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ORIGINAL ARTICLE

Comparison of clinical characteristics of real-life atrial fibrillation patients treated with vitamin K antagonists, dabigatran, and rivaroxaban: results from the CRAFT study

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Abstract

Background: The first-line drugs for the treatment of non-valvular atrial fibrillation (AF) are non-vitamin K antagonist oral anticoagulants (NOACs), which are preferred over vitamin K antagonists (VKAs). There is some evidence that there are discrepancies between everyday clinical practice and the guidelines.

Aim: The study aimed to compare the characteristics of patients on VKAs, dabigatran, and rivaroxaban in everyday practice (i.e. baseline characteristics, drug doses, risk factors for bleeding and thromboembolic events). Additionally, we assessed the frequency of prescription of different oral anticoagulants (OACs) in recent years.

Methods: This study consisted of data from the multicentre CRAFT (MultiCentre expeRience in AFib patients Treated with OAC) study (NCT02987062). This was a retrospective analysis of hospital records of AF patients (hospitalised in the years 2011–2016) treated with VKAs (acenocoumarol, warfarin) and NOACs (dabigatran, rivaroxaban). A total of 3528 patients with non-valvular AF were enrolled in the CRAFT study.

Results: The total cohort consisted of 1973 patients on VKA, 504 patients on dabigatran, and 1051 patients on rivaroxaban. Patients on rivaroxaban were older (70.5 ± 13.1 years) and more often female (47.9%), compared with those on VKAs (67.0 ± 12.8 years, $p < 0.001$; 35.5%, $p < 0.001$) and on dabigatran (66.0 ± 13.9 years, $p < 0.001$; 38.9%, $p = 0.001$). Among NOACs, patients with persistent and permanent AF were more likely to receive rivaroxaban (54.7% and 73.4%, respectively) than dabigatran (45.3%, $p < 0.001$ and 26.6%, $p = 0.002$, respectively). Patients on rivaroxaban had higher risk of thromboembolic events (CHA_2DS_2VASc 3.9 ± 2.0, $CHADS_2$ 2.2 ± 1.4) than those on VKAs (3.3 ± 2.0, 1.9 ± 1.3) and on dabigatran (3.1 ± 2.0, 1.8 ± 1.3). Patients on rivaroxaban had also a higher rate of prior major bleeding (11.2%) than those on VKAs (6.7%, $p < 0.001$) and on dabigatran (7.3%, $p = 0.02$). Patients on lower doses of dabigatran and rivaroxaban had a significantly higher risk of thromboembolic and bleeding events. Use of VKAs in the year 2011 was reported in over 96% of patients on OACs, but this proportion decreased to 34.6% in 2016. In the last analysed year (2016) AF patients were treated mainly with NOACs — dabigatran (24.2%) and rivaroxaban (41.3%).

Conclusions: The prescription of VKAs declined significantly after the introduction of NOACs. Patients treated with different OACs demonstrated a distinct baseline clinical profile. The highest risk of thromboembolic events and incidence of major bleedings was observed in patients on rivaroxaban, in comparison to patients on VKAs and dabigatran. Among NOACs, patients treated with lower doses of dabigatran and rivaroxaban were older and had a significantly higher risk of thromboembolic and bleeding events.

Key words: anticoagulation, atrial fibrillation, drug dose, non-vitamin K antagonist oral anticoagulants (NOACs), vitamin K antagonists (VKAs)

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INTRODUCTION

According to current European guidelines, the prevalence of atrial fibrillation (AF) is estimated at approximately 3% of adults [1]. What is more, among those in middle-age probably one in four will develop AF [1]. AF is associated with increased risk of all-cause mortality and ischaemic stroke, as well as high hospitalisation rates [1]. An integral element of management of patients with AF is anticoagulation to prevent thromboembolic events. According to the current guidelines for non-valvular AF treatment, the first-line drugs are non-vitamin K oral anticoagulants (NOACs), which are preferred over vitamin K antagonists (VKAs) [1]. However, the international GARFIELD-AF (Global Anticoagulant Registry in the FIELD) registry showed that everyday clinical practice is distant from the guidelines [2]. Although the rate of prescription of NOACs is increasing, in general the proportion of patients with an intermediate-high stroke risk receiving oral anticoagulants (OACs) is not increasing [2]. There is a lack of data describing differences in phenotypes of real-life populations according to the type of OAC.

This study aimed to compare the characteristics of patients on VKAs, dabigatran, and rivaroxaban met in everyday practice in terms of baseline characteristics, drug doses, and risk factors for bleeding and thromboembolic events. Additionally, we assessed the frequency of prescription of different OACs in recent years.

METHODS

Study design

This cohort study consisted of data from the multicentre CRAFT (MultiCentre expeRience in AFib patients Treated with OAC) study. The study was registered in ClinicalTrials.gov: NCT02987062. This was a retrospective analysis of hospital records of AF patients treated with VKAs (acenocoumarol, warfarin) and NOACs (apixaban, dabigatran, rivaroxaban). The study was approved by the local Ethical Review Board.

