CASE REPORT

Predictors of thromboembolic and bleeding complications in patients with non-valvular atrial fibrillation and atrial flutter using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants: A cross-sectional study

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ABSTRACT

BACKGROUND: Most common complications that could occur due to inadequate anticoagulant therapy are different types of bleeding or thromboembolic events.

OBJECTIVES: The aim of this study was to identify differences between patients using a different anticoagulant therapy and the occurrence of complications and their frequency. The second aim was to determine the predictors that may lead to these complications using the regression model.

METHODS AND RESULTS: We conducted a cross-sectional study. In total, 1401 AF/AFL patients were identified with prescriptions to either VKA or NOAC. Duration of follow-up was 22.5 months. The results showed no significant differences between NOAC and VKA users for ischaemic stroke or systemic embolism. On the other hand, in the VKA group, there were two times more fatal outcomes than in the NOAC group (p=0.002). Also, combined endpoint (stroke/systemic embolism/death) was statistically higher in the VKA group (p=0.039). We found a statistically significant difference in the rate of "total bleeding" between groups (NOAC: 7.6%, VKA group: 17.2%, p<0.001). Regression model identified that the factors that increased bleeding events were female gender, a higher level of creatinine and percutaneous coronary intervention, while usage of NOAC was related to a statistically significant reduction of bleeding (p<0.001).

CONCLUSION: This study shows that NOAC are an effective and safe alternative to VKA in clinical care settings. Individual patient characteristics including renal function, age or prior bleeding should be taken into account when choosing the VKA/NOAC with the best risk-benefit profile.

Keywords: *Atrial fibrillation/flutter; Thromboembolism; Bleeding; Oral anticoagulants*

INTRODUCTION

Usage of oral anticoagulants is necessary for treating patients with atrial fibrillation (AF) or Atrial Flutter (AFL). Atrial fibrillation is observed in 3% of adults aged 20 years or older [1, 2] while the overall incidence of AFL has been estimated at 88 cases per 100,000 person-years [3]. In these types of arrhythmia the risk of thromboembolic stroke is five times higher [4]. Patients with a thromboembolic stroke caused by atrial fibrillation have higher mortality and higher morbidity than patients with other stroke subtypes [5].

Due to the increased risk of clotting, it is most important to find adequate anticoagulant therapy for this type of arrhythmia. However, the use of anticoagulants can lead to a not so small number of complications. The most common complications are different types of bleeding or thromboembolic events that can occur if an adequate anticoagulant effect is not achieved. Most commonly prescribed anticoagulants in the last five decades are Vitamin K Antagonists (VKA) [6-8]. VKA, mainly warfarin, are effective for prevention and lowering of risks of stroke by about two thirds and mortality by one quarter. On the other hand, VKA increase the risk of bleeding, which is proven in many clinical trials [9]. A narrow therapeutic range, dietary interactions and permanent need for coagulation monitoring [10-12] are some of the problems that occur while using VKA. Uncontrolled bleeding and different types of bleeding complications are a very frequent cause of hospital admissions worldwide [13].

Today, we have several Non-Vitamin K Antagonists (NOAC) in every day practice. NOAC overcome some of the limitations of VKA, offering important benefits that can improve the quality of patient's life [14]. NOAC have a fixed dosage which is a big advantage compared to VKA. Several Randomized Controlled Trials (RCT) have demonstrated superiority of NOAC over warfarin for key indications [15-17]. In clinical trials, NOAC showed non-inferiority (dabigatran both doses, rivaroxaban, apixaban and edoxaban) and superiority (dabigatran 150 mg and apixaban) in terms of preventing stroke and systemic embolism in patients with non-valvular AF and their superiority (dabigatran 110 mg and apixaban) in terms of major bleeding, compared to warfarin [18, 19].

Several large world registers that collect data from big national databases provide results of single NOAC comparison with warfarin [19]. Ruff et al, showed that NOACs at standard dose, significantly reduce the risk of stroke and all-cause mortality but increase the risk of gastrointestinal bleeding [19]. Thus, in last guidelines NOACs are preferred treatment option over warfarin [20].

Given the available information, the aims of this study are as follows. Firstly, we wanted to present a difference between patients using a different anticoagulant therapy and frequency of complications in them. Secondly, we wanted to identify predictors that may lead to these complications using the regression model [21].

