Inappropriate prescription of a reduced dosage of NOAC in clinical practice: the results of the Polish Atrial Fibrillation (POL-AF) Registry in hospitalized patients

Niewłaściwe przepisywanie zredukowanej dawki NOAC w praktyce klinicznej — wyniki Polskiego Rejestru Migotania Przedsionków (POL-AF) u hospitalizowanych pacjentów

Olga Jelonek[1, 2], Iwona Gorczyca-Głowacka[2], Beata Uziębło-Życzkowska[3], Małgorzata Maciorowska[3], Maciej Wójcik[4], Robert Błaszczyk[4], Agnieszka Kapłon-Cieślicka[5], Monika Gawałko[5], Monika Budnik[5], Renata Rajtar-Salwa[6], Tomasz Tokarek[6], Jacek Bil[7], Michał Wojewódzki[7], Anna Szpotowicz[8], Małgorzata Krzciuk[8], Janusz Bednarski[9], Elwira Bakuła-Ostalska[9], Anna Tomaszuk-Kazberuk[10], Anna Szyszkowska[10], Marcin Wełnicki[11], Artur Mamcarz[11], Beata Wożakowska-Kapłon[1, 2]

[1]1st Clinic of Cardiology and Electrotherapy, Swietokrzyskie Cardiology Centre, Kielce, Poland
[2]*Collegium Medicum*, The Jan Kochanowski University, Kielce, Poland
[3]Department of Cardiology and Internal Diseases, Military Institute of Medicine, Warszawa, Poland
[4]Department of Cardiology, Medical University of Lublin, Lublin, Poland
[5]1st Chair and Department of Cardiology, Medical University of Warsaw, Warszawa, Poland
[6]Clinical Department of Cardiology and Cardiovascular Interventions, The University Hospital, Kraków, Poland
[7]Clinical Department of Interventional Cardiology, Central Clinical Hospital of the MSWiA, Warszawa, Poland
[8]Department of Cardiology, Ostrowiec Świętokrzyski, Poland
[9]Department of Cardiology, St John Paul II Western Hospital, Grodzisk Mazowiecki, Poland
[10]Department of Cardiology, University Hospital of Bialystok, Białystok, Poland
[11]3rd Department of Internal Diseases and Cardiology, Warsaw Medical University, Warszawa, Poland

Lekarz Olga Jelonek jest absolwentką Wydziału Lekarskiego Uniwersytetu Medycznego w Lublinie. Ukończyła szkolenie specjalizacyjne z kardiologii w I Klinice Kardiologii i Elektroterapii Świętokrzyskiego Centrum Kardiologii w Kielcach pod kierownictwem prof. dr hab. n. med. Beaty Wożakowskiej-Kapłon. Klinika specjalizuje się w diagnostyce i leczeniu zaburzeń rytmu serca (implantacja stymulatorów, ICD, CRT, badania elektrofizjologiczne, ablacje). W kręgu zainteresowań medycznych dr Jelonek pozostają: diagnostyka i leczenie choroby wieńcowej, terapia przeciwkrzepliwa, hipertensjologia. W wolnym czasie zajmują ją sport oraz muzyka.

Address for correspondence: Iwona Gorczyca-Głowacka MD, PhD, *Collegium Medicum*, Uniwersytet im. Jana Kochanowskiego w Kielcach, ul. Żeromskiego 5, 25–369 Kielce, Poland, e-mail: iwona.gorczyca@interia.pl

Abstract

Introduction. Prescribing non-vitamin K antagonist oral anticoagulants (NOACs) in a reduced or full dosage is important for providing patients with atrial fibrillation (AF) with efficacious and safe treatment. The study aimed to evaluate the administration frequency of reduced NOAC dosages against the guidelines and analysis of factors predisposing to such a choice in patients with AF included in the Polish Atrial Fibrillation (POL-AF) Registry.

Material and methods. The study included 1003 patients with AF treated with reduced dosages of NOACs hospitalized in ten Polish cardiology centers from January to December 2019. The criteria for appropriately reduced NOAC dosages was a dosage reduction of individual NOAC from the clinical studies, which was the basis for their registration.

Results. Among the 1003 patients who were treated with a reduced dosage of NOACs, inappropriately reduced dosages were observed in 242 patients (24.1%): in 120 patients (29.3%) treated with rivaroxaban, in 93 patients (33.8%) treated with apixaban and in 29 patients (9.1%) treated with dabigatran (p < 0.0001). Independent predictors of the use of inappropriately reduced dosages of NOACs were heart failure (odds ratio [OR] 1.55, confidence interval [CI]: 1.08–2.22) and hospitalization due to cardiac implantable electronic device (CIED) implantations/reimplantations (OR 2.01, CI: 1.27–3.17). Factors diminishing the chances of using inappropriately reduced dosages of NOACs were age (OR 0.98, CI: 0.97–0.998), vascular disease (OR 0.29, CI: 0.21–0.40) and creatinine clearance (CrCl) < 60 mL/min (OR 0.37, CI: 0.27–0.52).

Conclusions. In the group of patients treated with a reduced dosage of NOAC, 24.1% of patients had an inappropriately reduced dosage prescription, most frequently the patients receiving apixaban and rivaroxaban. The factor predisposing to prescribing an inappropriately reduced dosage of NOAC was heart failure and hospitalization due to CIED implantation/reimplantation. Label adherence to NOAC dosage is important to improve clinical outcomes in AF patients, and further investigation is needed to assess the best dosage of NOACs in the AF population.

Key words: atrial fibrillation, NOAC, reduced dosage, inappropriate prescription

Folia Cardiologica 2023; 18, 3: 113–125

Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia. It is estimated that it can involve about 2–4% of the general population, and the prevalence of AF increases with age [1, 2]. Thromboembolic complications, stroke included, are one of the most dangerous implications of AF, and the risk of their occurrence in patients not using anticoagulant treatment is about 5% yearly [3]. Multicenter randomized clinical studies showed the efficacy and safety of non-vitamin K antagonist oral anticoagulants (NOACs) in the prevention of thromboembolic complications in patients with AF. Dabigatran (thrombin inhibitor), apixaban, and rivaroxaban (Xa factor inhibitors), which belong to this group, are characterized by predictable pharmacokinetics enabling their application without monitoring parameters of coagulation and by a lower number of interactions with pharmaceuticals different from vitamin K antagonists. These medications differ from each other in terms of dosage and indications to reduce dosages. Based on the conducted clinical studies, recommendations for choosing the appropriate NOACs dosage in patients with AF were defined. Administering NOACs in a full or reduced dosage is vital for providing patients with efficacious and safe treatment, and the choice of the dosage depends on features such as age, weight, renal impairment, or higher risk of bleeding [4–6]. However, there are some reports that indicate inappropriate administering of NOACs dosages — especially prescription of reduced dosages too frequently, which is against the guidelines. Several studies have shown a higher percentage of patients who received inappropriate reduced NOAC dosages — in Whitworth et al. [7], 33% of patients received a reduced dosage of NOAC against guidelines, and in Barra et al. [8], this percentage was even higher — 46%. An inappropriate dosage reduction of NOAC was associated with reduced effectiveness for stroke prevention without any safety benefits [9].

