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Efficacy and safety of anticoagulant treatment for non-valvular atrial fibrillation in multimorbid patients

Objective	Assessment of the safety and efficacy of anticoagulant treatment in patients with nonvalvular atrial fibrillation (AF) in a multimorbidity setting.
Materials and Methods	The cross-sectional study included 104 patients diagnosed with nonvalvular AF and followed in the medical facilities of Yekaterinburg. The subjects were interviewed, anthropometric measurements were made, and the risk of thromboembolic complications was evaluated using the CHA_2DS_2-VASc score. The Charlson multimorbidity index was calculated, and patients were divided into two groups: Group 1 with a low level of multimorbidity (not more than 5 points) and Group 2 with a high level of multimorbidity (6 points or more). The data are presented as a median and interquartile range (25%; 75%).
Results	The study population included 40 males and 64 females. The median age was 71 (62.5; 80) years. The level of multimorbidity was estimated as 5 (3; 6) points. Group 1 included 64 patients, and Group 2 included 40 patients. Thirty-nine percent of the sample patients had a paroxysmal form of AF, 10% had a persistent form, and 51% had permanent AF. The group of patients with a high level of multimorbidity included more patients with permanent AF and fewer patients with paroxysmal AF as compared with a moderate level of multimorbidity ($p<0.01$). Anticoagulant treatment was indicated for 92 (88.5%) patients. It was administered to 70.7% of patients; 29.3% did not receive it. Among patients receiving anticoagulants, warfarin was administered to 18.5%, and new oral anticoagulants (NOACs) were administered to 81.5%. Complications were reported in 15.2% of anticoagulant treatment cases. Bleeding was reported in 21.7% of cases of warfarin administration and 12.5% of cases of NOAC treatment ($p=0.32$). The median number of risk factors for bleeding per patient was 5 (4; 5.5). The Charlson index and the total number of risk factors are significantly correlated ($R=0.37$, $p<0.05$).
Conclusion	In real-world clinical practice in Ekaterinburg, Russia, 7 of 10 patients with AF for whom anticoagulant treatment was indicated actually received it; NOACs are prescribed four times more often than warfarin. With a higher level of multimorbidity, the risk of bleeding under the pressure of anticoagulant treatment increases; thus, NOACs should be preferred over warfarin for treatment of multimorbid patients.

Keywords	Atrial fibrillation; anticoagulants; multimorbidity; comorbidity; pharmacotherapy; bleeding
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Introduction

Despite the published results of large, multicenter, randomized clinical trials of the use of anticoagulant drugs to prevent embolic complications in patients with atrial fibrillation (AF) (ROCKET-AF [1 –], ARISTOTLE [2], RE-LY [3], ACTIVE-W [4], AVERROES [5]), current practice makes it necessary to monitor the efficacy and safety of anticoagulant treatment. A fair number of both foreign and national registers of patients with AF has been created in recent years [6–11]. In real-world clinical practice, patients are mostly multimorbid and receiving therapy with multiple drugs simultaneously, which can significantly affect the efficacy, tolerability, and safety of the recommended treatment [12].

Objective

Estimate efficacy and safety of anticoagulant treatment in patients with nonvalvular AF, considering their multimorbidity.

Materials and Methods

The cross-sectional study included 104 patients with nonvalvular AF. The diagnosis of nonvalvular AF and signed informed consent to participate in the study

were the inclusion criteria. A valvular form of AF (mitral stenosis or a mitral valve prosthesis) was the exclusion criterion. The study was carried out in the medical facilities of Ekaterinburg, Russia, from June 1 to November 1, 2018. The local ethical committee of Ural State Medical University approved the study.

The patients were interviewed using a specially developed questionnaire. Indications for anticoagulant treatment were determined using the clinical risk score for thromboembolic complications in AF, CHA_2DS_2-VASc [13]. Anthropometry, blood pressure (BP), and heart rate were measured. The results of laboratory and instrumental examinations were obtained from the patients' medical records (inpatient and outpatient). The following conditions were taken into account: arterial hypertension, coronary artery disease, chronic heart failure (including without congestion phenomena, verified earlier by documented medical data, and ultrasound study of the heart in case of high pro-BNP or BNP levels), acute cerebrovascular accident, transient ischemic attack, pulmonary embolism, obesity, chronic kidney disease, osteoarthritis, gastroduodenal ulcer, hepatitis, liver cirrhosis, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, and cancer.

