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COMPARATIVE CHARACTERISTICS OF ANTICOAGULANTS AT ATRIAL FIBRILLATION IN COMORBID PATIENTS

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Abstract: Patients with Chronic Kidney Disease (CKD) develop a tendency to bleed and thromboembolism, so the indication for anticoagulants at the attachment of atrial fibrillation (AF) is complex. AF is the most common chronic heart arrhythmia, and thromboembolism and ischemic stroke in particular are the main complications. In recent years, new oral anticoagulants have been developed and they have shown superiority over the classic antivitamin K anticoagulants in preventing the risk of stroke, systemic embolism and bleeding, providing an effective alternative to these resources.
Keywords: chronic kidney disease, atrial fibrillation, new oral anticoagulants, rivaroxaban, warfarin.

In modern craniological practice, atrial fibrillation (AF) is the most common arrhythmia that requires close attention of doctors due to the high risk of thromboembolic complications (TEO). The prevalence of AF in the population is very high and continues to grow [1].

The problem of the prevention of feasibility studies associated with atrial fibrillation remains extremely relevant, as evidenced by the high frequency of strokes, 80% of which are ischemic. Every third patient with a stroke dies, 80% of surviving patients replenish the army of disabled people and only 20% are able to return to work [2, 11]. As you know, ischemic strokes differ in nature. The most common of these is an atherothrombotic stroke (50%). The second place (from 20 to 25%) is occupied by cardioembolic strokes, mainly associated with the formation of blood clots in the cavity of the left atrium with AF. Typically, one in six strokes occurs in a patient with AF [3]. The risk of stroke is present in the patient with both symptomatic and asymptomatic forms of AF. Moreover, it is the same in patients with paroxysmal and persistent AF [4]. That is why, regardless of which tactics of managing a patient with AF will be chosen - restoration of sinus rhythm or control of heart rate, the prevention of thromboembolic events should occupy the first place.

Almost every third patient with AF has either an initial or moderately severe stage of chronic kidney disease - this combination increases the risk of stroke by 1.4 times [5, 9]. The terminal stage of chronic kidney disease is also not uncommon among patients with AF. Approximately 20% of patients with chronic kidney disease in the terminal stage have additional AF [6]. And among patients with AF, about 5% have a decrease in glomerular filtration rate below 15 ml / min, which corresponds to the terminal stage of chronic kidney disease - in these patients, the risk of stroke increases many times, reaching a 5-10-fold increase [7]. The problem of treating patients with comorbidity - a combination of AF and renal failure - is that there are few special clinical studies that would focus on the use of oral anticoagulants for the prevention of strokes and thromboembolic complications in this category of patients.

However, with the combination of AF with CKD, in addition to increasing the frequency of strokes and thromboembolic complications, the frequency of serious bleeding also significantly increases, which makes it difficult to select adequate anticoagulant therapy in this situation [8]. For many years, vitamin K antagonists have been the only representatives of the class of anticoagulants for long-term therapy for AF. Their well-known shortcomings (narrow therapeutic window, the need for frequent laboratory monitoring, numerous interdrug and dietary interactions, the unpredictability of pharmacodynamics and pharmacokinetics in individual patients) contributed to the search for new, more convenient to use drugs [11]. New oral anticoagulants turned out to be easier to use, and according to the results of the main studies, they were not inferior or superior to warfarin in relation to the balance of effectiveness and safety [12]. However, in patients with impaired renal function, they have not been specifically studied. In clinical studies conducted earlier, only patients with mild renal failure participated, and patients with moderate and severe renal failure due to the high risk of hemorrhagic complications were excluded from the studies. The consensus of the Cardiovascular Society of Cardiology and the Society of Nephrologists recently revealed this gap in the treatment of patients with CKD and heart rhythm disturbance. This situation is currently undergoing change

The aim of our study was to study the effects of oral anticoagulants (warfarin and rivaroxaban) on the prevention of complications of AF in patients with CKD and without CKD, and to compare the efficacy and safety of drugs with each other.

Material and methods. The study was conducted at the Republican Specialized Scientific and Practical Medical Center for Therapy and Medical Rehabilitation. A total of 164 patients with AF were included in the study: 82 of them were diagnosed with CKD (1 group of CKD (+)) and 82 patients without CKD (2 group of CKD (-)). Each group, in turn, was divided into two subgroups: a - the subgroup received rivoraxaban, b - the subgroup received warfarin.