The study included all ages of patients with AF diagnosis, hospitalised in between 2011 and 2016 in two centres: one academic centre localised in a capital city and one district hospital. Patients who did not receive OACs at hospital discharge or had diagnosis of valvular-AF were excluded from the analysis. Patients on apixaban, due to the small group size, were also excluded. Another NOAC, edoxaban, was still unavailable on the Polish market. Investigators collected baseline characteristics regarding demographics, medical history, type of AF (paroxysmal, persistent, and permanent), diagnostic tests results, and pharmacotherapy. Major bleeding was defined as symptomatic bleeding in a critical area or organ (i.e. intracranial, intraocular, retroperitoneal, intramuscular with compartment syndrome), gastrointestinal, and life-threatening (bleeding causing a decrease in haemoglobin level of 20 g/L [1.24 mmol/L] or more or leading to transfusion of two or more units of whole blood or red cells).

Study population and group selection

A total of 3528 patients with non-valvular AF were enrolled in the CRAFT study. All patients were hospitalised and discharged on OAC pharmacotherapy. The total cohort consisted of 1973 patients on VKA, 504 patients on dabigatran, and 1051 patients on rivaroxaban. Figure 1 presents a flow chart of the patients' enrolment in the study.

Comparative analysis of patients treated with OAC

Patients treated with each drug were compared with regard to baseline characteristics and doses of NOACs (2 × 150 mg vs. 2 × 110 mg of dabigatran and 20 mg vs. 15 mg of rivaroxaban). Six patients on dabigatran and seven patients on rivaroxaban had missing dosage data.

Each patient was evaluated regarding common scales assessing risk of thromboembolic (CHA_2DS_2VASc) and bleeding (HAS-BLED, modifiable and non-modifiable risk factors for bleeding in anticoagulated patients, based on the current guidelines for AF treatment [1]) events. We also assessed the frequency of usage of different types of OACs in recent years.

Statistical analysis

Normally distributed continuous variables were presented as mean values and standard deviations. Ordinal variables and non-normally distributed continuous variables were presented as median values and interquartile ranges (IQR). Categorical data were presented as numbers of patients and percentages. The Fisher's exact test and the Mann-Whitney U test were used for categorical variables and continuous variables, respectively. P-values less than 0.05 were considered significant. All tests were two-tailed. Statistical analyses were performed using SPSS software, version 22 (IBM SPSS Statistics 22, Armonk, NY, USA).

RESULTS

Clinical characteristics

Baseline clinical characteristics of the study groups are presented in Table 1. The mean age of the total population was 67.9 ± 13.2 years, and 40.2% were female. Patients on rivaroxaban were older (70.5 ± 13.1 years) and more often female (47.9%), compared with patients on VKAs (67.0 ± 12.8 years, $p < 0.001$; 35.5%, $p < 0.001$) and on dabigatran (66.0 ± 13.9 years, $p < 0.001$; 38.9%, $p = 0.001$). Patients with all types of AF more frequently were on VKAs than on NOACs, but statistical significance was reached only for paroxysmal AF (54.2% vs. 45.8%, respectively; $p = 0.01$). NOAC patients with persistent and permanent AF were more likely to receive rivaroxaban (54.7% and 73.4%, respectively)

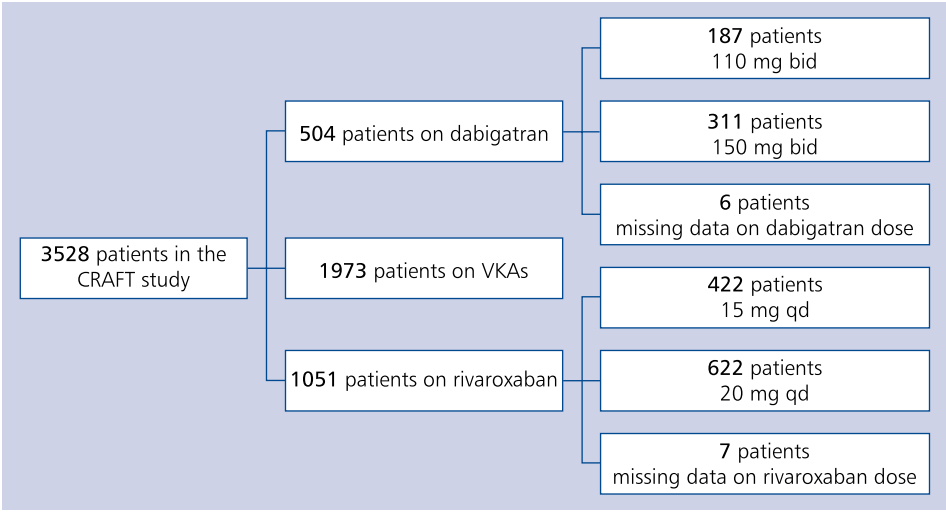

Figure 1. Flow chart of patient enrolment in the study; bid — twice daily; qd — once daily; VKAs — vitamin K antagonists

than dabigatran (45.3%, $p < 0.001$ and 26.6%, $p = 0.002$, respectively).

