Oral anticoagulation therapy in atrial fibrillation patients at high risk of bleeding: Clinical characteristics and treatment strategies based on data from the Polish multicenter register of atrial fibrillation (POL-AF)

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Editorial
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ABSTRACT

Background: Despite its benefits, oral anticoagulant (OAC) therapy in patients with atrial fibrillation (AF) is associated with hemorrhagic complications.

Aims: We aimed to evaluate clinical characteristics of AF patients at high risk of bleeding and the frequency of OAC use as well as identify factors that predict nonuse of OACs in these patients.

Methods: Consecutive AF patients hospitalized for urgent or planned reasons in cardiac centers were prospectively included in the registry in 2019. Patients with HAS-BLED ≥3 (high HAS-BLED group) were assumed to have a high risk of bleeding.

Results: Among 3598 patients enrolled in the study, 29.2% were at high risk of bleeding (44.7% female; median [Q1–Q3] age 72 [65–81], CHA_2DS_2-VASc score 5 [4–6], HAS-BLED 3 [3–4]). In this group, 14.5% of patients did not receive OACs, 68% received NOACs, and 17.5% VKAs. In multivariable analysis, the independent predictors of nonuse of oral OACs were as follows: creatinine level (odds ratio [OR], 1.441; 95% confidence interval [CI], 1.174–1.768; P <0.001), a history of gastrointestinal bleeding (OR, 2.918; 95% CI, 1.395–6.103; P = 0.004), malignant neoplasm (OR, 3.127; 95% CI, 1.332–7.343; P = 0.009), and a history of strokes or transient ischemic attacks (OR, 0.327; 95% CI, 0.166–0.642; P = 0.001).

Conclusions: OACs were used much less frequently in the group with a high HAS-BLED score than in the group with a low score. Independent predictors of nonuse of OACs were creatinine levels, a history of gastrointestinal bleeding, and malignant neoplasms. A history of stroke or transient ischemic attack increased the chances of receiving therapy.

Key words: antithrombotic treatment, atrial fibrillation, high bleeding risk

INTRODUCTION

Oral anticoagulants (OACs) significantly reduce the risk of strokes and systemic thromboembolism in patients with atrial fibrillation (AF) [1, 2]. Despite their high efficacy, OAC therapy is associated with an elevated risk of hemorrhagic complications [3]. Balancing the benefits of OACs against the risks they pose is crucial to ensuring their optimal use in clinical practice. The potential risk of bleeding should be assessed before initiating OAC therapy [4, 5]. Various bleeding risk scores, which include modifiable and non-modifiable risk factors, have been designed for this purpose [4]. According to a systematic review of 38 studies, the HAS-BLED score (hypertension, abnormal renal and/or liver function, history of stroke or thromboembolism, history of bleeding or bleeding diathesis [e.g., severe anemia], age >65 years, use of aspirin or nonsteroidal anti-inflammatory drugs, and alcohol abuse) is the best tool for predicting bleeding risk (moderate strength of evidence) [4, 6]. Following the European Society of Cardiology guidelines, a high bleeding risk score should not lead to discontinuation of OACs, as their clinical benefit in this patient population is even greater than that in patients with a low bleeding risk score [4]. Instead, given that bleeding risk is dynamic, after OAC therapy is initiated, modifiable risk factors should be reassessed and managed at each patient visit. High-risk patients with non-modifiable bleeding risk factors should be identified and monitored more frequently.

In a Taiwanese study, the mean HAS-BLED score of the study population increased from 1.54 to 3.33. After 12-month follow-up, 20.9% of patients had an increase of their HAS-BLED scores to ≥3, mainly due to newly diagnosed hypertension, stroke, bleeding, and concomitant drug therapies. In 4777 patients who consistently had a HAS-BLED score ≥3, 22.2% stopped their use of OACs, while patients who were kept on OACs (77.8%) even after their HAS-BLED scores increased to ≥3 had a lower risk of ischemic stroke, major bleeding, all-cause mortality, and any adverse events [7]. In the mAFA-II trial, in patients who had more frequent bleeding risk assessments according to the HAS-BLED score (together with holistic App-based management), incidental bleeding events decreased significantly (1.2% to 0.2%, respectively; P <0.001), while total OAC usage increased (from 63.4% to 70.2%) during 12-month follow-up. OAC use decreased significantly by 25% in AF patients receiving usual care when comparing baseline to 12 months (P <0.001) [8]. In the PREFER in AF study for each single point decrease on a modifiable bleeding risk scale, a 30% lower risk of major bleeding events was observed (OR, 0.70; 95% CI, 0.64 to 0.76; P <0.01) [9].