MATERIALS AND METHODS

Study design and population

We conducted a cross-sectional study (from January 2014 to July 2017). The patients who participated in the study were hospitalized in the clinical center of Serbia at the department of cardiology. Due to the first appearance of NOAC in the country during 2013, January of 2014 was taken as a starting point of this study. The clinical data were collected retrospectively from the patients' medical charts [22].

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All selected patients were treated for non-valvular atrial fibrillation and atrial flutter either with dabigatran, rivaroxaban, apixaban or VKA. We excluded patients with valvular atrial fibrillation (rheumatic mitral stenosis, a mechanical or bioprosthetic heart valves or mitral valve repair), based on the definition of "nonvalvular" AF in the 2014 American College of Cardiology, American Heart Association and Heart Rhythm Society guidelines. Also, we excluded patients with deep vein thrombosis, pulmonary embolism, terminal kidney disease [23].

Data collection and outcomes

In August 2017, phone follow-up was performed. All patients were informed about the planned research and all patients were asked questions about hemorrhagic and thromboembolic events in the period from discharge to the day of follow up. The questions were formulated as follows:

- **Q1:** Do you take anticoagulant therapy that was prescribed at your discharge from our hospital?
- **Q2:** Did you have any bleeding event: epistaxis, hematoma, hematuria, gastrointestinal bleeding (including melena and/or haematemesis), intracranial bleeding, bleeding in the eye or severe anemia?
- **Q3:** Did you have a stroke or systemic embolism?
- **Q4:** Did you have myocardial infarction?

Also, if patients asked that they stopped to take anticoagulant therapy that was prescribed at discharge letter, we asked them about reasons for that, or if they asked that they take anticoagulant therapy different from discharge letter, we asked them which anticoagulant drug they take. About patients who died, we received information from their relatives or spouses.

For each patient, we assessed demographic and social characteristics, including age, gender, weight, height, body mass index, medical history (hypertension, hypercholesterolemia, diabetes mellitus, previous bleeding, peptic ulcer disease, creatinine level, left ventricular ejection fraction, left atrial dimension, previous stroke, previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, peripheral vascular disease, heart failure, type of AF/AFL, cardio-ablation, cardioversion) and therapy. We combined covariate information into the CHA2DS2-VASc score for assessing stroke risk and the HAS-BLED score [23]. as a measure of bleeding risk. Creatinine clearance was calculated using the weight-adjusted Cockroft-Gault formula. We also examined the occurrence of discontinuation of VKA/NOAC therapy.

Effectiveness and safety outcomes were followed in order to examine the differences in treatments. The primary effectiveness outcomes of interest were stroke and systemic embolism. Also, we included all-cause mortality as a single endpoint and as a combined endpoint with stroke and systemic embolism. The secondary effectiveness outcome was a myocardial infarction. The primary safety outcomes were intracranial bleeding and major gastrointestinal bleeding. The secondary safety outcome was bleeding with severe anemia, hematuria, epistaxis, hematoma and bleeding in the eye [24].

In order to identify factors that could lead to thromboembolic complications, patients were divided into two groups, those who had a stroke, thromboembolism or death and controls. Also, for bleeding complications, patients were divided in those who had any bleeding complications, including epistaxis, hematoma, hematuria, gastrointestinal bleeding, intracranial bleeding, bleeding in the eye or severe anemia and controls.

Statistical analyses

All statistical analyses were performed using Statistical Package for Social Science (SPSS software package, version 22.0; SPSS Inc., Chicago, IL, USA). Primarily obtained data were analyzed by descriptive statistical methods and methods of regression modeling. Of descriptive statistical methods, we used: the middle value (arithmetical mean), measures of variability (standard deviation) and determinants of the structure presented as a percentage. For comparison of patients, we used the Pearson chi-square test or Fisher's exact test for categorical data and the Student's t-test or Mann-Whitney test for numerical data. A multivariate regression model was used to determine the predictors for bleeding or thromboembolic complications. The variables for the multivariate regression model were selected according to clinical importance. All predictors that were statistically significant in univariate comparative analyzes were included in the multivariate logistic regression model. Statistical hypothesis testing was conducted at the level of statistical significance of 0.05 [25].

RESULTS

Characteristics of the study patients

In total, 1401 AF/AFL patients were identified with a prescriptions to either VKA or NOAC. Of these, 1028 (73.3%) were in the VKA group and 373 (26.7%) were in NOAC group (dabigatran: n=297, apixaban: n=51, rivaroxaban: n=25). There were 1232 patients with atrial fibrillation (87.9%) and 298 patients with atrial flutter (12.1%), but 129 patients (9.2%) had both (AF and AFL). Duration of follow-up was 22.5 months.