Comparison of thromboembolic and bleeding risk factors

Table 2 presents thromboembolic and bleeding risk factors in patients with AF treated with different OACs. Patients on rivaroxaban had higher risk of thromboembolic events (CHA_2DS_2VASc 3.9 ± 2.0, $CHADS_2$ 2.2 ± 1.4) than those on VKAs (3.3 ± 2.0, 1.9 ± 1.3) and on dabigatran (3.1 ± 2.0, 1.8 ± 1.3). Patients on rivaroxaban had also a higher rate of prior major bleeding (11.2%) than patients on VKAs (6.7%, $p < 0.001$) and on dabigatran (7.3%, $p = 0.02$). Whereas, patients treated with VKAs had higher mean serum creatinine concentration (1.12 ± 0.43 mg/dL) than patients on rivaroxaban (1.08 ± 0.39 mg/dL, $p = 0.04$) and dabigatran (1.07 ± 0.54 mg/dL, $p = 0.04$), and they were treated with antiplatelets more often than patients on NOACs. Compared to dabigatran and VKAs, patients on rivaroxaban were more likely to have heart failure, history of myocardial infarction or peripheral artery disease, stroke or transient ischaemic attack (TIA), and chronic obstructive pulmonary disease (COPD).

Comparative analysis of patients receiving different doses of NOACs

Among NOACs, patients on higher daily doses (150 mg of dabigatran bid and 20 mg of rivaroxaban qd) were significantly younger (60.0 ± 12.4 years and 65.2 ± 12.9 years, respectively) than patients on lower doses of NOACs (75.8 ± 10.2 years, $p < 0.001$; 78.5 ± 8.6 years, $p < 0.001$, respectively) (Table 3). Patients on lower doses of NOACs were more likely to have permanent AF, while patients on the higher doses had paroxysmal or persistent AF. Patients receiving 110 mg of dabigatran bid or 15 mg of rivaroxaban qd had significantly higher serum creatinine levels, were more often female (significant only for rivaroxaban), and more often had a history of major bleeding, stroke or TIA, prior myocardial infarction and peripheral artery disease, heart failure, type 2 diabetes, and COPD than patients on 150 mg of dabigatran bid or 20 mg of rivaroxaban qd. Patients on lower doses of dabigatran and rivaroxaban had a significantly higher risk of thromboembolic events (CHA_2DS_2VASc: 4.4 ± 1.7 and 5.0 ± 1.7, respectively) than patients on higher doses (CHA_2DS_2VASc: 2.3 ± 1.7 [$p < 0.001$] and 3.1 ± 1.9 [$p < 0.001$], respectively). They had also a higher bleeding risk (HAS-BLED: 0.6 ± 0.6 and 0.6 ± 0.7 for dabigatran and rivaroxaban, respectively) than patients on regular doses (HAS-BLED: 0.2 ± 0.5; $p < 0.001$ and 0.3 ± 0.5; $p < 0.001$ for dabigatran and rivaroxaban, respectively). Patients on reduced doses of NOACs were more likely to receive concomitant treatment with antiplatelets, statins, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers than patients on higher doses of NOACs.

OAC prescription over the years

Data on frequency of prescription of different types of OACs in recent years are provided in Figure 2. Dabigatran and afterwards rivaroxaban were approved for the prevention of ischaemic stroke and systemic embolism in adults with non-valvular AF at the end of 2011. Use of VKA in 2011 was reported in over 96% of patients on OACs, but it decreased to as few as 34.6% in 2016. In the last analysed year, i.e. 2016, AF patients were treated mainly with NOACs — dabigatran (24.2%) and rivaroxaban (41.3%).

DISCUSSION

This study presents the clinical characteristics, as well as baseline thromboembolic and bleeding risk factors, of AF patients

Table 1. Clinical characteristics of patients with atrial fibrillation treated with vitamin K antagonists, rivaroxaban, and dabigatran

