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Adherence to anticoagulant treatment with apixaban and rivaroxaban in a real-world setting

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ABSTRACT

Aim: Low adherence to cardiovascular medications is often difficult to monitor and is associated with adverse outcomes. We investigated whether there is a difference between the estimated adherence (EA) of the two-dosed regimens of apixaban (A) and the one-dosed regimen of rivaroxaban (R) for stroke prophylaxis in patients with non-valvular atrial fibrillation (AF).

Method and results: This is a retrospective cohort study of AF patients referred to a well-structured nurse-based AF unit for the initiation of anticoagulation therapy. The adherence data was extracted from the Swedish national prescribed drug register. EA was calculated by dividing the number of daily doses dispensed from the prescription that occurred closest after 3 months from the first dispensed prescription of the respective agent until (but excluding) the last refill by the number of days in the interval. The study included 123 patients on A and 227 patients on R with a 12-month follow-up period. There were no significant demographic differences between the two patient groups except for previous vitamin K antagonist treatment, in the A patient group ($n = 29$, 24%) and in the R ($n = 31$, 14%), $p = 0.025$. The mean ± SD of EA after 3 months was high for both A 97 ± 7 ($n = 112$) and R 97 ± 9 ($n = 197$) $p = 0.97$. The EA ≥80% was for A 97% ($n = 109$) and for R 96% ($n = 189$) $p = 0.43$.

Conclusion: The two dosed regimens of apixaban and the one dosed regimen of rivaroxaban showed similar high estimated adherence when administered for stroke prophylaxis in patients with AF in a well-structured nurse-based AF clinic.

1. Introduction

The non-vitamin K antagonist oral anticoagulants (NOACs) are superior in efficacy and safety compared to vitamin K antagonists (VKA) when used for stroke prophylaxis in patients with non-valvular atrial fibrillation (AF) [1–3]. The NOACs offer life style advantages due to fast dosing regimen, lack of regular routine laboratory monitoring of the hemostatic system and significantly less interactions with food products and medical preparations.

However there are concerns that the lack of regular monitoring of the coagulation level might make it difficult to assess and enhance the drug adherence. Low adherence in AF patients taking NOACs was shown to be associated with higher mortality and morbidity [4].

Once daily dosed medication had been shown to have better adherence rates in comparison to twice daily dosed regimens in case of cardiovascular medications [5]. Therefore we planned this study to assess and compare adherence levels between the one-dosed regimen of rivaroxaban and the two-dosed regimens of apixaban among patients with non-valvular AF in a real world clinical setting within the framework of a well-structured atrial fibrillation clinic.

2. Methods

This is a retrospective cohort study of AF patients referred to our unit for initiation of NOACs in the period between December 2011 and May 2014. All the patients were treated in a single institution, which is a large tertiary referral cardiology outpatient clinic that incorporates a well-structured, nurse-based AF unit. The unit's nurses initiate NOAC treatment for patients with AF assessed initially by a referring cardiologist. The unit nurses review the treatment indication, the bleeding risk, provide information about the treatment, and give patient support during the follow-up period.

The nurse suggests to the referring cardiologist a follow-up plan and in addition they stand for future patient support during the follow-up period at the clinic. Patients are encouraged to make prompt contact

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with the unit nurses in case of bleeding, suspected side effects, and planned interventions that might necessitate study withdrawal, and even in case they for some reason decide or wish to stop the NOAC treatment. All patients had a scheduled appointment with the cardiologist 3 and 12 months after the initiation of the NOAC therapy. We did not include any patient with persistent atrial fibrillation requiring NOAC temporally for scheduled elective cardioversion.

The CHA_2DS_2-VASc score scale was used to estimate the risk of stroke. The score takes into account age, gender, congestive heart failure (current diagnosis of heart failure or left ventricular ejection fraction <40%), hypertension and/or diabetes mellitus requiring pharmacological treatment, and previous diagnosis of stroke/transient ischemic attack (TIA) or systemic embolism, vascular disease. Previous antiplatelet therapy comprised prior use of oral acetylsalicylic acid or clopidogrel that was stopped immediately or shortly before the start of NOAC therapy and the same for prior VKA therapy, which was either stopped shortly before or switched immediately to NOAC.