Although there are only a few absolute contraindications to OACs, such as serious active bleeding, associated comorbidities (e.g., severe thrombocytopenia: platelet levels between 51 000 and 21 000 microliters of blood, severe anemia under investigation), or a recent high-risk bleeding event (e.g., an intracranial hemorrhage) [4], underuse of anticoagulants remains a significant clinical problem [10, 11]. In this study, we aimed to evaluate the clinical characteristics of AF patients at high risk of bleeding, to assess the frequency of OAC use in these patients, and to identify factors that predict nonuse of OACs.

METHODS

Study design and patients

The Polish Registry of Patients with Atrial Fibrillation (POL-AF) is a multicenter, cross-sectional study, which includes AF patients hospitalized in 10 Polish cardiac centers. The registry aimed to assess clinical characteristics and pharmacotherapy of hospitalized Polish AF patients. The research methodology has been described in detail elsewhere [12, 13]. The present study was registered in ClinicalTrials.gov (NCT04419012). The study was approved by the ethics committee of the Swietokrzyska Medical Chamber, Kielce, Poland (104/2018). The ethics committee waived the requirement for obtaining informed consent from the patients.

Patients hospitalized for urgent and planned reasons were enrolled in the registry between January and December 2019, during two selected weeks each month. The inclusion criteria were age over 18 years and AF diagnosed

WHAT'S NEW?

To our knowledge, this is the largest study describing antithrombotic treatment strategies in patients with atrial fibrillation and high risk of bleeding in clinical practice in Poland. Patients at high risk of bleeding represented a significant proportion of the hospitalized patient population. Our results showed that oral anticoagulants were used less frequently in this group than in the low-risk group. Furthermore, we found that although the vast majority of our registry was based in academic centers, non-vitamin K antagonist oral anticoagulant doses were often inappropriately reduced contrary to existing recommendations.

on admission to the hospital or during hospitalization, except for patients who were scheduled for ablation (in centers with an electrotherapy team). To avoid a biased selection of patients and achieve a cohort close to reality, no explicit exclusion criteria were designed. In the present study, AF patients at high risk of bleeding were evaluated. To avoid the effect of antiplatelet drugs on oral anticoagulant dosing, patients who underwent percutaneous coronary angioplasty were excluded from the study. In our previous study, we presented the label adherence of a reduced non-vitamin K antagonist oral anticoagulant (NOACs) dose during combination therapy [13]. We also described everyday practice in antithrombotic therapy in 10 cardiology departments in a nationwide cohort of hospitalized AF patients undergoing elective or urgent PCI and its accordance or non-accordance with current guidelines [13]. In addition, patients who died during hospitalization were also excluded from the study.

Data were collected on demographics, medical histories, comorbidities, types of AF, laboratory and echocardiography results, and pharmacotherapies recommended at discharge, with particular emphasis on OAC use. Laboratory tests performed on admission to the hospital included evaluation of renal function (estimated glomerular filtration rate [eGFR] and creatinine level) and blood cell counts. eGFR was calculated from the Modification of Diet in Renal Disease or Chronic Kidney Disease Epidemiology Collaboration formula [14]. Chronic kidney disease was defined as diagnosed kidney damage or eGFR <60 ml/min/1.73 m^2 for 3 months or more, irrespective of cause. Previous bleeding was considered to be clinically relevant bleeding (including cerebrovascular bleeding) or a history of spontaneous bleeding. Echocardiography was performed during hospitalization. The following echocardiographic parameters were analyzed: left ventricular ejection fraction, left atrial diameter, intraventricular septum diameter, and left ventricular mass index. CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category [female]) and HAS-BLED scores were calculated for each patient according to the established guidelines [15, 16]. According to these guidelines, a HAS-BLED score ≥3 was assumed to represent a high risk of bleeding [4]. In the case of patients with malignant neoplasm history, the data concerning active disease or treatment completed <12 months were included in the registry. As an appropriate NOACs dosage reduction was considered: dabigatran 220 mg/day for patients aged ≥80 years; creatinine clearance (CrCl) 30–49 ml/min with high bleeding risk (defined as HASBLED ≥3); using antiplatelet drug/drugs with high bleeding risk (defined as HASBLED ≥3) or concomitant use of verapamil;

