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Stroke Prevention in Patients with Atrial Fibrillation in Real Clinical Practice, Emphasis on Efficacy and Safety of Anticoagulant Therapy

Aim	To evaluate frequency of administration of anticoagulant therapy (ACT) for atrial fibrillation and to study the effect of chronic antithrombotic therapy (ATT) on kidney function.
Materials and methods	Due to a high medical and social significance of AF, much attention is presently paid to appropriate administration of ACT for AF in clinical practice. The study retrospectively analyzed 776 case reports of hospitalized patients with AF. The effect of chronic ATT on kidney function was studied in 70 patients who were rehospitalized, including 25 patients treated with warfarin, 25 patients treated with direct oral anticoagulants (DOAC), and 20 patients treated with acetylsalicylic acid (ASA).
Results	In January 2014, at the prehospital stage, 74.3% of patients did not receive ATT, 14.7% of patients received antiplatelet therapy, and only 11% received anticoagulants. In the hospital in January 2014, ACTs were administered to 74.3% of patients (warfarin, 58.6%; DOAC, 15.7%), 20.6% of patients received antiplatelet drugs, and 5.1% of patients were discharged without ATT. In January 2019, the number of patients receiving ACT at the prehospital stage increased to 58.1% (warfarin, 13.8%; DOAC, 44.3%); 12% of patients received antiplatelet drugs; and 29.9% of patients did not receive ATT. The number of patients treated with warfarin and DOAC in the hospital increased to 14.8% and 70.6% (rivaroxaban, 33.4%; apixaban, 25.5%, and dabigatran, 11.7%), respectively. The number of patients taking antiplatelet drugs decreased to 3.7%, and the number of patients without ATT decreased to 10.9%. There were no statistically significant differences in glomerular filtration rate (GFR) between these three groups at baseline. Only in the warfarin treatment group, GFR was significantly decreased from baseline during the follow-up period. Comparison of GFR in three study groups at the finale stage of the study showed significant differences between mean GFRs in the warfarin treatment group and the DOAC treatment group and between the warfarin treatment group and the ASA treatment group.
Conclusion	Among the prescribed and taken anticoagulants, DOACs are presently in the first place. Among DOACs, the most frequently prescribed drug is rivaroxaban. GFR decreases with the DOAC treatment slower than with the warfarin treatment. Despite the slower decrease in GFR with the ASA treatment compared to warfarin, ASA is not indicated for prevention of stroke in AF due to its low efficacy.

Keywords	Atrial fibrillation; chronic kidney disease; direct oral anticoagulants; warfarin; rivaroxaban
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Atrial fibrillation (AF) is the most common cardiac rhythm disorder. The prevalence of this type of arrhythmia in the general population reaches 2–5% [1, 2]. However, AF very rarely occurs as a condition in and of itself. Most often, it occurs in the setting of other pathologies, such as hypertension, coronary artery disease, chronic heart failure, chronic kidney diseases (CKDs) and diabetes mellitus [1–4]. AF negatively affects prognosis and aggravates the progression of any associated pathology. The primary complications of AF are cardioembolic strokes: according to the literature, 20–30% of cases of ischemic stroke (IS) are caused by embolic complications of AF [1, 2, 5, 6]. The presence of AF is associated with a two-fold increase in the risk

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of dying of cardiovascular pathology and death of any cause [1, 2, 5]. Timely and well-chosen anticoagulant treatment (ACT) can reduce the risk of thromboembolic complications and improve prognosis [7]. Warfarin reduces the risk of stroke in AF by 64% compared to placebo [2, 8, 9]. Direct oral anticoagulants (DOACs), which appeared about ten years ago and are now commonly used in clinical practice, surpassed warfarin or were at least as effective and safe as warfarin in many major randomized clinical trials [1, 2, 5, 6, 9–17]. The use of anticoagulants is associated with the increased risk of bleeding [18]. Elderly patients with AF and concomitant CKD [1] are the most vulnerable in terms of increased risk of bleeding during ACT. Therefore, the physician must select the most effective and safe anticoagulant with an optimal risk-benefit ratio for each patient, taking into account his/her comorbidities [7]. Due to the high medical and social significance of AF, much attention is paid to the study of correct clinical administration of ACT in AF [2, 4, 19, 20].

