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Review Article

Atrial fibrillation in patients with chronic kidney disease: features of pathogenesis and treatment

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Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia in adults, the frequency of which increases in patients with chronic kidney disease (CKD). The substrate for the development of AF is atrial cardiomyopathy, which includes structural, electrophysiological and molecular remodeling of the atria. AF, in turn, can initiate and accelerate the progression of CKD. Such a bidirectional relationship causes a frequent combination of these two conditions, leading to both a prothrombotic state and an increased risk of bleeding. In patients with CKD, the pharmacokinetics of drugs used in AF are changing, what limits their use in CKD S4/S5. If previously patients with CKD S4-5 were excluded from randomized clinical trials (RCTs) on treatment strategies for AF, a number of such studies on their management have been published to date. The purpose of the article is to review existing ideas about the features of the pathogenesis of AF in CKD and strategies of recent years for the treatment of AF with advanced stages of CKD.

Keywords: chronic kidney disease (CKD); atrial fibrillation (AF); pathophysiology; inflammasoma; atrial fibrosis; treatment.

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Обзорная статья

Фибрилляция предсердий у пациентов с хронической болезнью почек: особенности патогенеза и лечения

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Фибрилляция предсердий (ФП) наиболее часто диагностируемая сердечная аритмия у взрослых, частота которой увеличивается при хронической болезни почек (ХБП). Субстратом развития ФП является предсердная кардиомиопатия, включающая в себя структурное, электрофизиологическое и молекулярное ремоделирование предсердий. ФП, в свою очередь, может инициировать и ускорять прогрессирование ХБП. Такая двунаправленная взаимосвязь обусловливает частое сочетание этих двух состояний, приводящее как к протромботическому состоянию, так и к повышению риска развития кровотечений. У пациентов с ХБП меняется фармакокинетика лекарственных препаратов, используемых при ФП, что ограничивает их применение при ХБП 4-5-й стадии. Ранее пациентов с ХБП 4-5-й стадии исключали из рандомизированных клинических исследований (РКИ) по лечебным стратегиям при ФП, однако к настоящему времени опубликован ряд исследований по их лечению. Цель статьи — обзор существующих представлений об особенностях патогенеза ФП при ХБП и стратегий последних лет по лечению ФП с поздними стадиями ХБП.

Ключевые слова: хроническая болезнь почек (ХБП); фибрилляция предсердий (ФП); патофизиология; инфламмасома; предсердный фиброз; лечение.

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ЭКО•ВЕКТОР

BACKGROUND

Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia in adults around the world, the global prevalence of which tends to increase [1]. AF is associated with serious complications such as stroke and heart failure leading to significant morbidity and mortality [2, 3]. Chronic kidney disease (CKD) is one of the risk factors for the development of AF, defined as the presence of markers of kidney damage (albumin/creatinine ratio > 30 mg/g in a single urinalysis is usually used for screening) or a decrease in glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2, persisting ⩾ 3 months. Based on the presence of markers of damage and the level of GFR, the following stages of CKD are distinguished: S1 — ⩾ 90 (high or optimal), S2 — 60-89 (slightly reduced), S3a — 45–59 (moderately reduced), S3b — 30–44 (significantly reduced), S4 — 15–29 (drastically reduced), S5 — < 15 ml / min / 1.73 m^2 (end-stage renal disease, ESRD) [4]. CKD is a rapidly growing public health problem, with a global prevalence of CKD estimated at 9.1–13.4% [4, 5]. Patients with CKD demonstrate an increased risk of developing AF and other cardiovascular diseases, which are the most common cause of death in CKD patients [4].

CKD and AF have a number of common predisposing factors, including arterial hypertension, coronary heart disease, and diabetes mellitus [6–8]. Patients with CKD are characterized by such comorbidity, however, even after adjustments for many co-factors, CKD remains an independent factor in the development of AF [6, 8]. In turn, AF can initiate and accelerate the progression of CKD. Such a bidirectional relationship causes a frequent combination of these two conditions, which worsens the prognosis, leads, on the one hand, to a prothrombotic state, and, on the other hand, to an increased risk of bleeding. Renal dysfunction is accompanied by a change in the pharmacokinetics of many drugs that are indicated for use in people with CKD, including direct oral anticoagulants (DOACs), which limits their use in S4-5 CKD. However, since the risk of thromboembolic complications increases with decreasing GFR, more so than the risk of bleeding, efforts continue to find the optimal treatment for AF in this patient population. While previously patients with AF and S4-5 CKD were excluded from randomized clinical trials (RCTs) on treatment strategies for AF, a number of RCTs on the tactics of managing these patients have been published to date [9–11].

EPIDEMIOLOGY

A meta-analysis of the risk of developing AF depending on kidney function in a study that included 16.769 participants of different ethnic groups, divided by categories of decrease in estimated GFR (eGFR), showed a gradual increase in the risk of developing AF: RR (95% CI) was 1.00, 1.09 (0.97–1.24), 1.17 (1.00–1.38), 1.59 (1.28–1.98) and 2.03 (1.40–2.96) at S1, S2, S3a, S3b, S4, respectively [12]. A South Korean study (*n* = 4,827,987) also noted an increase in the risk of developing AF depending on the severity of CKD: RR (95% CI) was 1.77 (1.69–1.85), 1.85 (1.85 80–1.91), 1.99 (1.95–2.04) and 4.04 (3.07–5.33) in persons with CKD stages 1, 2, 3 and 4, respectively, compared with persons without CKD [13]. In the ARIC study (*n* = 10328), a decrease in eGFR to 30–50 and 15–29 ml/min/1.73 m^2 was accompanied by an increase in the risk of developing AF by 1.6 and 3.2 times compared with that in individuals with normal renal function [14]. In a meta-analysis of 25 RCTs of patients with ESRD, the incidence of AF was 11.6% of patients [15]. In general, it is believed that the prevalence of AF in CKD is 2–3 times higher than AF in the general population [7]. And, conversely, as the analysis of the Russian REQUAZA registry showed, almost half of patients with AF may have concomitant renal pathology [16].

