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ORIGINAL ARTICLE

Evaluation of indications for reduced-dose non-vitamin K antagonist oral anticoagulants in hospitalised patients with atrial fibrillation

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Abstract

Background: Prevention of thromboembolic complications is a priority in patients with atrial fibrillation (AF). The use of non-vitamin K antagonist oral anticoagulants (NOACs) is more common and some patients have indications for a reduced dose.

Aim: We sought to evaluate the frequency of NOACs being prescribed to AF patients and to compare the groups of AF patients receiving standard and reduced doses.

Methods: The study included 1327 patients diagnosed with AF and hospitalised at an institution of the highest referral level in cardiology in the years 2015–2016. Final analysis encompassed 713 patients with nonvalvular AF, who were prescribed NOACs upon discharge.

Results: In the group of patients receiving NOACs, standard doses were used in 383 (53.7%) patients, while 330 (46.3%) patients received reduced doses. Among patients treated with reduced doses, dabigatran was prescribed to 186 (56.4%) patients, rivaroxaban to 124 (37.5%) patients, and apixaban to 20 (6.1%) patients. Absence of indications for dose reduction was identified in 54 out of 330 (16.4%) patients receiving reduced-dose NOACs, including six out of 20 patients receiving reduced-dose apixaban (30%), 21 out of 186 patients receiving reduced-dose dabigatran (11.3%), and 24 out of 124 patients receiving reduced-dose rivaroxaban (19.3%). Among patients treated with reduced dose of dabigatran (n = 186), one indication for dose reduction was observed in 75 patients, and at least two indications were observed in 90 patients. One indication was observed in 71 patients, and at least two indications were observed in 30 patients treated with a reduced dose of rivaroxaban (n = 124).

Conclusions: Standard doses of NOACs were prescribed to most hospitalised AF patients. Apixaban was prescribed more frequently in the reduced-dose regimen, while the frequencies of standard and reduced doses prescribed were similar for dabigatran and rivaroxaban. Absence of indications for dose reduction as defined in relevant guidelines and Summaries of Product Characteristics was identified in 15.5% of patients receiving reduced doses of NOACs. More than one indication for dose reduction was identified in most patients receiving reduced-dose dabigatran, while one indication was identified in most patients receiving reduced-dose rivaroxaban.

Key words: reduced dose, full dose, oral anticoagulants

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INTRODUCTION

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. It increases the risk of cerebral stroke by a factor of five and is responsible for 15% to 20% of all ischaemic brain strokes [1]. Non-vitamin K antagonist oral anticoagulants (NOACs) have been shown to be comparable or more effective in reducing the risk of cerebral stroke or systemic embolism in AF patients as compared to warfarin [2]. Currently used NOACs, such as apixaban, dabigatran, and rivaroxaban, are characterised by favourable safety profiles resulting in lower

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incidence of dangerous haemorrhages, particularly intracranial haemorrhages, and presenting with fewer interactions with other drugs [3–5]. Clinical factors such as age, weight, and comorbidities, including renal insufficiency, concomitant drugs, or high risk of bleeding, may require a reduced dose of NOACs being used in hospitalised patients [6].

The objective of this study was to evaluate the frequency of NOACs being prescribed to AF patients and to compare the groups of AF patients receiving standard and reduced doses of NOACs.

METHODS

The study was conducted in a population of 1327 patients diagnosed with AF and hospitalised at an institution of the highest referral level in cardiology in the years 2015–2016. The study population consisted of consecutive AF inpatients admitted to the referral clinic in elective or emergency mode.

The inclusion criteria were as follows: (1) nonvalvular AF; (2) nonfatal hospitalisation; (3) NOAC medication recommended upon hospital discharge.

Nonvalvular AF was defined as AF in patients without aortic or mitral valve replacements and without moderate or severe mitral stenosis.

The risk of cerebral stroke and the risk of bleeding were estimated using the CHA_2DS_2-VASc and HAS-BLED scoring systems, respectively.

