ORIGINAL ARTICLE

Comparison of different oral anticoagulant regimens in patients with atrial fibrillation undergoing ablation or cardioversion

Monika Gawałko, Agnieszka Kapłon-Cieślicka, Monika Budnik, Aldona Babiarz, Aleksandra Bodys, Robert Uliński, Maciej Żochowski, Michał Peller, Piotr Scisło, Janusz Kochanowski, Krzysztof J. Filipiak, Grzegorz Opolski

1st Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

KEY WORDS

atrial fibrillation, dabigatran, non–vitamin K antagonist oral anticoagulants, rivaroxaban, vitamin K antagonist

ABSTRACT

INTRODUCTION Non–vitamin K antagonist oral anticoagulants (NOACs) are an alternative to vitamin K antagonists (VKAs) for stroke prevention in atrial fibrillation (AF).

OBJECTIVES The aim of the study was to assess the incidence of left atrial appendage (LAA) thrombus and dense spontaneous echo contrast (SEC), as well as to compare the clinical characteristics of patients with AF treated with different anticoagulant regimens.

PATIENTS AND METHODS We studied 1033 consecutive patients with AF, who underwent transesophageal echocardiography (TEE) before AF ablation or cardioversion. We excluded 174 patients without any prior oral anticoagulation or who underwent bridging with heparin before TEE.

RESULTS In the study group of 859 patients (median age, 61 years; men, 66%), 437 patients (50.9%) received VKAs; 191 (22.2%), dabigatran; 230 (26.8%), rivaroxaban; and 1 patient (0.1%), apixaban. There were no differences in baseline characteristics or the incidence of LAA thrombus (VKAs, 6.9%; NOACs, 5.5%; $P = 0.40$) and dense SEC (VKAs, 5.3%; NOACs, 3.3%; $P = 0.18$) between patients on VKAs and those on NOACs. Compared with patients treated with dabigatran, those on rivaroxaban more often had paroxysmal AF, higher ejection fraction, LAA emptying velocity, and platelet count, as well as lower left ventricular end-diastolic dimension and hematocrit. The frequency of LAA thrombus in patients receiving dabigatran and those receiving rivaroxaban was comparable (6.8% vs 4.4%; $P = 0.29$), while dense SEC occurred more often in patients treated with dabigatran (5.2% vs 1.7%; $P = 0.06$). In a logistic regression analysis, none of the oral anticoagulation regimens predicted LAA thrombus in TEE, whereas maximal LAA emptying velocity was the only parameter independently associated with the presence of thrombus.

CONCLUSIONS In the studied group of patients with AF, the choice of anticoagulation did not depend on thromboembolic or bleeding risk.

Correspondence to:
Monika Budnik, MD, PhD,
I Katedra i Klinika Kardiologii,
Warszawski Uniwersytet Medyczny,
ul. Banacha 1a, 02-097 Warszawa,
Poland, phone: +48 22 599 29 58,
email: moni.budnik@gmail.com

Received: June 16, 2017.
Revision accepted:
September 21, 2017.
Published online:
September 30, 2017.
Conflict of interest: KJF received speaker honoraria from Bayer, Boehringer Ingelheim, MSD, and Pfizer.
Pol Arch Intern Med. 2017;
127 (12): 823-831
doi:10.20452/pamw.4117

INTRODUCTION Despite advancements in the management of atrial fibrillation (AF), this arrhythmia remains one of the major causes of ischemic stroke, heart failure, and cardiovascular morbidity.[1,2] More than 90% of thrombi in patients with nonvalvular AF originate in the left atrial appendage (LAA).[3] Thus, examination of the left atrial (LA) cavity (including LAA) on transesophageal echocardiography (TEE) is a reasonable approach to prevent thromboembolism in patients with AF undergoing pulmonary vein isolation or direct current cardioversion, and the presence of LA thrombi on TEE may be considered a surrogate efficacy endpoint in anticoagulant-treated patients with AF.[3,4]

With the advent of an era of non–vitamin K antagonist oral anticoagulants (NOACs), an increasing number of patients with AF are prescribed NOACs instead of vitamin K antagonists (VKAs), predominantly due to a lower risk of intracranial bleeding and hemorrhagic stroke as well as a predictable effect without a need for routine

monitoring.[5-10] The most recent European Society of Cardiology guidelines on AF favor NOAC over VKA treatment in nonvalvular AF.[1] However, in Poland, many patients with nonvalvular AF still receive VKAs instead of NOACs[11] because the latter are not reimbursed. Apart from the relatively high cost of NOAC therapy, some Polish physicians seem to believe that VKAs are superior to NOACs in terms of their anticoagulant efficacy, despite evidence from randomized clinical trials.[9-10,12-16]

The aim of the study was to compare the clinical characteristics of Polish patients with AF treated with different anticoagulant regimens (VKAs and NOACs), as well as to assess the incidence of LAA thrombus and dense spontaneous echo contrast (SEC) in a real-world population of patients with AF.

