

Analysis of antithrombotic therapy in elderly patients with nonvalvular atrial fibrillation in the Kyrgyz Republic and ways to increase treatment adherence

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Abstract

Aim. To analyze anticoagulant therapy in elderly patients with non-valvular atrial fibrillation and ways to increase adherence in the work of a specialized team.

Methods. The study followed 250 patients with non-valvular atrial fibrillation aged 65 to 74 years (mean age 70.7±4.39 years). The patients were divided into three groups: the first group included 105 people, who were prescribed warfarin in a retrospective study; the second group — 57 people treated with rivaroxaban, and the third group — 88 people treated with warfarin. The second and third groups were prospective study groups which were supervised by a specialized team of physicians. The groups were matched on sex and age, comorbidities. Statistical data analysis and mathematical processing were performed by using the methods of descriptive and variational statistics. Most parameters reported as absolute values and percentages, while quantitative data — the 25th and 75th percentiles.

Results. All patients included in the study had a high risk of developing thromboembolic complications by their CHA₂DS₂-VASc score (≥2) and a low risk of developing hemorrhagic complications on the HAS-BLED scale (average score 1.49±0.04). They were prescribed anticoagulant therapy. By the end of the year follow-up from the start of anticoagulant therapy, only 9.5% of patients were treatment adherent, in the second group — 43.8%, in the third group — 70.5% of patients. The reason for refusing to take warfarin in the vast majority of cases was the inability to control the international normalized ratio, medical contraindications, and the high cost of the drug in prescribing rivaroxaban. The results showed that the majority of patients with atrial fibrillation (90.5%) receive inadequate antithrombotic therapy in routine outpatient clinical practice. At the same time, in a very small number of patients (9.5%) receiving warfarin, this type of therapy can be considered adequate (60% or more of the stay time in the therapeutic range of international normalized ratio of 2.0 to 3.0).

Conclusion. Anticoagulant therapy prescription under the supervision of a specialized team contributes to a significant improvement in treatment adherence (from 43.8 to 70.5%); promising in the future is the use of drugs from the group of new oral anticoagulants that do not require routine monitoring of coagulogram.

Keywords: geriatrics, elderly, atrial fibrillation, anticoagulant therapy, warfarin, adherence to treatment.

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Background. Atrial fibrillation (AF) is the most common arrhythmia in older people, with a prevalence of 1%–2% in western populations. In Kyrgyzstan, the prevalence of pathology has not been studied. The number of patients with AF worldwide is expected to increase 2.5-fold over the next 50 years in an aging population [1]. According to the updated recommendation of the European Society of Cardiology, AF is designated as a polymorbid and continuously developing syndrome; its

treatment strategy is based on a comprehensive assessment of the patient, including the risk of stroke, presence and severity of symptoms, and assessment of structural heart disease and comorbidity [2].

Studies have forecasted a rapid increase in the number of patients with AF in the coming decades [3, 4]. Cardioembolic stroke is the most severe complication of AF, and it is associated with a doubling of mortality and an increased risk of disability compared with stroke not associated with AF [5].

Thus, long-term prevention of stroke in patients with AF is considered the most important area of treatment. The standard therapy for the prevention of AF-related stroke is the continuous administration of anticoagulants [1, 6], and its effectiveness is currently undeniable.

The prescription of oral anticoagulants and achievement of appropriate adherence to treatment in patients with AF in the Kyrgyz Republic remains an unresolved problem. A recent study of 377 patients with nonvalvular AF showed that proper anticoagulant therapy was prescribed only in 43% of the patients, and adequate anticoagulation after 1 year was achieved only in 12.2% of the patients [7].

In this regard, it appears very relevant to conduct a further objective assessment of anticoagulant therapy in patients with AF and to search for ways to increase their adherence to treatment.

This study aimed to analyze anticoagulant therapy in older patients with AF of nonvalvular etiology and to find ways to increase adherence under the supervision of a specialized team.

Materials and methods. This noninterventional retrospective and prospective study involved 250 patients with nonvalvular AF who were living in the Chui region of the Kyrgyz Republic.

The inclusion criteria of the study were as follows:

- Patients aged 65–74 years
- Presence of nonvalvular etiology in patients with AF
- Indications for the appointment of anticoagulant therapy (according to the CHA₂DS₂-VASc scale¹ ≥ 1 point)
- Provision of consent to participate in the study (signed informed voluntary consent)

Patients who did not meet all the inclusion criteria were excluded.

The retrospective part of the study included the analysis of outpatient medical records of 105 patients with nonvalvular AF, aged 65–74 (mean age, 70.4 ± 8.92) years, who were prescribed warfarin from 2017 to 2020 in the Chui region. These patients constituted the first study group.