Variable	VKAs (n = 1973)	Rivaroxaban (n = 1051)	Dabigatran (n = 504)	p
Age [years]	67.0 ± 12.8	70.5 ± 13.1	66.0 ± 13.9	< 0.001[a] 0.34[b] < 0.001[c]
Female sex	35.5% (721)	47.9% (503)	38.9% (196)	< 0.001[a] 0.33[b] 0.001[c]
BMI [kg/m^2]	29.6 ± 6.3 (n = 125)	29.3 ± 4.9 (n = 146)	28.2 ± 5.2 (n = 90)	0.82[a] 0.14[b] 0.07[c]
Mean daily NOAC dose [mg]	–	18.0 ± 2.5 (n = 1044)	135.0 ± 19.1 (n = 498)	–
Paroxysmal AF	52.1% (989/1900)	57.3% (566/987)	55.5% (269/485)	0.01[a] 0.19[b] 0.50[c]
Persistent AF	18.5% (351/1901)	13.6% (134/988)	22.9% (111/485)	0.001[a] 0.03[b] < 0.001[c]
Permanent AF	29.5% (561/1901)	29.3% (289/988)	21.6% (105/485)	0.90[a] 0.001[b] 0.002[c]
Haemoglobin [g/dL]	13.8 ± 2.0 (n = 1623)	13.6 ± 1.6 (n = 673)	13.9 ± 1.6 (n = 358)	< 0.001[a] 0.74[b] 0.01[c]
eGFR ≥ 50 [mL/min]	68.9% (898/1302)	76.6% (730/953)	82.5% (345/418)	< 0.001[a] < 0.001[b] 0.02[c]
eGFR 30–49 [mL/min]	26.0% (338/1298)	21.1% (201/952)	17.0% (71/417)	0.01[a] < 0.001[b] 0.09[c]
eGFR 15–29 [mL/min]	4.9% (64/1298)	2.2% (21/952)	0.7% (3/417)	0.001[a] < 0.001[b] 0.07[c]
eGFR ≤ 14 [mL/min]	0.2% (3/1299)	0.3% (3/954)	0.0% (0/419)	0.70[a] 1.00[b] 0.56[c]
Antiplatelets	17.0% (335)	10.0% (105)	8.1% (41)	< 0.001[a] < 0.001[b] 0.27[c]
Antiarrhythmics	16.9% (332/1969)	17.3% (182/1050)	16.9% (85/503)	0.76[a] 1.00[b] 0.89[c]
β-blockers	82.3% (1341/1630)	79.9% (540/676)	76.8% (275/358)	0.19[a] 0.02[b] 0.26[c]
ACEIs or ARBs	74.8% (1220/1631)	71.7% (485/676)	67.6% (242/358)	0.13[a] 0.01[b] 0.17[c]
Statins	64.1% (1045/1631)	64.9% (439/676)	54.7% (196/358)	0.70[a] 0.001[b] 0.002[c]
CCBs	18.5% (302/1630)	24.3% (164/676)	19.8% (71/358)	0.002[a] 0.55[b] 0.12[c]

[a]Refers to the comparison of VKAs with rivaroxaban; [b]Refers to the comparison of VKAs with dabigatran; [c]Refers to the comparison of rivaroxaban with dabigatran. Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as percentage and (number); ACEIs — angiotensin converting enzyme inhibitors; AF — atrial fibrillation; ARB — angiotensin receptor blockers; BMI — body mass index; CCBs — calcium channel blockers; eGFR — estimated glomerular filtration rate; NOACs — non-vitamin K antagonist oral anticoagulants; VKAs — vitamin K antagonists

Table 2. Thromboembolic and bleeding risk factors in patients with atrial fibrillation treated with vitamin K antagonists, rivaroxaban, and dabigatran (based on the current guidelines for AF treatment [1])

Variable	VKAs (n = 1973)	Rivaroxaban (n = 1051)	Dabigatran (n = 504)	p
THROMBOEMBOLIC RISK FACTORS				
Previous stroke or TIA	11.2% (220/1966)	16.2% (170/1049)	12.0% (60/501)	< 0.001 [a]
				0.64 [b]
				0.03 [c]
Prior MI or PAD	43.9% (864/1966)	48.1% (505/1049)	35.3% (177/501)	0.03 [a]
				< 0.001 [b]
				< 0.001 [c]
Heart failure	36.2% (712/1966)	41.7% (437)	32.3% (162/501)	0.003 [a]
				0.12 [b]
				< 0.001 [c]
Diabetes mellitus	26.4% (518/1959)	29.5% (309/1046)	20.2% (101/500)	0.07 [a]
				0.004 [b]
				< 0.001 [c]
Hypertension	71.8% (1412/1966)	71.5% (750/1049)	69.5% (348/501)	0.87 [a]
				0.29 [b]
				0.44 [c]
COPD	8.1% (160/1969)	12.8% (134/1050)	6.2% (31/503)	< 0.001 [a]
				0.16 [b]
				< 0.001 [c]
$CHADS_2$ score	1.9 ± 1.3 (n = 1959)	2.2 ± 1.4 (n = 1046)	1.8 ± 1.3 (n = 500)	< 0.001 [a]
				0.46 [b]
				< 0.001 [c]
0–1	45.2% (886/1959)	34.9% (365/1046)	48.6% (243/500)	< 0.001 [a]
				0.19 [b]
				< 0.001 [c]
2	24.2% (474/1959)	26.7% (279/1046)	25.4% (127)	0.15 [a]
				0.60 [b]
				0.62 [c]
3–6	30.6% (599/1959)	38.4% (402/1046)	26.0% (130/500)	< 0.001 [a]
				0.048 [b]
				< 0.001 [c]
CHA_2DS_2VASc score	3.3 ± 2.0 (n = 1959)	3.9 ± 2.0 (n = 1046)	3.1 ± 2.0 (n = 500)	< 0.001 [a]
				0.33 [b]
				< 0.001 [c]
0–1	22.6% (443/1959)	15.5% (162/1046)	25.8% (129/500)	< 0.001 [a]
				0.14 [b]
				< 0.001 [c]
2	16.1% (315/1959)	12.4% (130/1046)	17.6% (88/500)	0.01 [a]
				0.42 [b]
				0.01 [c]
3–9	61.3% (1201/1959)	72.1% (754/1046)	56.6% (283/500)	< 0.001 [a]
				0.06 [b]
				< 0.001 [c]

