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Prevalence of Advanced Chronic Kidney Disease in Patients with Nonvalvular Atrial Fibrillation Hospitalized in Cardiology Departments

Objective	To estimate the prevalence of chronic kidney disease (CKD) 3b – 5 stages and the newly diagnosed sustained reduction in glomerular filtration rate (GFR) <30 ml/min/1.73 m^2 in patients with atrial fibrillation (AF) in real clinical practice, as well as the features of their anticoagulant therapy.
Materials and Methods	Retrospectively, data of all discharge epicrisis from cardiological departments of five Moscow hospitals from June 1, 2016 to May 31, 2017 were analyzed. Patients over 18 years old with AF were enrolled. At the next stage, patients with CKD 3 b – 5 st and newly diagnosed sustained reduction in GFR <30 ml/min/1.73 m^2 (at least 2 measurements during hospitalization) were selected.
Results	Data of 9725 patients were analyzed, AF was diagnosed in 2983 (31%) cases, of which a decreased GFR <45 ml/min/1.73 m^2 was detected in 27% (n = 794) cases. Among them, 349 (44%) were diagnosed with CKD 3b st, 123 (15%) with CKD 4 st, 44 (6%) with CKD 5 st, 278 (35%) had a newly diagnosed sustained reduction in GFR. In 63% of patients with AF and GFR <45 ml/min/1.73 m^2, anemia was diagnosed, 39% of them had moderate and severe one. 711 (89%) patients were prescribed anticoagulants, 53% were assigned direct oral anticoagulants (DOACs). Patients with CKD 3 b st. more often rivaroxaban 15 mg (29%) was prescribed, with CKD 4 and CKD 5 – warfarin (48% and 25%, respectively), in patients with newly diagnosed sustained reduction in GFR <30 ml/min/1.73 m^2 – apixaban 10 mg/day (16.2%).
Conclusion	A quarter of patients with AF revealed a decreased GFR <45 ml/min/1.73 m^2, half of them were recommended DOACs. 42% of patients with GFR <30 ml/min/1.72 m^2 were prescribed DOACs, 27% – warfarin. Patients with CKD 5 st DOACs were not assigned; in half of cases, none of the anticoagulants was recommended. Most often, the dose of the prescribed anticoagulant was not counted according to GFR in patients with newly diagnosed sustained reduction in GFR <30 ml/min/1.73 m^2.

Keywords	Atrial fibrillation; advanced chronic kidney disease; direct oral anticoagulants; vitamin K antagonists; anemia
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Atrial fibrillation (AF) is a common cause of ischemic stroke and other thromboembolic complications [1]. AF and chronic kidney disease (CKD) are the complications of the same underlying medical conditions: hypertension, diabetes, and atherosclerosis. Almost 30% of patients with AF have CKD, and 10–15% of patients with CKD have AF [2]. In the Russian Federation, the prevalence data on CKD with AF are limited to a few small studies [3–5], which is problematic for two reasons. First, CKD changes the pharmacokinetics and pharmacodynamics of many drugs, affecting treatment efficacy and adherence to treatment, which are of particular importance in thromboprophylaxis in AF [6, 7]. Anticoagulant therapy is an essential pharmacotherapeutic approach in AF. Under current recommendations, direct oral anticoagulants (DOACs) are preferred to vitamin-K antagonists (VKAs), as supported by several randomized trials [8–10]. The efficacy and safety of DOACs have been confirmed in subgroups of CKD

of varying severity, except for patients with glomerular filtration rate (GFR) of less than 30 mL/min/1.73 m² [11–13]. However, based on pharmacokinetic studies, direct factor Xa inhibitors rivaroxaban and apixaban were approved for use in GFR of not less than 15 mL/min/1.73 m² as medicinal products with reduced renal clearance [14]. The direct thrombin inhibitor dabigatran, which is excreted in urine (up to 80%), can be administered only when GFR is greater than 30 mL/min/1.73 m² [15, 16]. The administration of DOACs in advanced CKD (GFR less than 45 mL/min/1.73 m²) has not been studied in Russia. The second reason involves the high prevalence of anemia in CKD [17], which is accompanied by an increased risk of bleeding complications in this population and influences the decision on whether to administer anticoagulant therapy. Little research exists on current real-world practice of the administration of anticoagulant therapy in anemia and AF.