POTENTIAL MECHANISMS FOR THE DEVELOPMNT OF ATRIAL FIBRILLATION IN CHRONIC KIDNEY DISEASE

The mechanisms of development of AF are not fully understood. The substrate for AF is atrial cardiomyopathy, which is a complex of structural, electrophysiological, and molecular changes in the atrial myocardium that can cause and maintain AF [2]. The term "atrial cardiomyopathy" and the definition were given by the experts of the international Working Group formed by the European Heart Rhythm Association (EHRA), the International and Asia-Pacific Heart Rhythm Societies (HRS and APHRS respectively) and the Latin American Society for Cardiac Pacing and Electrophysiology (SOLAECE). The consensus report published by EHRA/HRS/APHRS/SOLAECE presents a classification of atrial cardiomyopathy and summarizes the existing concepts of structural and electrophysiological remodeling of the heart in AF [17].

As already noted, the development of AF in CKD has a number of common risk factors with other diseases, however, non-traditional risk factors for the development of AF are identified. These include activation of the renin-angiotensin-aldosterone system (RAAS) and hyperactivity of the sympathoadrenal system (SAS), oxidative stress, systemic inflammation, electrolyte disturbances, accumulation of uremic toxins, and chronic anemia [6–8]. These factors are difficult to isolate from others involved in atrial remodeling and are common risk factors for the development of AF, leading to atrial volume or pressure overload, however, the contribution of “renal” factors to the development of AF is generally recognized [6, 8]. Traditional Framingham risk factors for cardiovascular disease have a weak predictive power in CKD, and the addition of specific renal factors significantly improves the correlation [18].

Renin-angiotensin-aldosterone system (RAAS). Activation of the RAAS and its mediators is a major factor in the pathogenesis and progression of CKD [7].

Angiotensin II (AngII) has profibrotic activity. AII in combination with aldosterone promotes the production of reactive oxygen species by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which in turn stimulates the production of transforming growth factor β1 (TGF-β1). In general, the RAAS, with the help of its mediators, initiates oxidative stress and the synthesis of profibrotic growth factors, the production of pro-inflammatory cytokines, cell adhesion molecules, extracellular matrix proteins, plasminogen activator inhibitor-1 (PAI-1), promotes the activation of macrophages [7]. RAAS activation is seen as an important link between CKD and AF. In the formation of an arrhythmogenic substrate in the heart in AF, three interrelated pathways are believed to be involved — RAAS, TGF-β1 and oxidative stress; the atria appear to be more susceptible to fibrosis than the ventricles [7, 19]. In a transgenic mouse model overexpressing the constitutively active form of TGF-β1, selective atrial fibrosis was observed, which led to heterogeneous conduction and increased atrial vulnerability to AF [20]. RAAS can also induce the activation of the TGF-β1/Smad2/3 pathway, which is also promoted by an increased level of reactive oxygen species and oxidative stress [21]. An experimental decrease in TGF-β1 expression with pirfenidone reduces the degree of fibrosis in the lungs, liver, kidneys, and heart [7]. A study in nephrectomy rats, which are used to model the pathogenesis of human CKD, demonstrates the role of oxidative stress mediated by NADPH oxidases in causing left atrial fibrosis and increased vulnerability to AF. Treatment with a powerful antioxidant, zinc sodium dihydrolipoyl histidinate, was effective in reducing the inducibility of AF [7, 22].

Inflammation. CKD is considered a systemic inflammatory disease with many causes [23]. Elevated levels of inflammatory markers (IL-6, tumor necrosis factor-α, C-reactive protein, etc.) are found in the early stages of CKD, which become more significant as the disease progresses [24]. It is also known that elevated blood levels of pro-inflammatory cytokines and inflammatory markers are associated with an increase in the frequency and persistence of AF [25]. There is no evidence of a direct relationship between the level of circulating inflammation markers and the formation of fibrosis in the atria, however, data have been obtained on the activation of the NLRP3 inflammosome in cardiomyocytes in AF and its role in atrial remodeling in CKD [21, 26]. Compared to the well-established canonical function of the NLRP3 inflammasome in innate immune cells, mediating caspase-1 activation and interleukin-1β (IL-1β) release, the role of the NLRP3 inflammasome in cardiac cells and other non-immune human cells is less well known. The first study that provided evidence of NLRP3 inflammasome activation in heart cells as a key event in the pathogenesis of AF was published in 2018 [26]. Cardiomyocyte-specific knockdown in a mouse model (CM-KI) expressing constitutively active NLRP3 inflammasomes only in cardiomyocytes caused 100% premature atrial contractions with a significant increase in induced AF. MCC950, a selective inflammasome inhibitor, successfully reduced induced AF in CM-KI mice [26].