Results showed that differences between NOAC and VKA users were statistically significant in ages (p=0.024), weight (p=0.038), follow-up time (p<0.001), creatinine level (p=0.012), creatinine clearance (p=0.008), left ventricle ejection fraction (p<0.001), dimension of left atrium (p=0.001), coronary artery disease (p<0.001), previous myocardial infarction (p<0.001), previous percutaneous coronary intervention (p=0.001), previous coronary artery bypass grafting (p=0.043), heart failure (p<0.001), cardio-ablation (p=0.022). CHA2DS2-VASc and HAS-BLED scores were statistically significantly higher in the VKA group (p<0.001). In NOAC users, the frequency of the paroxysmal type of arrhythmias was statistically significantly higher than in VKA users (p<0.001), while in VKA users the permanent type of AF/AFL was statistically dominant (p<0.001). VKA patients were taking antiplatelet therapy (aspirin and P2Y12-receptor inhibitors) more than NOAC patients. Other clinical characteristics of patients using NOAs or VKA are summarized in Table 1.

TABLE 1
Characteristics in NOAC and VKA users

Variables	NOAC N=373	VKAN=1028	p-value
Demographics			
Age, years, mean ± SD	63.5± 12.3	65.0 ± 11.1	0.024
Weight, kg, mean ± SD	87.9± 17.1	85.7 ± 17.0	0.038
BMI, kg/m2, mean ± SD	28.7 ± 12.5	28.4 ± 10.8	0.658
Follow-up time, months	18 ± 14.2	24.5 ± 11.8	<0.001
Medical history			
Hypertension, n (%)	271 (72.7)	794 (77.2)	0.076
Hypercholesterolemia, n (%)	145 (38.9)	435 (42.3)	0.248
Diabetes mellitus, n (%)	73 (19.6)	237 (23.1)	0.165
Previous bleeding, n (%)	19 (5.1)	41 (4.0)	0.366
Peptic ulcer disease, n (%)	13 (3.5)	48 (4.7)	0.337
Creatinine level (μmol/L)	96.5 ± 29.5	102.6 ± 43	0.012
CrCl, ml/min, mean ± SD	89.1 ± 33.6	85.8± 53.6	0.008*
LVEF, %, mean ± SD	53.8 ± 13.7	50.3 ± 4.3	<0.001
LA, cm, mean ± SD	4.7 ± 3.8	4.6 ± 2.1	0.001

Previous stroke, n (%)	32 (8.6)	98 (9.5)	0.586
Coronary artery disease, n (%)	60 (16.1)	337 (32.8)	<0.001
Previous myocardial infarction, n (%)	38 (10.2)	221 (21.5)	<0.001
Previous PCI, n (%)	37 (9.9)	173 (16.8)	0.001
Previous CABG, n (%)	12 (3.2)	61 (5.9)	0.043
Peripherial vascular disease, n (%)	10 (2.7)	39 (3.8)	0.316
Heart failure, n (%)	87 (23.3)	360 (35.1)	<0.001
Cardioablation, n (%)	146 (39.1)	335 (32.6)	0.022
Cardioversion, n (%)	45(12.1)	135 (13.1)	0.598
CHA2DS2-VASc, mean ± SD	2.4 ± 1.6	2.8 ± 1.7	<0.001
HAS-BLED, mean ± SD	0.9 ± 1.0	1.2 ± 1.0	<0.001
Type of AF/AFL			
Paroxysmal, n (%)	199 (53.5)	417 (41.1)	<0.001
Persistent, n (%)	105 (28.2)	289 (28.5)	0.928
Permanent, n (%)	67 (18.0)	307 (30.2)	<0.001
Medication use			
ASA, n (%)	69 (18.5)	353 (34.4)	<0.001
P2Y12-receptor inhibitors, n (%)	26 (7.0)	111 (10.8)	0.033
Amiodaron, n (%)	162 (43.4)	422 (41.1)	0.44
Digoxin, n (%)	18 (4.8)	77 (7.5)	0.079
Verapamil, n (%)	11 (2.9)	46 (4.5)	0.2
Propafenone, n (%)	81 (21.8)	140 (13.6)	<0.001
Flecainid, n (%)	1 (0.3)	4 (0.4)	1
ACE inhibitors, n (%)	190 (50.9)	633 (61.6)	<0.001
Angiotensin II receptor antagonist, n (%)	45 (12.1)	110 (10.7)	0.476
Statins, n (%)	158 (42.4)	495 (48.2)	0.053
Nitrates, n (%)	19 (5.1)	138 (13.4)	<0.001
Diuretics, n (%)	182 (48.8)	613 (59.7)	<0.001
Antiulcer agents, n (%)	161 (43.2)	437 (42.6)	0.838
Insulin, n (%)	12 (3.2)	52 (5.1)	0.144
Metformin, n (%)	37 (9.9)	154 (15.0)	0.014*
Sulfonylureas, n (%)	11 (2.9)	50 (4.9)	0.12
Other diabetes drugs, n (%)	6 (1.7)	19 (1.9)	0.214

