Original paper

Secondary prevention of thromboembolic complications in patients with nonvalvular atrial fibrillation – clinical practice in relation to guidelines

Wtórna profilaktyka powikłań zakrzepowo-zatorowych u pacjentów z niezastawkowym migotaniem przedsionków – praktyka kliniczna w odniesieniu do wytycznych

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Słowa kluczowe: udar mózgu, migotanie przedsionków, powikłania zakrzepowo-zatorowe, doustne leki przeciwzakrzepowe.

Abstract

Introduction: Atrial fibrillation (AF) patients after past thromboembolic complications are at high risk of such subsequent complications and should undergo anticoagulant therapy.
Aim of the research: To assess recommended anticoagulant prophylaxis in AF patients after past thromboembolic complications, and an attempt to identify predictors of oral anticoagulant (OAC) use and non-use among these patients.
Material and methods: The presented research is a retrospective, unicentric study comprising 1266 AF patients with thromboembolic complications and CHA_2DS_2-VASc score ≥ 2, subsequently hospitalized from January 2004 to December 2019 in the referential cardiology centre.
Results: In the group of 1266 patients, 1072 of them (84.7%) received OACs, 134 (10.6%) antiplatelet drugs, 36 (2.8%) low molecular weight heparin, and 24 (1.9%) remained without anticoagulant prophylaxis. Between 2004 and 2019 OAC application increased from 70.5% to 95.3% and antiplatelet pharmaceutical use decreased from 23.7% to 1.9%. Independent predictors of OAC use were female sex (OR = 1.57; 95% CI: 1.14–2.17; p = 0.006) and peripheral artery disease (PAD) (OR = 2.59; 95% CI: 1.48–4.51; $p = 0.001$). Factors determining no OAC use were age > 74 years (OR = 0.64; 95% CI: 0.46–0.89; $p = 0.007$) and acute coronary syndrome (ACS) hospitalization or planned coronarography or percutaneous coronary intervention (PCI) (OR = 0.41; 95% CI: 0.28–0.61; $p < 0.001$). Between 2004 and 2019 an increase in the number of high-risk thromboembolic patients treated with OACs was observed.
Conclusions: Independent predictors of OAC use were sex and PAD. The factors that reduced the chance of OAC use were age > 74 years, ACS hospitalization, or planned coronarography or PCI.

Streszczenie

Wprowadzenie: Pacjenci z migotaniem przedsionków (AF) po przebytym powikłaniu zakrzepowo-zatorowym są chorymi wysokiego ryzyka kolejnych takich powikłań i powinni otrzymywać leczenie przeciwkrzepliwe.
Cel pracy: Ocena zalecanej profilaktyki przeciwkrzepliwej u chorych z AF po przebytym powikłaniu zakrzepowo-zatorowym oraz próba identyfikacji predyktorów stosowania oraz niestosowania doustnych leków przeciwkrzepliwych (OAC) wśród tych chorych.
Materiał i metody: Prezentowane badanie jest retrospektywnym, jednoośrodkowym badaniem obejmującym kolejno 1266 hospitalizowanych pacjentów z AF oraz powikłaniami zakrzepowo-zatorowymi oraz wynikiem w skali CHA_2DS_2-VASc ≥ 2 pkt, w referencyjnym ośrodku kardiologicznym od stycznia 2004 do grudnia 2019 roku.
Wyniki: W grupie 1266 osób OAC były stosowane u 1072 (84,7%) pacjentów, leki przeciwpłytkowe u 134 (10,6%) pacjentów, heparyna drobnocząsteczkowa u 36 (2,8%) pacjentów; bez profilaktyki przeciwkrzepliwej pozostawało 24 (1,9%) pacjentów. W latach 2004–2019 zastosowanie OAC wzrosło z 70,5% do 95,3%, leków przeciwpłytkowych zmniejszyło się z 23,7% do 1,9%. Wykazano, że niezależnymi predyktorami zastosowania OAC były płeć żeńska (OR = 1,57; 95% CI: 1,14–2,17;

$p = 0{,}006$) oraz choroba tętnic obwodowych (PAD) (OR = 2,59; 95% CI: 1,48–4,51; $p = 0{,}001$). Następujące czynniki predysponowały do niezalecania OAC: wiek > 74 lat (OR = 0,64; 95% CI: 0,46–0,89; $p = 0{,}007$) oraz hospitalizacja z powodu ostrego zespołu wieńcowego (ACS), planowej koronarografii lub też plastyki tętnic wieńcowych (PCI) (OR = 0,41; 95% CI: 0,28–0,61; $p < 0{,}001$). Pomiędzy 2004 a 2019 rokiem zaobserwowano zwiększenie liczby chorych wysokiego ryzyka zakrzepowo-zatorowego leczonych OAC.
Wnioski: Niezależnymi predyktorami zastosowania OAC były płeć, PAD, natomiast czynnikami, które zmniejszały szansę na zastosowanie OAC, okazały się wiek > 74 lat, hospitalizacja z powodu ACS lub planowej koronarografii oraz PCI.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia. Almost 1% of population suffers from it. AF prevalence rises with age from around 0.1% in adults < 55 years old to 8% in people aged 80 years and older [1]. As a result of the rapid increase in AF attacks due to age and constant ageing of societies, the predicted number of people with AF in the European Union is expected to reach 17.9 million by 2060 [2]. Important clinical implications of AF include negative impact on quality of life, increased incidence of heart failure, stroke, and systemic thromboembolism and increased risk of death in this patient population. Patients with atrial fibrillation and stroke are at significantly increased additional risk of death, while those with atrial fibrillation and non-fatal stroke are at higher risk of severe disability than patients with stroke without atrial fibrillation [3]. Despite progression in AF therapy, patients with this condition still have an increased risk of cardiovascular events [4]. The most serious AF complications are the thromboembolic ones [5, 6]. AF is the cause of about 3-26% of ischaemic strokes, and the proportion increases with the patients' age [7]. Strokes connected with AF have a worse prognosis than those of different aetiology [8]. Patients with ischaemic stroke or transient ischaemic attack (TIA) and AF are at higher risk of recurrent stroke and of other vascular diseases; this is connected with the prevalence of multiple concomitant diseases, such as diabetes mellitus or heart failure [9], and as a result, with the higher number of points in the CHA_2DS_2-VASc score. Additionally, independent factors of thromboembolic events include stroke, TIA, or peripheral thromboembolic events [10]. Patients after thromboembolic complications are at risk of subsequent complications of this type, and regardless of other comorbidities, age, and sex they should receive anticoagulant treatment [11, 12]. According to the current guidelines, non-vitamin K antagonist oral anticoagulants (NOACs) are the advised therapy after stroke and other thromboembolic events [11].