According to the current guidelines of the European Society of Cardiology and the relevant Summaries of Product Characteristics, indications for reduced doses of NOACs are as follows:

- apixaban (2.5 mg twice daily [BID]): any two of the following: age ≥ 80 years, creatinine level ≥ 1.5 mg/dL, body weight ≤ 60 kg;
- dabigatran (110 mg BID): high risk of bleeding, age ≥ 80 years, simultaneous use of verapamil, creatinine clearance (CrCl) < 50 mL/min;
- rivaroxaban (15 mg once daily [OD]): high risk of bleeding, CrCl < 50 mL/min.

Additionally, simultaneous use of the aforementioned NOACs and antiplatelet drugs is an indication for reducing the dose of the NOAC.

Statistical analysis

The R statistical software package (The R Project for Statistical Computing, version 3.2.3, available from https://www.r-project.org/) was used for statistical analysis.

The differences between subpopulations were analysed using statistical tests adequate to the type of data: two-sided Student t test was used for continuous data, Fisher exact test was used for categorical data with at least one value of less than five appearing within a contingency table, and χ^2 test was used for the remaining categorical data (as default). Values of $p < 0.05$ were considered significant.

RESULTS

The presented study included a total of 1327 AF patients aged 26 to 102 years (mean age 72.3 ± 11.4 years). Oral anticoagulants (OACs), i.e. vitamin K antagonists (VKAs) or NOACs, were prescribed upon discharge to 1185 (89.3%) patients. Among them, NOACs were recommended to 713 (60.2%) patients, while VKAs were recommended to 472 (39.8%) patients. In the group of patients treated with NOACs (n = 713), apixaban was administered to 22 (3.1%) patients, dabigatran was administered to 414 (58.1%) patients, and rivaroxaban was administered to 277 (38.8%) patients. Standard doses of NOACs were used in 383 (53.7%) patients, while the remaining 330 (46.3%) patients received reduced doses (Fig. 1).

In the dabigatran group, consisting of 414 patients, the dose of 110 mg BID was prescribed to 186 (44.9%) patients. In the rivaroxaban group, consisting of 277 patients, the dose of 15 mg OD was prescribed to 124 (44.8%) patients. A total of 20 (90.9%) patients in the apixaban group were prescribed with the dose of 2.5 mg BID (Table 1).

The highest percentage of the group of patients prescribed with reduced-dose NOACs were patients receiving dabigatran (n = 186; 56.4%), followed by 124 (37.5%) patients receiving rivaroxaban, and 20 (6.1%) patients receiving apixaban.

Table 2 presents a comparison of the thromboembolic risk, the bleeding risk, age, renal function, and AF form in patients receiving standard and reduced doses of NOAC medications.

Table 3 shows a list of indications for the use of reduced doses of NOACs. For apixaban, the most common indications for dose reduction included age ≥ 80 years in 55% of patients and creatinine levels ≥ 1.5 mg/dL in 55% of patients receiving the reduced dose of the drug. For dabigatran, the most common indication for dose reduction was age ≥ 80 years in 58.6% of patients receiving the reduced dose of the drug. In the rivaroxaban group, the most common indication for dose reduction was ClCr < 50 mL/min in 59.7% of patients receiving the reduced dose of the drug.

In patients receiving the reduced dose of apixaban (n = 20; 6.1% of patients treated with apixaban), indications for dose reduction were observed in the following numbers of patients:

- one out of three indications in seven (35%) patients;
- two out of three indications in 11 (55%) patients;
- three out of three indications in one (5%) patient.

In patients receiving the reduced dose of dabigatran (n = 186; 56.4% of patients treated with dabigatran), indications for dose reduction were observed in the following numbers of patients:

- one indication in 75 (40.3%) patients;
- two indications in 68 (36.6%) patients;
- three indications in 18 (9.7%) patients;
- four indications in four (2.2%) patients.

