THROMBOEMBOLIC RISK IN CHRONIC KIDNEY DISEASE AND ATRIAL FIBRILLATION

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Abstract. *The risk of acute cerebrovascular accident and other systemic thromboembolic complications is very high in both atrial fibrillation and chronic kidney disease. However, it is currently unknown to what extent the prognostic value of these risks increases when these two conditions coexist. These risk factors lead to a sharp increase in disability and mortality, posing serious challenges to the healthcare system.*

Key words: *atrial fibrillation, chronic kidney disease, thromboembolic complications, anticoagulant therapy.*

Introduction. In recent years, interest in preventing thromboembolic complications (TEC) among patients with chronic kidney disease (CKD) and atrial fibrillation (AF) has grown. The incidence of transient ischemic attack (TIA), ischemic stroke, cardioembolic complications, and other systemic embolism in patients with AF and CKD has increased, as have the preventive potential of antithrombotic therapy, thanks to the advent of new oral anticoagulants (NOACs) and the development of new clinical guidelines [10, 11].

Chronic kidney disease significantly impacts the pharmacodynamics and pharmacokinetics of various drugs eliminated via the kidneys [1]. This complicates the selection of appropriate antithrombotic therapy. Many patients refuse therapy due to concerns about bleeding. This condition affects the increase in TEC, as a result of which an increase in disability and mortality is observed.

For a long time, vitamin K antagonists (VKAs) remained the drugs of choice for anticoagulant therapy. The use of VKAs has certain limitations: they require constant monitoring of the INR (international normalized ratio), have a narrow therapeutic window, interact with many medications and foods, and others [5].

Another significant problem with long-term warfarin use is the development of warfarin-induced nephropathy. In the general patient population, its incidence is 20.5% [4, 8]. With the development of this nephropathy, if the INR increases by >3, then within a week, plasma creatinine begins to rise above 26.5 μmol/L without obvious signs of hemorrhagic complications [4]. In warfarin-induced nephropathy, the glomerular basement membrane begins to thin or thicken. This in turn can lead to spontaneous massive hematuria.

Thus, given the above-mentioned results of various studies, a more thorough investigation of the use of vitamin K antagonists in patients with stage III CKD combined with AF is required, which prompted the development and search for NOACs.

Currently, an oral anticoagulant, having become the drug of choice, should provide safe yet effective prevention of thromboembolic and hemorrhagic events in patients with AF and moderate and pre-dialysis stages of CKD. NOACs have the best safety profile with the fewest hemorrhagic events [6, 7, 9].

In the ROCKET AF study, the average CHADS2 hemorrhagic complications risk score was 3.5. 62% of patients had a HAS-BLED hemorrhagic complications risk score of more than 3.0. With rivaroxaban treatment, the risk of stroke decreased by 21.0% compared with the VKA group. A high risk of stroke was observed among patients with CKD. Also, one of the subgroups of this study included participants with comorbid conditions such as AF and CKD stage 3b. The study demonstrated that the use of rivaroxaban resulted in fewer fatal bleeding events (odds ratio [OR] 0.39, 95% confidence interval [CI] 0.15-0.99) compared with warfarin with a favorable efficacy profile [5].

The efficacy and safety indicators of NOACs and VKAs were comparable among patients with AF, regardless of age category. The correct selection of antithrombotic therapy drug and its dose can become the key to more effective prevention of hemorrhagic and thromboembolic events among older patients compared to younger ones [2, 3].

Despite numerous positive research results, the correct selection of rivaroxaban dosage for different stages of CKD remains unclear. Concern about the risk of hemorrhagic complications leads to unnecessary reductions in rivaroxaban dosages, which may lead to adverse events and an increased risk of various thromboembolism. Therefore, further research into the correct renal dosage of rivaroxaban depending on CKD stages in combination with AF is a critical issue in both nephrology and cardiology.

The aim of the study is the early prediction of the risk of thromboembolic complications in patients with atrial fibrillation and chronic kidney disease.

