewhat flattened curve in between.

Another limitation is that only concomitant cardiovascular drugs were studied; the total number of medicines and the dosing regimens may have impacted adherence and persistence.

The variation between OACs in the proportion of patients who were followed up for the appropriate period was caused by the difference in launch dates. Therefore, patients initiated on a VKA had the highest proportion of follow-up at 360 days, whereas patients receiving rivaroxaban had the lowest proportion of follow-up over the same time frame. It cannot be excluded that different launch dates of dabigatran (September 2011) and rivaroxaban (January 2012) had some impact on our findings. However, rivaroxaban was launched in Germany only 4 months after dabigatran, and uptake of new treatments in the first few months is usually low. Therefore, we do not think that the short period of time between the launches of the two drugs led to a relevant selection bias that affected our overall findings.

Analysis was restricted to patients who were still alive after 180 and 360 days. Therefore, this group may represent a group of relatively healthy patients, as those who were lost to follow-up or who died during the first year were not included.

Despite these limitations, we conclude from our study that treatment persistence with dabigatran and rivaroxaban was better than persistence with VKA. Furthermore, within the group of patients prescribed a NOAC, persistence with and adherence to treatment were better with rivaroxaban compared with dabigatran.

Supplementary material

Supplementary material is available at *Europace* online.

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