Aim of the research

The aim of our study was to evaluate the recommended anticoagulant prophylaxis in patients with AF after thromboembolic complications and to attempt to identify predictors of OAC use or non-use in this group of patients.

Material and methods

Study group

The presented registry is a retrospective, unicentric study comprising 1266 patients with AF and CHA_2DS_2-VASc score ≥ 2 and thromboembolic complications. Patients with haemorrhagic stroke were not analysed. They were hospitalized in the referential cardiology centre. The study comprises all AF patients consecutively hospitalized during the research time due to urgent or planned reasons. The inclusion criteria were at least 18 years of age and AF documented by electrocardiography or in patients' history. Patients with incomplete anticoagulant treatment data, with a mechanical heart valve, without thromboembolic complications, and those who died during hospitalization were excluded from the study (Figure 1).

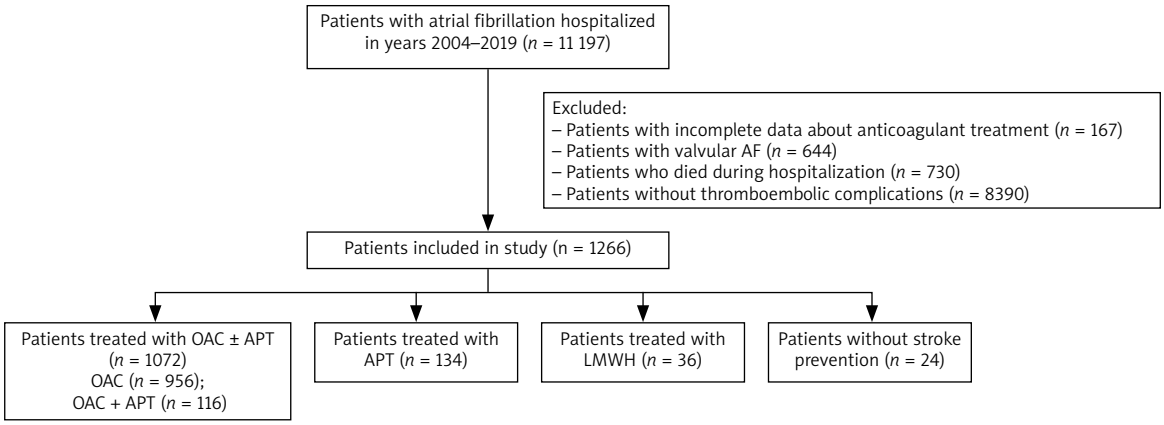

Figure 1. The flow chart of the study

AF – atrial fibrillation, APT – antiplatelet drug/s, OAC – oral anticoagulant therapy, LMWH – low molecular weight heparin.

Patients were assessed in 3 time periods (2004–2010, 2011–2016, 2017–2019), which were connected with the publication of consecutive guidelines on atrial fibrillation.

Assessed parameters

Patients were characterized in reference to sex, age, concomitant diseases, anaemia defined as the decrease of haemoglobin < 12 g/dl, thrombocythemia defined as the fall of platelets (PLT) < 150,000/µl, condition after past heart attack, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), type of atrial fibrillation, kidney parameters, type of treatment and proceeding in particular years, and their hospitalization.

The risk of bleeding was defined on the basis of HAS-BLED score, which includes arterial hypertension, impaired renal/liver function, stroke, bleeding, labile international normalized ratio (INR), older age (> 65 years), drugs, and alcohol.

The glomerular filtration rate (GFR), which is used to assess renal function, was calculated using the CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration).

Until 2010, the $CHADS_2$ score was used, and then the use of the CHA_2DS_2-VASc score was recommended. In the presented study, the CHA_2DS_2-VASc score was used to account for additional risk factors recommended by the ESC guidelines (vascular disease, age 65–74 years, female gender). The CHA_2DS_2-VASc score [11] included congestive heart failure, arterial hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischaemic attack or another thromboembolic event, vascular disease (past myocardial infarction, peripheral arteriosclerosis, atherosclerotic plaque in the aorta), age between 65 and 74 years, and sex.