Materials and methods. This study was conducted in patients with non-valvular atrial fibrillation and stage III chronic kidney disease who were receiving anticoagulant therapy with the vitamin K antagonist warfarin or the novel oral anticoagulant rivaroxaban. The study was conducted at the Republican Specialized Scientific and Practical Medical Center for Therapy and Medical Rehabilitation.

The study included patients with previously confirmed non-valvular AF based on ECG or Holter ECG monitoring. All patients underwent an analysis of their medical history, complete blood count and urine tests, blood chemistry, creatinine, and blood urea levels. Coagulation tests were performed, and SCF was determined using the CKD-EPI formula. The study included 64 patients with atrial fibrillation and stage III CKD. Anticoagulant therapy with warfarin was received by 45.3% (n = 29) of patients (subgroup a), and rivaroxaban was received by 54.7% (n = 35, subgroup b). Anticoagulant therapy doses were titrated individually. The warfarin dose was adjusted based on INR values. In the stage III CKD group, the rivaroxaban dose was 15 mg once daily.

At the beginning of the study, each patient underwent an assessment of their risk of developing thromboembolic complications and bleeding. Using the CHA2DS2-VASc scale, we assessed the risk of thromboembolic complications. Patients were reassessed dynamically at the third, sixth, and twelfth months of the study. Each patient's CHA2DS2-VASc risk was recalculated, and renal function and blood counts were assessed dynamically. Statistical analysis of the study results was performed using the Microsoft Excel 2019 statistical package. The odds ratio and 95% confidence interval were calculated from quantitative indicators. The significance of differences in mean indicators for paired samples was assessed using the Student's t-test (St). A two-tailed significance test (p) of less than 0.05 was considered statistically significant.

Results. Our study monitored the dynamics of renal filtration function parameters, such as plasma creatinine, and calculated the glomerular filtration rate using the CKD-EPI formula depending on the anticoagulant therapy received. Baseline renal filtration parameters did not differ between the VKA and NOAC groups.

When analyzing plasma creatinine levels in the warfarin group, the average was 139.7±27.9 μmol/L. However, monitoring every 3 months indicated an increase in plasma creatinine levels in this group of patients. At month 6 of the study, this indicator averaged 149.9±30.4 μmol/L. At the end of the study, plasma creatinine levels in patients taking warfarin increased to 160.2±32.7 μmol/L ($p<0.001$). In this group of patients, plasma creatinine increased by an average of 20.6 μmol/L over 12 months, indicating a significant deterioration in renal function in patients taking VKAs and the negative impact of warfarin on filtration (Table 1).

In the rivaroxaban group, on the contrary, positive dynamics of the renal filtration function was observed. Although the initial plasma creatinine values were almost equal (133.1 ± 23.9 μmol / L). The blood creatinine level at the 3rd month of observation slightly increased to 134.8 ± 23.9 μmol / L, at the 6th month to 136.4 ± 24.5 μmol / L. One year after the start of the study, the average value

was 139.3 ± 25.1 µmol / L ($p < 0.05$). Quarterly monitoring of blood creatinine in patients with AF and CKD stage III receiving rivaroxaban demonstrated an increase by an average of 6.2 µmol / L ($p < 0.001$). Our results indicate a nephroprotective effect of NOACs on renal function, in contrast to VKAs. Figure 1 shows significant differences in plasma creatinine levels among patients receiving different anticoagulant therapies.