Rivaroxaban 15 mg/day for patients:

— with CrCl 15–49 ml/min;

— using antiplatelet drug/drugs with high bleeding risk (defined as HASBLED ≥3);

Apixaban 5 mg/day for patients:

— with CrCl 15–30 ml/min;

— with more than two of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dl; concomitant using of antiplatelet drug/drugs. Following the guidelines of the Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society, NOACs are considered to have been inappropriately reduced if the dosage is reduced despite not meeting the above criteria [17].

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Swietokrzyska Medical Chamber in Kielce (104/2018). Patient consent was waived due to the observational character of the registry.

Statistical analysis

All data analyses were performed using Statistica 13.0 (StatSoft Inc., Tulsa, OK, US). Continuous variables were presented as mean (standard deviation [SD]) or median (interquartile range), and categorical variables were presented as numbers and percentages. The distribution patterns of continuous variables were evaluated by the Kolmogorov–Smirnov test. Independent t-tests, Mann–Whitney *U,* and χ^2 tests were applied to compare two groups of continuous and categorical variables. To identify the predictors of OAC nonuse, uni- and multivariable logistic regression analyses were performed. While selecting variables for the univariable and multivariable model, we were guided by statistically significant variables, i.e. differentiating the groups of people being compared (OAC use vs. OAC nonuse). If highly correlated parameters were present, only one representative was chosen for the multivariable analysis, based on its *P*-value in the univariable analysis and its biological validity. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Analysis of high HAS-BLED and low HAS-BLED risk groups

In total, 3999 patients were enrolled in the POL-AF study. Three hundred sixty-four patients who underwent percutaneous coronary angioplasty during hospitalization and 37 patients who died were excluded from the present study. The final analysis comprised 3598 patients. The main reasons for hospitalization were AF and heart failure symptoms (Supplementary material, *Table S1*).

In the study group, 29.2% (n = 1049) of patients had a high risk of bleeding (high HAS-BLED group). The patients at high bleeding risk, compared to those at low bleeding risk, were older and had more comorbidities. Hypertension, heart failure, vascular disease, coronary artery disease, in addition to a history of myocardial infarction, peripheral artery disease, stroke, previous bleeding, including gastrointestinal bleeding, chronic kidney disease, malignant neoplasm, and chronic obstructive pulmonary disease were more frequent in the high HAS-BLED group. In addition,