Patients were prescribed rivaroxaban at a dose of 20 mg/day once (15 mg/day in individuals with creatinine clearance of 15-49 ml/min) or warfarin under the control of INR.

The mean age of the patients involved was 59.9 ± 7.9 years. The risk of thromboembolic complications was assessed according to the CHA2DS2-VASc scale (*table* 1), the risk of hemorrhagic complications was assessed according to the HAS-BLED scale (*table* 2).

Table 1. CHA2DS2-VASc score for assessing the risk of stroke with atrial fibrillation.

C	(congestive heart failure)	1 p
H	(hypertension)	1 p
A	(age) ≥ 75 years	2 p
D	(diabetes mellitus)	1 p
S2	(stoke)	2 p
V	(Vascular disease)	1 p
A	(Age 65–74 годs)	1 p
Sc	(Sex)	1 p

Maximum: 9 points. Low risk: 0; intermediate risk: 1; high risk ≥2.

Table 2. Bleeding risk assessment: HAS-BLED.

H	(hypertension)	1 point
A	(abnormal renal / liver function)	1 point for each

S	(Stroke)	1 point
B	(Bleeding history or predisposition)	1 point
L	(Labile INR)	1 point
E	(Elderly) ≥ 65 years	1 point
D	(Drugs/alcohol concomitantly)	1 point for each

INR: international normalized ratio.

Patients had a high risk of thromboembolic complications (an average of 4 on the CHA2DS2-VASc scale) and a moderate risk of developing large bleeding (the average HAS-BLED score was 1.3). Of the concomitant pathologies, most often (in 92.7%) there was arterial hypertension (AH), a quarter of patients (28.7%) suffered from type 2 diabetes mellitus (DM). A number of patients had a history of cardiovascular complications (12.2% of patients had previous myocardial infarction (MI), and 17.7% had ischemic stroke or transient ischemic attack (TIA)). As concomitant therapy, most patients received drugs with proven nephroprotective properties: 74.8% - ACE inhibitors / ARBs, 62.2% - statins.

Comparative characteristics of patients with AF of groups 1 and 2 with their a and b subgroups are presented in *table 3*.

Table 3. Comparative characteristics of patients with AF depending on the presence of CKD

Patient Characterization	1a group (n-43)	1b group (n-39)	2a group (n-42)	2b group (n-40)
Women	22(51,2%)	19(48,7%)	21(50,0%)	18(45,0%)
Men	21(48,8%)	20(51,3%)	21(50,0%)	22(55,0%)
Average age, years	61,8±7,83	59,6±8,12	58,0±8,19	60,3±7,58
The average body mass index, kg / m2	29,7±5,23	28,8±4,64	29,4±4,81	29,3±4,69
HAS-BLED Scale, GPA	1,6±0,83	1,5±0,95	1,1±0,85	1,1±0,78
Scale CHA2DS2-VASc, average score	4,3±1,47	4,1±1,48	3,5±1,44	3,7±1,45
GFR (CKD-EPI) medium, ml / min / 1.73 m2	44,1±7,13	47,4±8,18	99,3±10,59	104,7±12,46
Stroke / TIA history	8 (18,6%)	7 (17,9%)	7 (16,7%)	7 (17,5%)
IM history	6 (13,9%)	5 (12,8%)	5 (11,9%)	4 (10,0%)
Diabetes	12 (27,9%)	12 (30,8%)	12 (28,6%)	11 (27,5%)
Arterial hypertension	40 (93,0%)	36 (92,3%)	39 (92,9%)	37 (92,5%)
CHF (PV ≤40%)	4 (9,3%)	3 (7,7%)	3 (7,1%)	3 (7,5%)

Significant differences between the two groups were obtained by the number of points on the CHA2DS2-VASc and HAS-BLED scales (in the 1st group of CKD (+) patients had a greater risk of both thromboembolic and hemorrhagic complications), as well as in terms of renal filtration function (GFR according to CKD-EPI), which is consistent with the characteristics of patients with CKD in the population.