Assessment of thromboembolic complications

Ischaemic stroke, TIA, and peripheral complications were considered to be thromboembolic complications. Peripheral complications included emboli located in upper and lower limbs and abdominal arteries.

Prophylaxis of thromboembolic complications

Anticoagulant therapy was assessed at discharge from hospital. The following regimens were defined: OAC ± APT therapy, APT alone, low-molecular-weight heparin (LMWH), and lack of anticoagulant treatment.

The OAC group comprised vitamin K antagonists (VKAs), apixaban, dabigatran, and rivaroxaban alone or with APT. Edoxaban, despite being registered in Europe as a pharmaceutical against thromboembolic complications in AF patients, is not obtainable in Poland. The APT group contained ticagrelor, acetylsalicylic acid (ASA), and/or clopidogrel and prasugrel.

The Ethics Committee of the Świętokrzyska Medical Chamber in Kielce approved the study (Approval No. 12/2011; 2/2023). The committee waived the requirement of obtaining informed consent from the patients.

Statistical analysis

Statistical analyses to find the answers to the researched questions and to test the formulated hypothesis were conducted using IBM SPSS Statistics, version 25. The tool enabled the analysis of basic descriptive statistics: χ^2 independence tests, Student's *t*-test for independent trials, Mann-Whitney test, and logistic regression analyses. The classic $\alpha = 0.05$ threshold was assumed to be the level of statistical significance. Distributions of quantitative variables were checked in the first stage of the analyses. To do this, basic descriptive statistics along with the Kolmogorov-Smirnov test, which assesses normality of distribution, were calculated. To obtain information about which factors influence the patients' use of OACs, a series of univariate logistic regression analyses was conducted. Additionally, to see the big picture, a multivariable logistic regression for OAC use was performed. Significant variables from univariate models were included as predictors. The model is statistically significant and explains 7% of the OAC use variance according to R^2 Nagelkerke.

Results

Characteristics of the study group

The presented group of patients with AF comprised 1266 people, almost half of whom were women – 49.4%. The mean age of patients was 74 ±10 years; most of them were over 74 years old – 52.8%.

Patients after thromboembolic complications were patients who had had a stroke –77.8%, TIA – 13.7%, or peripheral complications – 11.6%. 3.2% of the patients suffered from multiple thromboembolic complications (stroke and TIA, stroke and peripheral complications, TIA and peripheral complications).

The most common concomitant diseases were arterial hypertension – 80.9% of patients, and heart failure – 65%. Impaired renal function was most frequently observed among non-cardiac comorbidities (68.3%). 50.6% of patients had permanent AF.

The mean CHA_2DS_2-VASc score was 6.1±1.5 points. 60% of patients were at high risk of bleeding. Table 1 presents the clinical characteristics in the study cohort.

Prophylaxis of thromboembolic complications

Of the group of 1266 patients, OACs were used in 1072 (84.7%), APT in 134 (10.6%), LMWH in 36 (2.8%), and 24 patients (1.9%) did not receive any treatment.

Table 1. Baseline characteristics of the study group

Parameter	All (*n* = 1266)	2004–2010 (*n* = 410)	2011–2016 (*n* = 491)	2017–2019 (*n* = 365)
Sex (female), *n* (%)	625 (49.4)	204 (49.8)	254 (51.7)	167 (45.8)
Age:				
Mean (SD)	74 (10)	72.4 (9.7)	75.2 (9.3)	74.4 (10.8)
< 65, *n* (%)	223 (17.6)	86 (20.9)	69 (14.1)	68 (18.6)
65–74, *n* (%)	374 (29.6)	129 (31.5)	141 (28.7)	104 (28.5)
> 74, *n* (%)	669 (52.8)	195 (47.6)	281 (57.2)	193 (52.9)
Heart failure	823 (65)	252 (61.5)	335 (68.2)	236 (64.7)
Arterial hypertension	1024 (80.9)	315 (76.8)	413 (84.1)	296 (81.1)
Vascular disease	598 (47.2)	111 (27.1)	267 (54.4)	220 (60.3)
Diabetes mellitus	403 (31.2)	108 (26.4)	163 (33.2)	132 (36.2)
Past heart attack	326 (25.8)	92 (22.4)	131 (26.7)	103 (28.2)
PCI	169 (13.3)	34 (8.3)	66 (13.4)	69 (18.9)
CABG	86 (6.8)	10 (2.4)	39 (7.9)	37 (10.1)
PAD	201 (15.9)	4 (1)	62 (12.6)	135 (37)
Bleeding	44 (3.5)	12 (2.9)	17 (3.5)	15 (4.1)
Peptic ulcer disease	42 (3,3)	18 (4.4)	13 (2.6)	11 (3)
Cancer	54 (4.3)	18 (4.4)	15 (3.1)	21 (5.8)
Thrombocytopaenia	194 (15.3)	76 (18.5)	65 (13.2)	53 (14.5)
Anaemia	267 (21.1)	60 (14.6)	106 (21.6)	101 (27.7)
Paroxysmal	513 (40.5)	168 (40.1)	191 (38.9)	154 (42.2)
Persistent	112 (8.9)	25 (6.1)	46 (9.4)	41 (11.2)
Permanent	641 (50.6)	217 (52.9)	254 (51.7)	170 (46.6)
$CHADS_2$:				
Mean (SD)	4.3 (1)	4.1 (1)	4.4 (1)	4.3 (1)
2–4, *n* (%)	712 (56.2)	261 (63.7)	258 (52.5)	193 (52.9)
> 4, *n* (%)	554 (43.8)	149 (36.3)	233 (47.5)	172 (47.1)
CHA_2DS_2-VASc:				
Mean (SD)	6.1 (1.5)	5.7 (1.5)	6.4 (1.4)	6.2 (1.5)
2, *n* (%)	7 (0.6)	5 (1.2)	0 (0)	2 (0.6)
3, *n* (%)	41 (3.2)	23 (5.6)	8 (1.6)	10 (2.7)
4, *n* (%)	150 (11.9)	68 (16.6)	41 (8.4)	41 (11.2)
5, *n* (%)	238 (18.8)	88 (21.5)	91 (18.5)	59 (16.2)
6, *n* (%)	313 (24.7)	94 (22.9)	120 (24.4)	99 (27.1)
7, *n* (%)	287 (22.7)	90 (21.9)	125 (25.5)	72 (19.7)
8, *n* (%)	165 (13)	34 (8.3)	73 (14.9)	58 (15.9)
9, *n* (%)	65 (5.1)	8 (2)	33 (6.7)	24 (6.6)
2–4, *n* (%)	198 (15.6)	96 (23.4)	49 (10)	53 (14.5)
5–9, *n* (%)	1068 (84.4)	314 (76.6)	442 (90)	312 (85.5)