In patients receiving the reduced dose of rivaroxaban (n = 124; 37.5% of patients treated with rivaroxaban), in-

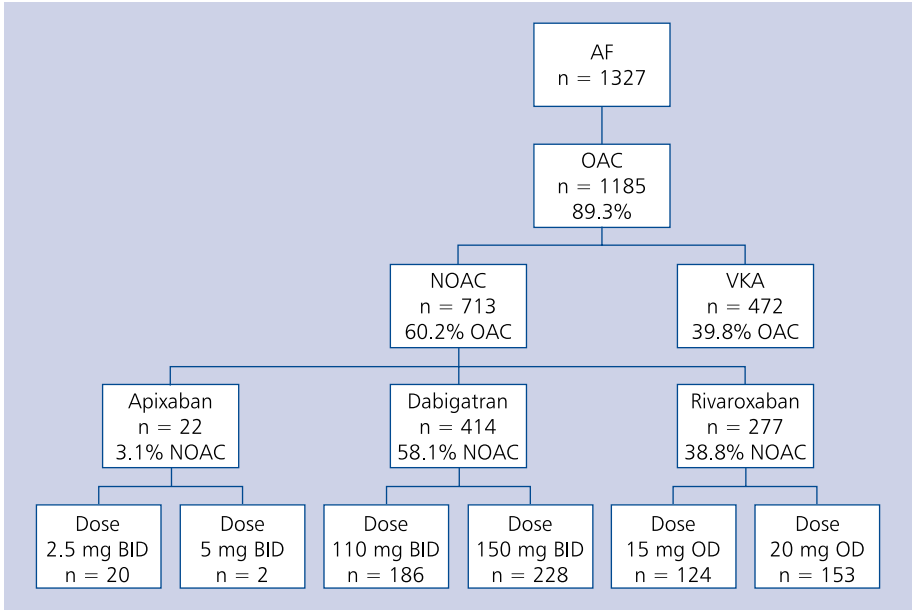

Figure 1. Number and percentage of patients treated with oral anticoagulants (OACs); AF — atrial fibrillation; VKAs — vitamin K antagonists; NOACs — non-vitamin K antagonist oral anticoagulants; BID — twice daily; OD — once daily

Table 1. Number of patients treated with full and reduced doses of non-vitamin K antagonist oral anticoagulants (NOACs)

NOAC	All	Full dose	Reduced dose	p
				< 0.001#
Dabigatran	414	228 (55.1%)	186 (44.9%)	0.436*
Rivaroxaban	277	153 (55.2%)	124 (44.8%)	0.568*
Apixaban	22	2 (9.1%)	20 (90.9%)	< 0.001*

Data are shown as number (percentage).
*Test for particular row-category vs. all the other considered together
#Test for the whole contingency table

dications for dose reduction were observed in the following numbers of patients:

— one indication in 71 (57.3%) patients;
— two indications in 29 (23.4%) patients;
— three indications in one (0.8%) patient.

Absence of indications for NOAC dose reduction as defined in relevant guidelines and Summaries of Product Characteristics was identified in 51 out of 330 (15.5%) patients receiving reduced-dose NOACs, including six out of 20 patients receiving reduced-dose apixaban (30%), 21 out of 186 patients receiving reduced-dose dabigatran (11.3%), and 24 out of 124 patients receiving reduced-dose rivaroxaban (19.3%).

Tables 4–6 present a comparison of demographic and clinical characteristics of patients receiving standard and reduced doses of apixaban, dabigatran, and rivaroxaban, respectively.

DISCUSSION

Randomised clinical trials such as Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY), and Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) compared the efficacies of standard and reduced doses of apixaban (5 mg vs. 2.5 mg), dabigatran (150 mg vs. 110 mg), and rivaroxaban (20 mg vs. 15 mg), respectively, against warfarin in the reduction of stroke or systemic embolism in AF patients. In the ARISTOTLE trial, apixaban 2.5 mg BID was administered to 831 patients. Indications for dose reduction included a positive status for at least two of the three following criteria: age ≥ 80 years, body weight ≤ 60 kg, and serum creatinine level ≥ 132.6 μmol/L (1.5 mg/dL). As revealed by the analysis of this subgroup of

Table 2. Comparison of patients receiving standard and reduced doses of non-vitamin K oral antagonist anticoagulants (NOACs)