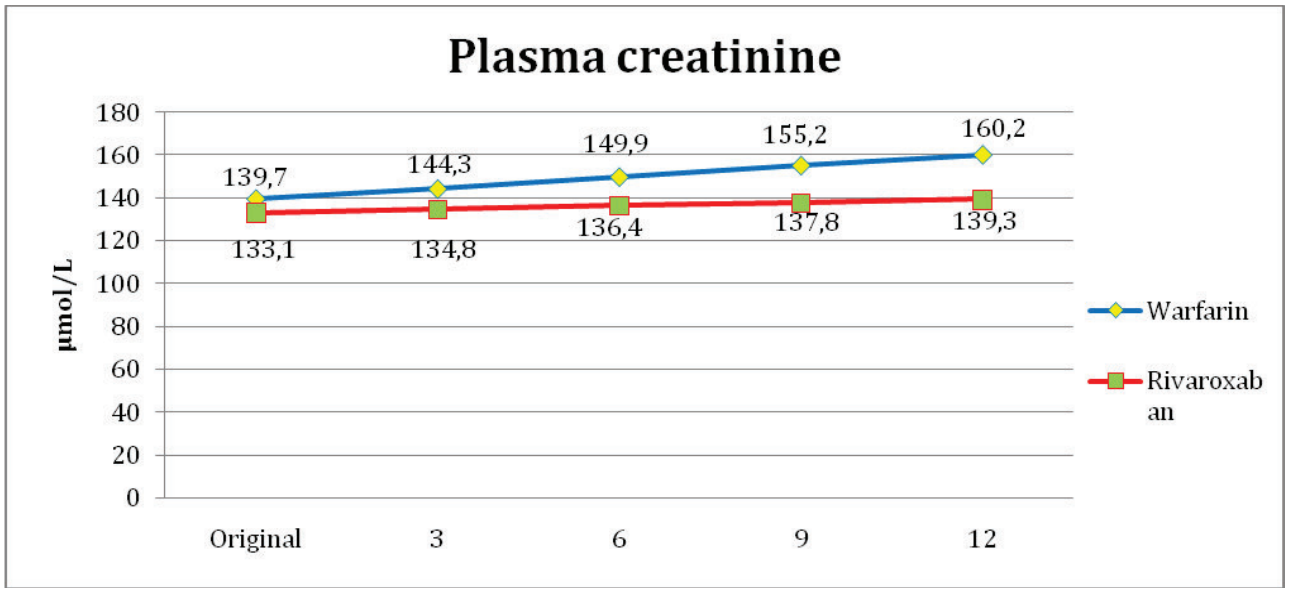


Fig. 1. Dynamics of blood creatinine (µmol/l) with various anticoagulants in CKD.

In the AF and CKD group, plasma creatinine increased from 139.7±27.9 µmol/L to 155.2±31.4 µmol/L during warfarin therapy. Analysis of the results demonstrated an increase in blood creatinine among patients with AF and stage III CKD. These results further demonstrate the negative impact of warfarin on renal filtration function.

During a study of annual plasma creatinine monitoring in patients receiving rivaroxaban therapy, a baseline of 133.1±23.9 µmol/L was recorded in AF with CKD. The average annual increase in blood creatinine in patients with AF and CKD was 6.2 µmol/L during rivaroxaban therapy. When comparing this indicator with that in patients receiving warfarin therapy in the AF/CKD group (20.5 µmol/L), it can be reliably concluded that rivaroxaban has a positive effect on renal filtration function ($p<0.01$).

In patients with AF and stage III CKD, NOAC therapy resulted in improved renal filtration function.

During the study, glomerular filtration rate (GFR) was also assessed using the CKD-EPI formula. A significant improvement in GFR dynamics was noted in the NOAC group compared with the VKA group. Baseline GFR values using the CKD-EPI formula in the warfarin group (AF and CKD) were 43.3 ± 6.7 ml/min/1.73 m2, while at month 6 they were 39.9 ± 6.3 ml/min/1.73 m2, and at month 12, 36.7 ± 6.1 ml/min/1.73 m2. The results indicate a significant deterioration in renal filtration function in patients taking warfarin ($p< 0.01$). On average, GFR decreased by 6.6 ml/min/1.73 m2 over the year.

Twenty-nine patients diagnosed with AF and stage III CKD were taking warfarin. Over the course of a year, seven patients with stage III CKD progressed to stage IV. This represents 24.1% of the total number of patients receiving warfarin. All of these patients initially had stage 3b CKD, compared to 13 in the warfarin group. Consequently, one in two patients taking warfarin with stage 3b CKD and AF progressed to stage IV CKD within a year (53.8%). These data demonstrate the negative impact of warfarin on the course of chronic kidney disease.