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Table 2 (cont). Thromboembolic and bleeding risk factors in patients with atrial fibrillation treated with vitamin K antagonists, rivaroxaban, and dabigatran (based on the current guidelines for AF treatment [1])

Variable	VKAs (n = 1973)	Rivaroxaban (n = 1051)	Dabigatran (n = 504)	p
MODIFIABLE BLEEDING RISK FACTORS				
History of labile INR	3.4% (55/1619)	1.3% (9/673)	2.0% (7/353)	0.01 [a]
				0.24 [b]
				0.44 [c]
Uncontrolled hypertension (SBP > 160 mmHg)	1.5% (25/1629)	3.4% (23/676)	4.2% (15/358)	0.01 [a]
				0.003 [b]
				0.60 [c]
NSAIDs or antiplatelets	17.1% (339)	10.1% (106)	18.7% (44)	< 0.001 [a]
				< 0.001 [b]
				0.41 [c]
Frequent current alcohol usage	0.8% (15/1967)	1.5% (16/1049)	1.2% (6/502)	0.06 [a]
				0.41 [b]
				0.82 [c]
POTENTIALLY MODIFIABLE BLEEDING RISK FACTORS				
Anaemia*	18.0% (291/1619)	20.8% (140/673)	17.9% (64/358)	0.13 [a]
				1.00 [b]
				0.29 [c]
Reduced platelet count or function	31.1% (526/1693)	24.2% (171/706)	19.4% (72/371)	0.001 [a]
				< 0.001 [b]
				0.08 [c]
Abnormal renal function	2.2% (35/1621)	1.0% (7/676)	0.3% (1/358)	0.09 [a]
				0.01 [b]
				0.28 [c]
Abnormal liver function	3.6% (67/1852)	4.2% (41/967)	3.4% (16/471)	0.41 [a]
				0.89 [b]
				0.48 [c]
NON-MODIFIABLE BLEEDING RISK FACTORS				
Major bleeding	6.7% (131/1970)	11.2% (118)	7.3% (37)	< 0.001 [a]
				0.62 [b]
				0.02 [c]
Malignancy	7.6% (124/1629)	8.9% (60/676)	7.8% (28/358)	0.31 [a]
				0.91 [b]
				0.64 [c]
Dialysis-dependent kidney disease or renal transplant	0.7% (11/1631)	0.3% (2/676)	0.0% (0/358)	0.37 [a]
				0.23 [b]
				0.55 [c]
Cirrhotic liver disease	2.2% (41/1852)	3.5% (34/967)	1.9% (9/471)	0.048 [a]
				0.86 [b]
				0.10 [c]
Serum creatinine [mg/dL]	1.12 ± 0.43 (n = 1622)	1.08 ± 0.39 (n = 675)	1.07 ± 0.54 (n = 357)	0.04 [a]
				0.04 [b]
				0.66 [c]
HAS-BLED score	0.4 ± 0.7 (n = 1611)	0.4 ± 0.6 (n = 673)	0.3 ± 0.6 (n = 352)	0.31 [a]
				0.01 [b]
				0.09 [c]

[a]Refers to the comparison of VKAs with rivaroxaban; [b]Refers to the comparison of VKAs with dabigatran; [c]Refers to the comparison of rivaroxaban with dabigatran. *Haemoglobin < 13 g/dL for men; Haemoglobin < 12 g/dL for women. Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as percentage and (number); $CHADS_2$ — Congestive heart failure, Hypertension, Age ≥ 75, Diabetes, Stroke (doubled); CHA_2DS_2VASc — Congestive Heart failure, hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, Sex (female); COPD — chronic obstructive pulmonary disease; HAS-BLED — Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; INR — international normalised ratio; MI — myocardial infarction; NSAIDs — nonsteroidal anti-inflammatory drugs; PAD — peripheral artery disease; SBP — systolic blood pressure; TIA — transient ischaemic attack; VKAs — vitamin K antagonists

Table 3. Clinical characteristics of patients with atrial fibrillation depending on the dose of dabigatran or rivaroxaban