Table 1. Cont.

Parameter	All (*n* = 1266)	2004–2010 (*n* = 410)	2011–2016 (*n* = 491)	2017–2019 (*n* = 365)
HAS-BLED:				
Mean (SD)	2.6 (0.8)	2.4 (0.7)	2.8 (0.9)	2.7 (0.8)
≥ 3, *n* (%)	759 (60)	213 (52)	309	237 (64.9)
Laboratory test results:				
eGFR, mean (SD)	52.6 (18.3)	53.5 (20.2)	52.2 (17.2)	52.2 (17.5)
eGFR < 60 ml/min/1.73 m^2, *n* (%)	861 (68.3%) *n* = 1260	276 (67.3)	343 (70.1) *n* = 489	242 (67) *n* = 361
Reason of hospitalization:				
Electrical cardioversion	80 (6.3)	10 (2.4)	34 (6.9)	36 (9.9)
Planned coronarography/PCI or ACS	166 (13.1)	78 (19)	58 (11.8)	30 (8.2)
Planned CIED implantation/ reimplantation	347 (27.4)	153 (37.3)	125 (25.5)	69 (18.9)
Heart failure	297 (23.5)	80 (19.5)	103 (21)	114 (31.2)
Ablation	22 (1.7)	2 (0.5)	6 (1.2)	14 (3.8)
Other	245 (19.4)	49 (12)	126 (25.7)	70 (19.2)
AF without any procedures	109 (8.6)	38 (9.3)	39 (7.9)	32 (8.8)

Data are presented as number (percentage) or mean (standard deviation) (SD). ACS – acute coronary syndrome, AF – atrial fibrillation, CABG – coronary artery bypass grafting, CIED – cardiac implantable electronic device, eGFR – estimated glomerular filtration rate, PAD – peripheral artery disease, PCI – percutaneous coronary interventions.

Table 2. Factors accompanying not prescribing OACs

Factors	All (*n* = 194)	2004–2010 (*n* = 121)	2011–2016 (*n* = 56)	2017–2019 (*n* = 17)
Anaemia, *n* (%)	49 (25.3)	24 (19.8)	19 (33.9)	6 (35.3)
Thrombocytopaenia, *n* (%)	35 (18.4)	27 (22.3)	6 (10.7)	2 (11.8)
Cancer, *n* (%)	12 (6.2)	6 (5)	1 (1.8)	5 (29.4)
Bleeding, *n* (%)	9 (4.6)	5 (4.1)	3 (5.4)	1 (5.9)
Labile INR, *n* (%)	4 (2.1)	1 (0.8)	2 (3.6)	1 (5.9)
Bilirubin, > 1 mg/dl, *n* (%)	*n* = 176 58 (33)	37 (30.6)	*n* = 43 18 (41.9)	*n* = 12 3 (25)
ALT > 40 IU/l, *n* (%)	*n* = 191 43 (22.5)	*n* = 120 23 (19.2)	*n* = 55 16 (29)	*n* = 16 4 (25)
eGFR < 60 ml/min/1.73 m^2, *n* (%)	*n* = 193 136 (70.5)	88 (72.7)	37 (66.1)	*n* = 16 11(68.8)

ALT – alanine aminotransferase, eGFR – estimated glomerular filtration rate, INR – international normalised ratio.

Table 2 shows the most common factors among patients who did not receive OACs.

Between 2004 and 2019, the use of OACs rose from 70.5% to 95.3%, and use of APTs decreased from 23.7% to 1.9%. 3.6% of patients received no treatment between 2004 and 2010, and 0.3% from 2017 to 2019 (Table 3).

Among the pharmaceuticals administered to patients with thromboembolic complications, the highest increase was observed in NOAC application. They were not used from 2004 to 2010, while between 2017 and 2019 they constituted 76.9% (Figure 2).

Figure 3 presents the proportion of patients treated with OACs in particular years of hospitalization. The use of VKAs from 2004 to 2010 was 100%, it decreased by 80.7% by 2019. The drug prescribed to the highest number of patients was dabigatran. Between 2011 and 2016, it accounted for 21.4% of prescribed OACs, and in 2017–2019 it accounted for 35%.

