ORIGINAL ARTICLE

Trends in antithrombotic management of patients with atrial fibrillation

A report from the Polish part of the EURObservational Research Programme – Atrial Fibrillation General Long-Term Registry

Piotr Lodziński[1], Monika Gawałko[1], Monika Budnik[1], Agata Tymińska[1], Krzysztof Ozierański[1], Marcin Grabowski[1], Agnieszka Janion-Sadowska[2], Grzegorz Opolski[1], Radosław Lenarczyk[2], Zbigniew Kalarus[3], Gregory Y. H. Lip[4,5], Paweł Balsam[1]

1 1st Department of Cardiology, Medical University of Warsaw, Warsaw, Poland
2 2nd Department of Cardiology, Świętokrzyskie Cardiology Center, Kielce, Poland
3 Department of Cardiology, DMS in Zabrze, Medical University of Silesia, Katowice, Poland
4 Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom
5 Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

KEY WORDS

antithrombotic therapy, atrial fibrillation, non-vitamin K antagonist oral anticoagulants, vitamin K antagonists

ABSTRACT

INTRODUCTION Data on antithrombotic treatment among patients with atrial fibrillation (AF) in Poland are limited.

OBJECTIVES We aimed to describe antithrombotic management within the Polish part of the EURObservational Research Programme on Atrial Fibrillation General Long-Term Registry.

PATIENTS AND METHODS We analyzed data collected at baseline and at 1-year follow-up from 701 Polish patients treated at 25 Polish centers between 2013 and 2016.

RESULTS Any antithrombotic therapy was administered to 94% of patients (vitamin K antagonists [VKAs], 53%; non-VKA oral anticoagulants [NOACs], 36%; antiplatelet therapy [APT], 4.8%). However, 78% of patients considered as "low-risk" (CHA_2DS_2-VASc = 0 in men or 1 in women) were prescribed oral anticoagulants and 12% were on APT. Independent predictors of NOAC and VKA use were first-detected AF and device therapy. Predictors of VKA use were lone AF, history of ischemic stroke, and pulmonary embolism or deep vein thrombosis; of NOAC use, permanent AF; of APT use, history of hemorrhagic events and first-detected or persistent AF; and of no antithrombotic treatment, young age. Incorrect NOAC prescription was more common in the reduced-dose group than in the full-dose group (30% vs 7%). During follow-up, the all-cause mortality rate was 5.2%, 0.8%, 15%, and 7% (P <0.0001) and the risk of thromboembolic events was 0.4%, 0.5%, 6.2%, and 0% (P = 0.04) in patients on VKA, NOAC, APT, and no treatment, respectively.

CONCLUSIONS Patients with the lowest stroke risk are often overtreated. The choice of proper antithrombotic strategy does not depend solely on factors incorporated in the CHA_2DS_2-VASc score. Higher mortality is observed among APT-treated patients and those without antithrombotic treatment.

Correspondence to:
Monika Gawałko, MD,
1st Department of Cardiology,
Medical University of Warsaw,
ul. Banacha 1a, 02-097 Warszawa,
Poland, phone: +48 22 599 29 58,
email: mongawalko@gmail.com
Received: November 15, 2019.
Revision accepted: January 20, 2020.
Published online: January 24, 2020.
Pol Arch Intern Med. 2020;
130 (3): 196-205
doi:10.20452/pamw.15157

INTRODUCTION Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is associated with a significant risk of morbidity and mortality, mainly due to an increased risk of stroke and systemic embolism.[1] Prevention of embolism with oral anticoagulation (OAC) is recommended for AF patients with at least 1 risk factor for stroke (ie, a CHA_2DS_2-VASc score of ≥1 in men or ≥2 in women).[2-4]

Randomized controlled trials are considered the gold-standard method to evaluate the effectiveness and safety of simple therapeutic interventions such as OAC. However, clinical trials have limited generalizability because they are

WHAT'S NEW?

The analysis of the Polish part of EURObservational Research Programme on Atrial Fibrillation General Long-Term Registry provides an overview of atrial fibrillation management in Poland. Treatment with antithrombotic drugs had a high frequency and was associated with various clinical features. Patients with the lowest risk of stroke (CHA_2DS_2-VASc = 0) were often overprescribed or received an inappropriate dose of antithrombotic drugs. One-year follow-up revealed an overall low occurrence of thromboembolic and hemorrhagic events, although mortality remains high, especially among patients treated with antiplatelet therapy alone or those without antithrombotic treatment.

performed in conditions that differ from routine clinical practice.[5,6] In consequence, recommended OAC may be underused in a significant proportion of patients, but antithrombotic drugs can be also overprescribed in many patients.[7-9]

There are limited data on contemporary antithrombotic treatment of patients with AF in Poland. Therefore, we aimed to describe antithrombotic management within the Polish part of the EURObservational Research Programme Atrial Fibrillation (EORP-AF) General Long-Term Registry. Moreover, we evaluated associations between patients' clinical characteristics and drug choice as well as between the type of antithrombotic management and long-term outcomes.

PATIENTS AND METHODS

Study population Data reported herein are based on the results calculated for Polish participants of the EORP-AF Long-Term General registry, which was conducted from 2013 to 2016. The methodology of this registry was described previously.[10] In brief, the aim of the registry was to assess the rate of complications related to AF across Europe in order to confirm adherence of cardiologists to the 2012 recommendations of the European Cardiac Society (ESC) on the treatment of AF.[3] The registry population consisted of consecutive patients presenting to cardiologists with AF as the main or comorbid condition. Additionally, patients included in the registry had to have AF within the last year, as recorded on electrocardiography, but they did not need to be in arrhythmia at the time of enrollment. Finally, 701 consecutive patients from 25 Polish centers were included in the registry. Participating investigator sites presented a broad range of medical care units (tertiary, secondary, general hospitals, and outpatient clinics). The registry schedule assumed 1 baseline visit and 1 visit per year over a 3-year follow-up, but only data collected at baseline and at 1 year were included in this analysis.

