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Review

Insights into Concomitant Atrial Fibrillation and Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) shows a high prevalence and is characterized by progressive and irreversible loss of renal function. It is also associated with a high risk of cardiovascular disease. The CKD population often suffers from atrial fibrillation (AF), which is associated with cardiovascular and all-cause mortality. There is a pernicious bidirectional relationship between CKD and AF: renal dysfunction can help promote AF initiation and maintenance, while unmanageable AF often accelerates kidney function deterioration. Therefore, it is necessary to determine the interactive mechanisms between CKD and AF for optimal management of patients. However, due to renal function impairment and changes in the pharmacokinetics of anticoagulants, it is still elusive to formulate a normative therapeutic schedule for the AF population concomitant with CKD especially those with end-stage kidney failure. This review describes the possible molecular mechanisms linking CKD to AF and existing therapeutic options.

Keywords: chronic kidney disease; atrial fibrillation; fibroblast growth factor; uremic toxin; anticoagulant; sodium-glucose cotransporter inhibitor; sacubitril/valsartan

1. Introduction

The prevalence of chronic kidney disease (CKD) and atrial fibrillation (AF) is rising annually. CKD is an insidious disease defined by a progressive drop in kidney function with or without renal structural changes and is a vital contributor to cardiovascular disease. Data from the health system shows that CKD affects 10% population worldwide (Fig. 1), and its global prevalence has augmented 29.3% since 1990 [1].

The most common cardiac dysrhythmia, AF, causes many adverse cardiovascular outcomes. Stroke, chronic heart failure, myocardial infarction, systemic embolic events, dementia, and venous thromboembolism are common complications of atrial fibrillation, and its prevalence ranges from 2% to 4% in adults [2]. Moreover, AF was associated with an increased risk of adverse cardiovascular events and cardiovascular mortality [3,4].

CKD and AF often share multiple common risk factors, such as age, male sex, cardiovascular disease, hypertension, diabetes, heart failure, and obesity (Fig. 2) [5–7]. A prospective cohort study including 235,818 general subjects indicated that estimated glomerular filtration rate (eGFR) decline increased the risk of AF, meanwhile, the occurrence of AF promoted the deterioration of renal function [8]. In CKD patients, 15–20% were estimated to suffer from AF, and 7.0% of the dialysis population had AF [9–11]. Conversely, CKD acts as an independent risk factor of AF. Urine albumin-to-creatinine ratio (UACR) represents a common kidney function indicator. A recent study focusing on the incidence of AF in CKD patients showed that the risk of AF increased approximately twice in UACR >300 mg/g compared with UACR <30 mg/g [Hazard Ratio (HR) 2.69; $p < 0.0001$] [12]. On the other hand, AF might play a significant role in CKD progression. In the Chronic Renal Insufficiency Cohort Study (CRIC) which included 3,091 participants, patients complicated with AF were at a considerably higher probability of progression to end-stage renal disease (ESRD) (HR 3.2; $p < 0.0001$) [13]. Similarly, a systematic review of 25 literature showed that the presence of AF among the dialysis population was associated with a higher risk of stroke (5.2 vs. 1.9 per 100 person-years) and mortality (26.9 vs. 13.4 per 100 person-years) [14]. Thus, management of AF in CKD patients is extremely imperative for physicians. This review aimed to elaborate our argument on the knowledge about patients with AF and CKD.

2. Clinical Outcomes of AF in CKD Patients

Ineffective and disordered atrial contraction and diastole lead to an impaired or loss of atrial contribution to ventricular filling. Thus, patients with AF may have symptoms like palpitation, breathlessness, fatigue, and dizziness due to irregular and inappropriately rapid ventricular rhythm and loss of "atrial kick", while some are asymptomatic. On the other hand, sympathetic nervous system hyperactivity in CKD patients promotes conduction of atrial impulses to the ventricles with rapid ventricular rate then influence cardiac output [15]. In addition to hemodynamic disturbance resulting from AF, AF is also associated with poor clinical consequence such as stroke and death in dialysis patients [16–18]. Moreover, a cohort study named CRIC indicated

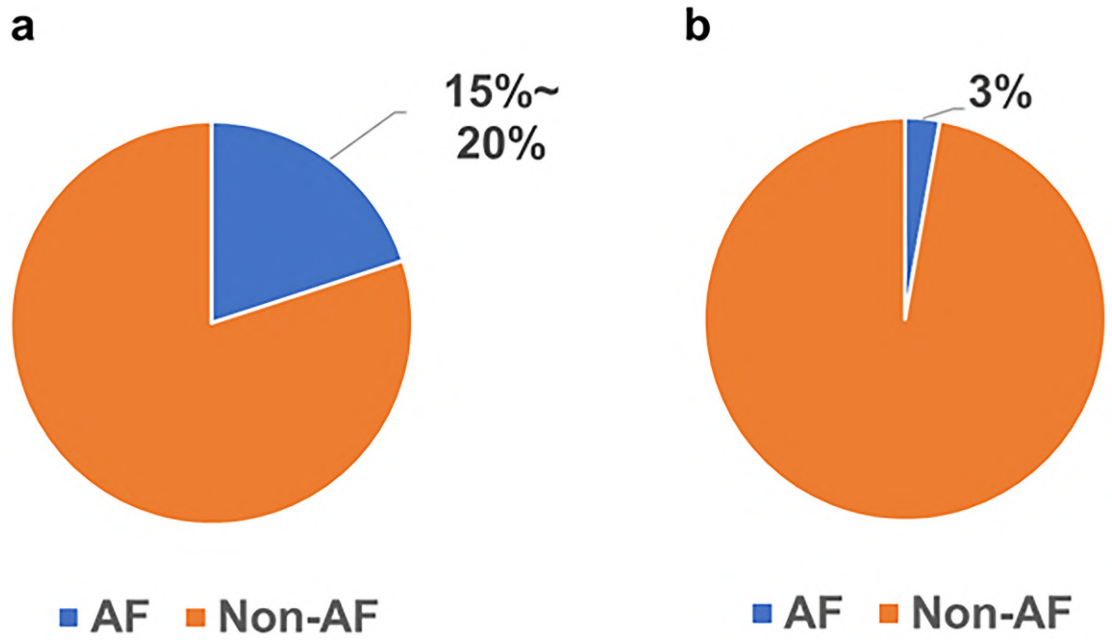

Fig. 1. The prevalence of AF in CKD (a) and non-CKD (b) population. AF, atrial fibrillation; CKD, chronic kidney disease.