Table 3. Anticoagulation in particular years of hospitalization

Parameter	All (*n* = 1266)	2004–2010 (*n* = 410)	2011–2016 (*n* = 491)	2017–2019 (*n* = 365)
APT	134 (10.6)	97 (23.7)	30 (6.1)	7 (1.9)
OAC ± APT	1072 (84.7)	289 (70.5)	435 (88.6)	348 (95.3)
LMWH	36 (2.8)	9 (2.2)	18 (3.7)	9 (2.5)
None	24 (1.9)	15 (3.6)	8 (1.6)	1 (0.3)

APT – antiplatelet drug/s, OAC – oral anticoagulant therapy, LMWH – low-molecular-weight heparin.

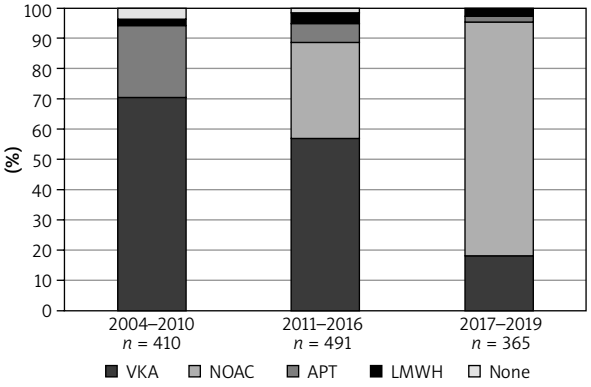

Figure 2. Stroke prophylaxis in patients with atrial fibrillation in particular years of hospitalization

APT – antiplatelet drug/s, NOAC – non-vitamin K antagonist oral anticoagulants, LMWH – low molecular weight heparin, VKA – vitamin K antagonist.

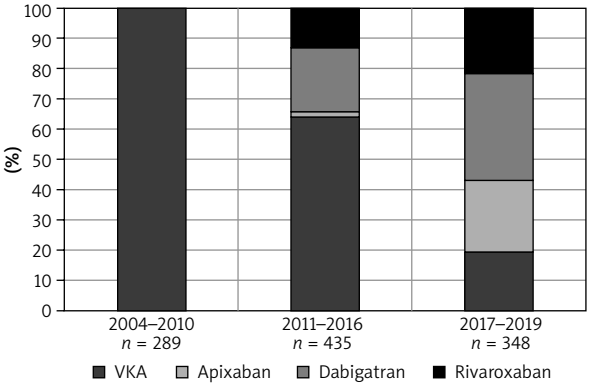

Figure 3. Proportion of patients treated with oral anticoagulants in particular years of hospitalization

VKA – vitamin K antagonist.

Comparison of patients using and not using OACs in terms of clinical characteristics

In the study cohort of 1266 patients, OACs were used by more females than males (50.6% vs. 42.8%; $p = 0.046$). What is more, patients administered OACs were significantly younger than those who did not receive them (73.8 ±0.1 vs. 75.4 ±9.4 years old; $p = 0.047$). Additionally, patients using OACs suffer from peripheral artery disease (PAD) more frequently than those not using them (17.4% vs 7.7%; $p = 0.001$). AF without any procedures was a more frequent reason for hospitalization of patients administered OACs (9.3% vs. 4.6%; $p = 0.032$) than planned coronarography, PCI, or acute coronary syndrome (ACS) (11.2% vs. 23.7%; $p < 0.001$). Table 4 presents a comparison of patients treated and not treated with OACs.

Predictors of OAC choice in the group of patients

In the univariate logistic regression analysis, numerous predictors of OAC prescription were found (Table 5).

In the multivariate statistical analysis (Table 6) it was shown that independent predictors of OAC use were: female sex (OR = 1.57; 95% CI: 1.14–2.17; $p = 0.006$) and PAD (OR = 2.59; 95% CI: 1.48–4.51; $p = 0.001$). Age > 74 years (OR = 0.64; 95% CI: 0.46–0.89; $p = 0.007$) and hospitalization due to ACS or planned coronarography and PCI (OR = 0.41; 95% CI: 0.28–0.61; $p < 0.001$) lessened the chance of receiving OACs.

Discussion

The presented study shows the current picture of anticoagulant treatment in patients with AF after thromboembolic complications.

In our study we identified predictors that predisposed and did not predispose to the administration of OACs.

OACs are strongly recommended in patients after thromboembolic complications. In the study group, as many as 84.7% of patients were prescribed OACs. Similarly, in other registries, such as ORBIT-AF II [13] and PREFER in AF [14], the use of OACs was, respectively, 87% and 85.6%. In the study of Gorczyca *et al.* [15] they were used in 92.8% of patients after a thromboembolic event, which proves their efficacy and the right procedures in this group of patients.