The study aimed to evaluate the administration frequency of NOAC dosages against the guidelines and analysis of factors predisposing to such a choice in patients with AF included in POL-AF (The Polish Atrial Fibrillation) Registry.
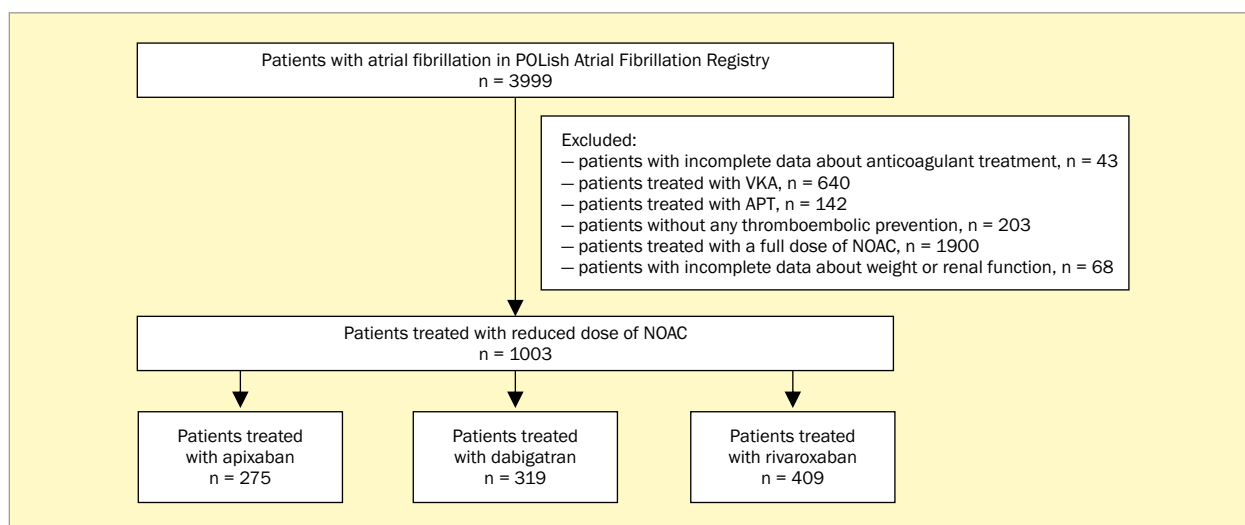
Figure 1. Flow chart of the study; APT — antiplatelet; NOAC — non-vitamin K antagonist oral anticoagulants; VKA — vitamin K antagonists

Material and methods

Study group
The Polish Atrial Fibrillation (POL-AF) Registry is a multi-center, prospective, observational study including patients with AF from ten cardiology centers — 7 academic ones, 2 regional hospitals, and one military hospital. The study was registered on clinicaltrials.gov (NCT04419012). The data was gathered from January to December 2019. The aim of the record was to obtain data concerning the clinical characteristics of patients with AF and to evaluate the undertaken steps — especially in terms of thromboembolic prophylaxis. Subsequent patients with AF, hospitalized in the centers for urgent and planned reasons — and who were over 18 years of age and suffered from arrhythmia documented with electrocardiographic examination or medical documents — were added to the record. No clear exclusion criteria were defined to gather a group well-representing Polish cardiological reality; however, patients admitted to the hospital to have ablation due to AF were not included in the record.

Based on the POL-AF record results, patients with AF treated with reduced dosages of NOACs were evaluated in the presented study. Patients receiving full NOACs doses, vitamin K antagonists, and antiplatelet therapy — i.e., those without anticoagulant treatment and with no data about weight or renal function — were excluded from the study (Figure 1).

Analyzed data
Atrial fibrillation was diagnosed based on medical records or electrocardiographic examination results upon admission to the hospital or during hospitalization. The researchers collected rudimentary data connected with demography, medical record, AF type, laboratory investigation results, and pharmacotherapy. The definitions of comorbidities are presented in *Table S1*. Creatinine clearance was achieved using the Cockroft-Gault equation. The thromboembolic risk was estimated based on the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age $\geq$ 75 years, diabetes, stroke/transient ischemic attack, vascular disorder, age 65–74 years, sex) [10]. The risk of bleeding was defined based on the HAS-BLED score (arterial hypertension, kidney/liver failure, stroke, bleeding, labile international normalized ratio [INR], older age > 65 years, pharmaceuticals/alcohol) [11]. The study was sanctioned by the Bioethical Commission of the Swietokrzyskie Chamber of Physicians in Kielce (104/2018). The commission waived the requirement of obtaining patients' informed consent.

Appropriateness of NOAC dosage
An evaluation of the appropriateness of reduced NOAC dosage was determined based on guidelines from The European Society of Cardiology, which refer to the treatment of patients with AF, and a summary of product characteristics registered in the European Medicine Agency [1]. The criteria for the approved dosage reduction for each NOAC was as follows: dabigatran 220 mg/day for patients with creatinine clearance (CrCl) 30–50 mL/min; rivaroxaban 15 mg/day for patients with CrCl 15–49 mL/min; apixaban 5 mg/day for patients with more than two of the following: age $\geq$ 80 years, body weight $\leq$ 60 kg, or serum creatinine $\geq$ 1.5 mg/dL. For all NOACs, concomitant use of P-glycoprotein inhibitors was an indication of reduced dosages (*Table S2*). Inappropriate

Table S1. Definitions of comorbidities

Coronary artery disease	Previous history of angina pectoris, myocardial infarction, coronary artery bypass graft burgery, percutaneous transluminal coronary angioplasty
Peripheral arterial disease	Previous history of intermittent claudication, arterial thrombosis, percutaneous or surgical intervention in the thoracic, abdominal aorta, or lower extremity vessels
Heart failure	Characterized by typical symptoms (e.g. fatigue, breathlessness) which may be accompanied by signs (such as pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress
Hypertension	Mean arterial blood pressure values (calculated from at least two measurements made during at least two different visits to the doctor) are $\geq$ 140 mm Hg for systolic blood pressure and/or $\geq$ 90 mm Hg for diastolic blood pressure
Diabetes mellitus	The level of fasting glucose $\geq$ 126 mg/dL twice (each test performed on a different day) or the glucose concentration measured at any time of the day $\geq$ 200 mg/dL with symptoms of hyperglycaemia or at the 120th minute of the Oral Glucose Load Test, the glucose level $\geq$ 200 mg/dL

Table S2. Indications for NOAC dose reduction

	Reduced dose	Recommendations for dose reduction
Apixaban	2.5 mg BID	1. More than two of the following: • age $\geq$ 80 years • body weight $\geq$ 60 kg • serum creatinine $\geq$ 1.5 mg/dL 2. Creatinine clearance 15–29 mL/min
Dabigatran	110 mg BID	1. Creatinine clearance 30–50 mL/min 2. Concomitant use of P-glycoprotein inhibitors 3. High risk of bleeding 4. Age > 80 years or age 75–80 years
Rivaroxaban	15 mg QD	1. Creatinine clearance 15–49 mL/min

BID (*bis in die*) — twice a day; QD (*quaque die*) — once a day

reduction of the NOAC dosage was defined as fulfilling $\geq$ 1 criterion of dosage against the guidelines. It referred to patients with a prescribed reduced NOAC dosage, despite qualification for the full dosage ('underdosed'), and to patients with a prescribed NOAC dosage higher than the one advised or allowed ('overdosed'). According to the guidelines in force at the time the POL-AF Registry was started, NOAC dosages should be reduced when one or two antiplatelet drugs are used concomitantly; so, we considered that reducing NOAC dosages in patients taking antiplatelet drugs is the correct management.