The prospective part of the study included 145 patients with nonvalvular AF, also aged 65–74 (mean age, 68.7 ± 6.82) years, who, depending on the type of anticoagulant taken, were assigned to the second and third groups.

– The second group was composed of 57 patients (average age, 69.1 ± 5.73 years) who were prescribed with the new oral anticoagulant rivaroxaban.

– The third group consisted of 88 people (average age, 71.8 ± 4.35 years) who were prescribed with warfarin.

The study was conducted in the City Clinical Hospital No. 1, where the Department of Hospital Therapy of the Kyrgyz State Medical Academy was named after I.K. Akhunbaeva.

Both groups were managed by a specialized team, which was created from the staff of the department and consisted of doctors (therapist, cardiologist, and hematologist), a laboratory assistant, and a nurse. The team's intervention to the patients was limited to timely adjustment of the warfarin dose and, if necessary, to timely examination and hospitalization, and they provided the patient with the necessary information about the lifestyle features associated with taking several drugs and all hemorrhagic complications. During the observation period, each patient had contacted their doctor by phone at least six times and received answers to all their questions.

The study was approved by the local committee on bioethics of the Kyrgyz State Medical Academy named after I.K. Akhunbaev (Minutes No. 6 of December 11, 2017).

In patients taking warfarin, the time spent by the international normalized ratio (INR) in the therapeutic window from 2.0 to 3.0 was calculated — the target level. Among patients with poorly controlled condition, a survey was conducted to determine the reasons for their irregular visits to the doctor and control the INR values.

To screen patients' adherence to the drug in all study groups, we performed the Morisky–Green test [8], which included the following three questions: Does the patient miss a drug intake if he feels good or bad? Did the patient forget to take his/her medication? Was the patient attentive to the recommended time of taking the medication? For each question, the participant was asked to choose a positive or a negative answer (yes/no). Each negative answer was scored 1 point. Patients who scored 4 points were considered adherent to therapy, 1–2 points as not adherent to treatment, and 3 points as insufficiently adherent, with the risk of moving to the group not adhering to treatment.

Statistical analysis of the data and mathematical processing were performed using Microsoft Excel, Statistica Excel, and Statistica 8.0. Descriptive and variation statistics methods were also used. Most parameters are presented as absolute numbers and percentages. Quantitative data are presented as median and 25th and 75th percentiles. Frequencies were compared using the z-test (site http://vassarstats.net/propdiff_ind.html). The Mann–Whitney U test was used to assess the sig-

¹ CHA₂DS₂-VASc: scale for assessing the risk of stroke in patients with atrial fibrillation.

Table 1. Clinical and demographic characteristics of the patients with atrial fibrillation (n = 250) treated with different anticoagulant drugs

Patient's characteristics	Value			Significance of differences between groups		
	First group, warfarin (retrospective study)	Second group, rivaroxaban	Third group, warfarin	P ₁₋₂	P ₂₋₃	P ₁₋₃
Total	105	57	88	0.005	0.005	0.005
Mean age, years	70 (65; 81)	69 (65; 79)	71 (65; 83)	0.25	0.32	0.41
Male, n (%)	31 (29.5)	18 (31.6)	27 (30.7)	0.37	0.47	0.72
Female, n (%)	74 (70.5)	39 (68.4)	61 (69.3)	0.18	0.22	0.19
Arterial hypertension, n (%)	69 (65.7)	39 (68.4)	60 (68.1)	0.43	0.039	0.032
CHD, n (%)	51 (48.6)	29 (50.8)	41 (46.6)	0.044	0.031	0.58
Including myocardial infarction in history, n (%)	19 (18.0)	9 (15.8)	17 (19.3)	0.18	0.27	0.62
Diabetes mellitus types 1 and 2, n (%)	21 (20.0)	17 (29.8)	15 (17.0)	0.015	0.026	0.020
Acute cerebrovascular accident, n (%)	15 (14.2)	9 (15.8)	11 (12.5)	0.27	0.033	0.19
Chronic heart failure, n (%)	14 (13.3)	8 (14.0)	7 (7.9)	0.19	0.23	0.037
Chronic kidney disease, n (%)	6 (5.7)	–	1 (1.1)	0.031	0.17	0.029
Bleeding risk according to HAS-BLED scale (mean value)	1.4	1.3	1.4	0.24	0.33	0.18
TEC risk according to CHA2DS2-VASc scale (mean value)	3.7	3.8	3.9	0.34	0.37	0.25

Note: p₁₋₂, significance of the differences between the first and second groups; p₂₋₃, significance of differences between the second and third groups; p₁₋₃, significance of differences between the first and third groups (Mann–Whitney test). Ischemic heart disease; TEC, thromboembolic complications; HAS-BLED, hypertension, abnormal renal-liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (65 years), drugs or alcohol concomitantly, a scale for assessing bleeding risk; CHA2DS2-VASc is a scale for assessing the risk of stroke in patients with atrial fibrillation.

nificance of the differences. Considering the effect of multiple comparisons, the Bonferroni correction was introduced. Differences were considered significant at $p < 0.05$.