In our registry it was indicated that the use of OACs in patients after thromboembolic complica-

Table 4. Clinical characteristics of patients with atrial fibrillation treated with oral anticoagulants and non-oral anticoagulants

Parameter	OAC (*n* = 1072)	Non-OAC (*n* = 194)	*P*-value
Female, *n* (%)	542 (50.6)	83 (42.8)	0.046
Age:			0.047
Mean (SD)	73.8 (10.1)	75.4 (9.4)	
Median (IQR)	75 (14.0)	78 (13.0)	
< 65, *n* (%)	191 (17.8)	32 (16.5)	0.656
65–74, *n* (%)	328 (30.6)	46 (23.7)	0.053
> 74, *n* (%)	553 (51.6)	116 (59.8)	0.035
Clinical characteristics, *n* (%):			
Heart failure	688 (64.2)	135 (69.6)	0.146
Hypertension	873 (81.4)	151 (77.8)	0.240
Vascular disease	513 (47.9)	85 (43.8)	0.300
Diabetes mellitus	338 (31.5)	65 (33.5)	0.587
Previous myocardial infarction	272 (25.4)	54 (27.8)	0.471
PCI	149 (13.9)	20 (10.3)	0.176
CABG	79 (7.4)	7 (3.6)	0.055
PAD	186 (17.4)	15 (7.7)	0.001
Bleeding	35 (3.3)	9 (4.6)	0.336
Ulcer disease	33 (3.1)	9 (4.6)	0.264
Cancer	42 (3.9)	12 (6.2)	0.150
Thrombocytopaenia	159 (14.8)	35 (18)	0.254
Anaemia	218 (20.3)	49 (25.3)	0.122
Type of atrial fibrillation, *n* (%):			
Paroxysmal	423 (39.5)	90 (46.4)	0.070
Persistent	100 (9.3)	12 (6.2)	0.156
Permanent	549 (51.2)	92 (47.4)	0.331
Thromboembolic risk:			
$CHADS_2$:			0.120
Mean (SD)	4.3 (1.0)	4.4 (1.1)	
Median (IQR)	4.0 (1.0)	5.0 (1.0)	
CHA_2DS_2-VASc:			0.911
Mean (SD)	6.1 (1.5)	6.1 (1.5)	
Median (IQR)	6.0 (2.0)	6.0 (2.0)	
Bleeding risk:			
HAS-BLED:			0.753
Mean (SD)	2.6 (0.8)	2.6 (0.8)	
Median (IQR)	3.0 (1.0)	3.0 (1.0)	
≥ 3, *n* (%)	642 (59.9)	117 (60.3)	0.912

Table 4. Cont.

Parameter	OAC (n = 1072)	Non-OAC (n = 194)	P-value
Laboratory tests:			
eGFR:			0.223
Mean (SD)	52.8 (17.9)	51.7 (20.7)	
Median (IQR)	51.8 (21.7)	48.6 (25.8)	
eGFR < 60 ml/min/1.73 m^2, n (%)	723 (67.4)	136 (70.1)	0.466
Reason for hospitalization:			
Electrical cardioversion	72 (6.7)	8 (4.1)	0.172
Planned coronarography/PCI or ACS	120 (11.2)	46 (23.7)	< 0.001
Planned CIED implantation/reimplantation	290 (27.1)	57 (29.4)	0.503
Heart failure	254 (23.7)	43 (22.2)	0.644
Other	214 (19.9)	31 (16)	0.196
AF without any procedures	100 (9.3)	9 (4.6)	0.032

Data are presented as number (percentage) or mean (standard deviation) (SD) or median (interquartile range) (IQR). ACS – acute coronary syndrome, AF – atrial fibrillation, CABG – coronary artery bypass grafting, CIED – cardiac implantable electronic device, eGFR – estimated glomerular filtration rate, PAD – peripheral artery disease, PCI – percutaneous coronary intervention.

tions rose gradually from 70.5% between 2004 and 2010 to 95.3% between 2017 and 2019.

In the GARFIELD-AF study conducted from 2010 to 2016 the use of OACs increased to 43%, and in ORBIT-AF II to 71% between 2013 and 2016 [13]. In our registry, the use of OACs in 2011–2016 accounted for 88.6%, which demonstrates the positive trend in prescribing these drugs and the consistent application of the guidelines. It is also necessary to mention the decrease in the proportion of patients receiving APT. The declining proportion of patients who have received APT is mainly due to the decline in the position of APT and its harmfulness in numerous conducted studies and the changing guidelines for AF.

It should be noted that our study shows that in the years 2004–2010, 3.6% of patients remained without treatment, while between 2017 and 2019, it was only 0.3%. This is probably due to greater clinical experience and the update of the guidelines. Patients with AF after thromboembolic complications, who have not received anticoagulation treatment, are patients with anaemia, thrombocytopaenia, history of bleeding, neoplasms, and abnormal laboratory test results (elevated bilirubin and creatinine values), which is associated with a high bleeding risk. Anaemia was noted in as many as 25.3% of patients who did not receive anticoagulant treatment, thrombocytopaenia in 18.4% of patients, and a large percentage of patients suffered from impaired renal function. Similar factors that influenced the use of caution during anticoagulant therapy were observed in different years. Similarly, in the study by Steinberg *et al.* [16], where the lack of OAC treatment was mainly associated with contraindications related to a high risk of bleeding, mainly abnormal blood morphotic parameters – thrombocytopaenia, anaemia, haemoglobinopathies, neoplasms of the haematopoietic and lymphatic system, or gastrointestinal bleeding in the history. A Japanese study [17] showed that complications such as stroke or systemic embolism and bleeding complications occurred in a group of cancer patients with AF who received anticoagulant treatment. After the introduction of NOACs, which have a high safety profile and do not necessitate monitoring of the INR, they were more likely to be prescribed to the elderly and to patients at increased risk of bleeding. A large retrospective study of a cohort of nonvalvular atrial fibrillation patients revealed that physicians make their treatment decisions based on the patient's individual risk factors, not on the values of the risk scores [18]. Therefore, anticoagulant therapy should be approached with caution in this group, taking into account the benefits and possible side effects.