Thromboembolic events

For ischaemic stroke or systemic embolism, no significant differences were evident between NOAC and VKA users. On the other hand, in the VKA group, there were two times more fatal outcomes than in the NOAC group (p=0.002). Also, combined endpoint (stroke-systemic embolism-death) was statistically higher in the VKA group (p=0.039). The difference in the frequency of myocardial infarction was not statistically significant between these two groups (p=0,130), although 13 VKA users had myocardial infarction versus one patient in the NOAC group.

Bleeding events

There was a statistically significant difference in the rate of "total bleeding" (NOAC group: 7.6%, VKA group: 17.2%, p<0.001). Also, in the NOAC group, there was a statistically lower rate of epistaxis (p=0.003) and hematoma (p<0.001). There were no differences in other types of bleeding: intracranial bleeding (p=0.564), gastrointestinal bleeding (p=0.271), hematuria (p=0.120), bleeding with severe anemia (p=0.717), intraocular bleeding (p=0.372).

Univariate and multivariate analysis for stroke, thromboembolism and death In univariate analyses, we investigated the differences in parameters between the group with the events (stroke, thromboembolism and death) and the control group. A statistical difference existed in the ages, creatinine level, hypertension, diabetes mellitus, coronary artery disease, previous myocardial infarction, coronary artery bypass grafting (CABG), peripheral vascular disease, heart failure, cardio-ablation, cardioversion, new-onset AF/AFL, persistent and permanent AF/AFL, NOAC and follow-up time (Table 2).

TABLE 2
Univariate analysis for stroke, thromboembolism and death

Variables	Univariate analysis		
	Cases (stroke, thromboembolism, death)	Controls	p-value
Age, years, mean ± SD	69.7 ± 11	63.5 ± 11.3	<0.001**
Male gender, n (%)	182 (73.4)	803 (69.6)	0.251
Creatinine, (μmol/L), mean ± SD	113.6 ± 50.9	98.3 ± 36.6	<0.001**
CrCl, ml/min, mean ± SD	79.6 ± 32.2	87.5 ± 50.1	0.096
Hypertension, n (%)	209 (84.3)	856 (74.2)	0.001*
Diabetes mellitus, n (%)	76 (30.6)	234 (20.3)	<0.001**
Coronary artery disease, n (%)	108 (43.5)	289 (25.1)	<0.001**
Myocardial infarction, n (%)	84 (33.9)	175 (15.2)	<0.001**
PCI, n (%)	39 (15.7)	171 (14.8)	0.72
CABG, n (%)	24 (9.7)	49 (4.2)	<0.001**
Peripheral vascular disease, n (%)	23 (9.3)	26 (2.3)	<0.001**
Heart failure, n (%)	117 (47.4)	330 (28.6)	<0.001**
Previous bleeding, n (%)	16 (6.5)	44 (3.8)	0.063
Peptic ulcer disease, n (%)	13 (5.2)	48 (4.2)	0.45
LA, cm, mean ± SD	4.74 ± 0.77	4.61 ± 2.93	0.501
Cardioablation, n (%)	48 (19.4)	433 (37.6)	<0.001**
Cardioversion, n (%)	11 (4.4)	169 (14.7)	<0.001**
New onset AF/AFL, n (%)	40 (16.4)	113 (9.9)	0.003*
Paroxysmal, n (%)	95 (39.3)	521 (45.5)	0.087
Persistent, n (%)	40 (16.5)	354 (30.9)	<0.001**
Permanent, n (%)	106 (43.8)	268 (23.4)	<0.001**
NOAC, n (%)	53 (21.4)	320 (27.8)	0.040*
Follow-up time, months, mean ± SD	25.0 ± 11.6	22.3 ±13.0	0.003*