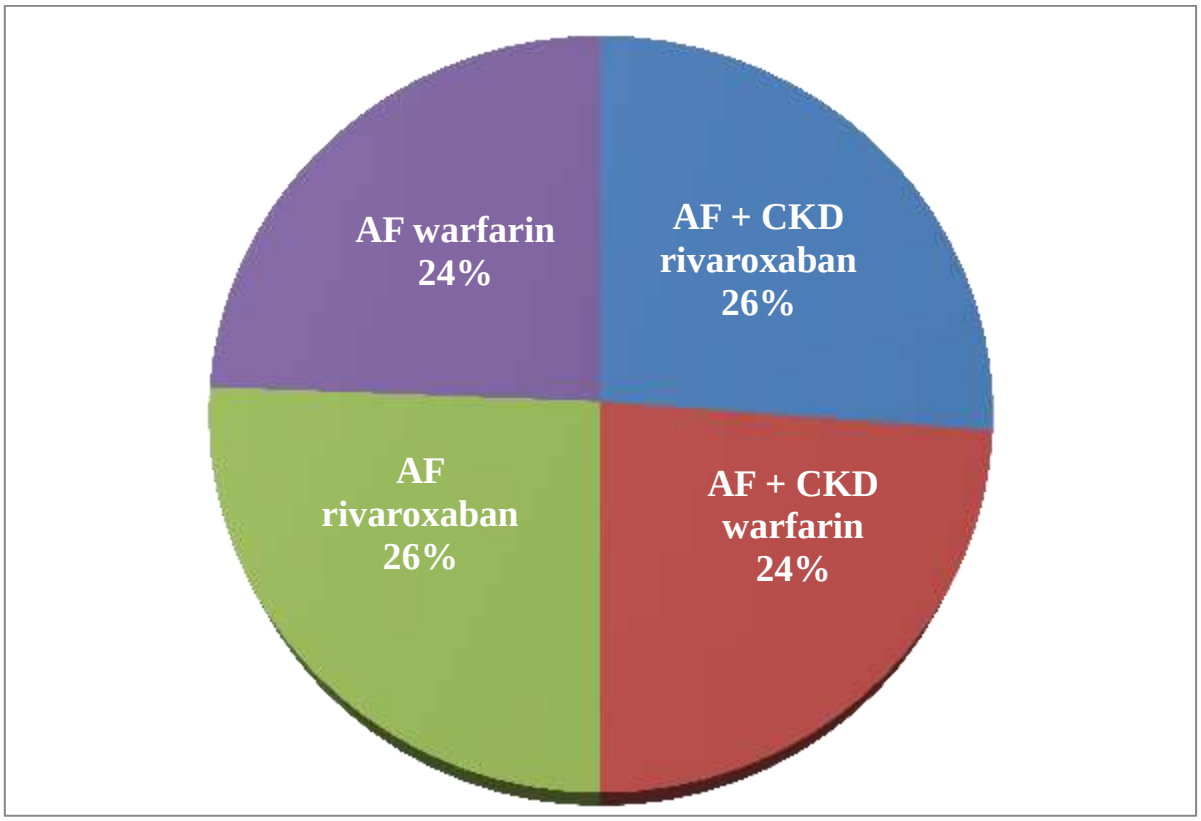
For comorbidity, there were no significant differences between the two groups. For concomitant therapy, significant differences were obtained by the frequency of prescriptions of the blockers of the renin-angiotensin system (ACE inhibitors and ARBs) and β-blockers:

they were significantly more often prescribed to patients with concomitant CKD. For other groups of drugs that are potentially capable of affecting kidney function (calcium channel blockers, proton pump inhibitors, diuretics and statins), no significant differences between the groups were found.

All patients of 4 subgroups during the observation every 3 months during the year assessed the dynamics of renal filtration function, as well as the effectiveness and safety of anticoagulant therapy.

Depending on the anticoagulant taken, patients in the CKD (+) group were divided as follows (*Fig*. 1).

Fig 1. The distribution of patients in groups depending on the presence of CKD and the treatment received



In our study, patients taking warfarin accounted for 48%, and the rest took rivaroxaban 52%.

Table 4 presents patients with AF and CKD, which are distributed in the study according to the stages of CKD.

Table 4. Distribution of patients with AF by stages of CKD

CKD stages	(CKD-EPI)	Number of patients
C2	60-89 ml / min /1,73м^2	23 (28,0%)
C3a	45-59 ml / min /1,73м^2	31 (37,8%)
C3b	30-44 ml / min /1,73м^2	26 (31,7%)
C4	15-29 ml / min / 1,73м^2	2 (2,5)

Our work was dominated by patients with 2-, 3- and 3b-stages of CKD (a total of 92.4% of the total number with AF and CKD). The baseline characteristics of renal filtration function (RFF) in patients with CKD taking rivaroxaban and warfarin did not differ significantly.