	NOAC overall (n = 713)	Full dose NOAC (n = 383; 53.7%)	Reduced dose NOAC (n = 330; 46.3%)	p
Age [years]	72.5 ± 11.5	66.3 ± 10.2	79.7 ± 8.4	< 0.001
Women/Men	326/387 (45.7%/54.3%)	143/240 (37.3%/62.7%)	183/147 (55.5%/44.5%)	< 0.001
Calculated creatinine clearance	59.3 ± 16.7	65.2 ± 14.5	52.4 ± 16.4	< 0.001
[mL/min/1.73 m^2]:				< 0.001#†
≥ 50	505 (70.8%)	341 (88.8%)	165 (50%)	< 0.001*
30–49	189 (26.5%)	42 (11.2%)	147 (44.6%)	< 0.001*
< 30	18 (2.7%)	0 (0%)	18 (5.4%)	< 0.001#**
Serum creatinine [mg/dL]	1.2 ± 0.3	1.1 ± 0.2	1.3 ± 0.4	< 0.001
Form of atrial fibrillation:				< 0.001†
Paroxysmal	348 (48.8%)	181 (47.3%)	167 (50.6%)	0.414*
Persistent	156 (21.9%)	131 (34.2%)	25 (7.6%)	< 0.001*
Permanent	209 (29.3%)	71 (18.5%)	138 (41.8%)	< 0.001*
CHA_2DS_2-VASc score:	4.3 ± 1.9	3.4 ± 1.7	5.3 ± 1.5	< 0.001
				< 0.001#†
0	9 (1.3%)	9 (2.4%)	0 (0%)	0.004#*
1	44 (6.2%)	42 (11%)	2 (0.6%)	< 0.001#**
≥ 2	660 (92.5%)	332 (86.6%)	328 (99.4%)	< 0.001#**
HAS-BLED score:	2 ± 0.9	1.7 ± 0.9	2.3 ± 0.8	< 0.001
0–2	538 (75.5%)	324 (84.6%)	214 (64.9%)	
≥ 3	175 (24.5%)	59 (15.4%)	116 (35.1%)	< 0.001†
Concomitant verapamil therapy	4 (0.6%)	2 (0.5%)	2 (0.6%)	1.000#
Prior bleeding episode	166 (23.3%)	63 (16.5%)	103 (31.2%)	< 0.001

Data are shown as mean ± standard deviation or number (percentage).
#Fisher exact test
*Test for particular row-category vs. all the other considered together
†Test for the whole contingency table

Table 3. Indications for using reduced doses of non-vitamin K oral antagonist anticoagulants

Indications	Number of patients (%)		
	Apixaban (n = 20)	Dabigatran (n = 186)	Rivaroxaban (n = 124)
Age ≥ 80 years	11 (55%)	109 (58.6%)	–
Serum creatinine ≥ 1.5 mg/dL	11 (55%)	–	–
Body weight ≤ 60 kg	10 (50%)	–	–
Age ≥ 80 years + serum creatinine ≥ 1.5 mg/dL	3 (15%)	–	–
Age ≥ 80 years + body weight ≤ 60 kg	4 (20%)	–	–
Serum creatinine ≥ 1.5 mg/dL + body weight ≤ 60 kg	4 (20%)	–	–
Age ≥ 80 years + serum creatinine ≥ 1.5 mg/dL + body weight ≤ 60 kg	1 (5%)	–	–
Calculated creatinine clearance < 50 mL/min	–	80 (43%)	74 (59.7%)
HAS-BLED score ≥ 3 points	–	63 (33.9%)	39 (31.5%)
Concomitant use of one or two antiplatelet agents	7 (35%)	26 (14%)	20 (16.1%)
Concomitant verapamil therapy	–	2 (1.1%)	–
No indications specified in the guidelines	6 (30%)	21 (11.3%)	24 (19.4%)

Data are shown as number (percentage). The sum > than 100% due to multiple dose reduction indications in one patient.