The objective of this study was to estimate the rate of administration of ACT in clinical practice for patients suffering from AF, who are at high risk of developing IS and systemic embolism, as well as to investigate the impact of long-term antithrombotic therapy (ATT) on kidney function.

Material and Methods

Retrospective analysis of 776 inpatient case records was carried out in the Antiarrhythmic Center of Pokrovskaya City Hospital in St. Petersburg in the period from January 1, 2014, to January 31, 2019. The patients suffered from non-valvular AF and AF with type 2 valvular heart defects according to the EHRA classification [16]. The presence of AF in the patient's clinical diagnosis was verified with a 12 lead electrocardiogram (ECG) or 24-hour ECG monitoring. The inclusion criterion consisted of patient ages of 18 or older.

Of the 776 patients, 70 patients with AF who continuously used antithrombotic drugs for the prevention of IS and systemic embolism (25 patients taking warfarin, 25 patients using DOACs, and 20 patients using acetylsalicylic acid (ASA)) were selected for assessing the effect of long-term ATT on kidney function. In the period from January 1, 2014, and June 30, 2018, the selected patients had been hospitalized at least once in 2014 and not less than once in 2018. During hospitalization, the levels of creatinine were determined, allowing the calculation of the glomerular filtration rate (GFR) and its observation over time. The risk of development of IS was assessed using the CHA_2DS_2 VASc score; the risk of bleeding – using the HAS-BLED score; the GFR – according to the CKD-EPI formula; creatinine clearance (CC) – by applying the Cockroft-Gault formula.

The findings were statistically processed using the descriptive statistics methods in the Statistica v.10.0 statistical software package.

Results

The age and sex compositions of the patient population are shown in Figure 1. AF is common for senior-age groups. The mean age of our patients was 67.5±12.3 years old; 62% were over 65 years old, while 37% were over 75 years old. Although male patients prevailed among patients with AF in the under 65 age group, the number of male and female patients in the 65–84 age group was comparable; moreover, there were more female patients in the above 85 age group. Idiopathic AF was rare and diagnosed in only 0.9% of