Results. The primary combined endpoint was the total frequency of thromboembolic complications (stroke, myocardial infarction and other vascular embolisms). Safety was assessed as a secondary endpoint by the total frequency of large and clinically significant bleedings. The period of observation was 346 days on average.

When analyzing the results of the primary endpoint study among patients with FP and HBP, who were treated with rivaroxaban, the number of thromboembolic events made up 11.62% of cases during the year. Acute cerebral circulation disorders accounted for 4.65% of these cases. And in the 1b group, where patients took a warfarin dose, which depends on the MNO indicators, the frequency of thromboembolic events was 20.49%. Ischemic stroke was found in 5.12% of patients in this group, hemorrhagic stroke in 2.56% of patients.

In patients with FP without renal function impairment thromboembolic complications were much less. It testifies to the fact that renal dysfunction increases the risk of complications in comparison with patients without PBP. Thromboembolic complications were recorded in 9.52% of patients in 2a-group suffering from PF of non-lapatic etiology and being treated with rivaroxaban. And in 2a-group (patients with PE taking warfarin) 12,5% during the year. The incidence of thromboembolic complications is presented in Table 5.

Table 5: Frequency of thromboembolic complications depending on the therapy and kidney function

Thromboembolic events	**1a group**	**1a group**	**Risk ratio, (95% CI) 2a-group**	**2a group**	**2b group**	**Risk Ratio, (95% CI)**	**P**
Primary Endpoint (PET)	3,87	5,10	0,75 (0,57-0,93)	3,17	4,17	0,76 (0,53-0,91)	0,43
vascular emboli	2,32	5,12	0,45 (0,23-0,67)	2,38	2,50	0,95 (0,70-0,98)	0,41
Myocardial infarction	4,65	7,69	0,60 (0,47-0,79)	4,76	5,00	0,95 (0,73-1,14)	0,43
Ischemic stroke	4,65	5,12	0,90 (0,71-1,13)	2,38	5,00	0,47 (0,29-0,76)	0,41
Hemorrhagic stroke	0,0	2,56	0,28 (0,17-0,41)	0,0	0,0	0,0	0,22

Rivaroxaban was significantly more effective than warfarin in preventing acute circulatory disorders and systemic embolisms in analysing all groups according to the intended treatment. But after the drug's cancellation, further observation showed that this advantage was levelled off, indicating the danger of cancelling therapy with new oral anticoagulants.

When assessing the secondary endpoints, it was revealed that the frequency of hemorrhagic complications did not significantly differ between subgroups in the groups themselves. But in the 1st group the number of bleedings was observed more than in the 2nd group (Table 6).

Table 6: Frequency of hemorrhagic complications depending on the therapy and renal function.

Frequency of bleeding	**1a-group**	**1b-group**	**Risk ratio , (95%CI)**	**2a-group**	**2б-group**	**Risk ratio, (95%CI)**	**P**
Secondary endpoint	3,71	5,12	0,72(0,54-0,94)	3,33	4,00	0,83(0,66-1.03)	0,44
Major bleeding	4,65	5,12	0,90(0,72-1,16)	4,76	5,00	0,95(0,71-1,26)	0,48
Reduction of hemoglobin≥2g/dL	4,65	5,12	0,90(0,77-1,08)	2,38	2,50	0,95(0,79-1,22)	0,48
Hemotransfusion	2,32	5,12	0,45(0,37-0,59)	2,38	2,50	0,95(0,79-1,25)	0,41
Clinically relevant	4,65	7,69	0,60(0,47-0,76)	4,76	5,00	0,95(0,65-1,19)	0,44
Fatal bleedings	2,32	5,12	0,45 (0,33-0,61)	2,38	5,00	0,47(0,33-0,61)	0,32
Intracranial hemorrhages	0,00	2,56	0,28 (0,17-0,41)	0,0	0,0	0,0	0,22

The total frequency of types of large bleedings and clinically significant bleedings that were not classified as large differed significantly between both groups (Table 7). However, the frequency of critical, fatal and, most importantly, intracranial bleeding was significantly lower in the group of patients receiving rivaroxaban.

Table 7. Localization of bleeding.