Variable	Dabigatran 110 mg (n = 187)	Dabigatran 150 mg (n = 311)	p	Rivaroxaban 15 mg (n = 422)	Rivaroxaban 20 mg (n = 622)	p
Age [years]	75.8 ± 10.2	60.0 ± 12.4	< 0.001	78.5 ± 8.6	65.2 ± 12.9	< 0.001
Female sex	43.9% (82)	36.3% (113)	0.11	55.0% (232)	43.4% (270)	< 0.001
BMI [kg/m^2]	28.0 ± 5.4 (n = 53)	28.5 ± 4.8 (n = 37)	0.62	28.8 ± 4.4 (n = 91)	30.2 ± 5.4 (n = 55)	0.19
Paroxysmal AF	47.3% (86/182)	59.7% (178/298)	0.01	51.5% (204/396)	60.9% (356/585)	0.004
Persistent AF	15.4% (28/182)	27.9% (83/298)	0.002	8.6% (34/397)	17.1% (100/585)	< 0.001
Permanent AF	37.4% (68/182)	12.4% (37/298)	< 0.001	40.3% (160/397)	22.1% (129/585)	< 0.001
GFR ≥ 50 [mL/min]	70.5% (124/176)	91.5% (216/236)	< 0.001	55.9% (232/415)	92.5% (493/533)	< 0.001
GFR 30–49 [mL/min]	28.6% (50/175)	8.5% (20/236)	< 0.001	39.0% (162/415)	7.3% (39/532)	< 0.001
GFR 15–29 [mL/min]	1.7% (3/175)	0.0% (0/236)	0.08	4.8% (20/415)	0.2% (1/532)	< 0.001
GFR < 15 [mL/min]	0.0% (0/177)	0.0% (0/236)	–	0.7% (3/415)	0.0% (0/534)	0.08
Serum creatinine [mg/dL]	1.21 ± 0.90 (n = 108)	1.01 ± 0.24 (n = 243)	< 0.001	1.25 ± 0.55 (n = 228)	1.00 ± 0.23 (n = 440)	< 0.001
Major bleeding	13.9% (26/187)	3.2% (10/311)	< 0.001	16.6% (70)	7.6% (47)	< 0.001
HAS-BLED score	0.6 ± 0.6 (n = 106)	0.2 ± 0.5 (n = 240)	< 0.001	0.6 ± 0.7 (n = 227)	0.3 ± 0.5 (n = 439)	< 0.001
CHA_2DS_2VASc score	4.4 ± 1.7 (n = 185)	2.3 ± 1.7 (n = 309)	< 0.001	5.0 ± 1.7 (n = 417)	3.1 ± 1.9 (n = 622)	< 0.001
0–1	5.9% (11/185)	37.2% (115/309)	< 0.001	1.7% (7/417)	24.6% (153)	< 0.001
2	4.9% (9/185)	25.6% (79/309)	< 0.001	6.2% (26/417)	16.6% (103)	< 0.001
3–9	89.2% (165/185)	37.2% (115/309)	< 0.001	92.1% (384/417)	58.8% (366)	< 0.001
Previous stroke or TIA	18.9% (35/185)	7.8% (24/309)	< 0.001	22.8% (95/417)	11.6% (7.2)	< 0.001
Prior MI or PAD	57.3% (106/185)	21.7% (67/309)	< 0.001	64.3% (268/417)	31.6% (234)	< 0.001
Heart failure	53.5% (99/185)	20.1% (62/309)	< 0.001	60.7% (253/417)	28.8% (179)	< 0.001
Diabetes mellitus	26.5% (49/185)	16.5% (51/309)	0.01	38.6% (161/417)	23.6% (147)	< 0.001
Hypertension	73.5% (136/185)	67.0% (207/309)	0.13	76.0% (317/417)	68.3% (425)	0.01
COPD [%]	12.3% (23/187)	2.6% (8/310)	< 0.001	15.6% (66)	11.0% (68/621)	0.03
Antiplatelets	13.4% (25/187)	4.8% (15/311)	0.001	14.7% (62)	6.9% (43)	< 0.001
ACEIs or ARBs	75.9% (82/108)	64.3% (157/244)	0.04	80.3% (183/228)	67.1% (296/441)	< 0.001
Beta-blockers	81.5% (88/108)	74.6% (182/244)	0.17	83.3% (190/228)	78.2% (345/441)	0.13
Antiarrhythmics	14.5% (27/186)	18.3% (57/311)	0.32	18.3% (77/421)	16.3% (103)	0.50
Statins	66.7% (72/108)	49.2% (120/244)	0.003	72.8% (166/228)	60.8% (268/441)	0.002
CCBs	22.2% (24/108)	18.9% (46/244)	0.47	25.4% (58/228)	23.8% (105/441)	0.64

Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as percentage and (number). AF — atrial fibrillation; ACEIs — angiotensin converting enzyme inhibitors; ARB — angiotensin receptor blockers; BMI — body mass index; CCBs — calcium channel blockers; CHA_2DS_2VASc — Congestive Heart failure, hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, Sex (female); COPD — chronic obstructive pulmonary disease; GFR — glomerular filtration rate; HAS-BLED — Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly; MI — myocardial infarction; NSAIDs — nonsteroidal anti-inflammatory drugs; PAD — peripheral artery disease; SBP — systolic blood pressure; TIA — transient ischaemic attack

treated with VKAs and NOACs (dabigatran and rivaroxaban). In the literature there are insufficient data on the pattern of use of available NOACs and their comparison with use of VKAs in real-life patients. Our study confirms the tendency of an increase in NOAC usage at the expense of decreased frequency of VKA prescription. Interestingly, in our population the highest risk of thromboembolic events and incidence of major bleedings were observed in patients on rivaroxaban in comparison to patients on VKAs and dabigatran. Patients with a high risk of thromboembolic and bleeding events were also more likely to receive lower doses of NOACs.