Figure 1. Age and sex composition of patients with atrial fibrillation

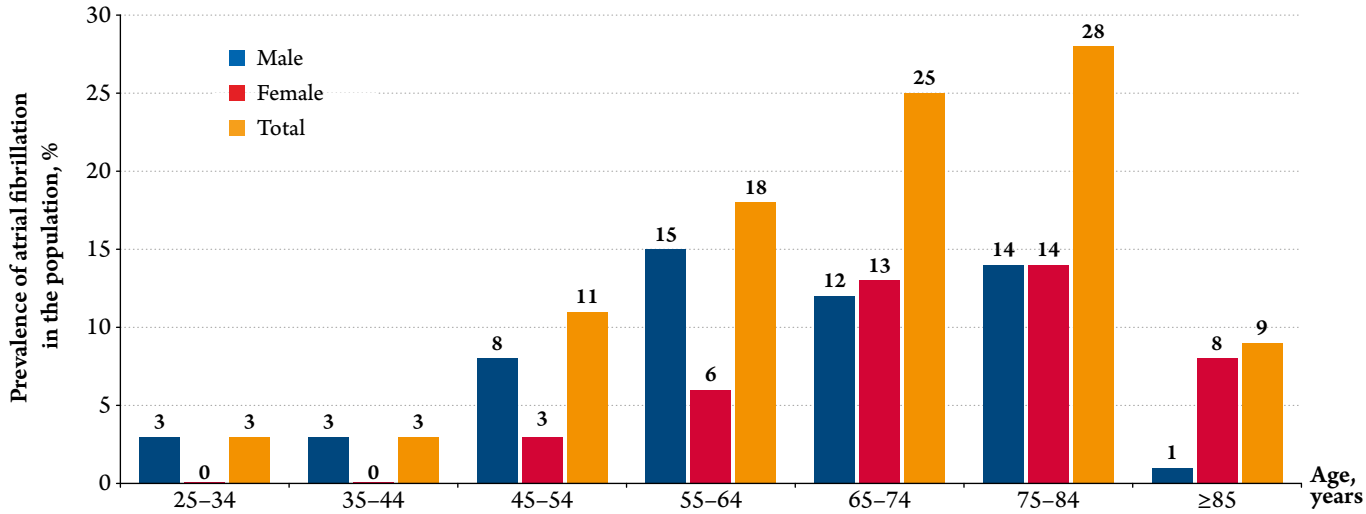
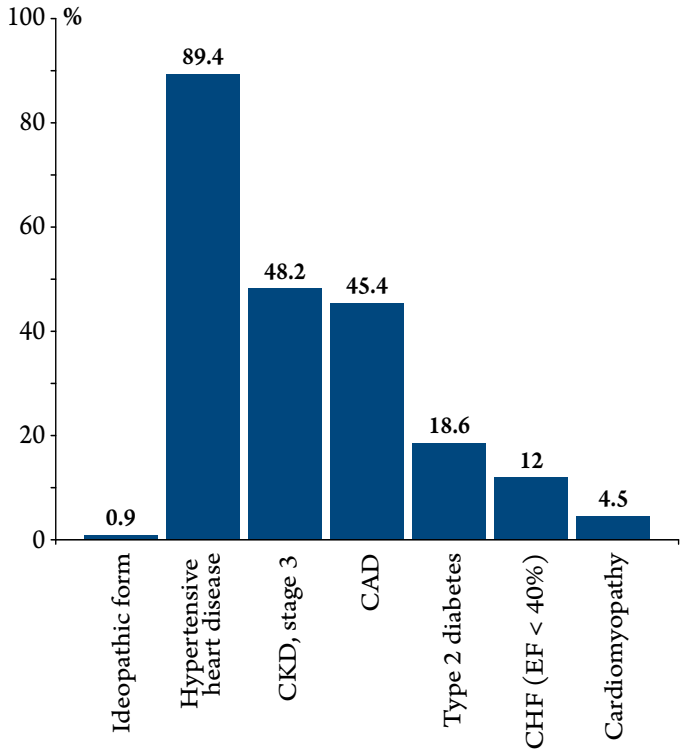
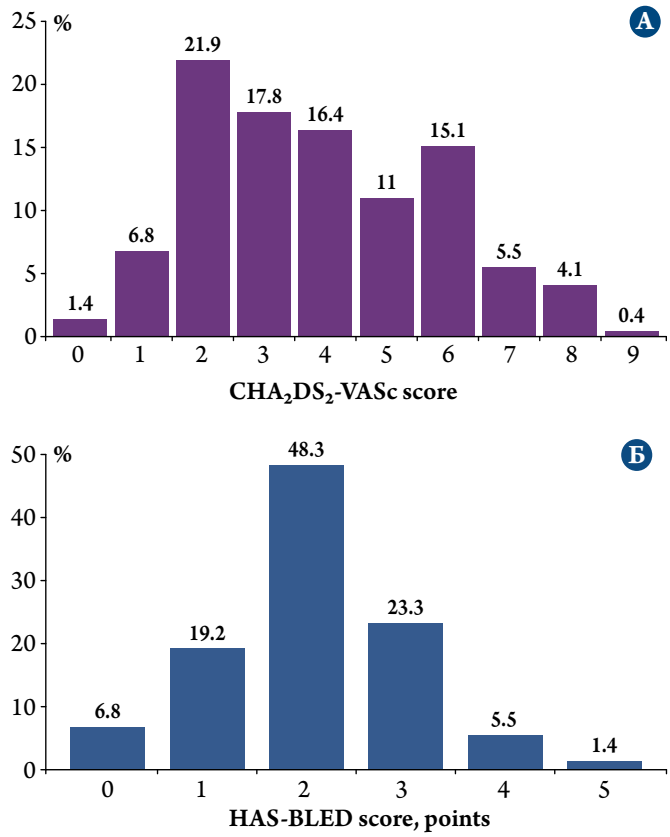


Figure 2. Prevalence of comorbidities in atrial fibrillation



CKD, chronic kidney disease;
CAD, coronary artery disease;
CHF, chronic heart failure; EF, ejection fraction.

