# Intersection of cardiovascular disease and kidney disease: atrial fibrillation

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**Purpose of review**
Atrial fibrillation is the most common sustained arrhythmia in patients with kidney disease. The purpose of this review is to describe the burden of atrial fibrillation in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD), postulate possible mechanisms to explain this burden of disease, understand the clinical consequences of atrial fibrillation and review the treatment options for atrial fibrillation specific to patients with kidney disease.

**Recent findings**
Recent literature has revealed that the clinical multiorgan impact of atrial fibrillation in patients with CKD and ESRD is substantial. Although novel oral anticoagulants to treat atrial fibrillation and prevent associated complications have been tested in large trials in the general population, there is a paucity of data on the efficacy and safety of these agents in patients with advanced CKD and ESRD.

**Summary**
Atrial fibrillation is a significant comorbidity in patients with CKD and ESRD with important prognostic implications. More research is needed to understand the mechanisms that contribute to the disproportionate burden of this arrhythmia in patients with kidney disease and in to treatment options specific to this population of high-risk patients.

**Keywords**
atrial fibrillation, chronic kidney disease, end-stage renal disease

## INTRODUCTION

Atrial fibrillation is the most common sustained arrhythmia in the general population. The burden of atrial fibrillation is even greater in patients with concomitant kidney disease. Recently published studies have highlighted the often underrecognized, yet highly prevalent relation between kidney disease and atrial fibrillation. Furthermore, evidence has suggested that the burden of atrial fibrillation will likely rise in this high-risk population, making the intersection of kidney disease and atrial fibrillation a highly relevant clinical problem.

Among the large population of patients with chronic kidney disease (CKD) not yet requiring dialysis, several studies have noted a high prevalence of atrial fibrillation, typically two to three-fold higher than that reported in the general population [1–5]. In participants with moderate-to-advanced CKD in the Chronic Renal Insufficiency Cohort (CRIC), the prevalence of atrial fibrillation was 18% overall and more than 25% in participants at least 70 years old [5]. Older age, female sex, tobacco use and history of cardiovascular disease, including heart failure, were significantly associated with prevalent atrial fibrillation in that study. Another study of the Medicare 5% sample with CKD found that the 2-year incidence of atrial fibrillation diagnosed by administrative codes was 14.4% among patients with stage 3–5 CKD [6]. In the Atherosclerosis Risk in Community (ARIC) Study, during 10 years of follow-up, there was a graded, increased risk of diagnosed incident atrial fibrillation with lower estimated glomerular filtration rate (eGFR) or higher level of albuminuria at cohort entry, even after adjustment for other clinical risk factors [1].

Among patients with end-stage renal disease (ESRD) on dialysis [7▪], the prevalence of atrial fibrillation is estimated to be 7–20% [8]. An analysis

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## KEY POINTS

- Atrial fibrillation is common in patients with CKD and ESRD, and is associated with significant morbidity and mortality.
- The biological pathways linking atrial fibrillation and kidney disease remain incompletely understood.
- Patients with kidney disease have unique considerations in the treatment of atrial fibrillation, and further studies are needed to study anticoagulation in patients with advanced CKD and ESRD.

of 63 884 Medicare/Medicaid-eligible dialysis patients found that age greater than 60 years, male sex, white race, being overweight or obesity, an inability to ambulate, and prior cardiovascular disease were significantly associated with prevalent atrial fibrillation [7▪]. Furthermore, recent data from the United States Renal Data System (USRDS) reported that the prevalence of atrial fibrillation continues to increase among patients with ESRD [8].

Although these data are compelling, our estimates of the burden of atrial fibrillation are likely conservative, given the current methods of ascertainment of atrial fibrillation, particularly incident atrial fibrillation. Most studies have relied on self-report, 12-lead electrocardiograms or administrative/ICD-9 diagnostic codes, which all may be insensitive measures given the often paroxysmal nature of atrial fibrillation and the fact that many patients are asymptomatic. Thus, innovative methods are needed to capture prevalent and incident atrial fibrillation more comprehensively and cost effectively in large studies of patients with kidney disease.

## MECHANISMS THAT CONTRIBUTE TO INCREASED RISK OF ATRIAL FIBRILLATION IN CHRONIC KIDNEY DISEASE

Several possible mechanisms may explain the high rate of identified atrial fibrillation in patients with CKD, including older age and a high burden of risk factors such as hypertension and cardiovascular disease [2], excessive inflammation which has been linked to both CKD and atrial fibrillation [9–16], larger left atrial and left ventricular sizes among CKD patients [2,17–23], and activation of the renin–angiotensin–aldosterone system [24,25]. Other plausible pathways linking kidney disease and atrial fibrillation include abnormalities in mineral metabolism. Specifically, elevations in phosphorus and fibroblast growth factor (FGF)-23 have been linked to increased left ventricular mass [26–28]. It is possible that alterations in these pathways may also contribute to the risk of atrial fibrillation in patients with CKD and ESRD through effects on cardiac structure, endothelial function and vascular calcification. Further investigations are needed to explore unique kidney-specific biological pathways linking atrial fibrillation and kidney disease, given the disproportionately high burden of disease in this population.