The estimated adherence was calculated by dividing the number of daily doses dispensed from the prescription that occurred closest after 3 months from the first dispensed prescription of the respective NOAC until (but excluding) the last refill by the number of days in the interval. Since rivaroxaban entered the market prior to apixaban we only included data for the first year following the first prescription in order to make the two groups comparable regarding follow-up time. Patients that did not have 12 month follow-up were excluded. A patient was defined as discontinued if the number of daily doses from the last refill did not last until the end of the 12-month period. In order to take into account possible non-adherence or saved doses from previous refills, we allowed a gap of 30 days from the last dose. However, if a patient was defined as discontinued, discontinuation was assumed to occur after half of the daily doses from the last refill. The adherence and persistence data was extracted from the Swedish national prescribed drug register since each resident in Sweden has a unique personal identification number. The Register performs online with automat registration of all dispensed prescriptions from all pharmacies throughout Sweden.

2.1. Ethics

The study complies with the Declaration of Helsinki, and the study protocol was approved by the regional ethics committee (DNR: 2014/738-31) and the Swedish Board of Health and Welfare (DNR: 30457/2014).

2.2. Statistics

Baseline characteristics were tested for distributional differences between apixaban and rivaroxaban using Fisher Exact test for categorical variables and *t*-test or Mann–Whitney U test for continuous variables. To compare outcomes (adherence and persistence) between the two groups Generalized Estimating Equation (GEE) models were used. Due to the small sample size we restricted adjustment to those variables that differed statistically significant between the two NOACs. Time to discontinuation was graphically presented in a Kaplan–Meier curve and tested with the log-rank test.

The level of significance was set to 5%, two-sided. All calculations were performed using R v 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The study included 127 patients on apixaban and 249 patients on rivaroxiban with a 12-month follow-up period. We then excluded patients who had only one prescription refill (3 apixaban and 21 rivaroxaban) and those who died during the follow-up period (1 apixaban and 1 rivaroxaban). Then for the calculation of the estimated adherence we excluded the first 3 months of treatment making the final number of patients 112 on apixaban and 197 on rivaroxaban. The total observation time (median, q1–q3) excluding the first 3 months of treatment was 184 (157–212) for apixaban and 188 (150–204) for rivaroxaban. The patient's clinical characteristics are described in Table 1. There were no significant differences between the patients on the two therapies except for previous VKA treatment for which there were more patients in the apixaban patient group (29, 24%) than in the rivaroxaban patient group (31, 14%), p = 0.025.

The number of patients that discontinued rivaroxaban was 39 (17%) and for apixaban was 16 (13%), which showed no statistical difference. The Kaplan–Meyer curve for discontinuation rates is shown in Fig. 1.

The risk ratio for discontinuation unadjusted is 1.32 (95% CI 0.77–2.26) p-value = 0.312, and risk ratio adjusted for prior VKA 1.28 (95% CI 0.75–2.21) p-value = 0.365.

The estimated mean and median adherence rates after 3 months for apixaban and rivaroxaban and the number of patients' adherence ≥80% are shown in Table 2.

The adherence rate including the initial 3 months was for apixaban, mean ± SD (96 ± 13) and for rivaroxaban (97 ± 9) p = 0.45, the median adherence rate (q1-13) was for apixaban 100 (100–100) and for rivaroxaban 100 (100–100) p = 0.67. The adherence rate ≥ 80% was for apixaban 95% (n = 117) and for rivaroxaban 96% (n = 218) p = 0.78.

The risk ratio for adherence ≥80% unadjusted is 1.52 (95% CI 0.41–5.60) p-value = 0.532, and risk ratio adjusted for prior VKA is 1.54 (95% CI 0.41–5.72) p-value = 0.523.