When monitoring the dynamics of SCF in 35 patients with AF and CKD during rivaroxaban therapy, a slight change was found from 44.0±7.3 ml/min/1.73m2 to 41.7±7.1 ml/min/1.73m2, with an average decrease in SCF of 2.3 ml/min/1.73m2 over the course of a year (Figure 2).

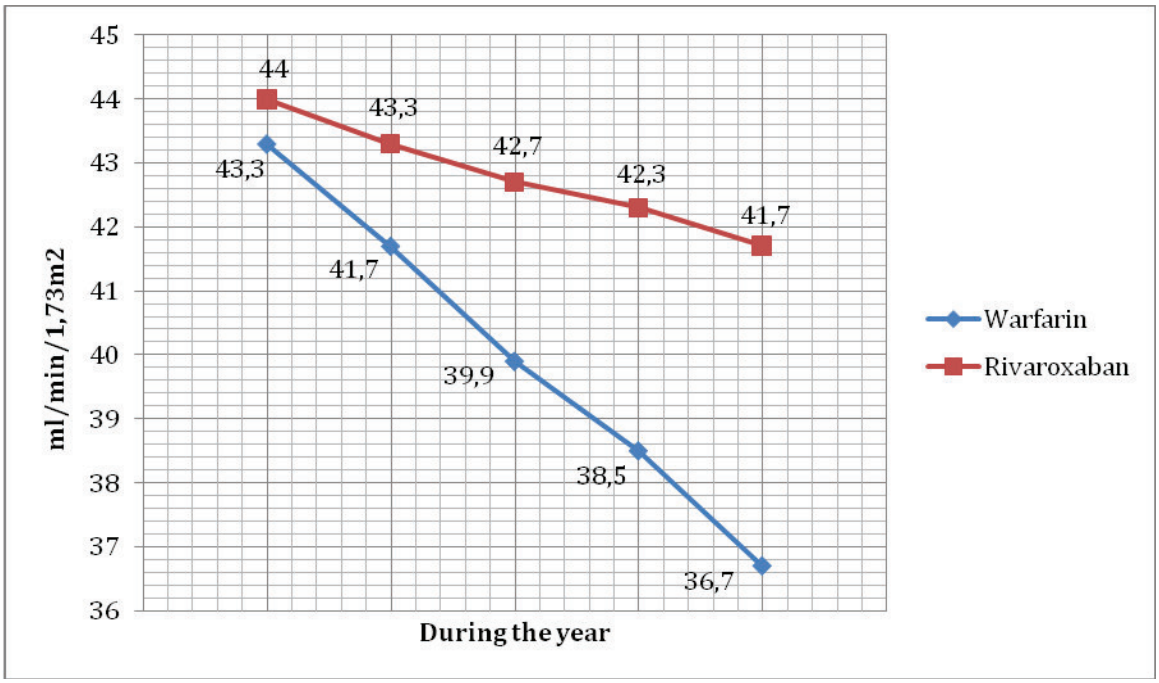


Fig. 2. Dynamics of GFR (ml/min/1.73m2) with various anticoagulants in CKD.

Table 1

Dynamics of plasma creatinine levels (μmol/l) and GFR according to the CKD-EPI formula depending on ACT (ml/min/1.73m2)

Research time	AF with CKD (creatinine)		p	AF with CKD (GFR)		p
	warfarin	rivaroxaban		warfarin	rivaroxaban	
Initial	139,7±27,9	133,1±23,9	139,7±27,9	43,3±6,7	44,0±7,4	0,67
At 3 months	144,3±28,9	134,8±23,9	144,3±28,9	41,7±6,5	43,3±7,2	0,55
At 6 months	149,9±30,4	136,4±24,5	149,9±30,4	39,9±6,3	42,7±7,2	0,1
At 9 months	155,2±31,4	137,8±24,4	155,2±31,4	38,5±5,9	42,3±7,0	0,02
At 12 months	160,2±32,7^^	139,3±26,1^	160,2±32,7^^	36,7±6,2^^	41,7±7,2^	0,004

Note: ^- p<0.05; ^^- p<0.001 (relative to the original data)

In an analysis of the overall incidence of thromboembolic complications during the study, 14.1% of cases were recorded among patients with CKD and AF. Of these, 9.4% received anticoagulant therapy with VKAs, and 4.7% took NOACs. A feasibility study was also conducted in

each subgroup, which also revealed 20.7% of cases in the warfarin group (p<0.001) and 8.6% of cases in the rivaroxaban group (p<0.001, Figure 3).