All NOACs have been shown to have a better safety profile and to be at least as effective as warfarin [3, 4]. According to guidelines on AF published in 2012, NOACs were recommended on a par with VKAs [5], but the current guidelines (published in 2016) clearly prefer NOACs over VKAs [1]. Adherence to changing guidelines was observed in our study. Dabigatran and subsequently rivaroxaban came onto the Pol-

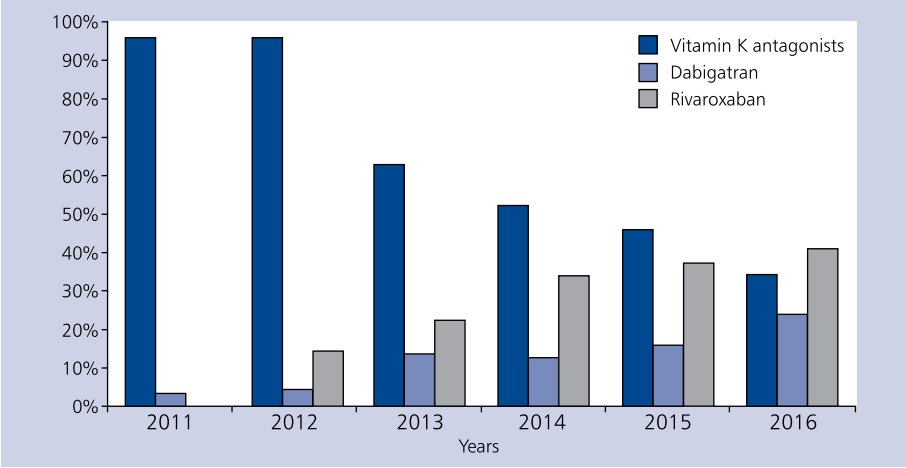

Figure 2. Frequency of prescription of vitamin K antagonists, dabigatran, and rivaroxaban in patients with atrial fibrillation in recent years

ish market at the end of 2011, and since that moment our study has observed an increasing rate of NOAC prescription of up to two-thirds of the total number of used OACs (Fig. 2). At the end of the study period dabigatran was prescribed in approximately 24%, while rivaroxaban was prescribed in as many as 41% of patients on OACs. These results are in line with data from a large Danish nationwide registry, which included 18,611 AF patients who initiated OAC treatment in the period between 2011 and 2013 [6]. In that registry most of the patients were still on VKAs (53%), but the prescription rate of NOACs was increasing (38% — dabigatran, 7% — rivaroxaban, 1% — apixaban) [6]. In the GARFIELD-AF registry conducted in Europe a decline in VKA treatment by 37% to 42% of patients receiving OACs was also observed [2].

In previous studies the following factors have been shown to be associated with an increased probability of NOAC prescription: hospitalisation due to AF, age ≥ 80 years, history of bleeding, paroxysmal AF, certain comorbidities (stroke, alcohol abuse), and living in a rural area [6, 7]. Whereas, factors strongly related with VKA prescription were ischaemic heart disease, heart failure, liver failure, and, in particular, chronic kidney disease [6]. In our analysis patients on VKAs had significantly worse kidney function (assessed by serum creatinine or estimated glomerular filtration rate [eGFR] levels) and more frequently were treated with antiplatelets than patients on rivaroxaban and dabigatran. According to the AF guidelines (published in 2012), NOACs were not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min) [5], but in our study 2.5% patients on rivaroxaban and 0.7% patients on dabigatran had eGFR < 30 mL/min. In the NOACs approval trials (ROCKET-AF [rivaroxaban] and RE-LY [dabigatran]) the creatinine clearance was calculated according to the Cockroft-Gault formula [3, 4], which was shown to be more useful than the Modification of Diet in Renal Disease (MDRD) study equation or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in predicting very late mortality [8].

Available data show that patients with paroxysmal AF less frequently receive antithrombotic therapy than patients with persistent or permanent AF, despite the fact that all types of AF should be treated similarly in terms of assessed thromboembolic risk [1, 9]. However, it was shown that patients with persistent AF had higher risk of stroke than patients with paroxysmal AF, due to more frequent presence of comorbidities such as diabetes, heart failure, ischaemic heart disease, prior stroke, and higher $CHADS_2$ or CHA_2DS_2VASc score [10, 11]. In our study patients with paroxysmal AF were more likely to be treated with VKAs than with NOACs (54.2% vs. 45.8%, respectively; $p = 0.01$), but without such a difference in those with persistent and permanent AF. However, among NOACs, patients with persistent and permanent AF were more likely to receive rivaroxaban (54.7% and 73.4%, respectively) than dabigatran (45.3%, $p < 0.001$ and 26.6%, $p = 0.002$, respectively).