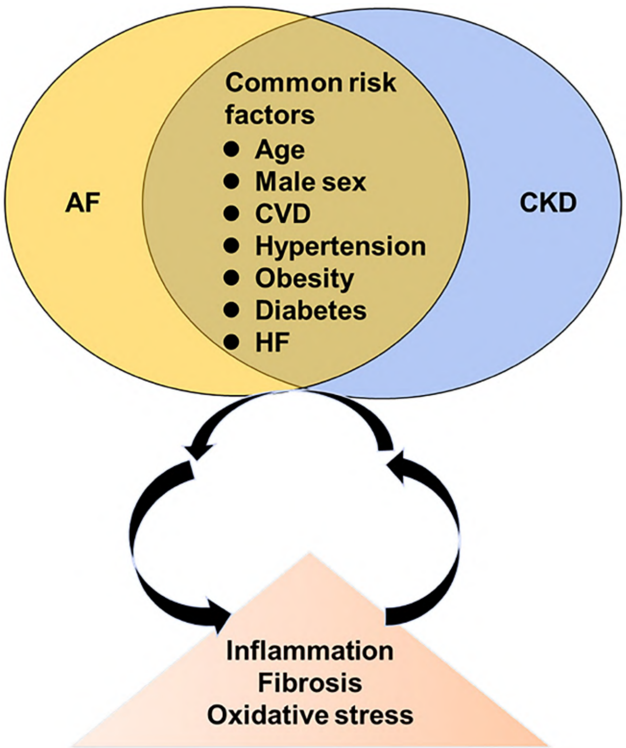

Fig. 2. Mutual influence between AF and CKD, sharing a series of common risk factors. AF, atrial fibrillation; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure.

that incident AF was linked independently with an elevated incidence of heart failure, stroke, and death [19]. In another study on stages 3–4 CKD population, incident AF elevated the risk of renal function deterioration [20]. Except for the poor prognosis of AF in the CKD population, changes in the CKD coagulation systems lead to an increased risk of thrombosis and bleeding. CKD's bleeding tendency is influenced by many aspects relevant to the secondary platelet function disorder and the heparin application in dialysis [21,22]. In conclusion, the pro-hemorrhagic state poses a challenge for the management of thromboembolism events prophylaxis in CKD patients.

3. AF in CKD

Generally, the AF pathophysiology includes three essential parts (Fig. 3): AF initiation, maintenance and progression to persistent state [23]. Atrial risk factors cause atrium changes like fibrosis, inflammation, cellular and molecular dysfunction, subsequently electrophysiological and structural remodeling raised by persistent AF leads to its perpetuation [3].

Pulmonary vein sleeves (PVs) play a major role in introducing AF [24]; its unique location, tissue construction, and ion channels conduce to ectopic electrical activity and re-entry [25]. The PV sleeves lack adjacent tissue and continuous fibers, leading to spontaneous activity and AF onset. The early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs) generation underlies ectopic activity. In the setting of prolonged action potential duration (APD), usually caused by reducing K^+ currents or enhanced depolarizing currents (including Na^+ and L-type Ca^{2+} currents), L-type Ca^{2+} channels recover from inactivation and facilitate the occurrence of inward current [26]. Compared with EADs, DADs have a more active role in triggering ectopic activity. Ca^{2+}-handling abnormalities resulting from cardiac ryanodine receptor channel type2 (RyR2) dysfunction, and spontaneous sarcoplasmic reticu-

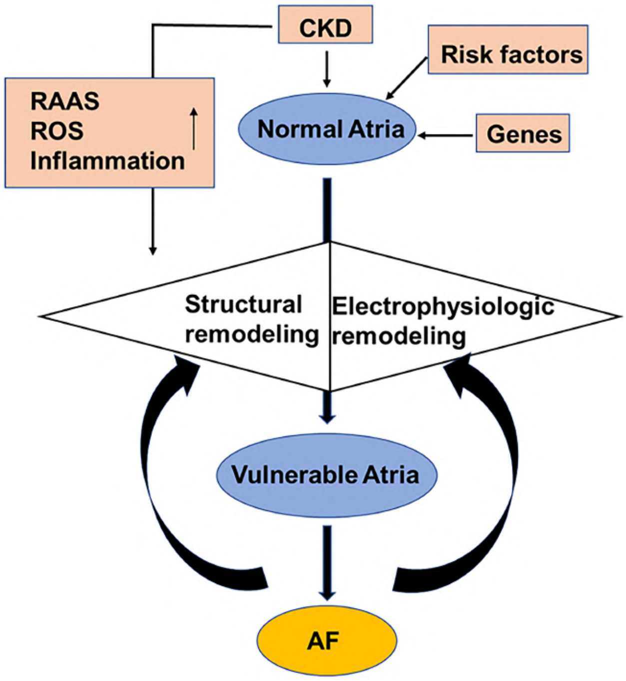

Fig. 3. The parts of the AF pathophysiology stage. AF, atrial fibrillation; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species.

lum (SR) Ca^{2+} release events (SCaEs) promote DAD both in animal models and patients with AF [27–29]. However, as the original link of DAD, Ca^{2+}/calmodulin-dependent kinase II (CaMK II) hyperphosphorylation is a crucial target in arrhythmia initiation and perpetuation. The autonomic system provides a substrate for AF development, and triggers the AF-pathophysiology by promoting Ca^{2+}-handling abnormalities. Sympathetic activation leads to CaMK II phosphorylation through β-adrenoceptor and cyclic adenosine monophosphate (cAMP) production [30]. In addition, sympathetic stimulation results in increased SR Ca^{2+} load, with concurrent positive inotropic action of cardiomyocytes.

Ca^{2+} overload plays a vital role in the persistence of CaMK II phosphorylation [30]. Oxidative stress is a feature of many diseases and is involved in Ca^{2+}-handling abnormalities. A study comparing patients with AF and sinus rhythm concluded that oxidative stress promotes AF through oxidating CaMK II. However, in CKD patients, overactive inflammatory response and the renin-angiotensin-aldosterone system (RAAS) promote reactive oxygen species (ROS) accumulation and atrial fibrosis; thus, contributing to AF progression [31,32].