The objective of this study was to estimate the prevalence of CKD stage IIIb – V and the sustained decrease newly detected in GFR <30 mL/min/1.73 m² in patients with AF in clinical practice, and clarify patterns in the administration of anticoagulant therapy.

Materials and Methods

This study is a retrospective analysis of data from cardiology department patients of five primarily emergency medical care – oriented hospitals in Moscow. Discharge summaries of all patients hospitalized from June 1, 2016, to May 31, 2017, were reviewed. All patients 18 years and older diagnosed with AF were included at the first stage. At the second stage, patients with advanced CKD were selected: IIIb (GFR 45–30 mL/min/1.73 m²), IV (GFR 29–15 mL/min/1.73 m²), V (GFR <15 mL/min/1.73 m²), and newly diagnosed decrease in GFR to less than 30 mL/min/1.73 m² (decrease is considered sustained if registered in at least two tests during the hospitalization period). CKD was diagnosed under the KDIGO 2012 criteria, and GFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula [18]. Patients were put into the CKD group if the diagnosis was registered in previous medical records or was based on serum creatinine levels at least 3 months before the current admission. Indications for anticoagulant therapy were determined according to the Russian and European guidelines for AF using thromboembolic complication (TEC) risk score CHA2DS2-VASc and bleeding risk scores HAS-BLED [15, 19]. The classification of anemia was performed according to the recommendations of the World Health Organization [20]. The study was approved by the local ethics committee of I. M. Sechenov First Moscow State Medical University.

Statistical data processing was carried out using the IBM SPSS Statistics v23 software. The nominal variables were compared using a common value of significance for the groups. The significance of intergroup differences was estimated using the chi-square test. The differences were considered significant at $p<0.05$.

Results

From June 1, 2016, to May 31, 2017, a total of 9,725 patients were hospitalized in the cardiology departments. AF was diagnosed in 2,983 (31%) patients; among these GFR <45 mL/min/1.73 m² was detected in 27% (n=794, 47% males). Of the latter group, 516 (65%) patients were diagnosed with CKD stage IIIb – V, and 278 (35%) with newly detected decrease in GFR (Figure 1).

Among patients with AF and GFR <45 mL/min/1.73 m², patients with CKD stage IIIb (44%) and newly diagnosed decrease in GFR (35%) (Figure 2) were the most prevalent.

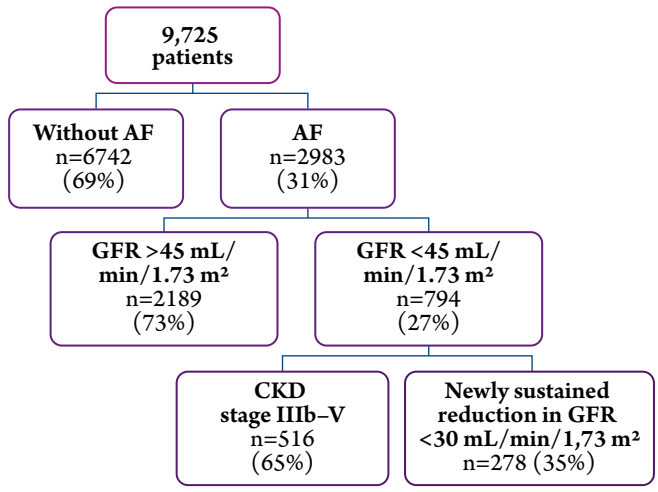
Most patients with AF had essential hypertension (n=2,804, 94%). Other comorbidities included: chronic heart failure (n=2117, 71%), coronary artery disease (n=1,938, 65%), and type 2 diabetes (n=686, 23%).