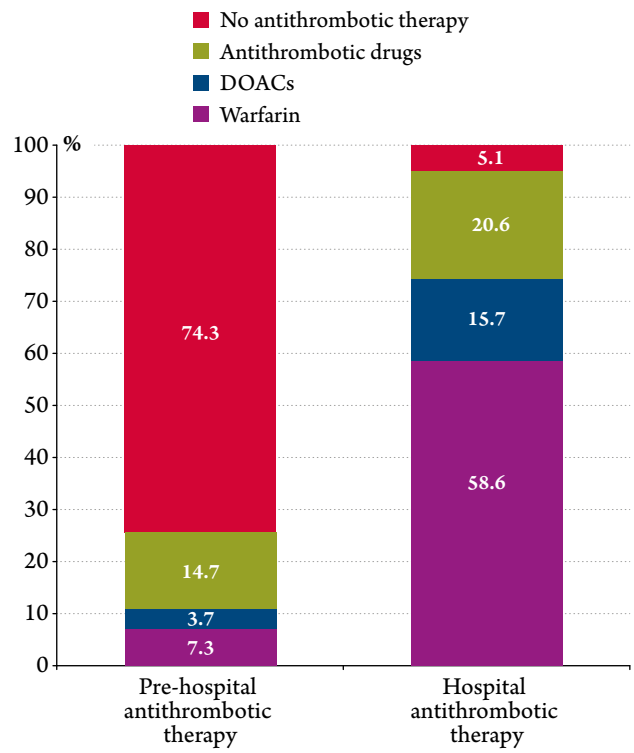
Figure 3. Assessment of stroke and systemic embolism using the CHA_2DS_2-Vasc (A) score and risk of bleeding using the HAS-BLED score (B)



patients (Figure 2). Most typically, AF was associated with hypertension (89.4% of patients). The second most common comorbidity was stage III–V CKD (48.2% of patients). Clinically-confirmed coronary artery disease was reported in 45.4%, diabetes mellitus in 18.6%, chronic heart failure with reduced ejection fraction in 12.0%, and cardiomyopathy in 4.5% of patients. Most patients had a high risk of developing IS and systemic embolism (Figure 3, A). The mean risk score, according to CHA_2DS_2 VASc, was 3.9±1.8, with one in four patients having an extremely high risk (≥6 points). The distribution of patients based on the bleeding risk score is shown in Figure 3, B. The mean HAD-BLED risk score was 2.1±1.1. 30.2% of patients had a high risk of bleeding (≥3 points).

In January 2014, 74.3% of patients who needed ACT at the pre-hospital stage did not receive ATT, 14.7% received antiplatelet drugs (ASA, clopidogrel, or their combination), while only 11.0% of patients took anticoagulants (7.3% warfarin, 3.7% DOACs; Figure 4). At the hospital stage, in January 2014, ACT was prescribed and recommended at discharge to 74.3% of patients (58.6% warfarin, 15.7% DOACs), 20.6% received antiplatelet drugs, and 5.1% of patients were discharged without ATT. It appeared that patients who did not receive

Figure 4. The rate of administration of antithrombotic drugs to patients with atrial fibrillation at the pre-hospital stage and in the hospital in January 2014



DOACs, direct oral anticoagulants.