There were no whatever significant differences between the patient group with high adherence ≥80% and those with poor adherence <80% (Table 3).

4. Discussion

Our study shows a very high estimated adherence levels for both apixaban and rivaroxaban when initiated in a well-structured atrial fibrillation clinic and no statistically significant difference in persistence during one-year treatment time. There was no significant difference in the overall adherence level and higher adherence (≥80%) between the two-dosed regimens of apixaban and the one-dosed regimen of rivaroxaban.

The findings are of extreme importance considering the short half-life of the NOAC and the lack of any mean of detecting and following the patient's adherence to the agent. These considerations have raised fears taking into account the high costs of the NOAC drugs and that a

Table 1
Basic characteristics of the patients.

Variable	Apixaban N = 123	Rivaroxaban N = 227	p-value
Age	72 + 8	73 + 8	0.56
Female	57 (46%)	112 (49%)	0.65
Male	66 (54%)	115 (51%)	
Body Mass Index	26 + 4	26 + 5	0.50
Prior antiplatelet	49 (40%)	85 (37%)	0.73
Prior VKA	29 (24%)	31 (14%)	0.03
Standard dose	102 (83%)	184 (81%)	0.77
Reduced dose	21 (17%)	43 (19%)	
CHA_2DS_2-VASc score	3 (2–4)	3 (2–4)	0.26
Heart failure	13 (11%)	23 (10%)	1.00
Hypertension	77 (63%)	153 (67%)	0.41
Diabetes mellitus	10 (8%)	25 (11%)	0.46
Stroke	14 (11%)	13 (6%)	0.09
Acute myocardial infarction	12 (10%)	11 (5%)	0.11
Peripheral artery disease	3 (2%)	6 (3%)	1.00
Glomerular filtration rate*	79 ± 25	79 ± 26	0.96

Categorical variables are presented with n (%) and tested with Fisher Exact Test, continuous variables are presented with mean ± SD or median (q1–q3) and tested with *t*-test or Man–Whitney U test respectively. VKA: Vitamin K antagonist. * ml/min, calculated using Cockroft–Gault.

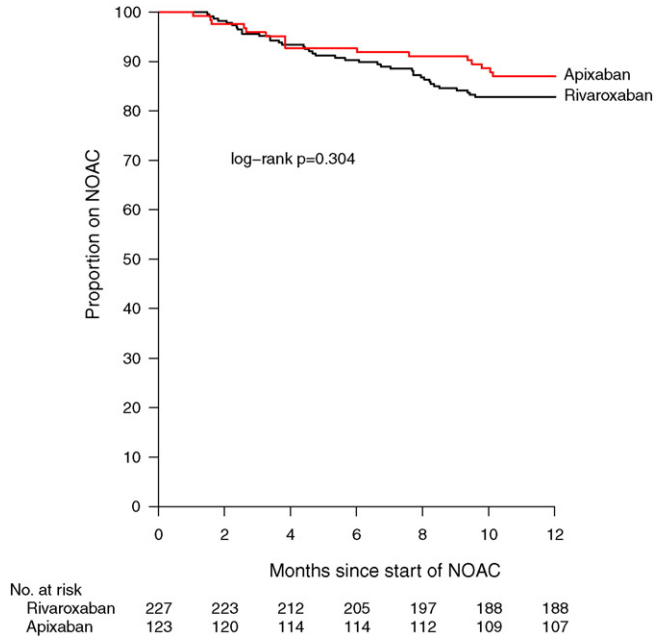

Fig. 1. Kaplan–Meyer curve of the discontinuation rates of patients on apixaban and rivaroxaban during 12 month period.

low adherence would probably expose the patients to a higher risk of stroke, which would then double the health system and personal costs.

A once daily dosed regimen of NOAC had been suggested to yield better adherence rates in comparison to twice daily dosed regimens since there seems to be a general concern that drug adherence is inverse to the number of doses per day.