Appropriateness of non–vitamin K antagonist oral anticoagulant dosing A prescription was reported as inappropriate if the patient met at least 1 inappropriate dosing criterion according to the ESC guideline for AF and the summary of product characteristics as registered with the European Medicine Agency.[11] The dosing criteria that were used to evaluate the appropriateness of the prescriptions are summarized in Supplementary material (*Table S1*). Prescriptions that were classified as inappropriate solely based on a missing value or multiple missing values were reported as "unknown inappropriateness."

Ethical approval The registry was approved by local ethical review boards according to the regulations of each participating country. The study was performed according to the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki. A signed informed consent was obtained from each patient after providing detailed information on the registry.[10]

Statistical analysis Data were presented as a median and interquartile range or number of patients and percentages, as appropriate. The statistical significance of differences was analyzed using the Kruskal–Wallis test. Frequencies of parameters or events were compared using the χ^2 test or Fisher exact test, as appropriate. For all tests, a P value of less than 0.05 was considered significant. To determine predictors of different type of antithrombotic management, univariable and multivariable logistic regression analyses were performed. Statistical analysis was performed with StatsModels: Statistic in Python – v0.10.1 documentation (Seabold, Skipper, and Josef Perktold. "Statsmodels: Econometric and statistical modeling with Python." Proceedings of the 9th Python in Science Conference 2010).

RESULTS

Baseline characteristics Of the 701 patients enrolled, 10 were excluded due to missing data on antithrombotic treatment (Supplementary material, *Figure S1*). Any antithrombotic regimens were administered during study enrollment to 94% of Polish patients. Vitamin K antagonists (VKAs) were the most commonly prescribed antithrombotic drugs, followed by non-VKA oral anticoagulants (NOACs), whereas antiplatelet therapy (APT) was administered only to a small fraction of Polish patients (53%, 36%, and 4.8%, respectively). Patients receiving various regimens of antithrombotic treatment differed with respect to several baseline characteristics. Those on APT were older, had a greater prevalence of coronary artery disease (mainly in the form of myocardial infarction), more often had a history of heart failure, current malignancy, as well as more often were diagnosed with first-detected or permanent AF as compared with the remaining patients. Patients on NOACs more often had persistent AF and hypertension, whereas those without antithrombotic treatment more often had lone AF as compared with the other groups. The median CHA_2DS_2-VASc and HAS-BLED scores were higher in patients treated with APT (TABLE 1). Both patients treated with reduced doses of rivaroxaban and dabigatran were characterized by older age, more often were female, more often had coronary artery disease, and had higher thromboembolic or bleeding risk compared with

TABLE 1 Clinical characteristics of patients with atrial fibrillation treated with different oral antithrombotic regimens

Variable	VKA (n = 366)	NOAC (n = 249)	APT (n = 33)	No antithrombotic therapy (n = 43)	*P* value
Demographics					
Age, y, median (IQR)	67 (61–74)	68 (61–76)	73 (63–80)	68 (51–73)	0.07
Female sex, n (%)	156 (43)	110 (44)	11 (33)	17 (40)	0.67
Atrial fibrillation					
First-diagnosed	10 (2.7); 365	24 (9.6); 248	5 (15)	2 (4.7)	<0.0001
Paroxysmal	107 (29); 365	80 (32); 248	10 (30)	20 (46)	0.14
Long-standing persistent	38 (10); 365	20 (8); 248	1 (3)	3 (7)	0.43
Persistent	67 (18); 365	67 (27); 248	1 (3)	5 (12)	0.001
Permanent	143 (39); 365	57 (23); 248	16 (49)	13 (30)	<0.0001
Lone	18 (4.9)	20 (8)	3 (9.1)	10 (23)	<0.0001
Concomitant diseases and interventions					
Hypertension	208 (57); 364	157 (64); 247	16 (49); 32	17 (40)	0.02
CAD	135 (39); 350	80 (34); 237	21 (64)	8 (21); 39	0.001
Previous MI	66 (19); 350	32 (14); 237	15 (46)	5 (13); 39	<0.0001
Previous PCI/PTCA	65 (19); 350	28 (12); 237	12 (36)	3 (7.7); 39	0.001
Heart failure	201 (55); 364	107 (43); 247	24 (73)	18 (42)	0.001
Dilated cardiomyopathy	35 (9.6); 364	14 (5.6); 245	3 (9.1)	3 (7)	0.37
Hypertrophic cardiomyopathy	11 (3); 364	2 (0.8); 245	0	2 (4.7)	0.15
Restrictive cardiomyopathy	0; 364	0; 245	0	1 (2.3)	0.002
Device therapy (PM/CRT/ICD)	88 (24); 361	27 (11); 248	7 (21)	4 (10); 39	<0.0001
Previous thromboembolic events	52 (14); 363	23 (9.2)	3 (9.1)	2 (4.7)	0.08
Hemorrhagic events	23 (6); 364	19 (7.6); 248	8 (24)	6 (14)	0.001
Current malignancy	4 (1.1); 360	2 (0.8)	2 (6.1)	2 (4.7)	0.03
Thromboembolic and bleeding risk, median (IQR)					
CHA_2DS_2-VASc score	3 (2–4)	3 (2–4)	4 (3–6)	3 (1–3)	0.01
HAS-BLED score	1.5 (1–2)	1 (0–2)	2 (1–3)	1 (0–2)	0.02

Data are presented as number (percentage) of patients unless otherwise indicated. Number provided after the semicolon indicates the total number of patients available for that variable.

Abbreviations: APT, antiplatelet therapy; CAD, coronary artery disease; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke or thromboembolism, vascular disease, age 65 to 74 years, female sex; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; MI, myocardial infraction; NOAC, non–vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; PM, pacemaker; PTCA, percutaneous transluminal coronary angioplasty; VKA, vitamin K antagonist

those on full NOAC doses (TABLE 2). Detailed characteristics of patients with AF treated with different antithrombotic regimens are presented in Supplementary material, *Table S2*, while detailed characteristics of rivaroxaban- and dabigatran-treated groups (both using standard and reduced doses) are shown in Supplementary material, *Table S3*.