In the same year, the results of a study were presented demonstrating the presence in the atrial myocardium of rats serving as a model of CKD, components of the NLRP3 inflammasome activation and other biological pathways (Fig. 1) involved in the formation of an arrhythmogenic substrate in CKD [21]. The CKD model in the study was rats, in which 3 months after partial nephrectomy (of the right kidney and nephrotomy 5/6 of the left kidney), the level of circulating creatinine and urea was significantly increased. Also, at that time there were signs of RAAS activation: the blood level of AngII and TGFβ1 was 3 times higher than in the control, which was served by rats without CKD after laparotomy without kidney resection. The left atrial tissue (LA) was quantitatively tested for the severity of fibrosis and inflammation, expression of type I collagen, α-SMA (α-smooth muscle actin), CTGF (connective tissue growth factor), N-cadherin, expression and distribution of connexins 40 and 43 (Cx40 and Cx43 are the two major functional subunits of intercellular gap junctions in the atria) using immunohistochemistry. Any changes in expression, phosphorylation (regulator of gap channel activity in the transport of molecules, Ca ions) and distribution of atrial connexins were considered as proarrhythmic. The amount of TGFβ1, phosphorylated (activated) Smad 2 and Smad 3 (signal transduction mediators), α-SMA, type I collagen, NLRP3, ASC (inflammasome component), caspase-1, IL-1β, IL-18, Rac-1, Cx40, Cx43 (total and phosphorylated) were assessed in the atria by Western blotting. According to echocardiography, uremia in rats led to an increase in LA and left ventricular hypertrophy (LVH) without functional changes in the latter. There was a significantly higher frequency of AF occurrence provoked by atrial electrical stimulation in the CKD group compared with the control group ($p < 0.001$) and the duration of AF paroxysms in CKD ($p < 0.001$). Studies using immunohistochemistry, biochemical, enzyme-linked immunosorbent assays, and Western blotting made it possible to identify participants in the activation of biological pathways in the atrial tissue (Fig. 1). TGF-β1/Smad2/3/CTGF, NLRP3 inflammasome and connexins (Cx), present in cardiac cells, have been shown to be potential mediators of increased vulnerability to AF in CKD. Fibrosis and remodeling of Cx40/43-gap intercellular junctions are regarded as the main pathological substrate in the development of AF. There was a decrease in phosphorylated Cx43 (activated), a decrease in Cx40 and a lateral distribution (instead of diffuse) of Cx40 and Cx43 on the cell surface against the background of an increase in Rac-1 (a signaling protein from the family of small G proteins), CTGF and N-cadherin, activating the synthesis of collagen, which disrupts the function of connexins (Fig. 1) [21].

Thus, the researchers demonstrated the activation of biological pathways in the atrial myocardium, leading to