Table 1. Characteristics of the high and low HAS-BLED risk groups

Clinical characteristics	Whole group	High HAS-BLED group (n = 1049)	Low HAS-BLED group (n = 2549)	*P*-value
Demography				
Age, years; median (Q1– Q3)	72 (65–81)	76 (70–83)	70 (63–79)	<0.001
Age ≥75 years, n (%)	1561 (43.4)	594 (56.6)	967 (37.9)	<0.001
Female, n (%)	1563 (43.4)	469 (44.7)	1094 (42.9)	0.32
BMI, kg/m^2; mean (SD)	29.2 (5.4)	28.9 (5.5)	29.4 (6.5)	0.01
Medical history				
Hypertension, n (%)	2995 (83.2)	1003 (95.8)	1992 (78.2)	<0.001
Diabetes mellitus, n (%)	1181 (32.8)	446 (42.5)	735 (28.8)	<0.001
Heart failure, n (%)	2339 (65)	785 (74.8)	1554 (61)	<0.001
Coronary artery disease, n (%)	1625 (45.2)	663 (63.2)	962 (37.7)	<0.001
Myocardial infarction, n (%)	700 (19.5)	316 (30.1)	384 (15.1)	<0.001
Peripheral artery disease, n (%)	500 (13.9)	248 (23.6)	252 (9.9)	<0.001
Stroke/TIA, n (%)	428 (11.9)	354 (33.7)	74 (2.9)	0.001
Peripheral embolism, n (%)	38 (1)	15 (1.4)	23 (8.8)	0.16
Bleeding, n (%)	112 (3.1)	97 (9.2)	15 (0.6)	<0.001
Gastrointestinal bleeding, n (%)	141 (3.9)	85 (8.1)	56 (2.2)	<0.001
Chronic kidney disease, n (%)	906 (25.2)	403 (38.4)	503 (19.7)	<0.001
Creatinine level, mg/dl; median (Q1–Q3)	1.1 (0.91–1.37)	1.21 (1–1.6)	1.07 (0.9–1.3)	<0.001
eGFR, ml/min/1.73 m^2; median (Q1–Q3)	58 (45–71.5)	54 (37.9–71)	61.6 (50–82.3)	<0.001
Hemoglobin, g/dl; mean (SD)	13.2 (1.9)	12.19 (2.3)	13.6 (1.6)	<0.001
Malignant neoplasm, n (%) (active or treatment completed less than 1 year)	181 (5)	69 (6.6)	112 (4.4)	0.006
Excessive alcohol consumption (defined as 8 or more drinks per week), n (%)	136 (3.8)	81 (8.1)	55 (2.3)	<0.001
Smoking (active or in the past), n (%)	785 (21.8)	281 (28.2)	504 (21)	<0.001
COPD, n (%)	314 (8.7)	109 (10.4)	205 (8)	0.02
CHA_2DS_2-VASc score; median (Q1–Q3)	4 (3–5)	5 (4–6)	4 (3–5)	<0.001
Echocardiographic parameters; median (Q1–Q3)				
EF, %	55 (40–60)	50 (40–60)	55 (42–60)	<0.001
LAd, mm	47 (42–51)	47 (42–52)	47 (42–51)	0.07
IVSd, mm	11 (10–13)	11 (11–13)	11 (10–12)	<0.001
LVMI, g/m^2	122 (102–143.3)	128 (111–155)	118 (101–140)	<0.001
Anticoagulant treatment, n (%)				
OAC	3295 (91.6)	897 (85.5)	2398 (94.1)	<0.001
VKA	599 (16.6)	184 (17.5)	415 (16.3)	0.36
NOAC	2696 (74.9)	713 (68)	1983 (77.8)	<0.001
Rivaroxaban	1099 (30.5)	244 (23.3)	855 (33.6)	<0.001
Rivaroxaban dose (15 mg once a day)	339 (30.8)	135 (55.3)	204 (23.8)	<0.001
Inappropriately reduced dose of rivaroxaban	32 (9.4)	11 (8.1)	21 (10.3)	0.58
Dabigatran	742 (20.6)	183 (17.5)	559 (21.9)	0.002
Dabigatran (110 mg twice daily)	265 (35.7)	102 (55.7)	163 (29.2)	<0.001
Inappropriately reduced dose of dabigatran	66 (24.9)	22 (21.6)	44 (27)	0.48
Apixaban	855 (23.8)	286 (27.3)	569 (22.3)	0.002
Apixaban dose (2.5 mg twice-daily)	280 (32.7)	136 (47.5)	144 (25.3)	<0.001
Inappropriately reduced dose of apixaban	117 (41.2)	49 (36)	68 (47.2)	0.06

Abbreviations: BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category (female); COPD, chronic obstructive pulmonary disease; EF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HAS-BLED, hypertension, abnormal renal and/or liver function, history of stroke or thromboembolism, history of bleeding or bleeding diathesis (e.g., severe anemia), age >65 years, use of aspirin or nonsteroidal anti-inflammatory drugs, and alcohol abuse; IVSd, intraventricular septum diameter; LAd, left atrial diameter; LVMI, left ventricular mass index; NOAC, non-vitamin K antagonists oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist

excessive alcohol consumption and smoking were more common in the high HAS-BLED group compared to the low HAS-BLED group. The patients in the high HAS-BLED group also had higher CHA_2DS_2-VASc scores than those in the low HAS-BLED group. Furthermore, as shown by the laboratory tests, they also had lower hemoglobin levels and worse kidney function (Table 1).

