RESEARCH LETTER

Efficacy and safety of apixaban in real-life patients at high bleeding risk

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Introduction Recent registries and observational studies increasingly support the view that apixaban has the most favorable safety profile among all age groups.[1,2] The AVERROES trial[3] showed that in patients with atrial fibrillation (AF) who were unsuitable for treatment with vitamin K antagonists (VKAs), apixaban compared with aspirin was associated with a lower risk of stroke and similar risk of major bleeding.[3] We aimed to assess the efficacy and safety of the treatment with apixaban in real-life Polish patients at high bleeding risk compared with those who received other therapeutic options.

Material and methods **Patients** We enrolled patients with AF or venous thromboembolism (VTE) at high bleeding risk and unstable anticoagulation while on warfarin or acenocoumarol, who were referred to the Center for Coagulation Disorders at the John Paul II Hospital in Kraków, Poland, between June 2014 and November 2016. The inclusion criteria were indications for long-term anticoagulation, namely, for AF: ≥2 points for male sex and ≥3 points for female sex in the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke, vascular disease, age 65–74, and sex [female]); or for VTE: recurrent unprovoked disease or severe thrombophilia-associated proximal deep vein thrombosis and/or pulmonary embolism, combined with the time in therapeutic range of less than 50%. The exclusion criteria were acute coronary syndrome or stroke within the preceding 6 months, active malignancy, current alcohol abuse, and chronic kidney disease stage 4 or 5. The local bioethics committee approved the study. All patients signed written informed consent.

A high bleeding risk was defined as 3 points or higher in the HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly >65 years, drugs/alcohol concomitantly), or a single strong risk factor for bleeding. In patients after VTE, other bleeding risk factors, in particular menorrhagia in women, were present.

A total of 36 patients agreed to switch to apixaban therapy. Patients with a history of recurrent bleedings were switched to apixaban at a dose of 2.5 mg twice daily, while patients with high thromboembolic risk, especially those after ischemic stroke, were switched to apixaban at a dose of 5 mg twice daily. The patients switched to apixaban were matched for age, sex, bleeding risk, and indications for anticoagulation, with 36 participants recruited at the same time who served as a control group. These patients refused to start treatment with apixaban largely due to no reimbursement for this anticoagulant in Poland, and they preferred to continue VKAs or use other less expensive non–vitamin K antagonists oral anticoagulants (NOACs) at reduced doses (ie, dabigatran, 110 mg twice daily, or rivaroxaban, 15 mg once daily).

During follow-up, we recorded major bleeding and clinically relevant non–major (CRNM) bleeding defined according to the International Society on Thrombosis and Haemostasis criteria.[4] Menorrhagia was defined as self-reported bleeding which occurred at normal intervals but lasted more than 7 days.[5] New documented stroke and VTE episode were also recorded. The follow-up was censored at the time of bleeding or thromboembolic episode.

Statistical analysis Continuous variables were expressed as mean (SD) or median and interquartile range (IQR). Normality was assessed by the Shapiro–Wilk test. Differences between the groups were compared using the *t* test for normally distributed variables. The Mann–Whitney test was used for nonnormally distributed continuous variables. Categorical variables were

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presented as numbers and percentages and compared by the Fisher exact test for 2×2 tables or by the Pearson χ^2 test for other tables. The rate of bleeding (%/year) was calculated using the following formula: the number of bleeding episodes in the group divided by the product of number of patients in the group and number of years of follow-up multiplied by 100. Bivariate Cox proportional hazards regression models were used to calculate the hazard ratios (HRs) of predictive factors and their 95% confidence intervals (CIs) for the incidence of clinical events. A 2-sided *P* value was considered statistically significant. All calculations were done with JMP®, Version 12.2.0 (SAS Institute Inc., Cary, North Carolina, United States, 1989–2007).