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Figure 5. The rate of administration of antithrombotic drugs to patients with atrial fibrillation at the pre-hospital stage and in the hospital in January 2019

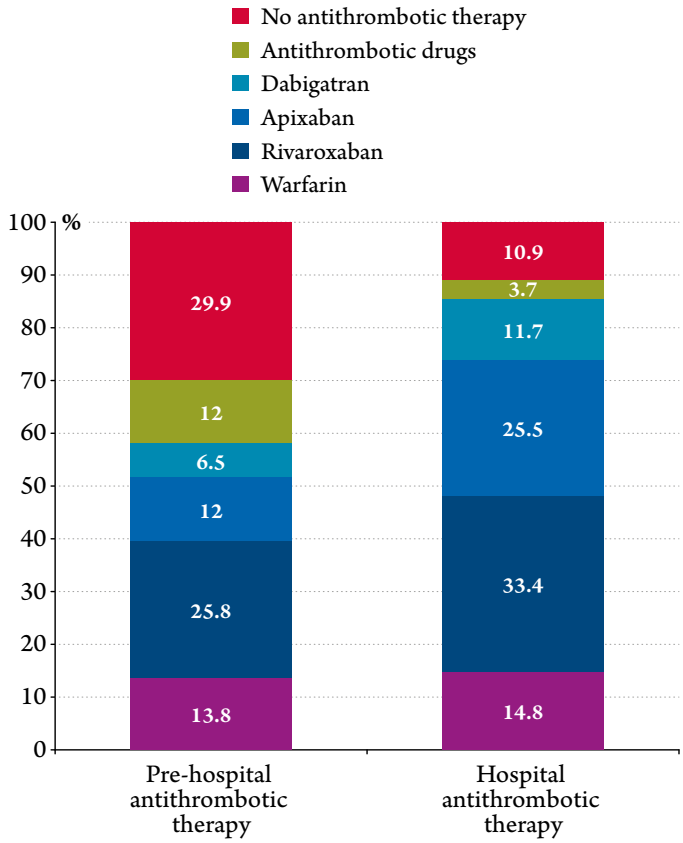
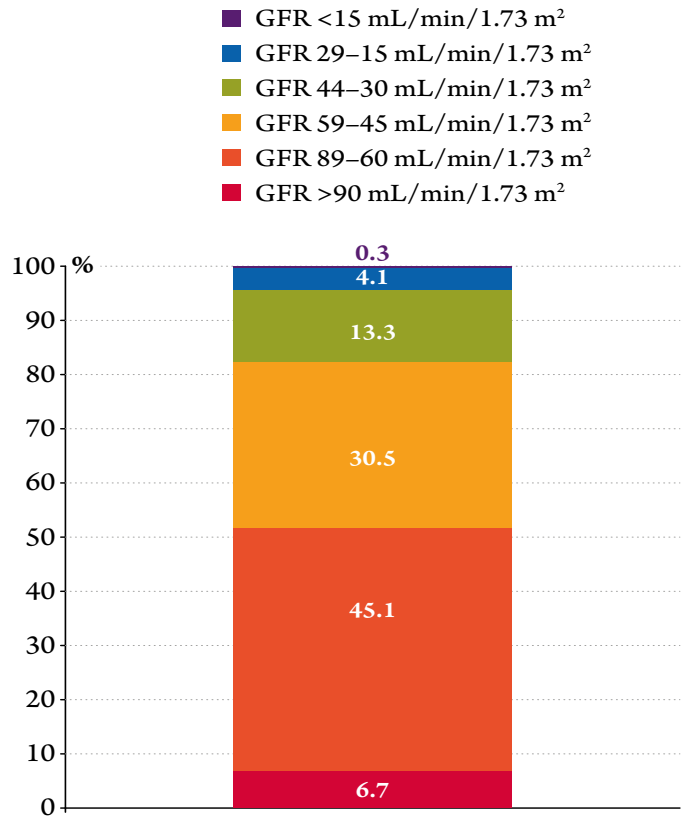


Figure 6. Prevalence of renal dysfunction in patients with atrial fibrillation



GFR, glomerular filtration rate.