Fibroblast growth factor-23 (FGF-23) is a hormone involved in the regulation of calcium-phosphorus metabolism balance and bone mineralization [33]. Elevated level of FGF-23 is associated with a higher risk of heart failure, all-cause mortality, cardiovascular mortality, and left-ventricular hypertrophy [34–36]. Both myocyte culture and animal experiments confirmed that FGF-23 can induce hypertrophic growth of cardiac cells [37,38]. Furthermore, in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS), increased FGF-23 concentration was associated with an increased risk of AF [39]. In addition, FGF-23 binds to the FGF-receptor 4 (FGFR4) in cardiac myocytes in the defect of klotho, and induces hypertrophy through activating phospholipase C (PLC) γ/calcineurin/Nuclear factor of activated T-cells (NFAT) pathway [37,40]. FGF-23 also stimulated PLC γ/calcineurin/NFAT cascade in hepatic cells during klotho deficiency, causing elevated inflammatory cytokine secretion (tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), and IL-6) [41]. FGF-23 and FGFR 4 expression increased in the atrial tissues of AF patients compared with the sinus rhythm population, consistent with the expression of α-smooth muscle actin (α-SMA) and collagen-1. Dong and his colleagues illuminated that FGF-23/FGFR4 accentuated atrial fibrosis by inducing ROS accumulation and then regulating signal transducer and activator of transcription 3 (STAT3) and small mother against decapentaplegic 3 (SMAD3) pathways [42]. Therefore, FGF-23/FGFR4 provides a vulnerable substrate for AF (Fig. 4). In patients with uremic syndrome, indoxyl sulfate (IS) and p-cresyl sulfate (pCS) are classic toxins with high protein affinity and cardiotoxicity. It has been shown that IS promotes AF by producing atrium fibrosis and inflammatory response, and treatment with uremic toxin absorbent AST-120 alleviated these undesirable effects and then attenuated AF [43,44]. Lekawanvijit *et al.* [45] also demonstrated that IS might play a role in pro-fibrotic and pro-inflammation via the P38 mitogen-activated protein kinase (MAPK), P22/44 MAPK, nuclear factor kappa-B (NF-κB) signaling pathway *in vitro*. In 5/6 nephrectomy rat models by Aoki *et al.* [43], oxidative stress is increased in the left atrium. In another animal experiment on rabbits, IS induced more DAD, burst firing events, and larger Ca^{2+} leakage in pulmonary vein cells, which trigger AF occurrence [44]. Furthermore, IS played a part in impairing the Mas receptor's ability to counter the pernicious effect of angiotensin II (Ang II) via the organic anion transporter 3 (OAT3)/aryl hydrocarbon receptor (AHR)/STAT3 pathway, which reduced the number of Mas receptor [46]. Thus, we conclude that IS plays a vital role in AF via the effects of inflammation, fibrosis, and oxidative stress on atrial remodeling (Fig. 4). Uremic toxin pCS may have effects similar to IS.

4. Management of AF in Patients with CKD

4.1 Rate and Rhythm Control

When the adverse effects of AF appear due to rapid ventricular rate or loss of available atrial contraction, medication strategy, including rate and rhythm control should be considered. β-blockers and non-dihydropyridines calcium channel blockers are recommended as first-line pharmaceutical strategies to realize rate control, and selective β_1 re-

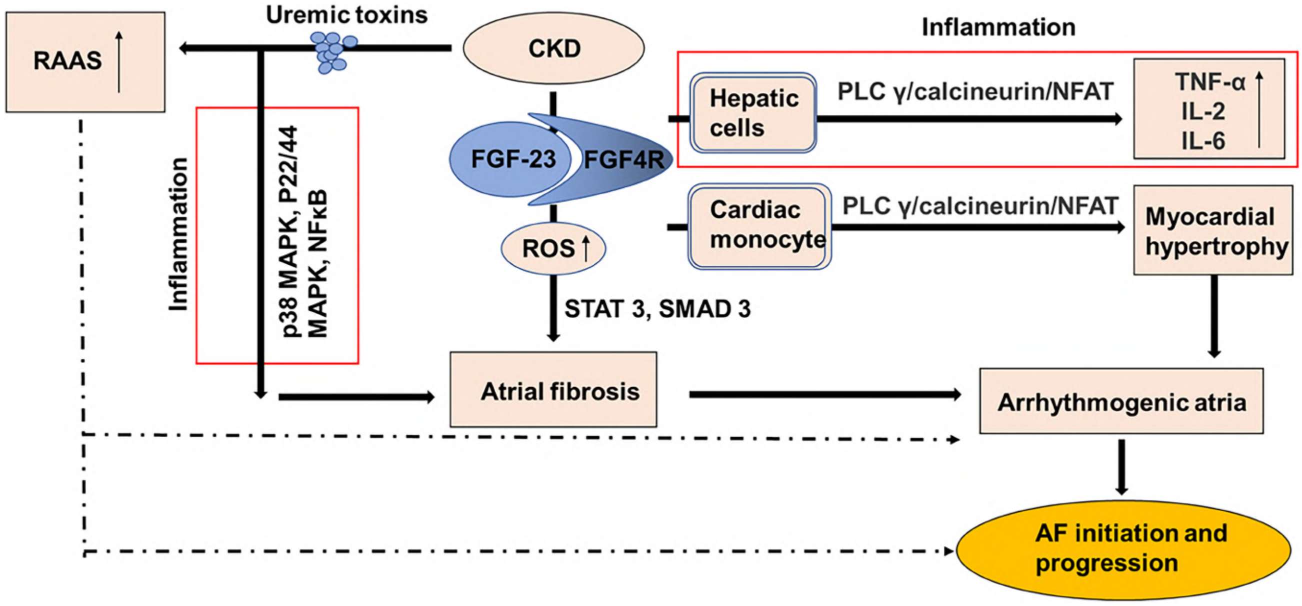

Fig. 4. The role of FGF-23 and uremic toxins in AF initiation and progression in patients with CKD. Here, we summarize the relevant molecular pathways and their effects. AF, atrial fibrillation; CKD, chronic kidney disease; FGF-23, fibroblast growth factor-23; IS, indoxyl sulfate; pCS, p-cresyl sulfate; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; TNF, tumor necrosis factor.