The Charlson index was calculated from the obtained data [14, 15]. Because it is difficult to interpret the pathogenetic relationship between diseases identified in the outpatient setting, the term multimorbidity was adopted to indicate the presence of multiple diseases in one patient. Patients with an index value between 0 and 5 were assigned to the group of moderate multimorbidity (Group 1); those having an index value of 6 and above corresponded to high multimorbidity (Group 2).

The indirect sign of the efficacy of anticoagulant treatment was the frequency of its administration in eligible patients (CHA_2DS_2-VASc score ≥2 points for males and ≥3 points for females) [13], the achievement of the target levels of international normalized ratio (INR) (2.0–3.0) for patients taking warfarin [13], and the rational choices of doses for patients treated with NOACs (nonvitamin-K-dependent oral anticoagulants).

The safety of anticoagulant treatment was assessed by the respective rates of bleeding associated with administration of the different types of anticoagulants. The history of hemorrhagic events of any location (intracranial, gastrointestinal, hemorrhoidal, nasal, gingival, scleral, ecchymoses) was considered. The risk factors for hemorrhagic complications were identified in all patients [13].

Statistical data analysis was carried out using Statistica 12.0. A median and interquartile range (25%; 75%) was used to describe the data. The differences between sample values were verified using the Mann-Whitney test, the differences of relative values were tested using the Fisher's exact test, and the Pearson chi-squared test. Correlation between signs was evaluated using the Spearman correlation coefficient. Differences and correlations were statistically significant when the level of confidence probability of $p<0.05$ was reached.

Results

The study population included 40 males and 64 females (Table 1). Comorbidities are characterized in Table 2.

The group of moderate multimorbidity (Group 1) included 64 subjects, and the high multimorbidity group (Group 2) included 40 subjects. Most patients were at high risk of systemic thromboembolism, which increased with a higher level of multimorbidity. Group 1 patients had a mean of 4 (3; 5) risk factors for cardioembolic stroke, and Group 2 patients had a mean of 5 (5; 7) risk factors, according to the CHA_2DS_2-VASc score ($p<0.01$).

The median serum levels of glucose and cholesterol in the sample were abnormally increased. Type 2 diabetes was diagnosed in every third patient. A significant portion of patients was overweight, and every third patient was obese.

Hypertension is the most significant risk factor for the development AF: it was diagnosed in 90% of patients. The median values of systolic and diastolic blood pressure were within the target level (below 140/90 mmHg).

Table 1. General characteristics of the study population

Parameter	Value, median (25%; 75%)
Age in years	71 (62.5; 80)*
Body mass index, kg/m^2	28.7 (25.7; 31.8)
Systolic blood pressure, mmHg	130 (120; 140)
Diastolic blood pressure, mmHg	80 (72; 85)
Heart rate, bpm	72 (65; 80)
CHA_2DS_2-VASc	5 (3; 6)
Charlson index	5 (3; 6)
Glucose, mmol/L	5.6 (5.1; 6.6)
Aspartate transaminase, U/L	24.7 (19; 31)
Alanine transaminase, U/L	24 (17.5; 31)
Creatinine, μmol/L	90.3 (82; 104)
GFR (CKD-EPI), mL/min/1.73m^2	61.3 (45.8; 73.8)
Creatinine clearance (Cockcroft-Gault equation), mL/min	71.2 (58.3; 92.5)
Hemoglobin, g/L	132.5 (121; 143)
Platelets, 109/L	214 (192; 245)

*– 30 (28.8%) patients were under 65 years old, 29 (27.9%) patients were 65–74 years old, and 45 (43.3%) patients were 75 years old or older. GFR, glomeruler filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