Smoking, n (%)			
Yes	92 (37.2)	426 (36.9)	0.058
No	106 (42.9)	563 (48.8)	
Former smoker	49 (19.8)	164 (14.2)	

The multivariate logistic regression model was performed to analyze the independent contribution of each factor in the development of stroke, thromboembolism and death. Results further demonstrated that ages (OR 1.036, 95% CI 1.019-1.053, p<0.001), myocardial infarction (OR 1.937, 95% CI 1.172-3.202, p=0.010), peripheral vascular disease (OR 2.698, 95% CI 1.420-5.129, p=0.002), heart failure (OR 1.505, 95% CI 1.064-2.128, p=0.021), cardioversion (OR 0.376, 95% CI 0.180-0.783, p=0.009), permanent AF/AFL (OR 1.541, 95% CI 1.040-2.285, p=0.031) and follow-up time (OR 1.016, 95% CI 1.004-1.028, p=0.008) were the independent risk factors of these events (Table 3).

TABLE 3
Predictors of stroke, thromboembolism or death during follow up: multivariate logistic regression

Variables	B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
					Lower	Upper
Age	0.035	0.008	<0.001	1.036	1.019	1.053
Creatinine	0.003	0.002	0.129	1.003	0.999	1.006
Hypertension	0.168	0.213	0.432	1.183	0.779	1.796
Diabetes mellitus	0.13	0.175	0.459	1.139	0.807	1.606
Coronary artery disease	-0.382	0.253	0.13	0.682	0.416	1.12
Myocardial infarction	0.661	0.256	0.010	1.937	1.172	3.202
CABG	0.269	0.306	0.379	1.309	0.719	2.383
Peripherial vascular disease	0.993	0.328	0.002	2.698	1.42	5.129
Heart failure	0.409	0.177	0.021	1.505	1.064	2.128
Cardioablation	-0.397	0.217	0.068	0.673	0.439	1.03
Cardioversion	-0.979	0.375	0.009	0.376	0.18	0.783
New onset AF/AFL	0.141	0.257	0.584	1.151	0.696	1.905
Persistent AF/AFL	0.179	0.24	0.456	1.196	0.747	1.913
Permanent AF/AFL	0.433	0.201	0.031	1.541	1.04	2.285
NOAC	0.037	0.188	0.846	1.037	0.717	1.501
Follow-up time	0.016	0.006	0.008	1.016	1.004	1.028

Univariate and multivariate analysis for bleeding

In the further analysis, univariate analyses revealed that age, female gender, creatinine level, creatinine clearance, hypertension, hypercholesterolemia, previous myocardial infarction, coronary artery disease, percutaneous coronary intervention (PCI), previous bleeding, peptic ulcer, radioablation, persistent and permanent AF/AFL, acetylsalicylic acid (ASA), P2Y12 receptor inhibitors (clopidogrel or ticagrelor) VKA and NOAC were risk factors of bleeding events (Table 4).

TABLE 4
Univariate analysis for bleeding

Variables	Univariate analysis		
	Cases (bleeding)	Controls	p-value
Age, years, mean ± SD	65.5 ± 10.9	63.7 ± 11.3	0.047*
Female gender, n (%)	70 (37.4)	299 (28.9)	0.019*
Creatinine, (μmol/L), mean ± SD	105.4 ± 44.0	97.6 ± 32.7	0.022*
CrCl, ml/min, mean ± SD	78.9 ± 35.0	88.1 ± 50.6	0.019*
Hypertension, n (%)	153 (81.8)	768 (74.2)	0.027*
Hypercholesterolemia, n (%)	94 (50.3)	423 (40.9)	0.017*
Diabetes mellitus, n (%)	41 (21.9)	216 (20.9)	0.744
Myocardial infarction, n (%)	44 (23.5)	149 (14.4)	0.002*
Coronary artery disease, n (%)	66 (35.3)	253 (24.4)	0.002*
Peripheral vascular disease, n (%)	8 (4.3)	30 (2.9)	0.317
Heart failure, n (%)	64 (34.2)	286 (27.6)	0.067
PCI, n (%)	46 (24.6)	137 (13.2)	<0.001**
CABG, n (%)	13 (7.0)	49 (4.7)	0.203
Previous bleeding, n (%)	13 (7.0)	39 (3.8)	0.047*
Peptic ulcer, n (%)	15 (8.0)	38 (3.7)	0.007*
LA, cm, mean ± SD	5.06 ± 4.74	4.53 ± 2.35	0.163
Radioablation, n (%)	53 (28.3)	401 (38.7)	0.007*
Paroxysmal AF/AFL, n (%)	85 (45.5)	461 (44.8)	0.869
Persistent AF/AFL, n (%)	45 (24.1)	330 (32.1)	0.031*
Permanent AF/AFL, n (%)	56 (29.9)	236 (22.9)	0.039*
ASA, n (%)	65 (34.8)	275 (26.6)	0.022*
P2Y12-receptor inhibitors, n (%)	31 (16.6)	83 (8.0)	<0.001**
NOAC, n (%)	27 (14.4)	316 (30.5)	<0.001**
Smoking, n (%)			
Yes	68 (36.4)	391 (37.8)	0.518
No	87 (46.5)	500 (48.3)	
Former smoker	31 (17.1)	144 (13.9)	