Interestingly, in previous studies the choice of NOACs and VKAs was not related to thromboembolic (CHA_2DS_2VASc score) and bleeding (HAS-BLED) risks [6]. In our study patients on rivaroxaban were older, had more comorbidities, and higher risk of stroke and bleeding than patients on dabigatran or VKAs. Similar findings regarding the profile of patients on rivaroxaban were revealed in the ORBIT-AF (Outcomes Registry for Better-Informed Treatment of Atrial Fibrillation) and Danish registries [6, 12].

In the previously published studies there was no difference in terms of thromboembolic and bleeding risk between patients on VKAs and those on NOACs [6, 7]. In a single-centre prospective study consisting of 550 patients with non-valvular

AF, patients on VKAs had a mean CHA_2DS_2VASc score of 3.8 ± 1.7 and HAS-BLED score of 2.2 ± 1.0, while patients on NOACs had a mean CHA_2DS_2VASc score of 4.1 ± 1.7 and a mean HAS-BLED score of 2 ± 0.9 [7]. In our study, significant baseline differences between groups were observed. Patients on rivaroxaban had a higher thromboembolic risk (mean CHA_2DS_2VASc score 3.9 ± 2.0, mean $CHADS_2$ score 2.2 ± 1.4; n = 1046) than patients on VKAs (mean CHA_2DS_2-VASc score 3.3 ± 2.0 and mean CHADS2 score 1.9 ± 1.3) and on dabigatran (mean CHA_2DS_2VASc score 3.1 ± 2.0 and mean $CHADS_2$ score 1.8 ± 1.3). Hence, in our study clinicians were prescribing rivaroxaban to high-risk patients and dabigatran or VKAs to low-intermediate (CHA_2DS_2VASc score 0–1)-risk patients; nonetheless, our population is more similar to the population included in the RE-LY study (mean $CHADS_2$ score 2.2 ± 1.2) than to the ROCKET AF study (rivaroxaban, mean $CHADS_2$ score 3.5 ± 0.9) [3, 4].

In the real-life setting an important factor conditioning the effectiveness of the therapy is the physicians' adherence to the guidelines, as well as patients' compliance. In the Polish part of the Heart Failure Pilot Registry of the European Society of Cardiology there was observed low use (66.1%) of oral anticoagulants in heart failure patients with concomitant AF, despite the fact that 98.1% patients had at least two points in the CHA_2DS_2VASc score [13]. It is worth emphasising that there are available tools based on three-dimensional movies, which might increase the patients' compliance and translate into higher effectiveness of OAC therapy [14].

The doses of dabigatran and rivaroxaban should be reduced (to 110 mg and 15 mg, respectively) in patients on dual-antiplatelet therapy, with a high risk of gastrointestinal bleeding (only dabigatran), renal impairment (serum creatinine clearance < 50 mL/min), and in the elderly (≥ 75 years) (only dabigatran) [15, 16]. According to those recommendations, in our study patients on lower doses of dabigatran and rivaroxaban were older (75.8 ± 10.2 and 78.5 ± 8.6 years, respectively), were more often female (significant only for rivaroxaban), had permanent rather than paroxysmal or persistent AF, worse kidney function, and more frequently were concomitantly treated with antiplatelets. Patients with reduced doses of NOACs had also higher thromboembolic and bleeding risk than patients on higher doses of NOACs. However, it should be stressed that the superiority of lower doses of dabigatran and rivaroxaban over VKA in reduction of the risk of stroke or systemic embolism was not shown in the NOAC trials [3, 4]. In the recently published propensity weighted nationwide study of reduced doses of NOACs by Nielsen et al. [17] rivaroxaban (15 mg once a day) and dabigatran (110 mg twice a day) presented lower thromboembolic event rates. Bleeding risk was lower only for dabigatran when compared with warfarin. This is a retrospective study and has several limitations. First, it was not a nation-wide registry with a truly representative cohort of AF patients on OAC. Second, we did not have information on time of first AF diagnosis or previous anticoagulant treatment. Third, there were no data regarding some important clinical variables including tobacco smoking, heart rate, and blood pressure. Fourth, due to the small number of patients on apixaban, we could not include this NOAC in the analysis.

In conclusion, the study revealed that prescription of VKAs has declined significantly since the introduction of NOACs. Patients treated with different OACs demonstrated a distinct baseline clinical profile. The highest risk of thromboembolic events and incidence of major bleedings were observed in patients on rivaroxaban in comparison to those on VKAs and dabigatran. Among NOACs, patients treated with lower doses of dabigatran and rivaroxaban were older and had significantly higher risk of thromboembolic and bleeding events.

Conflict of interest: *Paweł Balsam: grants, lectures expert committees of companies producing NOAC; Marcin Grabowski: grants, lectures, expert committees of companies producing NOAC; Piotr Lodziński: grants, lectures, expert committees of companies producing NOAC; Janusz Bednarski: fees for lectures from Bayer, Boehringer-Ingelhein and Pfizer; Krzysztof J. Filipiak: fees for lectures and expert committees of companies producing NOAC: Bayer, Boehringer Ingelheim, MSD and Pfizer; Grzegorz Opolski: grants, lectures, expert committees of companies producing NOAC.*

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