PATIENTS AND METHODS

Study population

We performed a single-center observational study of 1033 consecutive patients with AF, referred to our department between January 2012 and August 2016 for catheter ablation or direct current cardioversion for AF. All demographic, clinical, laboratory, and echocardiographic (including TEE) data, as well as information on medication, were retrieved retrospectively from medical records. To compare anticoagulant efficacy of different oral anticoagulant (OAC) regimens, we excluded patients on no anticoagulant treatment, patients in whom OACs were discontinued during the previous 3 weeks, and those who underwent bridging with heparin before TEE.

Transesophageal echocardiography

In our department, TEE is performed routinely in all patients scheduled for pulmonary vein isolation or for direct current cardioversion for AF (unless the latter is performed for emergency indications). TEE is routinely performed in all patients scheduled for cardioversion even if there are data indicating that it might be omitted.[17]

All TEE studies are performed within 48 hours before the scheduled procedure (usually directly or within a few hours prior to the procedure). All TEE studies were performed in our echocardiography laboratory (certified with grade C accreditation of the Section of Echocardiography of the Polish Cardiac Society) using EPIQ 7 Ultrasound Machine (Philips Medical Systems, Andover, Massachusetts, United States) or iE33 Ultrasound Machine (Philips Medical Systems), using a Philips X7-2t TEE ultrasound transducer (Philips Medical Systems). The LA cavity, including the LAA, was examined for the presence of a thrombus or SEC, including dense SEC, by experienced echocardiographers (all certified with the second-degree accreditation in echocardiography of the Echocardiography Working Group of the Polish Cardiac Society). Each TEE examination raising a suspicion of an LAA thrombus was assessed by 2 echocardiographers, and in case of doubt, by a third echocardiographer, to provide a reliable and unanimous diagnosis. The maximal LAA emptying velocity (LAAV) was recorded by placing the pulsed-wave Doppler gate within 1 cm of the LAA orifice. Emptying velocities of less than 20 cm/s were regarded as decreased. LA thrombus was defined as an independently mobile, round, oval, or irregularly shaped echodense structure, distinct from the surrounding endocardium or pectinate muscles, and detected in more than 1 imaging plane. Dense SEC was defined as dynamic "smoke-like" signal with a characteristic swirling motion, or a dynamic gelatinous precipitous echo density without a discrete mass, present throughout the cardiac cycle. In our department, all TEE studies are recorded and stored; thus, they were available for reevaluation during data collection for the current study. In patients with LAA thrombus, ablation or cardioversion was postponed and an intensified anticoagulant regimen was initiated.

Study endpoints

LAA thrombus on TEE was considered a study endpoint. Patients were not followed for periprocedural or postprocedural complications.

Statistical analysis

Continuous and ordinal variables were expressed as a median (interquartile range). Categorical data were presented as a number of patients and percentages. Group comparisons were performed using the *t* test for quantitative variables, and the Fisher exact test for qualitative variables. To determine whether any clinical variables and anticoagulant regimens were related to a relatively increased risk of LAA thrombus formation, univariate and multivariate logistic regressions were performed. A multivariate logistic regression analysis was performed using clinical variables with a *P* value of 0.10 or less in a univariate analysis. Coefficients from logistic regression were checked by the Wald test, and odds ratios (ORs) and referring 95% confidence intervals (CIs) were derived. All tests were 2-tailed. All calculations were performed using the SAS software, version 9.2 (SAS Institute, Cary, North Carolina, United States). For all analyses, a *P* value of less than 0.05 was considered statistically significant.

RESULTS

Of 1033 patients with AF scheduled for AF ablation or cardioversion who underwent TEE, 174 patients were excluded from the current analysis: 116 patients underwent TEE without any prior OAC therapy, and in 58 patients bridging with unfractionated heparin or low-molecular-weight heparin was used. The clinical characteristics as well as the frequency of LAA thrombus and dense SEC on TEE in patients with AF who did not receive any OAC, as compared with anticoagulant-treated patients with AF who constituted the study group are presented in Supplementary material, *Tables S1* and *S2*.

The study group consisted of 859 patients. A total of 437 patients (50.9%) were treated with VKAs; 191 (22.2%), with dabigatran; 230 (26.8%), with rivaroxaban; and 1 patient (0.1%),

TABLE 1 Comparison of patients treated with vitamin K antagonists and those treated with non–vitamin K antagonist oral anticoagulants based on medical history