In the high HAS-BLED group, 14.5% of patients did not receive OAC treatment, compared to 5.9% in the low HAS-BLED group (*P* <0.001). There was no difference in the frequency of use of vitamin K antagonists (VKAs) in the two groups, whereas NOACs were more commonly prescribed in the low HAS-BLED group. As shown in Figure 1, apart from rivaroxaban, reduced doses of the NOACs, apixaban

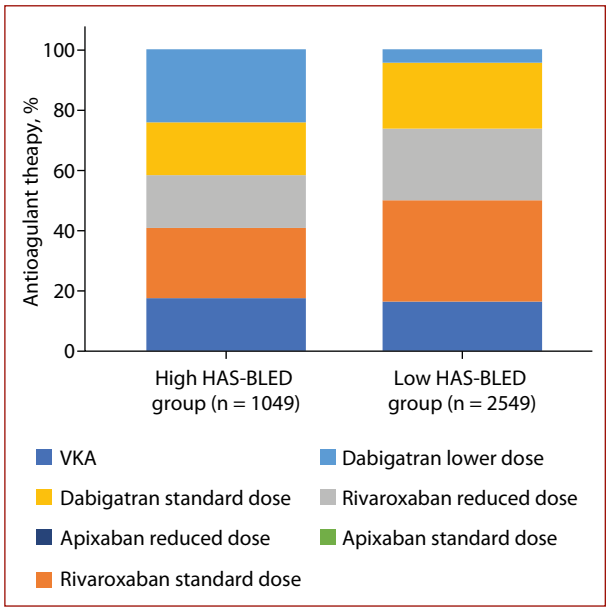

Figure 1. Anticoagulant treatment in the study cohort

and dabigatran, were more frequent in the high HAS-BLED group as compared to those in the low HAS-BLED group (55.7% vs. 29.2%; $P = 0.002$ and 47.5% vs. 25.3%; $P < 0.001$, respectively). The analysis demonstrated that the dose of apixaban was most often inappropriately reduced (Table 1) without a significant difference between the low and the high HAS-BLED group. Inappropriate dose reductions were the least common for rivaroxaban.

Comparison of clinical characteristics in the high HAS-BLED group according to use/non-use of OACs

When we compared the high HAS-BLED group that did not receive OACs with the high HAS-BLED group that received OACs, the former had a lower CHA_2DS_2-VASc score and fewer episodes of ischemic stroke or transient ischemic attack (TIA), in addition to a history of hemorrhagic stroke, bleeding, including gastrointestinal bleeding, chronic kidney disease, and cancer (active or with treatment completed less than 1 year earlier) (Table 2).

Predictors of OAC nonuse

In the multivariable analysis (Supplementary material, *Table S2*), creatinine level (OR, 1.441; 95% CI, 1.174–1.768; $P < 0.001$), a history of gastrointestinal bleeding (OR, 2.918; 95% CI, 1.395–6.103; $P = 0.004$), and malignant neoplasms (OR, 3.127; 95% CI, 1.332–7.343; $P = 0.009$) were independent predictors of OAC nonuse. A history of stroke or TIA increased the chance of recieiving treatment (OR, 0.327; 95% CI, 0.166–0.642; $P = 0.001$).

Table 2. Characteristics of the high HAS-BLED group according to the use (+) or nonuse (–) of OACs