It must be stated that in the presented registry, the highest increase among all OACs was observed in NOAC use. In 2017–2019 it was as high as 80.7%. This is due to the publication of the NOAC administering guidelines and important registries such as RE-LY [19], ROCKET-AF [20], AVERROES [21], and ARISTOTLE [22], which laid the foundation for growing popularity of NOAC. Currently, the drugs of first choice in pharmacological anticoagulation in patients with AF are NOACs, i.e. dabigatran (direct thrombin inhibitor) or apixaban, rivaroxaban, and edoxaban (direct factor Xa inhibitors), while VKAs, i.e. warfarin or acenocoumarol, are prescribed as second-line drugs [23].

Table 5. The results of univariate logistic regression analysis for the OAC use with the group's clinical characteristics as predictors

Factors	OR	95% CI	*P*-value
Gender (female)	1.37	1.01–1.86	0.047
Age:			
Per year	0.98	0.97–1.00	0.047
< 65	1.10	0.73–1.65	0.656
65–74	1.42	0.99–2.02	0.054
> 74	0.72	0.53–0.98	0.036
Clinical characteristics:			
Heart failure	0.78	0.56–1.09	0.147
Hypertension	1.25	0.86–1.81	0.241
Vascular disease	1.18	0.87–1.60	0.300
Diabetes mellitus	0.91	0.66–1.27	0.587
Previous myocardial infarction	0.88	0.63–1.24	0.471
PCI	1.40	0.86–2.30	0.178
CABG	2.13	0.97–4.68	0.061
PAD	2.51	1.45–4.34	0.001
Bleeding	0.69	0.33–1.45	0.339
Ulcer disease	0.65	0.31–1.39	0.267
Cancer	0.62	0.32–1.20	0.154
Thrombocytopaenia	0.79	0.53–1.18	0.254
Anaemia	0.76	0.53–1.08	0.123
Type of atrial fibrillation:			
Paroxysmal	0.75	0.55–1.02	0.071
Persistent	1.56	0.84–2.90	0.159
Permanent	1.16	0.86–1.58	0.332
Thromboembolic risk:			
$CHADS_2$	0.88	0.76–1.03	0.120
CHA_2DS_2-VASc	0.99	0.90–1.10	0.911
Bleeding risk:			
HAS-BLED	1.03	0.86–1.24	0.753
HAS-BLED ≥ 3			
Laboratory tests:			
eGFR	1.00	0.96–1.01	0.458
eGFR < 60 ml/min/1.73 m^2	0.88	0.63–1.23	0.466
Reason for hospitalization:			
Electrical cardioversion	1.67	0.79–3.53	0.176
Planned coronarography/PCI or ACS	0.41	0.28–0.59	< 0.001
Planned CIED implantation/reimplantation	0.89	0.64–1.25	0.503
Heart failure	1.09	0.76–1.57	0.644
Other	1.31	0.87-1.98	0.197
AF without any procedures	2.12	1.05–4.26	0.036

ACS – acute coronary syndrome, AF – atrial fibrillation, CABG – coronary artery bypass grafting, CIED – cardiac implantable electronic device, eGFR – estimated glomerular filtration rate, PAD – peripheral artery disease, PCI – percutaneous coronary intervention.

Table 6. The results of multivariate logistic regression analysis for the OAC use with the group's clinical characteristics as predictors

Factors	OR	95% CI	*P*-value
Gender (female)	1.57	1.14–2.17	0.006
Age > 74	0.64	0.46–0.89	0.007
Clinical characteristics:			
PAD	2.59	1.48–4.51	0.001
Reason for hospitalization:			
Planned coronarography/PCI or ACS	0.41	0.28–0.61	< 0.001
AF without any procedures	1.73	0.85–3.52	0.133

$\chi^2(5) = 48.01$; $p < 0.001$; Nagelkerke $R^2 = 0.07$. ACS – acute coronary syndrome, AF – atrial fibrillation, PAD – peripheral artery disease, PCI – percutaneous coronary intervention.

In our registry, the most willingly chosen NOAC was dabigatran. Similarly, in the study by Huisman *et al.* [24] it was observed that after introducing dabigatran into clinical use its application increased significantly, which is probably connected with the fact that it was introduced to the market as the first drug of the group. Our study also noted a dynamic increase in the number of apixaban and rivaroxaban prescriptions; the use of these drugs in 2017–2019 was 23.6% and 22.1%, respectively, among all OACs. In England [25] between 2014 and 2019, the most frequently used NOACs were apixaban and rivaroxaban. In Denmark, apixaban was the most frequently prescribed drug among new patients treated with NOACs in 2015 [26]. This is connected mainly with its later approval, bringing it into regular use, in comparison to dabigatran and rivaroxaban.

Female sex was the factor that predisposed to the choice of OAC. In the presented study, women were more often prescribed OACs than men. It probably refers to a higher CHA_2DS_2-VASc score and hence to thromboembolic risk and deeper concern over one's own health. In the study by Lee *et al.* [27], women also received OACs more frequently than men. Conversely, in the PINNACLE Registry [28], in a group of American patients with AF and recommended OACs, female sex was connected with significantly lower OAC use compared to male sex in the whole spectrum of thromboembolic risk. There are factors that worsen stroke prognosis according to gender [29]. Women may be more prone to refuse OAC treatment, especially warfarin, due to the fear of bleeding. The differences in sex hormones between sexes can influence the variability of haemostasis and blood vessel reactivity [30].