Table 4. Comparison of patients receiving standard and reduced doses of apixaban

Variables	Apixaban full dose (n = 2; 9.1%)	Apixaban reduced dose (n = 20; 90.9%)	p
Age [years]	76.5 ± 3.5	81.9 ± 9.1	0.327
Women/Men	1/1 (50%/50%)	13/7 (65%/35%)	1*
Calculated creatinine clearance [mL/min/1.73 m^2]:	76.3 ± 0.9	46.5 ± 15.8	< 0.001
≥ 50	2 (100%)	9 (45%)	0.619*
30–49	0 (0%)	8 (40%)	
15–29	0 (0%)	3 (5%)	
Serum creatinine [mg/dL]	0.9 ± 0.1	1.6 ± 0.8	0.012
Form of atrial fibrillation:			0.039*
Paroxysmal	0 (0%)	12 (60%)	
Persistent	1 (50%)	0 (0%)	
Permanent	1 (50%)	8 (40%)	
CHA_2DS_2-VASc score:	4.5 ± 0.5	6 ± 1.2	0.264
0	0 (0%)	0 (0%)	1*
1	0 (0%)	0 (0%)	
≥ 2	2 (100%)	20 (100%)	
HAS-BLED score:	2.5 ± 0.5	2.9 ± 0.5	0.568
0–2	1 (50%)	4 (20%)	0.411*
≥ 3	1 (50%)	16 (80%)	
Concomitant verapamil therapy	0 (0%)	0 (0%)	1*
Prior bleeding episode	1 (50%)	10 (50%)	1*

Data are shown as mean ± standard deviation or number (percentage).
*Fisher exact test

Table 5. Comparison of patients receiving standard and reduced doses of dabigatran

Variables	Dabigatran full dose (n = 228; 55.1%)	Dabigatran reduced dose (n = 186; 44.9%)	p
Age [years]	65.4 ± 9.7	79.4 ± 8.1	< 0.001
Women/Men	84/144 (36.8%/63.2%)	102/84 (54.8%/45.2%)	< 0.001
Calculated creatinine clearance [mL/min/1.73 m^2]:	65.6 ± 13.8	55.9 ± 15.7	< 0.001
≥ 50	207 (90.8%)	106 (57%)	< 0.001*
30–49	21 (9.2%)	78 (42%)	
15–29	0 (0%)	2 (1%)	
Serum creatinine [mg/dL]	1.1 ± 0.2	1.2 ± 0.3	< 0.001
Form of atrial fibrillation:			< 0.001
Paroxysmal	104 (45.6%)	90 (48.4%)	
Persistent	84 (36.8%)	18 (9.7%)	
Permanent	40 (17.6%)	78 (41.9%)	
CHA_2DS_2-VASc score:	3.3 ± 1.7	5.3 ± 1.5	< 0.001
0	2 (0.9%)	0 (0%)	< 0.001*
1	26 (11.4%)	2 (1.1%)	
≥ 2	200 (87.7%)	184 (98.9%)	
HAS-BLED score:	1.7 ± 0.9	2.3 ± 0.8	< 0.001
0–2	194 (85.1%)	123 (66.1%)	< 0.001
≥ 3	34 (14.9%)	63 (33.9%)	
Concomitant verapamil therapy	0 (0%)	2 (1.1%)	0.201*
Prior bleeding episode	36 (15.8%)	61 (32.8%)	< 0.001

Data are shown as mean ± standard deviation or number (percentage).
*Fisher exact test

Table 6. Comparison of patients receiving standard and reduced doses of rivaroxaban

Variables	Rivaroxaban full dose (n = 153; 55.2%)	Rivaroxaban reduced dose (n = 124; 44.8%)	P
Age [years]	67.4 ± 10.7	79.8 ± 8.6	< 0.001
Women/Men	58/95 (37.9%/62.1%)	68/56 (54.8%/45.2%)	0.007
Calculated creatinine clearance [mL/min/1.73 m^2]:	64.5 ± 15.5	48 ± 16	< 0.001
≥ 50	132 (85.6%)	50 (40.3%)	< 0.001*
30–49	21 (13.7%)	61 (49.2%)	
15–29	0 (0%)	13 (10.5%)	
Serum creatinine [mg/dL]	1.1 ± 0.2	1.4 ± 0.4	< 0.001
Form of atrial fibrillation:			
Paroxysmal	77 (50.3%)	65 (52.4%)	< 0.001*
Persistent	46 (30.1%)	7 (5.7%)	
Permanent	30 (19.6%)	52 (41.9%)	
CHA_2DS_2-VASc score:	3.4 ± 1.8	5.2 ± 1.6	< 0.001
0	7 (4.6%)	0 (0%)	0.006*
1	16 (10.5%)	0 (0%)	
≥ 2	130 (84.9%)	124 (100%)	
HAS-BLED score:	1.8 ± 0.9	2.2 ± 0.7	< 0.001
0–2	129 (84.3%)	87 (70.2%)	0.007
≥ 3	24 (15.7%)	37 (29.8%)	
Concomitant verapamil therapy	2 (1.3%)	0 (0%)	0.504*
Prior bleeding episode	26 (17%)	32 (25.8%)	0.100