Results **Baseline** The characteristics of the study groups are presented in TABLE 1. The median HAS-BLED score was 4 (IQR, 3–5), and a HAS-BLED score of 3 or more was observed in the majority of patients with AF (TABLE 1). The high bleeding risk in the other 3 patients with AF resulted from previous intracranial bleeding, von Willebrand disease in the second patient, and alcohol-related liver disease in the third patient. Among patients switched to apixaban at a dose of 2.5 mg twice daily (n = 26, 72.2%), there were fewer patients with previous stroke (4 [15.4%] vs 6 [60%], *P* = 0.01) compared with those on the 5-mg dose (10 [27.8%]). Patients on apixaban at a dose of 2.5 mg twice daily did not fulfill the criteria for reduced doses according to the product characteristics. In the control group, there were 7 patients (19.4%) on VKAs, 18 patients (50%) on dabigatran at a dose of 110 mg twice daily, and 11 patients (30.5%) receiving rivaroxaban at a dose of 15 mg daily.

Follow-up The median follow-up was 17 months (IQR, 14–21 months). A total of 18 patients (25%) reported major or CRNM bleeding, including 9 gastrointestinal (12.5%) bleedings, 4 heavy menstrual bleedings (5.6%), 1 intracranial hemorrhage (1.4%), 1 hemoptysis (1.4%), and 3 other bleedings (4.2%) (Supplementary material, *Table S1*). There were fewer CRNM or major bleedings among patients on apixaban compared with controls (3 [8.3%] vs 15 [41.7%], *P* = 0.01). The rate of major or CRNM bleedings was 5.8%/year on apixaban compared with 28.4%/year on other anticoagulant regimens (HR, 0.23; 95% CI, 0.05–0.70; *P* = 0.008). There were 2 major bleedings among patients treated with apixaban (2.5 mg twice daily) and 12 major bleedings in controls (3.9%/year and 22.7%/year, respectively; HR, 0.18; 95% CI, 0.03–0.7; *P* = 0.009). There was 1 CRNM bleeding on apixaban and 3 CRNM bleedings in the control group (1.9%/year and 5.7%/year, respectively; HR, 0.46; 95% CI, 0.02–3.66; *P* = 0.5). Gastrointestinal bleedings were less frequent among patients switched to apixaban (1 [2.8%] vs 8 [22.3%], *P* = 0.03), and the risk of gastrointestinal bleeding on apixaban was decreased compared with controls (1.9%/year and 15.1%/year, respectively; HR, 0.14; 95% CI, 0.01–0.76; *P* = 0.02). One control patient treated with rivaroxaban who experienced a gastrointestinal bleeding died during hospitalization. Other types of bleeding were comparable among the study groups.

There were 8 thromboembolic events (22.2%) during the follow-up, that is, 4 in each group. In the apixaban group, we observed 2 transient ischemic attacks (TIAs), 1 minor stroke, and 1 recurrent deep vein thrombosis episode, all on apixaban at a dose of 2.5 mg twice daily. In the control group, there were 2 strokes and 1 TIA, 2 at an international normalized ratio of less than 2 during VKA therapy and 1 TIA on rivaroxaban (Supplementary material, *Table S2*). The rate of thromboembolic events was similar in both groups (7.7%/year and 7.6%/year, respectively; HR, 1.30; 95% CI, 0.30–5.71; *P* = 0.7). The risk of thromboembolic episodes was similar among patients on apixaban and those on dabigatran at a dose of 110 mg twice daily and rivaroxaban at a dose of 15 mg daily.

Discussion Our study demonstrated that in real-life patients at high bleeding risk, the risk of major or CRNM bleeding on apixaban was reduced by 77% compared with the other anticoagulant regimens, including VKA, dabigatran (110 mg twice daily), and rivaroxaban (15 mg daily). In a previous study, the risk of major bleeding on apixaban, compared with other NOACs, was reduced similarly in patients with a HAS-BLED score of 3 or higher and those with a HAS-BLED score of 0 to 2 points.[6] In contrast to this large-scale study using administrative claims, we conducted a prospective real-life study with complete clinical characteristics of the participants and took into consideration also the rate of non–major bleedings, associated with an increased risk of death.[7] In patients on NOACs mostly with a HAS-BLED score below 3, Abraham et al[8] showed that apixaban was associated with a 61% lower risk of gastrointestinal bleeding than dabigatran. We extended those observations onto patients with 3 or more points in the HAS-BLED score. Previous findings suggested a superior benefit-to-risk profile with the lower-dose apixaban regimen than with the high-dose regimen.[9] The safety profile achieved by reducing the dose of apixaban was not associated with a higher risk of thromboembolic events compared with controls on VKAs, dabigatran (110 mg twice daily) and rivaroxaban (15 mg daily). However, all thromboembolic episodes during the follow-up in our study occurred in patients with a high risk of stroke treated with apixaban (2.5 mg twice daily). It indicated that reduced doses of apixaban may convey a relatively high thromboembolic risk which is typically associated with a high bleeding risk.