ATT were significantly older than patients who received some antithrombotic drugs (mean age 76.1±14.0 and 68.6±12.9 years old, respectively; p <0.05). Patients who received antiplatelet drugs (mean age 71.2±14.1 years old) were significantly (p=0.03) older than patients who used ACT (mean age 66.6±12.3 years old). Patients who received antiplatelet drugs had a significantly higher risk of developing IS (mean CHA_2DS_2 VASc score 4.6±1.9) than patients who received anticoagulants (mean CHA_2DS_2 VASc score 3.7±1.8; p=0.003). The risk of IS developing in patients without ATT was also high (3.7±0.9) and significantly did not differ from the risk in patients who received ACT (p=0.90).

Thus, it appeared that older patients with a higher risk of developing IS and in need of ACT either did not receive anticoagulants or received antiplatelet drugs with significantly lower protective effects than those of anticoagulants. The analysis of causes for the withdrawal of ACT in elderly patients showed that the primary cause was that patients could not control the international normalized relationship (INR) at the outpatient stage or buy expensive DOACs.

In 2016, the number of patients with AF receiving anticoagulants in the hospital increased to 89.0%; 48.9% of them used warfarin, 40.1% – DOACs, 8.8% received antiplatelet drugs, and 2.2% of patients did not receive ATT, although it was indicated.

In January 2019, of all patients who needed ACT, 58.1% received ACT at the pre-hospital stage, of whom 13.8% used warfarin, 44.3% – DOACs (rivaroxaban – 25.8%, apixaban – 12.0%, dabigatran – 6.5%), 12.0% took antiplatelet drugs, and 29.9% did not receive ATT (Figure 5). Anticoagulants were administered to 85.4% of hospitalized patients. The number of patients taking warfarin increased insignificantly to 14.8%. The number of patients taking DOACs increased to 70.6% (rivaroxaban – 33.4%, apixaban – 25.5%, dabigatran – 11.7%). The number of patients taking antiplatelet drugs decreased to 3.7%; the number of patients without ATT – to 10.9%.

Given the importance of assessing the kidney function to make sure that ACT is safe, GFR was estimated in all patients to detect CKD and assess its severity. In patients who needed ACT, CC was estimated together with GFR to choose an appropriate anticoagulant and its dose [21]. 6.7% of patients had GFR ≥90 ml/min/1.73 m², 45.1% from 89 to 60 ml/min/1.73 m², 30.5% from 59 to 45 ml/min/1.73 m² (stage IIIa CKD), 13.3% from 44 to 30 ml/min/1.73 m² (stage IIIb CKD), 4.1% from 29 to 15 ml/min/1.73 m² (stage IV CKD), 0.3%

<15 ml/min/1.73 m² (stage V CKD) (Figure 6). 70 of the 776 patients were selected to analyze the effects of long-term ATT on renal function. Twenty-five of them received warfarin, while the other 25 used DOACs (rivaroxaban–60%, dabigatran – 36%, apixaban 4%); twenty patients received ASA. The ASA group was included in this study despite the fact that it is no longer recommended for use in preventing IS in patients suffering from AF. Nevertheless, since it is still prescribed, it was therefore important to assess its effects on GFR.

The baseline differences between the groups in age and GFR were statistically insignificant. The mean baseline GFR was 63.7±14.7 ml/min/1.73 m² in the warfarin group, 63.8±21.2 ml/min/1.73 m² in the DOAC group, and 62.4±17.2 ml/min/1.73 m² in the ASA group ($p > 0.05$). The mean age reached 70.8±10.3 years old in the warfarin group, 69.6±10.6 years old in the DOAC group, and 72.06±12.29 years old in the ASA group ($p>0.05$). During the study period, a statistically more significant decrease in GFR versus the baseline (mean GFR 48.1±11.2 ml/min/1.73 m²; $p<0.002$) was observed in the warfarin group. Although the mean GFR in the DOAC group was also less than the baseline level (62.4±16.0 ml/min/1.73 m²), the difference was statistically insignificant. In the ASA group, the mean GFR decreased to 58.25±10.48 ml/min/1.73 m²; however, the difference was statistically insignificant as in the DOAC group. When the GFR levels were compared in the three groups, statistically significant differences between the mean GFR in the warfarin group and the DOAC group ($p=0.01$), as well as in the warfarin group and the ASA group ($p=0.02$), were detected at the final stage. Although there was a trend towards a more significant decrease in GFR over time in the ASA group versus the DOAC group, this difference was not statistically significant.