Sixty-three percent of patients with AF and GFR <45 mL/min/1.73 m² were diagnosed with anemia; 39% had moderate-to-severe anemia (Table 1). Among patients with CKD stage III, anemia was found in 207 (59%) patients, CKD stage IV in 110 (89%), CKD stage V in 43 (97%), and newly detected decrease in GFR in 145 (51%).

Distribution of patients according to the CHA2DS2-VASc and HAS-BLED scores is presented in Table 2.

In both the AF and AF+CKD groups, patients with high risk of bleeding (HAS-BLED >3 points) were prevalent: 1,850 (62%) and 612 (77%), respectively, as were as patients with the high risk of TEC (CHA2DS2-VASc 2–5 points): 1,789 (60%)

Figure 1. Distribution of patients by history of atrial fibrillation and chronic kidney disease



AF, atrial fibrillation; CKD, chronic kidney disease; GFR, glomerular filtration rate.

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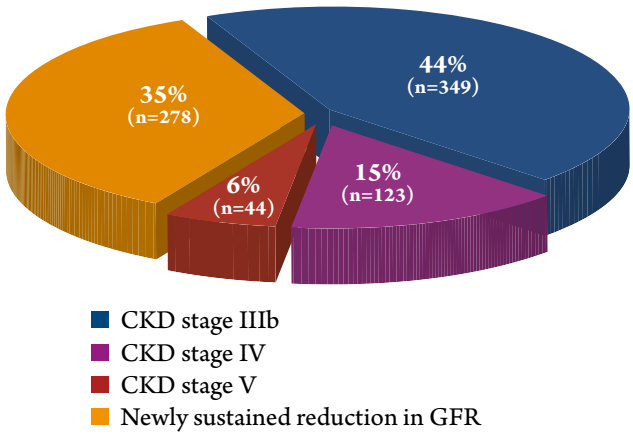
Table 1. Prevalence of anemia in patients with GFR <45 mL/min/1.73 m²

Severity of anemia (hemoglobin, g/L)		CKD stage IIIb (%)	CKD stage IV (%)	CKD stage V (%)	Newly detected decrease in GFR (%)
Mild	Males≤129	47 (13)	16 (13)	3 (7)	43 (15)
	Females ≤119	38 (11)	12 (9)	6 (13)	32 (11)
Moderate (≤109)		86 (25)	60 (48)	29 (66)	64 (23)
Severe (<80)		36 (10)	22 (19)	5 (11)	6 (2)
Total		207 (59)	110 (89)	43 (97)	145 (51)

Data are presented as the absolute number of patients (%). CKD, chronic kidney disease; GFR, glomeruler filtration rate.

Figure 2. Prevalence of CKD and VVS GFR in patients with AF (n=794)



CKD, chronic kidney disease; GFR, glomerular filtration rate.

and 420 (53%), respectively. There were more patients with CHA2DS2-VASc >6 points in the AF+CKD group.

Anticoagulant therapy recommendations made to study group patients at discharge were analyzed. Of the 2,983 patients with AF, anticoagulant therapy was recommended to 1,938 (65%); among patients with GFR <45 mL/min/1.73 m², anticoagulants were administered in 711 (89%). Distribution of the anticoagulant drugs recommended for each stage of CKD of interest and newly sustained reduction in GFR is shown in Figure 3 and Table 3.