In the analysis of the group of patients receiving warfarin, thromboembolic events in the form of acute cerebrovascular accidents occurred in 6.9% of patients, myocardial infarction and unstable angina were observed in 13.8% of patients, and no deaths were recorded. In these patients, ischemic stroke was observed in 6.9% of cases (p<0.05).

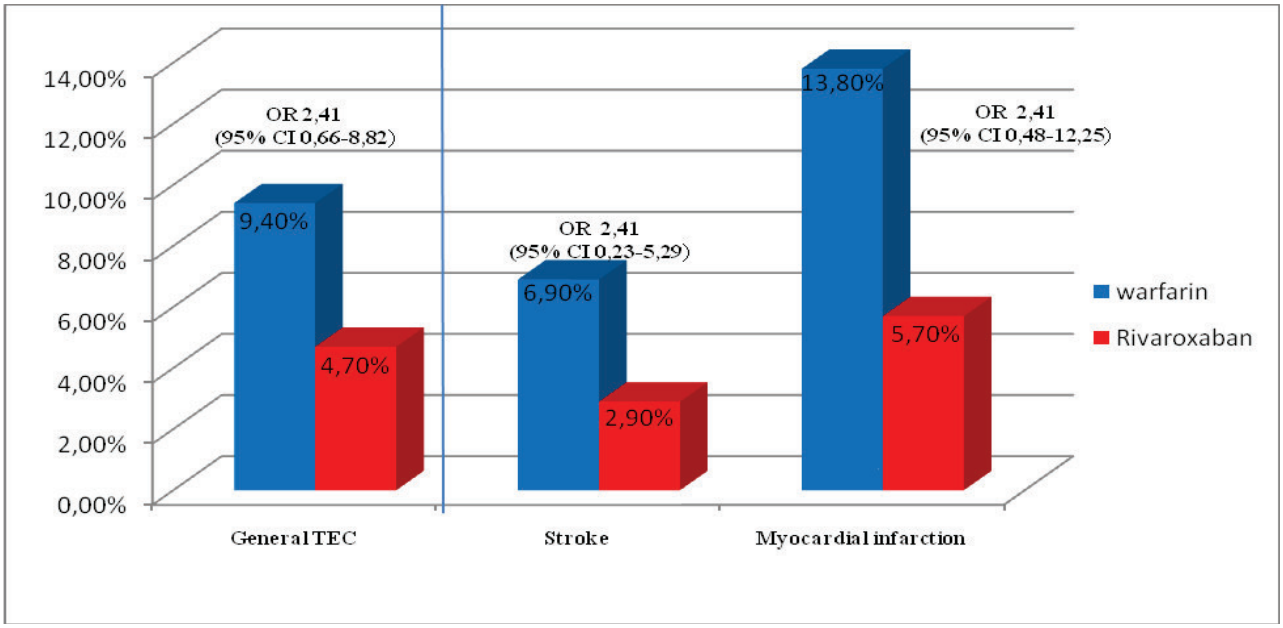


Fig. 3. Thromboembolic complications in patients with AF and CKD depending on the received ACT.

However, thromboembolic complications also occurred among patients taking rivaroxaban, but less frequently compared to the VKA group. In patients with stage III CKD and non-valvular AF, ischemic stroke was reported in 2.9% of cases, while myocardial infarction and unstable angina occurred in 5.7%. No death from any cause was recorded in this group during the study.

A comparative analysis of the effects of various oral anticoagulants on thromboembolic events revealed a statistically significant (p<0.05) reduction in events in patients with AF and stage 3 CKD taking rivaroxaban, despite a high risk of thromboembolic events based on the CHA2DS2-VASc score, compared to patients in the warfarin group.