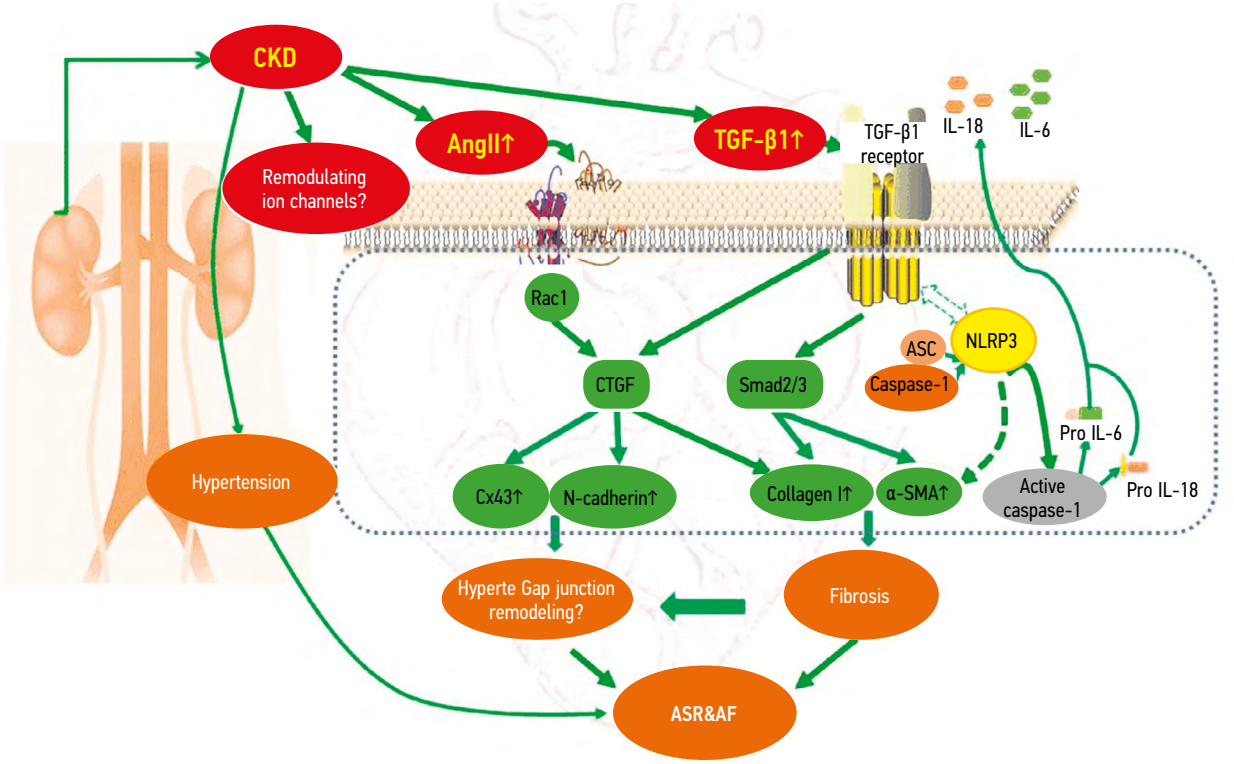

Fig. 1. Potential biological pathways involved in the formation of arrhythmogenic substrate of atrial fibrillation (AF) in chronic kidney disease (CKD). Atrial fibrosis induced by CKD may be associated with activation of the TGFβ1/Smads signaling pathway and NLRP3 inflammasome signaling pathway, and the CKD induced Cx40/43- gap junction remodeling may be connected with the Ang II-induced activation of Rac-1, CTGF and N-cadherin in atrial cells. Ang II — angiotensin II; ASC — apoptosis-associated Speck-like protein containing the C-terminal CARD domain; ASR — structural remodeling of the atria; α-SMA — α-smooth muscle actin; CTGF — connective tissue growth factor; Cx43 — connexin 43; IL-1β, -18 — interleukin-1β, -18; NLRP3 — NOD-like receptor (NLR) containing pyrin domain 3; Rac1 — intracellular protein involved in cellular signal transduction from a family of small G-proteins (small GTTases); TGF-β1 — transforming growth factor-β1 (adapted from [21])

inflammation and increased fibroplastic processes, which resulted in an extensive interstitial process in the atria and increased arrhythmogenicity, showed the relationship of these processes with azotemia, increased levels in the blood and in the atria RAAS mediators — AngII, TGF-β1 [21]. The role of RAAS in the pathogenesis of AF is supported by clinical data and studies in animal models showing that the use of angiotensin converting enzyme inhibitors reduces the incidence of AF and the level of atrial fibrosis [2, 7]. However, a complete understanding of the processes in atrial cells is still a long way off. Probably, in AF, both in the general population and in CKD, general processes in the atrial myocardium take place, and triggers may be more specific. Selective inhibition of various members of the NLRP3 inflammasome complex, the impact on participants in other biological pathways that implement the processes of atrial remodeling, may in the future become an effective therapeutic method in the prevention of AF. The large-scale clinical trial CANTOS showed that selective suppression of IL-1β with the monoclonal antibody canakinumab can significantly reduce the incidence of recurrent cardiovascular events [27].

Uremic toxins, oxidative stress, disorders of phosphorus-calcium (P-Ca) metabolism. Disruption of systemic and intracellular calcium homeostasis in CKD is a critical element in the pathogenesis of AF. Ca^{2+} plays a central role in atrial ectopic activity, re-entry formation, and electrophysiological atrial remodeling [7]. In a rat model of CKD, the effect of indoxyl sulfate (IS), a uremic toxin, on the calcium content in cardiomyocytes isolated from the left atrium (LA), right atrium (RA), sinoatrial node and orifice of the pulmonary veins (PV) was studied [28]. Important electrical changes were noted, including delayed post-depolarization in the PV, decreased spontaneous sinoatrial node activation, shortening of the LA action potential, and increased inducibility of AF. Ascorbic acid, as an antioxidant, weakened the effect of the toxin on the cardiomyocytes of LA PV, and sinoatrial node. According to the authors, the uremic toxin indoxyl sulfate promotes atrial and PV arrhythmogenesis by inducing oxidative stress and disturbances in Ca^{2+} current through ion channels, intracellular Ca^{2+} homeostasis, and may be a factor in the occurrence of AF in patients with CKD [28]. In another study, CKD led to significant disturbances in calcium homeostasis in pulmonary venous cardiomyocytes, such as an increase in the amplitude of calcium transport and calcium content in the sarcoplasmic reticulum, large sodium/calcium exchange currents, but a lower density of calcium currents in *L*-type channels due to the activation of protein kinase A and accumulation of reactive oxygen species [7]. Changes in Ca-P metabolism in CKD

predispose to valvular heart disease in the form of calcification of the mitral annulus or aortic valve, and may further contribute to the development of AF due to pressure overload. Vascular calcification, observed even in children with progressive CKD, increases afterload and is a risk factor for the development of LVH and subsequent LA overload [7].

Other uremic toxins (indole-3-acetic acid, *p*-cresol, and *p*-cresyl sulfate) that accumulate in CKD are also involved in oxidative stress, inflammation, and neurohumoral activation pathways leading to cardiovascular fibrosis and oxidative damage. The development of AF in CKD may be due to increased regulation of the SAS and an increased risk of cardiovascular diseases [7].

Molecular remodeling. In addition to the molecular processes described above that occur in atrial cardiomyopathy, new disturbances in various biological pathways in the atria are being identified. The use of next generation gene sequencing (NGS) methods allowed researchers to identify changes in 378 genes expressed in the heart in CKD [29]. Quantitative analysis of the expression of RNA transcripts showed genes with significantly increased expression, among which were the genes for stress-induced proteins — CIRP (cold-induced RNA-binding protein) and RBM3 (RNA-binding motif protein), associated with the functioning of ion channels, and changes in their expression may underlie ion channel remodeling in CKD.

Studies have appeared that emphasize the role of chronic anemia and the participation of hypoxia-inducible factor 1α (HIF-1α), as well as Klotho protein (co-factor FGF23) in the development of arrhythmogenicity. The authors believe that the responses of cardiac cells to stress are potential targets for pharmacological intervention in CKD-induced cardiac arrhythmias [29].

MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION AND CHRONIC KIDNEY DISEASE

Patient management includes stroke prevention (anticoagulation), treatment of AF in the form of symptom control (rhythm control or heart rate control), optimization of treatment of underlying and concomitant diseases.