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Table 2. Incidence of comorbidities

Disease	Yield, number of patients (%)
Hypertension	92 (88.5)
Type 2 diabetes	33 (31.7)
Stable angina	36 (34.6)
History of acute coronary syndrome	24 (23.1)
History of myocardial infarction	10 (9.6)
History of unstable angina	14 (13.5)
Chronic heart failure	82 (78.8)
History of acute ischemic cerebrovascular accident	20 (19.2)
History of transient ischemic attack	8 (7.7)
History of acute hemorrhagic cerebrovascular accident	1 (1.0)
History of pulmonary embolism	1 (1.0%)
Obesity (body mass index ≥30.0 kg/m^2)	39 (37.9)
Decreased glomerular filtration rate <90 mL/min/1.73m^2	85 of 93 patients with known GFR value (91.4)
Chronic hepatitis	8 (7.7)
Liver cirrhosis	0 (0.0)
Ulcer disease, exacerbation	2 (1.9)
History of ulcer disease	13 (12.5)
Gastric erosion at the time of examination	1 (1.0)
History of gastric erosion	13 (12.5)
Gastrointestinal bleeding	6 (5.8)
Bronchial asthma	12 (11.5)
Chronic obstructive pulmonary disease	10 (9.6)
Osteoarthritis	46 (44.2)
Rheumatoid arthritis	5 (4.8)
Back pain	44 (42.3)
Breast cancer	4 (3.8)
Colon cancer	3 (2.9)
Kidney cancer	5 (4.8)
Other oncological diseases	3 (2.9)

GFR, glomeruler filtration rate.

One-quarter of all patients had suffered an acute coronary syndrome. Stable exertional angina was detected in one-third of patients.

One-fifth of all patients examined had suffered an ischemic stroke. The vast majority of patients (80%) had clinical signs and symptoms of chronic heart failure (CHF). 90% had renal dysfunction of varying severity. The median glomerular filtration rate (GFR) and creatinine clearance levels were abnormally decreased.

The median values of hepatic transaminase activity, hemoglobin level, and platelet count were within normal limits.

Thirty-nine percent of patients had the paroxysmal form of AF, 10% had persistent AF, and 51% had permanent AF. The group of patients with high multimorbidity included significantly more patients with permanent AF and fewer patients with paroxysmal AF than did the moderate multimorbidity group ($p<0.01$) (Figure 1).

Structural analysis of anticoagulant treatment

Anticoagulant treatment was indicated for 92 (88.5%) patients (CHA_2DS_2-VASc score 3 points and above in females and 2 or above in males). Of these, 65 (70.7%) patients received anticoagulant treatment, and 27 (29.3%) did not. Figure 2 demonstrates the number of patients who received various anticoagulants. The administration of warfarin versus NOACs was 1:4.4. Of the 27 patients who did not receive the indicated anticoagulant treatment, six patients had previously received it and discontinued. AF was newly diagnosed in five patients, and the anticoagulant treatment had not been yet initiated. Thirteen patients had never been administered anticoagulant treatment. For 16 of 27 (59.3%) patients who did not receive anticoagulant treatment during the study, antiplatelet treatment was administered instead.

The ratio of the administration of various types of anticoagulants did not differ in patients with different levels of multimorbidity ($p>0.05$) (Figure 3).

Of the 12 patients treated with warfarin, only one patient controlled INR monthly, 10 patients did it less frequently, and one patient did not monitor it at all. The median INR value in patients treated with warfarin was 2.17 (1.32; 2.54). At the time of examination, five patients had INR within the target range, INR was below 2.00 in three patients, and INR could not be determined according to the medical records of four patients.

Eleven patients had previously received warfarin, which had been discontinued due to the failure to monitor INR or bleeding. In eight of these patients, NOACs were chosen as an alternative, and three patients did not resume treatment.

Safety analysis of anticoagulant treatment

Complications were reported in 12 of 79 (15.2%) cases of anticoagulant treatment. Bleeding was reported in 5 of 23 (21.7%) cases of warfarin administration and in 7 of 56 (12.5%) cases of NOAC treatment (the difference is insignificant, $p=0.32$).