The study has several limitations, including wide CIs of the calculated HRs, indicating low precision of our estimations due to a small sample size, arbitrary use of normal or reduced apixaban doses, and the possibility of omitting asymptomatic thromboembolic events.

TABLE 1 Characteristics of study participants

Variable		Apixaban-treated patients (n = 36)	Controls (n = 36)	*P* value
Demographic characteristics				
Age, y, median (IQR)		75 (66.8–79.8)	74.5 (65.5–78.8)	0.7
Female sex, n (%)		18 (50)	20 (55.6)	1.0
Body mass index, kg/m^2, median (IQR)		26.7 (24.1–28.9)	24.6 (21.9–32.8)	1.0
Indication for anticoagulation, n (%)	Venous thromboembolism	7 (19.5)	7 (19.5)	0.9
	Atrial fibrillation	30 (83.3)	30 (83.3)	
Time since diagnosis, y, median (IQR)		6 (2.6–12.8)	8 (5–10.8)	0.3
Time of anticoagulant treatment before enrollment, y, median (IQR)		3 (1–6)	3 (1–4)	0.4
Risk of stroke and bleeding in AF patients				
CHA_2DS_2-VASc, median (IQR)		4.5 (4–5)	4.5 (4–5)	1.0
CHA_2DS_2-VASc ≥2, n (%)		30 (83.3)	30 (83.3)	1.0
HAS-BLED, median (IQR)		4 (3–5)	4 (3–4)	1.0
HAS-BLED ≥3, n (%)		29 (96.7)	28 (93.3)	1.0
Comorbidities, n (%)				
Heart failure		15 (41.7)	10 (13.9)	0.3
Previous ischemic stroke		10 (13.9)	10 (13.9)	1.0
Peptic ulcer disease		10 (27.8)	8 (22.2)	0.8
Abnormal liver function		4 (11.1)	4 (11.1)	1.0
Medications, n (%)				
Acetylsalicylic acid		6 (16.7)	7 (19.5)	1.0
Amiodarone		4 (11.1)	2 (5.6)	0.7
Proton pump inhibitors		24 (66.7)	29 (80.6)	0.3
Laboratory investigations				
Hemoglobin, g/l, median (IQR)		129 (111–140)	138 (127–147)	0.03
Platelets, × 10^9/l, mean (SD)		225 (88.9)	192 (48.1)	0.05
eGFR, ml/min/1.73 m^2, median (IQR)		77 (44.25–91)	59 (43.50–65)	0.03
eGFR <60 ml/min/1.73 m^2, n (%)		16 (44.4)	18 (50)	0.2
Bleeding before enrollment, n (%)				
Severe gastrointestinal bleeding		16 (44.4)	16 (44.4)	1.0
Heavy menstrual bleeding		4 (11.1)	4 (11.1)	1.0
Intracranial hemorrhage		3 (8.3)	3 (8.3)	1.0
Hemoptysis		2 (5.6)	2 (5.6)	1.0
Other		7 (19.4)	7 (19.4)	1.0

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; CHA_2DS_2-VASc and HAS-BLED, see the Material and methods section

In conclusion, the current small study shows the first Polish experience with the use of apixaban in patients at high bleeding risk, given the low availability of this agent due to no reimbursement of such therapy for AF and VTE in Poland.

Supplementary material Supplementary material is available with the article at www.pamw.pl.

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