## ATRIAL FIBRILLATION IS ASSOCIATED WITH INCREASED RISK OF STROKE AND DEATH IN CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE

Impaired kidney function and atrial fibrillation are both associated with thromboembolic disease and the synergetic impact of these conditions enhances the risk of complications such as ischemic stroke. Atrial fibrillation and kidney disease lead to endothelial injury, abnormal blood flow and hypercoagulability, which result in substantial risk of thromboembolism (Fig. 1).

Among patients with CKD, several clinical studies have reported that atrial fibrillation is associated with increased risk of stroke and death. In a study of 132 372 patients with nonvalvular atrial fibrillation, patients with CKD had a 49% increased rate of stroke or systemic thromboembolism compared with those without kidney disease [30▪]. In a study of nearly 11 000 patients with atrial fibrillation, proteinuria increased the risk of thromboembolism by 54% and there was a graded, increased risk of stroke associated with a progressively lower level of eGFR [31]. In the Rivaroxaban Once-daily, oral direction factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), reduced creatinine clearance was a strong, independent predictor of stroke and systemic embolism, second only to prior stroke or transient ischemic attack, in the setting of anticoagulation [32▪]. A model that included creatinine clearance improved the net reclassification index by 8.2% [95% confidence interval (CI) 2.5–14%, $P = 0.005$] compared with the $CHADS_2$ score. When this new prediction score, that included kidney function, was validated in an external model, the net reclassification index improved by 17.4%, suggesting that stroke risk stratification in patients with atrial fibrillation should include kidney function [32▪]. A large study of the 2006 5% Medicare population found that incident atrial fibrillation was associated with a 27% increased rate of death among patients with CKD [6]. A single-center study of 387 Japanese patients with atrial fibrillation reported higher death rates in patients with a



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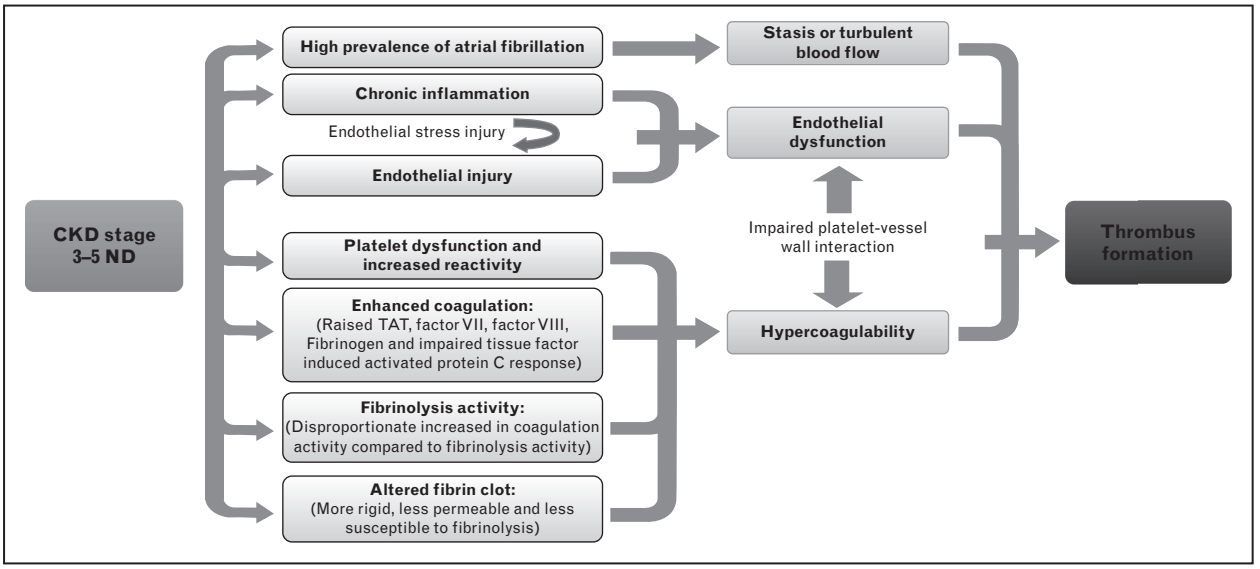