Clinical characteristics	OAC (+) group (n = 897)	OAC (–) group (n = 152)	*P*-value
AF pattern, n (%)			
Paroxysmal	419 (46.7)	66 (43.4)	0.54
Persistent	160 (17.8)	25 (16.4)	
Permanent	318 (35.4)	61 (40.1)	
Demography			
Age, years; median (Q1–Q3)	76 (70–83)	79 (71–85)	0.06
Female, n (%)	405 (45.1)	64 (42.1)	0.49
BMI, kg/m^2; mean (SD)	29.0 (5.5)	28.5 (4.7)	0.85
Medical history			
Hypertension, n (%)	861 (95.9)	142 (93.4)	0.15
Heart failure, n (%)	671 (74.8)	114 (75)	0.96
Vascular disease; n (%)	652 (72.7)	101 (66.4)	0.11
Coronary artery disease, n (%)	572 (63.8)	91 (59.9)	0.36
Myocardial infarction, n (%)	265 (29.5)	51 (33.5)	0.32
Peripheral artery disease, n (%)	212 (23.6)	36 (23.7)	0.99
Stroke/TIA, n (%)	328 (36.3)	26 (17.1)	<0.001
Peripheral embolism, n (%)	14 (1.6)	1 (0.6)	0.39
Any previous bleeding, n (%)	75 (8.4)	22 (14.5)	0.02
Gastrointestinal bleeding, n (%)	60 (6.7)	25 (16.4)	<0.001
Chronic kidney disease, n (%)	324 (36.1)	79 (51.9)	<0.001
Hemoglobin, g/dl; mean (SD)	12.3 (2.3)	11.5 (2.5)	<0.001
Creatinine level, mg/dl; median (Q1–Q3)	1.2 (0.99–1.53)	1.4 (1.05–2.06)	<0.001
eGFR, ml/min/1.73 m^2; median (Q1–Q3)	52.9 (38–66)	44.5 (29.3–60.1)	<0.001
Malignant neoplasm, n (%)	49 (5.5)	20 (13.1)	<0.001
Excessive alcohol consumption (defined as 8 or more drinks per week), n (%)	69 (8.1)	12 (8)	0.98
Smoking (active or in the past), n (%)	232 (27.3)	49 (32.9)	0.17
COPD, n (%)	90 (10)	19 (12.5)	0.36
CHA_2DS_2-VASc score; median (Q1–Q3)	5 (4–6)	5 (4–6)	0.03

Abbreviations: AF, atrial fibrillation; other — see Table 1

DISCUSSION

There were four major findings of our study. First, nearly one-third of the study group had a high risk of bleeding; second, OACs were used much less frequently in the group with a high HAS-BLED score than in the group with a low HAS-BLED score (85.5% vs. 94.1%; *P* <0.001). The former results seem to represent a comparable proportion to those found in other studies. Third, we identified independent predictors of OAC use or nonuse, such as creatinine levels, a history of gastrointestinal bleeding, malignant neoplasms, and a history of strokes or TIAs, which are consistent with other data reported in the literature, as discussed below. Finally, although most of our registry was based in academic centers, we showed that NOACs were often inappropriately reduced contrary to the existing recommendations.

It is also worth emphasizing that our registry was conducted in 2019, so it presents relatively current trends in the use of NOACs in AF patients. Meanwhile, most of the data presented in the literature cover both the beginnings of NOAC use and their use in later years.

In clinical practice, anticoagulation therapy in AF patients is often challenging. In our study, almost one-third of the patients had a high risk of bleeding. This is a similar proportion to that found in other studies [15, 18]. In a Swedish registry study of AF patients or atrial flutter (conducted in 2010–2017), 34.4% of patients had a high HAS-BLED score [18]. The patients in that study were older (aged 75–104 years; n = 2943) than those in our cohort. In a retrospective observational study conducted in the Macau Special Administrative Region of China (from 2010–2018), which enrolled 3895 consecutive patients with nonvalvular AF, 35.47% of patients had a HAS-BLED score of 3 or more [19]. Polo Garcia et al. [20], in a cross-sectional multicentre study on a population with AF and moderate-high embolic risk (CHA_2DS_2-VASc ≥2; n = 1310) not treated with OACs, reported that 55.9% of patients have a HAS-BLED score ≥3. Unlike previous studies (data from 2016–2018), the ANAFIE registry (n = 32 726), a prospective, multicenter, observational Japanese study, reported a lower proportion (17%) of AF patients at high risk of bleeding [21]. However, this finding is most likely due to the study's inclusion of a healthier population and multiple exclusion criteria.