The multivariate regression analysis identified female gender (OR 0.607, 95% CI 0.413-0.891, p=0.011), creatinine level (OR 1.005, 95% CI 1.000-1.010, p=0.045), percutaneous coronary intervention (OR 2.009, 95% CI 1.045-3.863, p=0.039) and NOAC (OR 0.392, 95% CI 0.252-0.609, p<0.001) as independent risk factors related to bleeding events (Table 5).

TABLE 5
Predictors of bleeding during follow up: multivariate logistic regression

Variables	B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
					Lower	Upper
Age, years	-0.006	0.01	0.597	0.995	0.974	1.015
Female gender	-0.5	0.196	0.011**	0.607	0.413	0.891

Creatinine	0.005	0.003	0.044**	1.005	1	1.01
CrCl	-0.001	0.003	0.642	0.999	0.992	1.005
Hypertension	0.077	0.231	0.738	1.08	0.687	1.699
Hypercholesterolemia	0.268	0.179	0.134	1.308	0.921	1.858
Myocardial infarction	0.254	0.289	0.381	1.289	0.731	2.273
Coronary artery disease	-0.369	0.373	0.322	0.691	0.333	1.436
PCI	0.698	0.333	0.036 **	2.009	1.045	3.863
Previous bleeding	0.532	0.415	0.2	1.702	0.755	3.837
Peptic ulcer	0.462	0.395	0.242	1.587	0.732	3.44
Radioablation	-0.232	0.204	0.256	0.793	0.532	1.183
Persistent	-0.169	0.209	0.419	0.844	0.56	1.272
Permanent	0.06	0.213	0.778	1.062	0.699	1.614
ASA	-0.264	0.298	0.374	0.768	0.428	1.376
P2Y12-receptor inhibitors	0.38	0.314	0.226	1.463	0.79	2.708
NOAC	-0.937	0.225	<0.001**	0.392	0.252	0.609

DISCUSSION

Atrial fibrillation is the most common sustained arrhythmia that is associated with significant morbidity and mortality. Atrial flutter is similar to atrial fibrillation and often degenerates into atrial fibrillation [24]. There is little evidence regarding thromboembolic risk factors in AFL patients. In current clinical practice, the risk estimation is carried out using score CHA2DS2-VASc, which mostly included patients with AF [25].

Effective stroke prevention in non-valvular AF and atrial flutter patients has the potential to not only reduce stroke-related deaths but also prevent stroke-related disability, which imposes an enormous burden on patients, their social environment and health insurance system [26].

This study explored the characteristics of non-valvular AF and AFL patients who were treated with NOAC compared to those treated with VKA. AF/AFL patients treated with VKA are usually older, with lower body weight, worse renal function and a lower dimension of a left atrium and lower left ventricular ejection fraction. The frequency of coronary artery disease, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting was twice as high in the VKA group than in the NOAC group. Also, the frequency of heart failure was higher in patients treated with VKA. Cardio-ablation was a procedure that was performed more in patients treated with NOAC. CHA2DS2-VASc and HAS-BLED scores were statistically higher in the VKA group. In randomized trials, CHA2DS2-VASc score in NOAC groups was only higher in ROCKET-AF trial (CHA2DS2-VASc in rivaroxaban group was 3.5), while in two other trails CHA2DS2-VASc score in patients treated with dabigatran or apixaban was lower than in our study (CHA2DS2-VASc: 2.1).