Data are shown as mean ± standard deviation or number (percentage).
*Fisher exact test

patients, the risk of cerebral stroke or systemic embolism was lower in patients receiving apixaban 2.5 mg BID as compared to those receiving warfarin (hazard ratio [HR] 0.52, 95% confidence interval [CI] 0.25–1.08) [7, 8]. In the RE-LY trial, dabigatran 110 mg BID was administered to 1196 patients, with indications for dose reduction including renal impairment as defined by CrCl < 50 mL/min. The incidence of ischaemic brain strokes or systemic embolism was lower in the dabigatran group as compared to the warfarin group, while the incidence of major bleedings was similar in both groups (HR 0.91, 95% CI 0.74–1.11) [8, 9]. The ROCKET-AF trial, evaluating the risk of cerebral stroke or systemic embolism in 1474 patients receiving rivaroxaban 15 mg compared to warfarin, demonstrated a lower incidence of ischaemic or thromboembolic complications in the rivaroxaban group, with comparable incidence of major bleedings in both study groups. The indication for a 15 mg dose of rivaroxaban was CrCl < 50 mL/min [8, 10, 11].

In the presented study conducted in AF patients hospitalised in the years 2015–2016, NOACs were prescribed at discharge to 60.2% of patients receiving anticoagulant treatment. In the study population, dabigatran, rivaroxaban, and apixaban were prescribed to 58.8%, 38.8%, and 3.1% of patients, respectively. The low percentage of patients receiving apixaban was because its registration in the prevention of thromboembolic complications of AF took place at the latest date. Reduced doses of NOACs were administered to 46.3% of patients receiving this class of medications. Among them, the most common reduced-dose drug was dabigatran (56.4%), followed by rivaroxaban (37.5%) and apixaban (6.1%).

In a study conducted in patients hospitalised in the years 2011–2014, Barra et al. [12] demonstrated that the percentage of patients treated with reduced-dose NOACs was 13.3%. In this group of patients, the most common reduced-dose medication was rivaroxaban (61.1%), followed by dabigatran (26.3%) and apixaban (12.5%). Similarly to our study, the lowest percentage of patients treated with a reduced dose of NOAC was observed for apixaban. Experience in the use of apixaban is still relatively low, although it has been increasing significantly in recent years.

In a Danish register encompassing a total of 31,522 AF patients, reduced doses of NOACs were used in 32.9% of patients [13]. The percentages of patients treated with individual NOACs were as follows: standard-dose dabigatran: 22.4%, reduced-dose dabigatran: 14%, standard-dose rivaroxaban: 21.8%, reduced-dose rivaroxaban: 6.7%, standard-dose

apixaban: 22.9%, and reduced-dose apixaban: 12.2% [13]. Of note is the fact that similar percentages of patients included in the Danish registry were treated with standard doses of apixaban, dabigatran, and rivaroxaban alike. Patients treated with reduced doses of dabigatran and apixaban accounted for half of the patients treated with standard doses of these drugs. In our study, the respective ratios differed; notably, the number of patients treated with reduced-dose rivaroxaban and dabigatran accounted for 45% of all patients treated with these medications.

Indications for the use of reduced doses of NOACs in hospitalised AF patients were also evaluated in this study. Numbers of patients receiving standard and reduced doses of NOACs were compared, with attention paid to such criteria as age, sex, creatinine clearance and serum levels, history of haemorrhagic episodes, concomitant use of verapamil, CHA_2DS_2-VASc score of brain stroke risk, HAS-BLED score of bleeding risk, or the AF form. The HAS-BLED scale was originally dedicated to patients treated with VKAs; however, because over the years the HAS-BLED scale has been the most popular scoring system to assess the risk of bleeding complications in patients with AF, it was used in the presented study. There are also available results of studies comparing the predictive value of different scales, including the HAS-BLED scale, in predicting bleeding complications in patients treated with NOACs [14].