Thromboembolic risk, bleeding risk, and antithrombotic therapy The use of different antithrombotic strategies stratified by CHA_2DS_2-VASc and HAS-BLED scores is shown in FIGURE 1. Almost 95% of patients with indications (CHA_2DS_2-VASc ≥2) were treated with antithrombotic drugs (including VKAs, NOACs, and APT). One-fifth of patients with indications who received antithrombotic treatment and one-fourth of those who, despite indications, did not receive any antithrombotic drugs were at high risk of bleeding (HAS-BLED ≥3) (Supplementary material, *Table S4*). However, still 78% of Polish patients who were considered "low-risk" (CHA_2DS_2-VASc = 0), were prescribed anticoagulation and 12% were receiving APT (FIGURE 1). In our study, 30% of patients were prescribed lower doses of NOACs despite indications for a standard dose, whereas 7% of patients were prescribed full instead of reduced NOAC doses (Supplementary material, *Figure S2*).

Predictors of oral antithrombotic drug use The predictors of the use of particular antithrombotic drugs are demonstrated in TABLE 3. Independent predictors of the use of both NOACs and VKAs were first-diagnosed AF and device therapy. Additionally, lone AF, history of ischemic stroke, and pulmonary embolism or deep vein thrombosis turned out to be predictors of VKA use, whereas permanent AF was a predictor of NOAC use.

TABLE 2 Clinical characteristics of patients with atrial fibrillation depending on the dose of dabigatran or rivaroxaban

Variable	Rivaroxaban		Dabigatran		*P* value
	Standard (n = 65)	Reduced (n = 24)	Standard (n = 114)	Reduced (n = 46)	
Demographic data					
Age, y, median (IQR)	67 (62–73)	80 (75–84)	64 (57–71)	78 (70–83)	<0.0001
Female sex	26 (40)	15 (63)	44 (39)	25 (54)	0.02
Atrial fibrillation					
First-diagnosed	6 (9.2); 64	2 (8.3)	14 (12)	2 (4.3)	0.28
Paroxysmal	24 (37); 64	9 (38)	34 (30)	13 (28)	0.61
Long-standing persistent	5 (7.7); 64	2 (8.3)	11 (9.6)	2 (4.3)	0.47
Persistent	9 (14); 64	2 (8.3)	43 (38)	13 (28)	0.001
Permanent	20 (31); 64	9 (38)	12 (11)	16 (35)	<0.0001
Lone	4 (6.2)	0	14 (12)	2 (4.3)	0.15
Concomitant diseases and interventions					
CAD	24 (38); 63	12 (55); 22	24 (21); 108	20 (44); 44	0.001
Previous MI	5 (7.7); 63	6 (25); 22	10 (8.8); 108	11 (24); 44	0.003
Previous PCI/PTCA	5 (7.7); 63	5 (23); 22	9 (7.9); 108	9 (20); 44	0.03
Angina	16 (25); 63	8 (36); 22	5 (4.4); 108	10 (22); 44	<0.0001
Valvular alterations moderate/severe	21 (32); 64	14 (58)	20 (18); 111	16 (35)	0.001
Previous thromboembolic events	2 (3.1)	1 (4.2)	16 (14)	4 (8.7)	0.14
Hemorrhagic events	4 (6.2); 64	2 (8.3)	7 (6.1)	6 (13)	0.26
CKD	3 (4.6)	5 (21)	12 (11)	18 (39)	<0.0001
Thromboembolic and bleeding risk, median (IQR)					
CHA_2DS_2-VASc score	3 (2–4)	4 (3–5)	2 (1–4)	4 (3–5)	<0.0001
HAS-BLED score	1 (0–2)	2 (1–2)	1 (0–2)	2 (1–2)	0.001

Data are presented as number (percentage) of patients unless otherwise indicated. Number provided after the semicolon indicates the total number of patients for that variable.

Abbreviations: CKD, chronic kidney disease; others, see TABLE 1

History of hemorrhagic events as well as first-diagnosed and persistent AF were all predictive for choosing APT, whereas young age predicted refraining from any antithrombotic treatment.

One-year outcomes During 1-year follow-up, of the 691 patients enrolled, 176 patients had withdrawn their consent or were lost to follow-up and 29 patients died. One-year all-cause mortality rates were 5.2%, 0.8%, 15%, and 7% for patients on VKA, NOAC, APT, and no antithrombotic treatment, respectively (P <0.0001). Most patients died from a cardiovascular cause (sudden cardiac death or heart failure). All patients treated with APT or who were on no antithrombotic treatment who died during follow-up had indications for OAC (CHA_2DS_2-VASc ≥2). Patients without antithrombotic treatment were more often subjected to cardiovascular interventions (mainly a valvular surgery), and those on APT, to thromboembolic events during follow-up. No significant differences between all analyzed groups were observed regarding rhythm control interventions and reasons for hospital admissions except more frequent general practitioner visits in the case of patients without antithrombotic treatment. Moreover, APT-treated patients more often experienced thromboembolic and noncardiovascular events as compared with the remaining groups (TABLES 4 and 5). According to patients on NOACs, there were no significant differences in long-term outcomes between the type of a NOAC as well as between standard or reduced doses (TABLES 6 and 7). During the 1-year follow-up, some patients were switched from one to another antithrombotic regimen, as shown in Supplementary material, *Figure S1*. Among patients without any antithrombotic treatment on enrollment, during 1-year follow-up, 9 patients were started on VKAs; 6 patients, on NOACs (mainly dabigatran); and 1 patient, on APT. Among the patients treated at baseline with NOACs, 10 were switched to VKAs (9 patients to dabigatran and 1 patient to rivaroxaban) or discontinued treatment (8 patients on dabigatran and 10 patients on rivaroxaban). On the other hand, 22 patients treated with VKAs were switched to NOACs (11 patients to dabigatran and 11 to rivaroxaban), and 3 patients, to APT. In the APT group, the majority of patients who were initially treated with APT and switched to another treatment, changed APT to VKA (5 patients).