Also during the study, the indicators of the relationship between the risk of thromboembolic events according to the CHA2DS2-VASc scale and the thromboembolic events that occurred among patients with AF and CKD on various anticoagulants were examined and assessed (Table 2).

Table 2

Relationship between thromboembolic risk and events on VKAs and NOACs in AF and CKD

Points on the scale CHA2DS2-VASc	Frequency of TEC	
	Warfarin	Rivaroxaban
0-1 points	-	-
2-3 points	1 (3,45%)	-
4-5 points	3 (10,3%)	1 (2,9%)
≥6 points	2 (6,9%)	2 (5,7%)

An increased incidence of thromboembolic events is predictably associated with an increased risk of developing thromboembolic events and CKD progression. Among patients receiving warfarin therapy, thromboembolic events were most frequently observed in those with a CHA2DS2-VASc score of 4-5. It is also noteworthy that in the warfarin group, thromboembolic events occurred in a patient with a low risk (2 points) of the complication. In the rivaroxaban group, thromboembolic events were most frequently observed in patients with a CHA2DS2-VASc score of 6 or more. Among patients with a low risk of thromboembolic events, no cases of stroke or MI were detected during NOAC therapy. These data reliably indicate the significant efficacy of rivaroxaban-based antithrombotic therapy compared to warfarin in the prevention of thromboembolic events.

The study examined the correlation between thromboembolic events and SCF values in patients with AF and stage III CKD (Figure 4). Further analysis of the study results demonstrated that with increasing renal function impairment, including a decrease in SCF, the incidence of thromboembolic complications increased in the warfarin group. However, in the rivaroxaban group, this rate remained virtually unchanged.