Parameter	OAC (n = 859)	VKA (n = 437)	NOAC (n = 422)	*P* value
Age, y, median (IQR)	61 (54–67)	61 (56–66)	61 (54–67)	0.96
Women, n (%)	290 (34)	143 (33)	147 (35)	0.52
BMI, kg/m^2, median (IQR)	29 (26–32)	29 (26–32)	29 (26–32)	0.29
Type of AF				
Paroxysmal, n (%)	492 (57)	260 (60)	232 (55)	0.19
Persistent, n (%)	310 (36)	148 (34)	162 (38)	0.18
Long-standing persistent, n (%)	57 (6.6)	29 (6.6)	28 (6.6)	1.00
EHRA class, median (IQR)	3 (2–3) n = 600	3 (2–3) n = 288	3 (2–3) n = 312	0.17
Clinical characteristics, n (%)				
Hypertension	577 (67)	305 (70)	272 (64)	0.11
Dyslipidemia	362 (42)	176 (40)	186 (44)	0.27
Diabetes	150 (17)	84 (19)	66 (16)	0.18
CAD	51 (6.0)	23 (5.0)	28 (6.6)	0.47
Previous MI	57 (6.6)	27 (6.2)	30 (7.1)	0.59
Previous PCI/CABG	64 (7.5)	30 (6.9)	34 (8.1)	0.52
Biological valve prosthesis	7 (0.8)	6 (1.4)	1 (0.2)	0.12
Mechanical valve prosthesis	3 (0.4)	3 (0.7)	0 (0.0)	0.25
Pacemaker	60 (7.0)	33 (7.6)	27 (6.4)	0.59
Chronic heart failure	107 (12)	55 (13)	52 (12)	0.92
PVD	12 (1.4)	5 (1.1)	7 (1.7)	0.57
Previous ischemic stroke/TIA	52 (6.1)	26 (6.0)	26 (6.2)	1.00
Previous peripheral embolism	11 (1.3)	9 (2.1)	2 (0.5)	0.06
Previous hemorrhagic stroke	2 (0.2)	1 (0.2)	1 (0.2)	1.00
Labile INR	–	11 (2.5)	–	–
Liver disease	14 (1.7)	9 (2.1)	5 (1.2)	0.42
Malignancy	57 (6.6)	23 (5.3)	34 (8.1)	0.13
Hyperuricemia	53 (6.2)	30 (6.9)	23 (5.5)	0.40
Smoking	305 (36)	152 (35)	153 (36)	0.63
Antiplatelets	42 (4.9)	20 (4.6)	22 (5.2)	0.75

P values are given for differences between VKA and NOAC groups.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; EHRA, European Heart Rhythm Association symptom classification; INR, international normalized ratio; IQR, interquartile range; MI, myocardial infarction; NOAC, non–vitamin K antagonist oral anticoagulants, OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIA, transient ischemic attack; VKA, vitamin K antagonist

with apixaban. In the dabigatran group, 89% of the patients received dabigatran at a dose of 150 mg twice daily; 6%, 110 mg twice daily; and 4%, 150 mg once daily. In the group of 7 patients who were given dabigatran at a dose of 150 mg once daily, 4 patients had persistent AF and 3 patients had paroxysmal AF. One patient was 78 years old, and 6 patients were treated with amiodarone in combination with dabigatran, which might have influenced the reduction of dabigatran dose in these patients. However, the reason for prescribing the dose of 150 mg daily instead of 110 mg twice daily is unknown. As no patient in this group (dabigatran, 150 mg once daily) presented with a thrombus on TEE, both cardioversions (n = 3) and ablations (n = 4) were subsequently performed.

In the rivaroxaban group, 92% of the patients were treated with a dose of 20 mg once daily and 8% received a dose of 15 mg once daily. In the VKA group, 296 patients (68%) were treated with acenocoumarol, and 141 (32%)—with warfarin. There were no differences between the VKA and NOAC groups with respect to the baseline clinical characteristics (including the CHA_2DS_2-VASc and HAS-BLED scores), as well as to the frequency of LAA thrombus (6.9% in the VKA group and 5.5% in the NOAC group; $P = 0.40$) and dense SEC (5.3% in the VKA group and 3.3% in

TABLE 2 Comparison of patients treated with vitamin K antagonists and those treated with non–vitamin K antagonist oral anticoagulants based on data collected on admission and echocardiographic results

Parameters		OAC (n = 859)	VKA (n = 437)	NOAC (n = 422)	*P* value
Type of procedure, n (%)					
Cardioversion		177 (20.5)	59 (13.5)	118 (27.5)	<0.0001
Ablation		686 (79.5)	478 (86.5)	308 (72.5)	<0.0001
Laboratory parameters					
Hemoglobin, g/dl, median (IQR)		14 (13–15)	14 (13–15)	14 (13–15)	0.37
Hematocrit, %, median (IQR)		43 (40–46)	43 (40–46)	43 (40–46)	0.36
Platelet count, K/μl, median (IQR)		216 (182–248)	213 (182–242)	221 (183–253)	0.07
eGFR, ml/min/1.73 m^2, n (%)	≥60	572 (67)	290 (67)	282 (67)	0.94
	30–59	274 (32)	140 (32)	134 (32)	0.94
	<30	13 (1.5)	7 (1.6)	6 (1.4)	1.00
eGFR ml/min/1.73 m^2, median (IQR)		68 (55–80)	52 (44–56)	51 (44–55)	0.86
CHA_2DS_2-VASc score, n (%)	0	125 (15)	60 (14)	65 (15.5)	0.49
	1	283 (33)	139 (32)	144 (34)	
	≥2	451 (53)	238 (54)	213 (50.5)	
CHA_2DS_2-VASc score, median (IQR)		2 (1–3)	2 (1–3)	2 (1–3)	0.28
$CHADS_2$ score, median (IQR)		2 (2–3)	2 (2–3)	2 (1–3)	0.28
HAS-BLED score, n (%)	0–2	796 (93)	402 (92)	394 (93)	0.60
	≥3	62 (7)	34 (7.8)	28 (6.6)	
HAS-BLED score, median (IQR)		1 (1–2)	1 (1–2)	1 (1–2)	0.22
TTE results, median (IQR)					
EF, %		56 (45–60) n = 121	55 (44–60) n = 55	56 (45–60) n = 66	0.59
LVDD, cm		5.1 (4.7–5.5) n = 114	5.2 (4.7–5.5) n = 55	5.0 (4.6–5.6) n = 59	0.41
LAD, cm		4.5 (4.1–4.8) n = 338	4.6 (4.1–4.9) n = 199	4.4 (4.1–4.8) n = 139	0.18
TEE results					
Thrombus, n (%)		53 (6.2)	30 (6.9)	23 (5.5)	0.40
Dense SEC, n (%)		37 (4.3)	23 (5.3)	14 (3.3)	0.18
Thrombus or dense SEC, n (%)		75 (8.7)	44 (10)	31 (7.4)	0.18
SEC, n (%)		146 (17)	69 (16)	77 (18)	0.36
$LAAV_{max}$, cm/s, median (IQR)		55 (35–79)	55 (35–79)	57 (37–80)	0.35