DISCUSSION

The EORP-AF General Long-Term registry provides an important view on contemporary antithrombotic strategies used in Polish

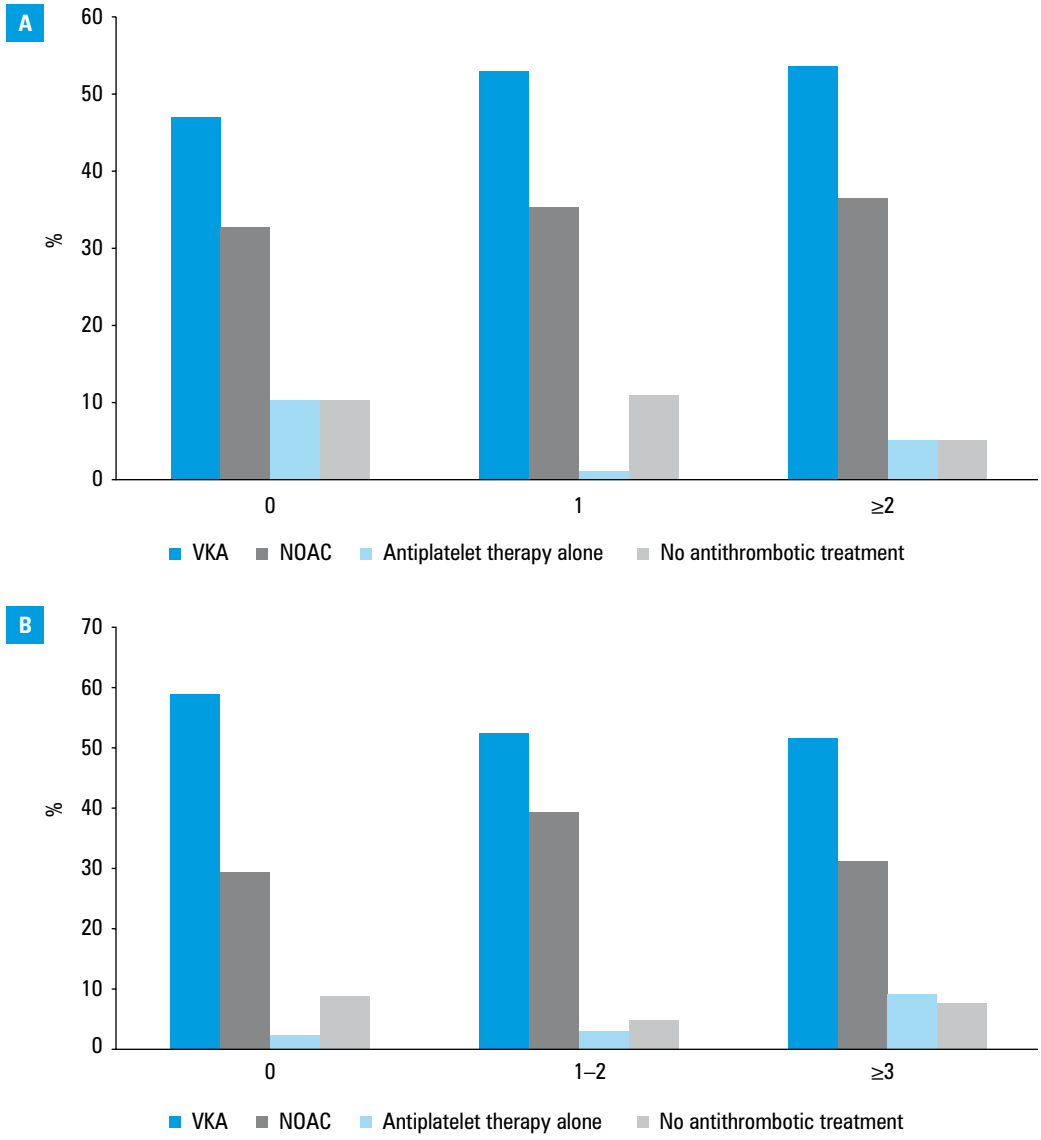

FIGURE 1 Proportion of patients treated with antithrombotic drugs by the CHA_2DS_2-VASc score (**A**) and HAS-BLED score (**B**)
Abbreviations: see TABLE 1

TABLE 3 Regression analysis for predictors of different antithrombotic regimens

Variable	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Predictors of NOAC use						
First-diagnosed AF	2.66	1.4–5.07	0.003	1.97	1.00–3.84	0.047
Permanent AF	0.46	0.32–0.66	<0.0001	0.58	0.39–0.88	0.01
Device therapy (PM/CRT/ICD)	0.41	0.26–0.65	<0.0001	0.51	0.31–0.84	0.008
Predictors of VKA use						
Lone AF	0.46	0.25–0.83	0.01	0.49	0.27–0.88	0.02
Ischemic stroke	2.20	1.18–4.11	0.01	4.34	1.31–14.45	0.02
Pulmonary embolism/DVT	9.15	1.17–71.89	0.04	23.06	2.29–231.85	0.008
First-diagnosed AF	0.27	0.13–0.55	<0.0001	0.33	0.16–0.68	0.003
Device therapy (PM/CRT/ICD)	2.38	1.57–3.61	<0.0001	1.91	1.24–2.95	0.003
Predictors of APT use						
Hemorrhagic events	4.24	1.81–9.93	0.001	0.24	0.11–0.53	<0.0001
First-diagnosed AF	3.09	1.12–8.46	0.03	0.14	0.05–0.36	<0.0001
Persistent AF	0.12	0.02–0.86	0.04	0.01	0.01–0.06	<0.0001
Predictors of no antithrombotic treatment						
Age (every 10 years)	0.76	0.62–0.94	0.01	0.96	0.95–0.87	<0.0001

Abbreviations: AF, atrial fibrillation; DVT, deep vein thrombosis; OR, odds ratio; others, see TABLE 1

TABLE 4 Associations between the type of antithrombotic treatment and long-term outcomes in all study groups