Assessment of the risk of thromboembolic complications in patients with AF and chronic kidney disease

AF and CKD, each by itself, are risk factors for acute cerebrovascular accident (ACV). AF and CKD contribute to the formation of blood clots due to the influence on individual components of the Virchow triad [30]. In AF, ischemic stroke (IS) and systemic thromboembolism (SE) most often have a cardioembolic origin, which is associated with stagnation of blood in the LA and the formation of a thrombus in the ear, less often — in the cavity of the LA. On the other hand, endothelial dysfunction and platelet activation are noted already in the early stages of CKD, and the risk of thromboembolic complications (TEC) is increased both at the pre-dialysis stage of CKD and during dialysis [30]. The high risk of TEC is the most important problem in CKD patients with AF [6, 8]. The CHA2DS2-VASc score is recommended for stratifying the risk of stroke and systemic embolism in patients with AF in the general population and in AF with CKD. Continuous use of oral anticoagulants (OAC) with a score of ⩾ 2 in men and ⩾3 in women is associated with favorable effects in AF, including CKD (with a lower risk, the issue of prescribing OAC is decided individually) [6, 31].

Bleedings risk assessment

Patients with CKD have an increased risk of bleeding compared with the general population. Thus, the presence of reduced kidney function (GFR < 60 ml/min/1.73 m^2) leads to an increase in the risk of hemorrhagic stroke by more than 4 times in men and 7 times in women [32]. Bleeding risk scales, in particular the HAS-BLED scale, take into account the presence of CKD, and the risk of bleeding when prescribing oral anticoagulants (OAC) should be taken into account [2, 3, 6]. The value of the HAS-BLED index ⩾ 3 indicates a high risk of bleeding, but does not exclude the possibility of anticoagulant therapy, since in most cases the risk of IS and SE is higher than the risk of bleeding. Absolute contraindications to OAC therapy in CKD are the same as in the general population [6].

Prescription of OAC in CKD S1-3. VKAs (vitamin K antagonists) are effective and relatively safe in maintaining international normalized ratio (INR) in the therapeutic range > 70% of the time (TRT). The frequency of hemorrhagic and thromboembolic events correlates with the quality of VKA treatment, as assessed by TRT [2, 3, 32].

All DOACs including direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban) have a certain degree of renal excretion, ranging from 25% for apixaban to 80% for dabigatran, which should be taken into account in the treatment of patients with CKD [2, 3, 6].

The results of RCTs and observational studies have shown that in patients with mild to moderately reduced renal function — creatinine clearance (CC) 30–50 ml/min (for apixaban 25–50 ml/min), calculated according to Cockcroft-Gault, dabigatran, rivaroxaban and apixaban are equally comparable to warfarin in terms of its effect in stroke prevention [6, 32]. Also, in all major RCTs, the use of DOACs in patients with CC in the range of 30–50 ml/min (for apixaban — 25–50 ml/min) was associated with a significant reduction (~ 50%) in the risk of intracranial hemorrhage compared with warfarin [33].

In patients with moderate renal impairment, the concentration of rivaroxaban in the plasma after a dose of 15 mg once per day was identical to the concentration of rivaroxaban in the blood plasma in people with normal renal function after taking 20 mg once per day. A renal dose study was planned in the ROCKET AF design, where all patients

Table 1. Recommendations for the use of oral anticoagulant drugs in atrial fibrillation, depending on creatinine clearance[1]

CKD stage	CC, ml/min	Drug, dose, frequency
1 и 2	⩾ 90 и 60–89	Warfarin, target INR 2.0–3.0 Dabigatran[2] 150 mg twice per day or 110 mg twice per day Rivaroxaban 20 mg once per day Apixaban, 5 mg, twice per day
3	30–59	Warfarin, target INR 2.0–3.0 Dabigatran[2] 150 mg twice per day or 110 mg twice per day Rivaroxaban [3] 15 mg once per day or Rivaroxaban 20 mg once per day if CC ⩾ 50 ml/min Apixaban[4] 5 mg or 2.5 mg twice per day
4	15–29	Warfarin, target INR 2.0–3.0 Rivaroxaban [3] 15 mg once per day Apixaban [4] 2,5 mg twice per day
5	< 15 ml/min, hemodialysis	Warfarin, target INR 2.0–3.0

[1] CC — creatinine clearance estimated by Cockcroft–Gault formula;
[2] reducing the dose is not associated with CC; see Table 2 for reducing the dose criteria;
[3] reducing the dose if CC is equal to 15–49 ml/min;
[4] reducing the dose if creatinine ⩾ 133 mmol/l; for additional criteria, see Table 2.

Table 2. Recommendations for reducing the dose of oral anticoagulant drugs in atrial fibrillation [3]

	Dabigatran	Rivaroxaban	Apixaban
Standard dose	150 mg twice per day	20 mg once per day	5 twice per day
Reduced dose	110 mg twice per day	15 mg once per day	2,5 twice per day
Dose reduction criteria	• Age ⩾ 80 years • Concomitant use of verapamil or • Increased risk of bleeding	CC 15–49 ml/min[1]	At least 2 of 3 criteria: • Age ⩾ 80 years • Body weight ⩽ 60 kg or • Serum creatinine ⩾ 133 μmol/l

[1] CC — creatinine clearance estimated by Cockcroft-Gault formula

with CC 30–49 ml/min received rivaroxaban at a dose of 15 mg once per day [34]. Recommended doses of OAC are presented in Table 1.