The efficacy of novel oral anticoagulants has been well established in clinical trials, so the goal of many registers is to assess how these drugs performed under usual clinical conditions in real-world populations. The questions can be answered only by observational studies [27].

All prescribed NOAC in Serbia are not reimbursed and many of our patients have financial difficulties to buy them. Because of that, most of our patients are on VKA treatment (73.4%). Dabigatran was the first NOAC that appeared on the market, so during 2014 and 2015 it was prescribed in most patients, rivaroxaban came as the second and the last NOAC introduced was apixaban, which also became frequently used NOAC because of the results of the ARISTOTLE clinical trial.

For ischaemic stroke only, no significant differences were evident between NOAC and VKA. However, for the combined endpoint of ischaemic stroke-systemic embolism-death, NOAC were associated with a statistically significant lower rate than VKA. In the big observational study, conducted by Larsen et al [28], the combined endpoint of ischaemic stroke, systemic embolism or death displayed lower relative risks for all NOAC compared to VKA. In our study, mortality risk was lower in patients treated with NOAC compared to VKA. A meta-analysis of NOAC trials found a 10% reduction in all-cause mortality with standard dose NOAC compared to VKA. Mortality was borderline significant for dabigatran 150 mg twice daily [28].

In our study, the rate of myocardial infarction was higher in the VKA group compared with the NOAC group although not statistically significant. In the RE-LY study, the rate of myocardial infarction was higher in the dabigatran group. Our results are in contrast to the conclusion that VKA have a cardioprotective effect but they are in line with the results of Graham 's findings [29]. In an observational study conducted by and in a meta-analysis conducted by Loffredo it has been published that the anti-Xa NOAC may increase the risk of myocardial infarction. A recent study, conducted by Patti et al, showed that protection from cardiovascular events was more prominent with the NOAC [30].

The most devastating complication of VKA therapy is intracranial hemorrhage (ICH), especially hemorrhagic stroke. Among our patients, only three patients had ICH and no one in the NOAC group. In general, the reduction of ICH is the most important advantage of all NOAC compared with VKA and mostly with dabigatran. In RE-LY, independent predictors of ICH were concomitant aspirin use, age and previous stroke or transient ischemic attack. Our results might reflect a smaller number of patients, a smaller number of events and a shorter follow-up time.

There was a statistically significant difference in the rate of "total bleeding". Also, in the NOAC group, there was a statistically significant lower rate of epistaxis and hematoma. In RE-LY study the rate of major bleeding was lower in patients treated with dabigatran compared with warfarin, but the rate of gastrointestinal bleeding was higher in dabigatran 150 mg group. In ROCKET-AF study there was more gastrointestinal bleeding in the rivaroxaban group compared with the warfarin group. In our study, there were no differences between the NOAC and VKA groups in gastrointestinal bleeding. Maybe the reason for this could be due to a proper patient and dosage selection. The usage of apixaban is associated with a lower rate of gastrointestinal bleeding compared to warfarin .

Predictors of stroke, thromboembolism and death in our study were older ages, previous myocardial infarction, peripheral vascular disease, heart failure, cardioversion, permanent AF/AFL and longer follow up time.

Hohnloser et al, showed that the risk of thromboembolic events was similar in patients with paroxysmal AF and those with sustained arrhythmia [34]. In contrast, a recent meta-analysis conducted by Ganesan et al, reported that there was a higher rate of stroke/systemic embolism in patients with sustained AF compared to patients with paroxysmal. Also, sustained AF was independently associated with a higher rate of stroke/systemic embolism in the study based on a Fushimi AF Registry. In our study, patients with a permanent type of arrhythmia had 1.5 times higher risk of thromboembolic events.

Advanced age, heart failure and vascular disease (previous myocardial infarction, peripheral vascular disease) are widely recognized as risk factors for stroke in patients with AF, including in the CHA2DS2-VASc score. Increased age is one of the strongest independent predictors of thromboembolic events in patients with AF, accounting for a 1.5-fold increase in the relative risk of stroke for every additional decade. Our results showed that with each increasing age, increases the risk of thromboembolic events in 3.6%. Patients who had heart failure had 1.5 times higher risk for these events. Also, in our study, patients who had a peripheral vascular disease had 2.7 times higher risk of thromboembolic events. In contrast, diabetes mellitus and hypertension, which are commonly listed as risk factors for any ischemic stroke in AF patients,

weren't found to be significant risk factors for these events. The study of Yasuda et al confirmed the same result. Our patients with myocardial infarction had almost two times higher risk of stroke, thromboembolism or death. The longer follow-up time is, the more likely to occur a thromboembolic event.