Statistical analysis

The distribution of quantitative features (age, sex, AF type, medical record, results of laboratory investigation, pharmacotherapy) was verified with the Shapiro–Wilk test.

To define the significance of the differences between the groups for particular quantitative features, the Kruskal––Wallis test was used. In the case of features for which the differences appeared to be significant, *post hoc* Dunn Bonferoni tests were also used. All the qualitative variables were coded in a zero-one system, where 0 means the lack of a particular feature and 1 means its presence. In individual NOAC groups, and later in appropriate/inappropriate dosage groups, stratum weights were calculated and the relationship between variables was estimated using a non-parametric χ^2 test. To determine the influence of chosen variables on medication dosage, a logistic regression analysis was used (the full model was presented). The effects were shown for the inappropriate dosage, whereas the appropriate dosage was the referential level. The value $p \leq 0.05$ was assumed to be

statistically significant. The data was analyzed using Statistica 13.3 software.

Results

Baseline characteristics

Among the 1003 patients treated with the reduced dose of NOACs, 409 were prescribed rivaroxaban (40.8%), 275 were prescribed apixaban (27.4%) and 319 were prescribed dabigatran (31.8%). The average age of the patients was 77.9 (± 9.4) years, patients over 74 years accounted for 68.7% of the researched population. Women accounted for 47.9% of the patients. The average result in the CHA_2DS_2-VASc score was 5.1 points, whereas, in the HAS-BLED score, it was 2.3 points. Renal impairment, defined as creatinine clearance < 60 ml/min, was diagnosed in 640 patients (63.8%). Previous bleeding, including bleeding from the digestive tract, appeared in 64 patients (6.4%) — most frequently in the group of patients treated with apixaban (28 patients, 10.2%), least frequently in patients using rivaroxaban (15 patients, 3.7%). In the studied population, the first-time episode of AF was observed in 61 patients (6.1%). Heart failure (HF) was the most frequent reason for hospital admission; it referred to 268 patients (26.7%) — most of them from the group treated with apixaban (101 patients, 36.7%). Planned reasons for hospitalization, such as electrical cardioversion and ablation of arrhythmia different

from AF, were observed most often in the group treated with rivaroxaban — respectively, 67 patients (16.4%) and 21 patients (5.1%). The clinical characteristics of patients included in the study are presented in Table 1.

Assessment of the propriety of using a reduced dose of NOAC

An appropriate NOAC dosage reduction was observed in 761 patients (75.9%), and an inappropriate NOAC dosage reduction was observed in 242 patients (24.1%). An inappropriate reduced dosage was observed in 120 patients (29.3%) treated with rivaroxaban, in 93 patients (33.8%) treated with apixaban, and in 29 patients (9.1%) treated with dabigatran (p < 0.0001). The frequency of an appropriate and inappropriate NOAC dosage reduction in each NOAC group is shown in Table 2, while a comparison of patients treated with appropriate/inappropriate reduced NOAC dosages is shown in Table 3. Patients using inappropriately reduced NOAC dosages, in comparison to patients receiving appropriately reduced dosages, were younger (the average age was 76.9 years vs. 78.3 years, p > 0.05), and the proportion of women in this group was higher (51.2% vs. 46.8%, p > 0.05). The occurrence frequency of HF, vascular diseases, and renal impairment was lower in the group of patients treated with inappropriately reduced dosages than in the group with appropriately reduced dosages (p < 0.05 for all). Moreover, in this group, the number

Table 1. Clinical characteristics of patients treated with reduced dosages of NOACs

Clinical characteristic	All patients n = 1003	Patients treated with apixaban n = 275 (27.4)	Patients treated with dabigatran n = 319 (31.8)	Patients treated with rivaroxaban n = 409 (40.8)	p-value
Age, years (mean ± SD)	77.9 ± 9.4	79.6 ± 9.7	77.6 ± 9.0	77.1 ± 9.5	**< 0.003**
Age, years, n (%)					
< 65	89 (8.9)	19 (7.0)	33 (10.4)	37 (9.1)	0.336
65–74	225 (22.4)	51 (18.5)	70 (21.9)	104 (25.4)	0.103
> 74	689 (68.7)	205 (74.5)	216 (67.7)	268 (65.5)	**0.040**
Female, n (%)	480 (47.9)	136 (49.5)	147 (46.1)	197 (48.2)	0.704
Type of atrial fibrillation, n (%)					
Paroxysmal	512 (51.0)	140 (50.9)	157 (49.2)	215 (52.6)	0.668
Persistent	171 (17.0)	39 (14.2)	59 (18.5)	73 (17.8)	0.324
Permanent	320 (32.0)	96 (34.9)	103 (32.3)	121 (29.6)	0.337
Medical history, n (%)					
Hypertension	874 (87.1)	234 (85.1)	287 (90.0)	353 (86.3)	0.169
HF	729 (72.7)	211 (76.7)	222 (69.6)	296 (72.4)	0.148
CAD	633 (63.1)	181 (65.8)	202 (63.3)	250 (61.1)	0.457
Previous MI	331 (33.0)	113 (41.1)	89 (27.9)	129 (31.5)	**0.002**
PAD	189 (18.8)	58 (21.1)	58 (18.2)	73 (17.8)	0.531

$\rightarrow$

Table 1. (cont.) Clinical characteristics of patients treated with reduced dosages of NOACs