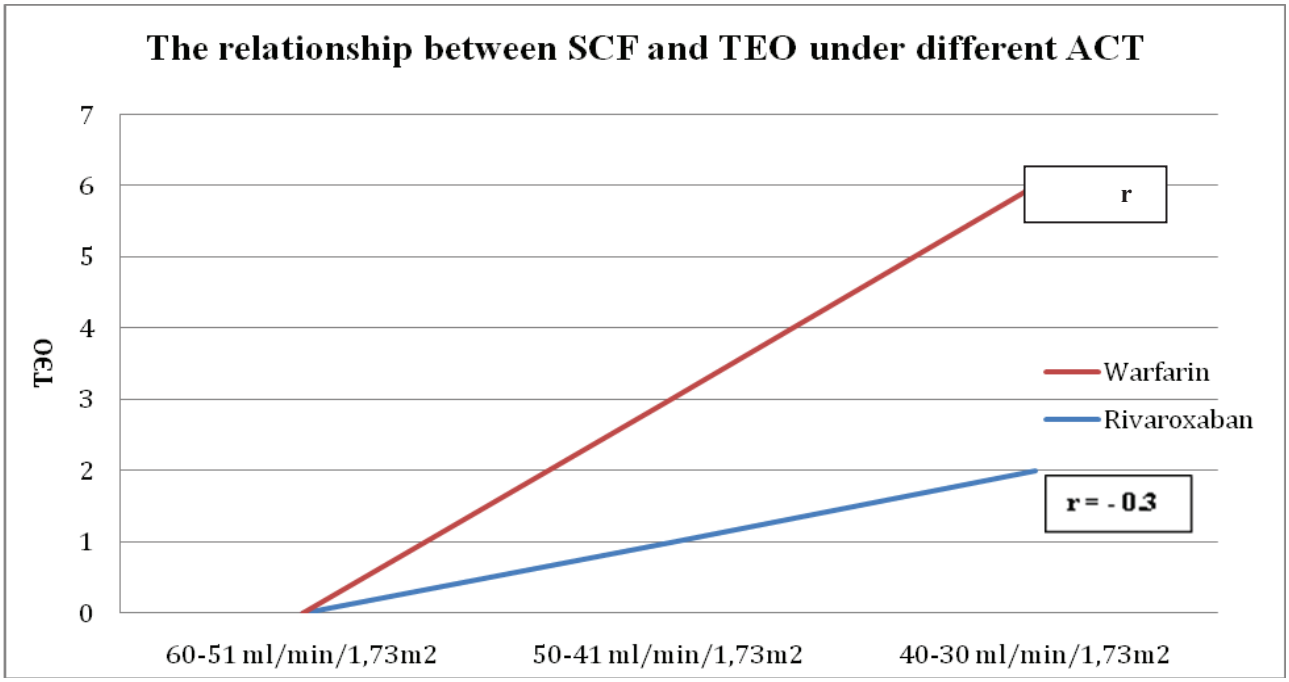


Fig. 4. Correlation between TEC and GFR in patients with CKD and AF on VKA or NOAC

Based on our data, a strong inverse correlation was found between the increased incidence of thromboembolic events and a decrease in GFR among patients with AF and CKD treated with warfarin (r = -0.7). In the group of patients receiving rivaroxaban, a weak inverse correlation was observed between SCF and TEC (r = -0.3). These results further demonstrate the superior efficacy of NOACs compared to VKAs.

Discussion. In recent years, the incidence of decreased renal filtration function in the general population has increased sharply. The increased risk of developing CKD may be associated with the increasing prevalence of major risk factors, such as diabetes mellitus and hypertension. Age-related declines in renal function, which are associated with increased life expectancy worldwide, are also significant. All of the above factors are common risk factors for the development of both renal pathologies and cardiovascular diseases, specifically atrial fibrillation. The risk of cardiovascular disease is highest and most prevalent among patients with moderate to severe CKD.

Our study is one of the few randomized prospective studies comparing VKA (warfarin) and NOAC (rivaroxaban). Our study included patients with atrial fibrillation and a glomerular filtration rate (GFR) between 30 ml/min/1.73 m2 and 60 ml/min/1.73 m2, corresponding to stage 3 CKD, receiving various anticoagulant therapies. These patients had CHA2DS2-VASc scores of 2-8 and HAS-BLED scores of 0-4. Thus, all participants had a high risk of stroke and systemic embolism with a moderate to low risk of hemorrhagic events.

Our study revealed significant differences in the incidence of thromboembolic events in both groups, despite the small number of these complications. However, the incidence of thromboembolic events was 20.9% in the warfarin group, compared to 8.6% in the rivaroxaban group ($p < 0.005$). The situation was further complicated by a fatal event in a patient taking warfarin. It should be noted that the cause of death was hemorrhagic stroke. It occurred in a patient with a TTR INR of 87%.

In moderate and severe CKD, achieving a target TTR>70% is very difficult. To ensure safe use of warfarin, all patients were prescribed a starting dose of 2.5 mg, and frequent INR monitoring (every 2-3 days) was introduced until the dose was titrated. For some patients, dose titration lasted up to six months, and each significant change in plasma creatinine levels required even more careful monitoring of INR and GFR, as well as therapy adjustments. In some cases, patients measured INR up to 15 times per month. This requirement for frequent laboratory visits in most cases was inconvenient for patients' daily lives. Unfortunately, this led to low patient adherence in the warfarin group, where the TTR was approximately 26%. In these cases, the superiority of NOACs, which do not require such frequent monitoring, cannot be overlooked.

Another important aspect of the study was monitoring the dynamics of kidney function during therapy with various anticoagulants. To assess kidney function, mixed linear models were created using SCF and plasma creatinine. The advantage of this method is the ability to assess time trends and minimize individual differences between patients. During the study, positive dynamics in GFR and plasma creatinine were observed among patients in the rivaroxaban group. An improvement in kidney function was observed in the NOAC group. However, opposite results were observed in the warfarin group. A divergence of the curves was already observed at month 6 of the study.

When comparing patients with AF and CKD in the warfarin and rivaroxaban groups, a trend toward improved kidney function was noted in the NOAC group ($p<0.005$). Transition from stage 3 CKD to stage 2 was observed in 25.7% of patients treated with rivaroxaban, and from stage 3b to stage 3a in 37.1%. This further demonstrates the renoprotective potential of NOACs. However, the opposite pattern was observed in the warfarin group. Unfortunately, there were cases of CKD transition from stage 3 to stage 4 (20.7%) recorded during the study. These figures demonstrate the negative impact of VKAs on renal filtration function.