Results and discussion. In this study, the groups were comparable by age and sex ($p > 0.05$). Among patients with AF of nonvalvular etiology, comorbidities identified are presented in Table 1.

All patients had a high risk of TEC on the CHA2DS2-VASc scale ≥ 2 and a low risk of hemorrhagic complications (mean 1.49 ± 0.04 on the HAS-BLED scale), that is, they had direct indications for anticoagulant therapy.

According to the review by Rodriguez et al. (2013), adherence to treatment with vitamin K antagonists varied from 42% to 78% in different studies [9]. According to the large registry of patients with AF (ORBIT-AF), 10% of the patients taking warfarin stopped this drug after 1 year [10]. In the present study, in the first group of patients who were prescribed warfarin, 43.8% refused to take

warfarin after 3 months, 74.3% after 6 months, 82.9% after 9 months, and 90.5% after 1 year. This means that in the actual clinical practice of a family medicine doctor, only 9.5% of the patients remain adherent to anticoagulant therapy.

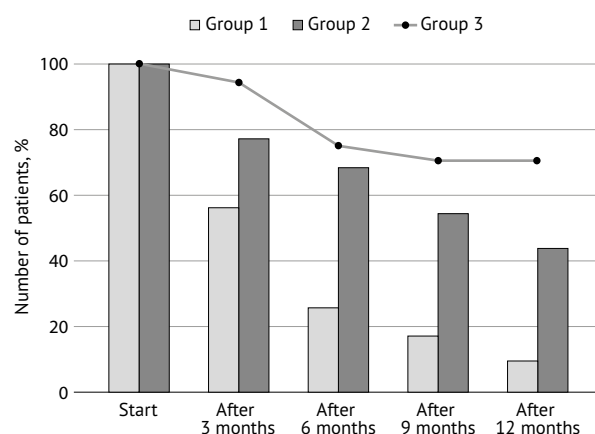
However, the situation is different when anticoagulant therapy was prescribed under the supervision of a specialized team of doctors. If, according to the findings of observational studies, adherence to oral anticoagulants after 1 year varied from 38% to 99.7% [11], it was 43.8% after 12 months in the second group (rivaroxaban group). However, during the observation period, the number of patients who were adherent to the oral anticoagulant therapy also tended to significantly decrease (Fig. 1).

Promising results were obtained in the third group, where patients took warfarin and were always under the supervision of a team of specialists. After the observation period, 70.5% of the patients remained adherent, which is significant-

Table 2. Results of the assessment using the Morisky–Green scale in the comparison groups at 12 months after the start of therapy

Questions of the Morisky–Green scale	Values			Significance of differences between groups		
	First group, warfarin (retrospective study) (n = 55)	Second group, rivaroxaban (n = 57)	Third group, warfarin (n = 57)	P ₁₋₂	P ₂₋₃	P ₁₋₃
Forget to take medications, n (%)	47 (85.5)	29 (50.9)	27 (47.3)	0.003	0.411	0.003
Attentive to the hours of taking the drug, n (%)	13 (23.6)	28 (49.1)	30 (52.6)	0.002	0.372	0.002
Skipped medications if they were feeling well, n (%)	39 (70.9)	9 (15.8)	7 (12.3)	0.001	0.257	0.001
Missed medication, n (%)	43 (78.2)	6 (10.5)	9 (15.8)	0.0001	0.182	0.0001

Note: p₁₋₂, significance of the differences between the first and second groups; p₂₋₃, significance of differences between the second and third groups; p₂₋₃, significance of differences between the first and third groups (Mann–Whitney test)

**Fig. 1.** Dynamics of the number of patients in the study groups adhering to oral anticoagulant therapy during 12 months of follow-up

ly high compared with those of the first ($p < 0.001$) and second ($p < 0.032$) groups.

According to the literature, frequent reasons for discontinuation of treatment were directly related to the doctor's preference (47.7%), patient refusal (21.1%), and bleeding while taking the drug (20.2%) [10].