ceptors blocking agents are more desirable [47]. Metoprolol and carvedilol are usually prescribed by physicians to ESRD patients, metoprolol is selective β_1 receptor blockers, while carvedilol is nonselective and it has greater α_1 antagonism [48,49]. In a large retrospective cohort study, subgroup analysis of dialysis patients with AF showed that carvedilol was associated with higher all-cause and cardiovascular mortality. Besides, carvedilol caused more hypotension during dialysis sessions [50]. Beta-blockers are also effective in the primary prevention of atrial fibrillation in ESRD patients [51]. Nevertheless, several large-scale randomized clinical trials (RCTs) are required to provide scientific and solid evidence to explicit beta-blockers administration in patients with concomitant AF and ESRD. When rate control treatment is ineffective or has serious side effects, it is time to consider initiating rhythm control, especially in those requiring dialysis [52]. A commonly administrated rhythm control drug is amiodarone, there is no need to adjust the prescription dose even in the dialysis population [52]. Of specific interest, a novel rate control agent ivabradine is not recommended in patients with CKD at present. A meta-analysis showed an elevated risk of AF with ivabradine treatment [53]. However, another meta-analysis found that ivabradine can reduce the ventricular rate in patients with AF [54]. An uncompleted RCT Ivabradine Block of Funny Current for Heart Control in Permanent Atrial Fibrillation (BRAKE-AF, NCT03718273) is going to demonstrate ivabradine's inferiority in heart rate control (Table 1) [55]. We still need to keep an eye on ivabradine treatment to control heart rate in persistent AF patients.

Apart from medical treatment, catheter ablation (CA) is now a safer and effective option for patients with symptomatic and refractory AF. An observational study showed that CA improves the eGFR of CKD patients with AF [56]. However, the presence of CKD increased the recurrence of AF after CA, and we should perform an assessment of the risks and benefits before atrial fibrillation ablation.

4.2 Stroke Prevention in AF and CKD Patients

One of the irreversible outcomes caused by AF is thromboembolism, which usually results from a detachment of thrombus in the atrium cordis. For long-term management of the risk between thromboembolism and bleeding, the widely recognized CHA_2DS_2-VASc (congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, and sex) guideline system identifies the population warranted prophylactic anticoagulation in patients with paroxysmal, persistent, or permanent atrial fibrillation. Oral anticoagulants are recommended strongly for AF patients with CHA_2DS_2-VASc score of 2 or greater in males or 3 or greater in females [57]. Anticoagulant options include the traditional drug warfarin and non-vitamin K oral anticoagulants (NOACs) (dabigatran, rivaroxaban, apixaban, and edoxaban). Compared with NOACs, warfarin administration has high-quality scientific evidence in clinical practice. However, in RCTs, the NOACs are not inferior to warfarin in preventing stroke and superior to warfarin in decreasing hemorrhage [58–61]. A meta-analysis of randomized trials and observational studies in the Asian population published in 2019 indicated that NOACs improved thera-

Table 1. On-going RCTs in patients with AF and ESRD and an unaccomplished trial on ivabradine in patients with persistent AF.

Registration of the trial	Study design		Estimated date of completing
	Drug	Primary outcome	
NCT03987711	Warfarin vs. apixaban vs. no antithrombotic therapy	Treatment effect and safety	2021.12
NCT02933697	Low-dose apixaban vs. warfarin	Treatment safety	2022.07
NCT02886962	Warfarin vs. nonuse	Adverse effect	2023.01
NCT03862359	Warfarin	Treatment effect and safety	2024.09
NCT03718273	Ivabradine vs. digoxin	Treatment effect and serious adverse outcome	2021.08

peutic effect and safety [62]. Nevertheless, ESRD patients were excluded from the study, which poses a handicap in the use of NOACs.

4.2.1 Warfarin

Warfarin is a commonly used anticoagulant that mainly inhibit the vitamin K reductase and vitamin K recirculation. After being completely absorbed, warfarin takes nearly a week to reach a steady-state and is eliminated totally by metabolism [63]. Although its renal excretion is negligible, a lower dose is needed in patients with stages 4–5 CKD to achieve the correct international normalized ratio (INR).

In ESRD patients complicated with AF, high-level RCTs to provide the most striking evidence for decision-making are lacking. Previous observational real-world studies on warfarin prescription in ESRD patients do not provide consistent idea (Fig. 5) [64]. Some cohort studies showed the benefits of warfarin in stroke prevention and survival (Fig. 5a,c) [65,66], while others showed no beneficial effects but greater harm (Fig. 5b) [67,68]. The American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) 2019 Guideline for AF management ranked warfarin prescription as II b indication, but in patients with ESRD and AF, less than 50% receive oral anticoagulant, and only about 34% of people receive warfarin in the dialysis population [69]. In end-stage CKD patients treated with warfarin, there were no survival benefits and decreased rate of stroke, but an elevated risk of hemorrhage events (Fig. 5) [67,70,71]. Warfarin therapy has one obvious drawback compared with direct oral anticoagulants (DOACs). The warfarin therapeutic range is critically questionable to overcome, especially for patients with poor treatment compliance. According to the AHA/ACC/HRS 2019 Guideline, patients should take coagulation function examination to determine the INR at least once a week at the initiation of warfarin treatment, and at least once a month until its efficacy is stable [57].

Moreover, warfarin may have side effects other than bleeding due to its pharmacological mechanism to inhibit vitamin K-dependent gamma-glutamyl carboxylase enzyme. Decreased vitamin K-dependent gamma-glutamyl carboxylase enzyme activation impairs matrix G1a protein (MPG). However, MPG is demonstrated to attenuate vascular calcification significantly [72]. Vascular calcification is prevalent in CKD patients, and is associated with an increased risk of cardiovascular, cerebrovascular, peripheral vascular disease [73,74]. Despite the untoward effects limit warfarin application, it is still a deemed medicine for anticoagulation when the INR is stable and the risk of bleeding is lower than stroke.

4.2.2 Non-Vitamin K Oral Anticoagulant

NOACs, also known as DOACs, and currently dabigatran, rivaroxaban, apixaban, and edoxaban are commonly used for anticoagulation. Dabigatran is a thrombin inhibitor unlike other three coagulation factor Xa inhibitors. NOACs are preferable to warfarin in NOACs-eligible AF patients [57]. However, top-level evidence for NOACs prescription is scarce in AF patients with severe renal dysfunction. Food and Drug Administration (FDA) approved only apixaban for anticoagulation in patients with ESRD, and the AHA/ACC/HRS 2019 Guideline for AF management is consistent with FDA [57]. On the contrary, the 2018 European practical guideline refused apixaban therapy in ESRD patients [75].