P values indicate differences between the VKA and NOAC groups.

Abbreviations: EF, ejection fraction; eGFR, estimated glomerular filtration rate; $LAAV_{max}$, maximal left atrial appendage emptying velocity; LAD, left atrial dimension; LVDD, left ventricular end-diastolic diameter; SEC, spontaneous echo contrast; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; others, see **TABLE 1**

the NOAC group; *P* = 0.18). Detailed characteristics of the NOAC and VKA groups are presented in **TABLES 1** and **2**.

Compared with patients treated with dabigatran, those on rivaroxaban more often had paroxysmal AF. They also had higher ejection fraction, LAAV, and platelet count, as well as lower left ventricular end-diastolic dimension and hematocrit, with no other significant differences in clinical characteristics (including the CHA_2DS_2-VASc and HAS-BLED scores). The frequency of LAA thrombus in both groups was comparable (6.8% in the dabigatran group vs 4.4% in the rivaroxaban group; *P* = 0.29), while dense SEC more often occurred in dabigatran-treated patients (5.2% vs 1.7%; *P* = 0.06). **TABLES 3** and **4** demonstrate detailed characteristics of both NOAC groups.

There were no differences between the acenocoumarol and warfarin groups with respect to baseline clinical characteristics, but both groups differed in the frequency of LAA thrombus (8% in the acenocoumarol group and 4% in the warfarin group; *P* = 0.07). The proportion of patients with LAA thrombus on TEE depending on OAC therapy is shown in **FIGURE 1**.

In the logistic regression analysis, none of the OAC regimens predicted LAA thrombus on TEE. In univariate analyses, the predictors of LAA thrombus included age, type of AF (persistent and permanent vs paroxysmal), diabetes, heart

TABLE 3 Comparison of patients treated with dabigatran and those treated with rivaroxaban based on medical history

Parameter	Dabigatran (n = 191)	Rivaroxaban (n = 230)	*P* value
Age, y, n (%)	61 (53–67)	61 (54–67)	0.97
Female sex, n (%)	58 (30)	88 (38)	0.10
BMI, kg/m^2, median (IQR)	29 (26–32)	29 (26–32)	0.33
Type of AF, n (%)			
Paroxysmal	92 (48)	139 (60)	0.01
Persistent	83 (43)	79 (34)	0.06
Long-standing persistent	16 (8.4)	12 (5.2)	0.24
EHRA class, median (IQR)	3 (2–3) n = 153	3 (2–3) n = 159	0.31
Clinical characteristics, n (%)			
Hypertension	121 (63)	150 (65)	0.76
Dyslipidemia	78 (41)	108 (47)	0.24
Diabetes	30 (16)	36 (16)	1.00
CAD	12 (6.3)	16 (7.0)	0.85
Previous MI	14 (7.3)	16 (7.0)	1.00
Previous PCI/CABG	15 (7.9)	19 (8.3)	1.00
Biological valve prosthesis	1 (0.5)	0 (0.0)	0.45
Pacemaker	8 (4.2)	19 (8.3)	0.11
Chronic heart failure	28 (15)	24 (10)	0.23
PVD	3 (1.6)	4 (1.7)	1.00
Previous ischemic stroke/TIA	10 (5.2)	15 (6.5)	0.68
Previous peripheral embolism	0 (0.0)	2 (0.9)	0.50
Previous hemorrhagic stroke	1 (0.5)	0 (0)	0.45
Liver disease	1 (0.5)	4 (1.8)	0.38
Pulmonary disease	10 (5.2)	16 (7.0)	0.54
Malignancy	13 (6.8)	21 (9.1)	0.47
Hyperuricemia	14 (7.3)	9 (3.9)	0.14
Smoking	73 (38)	80 (35)	0.21
Antiplatelets	10 (5.2)	12 (5.2)	1.00

P values indicate differences between the dabigatran and rivaroxaban groups.