Even though over the years, the frequency of OAC use has increased significantly (35.63% in 2010–2012 vs. 61.18% in 2019–2021), there is still a proportion of patients who do not receive OAC therapy despite indications. In an Italian retrospective observational study [22], a higher predicted bleeding risk in clinical practice was associated with a lower OAC prescription rate, but the data analyzed in that study cover the years 2010–2014. In our study, 14.5% of patients in the high HAS-BLED group did not receive OAC treatment, compared to 5.9% in the low HAS-BLED group. The detailed characteristics of this group were discussed in a previous study based on an analysis of the POL-AF register [23]. In the GLORIA-AF study conducted quite long ago (2011–2014), 20% of patients did not receive OACs [24], with lower OAC use rates in patients with a high HAS-BLED score, compared to those with a low HAS-BLED score (75% vs. 83%, respectively).

In our study, a high proportion of NOAC dose reduction in the group with a high HAS-BLED score was observed. With regard to dabigatran and apixaban (but not rivaroxaban), reduced-dose NOACs were used much more frequently in the high HAS-BLED group in comparison with the low group (55.5 vs. 29.2% for dabigatran and 47.5 vs. 25.3% for apixaban). Prescribing NOACs in a reduced or full dose is important for providing AF patients with efficacious and safe treatment. In the group of patients treated with reduced doses of NOACs, a high proportion of people had inappropriate dose reduction on hospital discharge (apixaban 41.2%, dabigatran 24.9%, rivaroxaban 9.4%). This proportion of patients treated with an inappropriately reduced NOAC dose in our study was similar to other studies. In a large retrospective cohort study, which included 1020 patients from outpatient centers, inappropriate dosages of NOACs were found in 33% of cases [25]. Similar to our study, apixaban was dosed inappropriately most frequently. There was no difference in dosing appropriateness between primary and secondary care centers. That study was conducted on patients in America in 2010–2014 and consisted of both non-valvular AF patients and patients with thromboembolism. In another real-world retrospective cohort study by Gustafson et al. [26] including only patients with non-valvular AF, underdosing of NOACs was 47.5% and 42.5% for rivaroxaban and apixaban, respectively. In another large population of Asian AF patients, assessed retrospectively in 2013–2016 (a total of 53 649 patients with prevalent AF treated with NOACs), 31.2% of them were underdosed with NOACs [27]. Patients taking dabigatran and apixaban were prescribed too low doses more frequently. That study refers to both outpatient and hospitalized patients with prevalent AF. In the Polish literature, we did not find such extensive data on the evaluation of inappropriate NOAC dose reduction in AF patients. In an analysis including the entire population of the POL-AF trial [12], 36% of patients were treated with reduced NOAC doses, of whom 22.6% had inappropriate dose reductions.

Such frequent NOAC dose reductions in our analysis despite the lack of guideline-specific indications may be due to the presence of other less common factors that significantly increase the risk of bleeding, such as frailty syndrome or psycho-organic disorders, which were not evaluated in our registry. Another factor may be the high mean age of our patients (median 72 years [65–81]). It has been shown that in the elderly patient population, up to 51% of patients received a reduced dose despite not meeting formal dose reduction criteria [28]. Finally, it is important to note one factor that may have contributed to such frequent inadequate dose reductions in our analysis. The first is the relatively large group of patients hospitalized

for device implantation and the associated fear among physicians of local anticoagulation-related complications.

In conclusion of this part of the discussion, it should be strongly emphasized that a high risk of bleeding assessed by a high HAS-BLED score should not be a reason for inappropriate NOAC dose reduction, as this may increase the risk of thromboembolic complications in our patients. A recent large systematic review with meta-analysis showed again that inadequate dosing of NOACs beyond the indications does not reduce bleeding and may be associated with an increased risk of mortality [29].

Our results provide more evidence about factors favoring withdrawal of anticoagulant therapy. In our study, the predictors of OAC nonuse included a higher-than-average (median) creatinine level, history of gastrointestinal bleeding, and malignant neoplasms. A history of stroke or TIA increased the chance of receiving treatment. These results are consistent with most data in the literature but not equivalent. In a few previous registries, treatment with antiplatelet drugs was associated with a lower likelihood of OAC use [10, 20]. Analysis of antiplatelet therapy in the POL-AF study group, which was the subject of a previous publication, showed that triple antithrombotic therapy (dual antiplatelet therapy and OAC) was used more frequently than recommended by the guidelines [30]. On the other hand, patients received reduced doses of NOACs much more frequently than recommended in guidelines. In the GLORIA-AF study, a history of falls was another factor favoring OAC therapy withdrawal. According to guidelines, it is one of the potentially modifiable bleeding risk factors. Unfortunately, the data on the history of falls were not collected in the POL-AF study.