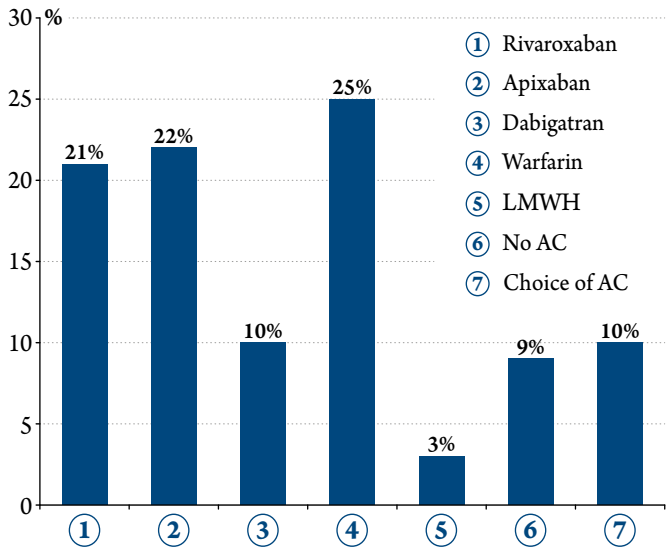
CKD stage IIIb patients were most commonly recommended rivaroxaban 15 mg; patients with CKD stage IV were most often recommended warfarin; patients with CKD stage V were most often not recommended an anticoagulant (p<0.005). Warfarin was administered more frequently in all patients with GFR <45 mL/min/1.73 m² than in patients with a newly sustained reduction in GFR. DOACs were administered in 53% of patients with GFR <45 mL/min/1.73 m² and in 42% of patients with GFR <30 mL/min/1.73 m². In the group with CKD stage IIIb, rivaroxaban 15 mg (29%) was the most commonly administered drug; in the group with CKD stage IV, warfarin (48%) was the most commonly administered; in the group with newly sustained reduction in GFR, apixaban 10 mg/day was most commonly administered.

Table 2. . Distribution of patients with AF and AF with GFR <45 mL/min/1.73 m2 in terms of risks of bleeding and thromboembolic complications

Score	AF, n=2,983 (%)	AF + CKD, n=794 (%)	p
HAS-BLED			
0–1 point	342 (11)	64 (8)	<0.001
2 points	791 (27)	118 (15)	
>3 points	1850 (62)	612 (77)	
CHA_2DS_2 -VASc			
0–1 point	269 (9)	11 (1)	<0.001
2–5 points	1789 (60)	420 (53)	
>6 points	2058 (31)	363 (46)	

AF, atrial fibrillation; CKD, chronic kidney disease..

Figure 3. Rate of administration of anticoagulant drugs at GRF <45 mL/min/1.73 m²



LMWH, low-molecular-weight heparins; AC, anticoagulant. Choice of AC, a new oral anticoagulant or warfarin is recommended.

Discussion

The relationship between AF and renal dysfunction has been described in many studies [21].

For the first time, however, this study presents data on the prevalence of CKD in patients with AF based on a sample of about 10,000 patients in Russia. Renal dysfunction (GFR

Table 3. Anticoagulant doses administered to patients with atrial fibrillation and GFR <45 mL/min/1.73 m²

Anticoagulant	CKD stage IIIb (%)	CKD stage IV (%)	CKD stage V (%)	Newly newly sustained reduction in GFR(%)	$p_{1,2}$	$p_{1,3}$	$p_{1,4}$	$p_{2,3}$	$p_{2,4}$	$p_{3,4}$
Rivaroxaban 15 mg/day	101 (29)	9 (7.4)	–	26 (9.1)	<0.001	<0.001	<0.001	0.06	0.56	0.036
Rivaroxaban 20 mg/day	6 (1.7)	2 (1.6)	–	21 (7.4)	0.95	0.37	0.005	0.39	0.021	0.06
Apixaban 5 mg/day	51 (14)	13 (10.6)	–	22 (7.6)	0.43	0.03	0.016	0.06	0.017	0.004
Apixaban 10 mg/day	34 (9)	9 (7.4)	–	46 (16.2)	0.27	0.006	0.006	0.023	0.33	0.06
Dabigatran 220 mg/day	30 (8.6)	3 (2.4)	–	27 (9.5)	0.02	0.04	0.7	0.29	0.013	0.032
Dabigatran 300 mg/day	9 (2.6)	1 (0.8)	–	12 (4.2)	0.24	0.27	0.25	0.07	0.54	0.16
Warfarin	79 (22.8)	59 (48)	11 (25)	51 (18)	<0.001	0.74	0.13	0.006	<0.001	0.27
LMWH	7 (2)	4 (3.3)	9 (20.5)	4 (1.4)	0.72	0.13	<0.001	0.17	0.001	0.005
Choice of AC*	17 (4.9)	5 (4.1)	–	43 (15.1)	0.42	<0.001	0.56	0.003	0.21	<0.001
AC not recommended	12 (3.4)	16 (13.2)	24 (54.5)	31 (10.9)	0.001	<0.001	0.002	<0.001	0.51	<0.001

XData are presented as the absolute number of patients (%). CKD, chronic kidney disease;
LMWH, low-molecular-weight heparins; AC, anticoagulant. *Choice of AC, a new oral anticoagulant or warfarin is recommended.