4.2.2.1 Apixaban. In studies comparing the efficacy and safety of apixaban with warfarin, apixaban showed its advantage in stroke and embolism prevention or less major bleeding events with fewer mortality [59,76,77]. Although warfarin was associated with a lower risk of stroke and systematic embolism in the subgroup analysis of severe or moderate renal impairment, it was statistically insignificant [59]. In a matched-cohort study, apixaban had a lower major bleeding occurrence; however, there was no significant difference [77]. In another retrospective cohort study, there were significant differences in both overall and major hemorrhagic events between apixaban and warfarin groups (18.9% vs. 42.0%; p = 0.01 and 5.4% vs. 22.0%; p =

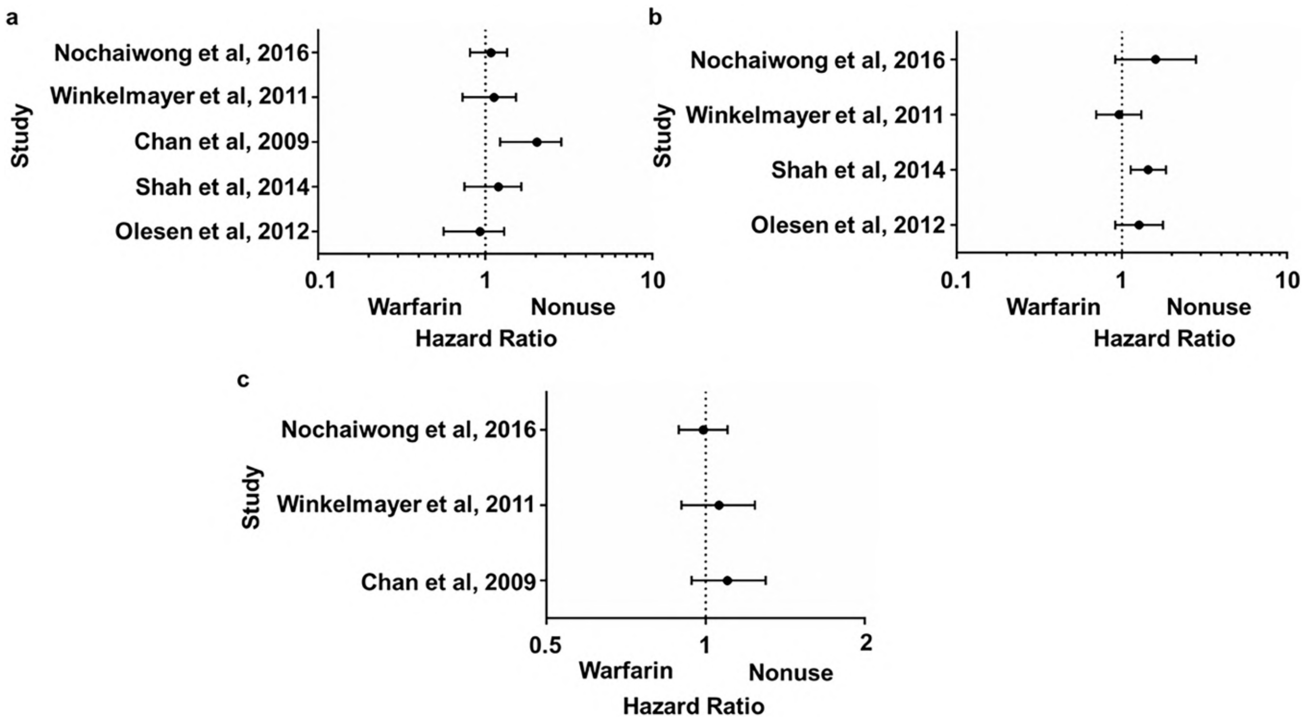

Fig. 5. Efficiency and safety of warfarin in patients with AF and ESRD. (a) Hazard ratio (HR) for stroke treated with warfarin. (b) Hazard ratio (HR) for bleeding treated with warfarin. (c) Hazard ratio (HR) for mortality treated with warfarin. AF, atrial fibrillation; ESRD, end-stage renal disease.

0.01 respectively) (Fig. 6, Ref. [78]) [76]. A meta-analysis of observational studies in dialysis population showed that apixaban was significantly associated with lower risk of bleeding than warfarin and other DOACs (Fig. 6b) [78]. Thus, apixaban may be effectively and safely used in ESRD patients (Fig. 6a,c). We have to be aware that the therapeutic dosage of apixaban needs to be prudently adjusted according to the stroke and bleeding risks. In a small-scale study including seven dialysis patients, 5 mg twice daily was beyond a reasonable therapeutic level [79]. On the contrary, routine 5 mg twice daily was significantly associated with reduced risks of stroke and mortality (HR 0.61, 95% CI 0.37–0.98, p = 0.04) [80]. Thus, ESRD is not a contraindication to apixaban, but a standard dose of 5 mg twice daily is not recommended for all patients.

4.2.2.2 Dabigatran. Dabigatran is not approved in patients with eGFR $\leq$15 mL/min/1.73 m^2. As the only thrombin inhibitor, dabigatran is distinguished from other NOACs because more than half of it can be eliminated by dialysis [22]. In an analysis comparing two fixed-doses (110 mg twice daily and 150 mg twice daily) of dabigatran with warfarin, higher doses gave a better response to stroke prevention but did not reduce major bleeding risks [1.11% vs. 1.69%; Risk Ratio (RR) 0.66; $p < 0.01$ and 3.36% vs. 3.1%; p = 0.31]. Conversely, the 110 mg twice daily strategy was independently associated with the decreased major bleeding rate (3.36% vs. 2.71%; p = 0.003) [58]. In another study on dialysis patients, dabigatran was at greater risk of not only lethal hemorrhage (RR 1.48; 95% CI 1.21–1.81, p = 0.0001) but also minor bleeding (RR 1.17; 95% CI 1.00–1.38, p = 0.05) after adjusting covariates (Fig. 6b) [81]. However, it did not show a trend to lower stroke due to the relatively short follow-up time. In severe renal impaired patients, dabigatran exposure was approximately a 6-fold increase compared with general subjects, and its elimination time was prolonged [82]. A treatment simulation suggested once-daily over twice-daily dosing in patients undergoing hemodialysis [83]. However, further studies are needed to support the use of dabigatran therapy in patients with severe kidney dysfunction.