Discussion

Our findings confirmed the results of previous Russian epidemiological studies, which revealed many concomitant diseases in patients with AF. The studied patients had a common combination of AF and CKD, requiring careful monitoring of kidney function and choice of an anticoagulant drug, whose efficacy and safety had been carefully studied in patients with concomitant AF and CKD. With such patients, it is important to regularly assess, not only CC to promptly correct ACT if the kidney function progressively deteriorates, but also GFR to assess the severity of CKD in order to refer the patient to a nephrologist in good time. At our center, the recommended rate of CC and thus GFR evaluation for patients taking DOACs is determined according to the European Heart Rhythm Association Practical Guide on the use of DOACs [22]. The baseline levels of GFR and CC were determined in all patients prior to the administration of oral anticoagulant. When the baseline CC >60 mL/min and the patient's age <75 years old, further CC assessment is recommended once a year (if ≥75 years old, at least once every six months). When CC ≤60 mL/min, the date for the next CC evaluation is calculated using the formula: CC:10 [22].

The ACT paradigm for the prevention of IS and systemic embolism in AF changed in response to the adoption of DOACs in clinical practice. Significant improvements in the prevention of IS and systemic embolism in AF as a consequence of the practicality of DOACs led to an increase in the number of patients taking anticoagulant drugs due to the removal of the need to conduct regular monitoring of blood clotting parameters and the drugs' overall efficacy and safety. Our study showed a 5-year (from January 2014 to January 2019) increase in the administration rate of anticoagulants from 11% to 58.1% at the pre-hospital stage, and from 74.3% to 85.4% during hospitalization. At the same time, although there is still a small percentage of patients who take ASA to prevent IS and systemic embolism, this is not recommended according to the current national and international guidelines. Senile patients who are the most vulnerable to IS sometimes do not receive ACT. Physicians who justify the failure to prescribe ACT for AF in terms of a patient's advanced age without providing sufficient additional grounds expose him/her to the risk of disabling IS and premature death. The use of DOACs in elderly patients allows for effective prevention of IS without increasing the risk of intracranial bleeding [1].

Currently, many patients use DOACs both at the pre-hospital stage and during the hospitalization. The administration rate of warfarin in the hospital decreased from 58.6% in 2014 to 14.8% in 2019. Rivaroxaban is the most commonly administered DOAC both in the hospital and at the pre-hospital stage. This is primarily due to the ROCKET AF trial, which studied the efficacy and safety of rivaroxaban versus warfarin in AF in patients with a high risk of developing IS and systemic embolism. The clinical characteristics of these patients were as close as possible to real-world clinical practice in Russian hospitals. For example, in the ROCKET AF trial, the mean risk score for IS and systemic embolism according to the $CHADS_2$ score was 3.5; in patients of our population (CHA_2DS_2 VASc), the $CHADS_2$ was 3.9. Physicians are more likely to prescribe a drug that has been studied in randomized clinical trials in patients with risks comparable to the those of his/her patients

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due to such drugs providing a more predictable clinical outcome.

The choice of the drug – not only by physicians, but also by patients – is significantly influenced by the dosage frequency and the simplicity of the treatment regimen. Of the DOACs approved in the Russian Federation, only rivaroxaban is administered once a day, which improves treatment compliance, especially in elderly patients.

Given the prevalence of concomitant AF and CKD of any degree, which has recently been progressively increasing – not only in Russia, but also worldwide – it is important to be guided by the existing evidence base of efficacy and safety of the drugs when ordering ACT for any such category of patients [21]. ROCKET AF is the only randomized clinical trial that studied a specific «renal» dose of DOACs in AF. The study was designed to administer a reduced dose of rivaroxaban (15 mg) in patients with CC 49–30 mL/min (patients with CC < 30 mL/min were not included) [11].