PAD, defined as a group of artery diseases that lead to stenosis or occlusion of large arteries, appeared to predispose OAC choice in the presented group of patients. Recent surveillance studies showed a high prevalence of PAD (12.2–16.8%) in patients with AF [31]. Observation and optimization of medical proceedings in this group of patients is justified due to the high risk of peripheral artery disease, which is accompanied by atrial fibrillation. Peripheral arterial disease (PAD), the third leading cause of atherosclerosis, shares many risk factors with AF. Both PAD and AF are more common in elderly patients and have a higher rate of vascular events, including stroke and myocardial infarction, compared to the general population [32]. Both PAD and AF are independent risk factors for stroke. Screening for asymptomatic PAD and making decisions regarding thromboprophylaxis are of key importance in patients with AF. Lopes *et al.* compared NOAC and warfarin treatment in patients with nonvalvular AF and diagnosed coronary disease/peripheral artery disease. All NOACs, compared to warfarin, were connected with lower indicators of stroke, myocardial infarction, and mortality due to any reason. Differences in prevalence of stroke, systemic embolism, and serious bleeding were also observed [33]. The same result was seen in the studies of Baker *et al.* [34] and Coleman *et al.* [35], in which rivaroxaban treatment and warfarin treatment were compared in terms of prevention against serious adverse cardiovascular and serious adverse limb events. These studies indicate a significant superiority of NOACs. It proves that OACs are safe and effective, which is consistent with our findings.

In the presented study, age > 74 years was a factor that predisposed against use of OACs. Advanced age was also a factor that reduced the chance of using OACs in PREFER in AF [36]. Seniors are at a higher risk of haemorrhagic complications, more frequent drug interactions associated with their use, and a risk of falls. Data from ENGAGE AF [37] in warfarin patients showed, respectively, a 2- and 3-fold increase of thromboembolic events and serious bleeding complications comparing patients ≥ 75 years old to those < 65 years old. It was also confirmed in subanalyses of the elderly from other phase III studies comparing NOACs to warfarin in patients with nonvalvular AF [38, 39]. It was probably the reason for less frequent

OAC prescription to elderly patients. The risk of serious bleeding seems to be similar or lower in the case of NOACs compared to VKAs (depending on the dose, renal function, site of bleeding, or type of NOAC). In light of the latest guidelines [11], these are NOACs that should be recommended to elderly patients. Due to cross-sectional observation from 2004, in the early phase of treatment there was probably some anxiety about OACs; therefore, in our registry, elderly patients were administered OACs less frequently.

In the presented study, ACS or planned coronarography and PCI lessen the chance of receiving OACs. It is probably dictated by treatment regimens prior to publication of the new guidelines on NOACs. Concomitant prescription of OACs and an antiplatelet drug, especially triple therapy, increases the absolute risk of serious bleeding. What is more, serious bleeding is connected with even a 5-fold higher risk of death as a result of acute coronary syndrome. Similarly, in the study of Vergheut *et al.*, which compared anticoagulant therapy in groups with acute coronary syndromes and without them, it was observed that most of the patients received OACs ± APT in the group without ACS [40]. Currently, among anticoagulants, these are NOACs that are recommended in the long-term treatment of patients with AF and concomitant ACS and PCI [41]. There is a tendency to abandon triple antiplatelet therapy in favour of double therapy and ultimately OACs alone. It is connected with lower bleeding risk. Each time, the clinical profile and thromboembolic risk must be considered in the process of making a decision about appropriate therapy.

Limitations: The present registry is limited by the retrospective nature of the gathered data. It is a unicentric study; however, it was conducted in a referential centre admitting ambulatory patients and those from other hospitals. In the presented study, there are no data on atrial fibrillation as an exact cause of thromboembolic complications. There are many causes of stroke, especially in the elderly, with additional risk factors such as obesity, hypertension, diabetes, or smoking [3]. Currently, there are no diagnostic tools that can confirm or exclude the relationship between these conditions, especially in patients receiving OACs; therefore, the actual incidence of strokes directly related to AF is unknown [42]. In the present study, hospitalized patients with AF were assessed; among them, only some were diagnosed with AF for the first time, and only these patients started anticoagulant treatment. Due to the long observation time and thereby the reference to AF guidelines published at different times, the indications for OAC use differed slightly. Our study does not contain data on edoxaban because currently it is not available in Poland. Nevertheless, our data show a comprehensive picture of patients with AF and of cardiological proceedings, which will provide useful and reliable insight into real clinical practice.

Conclusions

The presented study comprises trends referring to anticoagulant prophylaxis in patients with AF hospitalized from 2004 to 2019. It was possible to observe an increase in the number of patients after thromboembolic complications treated with OACs. Independent predictors of OAC use were sex and PAD. The factors that reduced the chance of using OACs were age > 74 years, hospitalization due to ACS, and planned coronarography or PCI.

Conflict of interest

Iwona Gorczyca-Głowacka – paid lectures for Bayer, Boehringer Ingelheim, Beata Wożakowska-Kapłon – paid lectures for Bayer, Boehringer Ingelheim, Pfizer. Others authors declare no conflict of interest.

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