Clinical characteristic	All patients n = 1003	Patients treated with apixaban n = 275 (27.4)	Patients treated with dabigatran n = 319 (31.8)	Patients treated with rivaroxaban n = 409 (40.8)	p-value
Vascular disease (CAD and/or PAD)	686 (68.4)	191 (69.5)	224 (70.2)	271 (66.3)	0.473
Diabetes mellitus	405 (40.4)	119 (43.3)	119 (37.3)	167 (40.8)	0.326
Previous stroke/TIA/peripheral embolism	201 (20.0)	46 (16.7)	67 (21.0)	88 (21.5)	0.337
Any previous bleeding	64 (6.4)	28 (10.2)	21 (6.6)	15 (3.7)	**0.003**
Previous gastric bleeding	46 (4.6)	22 (8.0)	13 (4.1)	11 (2.7)	**0.004**
Previous CNS bleeding	9 (0.9)	3 (1.1)	3 (0.9)	3 (0.7)	0.884
Thromboembolic risk					
CHA_2DS_2-VASc score (mean ± SD)	5.1 ± 1.5	5.2 ± 1.4	5.1 ± 1.5	5.1 ± 1.5	0.215
CHA_2DS_2-VASc score, n (%)					
= 0	3 (0.3)	1 (0.4)	0 (0.0)	2 (0.5)	0.475
= 1	3 (0.3)	0 (0.0)	3 (0.9)	0 (0.0)	**0.040**
> 1	997 (99.4)	274 (99.6)	316 (99.1)	407 (99.5)	0.617
Bleeding risk					
HAS-BLED score (mean ± SD)	2.3 ± 0.8	2.4 ± 0.9	2.2 ± 0.8	2.2 ± 0.8	**0.014**
HAS-BLED score > 2, n (%)	353 (35.2)	118 (42.9)	95 (29.8)	140 (34.2)	**0.003**
Laboratory tests					
Hemoglobin, g/dL (mean ± SD)	12.7 ± 1.8	12.2 ± 2.0	12.9 ± 1.7	12.9 ± 1.7	**< 0.001**
WBC, K/µL (mean ± SD)	8.2 ± 3.3	8.1 ± 3.2	8.2 ± 4.0	8.3 ± 2.8	0.096
Platelet count, K/µL (mean ± SD)	217.5 ± 75.3	208.6 ± 74.3	216.5 ± 70.7	224.3 ± 78.8	**0.044**
CrCl < 60 mL/min, n (%)	640 (63.8)	195 (70.9)	177 (55.5)	268 (65.5)	**< 0.0001**
Reason for hospitalization, n (%)					
Electrical cardioversion	125 (12.5)	7 (2.5)	51 (16.0)	67 (16.4)	**< 0.0001**
Planned coronarography/PCI	123 (12.3)	40 (14.5)	38 (11.9)	45 (11.0)	0.373
Planned CIED implantation/reimplantation	120 (12.0)	37 (13.5)	31 (9.7)	52 (12.7)	0.312
Acute coronary syndrome	112 (11.2)	37 (13.5)	32 (10.0)	43 (10.5)	0.360
HF	268 (26.7)	101 (36.7)	69 (21.6)	98 (24.0)	**< 0.0001**
Ablation other than AF	46 (4.6)	8 (2.9)	17 (5.3)	21 (5.1)	0.294
AF without any procedures	40 (4.0)	9 (3.3)	16 (5.0)	15 (3.7)	0.507
Other reasons for hospitalization	169 (16.8)	36 (13.1)	65 (20.4)	68 (16.6)	0.060
Concomitant treatment, n (%)					
Antiplatelets	259 (25.8)	75 (27.3)	70 (21.9)	114 (27.9)	0.157
Verapamil	4 (0.4)	1 (0.4)	2 (0.6)	1 (0.2)	0.715
Treatment before hospitalization, n (%)					
The same NOAC	773 (77.1)	144 (52.4)	272 (85.3)	357 (87.3)	**< 0.0001**
Other NOAC	43 (4.3)	37 (13.5)	5 (1.6)	1 (0.2)	**< 0.0001**
VKA	36 (3.6)	19 (6.9)	10 (3.1)	7 (1.7)	**< 0.0001**
APT	52 (5.2)	27 (9.8)	10 (3.1)	15 (3.7)	**< 0.0001**
None	99 (9.9)	48 (17.5)	22 (6.9)	29 (7.1)	**< 0.0001**

AF — atrial fibrillation; APT — antiplatelet; CAD — coronary artery disease; CHA_2DS_2-VASc — congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischemic attack, vascular disorder, age 65–74 years, sex; CIED — cardiac implantable electronic device; CNS — central nervous system; CrCl — creatinine clearance; HAS-BLED — arterial hypertension, kidney/liver failure, stroke, bleeding, labile INR, age > 65 years, pharmaceuticals/alcohol; HF — heart failure; MI — myocardial infarction; NOAC — non vitamin K antagonist oral anticoagulants; PAD — peripheral artery disease; PCI — percutaneous coronary intervention; SD — standard deviation; TIA — transient ischaemic attack; WBC — white blood cells; VKA — vitamin K antagonist

of patients concurrently using antiplatelet treatment was lower compared to the group administered appropriately reduced dosages (0.4% vs. 33.9%, p < 0.05).

The average number of points in the CHA_2DS_2-VASc score was lower in the group with inappropriately reduced doses (4.8 vs. 5.2, p < 0.05) (Table 3). Figure 2 shows the proportion of patients treated with appropriately/inappropriately reduced dosages according to the CHA_2DS_2VASc score. Electrical cardioversion and CIED implantation/reimplantation were more frequent reasons for hospitalization among patients treated with inappropriately reduced NOAC doses (p < 0.05 for both).

Predictors of the use of inappropriately reduced dosages of NOACs

The univariate logistic regression analysis found numerous predictors of inappropriately reduced dosages of NOACs prescription (*Table S3*).

In the multivariable model, factors associated with the selection of the inappropriately reduced dosages of NOACs included the following: age, HF, vascular disease, CrCl < 60 mL/min, and hospitalization due to CIED implantations//reimplantations.

Table 4 demonstrates the predictors of the use of inappropriately reduced doses of NOACs. Independent predictors of using inappropriately reduced doses of NOACs were HF (OR 1.55, CI: 1.08–2.22) and hospitalization due to CIED implantations/reimplantations (OR 2.01, CI: 1.27––3.17). Factors diminishing chances to administer inappropriately reduced doses of NOACs were age (OR 0.98, CI: 0.97–0.998), vascular disease (OR 0.29, CI: 0.21–0.40), and CrCl < 60 mL/min (OR 0.37, CI: 0.27–0.52).