In an American ambulatory-based cardiology registry, in contrast to our observations, a history of bleeding or bleeding predisposition were associated with a greater likelihood of OAC use, although in individuals with a higher estimated bleeding risk, the proportion of individuals prescribed OAC was substantially lower [10].

All types of cancer show an increased risk of causing AF. Furthermore, AF can be a marker of the disease or may develop in patients undergoing surgery, chemotherapy, or radiotherapy [31]. The decision-making process for long-term therapy should include analysis of thromboembolic risk, bleeding risk assessment, drug-drug interactions, and patient preferences. In our study, malignancy was one of independent factors of nonuse of OAC therapy, which is consistent with previous publications [32]. What is interesting, the GLORIA-AF study reported an even higher proportion of cancer patients (17.1% in the whole study group), compared to the POL-AF population; however, cancer did not turn out to be a statistically significant factor in the decision to start OAC therapy. In a retrospective analysis of a post-stroke cohort of Danish patients, the predictors of OAC nonuse were consistent with our findings (cancer, chronic kidney disease, and prior bleeding events). Age older than 74 years, alcohol abuse, chronic obstructive pulmonary disease, dementia, and ischemic heart disease also proved to be significant [32]. It may be related to a much bigger study population (n = 33 308) and different baseline characteristics (patients were admitted to the hospital with ischemic stroke or TIA, older than in our study). In an Australian study on factors that influenced antithrombotic treatment initiation in general practice among patients newly diagnosed with AF (based on a general practice dataset), a low risk of bleeding, male sex, and no history of dementia were independently associated with OAC initiation [33]. In a Balkan-AF survey, age ≥80 years, prior myocardial infarction, and paroxysmal AF were independent predictors of OAC nonuse [34]. Unlike our study, almost one-third of that cohort was enrolled in outpatient health centers, the patients were younger, had lower HAS-BLED, and had fewer comorbidities. In the EUROobservational Research Programme on AF, which analyzed consecutive AF patients presenting to cardiologists in 250 centers from 27 European countries, there were a few independent predictors of OAC use in multivariable analysis: age, previous ischemic stroke, but also symptomatic AF, planned cardioversion or ablation. On the other hand, previous hemorrhagic events, chronic kidney disease, and admission for acute coronary syndrome or non-cardiovascular causes independently predicted OAC nonuse [35].

Strengths and limitations

The present study provides insights into OAC treatment and prescribing practices in Poland in daily clinical practice. The main limitation of this study was its observational nature. Thus, some data are missing for some patients. The information concerning the history of falls was not included in the registry. Another limitation is the absence of long-term follow-up of the patients in the POL-AF registry. For this reason, the long-term prognosis for AF patients who were not treated with NOACs and a high bleeding risk cannot be assessed. In addition, as previous publications have shown, there may be differences in patient characteristics and applied treatment between academic and district hospitals [36]. However, we would like to point out that due to their relatively large size, the results of the carried-out analyses may be conclusive enough. Finally, we evaluated hospitalized AF patients. Among these, only a proportion had a first-time diagnosis of AF, and only these patients started NOACs. For this reason, although our registry refers to hospitalized patients, in most patients OAC treatment was started in the outpatient setting. It is difficult to say what impact this factor had on the decision to start NOAC treatment in previously untreated patients.

CONCLUSIONS

Oral anticoagulants were used much less frequently in the group with a high HAS-BLED score as compared to the group with a low score. Creatinine levels, a history of gastrointestinal bleeding, and malignant neoplasms were independent predictors of nonuse of OACs, and a history

of strokes or TIAs increased the chances of getting OAC treatment. Furthermore, although the vast majority of our data was collected in academic centers, NOAC doses were often inappropriately reduced contrary to existing recommendations. The results of our registry indicate that we should strictly adhere to existing European and, especially, national expert recommendations when deciding on OAC dosing in AF patients.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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