The rate of bleeding complications did not differ (warfarin vs. NOAC administration) in the groups of moderate multimorbidity (warfarin – 2 of 13 [15.4%], NOACs – 3 of 30 [10.0%] cases of anticoagulant treatment) and high multimorbidity (warfarin – 3 of 10

[30.0%], NOACs – 4 of 26 [15.4%] cases of anticoagulant treatment) (p>0.05).

No significant differences in the rate of bleeding with warfarin versus NOAC treatment were detected. In the group of moderate multimorbidity, the relative risk of warfarin versus NOACs is 1.6 (95% confidence interval: 0.2–11.2, p>0.05; in the high multimorbidity group, the relative risk of warfarin versus NOACs is 2.4 (95% confidence interval: 0.4–13.2; p>0.05).

The incidence of individual risk factors [13] in the examined sample of patients is provided in Table 3.

The median total number of risk factors for bleeding per patient of the total sample was 5 (4; 5.5). In the group of moderate multimorbidity it was 4.5 (3; 5), and in the high multimorbidity group it was 5 (4; 6); the difference is statistically significant (p=0.02). The Charlson index and the total number of risk factors are significantly correlated (R=0.37, p<0.05).

The presence of hypertension is considered a modifiable risk factor for the development of bleeding in anticoagulant treatment, specifically when BP is not uncontrolled and systolic BP is more than 160 mmHg [13]. In the examined sample, virtually all patients were diagnosed with hypertension. Target BP values (below140/90 mmHg) were achieved in 58 of 92 (63.0%) patients for whom anticoagulant treatment was indicated, without any significant differences between the groups of moderate (61.5%) and high (65.0%) multimorbidity (p>0.05).

Administration of antiplatelet and nonsteroidal anti-inflammatory drugs was more frequent in Group 2 versus Group 1, but the differences were not significant.

Renal dysfunction is a multimodal risk factor for bleeding in anticoagulant treatment. Decreased GRF, less than 90 mL/min/L.73m^2, was detected in 90% of patients examined. The Charlson index was negatively correlated with the GFR (R= –0.54, p<0.05). Figure 4 shows the distribution of the frequency of various GRF categories according to level of multimorbidity. Notably, the distribution of GRF categories in highly multimorbid patients is significantly shifted toward progressive renal lesions (p=0.02).

If a patient has several risk factors, the NOAC dose should be adjusted. According to the instruction for the use of Pradaxa© (dabigatran etexilate), the dose should be reduced from 150 mg bid to 110 mg bid in patients aged 80 years and older.

Xarelto® (rivaroxaban) should be administered at a dose of 15 mg instead of 20 mg once a day in patients with moderate renal function (creatinine clearance <50 mL/min). Eliquis® (apixaban) requires dose reduction from 5 mg to 2.5 mg bid if a patient has at least two risk