Abbreviations: see **TABLE 1**

failure, a history of stroke, transient ischemic attack or peripheral embolism, glomerular filtration rate, and maximal LAAV. All those variables were consequently included in the multivariate analysis. In the multivariate model, only maximal LAAV remained an independent predictor of LAA thrombus on TEE. The results of the univariate and multivariate analyses of the predictors of LAA thrombus are presented in Supplementary material online, *Table S3*.

DISCUSSION Based on the European Heart Rhythm Association and the European Society of Cardiology guidelines, in patients with AF lasting more than 48 hours (or AF of unknown duration) undergoing cardioversion, effective OAC therapy should be given for at least 3 weeks prior to cardioversion or TEE should be performed to exclude LA thrombi.[1,2] Left pulmonary vein isolation requires continuation of VKA therapy (international normalized ratio, 2–3), and recent studies have also suggested safety of uninterrupted NOAC therapy in the periprocedural period.[18-23] Moreover, a recent report revealed that in patients with AF undergoing catheter ablation, uninterrupted anticoagulation with dabigatran reduces the number of major bleeding events compared with uninterrupted anticoagulation with warfarin.[24]

When the last dose of NOACs is taken at least 36 hours before the intervention, TEE should be considered before ablation.[2] In our department, routine TEE is performed before each cardioversion and ablation, irrespective of the anticoagulation strategy. This is because there is no coagulation assay available for any NOAC that provides information on effective anticoagulation over the previous 3 weeks. Moreover, patient adherence to NOAC treatment may be doubtful, and LA thrombus may occur even despite adequate VKA

TABLE 4 Comparison of patients treated with dabigatran and those treated with rivaroxaban based on data collected on admission and echocardiographic results

Parameter		Dabigatran (n = 191)	Rivaroxaban (n = 230)	*P* values
Type of procedure, n (%)				
Cardioversion		52 (27)	62 (27)	0.91
Ablation		139 (73)	168 (73)	1.00
Laboratory parameters				
Hemoglobin, g/dl, median (IQR)		14.5 (13–15)	14.0 (13–15)	0.09
Hematocrit, %, median (IQR)		43 (41–46)	42 (40–45)	0.03
Platelet count, K/μl, median (IQR)		212 (180–245)	225 (186–262)	0.03
eGFR, ml/min/1.73 m^2, n (%)	≥60	128 (67)	153 (67)	1.00
	30–59	60 (31)	76 (33)	0.75
	<30	3 (1.6)	1 (0.4)	0.33
eGFR, ml/min/1.73 m^2, n (%)	≥50	157 (83)	201 (87)	0.21
	30–49	30 (16)	28 (12)	0.32
	<30	3 (1.6)	1 (0.4)	0.33
eGFR, ml/min/1.73 m^2, median (IQR)		67 (55–78)	67 (56–83)	0.17
CHA_2DS_2-VASc, n (%)	0	34 (18)	31 (13)	0.36
	1	60 (31)	84 (37)	
	≥2	97 (51)	115 (50)	
CHA_2DS_2-VASc, median (IQR)		2 (1–2)	1.5 (1–3)	0.71
$CHADS_2$, median (IQR)		2 (1–3)	2 (1–3)	0.86
HAS-BLED, n (%)	0–2	174 (91)	220 (96)	0.07
	0–2	17 (8.9)	10 (4.4)	
HAS-BLED, median (IQR)		1 (0–2)	1 (1–2)	0.96
TTE results				
EF, %		55 (40–60) n = 39	60 (55–64) n = 27	0.005
LVDD, cm		5.3 (4.8–5.7) n = 36	4.8 (4.6–5.2) n = 23	0.03
LAD, cm		4.5 (4.1–4.9) n = 67	4.3 (4.1–4.8) n = 72	0.21
TEE results				
Thrombus, n (%)		13 (6.8)	10 (4.4)	0.29
Dense SEC, n (%)		10 (5.2)	4 (1.7)	0.06
Thrombus or dense SEC, n (%)		19 (10)	12 (5.2)	0.09
SEC, n (%)		37 (19)	40 (17)	0.61
$LAAV_{max}$, cm/s, median (IQR)		50 (35–75)	60 (40–80)	0.03

Continuous and ordinal variables are shown as a median (interquartile range). *P* values are given for differences between dabigatran and rivaroxaban groups.

Abbreviations: see TABLES 1 and 2

or NOAC therapy. Approximately 50% of centers perform TEE in all patients undergoing left pulmonary vein isolation, regardless of the presenting rhythm and of the $CHADS_2$ or CHA_2DS_2-VASc score.[25]

According to the updated European Heart Rhythm Association practical guidelines on the use of NOACs in patients with nonvalvular AF, the choice of anticoagulant (VKA or NOAC; type of NOAC) has to be made on the basis of a risk-benefit analysis. Furthermore, patient-related clinical factors and patient preference after discussion of different options need to be considered.[2] However, in our study, the choice of anticoagulation did not depend on patients' thromboembolic or bleeding risk, and there were no significant differences between patients treated with NOACs and those treated with VKAs with respect to clinical characteristics, including components of the SAMe-TT_2R_2 score, which has been previously suggested as a helpful tool to predict the time in therapeutic range of less than 65% on VKA therapy, and thus to assist the decision making in choosing between a NOAC and VKA in treatment-naive patients with AF.[26-30] Thus, the choice of a particular anticoagulant regimen