Despite the prompt restoration of sinus rhythm with cardioversion, the risk of stroke/systemic embolism remains over time because of the atrial stunning phenomenon with local hypocontractility in the left atrium (mostly in the left atrial appendage) even after the restoration of sinus rhythm. Additionally, the DC shock is able to damage myocardial cells, increasing the prothrombotic milieu as in the Virchow's triad. In contrast, our results showed that the risk of thromboembolic events was 2.66 times lower in patients who were undergoing cardioversion.

Independent predictors of bleeding events in this study were female gender, a higher level of creatinine, percutaneous coronary intervention and NOAC. The higher level of creatinine is associated with worsening of renal function. Abnormal renal function is a component of HAS-BLED score. PCI procedures are associated with the use of dual antiplatelet therapy which increases the risk of bleeding complications. In this study, we had patients who were treated with VKA or NOAC with antithrombotic therapy (aspirin and P2Y12 inhibitors) which increase the risk of hemorrhage. Patients who had some PCI procedure had two times higher risk of bleeding. Duration of triple therapy should depend on risks for stroke, bleeding and thrombosis. Also, our results showed that gender had an influence on bleeding events. Female had 1.64 higher risk of bleeding. Usage of NOAC was related to a statistically significant reduction of bleeding ($p<0.001$). In this study, patients who were using NOAC had 2.55 times lower risk of hemorrhage. In contrast, hypertension, previous bleeding, previous peptic ulcer, previous myocardial infarction, advanced ages, type of arrhythmia were not found to be significant risk factors for these events.

The discontinuation rates of NOAC in the major clinical trials were in the range of 21-25%, of which patient's decisions accounted for 8-10% of the total treated population. Recent studies suggest that VKA is discontinued at much higher rates in community practice than in clinical trials resulting in an increased risk of thromboembolic stroke.

In our study, the incidence of patient's decisions to discontinue treatment was 2.6%. For 1.1% of patients, the reason for discontinuation was unknown and 2.9% changed NOAC to VKA often due to financial reasons. In most patients, discontinuation of anticoagulants was after cardioablation and cardioversion and it was a cardiologist decision (16%). Only 3.2% of our population changed VKA to NOAC mainly due to difficulty maintaining a therapeutic INR. 3.3% of all patients in our study discontinued anticoagulant therapy due to bleeding events. In a recent study, O'Brien et al. found that fewer than 4% of patients had VKA discontinued after a nuisance bleeding in routine practice. In high risk patients, bleeding events are often the reason for discontinuation.

Limitations of this study

Our study had several limitations. Short follow-up and a small number of patients were the main limitations. Also, this was the experience of one single center although the biggest one in our country. Other registers included many more patients based on national databases. Despite this fact, we have a good experience with anticoagulant therapy in different profiles of patients. All NOAC in Serbia are not reimbursed and many patients can't afford them, consequently, more patients are on VKA treatment. Although most countries reimburse costs of NOAC, our goal was to explore characteristics of AF and ALF in one that does not reimburse them.

This study was observational. Phone follow-up was performed to collect data about bleeding and thromboembolic events. It is possible that some events were not reported. We included patients treated with both doses of all NOAC. In most registers, investigators excluded patients treated with a reduced dosage of NOAC.

We included patients with atrial flutter. Most of the registers included only patients with non-valvular atrial fibrillation. AFL and AF generally coexist and may also share similar pathophysiological mechanisms. Patients with AFL also take vitamin K antagonists or NOAC in the prevention of stroke and thromboembolic events.

We did not exclude patients with prior experience of oral anticoagulants. In a large meta-analysis of the pivotal trials of NOAC versus VKA, the benefit of NOAC seemed to be consistent regardless of prior anticoagulation experience.

CONCLUSION

This single-center, cross-sectional study, found that NOAC are an effective and safe alternative to VKA in clinical care settings. We can also conclude that we prescribe NOAC according to Prescribing Information to appropriate patients, taking into consideration patients ages, comorbidities, renal function and risk of bleeding.

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DISCLOSURES

The authors declare no potential conflict of interests..

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