4.2.2.3 Rivaroxaban and Edoxaban. Rivaroxaban therapy did not show significantly reduced rates of stroke and systematic embolism (RR 1.8; 95% CI 0.89–3.64) [81], and was associated with adverse effects of both severe (RR 1.38; 95% CI 1.03–1.83, p = 0.04) and slight (RR 1.35; 95% CI 1.11–1.65, p = 0.001) bleeding events. In a double-blinded trial, the rivaroxaban (20 mg) group did reduce stroke and systemic embolism compared with the warfarin group (RR 0.88; 95% CI 0.74–1.03, $p < 0.001$ for inferiority) [58]. Edoxaban did not show a favorable trend in stroke and thromboembolic events prevention compared with warfarin. Thus, rivaroxaban and edoxaban may not have their place as anticoagulation options for ESRD patients.

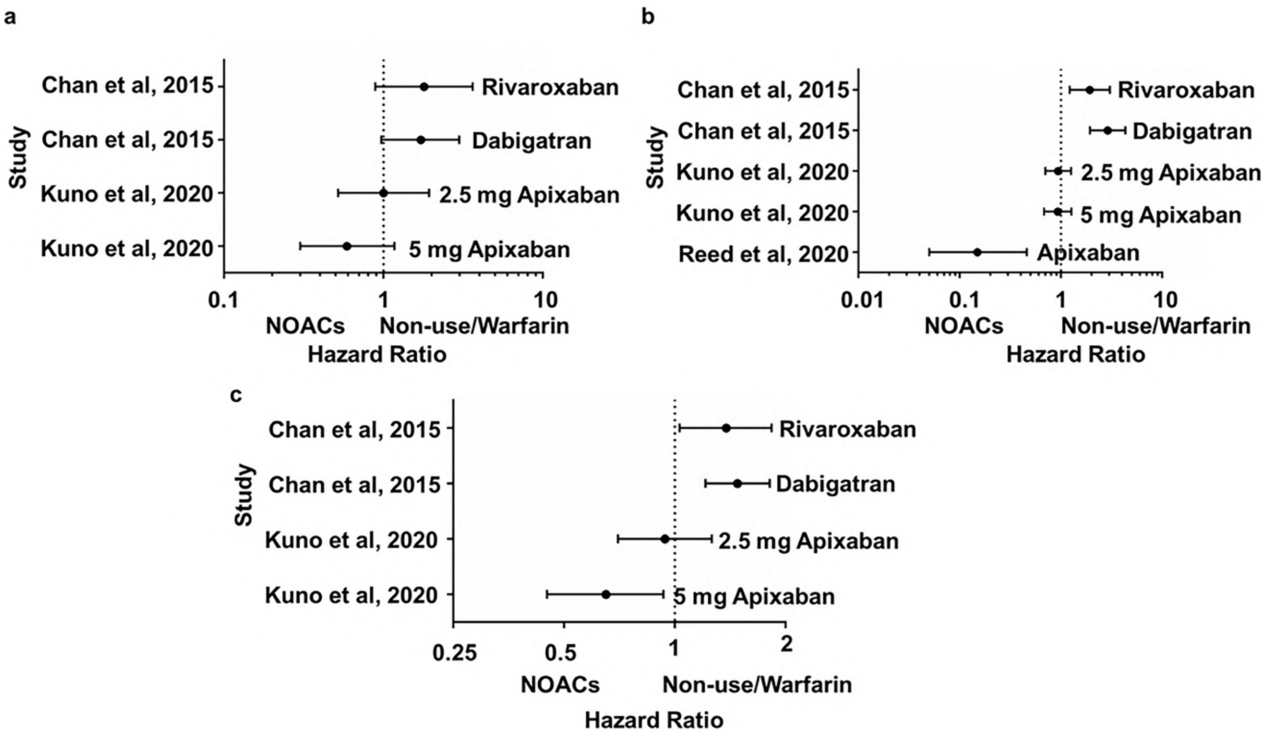

Fig. 6. Efficiency and safety of NOACs in patients with AF and ESRD. (a) Hazard ratio (HR) for stroke treated with NOACs. (b) Hazard ratio (HR) for bleeding treated with NOACs. (c) Hazard ratio (HR) for mortality treated with NOACs. Kuno *et al.* [78] is a systematic review that compared high and low-dose apixaban with no anticoagulants. AF, atrial fibrillation; ESRD, end-stage renal disease; NOACs, the non-Vitamin K oral anticoagulant.

Although we can get instructive information from observational studies with large subjects, the surrounding evidence from RCTs is limited. Several ongoing RCTs on anticoagulation drugs may provide a direction for improving embolism prophylaxis (Table 1).

5. Our New Idea on AF Management in CKD

5.1 SGLT-2 Inhibitor: Will It be a Good Choice for Patients with Mild-Moderate Renal Insufficiency to Prevent AF?

Sodium glucose cotransporter-2 (SGLT-2) is a cotransporter of Na^+-glucose located in the apical membrane of renal proximal convoluted tubule that plays a role in glucose reabsorption [84]. The latest hypoglycemic drug, SGLT-2 inhibitor acts on this transporter to decrease blood glucose. However, animal experiments indicated that SGLT-2 is widely involved in inflammation [85], tissue fibrosis and cell signaling pathways regulation [86]. More attention was given to its protective effect on the cardiovascular system than to its hypoglycemic effects. Several reviews have evidence for SGLT2i cardioprotective effects [87,88]. A meta-analysis of 22 RCTs revealed that SGLT2i was associated with decreased risk of AF (RR 0.82, 95% CI 0.70–0.96) and embolic stroke (RR 0.32, 95% CI 0.12–0.85) [89], consistent with a Chinese cohort study demonstrating that SGLT2i decreased the risk of new-onset arrhythmia [90]. Nevertheless, a previous systematic review with fewer participants took an opposite view that SGLT2i was not associated with a reduced risk of AF independently (OR 0.61, 95% CI 0.31–1.19) [91]. In patients with diabetes mellitus (DM), the application of SGLT2i ameliorated the AF occurrence events, regardless of whether the AF is absent or not previously [92]. SGLT2i can cause significant reduction in weight and blood pressure [93], which further reduces the risk of AF. Thus, it is suggested that that SGLT2i can decrease the chance of AF in patients with mild-moderate kidney failure. SGLT2i exerted the anti-inflammatory effects in rats with colitis by reducing the overexpression of proinflammatory cytokines IL-1β and TNF-α, and making the anti-inflammatory cytokine IL-10 work properly [85]. Following SGLT2 inhibition, AMP-activated protein kinase (AMPK) signal activation suppresses the nucleotide-binding domain and leucine-rich repeat-containing (NLR) family pyrin domain containing 3 (NLRP3) to mitigate inflammation [94]. It has also been proven that SGLT2i observably suppressed inflammation response in immune cells [95]. Indeed, one hallmark feature in CKD is chronic exposure to a low-grade inflammatory state. However, inflammation is a fundamental part of AF initiation and maintenance. Consequently, it is reasonable to suggest that SGLT2i can be prescribed for mild-moderate kidney dysfunction patients to prevent AF and other adverse cardiovascular events.