Discussion

The use of NOAC in clinical practice is becoming increasingly common; therefore, numerous international registers are being kept to assess the factors influencing the choice of anticoagulant therapy in the prevention of thromboembolic complications in patients with AF [12–14]. Despite the definite indications to reduce NOACs doses in randomized clinical studies — ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) [4], RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) [5] and ROCKET-AF (Rivaroxaban once-daily, direct oral factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) [6] — the selection of an appropriate NOAC dosage in clinical practice still remains a huge challenge for doctors. Several studies have reported clinical outcomes according to label adherence to NOAC dosage. Using a reduced NOAC dose without any dosage-reduction criteria could lead to a below-par reduction of stroke risk [15]. Steinberg et al. [16] showed that NOAC overdosing was

Table 2. Assessment of the frequency of use of appropriately/inappropriately reduced dosages in patients treated with particular NOACs

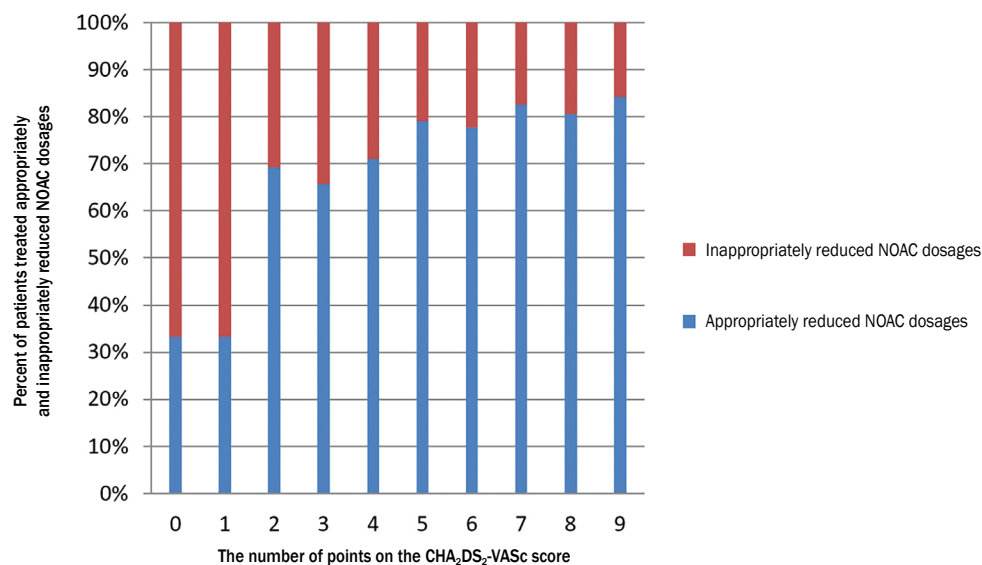|	All patients n = 1003	Patients treated with apixaban n = 275 (27.4)	Patients treated with dabigatran n = 319 (31.8)	Patients treated with rivaroxaban n = 409 (40.8)	p-value
Appropriately reduced doses	761 (75.9)	182 (66.2)	290 (90.9)	289 (70.7)	**< 0.0001**
Inappropriately reduced doses	242 (24.1)	93 (33.8)	29 (9.1)	120 (29.3)	**< 0.0001**
• overdosed	12 (1.2)	1 (0.4)	9 (2.8)	2 (0.5)	**0.005**
• underdosed	230 (22.9)	92 (33.5)	20 (6.3)	118 (28.9)	**≤ 0.001**

Table 3. A comparison of patients treated with appropriately/inappropriately reduced dosages of NOACs

Clinical characteristics	Appropriately reduced dosages n = 761	Inappropriately reduced dosages n = 242	p-value
Age, years (mean ± SD)	78.3 ± 9.1	76.9 ± 10.3	0.157
Age, years, n (%)			
< 65	66 (8.7)	23 (9.5)	0.692
65–74	162 (21.3)	63 (26.0)	0.123
> 74	533 (70.0)	156 (64.5)	0.103
Female, n (%)	356 (46.8)	124 (51.2)	0.226

$\rightarrow$

Table 3. (cont.) A comparison of patients treated with appropriately/inappropriately reduced dosages of NOACs

Clinical characteristics	Appropriately reduced dosages n = 761	Inappropriately reduced dosages n = 242	p-value
Type of atrial fibrillation, n (%)			
Paroxysmal	383 (50.3)	129 (53.3)	0.420
Persistent	129 (17.0)	42 (17.4)	0.884
Permanent	249 (32.7)	71 (29.3)	0.326
Medical history, n (%)			
Hypertension	668 (87.8)	206 (85.1)	0.282
HF	565 (74.2)	164 (67.8)	**0.049**
Coronary artery disease	532 (69.9)	101 (41.7)	**< 0.0001**
Previous MI	276 (36.3)	55 (22.7)	**< 0.0001**
PAD	152 (20.0)	37 (15.3)	0.105
Vascular disease (CAD and/or PAD)	570 (74.9)	116 (47.9)	**< 0.0001**
Diabetes mellitus	311 (40.9)	94 (38.8)	0.576
Previous stroke/TIA/peripheral embolism	146 (19.2)	44 (18.2)	0.729
Any previous bleeding	46 (6.0)	18 (7.4)	0.440
Previous gastric bleeding	33 (4.3)	13 (5.4)	0.502
Previous CNS bleeding	6 (0.8)	3 (1.2)	0.517
Thromboembolic risk			
CHA_2DS_2-VASc score (mean ± SD)	5.2 ± 1.5	4.8 ± 1.6	**< 0.0001**
CHA_2DS_2-VASc score, n (%)			
= 0	1 (0.1)	2 (0.8)	0.085
= 1	1 (0.1)	2 (0.8)	0.085
> 1	759 (99.8)	238 (98.2)	**0.015**
Bleeding risk			
HAS-BLED score (mean ± SD)	2.3 ± 0.8	2.3 ± 0.9	0.839
HAS-BLED score > 2, n (%)	269 (35.3)	84 (34.7)	0.856
Laboratory tests			
Hemoglobin, g/dL (mean ± SD)	12.7 ± 1.8	12.7 ± 1.9	0.349
Platelet count, K/µL (mean ± SD)	218.7 ± 77.6	213.7 ± 67.3	0.839
CrCl ml/min (mean ± SD)	50.6 ± 18.5	59.2 ± 18.3	**< 0.0001**
CrCl < 60 ml/min, n (%)	522 (68.6)	118 (48.8)	**< 0.0001**
Concomitant treatment, n (%)			
Antiplatelets	258 (33.9)	1 (0.4)	**< 0.0001**
Reason for hospitalization, n (%)			
Electrical cardioversion	81 (10.6)	44 (18.2)	**0.002**
Planned coronarography/PCI	110 (14.5)	13 (5.4)	**< 0.0001**
Planned CIED implantation/reimplantation	79 (10.4)	41 (16.9)	**0.006**
Acute coronary syndrome	110 (14.5)	2 (0.8)	**< 0.0001**
Heart failure	194 (25.5)	74 (30.6)	0.119
Ablation other than AF	31 (4.1)	15 (6.2)	0.169
AF without any procedures	28 (3.7)	12 (5.0)	0.376
Other reasons for hospitalization	128 (16.8)	41 (16.9)	0.965

AF — atrial fibrillation; CAD — coronary artery disease; CHA_2DS_2-VASc — congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischemic attack, vascular disorder, age 65–74 years, sex; CIED — cardiac implantable electronic device; CNS — central nervous system; CrCl — creatinine clearance; HAS-BLED — arterial hypertension, kidney/liver failure, stroke, bleeding, labile INR, age > 65 years, pharmaceuticals/alcohol; HF — heart failure; MI — myocardial infarction; PAD — peripheral artery disease; PCI — percutaneous coronary intervention; SD — standard deviation; TIA — transient ischaemic attack

Figure 2. Prescription pattern of appropriately and inappropriately reduced non-vitamin K antagonist oral anticoagulants (NOAC) dosages based on the CHA$_2$DS$_2$-VASc score

associated with increased all-cause mortality compared to recommended doses, and underdosing was associated with increased cardiovascular hospitalization.