Conclusions. A high frequency of VTE was recorded in the group with CKD and AF 14.1% (OR - 2.1 (CI 95% 0.60-7.36)). In AF and CKD during warfarin therapy, VTE occurred in 20.7% of cases, which is significantly less compared to patients taking NOACs (8.6%, $p < 0.001$). Against the background of oral anticoagulant therapy with warfarin in patients with non-valvular atrial fibrillation and chronic kidney disease stage III, a significant increase in creatinine levels (12.8%) and a decrease in GFR (by 15.2%) were observed according to the CKD-EPI formula. Patients receiving rivaroxaban showed an improvement in renal function (creatinine increased by 4.7%, GFR decreased by 5.2%, $p < 0.01$), indicating the renoprotective effect of NOACs.

It is recommended that general practitioners use NOACs in clinical practice in patients with AF and stage III CKD, as these drugs are highly effective in preventing thromboembolic complications and are safe against the development of various hemorrhagic events. All patients with AF and stage III CKD are recommended to have quarterly plasma creatinine monitoring and GFR calculation using the CKD-EPI formula to monitor renal function and early detection of bleeding to reduce the risk of major and fatal complications, thereby allowing for appropriate titration of anticoagulant therapy.

REFERENCES

1. Jones A, Patel K, Smith T. Anticoagulation in chronic kidney disease: current status. J Thromb Haemost. 2023;21(11):2857-2871. doi:10.1111/jth.16497

2. Lee SR, Choi EK, Park CS, et al. Renal outcomes of rivaroxaban compared with warfarin in Korean patients with atrial fibrillation. Kidney Res Clin Pract. 2023;42(1):51-63. doi:10.23876/j.krcp.22.099

3. Lee WC, Fang CY, Hsieh MJ, et al. The impact on renal function after long-term use of anticoagulants in atrial fibrillation patients. Thromb J. 2021;19(1):78. doi:10.1186/s12959-021-00351-1

4. Mezue K, Gopal DM, Reddy VY. Anticoagulation-related nephropathy for the internist. Cleve Clin J Med. 2020;87(11):663-670. doi:10.3949/ccjm.87a.20044

5. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-891. doi:10.1056/NEJMoa1009638

6. Sitticharoenchai P, Chaikriangkrai K, Srivali N, et al. Non–Vitamin K antagonist oral anticoagulants provide lower risk of acute kidney injury and end-stage renal disease compared with warfarin. J Am Heart Assoc. 2021;10(13):e019609. doi:10.1161/JAHA.120.019609

7. Vestergaard AEF, Adelborg K, Skjøth F, et al. Oral anticoagulant treatment and risk of kidney disease: a population-based study. Clin Kidney J. 2024;17(1):sfad252. doi:10.1093/ckj/sfad252

8. Wheeler DS, Giugliano RP, Rangaswami J. Anticoagulation-related nephropathy. J Am Coll Cardiol. 2022;79(11):1074-1086. doi:10.1016/j.jacc.2021.12.025

9. Yang J, Zhang Y, Yang S, et al. Efficacy and safety of direct oral anticoagulants in patients with atrial fibrillation and chronic kidney disease: a systematic review and meta-analysis. Thromb J. 2024;22(1):9. doi:10.1186/s12959-024-00608-5

10. Yao X, Tangri N, Gersh BJ, et al. Oral anticoagulation use in individuals with atrial fibrillation and chronic kidney disease. J Am Coll Cardiol. 2024;83(6):567-582. doi:10.1016/j.jacc.2023.11.031

11. Zaleski AL, Kolte D, Aronow HD, et al. Anticoagulation for patients with concomitant atrial fibrillation and chronic kidney disease. J Am Heart Assoc. 2023;12(23):e034176. doi:10.1161/JAHA.123.034176