Figure 1. Forms of atrial fibrillation in the sample patients

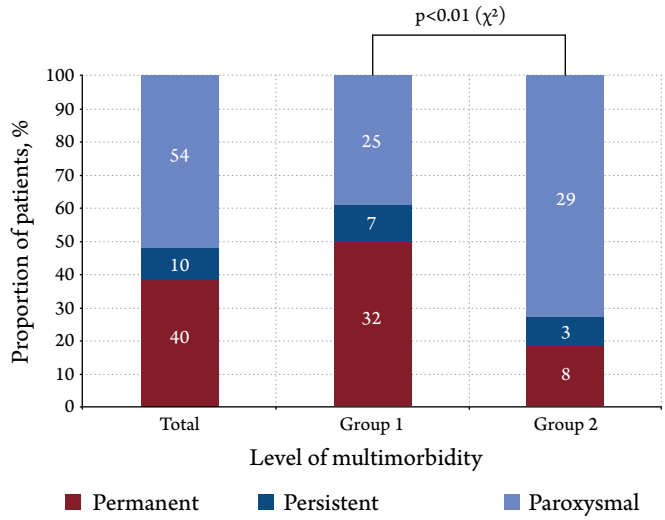

Figure 2. Anticoagulants administered by patients

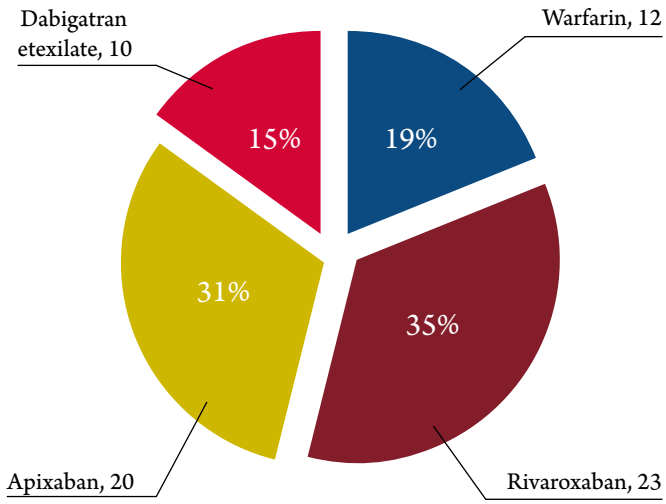

Figure 3. Rate of administration of different types of anticoagulants

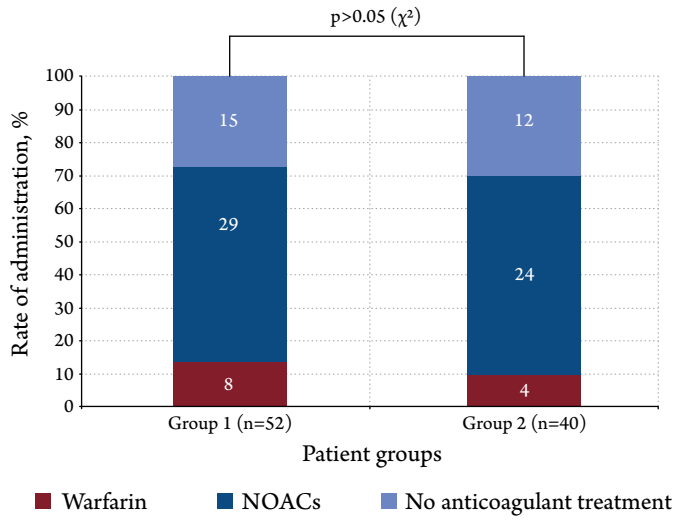

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Figure 4. GFR categories according to level of multimorbidity

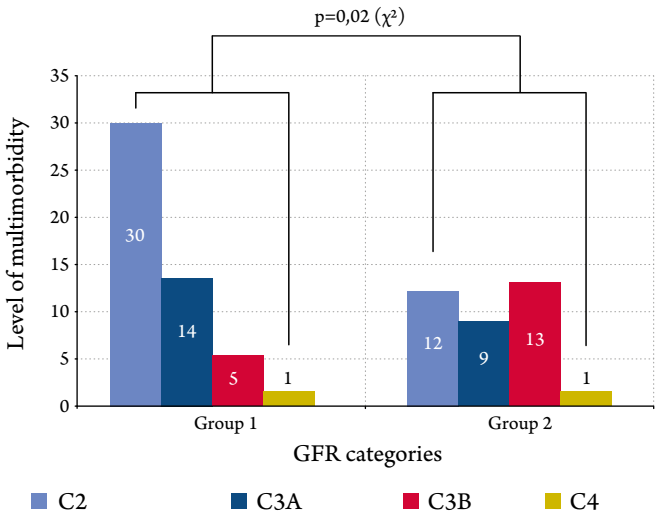

Table 3. Rate of risk factors for bleeding in anticoagulant treatment [13]