There are multiple possible molecular signaling pathways through which SGLT2i reduce the underlying risk of AF (Fig. 7). Sesterins are cytoplastic stress proteins that prevent atria from oxidative damage and structural remodeling by alleviating ROS accumulation and fibrosis in cardiac fibroblasts [96]. SGLT2i upregulated Sesterin2 and then activated downstream AMPK/mammalian target of rapamycin complex 1 (mTORC1) signaling pathway, thus accounting for SGLT2i's role in abating inflammation response, oxidative stress, and atrial fibrosis [97]. Normal physiological activities and energy metabolism of cells or organs depend on effective and functional mitochondrial respiration. Sesterin2/AMPK pathway activation enhances peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC-1α) expression, restraining ROS's excessive production through more dynamic mitochondrial function [98,99]. Shao *et al.* [99] disclosed the PGC-1α nuclear respiratory factor-1 (NRF-1)/mitochondrial transcription factor A (TFAM) as the relevant molecular pathway in rat models. Another key downstream molecule of Sesterin2 is liver kinase B1 (LKB1), a crucial protein kinase for normal atrial development and electrophysiological activities. Ion channel and connexin dysfunction in LKB1 knockdown mice resulted in electrophysiological abnormalities and fibrosis of the atrium, which predispose to the AF occurrence [100]. Animal studies also revealed that SGLT2i could ameliorate electrical remodeling of the atrium [99]. These intricate and diverse molecular signaling pathways illustrated that SGLT2 inhibitions has a positive impact on the prevention of cardiovascular disease and arrhythmia. Hence, extending the SGLT2i application to treat cardiovascular events is of great significance. Thus, we suggest SGLT2i's application to mild-moderate kidney failure population, especially with comorbid DM, HF, or multiple metabolic disorders.

5.2 LCZ696 (Sacubitril/Valsartan): Will It be Available for AF and Stroke Prevention in the CKD Population?

Sacubitril/Valsartan (SAC/VAL) is an inhibitor of Ang II and neprilysin receptor that blocks Ang II binding to angiotensin receptor 1 (AT-R1) and amplifies the effects of natriuretic peptides by decreasing their degradation [101]. It has been a first-class medicine for chronic heart failure, and trials by Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) investigators showed that sacubitril/valsartan significantly reduced the risk of cardiovascular mortality and admission in patients with reduced ejection fraction heart failure [102]. In severe renal insufficiency patients, the risk of death from cardiovascular disease reduced 28% in the sacubitril/valsartan group compared with conventional management [103]. Treatment with sacubitril/valsartan improved systolic cardiac function after myocardial infarction (MI), and decreased the arrhythmias tendency by decreasing CaMK II phosphorylation in rodent chronic MI and HF model [104]. Martens *et al.* [105] used a retrospective study including 151 eligible patients with heart failure with reduced ejection fraction (HFrEF) to demonstrate the benefit of sacubitril/valsartan therapy for ventricular arrhythmia and reversal of left ventricular structural remodeling. Data from pre-clinical trials suggested that sacubitril/valsartan ameliorates cardiac fibroblast transition by accommodating protein kinase G (PKG) signaling [106]. Li *et al.* [107] also found NF-κB/NLRP3 signaling pathway involved in positive effects of LCZ696 to prevent cardiac fibrosis in mice. Except for averting ventricular reconstruction, atrial electrophysiological dysfunction and structural remodeling in rabbits afflicted with AF were converted significantly by sacubitril/valsartan through the calcineurin/NFAT pathway [108], which further hindered initiation and progression of AF.

Li *et al.* [109] demonstrated that SAC/VAL altered atrial fibrillation propensity by suppressing Ang II-induced AF in rat models. Interestingly, they also noticed p-Smad 2/3, phosphorylation of c-jun-NH2-terminal kinase (p-JNK) and p-p38MAPK downregulated expression, indicating that it might be a potential therapeutic target pathway. Sacubitril/valsartan could strongly improve left atrial (LA) and left atrial appendage (LAA) function even in AF patients [110]. Fully effective LA and LAA function are essential for escaping from blood stagnation and thrombogenesis and reducing cardioembolic stroke risk [111]. A meta-analysis of SAC/VAL in renal failure and AF patients showed that it reserved kidney function without adverse drug reaction [112]. In a mouse model of CKD, LCZ696 attenuated oxidative stress, fibrosis and inflammation in the kidney as well as the cardiovascular system [113,114]. The above evidence (Fig. 8) adds to our understanding of sacubitril/valsartan therapy's role in preventing AF occurrence and stroke in patients with AF and CKD. Atrial disease is an important part in the development and progression of HF, meanwhile, patients with HF prone to AF [115], which suggests that it is necessary to treat HF in patients with CKD.

6. LAAO in Patients with AF and CKD

The left atrial appendage (LAA) is the main thrombogenesis region in AF for its poor function, and if that the thrombus falls off, a systematic embolic outcome follows. The left atrial appendage occlusion (LAAO) is an optimal mechanical strategy for preventing AF-related stroke [116]. In real-world clinical practice, patients who received LAAO therapy had a lower risk of stroke and hemorrhage [117]. Considering the uncertainty in the pros and cons of anticoagulants use in patients with advanced renal failure, LAAO may be a suitable stroke prevention strategy [118]. Kefer *et al.* [119] highlighted that LAAO greatly reduced the risk of stroke, transient ischemic attacks (TIA), and bleeding events. In a meta-analysis comparing the benefits and adverse outcomes between LAAO and anticoagulants, it has been indicated that LAAO acquired more ef-