The presented study showed that in 24.1% of patients, inappropriately reduced NOACs dosages were used. Yu et al. [17] showed that 31% of NOAC-treated patients were undertreated. In the population of elderly patients, it was shown that 51% of them received a reduced dosage despite the lack of formal criteria for dosage reduction [18]. The proportion of patients treated with an inappropriately reduced NOAC dose in our study is higher compared to studies of other authors — reduction of a NOAC dose against the guidelines was observed in 14.4% of patients in the study of Ono et al. [19]; in 16.1% in the study of Gustafson et al. [20], whereas in the ORBIT AF II study, an inappropriate dosage reduction was observed in only 9.4% of patients [16]. The presented study is multicenter; it included hospitalized patients, administering a reduced NOAC dose despite the lack of indications defined in the guidelines could result from the presence of different from those commonly acknowledged factors substantively increasing the risk of bleeding (e.g., frailty syndrome, psycho-organic syndrome).

In the discussed study, the highest proportion of inappropriate dosage reduction referred to patients receiving rivaroxaban (29.3%) and apixaban (33.8%), which is reflected in the results of some other authors' studies. In the study of Ono et al. [19], inappropriately reduced dosages were observed in 12.8% of patients administered rivaroxaban and in 19.6% of patients treated with apixaban, whereas in the study of Gustafson et al. [20], the proportion was even higher — 47.5% and 42.5% for rivaroxaban and apixaban, respectively. One of the probable reasons for

using an inappropriate dose reduction of rivaroxaban or apixaban can be an underestimation of renal function caused by different models of CrCl calculation — most laboratories present the CrCl value calculated based on MDRD (Modification of Diet in Renal Disease) formula, whereas customizing NOACs dosages in clinical studies was based on CrCl result achieved from the Cockroft–Gault equation [21, 22].

In the presented study, CrCl < 60 mL/min was shown to be a significant factor in diminishing the risk of using an inappropriate NOAC dose. It has been proven that using NOAC was associated with a reduced risk of thromboembolic and hemorrhagic complications compared to warfarin in patients with mild and moderate renal impairment [23–25]. Recent studies have also confirmed the effectiveness of reduced doses of NOAC in patients with concomitant chronic kidney disease, showing a promising benefit--risk balance in populations at high risk for cardiovascular complications [26].

In the POL-AF registry, the chance of using the inappropriately reduced NOAC dosage decreases by one percent every year. Older age was an independent factor in diminishing the risk of prescribing inappropriately reduced doses of NOACs in our study. Such conclusions were also drawn in the study of Jacobs et al. [27]; however, for the age group of ≥ 80 years — age was also a predictor of administering the appropriate reduction of doses for all researched NOACs. Interestingly enough, in the presented study, renal impairment and vascular disorder also appeared to be factors that diminished the risk of inappropriate dosage reduction. The study of Ono et al. [19] demonstrates that both older age (> 65 years), as well as renal impairment (CrCl < 60 mL/min), was independently connected with

Table S3. Factors determining the choice of inappropriately reduced dosages of NOACs: the results of univariate logistic regression analysis

Parameter	Univariate logistic regression analysis	
	OR (95% CI)	p-value
Age, years	0.99 (0.97–1.001)	0.059
< 65	1.11 (0.67–1.82)	0.692
65–74	1.30 (0.93–1.82)	0.123
> 74	0.78 (0.57–1.05)	0.103
Female	1.19 (0.89–1.60)	0.226
Paroxysmal AF	1.13 (0.84–1.51)	0.420
Persistent AF	1.03 (0.70–1.51)	0.884
Permanent AF	0.85 (0.62–1.17)	0.326
Hypertension	0.80 (0.53–1.21)	0.282
HF	**0.73 (0.53–0.99)**	**0.049**
Coronary artery disease	**0.31 (0.23–0.42)**	**< 0.0001**
Previous MI	**0.52 (0.37–0.72)**	**< 0.0001**
PAD	0.72 (0.49–1.07)	0.105
Vascular disease (CAD and/or PAD)	**0.31 (0.23–0.42)**	**< 0.0001**
Diabetes mellitus	0.92 (0.68–1.24)	0.576
Previous stroke/TIA/peripheral embolism	0.94 (0.64–1.36)	0.729
Any previous bleeding	1.25 (0.71–2.20)	0.440
Previous gastric bleeding	1.25 (0.65–2.42)	0.502
Previous CNS bleeding	1.58 (0.39–6.36)	0.517
CHA$_2$DS$_2$-VASc score	**0.83 (0.75–0.91)**	**< 0.0001**
= 0	6.33 (0.57–70.15)	0.085
= 1	6.33 (0.57–70.15)	0.085
> 1	**0.16 (0.03–0.86)**	**0.015**
HAS-BLED score	1.0 (0.84–1.19)	0.980
HAS-BLED score > 2	0.97 (0.72–1.32)	0.856
Hemoglobin (g/dL)	1.02 (0.94–1.11)	0.609
Platelet count (K/µL)	0.999 (0.997–1.001)	0.369
CrCl (mL/min)	**1.02 (1.016–1.033)**	**< 0.0001**
CrCl < 60 ml/min	**0.97 (0.72–1.32)**	**< 0.0001**
Antiplatelets	**0.008 (0.001–0.06)**	**< 0.0001**
Reason for hospitalization		
Electrical cardioversion	**1.87 (1.25–2.78)**	**0.002**
Planned coronarography/PCI	**0.34 (0.19–0.61)**	**< 0.0001**
Planned CIED implantation/reimplantation	**1.76 (1.17–2.65)**	**0.006**
Acute coronary syndrome	**0.05 (0.01–0.20)**	**< 0.0001**
HF	1.29 (0.94–1.77)	0.119
Ablation other than AF	1.56 (0.82–2.93)	0.169
AF without any procedures	1.37 (0.68–2.73)	0.376
Other reasons for hospitalization	1.01 (0.69–1.48)	0.965

AF — atrial fibrillation; CAD — coronary artery disease; CHA$_2$DS$_2$-VASc — congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischemic attack, vascular disorder, age 65–74 years, sex; CIED — cardiac implantable electronic device; CNS — central nervous system; CrCl — creatinine clearance; HAS-BLED — arterial hypertension, kidney/liver failure, stroke, bleeding, labile INR, age > 65 years, pharmaceuticals/alcohol; HF — heart failure; MI — myocardial infarction; PAD — peripheral artery disease; PCI — percutaneous coronary intervention; TIA — transient ischaemic attack