<45 mL/min/1.73 m²) was reported in 27% of patients with AF. Patients with CKD stage IIIb (44% of patients with GFR <45 mL/min/1.73 m² and 13% of all patients with AF) were prevalent; most had a newly detected decrease in GFR (35%, and 7% respectively). CKD stage IV was found in 15% (4% of all patients with AF); CKD stage V was found in 4% (1% of all patients with AF). The data obtained are closest to the results of the Barrios et al. register [22], in which of 3,287 patients hospitalized with newly registered AF paroxysm, GFR <60 mL/min/1.73 m² was detected in 33.8% – of whom 1.6% had GFR <30 mL/min/1.73 m² (in our study, 5% of patients had GFR <30 mL/min/1.73 m²). According to a national register, of the 388 patients with AF, CKD stage III was diagnosed in 39% and CKD stage IV in 5% [4]; in a similar retrospective analysis of 897 patients with AF, CKD stage IIIb was identified in 16.2% and CKD stage IV in 2.7% [23].

The present work represents the first time that patients with a newly sustained reduction in GFR were distinguished in such a study; it should be noted that the criteria for CKD diagnosis were not met in this case because of the unknown duration of the decrease in GFR [24]. However, we suggest that patients with a newly detected decrease in GFR did have CKD of an unknown duration, although it is impossible to identify the stage in such cases. These patients have no history of kidney disorders, and therefore blood levels of creatinine before the current hospitalization are not known. The proportion of patients with a newly detected decrease in GFR in the study is rather high (15% of all patients with CKD and 7% of all patients with AF). As yet, there are no guidelines for the doses of anticoagulants for such patients. In routine clinical practice, DOAC doses are adjusted based on drug serum levels, and later therapy is corrected depending on the dynamics of GFR. Due to irregular dynamics of creatinine levels, patients in this group should be monitored.

Anemia is a common complication of CKD [5]. According to this and similar studies [25, 26], the severity of anemia regularly increases as CKD progresses. In this study, mild anemia was found in 25% of patients, moderate-to-severe anemia in the majority of patients with CKD stage V (77%) and in 67% of patients with CKD stage IV; anemia was less frequently in CKD stage IIIb and newly detected decrease in GFR (35% and 25%), respectively. Patients with anemia (hemoglobin <100 g/L) and AF have not been included in large studies of antithrombotic drugs because of the high risk of bleeding. Only one study on the efficacy and safety of anticoagulants in AF and anemia has been published to date [27]. The study included 20,325 patients with AF; anticoagulants were administered in 33.3% of cases with mild anemia (20% of total patients) and in 23.1% of cases with moderate-to-severe anemia (13.7% of total patients). In mild anemia, anticoagulant therapy decreased the risk of TEC (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.39–0.80). In moderate-to-severe anemia, the risk of thromboembolic events did not decrease (OR 1.01, 95% CI 0.66–1.55), but bleeding risk increased (OR 1.59, 95% CI 1.15–2.18).