Variable	VKA (n = 366)	NOAC (n = 249)	APT (n = 33)	No antithrombotic treatment (n = 43)	*P* value
Follow-up completed	253 (69)	187 (75)	18 (55)	28 (65)	0.06
Death	19 (5.2)	2 (0.8)	5 (15)	3 (7)	<0.0001
Withdrawn consent/lost to follow-up	94 (26)	60 (24)	10 (30)	12 (28)	0.86

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: see **TABLE 1**

TABLE 5 Associations between the type of antithrombotic treatment and long-term outcomes among patients who presented at follow-up visit

Variable	VKA (n = 253)	NOAC (n = 187)	APT (n = 18)	No antithrombotic treatment (n = 28)	*P* value
Clinical visits for CV reasons during follow-up					
Cardiology visits	208 (90); 232	147 (81); 182	13 (81); 16	19 (76); 25	0.04
Emergency room admissions	34 (15); 234	28 (15); 184	2 (13); 16	3 (12); 26	0.96
GP visits	167 (74); 225	148 (86); 172	11 (73); 15	22 (96); 23	0.006
CV interventions					
Overall	26 (11); 239	5 (2.7); 184	2 (13); 16	3 (12); 26	0.01
PCI/PTCA	5 (2.1); 239	4 (2.2); 184	0 (0); 16	1 (3.8); 26	0.87
CABG	4 (1.7); 239	0 (0); 184	1 (6.2); 16	0 (0); 26	0.07
LAAO	2 (0.8); 239	0 (0); 184	0 (0); 16	0 (0); 26	0.59
Transcatheter valve intervention	2 (0.8); 239	0 (0); 184	0 (0); 16	0 (0); 26	0.59
Valvular surgery	13 (5.4); 239	0 (0); 184	1 (6.2); 16	2 (7.7); 26	0.01
Heart transplant	0 (0); 239	0 (0); 184	0 (0); 16	0 (0); 26	1.00
Other	4 (1.7); 239	1 (0.5); 184	0 (0); 16	0 (0); 25	0.63
Reasons for hospital admission					
AF/AFl/AT	19 (8.2); 233	26 (14); 181	0 (0); 16	4 (15); 26	0.09
Thromboembolic events	1 (0.4); 241	1 (0.5); 183	1 (6.2); 16	0 (0); 26	0.04
Hemorrhagic events	3 (1.2); 241	3 (1.6); 183	0 (0); 16	0 (0); 26	0.87
ACS	4 (1.7); 241	2 (1.1); 183	0 (0); 16	0 (0); 26	0.83
Overall CV events	28 (12); 240	16 (8.7); 183	4 (25); 16	0 (0); 26	0.054
Non-CV events	8 (3.3); 240	15 (8.2); 183	3 (19); 16	1 (3.8); 26	0.02
Rhythm control interventions and device therapy					
Pharmacological cardioversion	11 (4.8); 231	11 (6.2); 178	0 (0); 16	1 (4.2); 24	0.71
Electrical cardioversion	14 (6); 233	18 (10); 180	0 (0); 16	2 (8); 25	0.30
Catheter ablation for AF	5 (2.2); 231	7 (3.9); 180	0 (0); 16	1 (4); 25	0.65
Catheter ablation for AFl	1 (0.4); 232	1 (0.6); 180	0 (0); 16	1 (4); 25	0.21
AF surgery	2 (0.8); 233	0 (0); 180	0 (0); 16	0 (0); 25	0.59
Device therapy (PM/ICD/CRT)	7 (3); 233	5 (2.2); 180	0 (0); 16	1 (4); 25	0.84

Data are presented as number (percentage) of patients unless otherwise indicated. Number provided after the semicolon indicates the total number of patients for that variable.

Abbreviations: ACS, acute coronary syndrome; AFl, atrial flutter; AT, atrial tachycardia; CABG, coronary artery bypass graft; CV, cardiovascular; GP, general practitioner; LAAO, left atrial appendage occlusion; others, see **TABLES 1–3**

patients with AF. There are several major findings of the present study. First, our country-specific registry data suggest overuse of antithrombotic treatment in a significant proportion of patients at low risk of stroke or systemic embolism. Second, physicians' clinical assessment of stroke risk and the subsequent choice of proper AF management appear to incorporate also factors beyond those included in the CHA_2DS_2-VASc score. Third, there is no association between the type of appropriate antithrombotic management (VKAs or NOACs) and long-term thromboembolic and hemorrhagic outcomes in AF patients; however, higher mortality is observed among patients treated with APT only or those without antithrombotic treatment.

TABLE 6 Associations between standard and reduced doses of non–vitamin K oral anticoagulants and long-term outcomes among all study groups

Variable	Rivaroxaban (n = 89)		Dabigatran (n = 160)		*P* value
	Standard (n = 65)	Reduced (n = 24)	Standard (n = 114)	Reduced (n = 46)	
Death	1 (1.5)	0 (0)	0 (0)	1 (2.2)	0.45
Follow-up completed	46 (71)	17 (71)	87 (76)	37 (80)	0.64
Withdrawn consent/ lost to follow-up	18 (28)	7 (29)	27 (24)	8 (17)	0.59

Data are presented as number (percentage) of patients unless otherwise indicated.

TABLE 7 Associations between standard and reduced doses of non–vitamin K oral anticoagulants and long-term outcomes among patients who presented at follow-up visit