Table 4. Factors determining the choice of inappropriately reduced dosages of non-vitamin K antagonist oral anticoagulants: the results of multivariable logistic regression analysis

Parameter	Multivariable logistic regression analysis	
	OR (95% CI)	p-value
Age	0.98 (0.97–0.998)	0.031
CrCl < 60 mL/min	0.37 (0.27–0.52)	< 0.0001
Vascular disease	0.29 (0.21–0.40)	< 0.0001
Heart failure	1.55 (1.08–2.22)	0.017
Planned CIED implantation/reimplantation	2.01 (1.27–3.17)	0.003

CI — confidence interval; CIED — cardiac implantable electronic device; CrCl — creatinine clearance; OR — odds ratio

the risk of using inappropriately reduced doses — while vascular disease was a predisposing factor for prescribing an appropriately reduced dose of NOAC. The reason for the appropriate NOAC dosage reduction in patients with vascular disorders in our study could be the simultaneous use of antiplatelet drugs. In the methodology, we assumed that reducing NOAC doses in patients taking antiplatelet drugs is the correct management — according to the guidelines in force at the time the POL-AF Registry was started, which recommend considering a NOAC dose reduction when one or two antiplatelet drugs are used concomitantly. However, guidelines from the second half of 2019 allow using full doses of NOACs with simultaneous antiplatelet therapy.

There are many potential reasons why clinicians might prescribe inappropriate NOAC doses. In the discussed study, two factors predispose to prescribing inappropriately reduced dosages of NOACs. The first of them is hospitalization due to CIED implantation/reimplantation. The probable reason for such a study result could be doctors' fear of a hematoma when administering full doses of NOACs directly after the surgery. Because the influence of hospitalization reasons on the potential of using improper decreased doses was not examined in the papers that are readily available, it is not possible to compare the acquired result with other authors' investigations.

Another factor predisposing to an inappropriate prescription of reduced dosages of NOACs in our study is HF, as in the study by Ono et al. [19]. The reason for the inappropriate reduction of NOAC dosage in patients with HF could be the fear of worsening renal function in patients concomitantly taking diuretics in the absence of proper fluid balance control. However, it should be remembered that HF is one of the factors in the CHA$_2$DS$_2$-VASc score, which measures the risk of thromboembolic complications in patients with AF and, therefore, the selection of the appropriate NOAC dosage is important to ensure effective treatment of patients.

What is important in the presented study is the risk of bleeding estimated based on the HAS-BLED score was not a significant predictive factor of using inappropriately reduced NOAC doses, just as in the studies of Ono et al. [19] and Jacobs et al. [27]. In the SAFE-NOACS study, past hemorrhagic complication was also not a factor predisposing to an inappropriate NOAC dose correction [28]. The risk of bleeding during anticoagulant treatment is higher in some of the patients; however, it should not be the reason for an inappropriate reduction of NOAC dosages because it can increase the risk of thromboembolic complications in patients.

Conclusions

In the group of hospitalized patients with AF treated with a reduced dosage of NOAC, 24.1% of them inappropriately reduced the dosage of NOAC prescription, most frequently in patients treated with apixaban and rivaroxaban. The factors predisposing to the prescription of an inappropriate reduced dosage of NOAC were HF and hospitalization due to CIED implantation/reimplantation. Age, vascular disorder and renal impairment were independent predictors lowering the risk of prescribing an inappropriate reduced dosage of NOAC.

Acknowledgments

Conflict of interest

IGG — speaker for Bayer and Boehringer-Ingelheim; AKC — speaker for Bayer; JBednarski, AM and BWK — speaker for Bayer, Boehringer-Ingelheim and Pfizer; ATK — speaker for Boehringer-Ingelheim; MWełnicki — speaker for Bayer and Pfizer; other authors have no conflict of interest to declare.

Data availability

The data used to support the findings of this study is available from the corresponding author upon request.

Funding statement

Streszczenie

Wstęp. Przepisywanie doustnych przeciwkrzepliwych leków niebędących antagonistami witaminy K (NOAC) w dawce zredukowanej lub pełnej jest istotne dla zapewnienia pacjentom z migotaniem przedsionków (AF) skutecznego i bezpiecznego leczenia. Celem badania było ocenienie częstości stosowania zredukowanych dawek NOAC w stosunku do wytycznych oraz analiza czynników predysponujących do takiego wyboru u pacjentów z AF zarejestrowanych w Polskim Rejestrze Migotania Przedsionków (POL-AF).

Materiał i metody. Badanie obejmowało 1003 pacjentów z AF leczonych zredukowanymi dawkami NOAC, hospitalizowanych w 10 polskich ośrodkach kardiologicznych od stycznia do grudnia 2019 roku. Kryterium stosowania odpowiednio zredukowanych dawek NOAC była redukcja dawki indywidualnego leku NOAC na podstawie badań klinicznych, które były podstawą ich rejestracji.

Wyniki. Spośród 1003 pacjentów leczonych zredukowanymi dawkami NOAC, nieodpowiednio zredukowane dawki zaobserwowano u 242 pacjentów (24,1%): u 120 pacjentów (29,3%) leczonych rywaroksabanem, u 93 pacjentów (33,8%) leczonych apiksabanem oraz u 29 pacjentów (9,1%) leczonych dabigatranem (p < 0,0001). Niezależnymi czynnikami predykcyjnymi stosowania nieodpowiednio zredukowanych dawek NOAC były: niewydolność serca (iloraz szans [OR] 1,55; przedział ufności [CI]: 1,08–2,22) oraz hospitalizacja związana z wszczepieniem/reimplantacją kardioelektronicznych urządzeń wszczepialnych (CIED) (OR 2,01; CI: 1,27–3,17). Czynnikiem zmniejszającym szanse na stosowanie nieodpowiednio zredukowanych dawek NOAC były: wiek (OR 0,98; CI: 0,97–0,998), choroba naczyniowa (OR 0,29; CI: 0,21–0,40) i klirens kreatyniny (CrCl) < 60 ml/min (OR 0,37; CI: 0,27–0,52).

Wnioski. W grupie pacjentów leczonych zredukowaną dawką NOAC, 24,1% pacjentów miało nieodpowiednio przepisane dawki, najczęściej pacjenci otrzymujący apiksaban i rywaroksaban. Czynnikami predysponującymi do przepisywania nieodpowiednio zredukowanej dawki NOAC były niewydolność serca oraz hospitalizacja związana z wszczepieniem//reimplantacją CIED. Przestrzeganie zaleceń dotyczących dawek NOAC jest istotne dla poprawy wyników klinicznych u pacjentów z AF, konieczne jest również dalsze badanie w celu oceny optymalnej dawki NOAC w populacji z AF.

Słowa kluczowe: migotanie przedsionków, NOAC, zredukowana dawka, niewłaściwe przepisywanie

Folia Cardiologica 2023; 18, 3: 113–125

References

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021; 42(5): 373–498, doi: 10.1093/eurheartj/ehaa612, indexed in Pubmed: 32860505.

2. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006; 114(2): 119–125, doi: 10.1161/CIRCULATIONAHA.105.595140, indexed in Pubmed: 16818816.

3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991; 22(8): 983–988, doi: 10.1161/01.str.22.8.983, indexed in Pubmed: 1866765.

4. Granger CB, Alexander J, McMurray J, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365(11): 981––992, doi: 10.1056/nejmoa1107039, indexed in Pubmed: 21870978.

5. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361(12): 1139–1151, doi: 10.1056/nejmoa0905561, indexed in Pubmed: 19717844.

6. Patel M, Mahaffey K, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365(10): 883–891, doi: 10.1056/NEJMoa1009638, indexed in Pubmed: 21830957.

7. Whitworth MM, Haase KK, Fike DS, et al. Utilization and prescribing patterns of direct oral anticoagulants. Int J Gen Med. 2017; 10: 87––94, doi: 10.2147/IJGM.S129235, indexed in Pubmed: 28331354.

8. Barra ME, Fanikos J, Connors JM, et al. Evaluation of dose-reduced direct oral anticoagulant therapy. Am J Med. 2016; 129(11): 1198–1204, doi: 10.1016/j.amjmed.2016.05.041, indexed in Pubmed: 27341955.

9. Yao X, Shah ND, Sangaralingham LR, et al. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. J Am Coll Cardiol. 2017; 69(23): 2779–2790, doi: 10.1016/j.jacc.2017.03.600, indexed in Pubmed: 28595692.

10. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011; 342: d124, doi: 10.1136/bmj.d124, indexed in Pubmed: 21282258.

11. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS--BLED) to assess 1-year risk of major bleeding in patients with atrial

fibrillation: the Euro Heart Survey. Chest. 2010; 138(5): 1093–1100, doi: 10.1378/chest.10-0134, indexed in Pubmed: 20299623.

12. Huisman MV, Lip GYH, Diener HC, et al. Design and rationale of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation: a global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation. Am Heart J. 2014; 167(3): 329–334, doi: 10.1016/j.ahj.2013.12.006, indexed in Pubmed: 24576516.

13. Kakkar AK, Mueller I, Bassand JP, et al. 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(5): e63479, doi: 10.1371/journal.pone.0063479, indexed in Pubmed: 23704912.

14. Lopatowska P, Tomaszuk-Kazberuk A, Mlodawska E, et al. Do CHA$_2$DS$_2$VASc and HAS-BLED scores influence 'real-world' anticoagulation management in atrial fibrillation? 1556 patient registry from the reference cardiology centre. Pharmacoepidemiol Drug Saf. 2015; 24(12): 1297–1303, doi: 10.1002/pds.3878, indexed in Pubmed: 26419506.

15. Nielsen PB, Skjøth F, Søgaard M, et al. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. 2017; 356: j510, doi: 10.1136/bmj.j510, indexed in Pubmed: 28188243.

16. Steinberg BA, Shrader P, Thomas L, et al. Off-label dosing of non--vitamin K antagonist oral anticoagulants and adverse outcomes: the ORBIT-AF II registry. J Am Coll Cardiol. 2016; 68(24): 2597–2604, doi: 10.1016/j.jacc.2016.09.966, indexed in Pubmed: 27978942.

17. Yu HT, Yang PS, Jang E, et al. Label adherence of direct oral anticoagulants dosing and clinical outcomes in patients with atrial fibrillation. J Am Heart Assoc. 2020; 9(12): e014177, doi: 10.1161/JAHA.119.014177, indexed in Pubmed: 32495677.

18. de Almeida JP, Martinho AS, Girão A, et al. Novel anticoagulants in an older and frail population with atrial fibrillation: the effect of inappropriate dosing on clinical outcomes. Eur Geriatr Med. 2020; 11(5): 813–820, doi: 10.1007/s41999-020-00343-w, indexed in Pubmed: 32557249.

19. Ono T, Ikemura N, Kimura T, et al. Contemporary trend of reduced--dose non-vitamin K anticoagulants in Japanese patients with atrial fibrillation: A cross-sectional analysis of a multicenter outpatient regi-

stry. J Cardiol. 2019; 73(1): 14–21, doi: 10.1016/j.jjcc.2018.09.003, indexed in Pubmed: 30487057.

20. Gustafson W, Saunders J, Vazquez S, et al. Real-world study of direct oral anticoagulant dosing patterns in patients with atrial fibrillation. Pharmacy Practice. 2019; 17(4): 1709, doi: 10.18549/pharmpract.2019.4.1709.

21. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 130(6): 461–470, doi: 10.7326/0003-4819-130-6-199903160-00002, indexed in Pubmed: 10075613.

22. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16(1): 31–41, doi: 10.1159/000180580, indexed in Pubmed: 1244564.

23. Hart RG, Eikelboom JW, Brimble KS, et al. Stroke prevention in atrial fibrillation patients with chronic kidney disease. Can J Cardiol. 2013; 29(7 Suppl): S71–S78, doi: 10.1016/j.cjca.2013.04.005, indexed in Pubmed: 23790601.

24. Del-Carpio Munoz F, Gharacholou SM, Munger TM, et al. Meta-Analysis of renal function on the safety and efficacy of novel oral anticoagulants for atrial fibrillation. Am J Cardiol. 2016; 117(1): 69–75, doi: 10.1016/j.amjcard.2015.09.046, indexed in Pubmed: 26698882.

25. Lutz J, Jurk K, Schinzel H. Direct oral anticoagulants in patients with chronic kidney disease: patient selection and special considerations. Int J Nephrol Renovasc Dis. 2017; 10: 135–143, doi: 10.2147/IJNRD.S105771, indexed in Pubmed: 28652799.

26. Ha JT, Badve SV, Jun M. Recent evidence for direct oral anticoagulants in chronic kidney disease. Curr Opin Nephrol Hypertens. 2019; 28(3): 251–261, doi: 10.1097/MNH.0000000000000493, indexed in Pubmed: 30789840.

27. Jacobs MS, van Hulst M, Campmans Z, et al. Inappropriate non--vitamin K antagonist oral anticoagulants prescriptions: be cautious with dose reductions. Neth Heart J. 2019; 27(7-8): 371–377, doi: 10.1007/s12471-019-1267-9, indexed in Pubmed: 30949972.

28. Pharithi RB, Ranganathan D, O'Brien J, et al. Is the prescription right? A review of non-vitamin K antagonist anticoagulant (NOAC) prescriptions in patients with non-valvular atrial fibrillation. Safe prescribing in atrial fibrillation and evaluation of non-vitamin K oral anticoagulants in stroke prevention (SAFE-NOACS) group. Ir J Med Sci. 2019; 188(1): 101–108, doi: 10.1007/s11845-018-1837-7, indexed in Pubmed: 29860595.