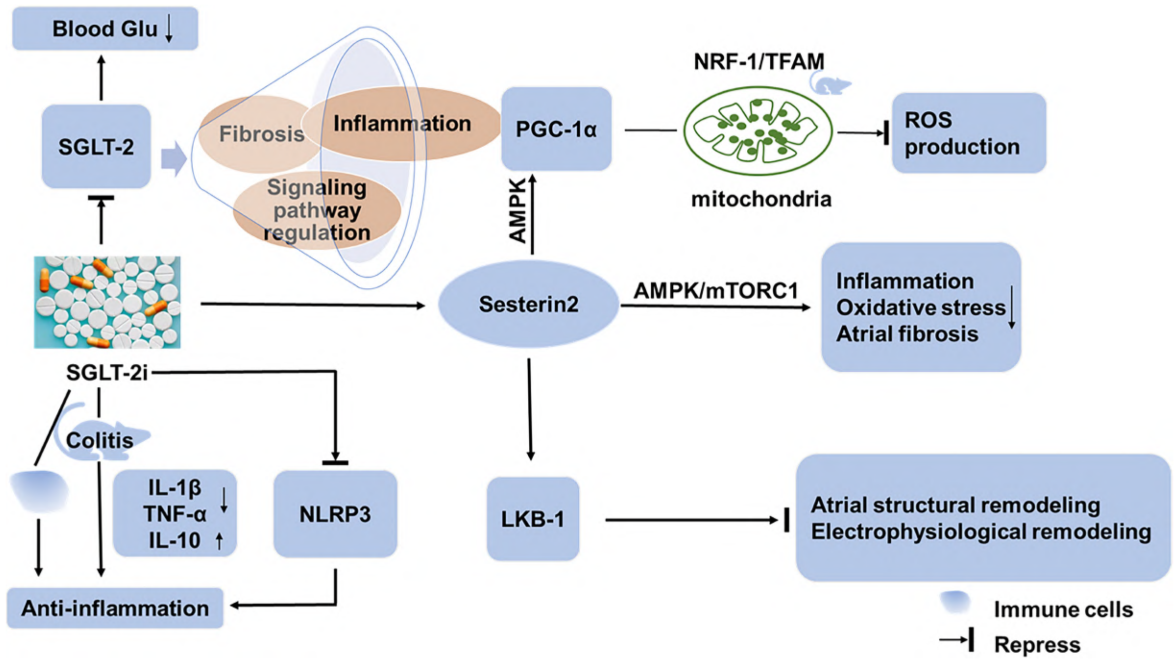

Fig. 7. SGLT2i exerts an influence on protecting the cardiovascular system. SGLT2i, sodium-glucose cotransporter inhibitor; Glu, glucose.

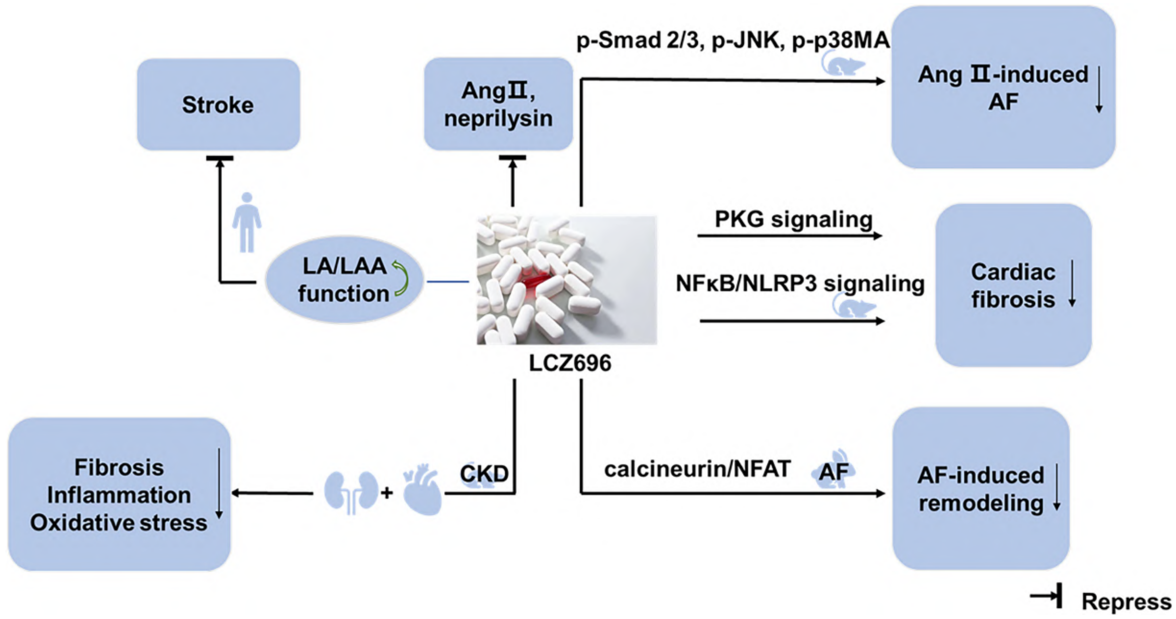

Fig. 8. Sacubitril/valsartan was demonstrated to be a beneficial option for AF patients. AF, atrial fibrillation; CKD, chronic kidney disease; LA, left atrium; LAA, left atrial appendage.

fective embolism prevention with a lower risk of bleeding than oral anticoagulants [120]. Therefore, LAAO can be proposed for CKD patients with absolute contraindication to oral anticoagulants.

7. Early Identification of AF is Required in Patients with CKD

Early identification of AF is beneficial for patients with renal insufficiency, and early diagnosis of asymptomatic AF helps prevent stroke effectively. However, screening for AF is not routinely performed in patients with CKD. LA imaging technology, such as 2-dimensional echocardiogram, 3-dimensioanl echocardiogram, cardiac magnetic resonance, and cardiac computed tomography, have been used to accurately assess LA size and function [121]. Besides, cardiac troponin and natriuretic peptide are serological markers suggestive of cardiovascular dysfunction. Molecular imaging may also enable accurate and early detection of AF [122]. Patients with CKD are at high risk for AF, therefore, we need a comprehensive strategy, which includes risk factor assessment, sensitive serum biomarkers, precise imaging, and promising molecular imaging for better management.

8. Summary

AF and CKD usually coexist and share several common traditional risk factors. CKD patients possess underlying pathophysiological mechanisms in the initiation and development of AF, and making treatment decisions for stroke prevention in this population remains a challenge. In this review, a series of innovative measures for AF management in CKD patients were brought forward, but these strategies were just hypotheses with sound reasoning. Thus, individualized prevention and therapy strategies for AF are still required in patients with CKD.

Author Contributions

FH and YY provided conceptualization. YW prepared the original draft. YY and YW contributed to editorial changes in the manuscript. FH contributed to supervision. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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