The choice of the dose of dabigartan and apixaban in patients with CC > 30 ml / min takes into account several risk factors for bleeding indicated in the instructions (Table 2). In the absence of these recommendations for dose reduction, it is necessary to strive for the appointment of a full dose of drugs [2, 3].

Prescription of OAC in CKD S4. Given the recommendations of drug manufacturers, patients with CC < 30 ml/min have historically been excluded from RCTs on treatment strategies, so there is no evidence base for prescribing DOACs with CC ⩽ 15–29 ml/min [6]. However, according to Russian and European recommendations, the use of direct factor Xa inhibitors, apixaban and rivaroxaban (but not dabigatran) at reduced doses is allowed in patients with AF and CC 15–29 ml/min (Table 1, 2), taking into account their pharmacokinetic properties, and relying on the results obtained in 2 cohort controlled studies [2, 3, 35, 36]. At the same time, the US FDA approved the use of dabigatran at a reduced dose of 75 mg twice daily, with a CC of 15–29 ml/min [6]. VKAs have conflicting observational data on their efficacy and safety, ranging from an increased risk of death in warfarin users to a clear benefit, but their use is independent of kidney function and is not contraindicated for the prevention of stroke and SE in CKD S4-5 [6, 32].

Prescription of OAC in CKD S5 and CKD S5(D). According to the latest recommendations for AF, instructions from manufacturers of drugs registered in the Russian Federation, the use of DOACs is not indicated for patients with CC < 15 ml/min (CKD S5 and CKD S5(D)), that is, both for people without dialysis and receiving chronic hemodialysis (CHD) [2, 3]. VKAs are approved for use in patients with AF and CKD S5/S5(D) with recommendations for individual risk assessment; an important condition for efficacy and safety is the patient's stay ⩾70% of the time in the recommended INR range. It has been noted that more severe stages of CKD are associated with a decrease in the period of INR stay in the therapeutic range [37, 38]. VKA can lead to CKD/exacerbation of CKD stage as a result of recurrent subclinical glomerular hemorrhages or accelerated tissue

and vascular calcification [37–39]. Available information on the efficacy and safety of VKA use in patients with AF and CKD S5/S5(D) is conflicting, and there are no large RCTs [37]. The results of a prospective study evaluating hemorrhagic and thrombotic risks with VKAs versus no anticoagulants in patients with AF and CKD on CGD are pending (AVKDIAL, NCT02886962). According to Russian clinical guidelines 2020, the decision on the need for OAC and the choice of an anticoagulant in patients with S5/S5(D) CKD should be made by a multidisciplinary team of specialists, taking into account all the characteristics of the patient. If, during warfarin therapy, INR values are often outside the target range (TRT < 70%), the possibility of prescribing DOACs should be discussed [2]. Experts participating in the KDIGO 2016 consensus conference suggest the use of apixaban at a reduced dose of 2.5 mg twice daily in CKD S5/S5(D) [6]. Apixaban is also licensed in some European countries for the prevention of stroke/SE in patients with S5/S5(D) CKD at a reduced dose of 2.5 mg twice daily [9]. The US FDA approved the use of apixaban 5 mg twice daily (with dose reduction if necessary) and rivaroxaban 15 mg twice daily in CKD S5 and CKD S5(D) based on limited pharmacokinetic and pharmacodynamic data without clinical data security [6]. Recently, the results of small RCTs have appeared, indicating a comparable safety with warfarin for the use of apixaban in patients with CC < 15 ml/min, or who need chronic hemodialysis.

A South Korean study published in 2023 examined the relative safety and efficacy of DOACs versus warfarin or no OAC in 260 patients with AF and S4/S5(D) CKD from the CODE-AF registry, divided into 3 equivalent group, with a median follow-up of 24 months. [10]. Serious/clinically significant bleeding happened less often in the DOAC group compared to the warfarin group (*RR* = 0.11; 95% CI 0.01–0.93; *p* = 0.043). There were also fewer adverse outcomes summarizing efficacy (thromboembolic complications, death) in the DOAC group compared to the group without OAC (RR 0.16; 95% CI 0.03-0.91; *p* = 0.039) [10].

An expected prospective RCT AXADIA comparing the efficacy and safety of apiscaban 2.5 mg twice daily with VKA, phenprocoumon (INR 2.0-3.0) was published in 2023 involving 97 patients with CKD S5(D) out of 39 medical centers [9]. Serious or clinically significant bleedings were observed in 45.8% of those treated with apixaban, and insignificantly more often in 51.0% of those treated with phenprocoumon; *RR* = 0.93 (95% CI 0.53–1.65), *p* = 0.157. TEC was also non-significantly more common in those treated with phenprocoumon than with apixaban, 30.6% vs 20.8%, respectively (*p* = 0.51; logarithmic rank). There were no significant differences in individual outcomes when comparing apixaban with phenprocoumon (all-cause mortality, 18.8% vs 24.5%; major bleeding, 10.4% vs 12.2%; myocardial infarction, 4, 2% vs 6.1% respectively). Thus, patients with AF and S5(D) CKD who receive an OAC-VKA or DOAC are still at high risk of cardiovascular complications, with no significant difference (perhaps due to the small number of participants) in safety or efficacy when using apixaban at a dose of 2.5 mg twice daily or phenprocoumon. The authors emphasize the need for larger studies and the development of additional measures to reduce the very high risk of TECs and bleedings in the chronic hemodialysis patient population [9].