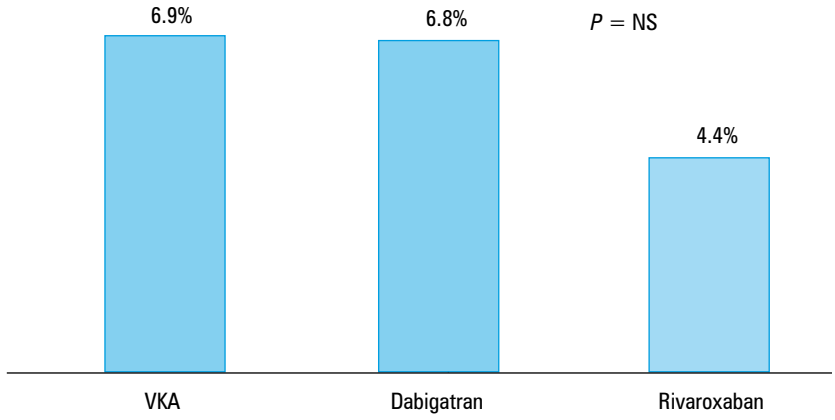

FIGURE 1 Proportion of patients with left atrial thrombus on different anticoagulant regimens
Abbreviations: NS, nonsignificant; others, see **TABLE 1**

in the real-world population of patients with AF in our study seems to have been affected predominantly by personal preferences of the attending physician or the patient (possibly including patients' financial capacities).

The results of our research indicate similar efficacy of different anticoagulant regimens in preventing LAA thrombus formation. The frequencies of LAA thrombus on VKA, dabigatran, and rivaroxaban therapies were 6.9%, 6.8%, and 4.4%, respectively. Recently, Kawabata et al[31] assessed the prevalence of LAA thrombi in 559 patients on at least a 3-week course of anticoagulation therapy. Similarly to our study, they found no difference in the prevalence of LAA thrombi between patients on warfarin and those on NOACs (2.8% vs 2.6%; $P = 0.86$).[31] In most studies, the incidence of LA thrombus under VKA treatment ranged between 2% and 7.9%.[32-36] Thus, the present data are in line with these studies.

Compared with our study group, the frequency of LA thrombus in the RE-LY trial[9] was significantly lower and reached 1.8%, 1.2%, and 1.1% in the group receiving dabigatran at a dose of 110 mg twice daily, the group receiving dabigatran at a dose of 150 mg twice daily, and the VKA group, respectively.[9] The same applies to the comparison of our results to the study by Mitamura et al,[37] who reported the frequency of LA thrombus at 0.5% in patients treated with dabigatran at a dose of 150 mg twice daily and 3.5% in those treated with dabigatran at a dose of 110 mg twice daily. In the study by Reers et al,[38] LA thrombus was observed in 4% of patients treated with VKAs, 0% in patients treated with dabigatran, and 2% in patients treated with rivaroxaban. However, a study by Zylla et al[39] revealed a significantly higher prevalence of intracardiac thrombi in patients on VKA therapy (17.8%) than those on dabigatran (3.8%) or rivaroxaban (4.1%). In a study by Wyrembak et al,[40] the incidence of LAA thrombi was also higher in patients treated with warfarin (1.55%), as compared with patients treated with NOACs (0.24%; $P = 0.047$).

Although we observed no difference in the prevalence of LAA thrombus between patients treated with dabigatran and those treated with rivaroxaban, there was a trend for a lower occurrence of dense SEC in the rivaroxaban group. However, this difference may be explained by higher emptying LAA velocities, as well as lower hematocrit in the rivaroxaban group. Better LAA hemodynamic function in the rivaroxaban group was probably related to a higher prevalence of paroxysmal (instead of persistent or permanent) AF. Still, despite these differences, the frequency of LAA thrombus formation in both NOAC groups was comparable.

Although it is beyond the scope of the present publication, it is worth noting that in the group receiving bridging therapy (58 patients), LAA thrombus was not observed. Previous nonrandomized studies have shown that the strategy without the use of bridging anticoagulation is noninferior to that with the use of bridging therapy for the prevention of arterial thromboembolism. A meta-analysis of observational studies involving a total of 12 278 patients with AF or mechanical heart prostheses who received or did not receive bridging with low-molecular-weight heparin showed no significant difference in the rate of arterial thromboembolism (OR with bridging, 0.80; 95% CI, 0.42–1.54), but a higher rate of major bleeding (OR, 3.60; 95% CI, 1.52–8.50) in association with bridging.[41] In our study, the lower prevalence of LAA thrombus in patients receiving bridging therapy may be related to a relatively small number of patients in this group. Furthermore, it needs to be emphasized that we did not assess the rate of bleeding complications in the study population.

Finally, it is worth noting that in our real-life population of patients with AF referred for ablation or cardioversion, 15% of the patients on OAC therapy had a CHA_2DS_2-VASc score of 0 (with only 0.4% of patients having an indication for OAC therapy due to mechanical valve prosthesis), and 24% of the patients receiving no form of OAC had a CHA_2DS_2-VASc score of 2.