In the first group, the reason for refusing to take warfarin was the impossibility of controlling the INR (41.0%), doctor's fear of bleeding (33.3%), and drug withdrawal during bleeding (16.2%). Among the reasons for refusal to prescribe the drug were medical contraindications, such as anemia, impaired renal function, exacerbation of gastric ulcer, and drug intolerance, in 21 (8.3%) patients.

In the second group, 56.2% of the patients refused rivaroxaban because of its high cost. However, these patients, on the recommendation of the

specialized team and with their consent, switched to cheaper warfarin, and they still continue anticoagulant therapy to date.

In the third group, 29.5% of the patients refused warfarin because it was impossible to control the INR.

Treatment adherence can also be influenced by therapy duration as confirmed by the UK General Practice Research Database. Thus, their results revealed a 1-year adherence rate of 70% [11]. In the present study, the 1-year adherence rate in the first group was 9.5%, while in the third group, which was under the supervision of a specialized team, it was 70% ($p < 0.001$).

According to a survey using the Morisky–Green scale (Table 2), the adherence rate of the patients in the first group to warfarin treatment was low, since patients did not adhere to the treatment regimen: 85.5% of the patients forgot to take the prescribed drug, 76.4% did not comply with the time of admission, 70.9% missed the drug if they felt well, and 78.2% did not take the drug at all.

The results of the analysis in the second and third groups were significantly better ($p < 0.003$) than those in the first group. This means that under the supervision of a specialized team, patients were more disciplined and adherent to treatment. Thus, 50.9% and 47.3% of the patients in the second and third groups forgot to take the prescribed drug, respectively (85.5% in the first group, $p < 0.003$), 49.1% and 52.6% were attentive to the hours of admission (23.6% in the first group, $p < 0.002$), 15.8% and 12.3% missed the drug if they felt well (70.9% in the first group, $p < 0.001$), and 10.5% and 15.8% did not take the drug at all (78.2% in the first group, $p < 0.0001$).

The low compliance in the first group was also reported in the Russian study by Eliseeva and Garina (2014) [12]. In their study using the Morisky–Green compliance scale, 81% of the patients with AF were not adherent to therapy (they forgot to take the drug, were inattentive to the hours of admission, and missed the drug if they felt well) [12].

In the present study, the analysis of the calculation of the INR time showed that 90.5% of the patients in the first group received warfarin and the INR indicator was in the therapeutic range for <60% of the time (in the remaining 9.5%, the INR indicator was in the therapeutic range for >60% of the time), which, according to generally accepted concepts, may indicate the ineffectiveness and/or unsafe use of the anticoagulant therapy. In the third group of patients who took warfarin under the supervision of a specialized team, the therapeutic range of INR was >60% of the time, and the INR value was maintained within the target values of 2.0–3.0 ($p < 0.002$).

Regarding hemorrhagic events, complications of therapy, such as bleeding, were recorded in 16.2% of the patients in the first group, 8.7% in the second group ($p < 0.01$, for differences with the first group), and 4.5% in the third group ($p < 0.003$, for differences with the first and second groups). During the observation period, feasibility studies were noted in only two patients of the first group, and feasibility studies were not detected in the second and third groups, which is most likely due to the short follow-up period in our study.

Studies have confirmed the efficacy and good safety profile of rivaroxaban, which demonstrates that patients had significantly higher rates of adherence to rivaroxaban treatment than to warfarin. Thus, the XANTUS study confirmed a high adherence to rivaroxaban therapy. The high rates of the constancy of therapy and satisfaction with the treatment were noted in 80% of the patients who continued to take the drug for 1 year, of which 75% of the patients were satisfied or very satisfied with the treatment [13]. The prospective Dresden registry (1204 patients with AF) revealed that more than 78% of the patients continue to take rivaroxaban after 2 years of therapy [14]. In the present study, patients who were taking rivaroxaban also expressed satisfaction with the treatment; all refusal cases were related to the high cost of the drug.

CONCLUSIONS

1. The majority of the patients with AF (90.5%) in the routine clinical practice of outpatient admission in the Kyrgyz Republic receive inadequate

antithrombotic therapy. Moreover, in 9.5% of the patients taking warfarin, warfarin therapy can be considered adequate ($\geq 60\%$ of the time spent in the therapeutic range of the INR –2.0 to 3.0).

2. Prescription of anticoagulant therapy under the supervision of a specialized team improves adherence to treatment in 25 (43.8%) of the 57 patients in the second group ($p < 0.002$ for differences with the first and third groups) and 62 (70.5%) of the 88 patients in the third group ($p < 0.001$ for differences with the first and second groups).

3. The use of new oral anticoagulants that do not require routine monitoring of coagulogram parameters is promising.

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