Variable	Rivaroxaban (n = 63)		Dabigatran (n = 124)		*P* value
	Standard (n = 46)	Reduced (n = 17)	Standard (n = 87)	Reduced (n = 37)	
Cardiology visits	38 (83); 44	12 (75); 16	71 (84); 85	26 (70)	0.24
Emergency room admissions	10 (23); 44	4 (24)	13 (15); 86	1 (2.7)	0.06
GP visits	35 (83); 42	14 (100)	68 (84); 81	31(89); 35	0.39
CV interventions					
Overall	2 (4.5); 44	1 (5.9)	1 (1.2); 86	1 (2.7)	0.58
PCI/PTCA	1 (2.3); 44	1 (5.9)	1 (1.2); 86	1 (2.7)	0.67
CABG	0 (0); 44	0 (0)	0 (0); 86	0 (0)	1.00
LAAO	0 (0); 44	0 (0)	0 (0); 86	0 (0)	1.00
Transcatheter valve intervention	0 (0); 44	0 (0)	0 (0); 86	0 (0)	1.00
Valvular surgery	0 (0); 44	0 (0)	0 (0); 86	0 (0)	1.00
Heart transplant	0 (0); 44	0 (0)	0 (0); 86	0 (0)	1.00
Other	1 (2.3); 44	0 (0)	0 (0); 86	0 (0)	0.36
Reasons for hospital admission					
AF/AFl/AT	6 (14); 44	0 (0)	15 (18); 84	5 (14); 36	0.30
Thromboembolic events	0 (0); 44	0 (0)	1 (1.2); 85	0 (0)	0.76
Hemorrhagic events	2 (4.5); 44	0 (0)	1 (1.2); 85	0 (0)	0.35
ACS	0 (0); 44	0 (0)	1 (1.2); 85	1 (2.7)	0.67
Overall CV events	3 (6.8); 44	0 (0)	9 (11); 85	4 (11)	0.50
Non-CV events	7 (16); 44	1 (5.9)	4 (4.7); 85	3 (8.1)	0.18
Rhythm control interventions and device therapy					
Overall	8 (17)	1 (5.9)	20 (22)	4 (12)	0.36
Pharmacological cardioversion	3 (7); 43	1 (6.2); 16	7 (8.3); 84	0 (0); 35	0.39
Electrical cardioversion	2(4.5); 44	1 (6.2); 16	14 (17); 85	1 (2.9); 35	0.06
Catheter ablation for AF	2 (4.5); 44	0 (0); 16	4 (4.7); 85	1 (2.9); 35	0.84
Catheter ablation for AFl	0 (0); 44	0 (0); 16	0 (0); 85	1 (2.9); 35	0.19
AF surgery	0 (0); 44	0 (0); 16	0 (0); 85	0 (0); 35	1
Device therapy (PM/ICD/CRT)	1 (2.2); 44	0 (0); 16	3 (3.5); 85	1 (2.9); 35	0.56

Data are presented as number (percentage) of patients unless otherwise indicated. Number provided after the semicolon indicates the total number of patients for that variable.

Abbreviations: see TABLES 1–3 and 5

For decades, VKAs were the only available OAC therapy in patients with AF, reducing the risk of stroke by almost two-thirds.[12] The introduction of NOACs in 2010 changed the landscape of stroke prevention in AF. Indeed, the proportion of incident OAC users for NOACs increased rapidly from 8.1% in the fourth quarter of 2010 to 78.9% in the first quarter of 2017 and surpassed that of VKAs in the third quarter of 2013.[13] In our study, among AF patients who received OAC, 41% and 59% were treated with NOACs and VKAs, respectively. It is in line with data from the CRAFT study

(Multicentre Experience in AFib Patients Treated with OAC), which was recruiting Polish patients with AF at a similar period of time (2011–2016), in which 44% and 56% of patients were prescribed NOACs and VKAs, respectively.[14]

Even though the presented findings may seem outdated as a rapid increase in the NOAC use has changed trends in prescription patterns for anticoagulants with a consensual decrease of antiplatelet drugs, they strengthen the concept that OAC use has significantly reduced risk for thromboembolic complications, without an excess of bleeding complications in real-life AF population. Obviously, our results do not allow to reconsider the role of APT in thromboembolic risk management but highlight the role of antiplatelet drugs in the management of concomitant vascular disease, which is often reported in AF patients.

In recent years, contemporary ESC guidelines have recommended prophylaxis with antithrombotic agents in people with AF and at least 1 other risk factor for stroke.[15-17] However, a discordance between AF guideline recommendations,[3,4,18,19] educational and organizational barriers in the implementation of guideline-recommended AF,[20] as well as anticoagulant prescription patterns has been reported in various international studies.[21-25] The current study assessed adherence of cardiologists to the 2012 ESC recommendations as it was conducted in the years 2013 to 2016. According to those guidelines, anticoagulation was recommended in patients with a CHA_2DS_2-VASc score of 2 or higher and assigned a IIa A recommendation in patients with a CHA_2DS_2-VASc score of 1. Anticoagulation was not recommended in patients with a CHA_2DS_2-VASc score of 0 (I A); however, it was only not considered (IIa B) in female patients without any additional risk factors.

The current 2016 ESC guidelines[4] strengthen the usefulness of the CHA_2DS_2-VASc score for predicting thromboembolic risk. Anticoagulation is not recommended in patients with a CHA_2DS_2-VASc score of 0, even in women (III A). Anticoagulation is assigned a IIa B recommendation in men and women with a single stroke risk factor and a I A recommendation in men with 2 or more risk factors and women with at least 3 risk factors. Thus, the female sex is no longer considered an independent risk factor when indications for anticoagulation are being assessed.

Two important differences regarding antithrombotic treatment in comparison with previous ESC guidelines (2012) are a clear declaration of preference for NOACs over VKAs (I A) and the fact that APT is no more recommended for stroke prevention in AF patients, regardless of stroke risk (III A). Interestingly, the recommendation for a switch to a NOAC when inadequate control of the international normalized ratio is achieved with a VKA was changed from I B in the 2012 guidelines to IIb A in the 2016 guidelines.