Our study adds to the knowledge on the efficacy of NOAC in comparison with VKAs in real-world population of patients with AF. Furthermore, it shows the prevailing trends in anticoagulant treatment in Poland, as our center gained the status of a tertiary referral hospital and

included patients referred from many different Polish regional centers.

Limitations of the study In contrast to ischemic stroke and other thromboembolic events, LAA thrombus on TEE is only a surrogate endpoint. However, as the pathophysiology of ischemic stroke in AF is related to LAA thrombus formation, the design of our study seems appropriate to address the issue of OAC treatment efficacy.

As this was a retrospective study, we did not perform a blinded assessment of LAA on TEE by different echocardiographers. However, when LAA thrombus was suspected on TEE, it was assessed by at least 2 echocardiographers to provide a reliable diagnosis and enable a safe referral of patients for ablation or cardioversion.

As the main purpose of the study was to assess the efficacy of different anticoagulant regimens in patients with AF and not to identify the most suitable mode of periprocedural anticoagulant treatment, we have not analyzed periprocedural or postprocedural complications, such as periprocedural bleeding or stroke.

Another limitation of our study results from its retrospective design (ie, data on some of the variables were not available for all the patients, as indicated in tables). However, we were striving to meet the requirements of a prospective observation (ie, all consecutive patients with AF undergoing TEE in our department were included). Nevertheless, it needs to be emphasized that the retrospective design of our study does not allow to draw any definite conclusions on the effectiveness (in terms of superiority or noninferiority) of different OAC regimens or to verify whether patients on NOAC missed any doses of their medication in the period before TEE. Finally, we were not able to assess the time in therapeutic range for patients on VKAs.

Conclusions Every second patient scheduled for AF ablation or cardioversion was treated with a NOAC, with a similar frequency of dabigatran and rivaroxaban treatment in the NOAC group. The choice of preprocedural anticoagulation did not depend on patients' thromboembolic or bleeding risk. There were no significant differences in the frequency of LAA thrombus between VKA and NOAC therapy.

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

Contribution statement AK-C and MB were responsible for the concept and design of the study. AK-C, MB, and MG contributed to the design of the research. MG, AB, AB, RU, and MZ were involved in data collection. AK-C, MB, PS, and JK performed echocardiographic analysis. AK-C, MB, and MG analyzed the data. MG and MP were responsible for statistical analysis. MG, AK-C, and MB wrote the manuscript. All authors edited and approved the final version of the manuscript.

REFERENCES

1 Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37: 2893-2962.

2 Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015; 17: 1467-1507.

3 Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg. 1996; 61: 755-759.

4 Healey JS, Crystal E, Lamy A, et al. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. Am Heart J. 2005; 150: 288-293.

5 Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014; 383: 955-962.

6 Gómez-Outes A, Terleira-Fernández AI, Calvo-Rojas G, et al. Dabigatran, rivaroxaban, or apixaban versus warfarin in patients with nonvalvular atrial fibrillation: a systematic review and meta-analysis of subgroups. Thrombosis. 2013; 2013: 640723.

7 Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. J Am Heart Assoc. 2016; 5: e003725.

8 Hankey GJ, Stevens SR, Piccini JP, et al. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: the rivaroxaban once daily, oral, direct factor xa inhibition compared with vitamin k antagonism for prevention of stroke and embolism trial in atrial fibrillation. Stroke. 2014; 45: 1304-1312.

9 Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361: 1139-1151.

10 Committee ES, Investigators RAs. Rivaroxaban – once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: rationale and design of the ROCKET AF study. Am Heart J. 2010; 159: 340-347.

11 Lenarczyk R, Mitręga K, Mazurek M, et al. Polish and European management strategies in patients with atrial fibrillation. Data from the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot). Pol Arch Med Wewn. 2016; 126: 138-148.

12 Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365: 981-992.

13 Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011; 364: 806-817.

14 Pruszczyk P, Stępińska J, Banasiak W, et al. Zastosowanie nowych doustnych leków przeciwkrzepliwych w prewencji powikłań zatorowych u chorych z migotaniem przedsionków. Kardiol Pol. 2012; 70: 979-988.

15 Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace. 2010; 12: 1360-1420.

16 Camm J, Lip GYH, De Caterina R, et al. [ESC guidelines on the management of atrial fibrillation: a 2012 update]. Kardiol Pol. 2012; 70 (Suppl IV): 197-234. Polish.

17 Cozma D, Streian CG, Vacarescu C, et al. Back to sinus rhythm from atrial flutter or fibrillation: dabigatran is safe without transoesophageal control. Kardiol Pol. 2016; 74: 425-430.

18 Di Biase L, Burkhardt JD, Santangeli P, et al. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the role of coumadin in preventing thromboembolism in atrial fibrillation (AF) patients undergoing catheter ablation (COMPARE) randomized trial. Circulation. 2014; 129: 2638-2644.

19 Di Biase L, Briceno DF, Trivedi C, et al. Is transesophageal echocardiogram mandatory in patients undergoing ablation of atrial fibrillation with uninterrupted novel oral anticoagulants? Results from a prospective multicenter registry. Heart Rhythm. 2016; 13: 1197-1202.