Risk factors	Rate of detection		
	All patients for whom anticoagulant treatment was indicated, n=92	Group 1, n=52	Group 2, n=40
1. Modifiable			
Hypertension	96.7%	96.2%	97.5%
Antiplatelet drugs	41.3%	34.6%	50.0%
Nonsteroidal anti-inflammatory drugs	45.7%	36.5%	57.5%
More than 8 units of alcohol a week	8.9%	13.7%	2.6%
Gastrointestinal ulcers or erosion	21.7%	15.4%	30.0%
2. Potentially modifiable			
Anemia	27.2%	28.8%	25.0%
Decreased GFR <90 mL/min/1.73m²	98.6%	95.7%	100.0%
Liver dysfunction	1.1%	1.9%	0.0%
Thrombocytopenia	15.2%	11.5%	20.0%
3. Nonmodifiable			
65 years old and older	80.4%	71.2%	92.5%*
History of massive bleeding (ulcer bleeding, hemorrhagic stroke)	5.4%	7.7%	2.5%
Liver cirrhosis	0.0%	0.0%	0.0%
Malignancies	17.4%	7.7%	30.0%

* – significant difference in the rate of risk factor between groups of moderate and high multimorbidity (p<0.05, two-tailed Fisher's exact test).

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factors of three: age of 80 years or older, weight of 60 kg or less, serum creatinine levels 133 μmol/L or higher.

In general, 32 of 92 (36.4%) patients for whom anticoagulant treatment was indicated needed dose correction. With a higher level of multimorbidity, the number of patients in need of NOAC dose adjustment increased significantly: 12 of 64 (18.8%) moderately multimorbid patients and 24 of 40 (60.0%) highly multimorbid patients ($p<0.01$).

The appropriate dosing schedule of NOAC was chosen for 31 (58.5%) patients, the incorrect schedule was used for 20 (37.7%) patients, and we failed to evaluate the appropriateness of NOAC dosing in two patients (3.8%) due to lack of data on creatinine clearance. Notably, the dose was unreasonably low in 18 (90.0%) patients and unreasonably high in 2 patients. The mean of 4 of 10 patients received an inappropriate dose of NOAC.

Discussion

A majority of patients observed in the outpatient facilities in Ekaterinburg have the permanent form of AF (51%), slightly fewer number have paroxysmal AF (39%), and fewer yet have the persistent form (10%). Similar data were obtained in the analysis of data from the REKVAZA-FP register based on data from medical facilities in several cities: in Yaroslavl, the permanent form of AF was detected in 65.6% of cases, paroxysmal AF in 30.2% of cases, and persistent AF in 4.2% of cases [6]; in Kursk, the permanent form of AF was identified in 51.3% of cases, paroxysmal AF in 12.8%, and persistent AF in 35.8% [10]. A completely different situation is observed in the global registers, where the paroxysmal form of AF is most prevalent. Specifically, in the population of patients included in the GLORIA-AF register, it occurs in 53.4% of cases, in the GARFIELD register population it occcurs in 71.3%, which can be associated with specific inclusion criteria. The analyses of the GLORIA-AF and GARFIELD registers included only patients who had been diagnosed with AF not earlier than 3 months and 6 weeks, respectively, before the initial facility visit.

If there is a high risk of thromboembolic complications, anticoagulant treatment is indicated in all cases of AF regardless of the chosen strategy of patient management (rhythm or heart rate control) [16]. Despite strong evidence of the benefits of NOAC in the prevention of cardioembolic complications over warfarin [16], the situation of inadequate dosing, early discontinuation, or withholding the treatment is still common. The main reasons cited are hemorrhagic complications, alleged high risk of bleeding, and inconvenient monitoring of coagulation profile [13].

According to different registers, the real-world rates of administration of anticoagulant treatment vary. The 2014 analysis of the REKVAA-FP (Ryazan) showed that only 4.2% of patients with AF received the indicated anticoagulant treatment; a similar proportion (4.3%) of patients was receiving it as noted in the Omsk regional register for 2013 [7]. At the same time, the multicenter trial GLORIA-AF, for which enrollment was completed in 2014, showed quite a different value of 88.4% for the Russian population [9]. This discrepancy might be due to the peculiarities of patient management in different regions of the Russian Federation. Moreover, most centers that include patients in the GLORIA-AF register were localized in large medical facilities and academic clinical centers, a factor that alienates this study from real-world clinical practice. A retrospective analysis of data obtained in the clinical hospital of I.M. Sechenov First Moscow State Medical University, Moscow, Russia, showed that anticoagulant treatment was administered to 61% of patients with AF who needed to prevent thromboembolic complications (2015) [7]. The data in the REKVAA-PF register (Kursk) for 2014 showed that the rate of anticoagulant treatment did not exceed 33.2% [10].