Types of large bleedings	**1a- group**	**1b- group**	**P**	**2a- group**	**2b- group**	**P**
Gastrointestinal .	6,97	7,69	0,47	4,76	5,00	0,48
Intraranial	0,0	2,56	0,22	0,0	0,0	0,0
Macrohematuria	4,65	5,12	0,47	4,76	5,00	0,48
Bleeding associated with non-cardial surgery	2,32	5,12	0,31	2,38	2,50	0,13
Intraarticular	6,97	10.25	0,40	4,76	5,00	0,98
Epistaxis	11,62	15,38	0,43	9,52	12,50	0,43

It is particularly noteworthy that rivaroxaban was significantly more effective and safer than warfarin. This was more often due to difficulty in controlling MOE levels in patients receiving warfarin.

The main limitations of our study are the lack of randomization, the open nature of the study, the short follow-up period and the limited number of patients involved. Therefore, the data obtained on differences between drug groups should be interpreted with caution.

In any case, the role of kidney dysfunction should not be underestimated due to the fact that it is they who often cause difficulties in choosing anticoagulant therapy, and this, in its turn, increases the risks of thromboembolic and hemorrhagic complications of FP, and is also an unfavorable predictor of total mortality in patients with FP.

Conclusion. Research results suggest that patients with FP and HBP have a higher chance of developing thromboembolic complications compared to the population without HBP, as well as a higher risk of various bleedings. In order to prevent thromboembolic complications in patients with creatinine clearance of 30-50 ml/min the use of a new oral anticoagulant (rivaroxabana) is not inferior to warfarin and is safer.

Thus, it can be concluded that rivaroxaban is an effective and safe alternative to warfarin, but unlike the latter, it does not require constant monitoring of coagulation levels and does not require dose selection even in severe patients with kidney dysfunction, low adherence to treatment and have an additional risk of bleeding in the background of anticoagulant therapy.

References.

[1] Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation. Eur Heart J 2016; doi:10.1093/eurheartj/ehw210.
[2] Gorst-Rasmussen A, Lip GYH, Larsen TB. Rivaroxaban versus warfarin and dabigatran in atrial fibrillation: comparative effectiveness and safety in Danish routine care. Pharmacoepid Drug Saf 2016; doi: 10.1002/pds.4034.
[3] Lip GYH, Keshishian A, Kamble S, et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. Thromb Haemost. 2016; 19; 116 (5).
[4] Hernandez I, Zhang Y. Comparing Stroke and Bleeding with Rivaroxaban and Dabigatran in Atrial Fibrillation: Analysis of the US Medicare Part D Data. Am J Cardiovasc Drugs. 2016; Sep 14.
[5] Graham DJ, Reichman ME, Wernecke M, et al. Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation. JAMA Intern Med. 2016 Oct 3. doi: 10.1001/ jamainternmed.2016.5954.
[6] Raccah B.H. et al. Major bleeding and hemorrhagic stroke with direct oral anticoagulants in patients with renal failure: Systematic Review and Meta-Analysis of Randomized Trials. Chest.2016;149(6):1516-24.
[7] Wheeler D.S., Giugliano R.P. and Rangaswami J. Anticoagulation-related Factor XA – Inhibition in RENal patients with Non-valvular Atrial fibrillation - Observational Registry (XARENO). Cited 2019 18/02.
[8] Rivoraxaban vs Warfarin in AF patients with T2D and CKD (RE-ELECT). Cited 2019 18/02.
[9] Bohm M. et al. Changes in renal Function in Patients With Atrial Fibrillation: An Analysis From the RE-LY Trial. J AM Coll Cardiol 2015;65(23):2481-93.
[10] Fumagally S., Said S.A.M., Laroche C., Gabbai D., Marchionni N, Boriani G., Maggioni A.P., Popescu M.I., Rasmussen R.H. et al. Age-Related Differences in Presentation, Treatment, and Outcome of Patients With Atrial Fibrillation in Europe: The EORP-AF General Pilot Registry (EURObservational Research Programme-Atrial Fibrillation). J Am Coll Cardiol EP. 2015;1:326-34.
[11] Abdullaev Sh.S., Igamberdieva R.Sh. The use of new oral anticoagulants for atrial fibrillation in patients with chronic kidney disease. Therapeutic Bulletin of Uzbekistan 2018; 4: 151-155.
[12] Tamayo S, Frank PW, Patel M, Sicignano N, Hopf KP, Fields LE, Sarich T, Wu S, Yannicelli D, Yuan Z. Characterizing major bleeding in patients with nonvalvular atrial fibrillation: a pharmacovigilance study of 27 467 patients taking rivaroxaban. Clin Cardiol 2015;38:63–68.