20 Lakkireddy D, Reddy YM, Di Biase, et al. Feasibility and safety of uninterrupted rivaroxaban for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. J Am Coll Cardiol. 2014; 63: 982-988.

21 Aryal MR, Ukaigwe A, Pandit A, et al. Meta-analysis of efficacy and safety of rivaroxaban compared with warfarin or dabigatran in patients undergoing catheter ablation for atrial fibrillation. Am J Cardiol. 2014; 114: 577-582.

22 Kaess BM, Ammar S, Reents T, et al. Comparison of safety of left atrial catheter ablation procedures for atrial arrhythmias under continuous anticoagulation with apixaban versus phenprocoumon. Am J Cardiol. 2015; 115: 47-51.

23 Nairooz R, Ayoub K, Sardar P, et al. Uninterrupted new oral anticoagulants compared with uninterrupted vitamin K antagonists in ablation of atrial fibrillation: a meta-analysis. Can J Cardiol. 2016; 32: 814-823.

24 Calkins H, et al. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation. N Engl J Med. 2017; 376: 1627-1636.

25 Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/ EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace. 2012; 14: 528-606.

26 Apostolakis S, Sullivan RM, Olshansky B, et al. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT(2)R(2) score. Chest. 2013; 144: 1555-1563.

27 Roldan V, Cancio S, Galvez J, et al. The SAMe-TTR score predicts poor anticoagulation control in AF patients: a prospective "Real-World" Inception Cohort Study. Am J Med. 2015; 128: 1237-1243.

28 Lip GY, Haguenoer K, Saint-Etienne C, et al. Relationship of the SAMe-TT(2)R(2) score to poor-quality anticoagulation, stroke, clinically relevant bleeding, and mortality in patients with atrial fibrillation. Chest. 2014; 146: 719-726.

29 Proietti R, Lip GYH. Simple decision-making between a vitamin K antagonist and a non-vitamin K antagonist oral anticoagulant: using the SAMe--TT2R2score. Eur Heart J. 2015; 1: 150-152.

30 Gorzelak-Pabiś P, Zyzak S, Krewko Ł, Broncel M. Assessment of the mean time in the therapeutic INR range and the SAME-TT2R2 score in patients with atrial fibrillation and cognitive impairment. Pol Arch Med Wewn. 2016; 126: 494-501.

31 Kawabata M, Goya M, Sasaki T, et al. Left atrial appendage thrombi formation in Japanese non-valvular atrial fibrillation patients. Warfarin vs. direct oral anticoagulants. Circ J. 2017; 81: 645-651.

32 Dorenkamp M, Sohns C, Vollmann D, et al. Detection of left atrial thrombus during routine diagnostic work-up prior to pulmonary vein isolation for atrial fibrillation: role of transesophageal echocardiography and multidetector computed tomography. Int J Cardiol. 2011; 163: 26-33.

33 Ono K, Iwama M, Kawasaki M, et al. Motion of left atrial appendage as a determinant of thrombus formation in patients with a low CHADS2 score receiving warfarin for persistent nonvalvular atrial fibrillation. Cardiovasc Ultrasound. 2012; 10: 50.

34 Saksena S, Sra J, Jordaens L, et al. A prospective comparison of cardiac imaging using intracardiac echocardiography with transesophageal echocardiography in patients with atrial fibrillation: the intracardiac echocardiography guided cardioversion helps interventional procedures study. Circ Arrhythm Electrophysiol. 2010; 3: 571-577.

35 Seidl K, Rameken M, Drogemuller A. Embolic events in patients with atrial fibrillation and effective anticoagulation: value of transesophageal echocardiography to guide direct-current cardioversion. Final results of the Ludwigshafen Observational Cardioversion Study. J Am Coll Cardiol. 2002; 39: 1436-1442.

36 Sikorska A, Baran J, Pilichowska-Paszkiet E, et al. Risk of left atrial appendage thrombus in patients scheduled for ablation for atrial fibrillation: beyond the CHA2DS2VASc score. Pol Arch Med Wewn. 2015; 125: 921-928.

37 Mitamura H, Nagai T, Watanabe A, et al. Left atrial thrombus formation and resolution during dabigatran therapy: A Japanese Heart Rhythm Society report. J Arrhythm. 2015; 31: 226-231.

38 Reers S, Agdirlioglu T, Kellner M, et al. Incidence of left atrial abnormalities under treatment with dabigatran, rivaroxaban, and vitamin K antagonists. Eur J Med Res. 2016; 21: 41.

39 Zylla MM, Pohlmeier M, Hess A, et al. Prevalence of intracardiac thrombi under phenprocoumon, direct oral anticoagulants (dabigatran and rivaroxaban), and bridging therapy in patients with atrial fibrillation and flutter. Am J Cardiol. 2015; 115: 635-640.

40 Wyrembak J, Campbell KB, Steinberg BA, et al. Incidence and predictors of left atrial appendage thrombus in patients treated with nonvitamin K oral anticoagulants versus warfarin before catheter ablation for atrial fibrillation. Am J Cardiol. 2017; 119: 1017-1022.

41 Siegal D, Yudin J, Kaatz S, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. Circulation. 2012; 126: 1630-1639.