AF and CKD have a close bidirectional causal relationship. Renal dysfunction predisposes an individual to the development of AF. AF is associated with an increased incidence of renal dysfunction and an increased risk of the development and progression of CKD due to hemodynamic disturbances of renal blood supply caused by low stroke volume during short cardiac cycles [21]. Deterioration of kidney filtration function in AF also contributes to renal artery thromboembolism, which does not always have clinical symptoms and can go undiagnosed. In a large cohort study including patients with CKD (n=206,229), the presence of concomitant AF was accompanied by a 67% increase in the risk of developing terminal stage CKD within the mean follow-up period of 5 years [23]. The prospective CRIC trial reported a three-fold increase in the risk of developing terminal stage CKD in patients with concomitant CKD and AF within the mean follow-up period of 5.9 years [24]. Given the prevalence of stage III CKD (43.8%) in our population, the use of a special «renal» dose of anticoagulants, the efficacy and safety of which is studied in a large randomized clinical trial, is extremely important.

When we followed up 70 patients with repeated hospitalizations over 4.5 years, we found a statistically less significant decrease in GFR in the DOAC group versus the warfarin group, which is entirely consistent with a post hoc analysis in the RE-LY trial [25]. The systemic effects of warfarin are not limited to the suppression of synthesis of the active forms of four coagulation factors (X, IX, VII, II). Warfarin disturbs the functioning of all vitamin K-dependent proteins [26]. One of the side effects of warfarin is the inhibition of vitamin K-dependent carboxylation of the regulatory bone morphogenetic proteins, such as osteocalcin, matrix Gla protein (MGP), and Gla-rich protein (GRP). These carboxylated proteins form calcium-binding centers in bone tissue and ensure that bone tissue captures calcium. The carboxylated MGP and GRP proteins also inhibit the calcification of smooth-muscle cells. If there is a deficiency of vitamin K, the processes of regulatory bone protein carboxylation are disturbed, which results in the increasing calcification of the vessel intima and media, including renal vessels. Calcification of small-diameter renal arteries causes the deterioration of renal blood supply and violation of the filtration function. The processes of vitamin K conversion in the human body are complex. Warfarin blocks one of the stages of vitamin K conversion, depressing vitamin K-epoxide reductase and thus preventing the formation of the biochemical form of vitamin K necessary for the synthesis of coagulation factors and the activation of inhibitors of smooth muscle cell calcification. The situation worsens if the patient initially has low levels of vitamin C. CKD was found to be associated with vitamin K deficiency [27]. Thus, the administration of warfarin for a comorbid patient with AF and CKD can significantly accelerate the processes of vessel calcification and interfere with the filtration function of the kidneys. DOACs, on the other hand, not only do not accelerate calcification of the renal arteries but also display non-hemostatic vascular effects [26]. DOACs inhibit signal transmission through protease-activated receptor – 1 (PAR1) responsible for coagulation, atherogenesis, and inflammation. Thus, DOACs can inhibit inflammation and the formation of atherosclerotic plaques in the vessel wall.

Conclusion

The adoption of direct oral anticoagulants into clinical practice contributed to an increase in the number of patients who take anticoagulants to prevent stroke and systemic embolism in non-valvular atrial fibrillation and atrial fibrillation with type II valvular heart disease according to the EHRA classification. Direct oral anticoagulants are the most commonly prescribed and administered anticoagulants. Such wide prevalence is justified because they are more effective and safer across several parameters than warfarin. Direct oral anticoagulants do not adversely affect kidney function. The rates of decrease in glomerular filtration with direct oral anticoagulants are lower than in the case of warfarin. Rivaroxaban is the most regularly prescribed direct oral anticoagulant in Russia. It is well-studied in the population of comorbid patients and has a special «renal» dose tested in the randomized clinical trial. In our study, acetylsalicylic acid generally showed lower rates of decrease in glomerular

filtration compared to warfarin. However, these results do not provide grounds for using acetylsalicylic acid in patients suffering from atrial fibrillation. Currently, acetylsalicylic acid is not recommended for stroke prevention in atrial fibrillation due to lack of efficacy.

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