Compared with our results, in the whole EORP-AF General Long-Term registry, 42.1% of AF patients were treated with VKAs, 32.8% with NOACs, 7% with APT, and 6.1% received no antithrombotic treatment. The registry reported a low occurrence of thromboembolic and hemorrhagic events, although mortality was high. All-cause death more often occurred in APT-treated patients (8.8%) as compared with those on no antithrombotic therapy (5.1%), those on VKAs (4.8%), and those on NOACs (3.2%), which is in line with our results. Both VKAs and NOACs were associated with a lower risk of all main adverse outcomes, similarly to our study.[26]

Based on our study, there is still some overuse of antithrombotic treatment observed in real-life patients with AF. Nearly 78% of patients with a CHA_2DS_2-VASc score of 0 in men and of 1 in women, who are considered "low-risk", received OAC, including 12% who received APT. This overuse pattern of anticoagulation is higher than that reported in such registries as GARFIELD (Global Anticoagulant Registry in the Field; 38.7%), Euro Heart (49.0%), or PREFER (Prevention of Thromboembolic Events – European Registry; 62.5% of ineligible patients received OAC). Almost 95% of patients with indications for anticoagulation (CHA_2DS_2-VASc ≥2) were taking at least 1 OAC, which suggests a better adherence to recommendations for OAC, as compared with the above studies (ie, GARFIELD, 59.3%; Euro Heart, 67%; PREFER, 85.6% of eligible patients received OAC).[6-8] Compared with previous data from EORP-AF Pilot where 65% of Polish patients with indications (CHA_2DS_2-VASc ≥2) and 67% of those without indications (CHA_2DS_2-VASc = 0) were prescribed OACs,[27] our results demonstrate a clear trend towards more frequent OAC prescription. Also, APT was less frequently prescribed in patients at high risk of thromboembolic event (but still), as compared with previous studies.[6,7]

Recent studies have demonstrated a strong association between APT and an increased risk of all-cause mortality.[28,29] Vazquez et al[29] reported that aspirin monotherapy was associated with a 66% increased likelihood of mortality. Our study also demonstrated that patients on APT were at higher risk of mortality and thromboembolic events as compared with other antithrombotic groups, even with patients on no antithrombotic treatment. Our finding of higher mortality in patients on no antithrombotic treatment is in line with previous studies.[30,31]

Despite differences in the mortality rate and thromboembolic events between study groups, there were no significant differences in terms of hemorrhagic events during follow-up. This is in line with the results from the BLED-AC study (Bleeding Effected by Direct Oral Anticoagulants), which demonstrated that among patients with OAC-related hemorrhage, in-hospital mortality was lower among patients with NOAC- than among those with VKA-associated bleeding events (9.8% vs 15.2%). However, no significant

differences in the risk of 30-day mortality (12.6% vs 16.3%) was observed between groups.[32]

In our study, 30% of patients were prescribed lower doses of NOACs despite indications for a standard dose, whereas 7% of patients were prescribed full instead of reduced doses. This trend was more notable among patients prescribed rivaroxaban (Supplementary material, *Table S1* and *Figure S2*). This is in line with previous studies.[33,34] The absence of indications for NOAC dose reduction was identified in 16.4% of patients receiving reduced-dose NOACs, as demonstrated by Jelonek et al.[35] Steinberg et al[30] found that 9.4% of patients receiving NOACs were underdosed and 3.4% received an inappropriately high dose. Importantly, they showed that over- and underdosing was associated with an increased risk of bleeding and cardiovascular events, respectively.[30] A Danish registry reported no significant difference in the risk of stroke or other thromboembolic events between standard and reduced doses of NOAC.[36]

Our data indicate that physicians' clinical judgment of stroke risk appears to incorporate factors beyond those included in the CHA_2DS_2-VASc score. In our study, patients were considered eligible for antithrombotic treatment not only on the basis of recommended factors such as the history of thromboembolic or hemorrhagic events and elderly age but also the type of AF. Similarly, a higher adjusted probability for prescription of OAC treatment in the GLORIA-AF registry was found in patients with nonparoxysmal AF, previous stroke or transient ischemic attack, and those aged 65 years or older.[37] On the other hand, younger age, heart failure, and history of embolic disease were significant predictors of OAC treatment in a study by Bista et al.[38]

Limitations of the study The major limitation of our study was the lack of a significant part of data either because patients were lost to follow-up or data were missing in the database. Moreover, registry-based studies such as this are limited by numerous other shortcomings, including selection bias (patients included by cardiologists only) or inclusion of nonconsecutive patients (no log-book). Consequently, our results should be interpreted with caution when attempting to extend them to the general AF population, as AF patients are often under the care of noncardiologists.

Compliance with treatment recommendations among patients with the lowest stroke risk remains suboptimal. The choice of proper antithrombotic strategy does not depend solely on factors incorporated into the guideline-recommended scales but also on physicians' and patients' preference. There is no association between the type of appropriate antithrombotic management (VKAs or NOACs) and long-term thromboembolic or hemorrhagic outcomes among AF patients; however, higher mortality was observed among those treated with APT alone and those without antithrombotic treatment.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

ACKNOWLEDGMENTS We thank Paweł Pilkowski for his assistance in statistical analysis as well as all Polish participating centers, investigators, and data collection officers (Supplementary material, *Table S5*).

CONTRIBUTION STATEMENT PL, PB, and MB conceived the concept of the study. PL, PB, and MG contributed to research design. MB, AT, and KO were involved in data collection. MG analyzed the data. PL, PB, and GO coordinated funding for the project. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST PL, GO, and PB received honoraria and speaker fees from Bayer, Boehringer Ingelheim, and Pfizer. GYHL served as a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees were directly received personally. Other authors declare no conflict of interest.

HOW TO CITE Lodziński P, Gawałko M, Budnik M, et al. Trends in antithrombotic management in patients with atrial fibrillation: a report from the Polish part of the EURObservational Research Programme – Atrial Fibrillation General Long-Term Registry. Pol Arch Intern Med. 2020; 130: 196-205. doi:10.20452/pamw.15157

REFERENCES

1 Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future. Comparing the guidelines and practical decision-making. Thromb Haemost. 2017; 117: 1230-1239.

2 Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest. 2018; 154: 1121-1201.

3 Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012; 33: 2719-2747.

4 Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016; 50: e1-e88.

5 Freedman B, Lip GY. "Unreal world" or "real world" data in oral anticoagulant treatment of atrial fibrillation. Thromb Haemost. 2016; 116: 587-589.

6 Lip GY, Laroche C, Dan GA, et al. 'Real-world' antithrombotic treatment in atrial fibrillation: the EORP-AF pilot survey. Am J Med. 2014; 127: 519-529.e1.

7 Kakkar AK, Mueller I, Bassand JP, et al; GARFIELD Registry Investigators. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PLoS One. 2013; 8: e63479.