Evaluation of kidney function when using DOACs. According to the European and Russian 2020 guidelines for AF, the protocols of the main RCTs for evaluating the efficacy and safety of DOACs, as well as instructions for the use of drugs registered in the Russian Federation, the assessment of kidney function when prescribing DOACs should be carried out by calculating the CC [2, 3]. The most common methods for assessing kidney function in clinical practice are creatinine clearance calculated according to Cockcroft–Gault (CC) and estimated glomerular filtration rate (eGFR) using the MDRD or CKD-EPI formulas [4]. Nephrologists prefer to use eGFR according to the CKD-EPI formula, avoiding the Cockcroft-Gault formula, considering it to overestimate true GFR in advanced CKD, which is in conflict with the documents described above. It was proposed to calculate CC and pCKD in a particular patient and use the lowest value when choosing a dose of DOACs. However, this is not consistent with the indication of the Russian Clinical Guidelines 2020 on AF, which read to use CC to assess kidney function and prescribe a full dose of DOACs, if there are no additional restrictions [2].

A recent study assessed the value of the method of assessing kidney function when prescribing DOACs in patients with AF and CKD for the treatment outcomes of patients enrolled in the ORBIT-AFII program [40]. Dosing was considered inadequate when the use of eGFR rather than CC resulted in lower doses (undertreatment) or higher doses (overtreatment). The primary serious adverse outcome was considered combined cardiovascular death, stroke or SE, new onset heart failure and myocardial infarction. Among 8727 patients in the total registry cohort, there was a correspondence between CC and eGFR in 93.5–93.8% of patients. Among 2184 patients with AF and CKD, the correspondence between CC and eGFR was noted in 79.9–80.7% of cases. A discrepancy between CC and eGFR was noted in 41.9% of rivaroxaban users, 5.7% of dabigatran users, and 4.6% of apixaban users. In 1 year, patients treated with eGFR-adjusted doses of DOACs, as undertreated patients, had significantly more serious cardiovascular and neurological events compared with the group treated with CC-adjusted doses of DOACs (adjusted *RR* = 2.93; 95% CI 1.08–7.92; *p* = 0.03). The authors point out the importance of using the calculation of CC for the selection of the dose of DOACs [40].

Customization of the dose of DOACs based on a different method of determining renal function may be justified, but requires discussion with the participation of nephrologists, cardiologists / arrhythmologists, primary care physicians

and, preferably, clinical pharmacologists to assess the risk/benefit ratio in a particular patient [1].

Left atrial appendage occlusion in CKD. The left atrial appendage (LAA) is considered the site of thrombus formation in most AF-associated cardioembolic strokes. LAA occlusion has emerged as an alternative to OAC for stroke prevention in patients with AF. To date, there are no optimal regimens for the treatment of OAC in patients with AF and ESRD. The effectiveness of LAA occlusion in these patients has also not been proven in prospective RCTs until recently. This year, the results of an expected study evaluating the safety and efficacy of LAA occlusion in patients with ESRD were published [11]. The study included 604 patients from the German multicenter Realworld registry who underwent LAA occlusion, including 57 patients with S5/S5 (D) and 57 with CKD S1/S2. The composite endpoint was the occurrence of IS or transient ischemic attack, SE, and/or major or clinically significant bleeding. Patients with CKD S5/S5(D) were compared with patients with CKD S1/S2. A total of 596 endocardial and 8 epicardial LAA occlusion procedures were performed. The incidence of serious complications was 7.0% (42/604 patients) in the total cohort, 8.8% (5/57 patients) in patients with ESRD and 10.5% (6/57 patients) in a comparable CKD control group S1/S2 ($p = 0.75$). Estimated recurrence-free survival after 500 days was observed in 90.7 ± 4.5% in patients with ESRD and 90.2 ± 5.5% in a comparable control group ($p = 0.33$). Thus, the study showed that the LAA occlusion procedure can be the method of choice for medium-high risk of stroke in patients with CKD, including those with contraindications to long-term use of NOACs [11].

Treatment strategy for patients with atrial fibrillation and chronic kidney disease

For the treatment of patients with AF and CKD, as well as patients with AF in the general population, two alternative therapeutic strategies are recommended: 1) rate control; 2) heart rythm control. Treatment is carried out in order to reduce the severity of AF symptoms, improve hemodynamic parameters, and prevent possible complications [2, 3, 6].

The strategies of "rate control" and "rhythm control" in the treatment of patients with AF are equivalent in reducing the risks of development and progression of heart failure, readmissions, deaths from cardiovascular and other causes. When choosing antiarrhythmic therapy (AAT) — the "rhythm control" strategy, the goal is to reduce the symptoms of AF, and not improve the prognosis of health and life. In patients without a clear indication for rhythm control, the "rate control" strategy should be followed by default. The indications for choosing a rhythm control strategy in patients with CKD are similar to those in patients in the general population [6]. "Renal" factors in favor of the "rhythm control" strategy are presented in Fig. 2.