This study included patients followed by the medical facilities of Ekaterinburg, Russia, in 2018. A high rate of administration of anticoagulant treatment (70.7%), considerably higher than that found in the data from various registers, was observed. The difference may be due to the progressive changes in approach to assigning anticoagulant treatment as compared with 2014–2015. In 2007–2008, all patients with AF for whom anticoagulant treatment was indicated received warfarin [17]. Pradaxa® was approved in 2009, and Xarelto© and Eliquis© in 2012. In 2014 and 2015, recommendations for the administration of anticoagulant treatment differed significantly [18]; in 2015, the rate of NOAC administration increased dramatically. In 2016, new clinical recommendations from the European Society of Cardiology for the treatment of patients with AF were published, which supported the safety and efficacy of NOACs.

NOACs are preferable oral anticoagulants for patients with AF with no contraindications rather than indirect anticoagulants (recommendation class I, evidence level A) [13]. Based on the meta-analysis of large multicenter randomized clinical trials, it was concluded that NOACs are safer than warfarin and at least as effective [19, 20].

This analysis showed the rate of NOAC administration at 81.5%, and that of warfarin at 18.5%, which is in line with the clinical recommendations [13]. There was no association between the number of comorbid conditions and the ratio of the rate of administration of direct and indirect anticoagulants.

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Warfarin treatment is effective and safe only if the target level of INR for most patients of 2.0–3.0 is achieved and maintained for not less than 65% of the time of monitoring. According to the general REEKVAA register for 2012–2013, the target level of INR was achieved only in 26.3–39.5% of cases [21]. In this analysis, 5 (41.7%) of 8 patients taking warfarin with the known value of INR achieved the target level; the median INR was 2.17 and was within the therapeutic range.

Patient adherence to treatment with warfarin also represents a challenge. According to the instructions for the use of the warfarin brand Nycomed©, it is best to control INR levels at least once a month. Of 12 patients taking warfarin, only one person controlled the INR levels as often as recommended. Other patients did it much less frequently or did not do it at all. The lack of adequate monitoring of INR significantly increases the risk of complications of anticoagulant treatment [13]. Warfarin is also known for an extremely high potential for drug and food interaction [6]. This explains why, in some cases, treatment with warfarin involves a higher risk of bleeding than treatment with NOACs.

A significant proportion of patients followed in real-world clinical practice are highly multimorbid. Given the challenges of the treatment with warfarin and increased risk of bleeding with higher levels of multimorbidity, it is reasonable to prefer the administration of NOACs. Moreover, the high risk of complications of anticoagulant treatment is not a contraindication for its administration but requires careful analysis and close clinical monitoring of patients. However, NOACs must be administered at correct doses. Irrational administration of partial doses of anticoagulant treatment makes it impossible to compare the results of real-world prevention of repeated events with clinical trial findings. In this study, wrong doses were chosen for 37.7% of patients taking NOACs: doses were unreasonably low in 90% of cases and high in 1 case.

These results point to the high relevance of continuous training of primary care physicians on the correct administration and dosing of NOACs.

Conclusion

1. In real-world clinical practice in Ekaterinburg, Russia70% with AF for whom anticoagulant treatment is indicated actually receive it; NOACs are prescribed four times more often than warfarin.
2. With a higher level of multimorbidity, the risk of bleeding under the pressure of anticoagulant treatment increases, which is why choosing treatment with NOACs rather than warfarin is reasonable if there are no contraindications.
3. It is essential to work with first-contact physicians to increase the number of patients who receive appropriate doses of NOACs.

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