Warfarin treatment for AF related stroke has been shown to be associated with 45% low adherence (<80%) in a study on pharmacy refill data from drug prescription data in Sweden [6]. However adherence to the two dosed regimens of dabigatran has been proven to be much better in the data from the Veterans Administration Health study, in which the ≥80% adherence was 72% using the proportion of days covered method to calculate the adherence [4]. In this study the majority was men 98.3% and the mean age was 71.3 years. In addition a nationwide cohort study in Denmark showed a 76.8% of the AF patients taking dabigatran hade ≥80% adherence after 1 year using the proportion of days covered [7]. Persistence has also been shown to be higher for patients taking dabigatran than for warfarin at one year (63% versus 39%) in a study by the United States Department of Defense administrative claims [8].

A clinical trial study of patients taking dabigatran versus warfarin for patients with acute deep venous thromboembolism showed a very high adherence of 98% [9]. This high adherence was most probably driven by frequent follow-up in the trial with the procedure of regular pill counts. In addition clinical trials tend to exclude patients with previous serious adverse events.

However a high adherence (88% of the patients had adherence ≥80%) was also shown by a clinical practice study of small cohort of patients taking dabigtran in a single thrombosis clinic [10].

Table 2
Adherence after 3 months in the apixaban and rivaroxaban patients.

Variable	Apixaban n = 112	Rivaroxaban n = 197	p-value
Adherence, mean ± SD	97 ± 7	97 ± 9	0.97
Adherence, median (q1–q3)	100 (99–100)	100 (98–100)	0.82
Adherence ≥ 80%, n (%)	109 (97%)	189 (96%)	0.43

Table 3
Characteristics of the patients with adherence < 80% compared with those with adequate adherence.

Adherence after 3 months			
Variable	<80% (n = 11)	≥80% (n = 298)	p-value
Treatment duration, days			
Mean ± SD	170 ± 38	179 ± 50	0.58
Median (q1–q3)	163 (142–186)	186 (156–208)	0.26
Female	6 (55)	141 (47)	0.76
Male	5 (45%)	157 (53%)	
Age	74 ± 11	72 ± 8	0.59
Body Mass Index	24 ± 4	27 ± 5	0.12
Prior VKA	2 (18%)	51 (17%)	1.00
None	9 (82%)	247 (83%)	
CHADSVASc	4 (2–4)	3 (2–4)	0.50
Creatinine clearance[a]	73 ± 30	80 ± 25	0.36

Categorical variables are presented with n (%) and tested with Fisher Exact Test, continuous variables are presented with mean + SD or median (q1–q3) (min–max) and tested with ANOVA or Kruskal–Wallis test respectively.
[a] GFR calculated by Cocroft–Gault formula.

Recent paper from Germany assessing the adherence to NOACs for one year based on the proportion of days covered ≥80% showed significantly higher adherence in rivaroxaban users (72.2%) compared to dabigatran (67.2%) and apixaban (69.5%) users [11].

In our study the high adherence in both rivaroxaban and apixaban users is probably attributed not only to proper patient education using motivational interviewing but also to proper patient selection and very well structured patient support and follow-up system.

Shore s. et al. showed that patient education alone is inferior to appropriate patient selection or patient adverse events monitoring to enhance dabigatran adherence in different prescription sites [12].

The limitation of the study is that it was retrospective and that the estimated adherence method we used to calculate adherence using the pharmacy refill data is not fully reliable as no any other available method neither [13]. Others are the small study population and that the study did not extend more than one-year treatment in looking at the adherence data.

5. Conclusion

Our study shows a high estimated adherence for both the two-dosed regimen of apixaban and the one-dosed regimen of rivaroxaban when administered for stroke prophylaxis in patients with non-valvular atrial fibrillation. There was no difference in the estimated adherence between the two agents of different dosed regimens.

Conflict of interests

Faris Al-Khalili and Catrine Lindström received honorarium for acting as speakers for Bayer, Boehringer Ingelheim and Pfizer.

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