Frequency control. The main indication for choosing heart rate control in CKD is the presence of a structural heart lesion. β-blockers, veropamil/diltiazem, digoxin are used. In CKD, water-soluble drugs should be avoided, since they can accumulate in the body due to a decrease in renal excretion (atenolol and sotalol), it is necessary to adjust the dose of drugs with a mixed metabolism (bisoprolol). In patients with CKD, it is preferable to prescribe lipophilic

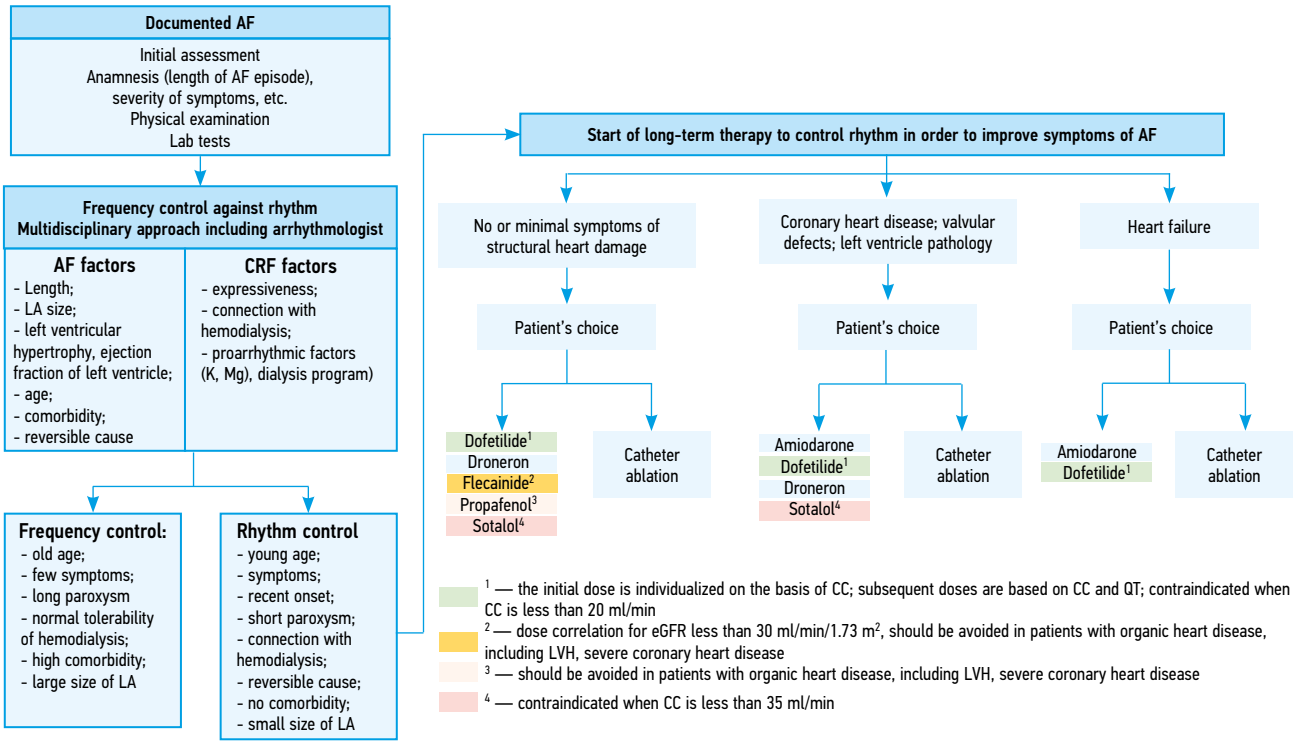

Fig. 2. Decision-making algorithm for frequency control or rhythm control in chronic kidney disease (CKD). AF — atrial fibrillation; LA — left atrium; CRF — chronic renal failure; LVH — left ventricular hypertrophy (Adapted from [6])

drugs that are metabolized in the liver (such as metoprolol and carvedilol) [2, 6].

The results of a cohort study evaluating the risk of using digoxin in patients with CKD for the treatment of AF and heart failure, which included a total of 31.933 patients with CKD, showed that all-cause mortality was higher in the digoxin group than in the non-digoxin group [41]. In cases where medical therapy does not control the ventricular rate, ablation of the AV junction and implantation of a pacemaker (pacer) should be considered. However, the high incidence of complications with transvenous access of the pacemaker in patients on hemodialysis limits the use of this method [6].

Rhythm control. Direct current cardioversion (DCVC) is more effective in restoring sinus rhythm than antiarrhythmic drugs, and, unlike most antiarrhythmic drugs, does not depend on kidney function (Fig. 2). However, the risk of AF recurrence is higher as the stage of CKD worsens; on the other hand, CKD patients who remain in sinus rhythm show improvement in renal function. The use of class IA (disopyramide, quinidine), IC (flecainide, propafenone) and class III (dofetilide, dronedarone, sotalol) rhythm control agents in patients with CKD is limited in those with decreased renal clearance and structural heart damage due to proarrhythmic risks. It remains unknown whether or not there is more pronounced organ toxicity of amiodarone in patients with chronic renal failure. Catheter ablation to maintain sinus rhythm is more effective than antiarrhythmic drugs alone in patients with CKD, as in the general population [2, 6].

CONCLUSIONS

An increase in the number of patients with both AF and CKD is expected, including patients with AF on hemodialysis. The coexistence of both conditions leads to an increased risk of both thromboembolism and hemorrhage, and which is especially high among patients with ESRD receiving hemodialysis. The substrate for AF is atrial cardiomyopathy, with structural, electrophysiological, and molecular atrial remodeling. The study of the pathogenesis of AF at the molecular level has begun recently. Understanding the biological pathways of the pathogenesis of AF may help in the future to develop new approaches to the treatment of both patients with AF and CKD, and AF in the general population.

Currently, among patients with ESRD, the methods of TEC prophylaxis and treatment strategies are being introduced, and the evidence base for their use among patients with S4/S5 CKD, including patients on hemodialysis, is being gathered, which requires large-scale RCTs.

ADDITIONAL INFORMATION

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