According to our data, the rate of anticoagulant administration in patients with AF and advanced CKD is very high (89%). This is likely due to a regular increase in the risk of TEC as CKD progresses, as shown by our analysis (see Table 2) and similar studies [28]. Interestingly, in some cases doses of anticoagulants were not adjusted depending on GFR, predominantly in patients with a newly detected decrease in GFR (see Table 3). The highest rate of mistakes was observed for the administration of apixaban (dose was in 16% of cases) and dabigatran (it was recommended to 13% of patients, at a dose of 300 mg/day to 4% of them, yet it is contraindicated in GRF <30 mL/min/1.73 m²); more rarely, mistakes were observed in the case of rivaroxaban (a full dose was administered in 7% of cases). This may indicate that if there is no history of CKD, the current state of renal function does not always receive the proper clinical attention. In the CKD stage IV group, dosage was most frequently exceeded for apixaban 10 mg, followed by

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dabigatran or rivarixaban 20 mg, apixaban was most frequently administered, at a dose higher than the recommended 10 mg (7.4%);. In group CKD stage IV, apixaban was the most frequently administered, prescribed at a dose exceeding the recommended 10 mg (7.4%); less frequently, dabigatran (3%) or rivaroxaban 20 mg (1.6%) was administered. It should be noted that no anticoagulant was recommended to a large number of patients, predominantly in CKD stage V (54.5%) group, which may be attributed to the lack of clinical studies of DOACs in such patients, as well as increased risk of bleeding as CKD progresses (see Table 2).

In a similar study by Ramagopalan et al. [29], carried out between 2013 and 2017 among 18,419 patients with newly diagnosed AF, a group of patients with AF and GFR <30 mL/min/1.73 m^2 was identified (n=1,857). DOACs were recommended to 13% of patients with CKD stage IV and 14% of patients with CKD stage V. Anticoagulant therapy was not administered in half of the total cases; most patients took warfarin (30% and 37% with CKD stage IV and stage V, respectively). Data received suggest that cardiologists have begun to prescribe DOACs to patients with advanced CKD.

It should be noted that according to a recent systematic review of the 8,008 clinical studies of thromboprophylaxis, only 10 studies compared DOACs with warfarin in patients with CKD stage III–V [30]. Coleman et al. [31] conducted a retrospective analysis of two groups of patients (n=777) with a moderate-to-severe decrease in GFR who took rivaroxaban (20 mg or 15 mg) or warfarin at the ratio 1:1. Their findings are consistent with the results of the ROCKET-AF study, and outcomes of patients receiving the lower dose (15 mg) were comparable with the results of the ROCKET-AF study cohort. In 2017, Stanton et al. [32] carried out a retrospective multicenter study, including 146 patients with AF and GFR <25 mL/min/1.73 m^2 who took warfarin or apixaban 5 mg/day. No significant differences were found in the incidence of major bleeds and ischemic stroke (9.6% vs. 17.8%, p=0.149 and 21.9% vs. 27.4%, p=0,442, respectively).

Particular attention should be given to patients with CKD stage V, including those who receive renal replacement therapy. Coleman et al. [33] performed a prospective study, including 1,896 patients receiving rivaroxaban (38.7% < 20 mg/day) and 4,848 patients receiving warfarin, with CKD stage IV and stage V (88%) and newly diagnosed AF (mean follow-up period was 16 months). The findings indicate a better safety profile for rivaroxaban versus warfarin: 32% (95% CI from 1% to 53%) fewer major bleeds (including intracranial and gastrointestinal). Siontis et al. confirmed the safety of direct factor Xa inhibitors in patients with CKD stage V [34].

Conclusion

One in four patients included in the study with atrial fibrillation had a decrease in glomerular filtration rate <45 mL/min/1.73 m^2; of these, a newly sustained reduction in glomerular filtration rate <30 mL/min/1.73 m^2 was detected in one in three – these were patients in whom a dose of the administered anticoagulant was most commonly not in line with glomerular filtration rate. Direct oral anticoagulants were recommended to 50% of patients with glomerular filtration rate <45 mL/min/1.73 m^2 and 42% patients with glomerular filtration rate <30 mL/min/1.73 m^2. Direct oral anticoagulants are not administered in patients with chronic kidney disease stage V; in 50% of the cases, no anticoagulant drugs were recommended.

Study limitations

This retrospective study was limited to the period of hospitalization, which does not allow extrapolating the findings, in general, to patients with advanced chronic kidney disease and atrial fibrillation. The study was not aimed at the assessment of adherence to treatment or the incidence of bleeding and ischemic complications.

No conflict of interest is reported.

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