Analysis of the study data revealed that a standard dose was prescribed more frequently than a reduced dose to hospitalised AF patients. This was the case particularly in patients with high thromboembolic risk who scored ≥ 2 in the CHA_2DS_2-VASc system and thus required standard doses of medications. An exception was observed in the apixaban group, where the dose of 2.5 mg was prescribed more frequently due to the presence of additional indications for dose reduction despite the CHA_2DS_2-VASc score of ≥ 2. In a prospective study by Lasek-Bal et al. [15] in patients with nonvalvular AF and cerebrovascular events, standard doses of rivaroxaban were also used more frequently than the reduced doses (171 vs. 38), which was due to the high CHA_2DS_2-VASc score (the mean CHA_2DS_2-VASc in the study group was 4.16) and was associated with high efficacy and safety of therapy. In the study by Yao et al. [16], potential overdose of NOACs (e.g. administration of standard doses to patients with renal impairment) was not associated with a reduction in the risk of brain stroke while simultaneously being associated with a twofold increase in the risk of bleeding.

The form of AF in the hospitalised patients had no impact on the decision to use anticoagulation; however, standard doses of NOACs were more common in patients with persistent AF. Appropriate preparation of these patients for an electrical cardioversion procedure to prevent thromboembolic complications required the use of standard doses of NOACs. Patients in whom sinus rhythm restoration was not attempted (i.e. patients with chronic AF) were more often prescribed with reduced-dose NOACs.

Reduced doses of NOACs were prescribed more frequently to patients with high risk of bleeding as defined by HAS-BLED score ≥ 3 and in patients with a history of bleeding episodes. Also, the thromboembolic risk in patients receiving reduced doses of medications was significantly higher compared to standard-dose patients; all patients receiving reduced doses of rivaroxaban and apixaban were at high risk of thromboembolic events. Standard and reduced doses of rivaroxaban were used with equal frequency in patients with a history of bleeding episodes. As demonstrated by Barra et al. [12], history of bleeding episodes was associated with reduced doses of NOACs being prescribed; however, bleedings continued to occur in ~20% of patients despite the reduction in NOAC doses.

In our study, no factors defined as indications for dose reduction in relevant guidelines or Summaries of Product Characteristics were identified in 15.5% of hospitalised AF patients treated with reduced doses of NOACs, most commonly in patients receiving reduced doses of apixaban. Barra et al. [12] identified no indications for dose reduction in 14.7% of patients treated with reduced doses of NOACs. In these patients, the appropriate dose of NOAC was determined on the basis of physicians' experience and the analysis of risk-to-benefit ratio for anticoagulation treatment to prevent thromboembolic events as compared to the increased risk of bleeding due to the administration of anticoagulants. However, one should keep in mind that administration of reduced doses of NOACs outside the established guidelines is associated with an increased risk of adverse events [17].

Our study has several limitations. Firstly, it was a retrospective study based on the assumption that all patients received their medications as prescribed. Secondly, factors such as treatment received prior to hospitalisation, socioeconomic status, or patients' preference, possibly affecting the choice of NOAC molecule and dose of hospitalised AF patients, were not taken into account.

In conclusion: 1) Standard doses of NOACs were prescribed to most hospitalised AF patients; 2) Apixaban was prescribed more frequently in the reduced-dose regimen, while the frequencies of standard and reduced doses prescribed were similar for dabigatran and rivaroxaban; 3) The most common causes for dose reduction included advanced age and renal impairment for apixaban, advanced age for dabigatran, and renal impairment for rivaroxaban; 4) Absence of indications for dose reduction as defined in relevant guidelines and Summaries of Product Characteristics was identified in 15.5% of patients receiving reduced doses of NOACs, most commonly in patients receiving reduced doses of apixaban; 5) More than one indication for dose reduction was identified in most patients receiving reduced-dose dabigatran, while one indication for dose reduction was identified in most patients receiving reduced-dose rivaroxaban.

Conflict of interest: *none declared*

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