8 Kirchhof P, Ammentorp B, Darius H, et al. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events-European Registry in Atrial Fibrillation (PREFER in AF). Europace. 2014; 16: 6-14.

9 Nieuwlaat R, Capucci A, Lip GY, et al. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on atrial fibrillation. Eur Heart J. 2006; 27: 3018-3026.

10 Boriani G, Proietti M, Laroche C, et al. Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. Europace. 2018; 20: 747-757.

11 Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018; 39: 1330-1393.

12 Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007; 146: 857-867.

13 Zhu J, Alexander GC, Nazarian S, et al. Trends and variation in oral anticoagulant choice in patients with atrial fibrillation, 2010-2017. Pharmacotherapy. 2018; 38: 907-920.

14 Balsam P, Ozierański K, Tymińska A, et al. Comparison of clinical characteristics of real-life atrial fibrillation patients treated with vitamin K

antagonists, dabigatran, and rivaroxaban: results from the CRAFT study. Kardiol Pol. 2018; 76: 889-898.

15 Lip GY, Nielsen PB. Should patients with atrial fibrillation and 1 stroke risk factor (CHA2DS2-VASc score 1 in men, 2 in women) be anticoagulated? Yes: even 1 stroke risk factor confers a real risk of stroke. Circulation. 2016; 133: 1498-1503.

16 Lip GY, Skjøth F, Rasmussen LH, et al. Net clinical benefit for oral anticoagulation, aspirin, or no therapy in nonvalvular atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex). J Am Coll Cardiol. 2015; 66: 488-490.

17 Lip GY, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest. 2018; 154: 1121-1201.

18 January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019; 74: 104-132.

19 Macle L, Cairns J, Leblanc K, et al. 2016 Focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Can J Cardiol. 2016; 32: 1170-1185.

20 Farkowski MM, Karliński MA, Sterliński M, et al. Educational needs among physicians treating patients with atrial fibrillation: lessons for Poland from the European Society of Cardiology international educational needs assessment study. Pol Arch Intern Med. 2019; 129: 586-591.

21 Sabouret P, Bricard M, Hermann MA. Discrepancy between guidelines for stroke prevention in atrial fibrillation and practice patterns in primary care. The nationwide French AFIGP survey. Arch Cardiovasc Dis. 2015; 108: 544-553.

22 Riva N, Lip GY. A new era for anticoagulation in atrial fibrillation. Which anticoagulant should we choose for long-term prevention of thromboembolic complications in patients with atrial fibrillation? Pol Arch Med Wewn. 2012; 122: 45-53.

23 Potpara TS, Mujovic N, Lip GY. Meeting the unmet needs to improve management and outcomes of patients with atrial fibrillation: fitting global solutions to local settings. Pol Arch Intern Med. 2019; 129: 574-576.

24 Litwinowicz R, Bartuś M, Ceranowicz P, et al. Stroke risk reduction after left atrial appendage occlusion in elderly patients with atrial fibrillation: long-term results. Pol Arch Intern Med. 2018; 128: 327-329.

25 Gawałko M, Kapłon-Cieślicka A, Budnik M, et al. Comparison of different oral anticoagulant regimens in patients with atrial fibrillation undergoing ablation or cardioversion. Pol Arch Intern Med. 2017; 127: 823-831.

26 Boriani G, Proietti M, Laroche C, et al. Association between antithrombotic treatment and outcomes at 1-year follow-up in patients with atrial fibrillation: the EORP-AF General Long-Term Registry. Europace. 2019; 21: 1013-1022.

27 Lenarczyk R, Mitręga K, Mazurek M, et al. Polish and European management strategies in patients with atrial fibrillation. Pol Arch Med Wewn. 2016; 126: 138-148.

28 Sabir IN, Matthews GD, Huang CL. Antithrombotic therapy in atrial fibrillation: aspirin is rarely the right choice. Postgrad Med J. 2013; 89: 346-351.

29 Vazquez F, Gonzalez J, Gandara E. Aspirin compared to low intensity anticoagulation in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. PLoS One. 2015; 10: e0142222.

30 Gorin L, Fauchier L, Nonin E, et al. Antithrombotic treatment and the risk of death and stroke in patients with atrial fibrillation and a CHADS2 score = 1. Thromb Haemost. 2010; 103: 833-840.

31 Cheng CM, Lin CH, Chou P, et al. Antithrombotic treatment may reduce mortality among new-onset atrial fibrillation patients with gray-zone risk of stroke. Int Heart J. 2019; 60: 303-309.

32 Xu Y, Schulman S, Dowlatshahi D, et al. Direct oral anticoagulant- or warfarin-related major bleeding: characteristics, reversal strategies, and outcomes from a multicenter observational study. Chest. 2017; 152: 81-91.

33 Steinberg BA, Shrader P, Pieper K, et al. Frequency and outcomes of reduced dose non-vitamin k antagonist anticoagulants: results from ORBIT-AF II (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II). J Am Heart Assoc. 2018; 7: e007633.

34 Pattullo CS, Barras M, Tai B, et al. New oral anticoagulants: appropriateness of prescribing in real-world setting. Intern Med J. 2016; 46: 812-818.

35 Jelonek O, Gorczyca I, Bączek M, et al. Evaluation of indications for reduced-dose non-vitamin K antagonist oral anticoagulants in hospitalised patients with atrial fibrillation. Kardiol Pol. 2018; 76: 1073-1080.

36 Staerk L, Gerds TA, Lip GY, et al. Standard and reduced doses of dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation: a nationwide cohort study. J Intern Med. 2018; 283: 45-55.

37 Mazurek M, Huisman MV, Rothman KJ, et al. Regional differences in antithrombotic treatment for atrial fibrillation: insights from the GLORIA-AF phase II registry. Thromb Haemost. 2017; 117: 2376-2388.

38 Bista D, Chalmers L, Peterson GM, Bereznicki LR. Patient characteristics and antithrombotic prescribing patterns in patients with atrial fibrillation in tasmania. Clin Appl Thromb Hemost. 2017; 23: 438-444.