**FIGURE 1.** Potential mechanisms of increased thromboembolic risk in patients with chronic kidney disease stages 3–5 nondialysis (CKD 3–5 ND). Factors known to be associated with CKD lead to abnormalities in all three factors in Virchow's triad, enhancing the risk of thrombus formation. Adapted with permission from [29].

decreased eGFR and high $CHADS_2$ score compared with those with preserved eGFR and low $CHADS_2$ score [33]. Among patients with an eGFR less than 60 ml/min/1.73 $m^2$, there was a 2.8-fold (95% CI 1.3–5.8) higher rate of death in patients with $CHADS_2$ score less than 2 and 6.9-fold (95% CI 3.5–13.5) higher rate of death in patients with $CHADS_2$ score of at least 2 [33]. Furthermore, change in kidney function may also be an important predictor of atrial fibrillation complications. A study of 617 atrial fibrillation patients followed over 2 years (with measures of kidney function every 6 months) found that a decline in eGFR of more than 25% over 6 months was associated with a greater than two-fold increased rate of stroke and death [34].

Complications associated with atrial fibrillation among ESRD patients on dialysis appear to be even greater [35,36]. In a study of 132 372 patients with nonvalvular atrial fibrillation, patients with ESRD had an 83% increased rate of stroke compared with patients without kidney disease [30▪]. In another study of dually eligible Medicare–Medicaid chronic dialysis patients, chronic atrial fibrillation was significantly associated with 26% higher rates of ischemic strokes [37]. A similar study of incident dialysis patients found that atrial fibrillation was one of the strongest risk factors for ischemic stroke, even stronger than age or hypertension [38]. Among more than 17 000 dialysis patients enrolled in the international Dialysis Outcomes and Practice Patterns Study (DOPPS), atrial fibrillation at study enrollment was associated with higher rates of stroke (adjusted hazard ratio 1.28, 95% CI 1.01–1.63) and death (adjusted hazard ratio 1.16, 95% CI 1.08–1.25) [36]. Within the nationally comprehensive USRDS between 1989 and 2006, the adjusted 1-year risk of death was 45% higher in dialysis patients with atrial fibrillation compared with those who did not have documented atrial fibrillation [8].

These large studies are the first step in elucidating the complex interaction between kidney disease and atrial fibrillation, and highlight that atrial fibrillation is far from a 'benign' arrhythmia.

## ATRIAL FIBRILLATION AND RENAL OUTCOMES

Although it is generally accepted that CKD increases the risk of developing atrial fibrillation, few studies have evaluated the potential bidirectional relationship between atrial fibrillation and CKD. One cohort study of Japanese participants in the Niigata Preventive Medicine Study found that participants with preserved kidney function (defined as eGFR >60 ml/min/1.73 $m^2$ and absence of dipstick detectable proteinuria) with atrial fibrillation at entry was associated with 80% higher adjusted rate of developing an eGFR less than 60 ml/min/1.73 $m^2$ and a 116% higher adjusted rate of developing proteinuria [39]. We recently extended the work from this study to a large integrated healthcare delivery system in Northern California [40▪]. In a study of 206 229 adults with confirmed CKD, we identified outpatient and inpatient atrial fibrillation using validated approaches. Our primary outcome was progression to ESRD, defined as the receipt of chronic dialysis or



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a kidney transplant. Over a mean follow-up time of 5 years, there was a 67% increased rate of ESRD among CKD patients who developed incident atrial fibrillation compared with those without atrial fibrillation, even after statistical adjustment for demographic characteristics, household income, educational status, entry eGFR level, comorbid conditions, outpatient blood pressure level, albuminuria, hemoglobin level and medication use [40▪]. In adjusted models stratified by age, sex, race and baseline eGFR level, we found a consistently higher adjusted rate of ESRD associated with incident atrial fibrillation in all of the targeted patient subgroups, except for baseline eGFR less than 30 ml/min/1.73 $m^2$. Adjustment of interim hospitalizations for heart failure and myocardial infarction only slightly attenuated the association between incident atrial fibrillation and ESRD. Although previous literature has shown that CKD is associated with a high incidence and prevalence of atrial fibrillation [1–5], our novel results support the hypothesis that atrial fibrillation may contribute to an accelerated progression of CKD to ESRD independent of other known risk factors.

Several possible mechanisms may explain how atrial fibrillation could increase the risk of ESRD. Atrial fibrillation promotes systemic inflammation [12–16], which has been strongly associated with progression of ESRD in patients with CKD [41,42]. Given that atrial fibrillation can also induce fibrosis within the myocardium [43], it is possible that this same fibrosis process is activated within the kidney as well, perhaps through a systemic profibrotic tendency (although there is no definitive evidence for this mechanism). Atrial fibrillation also contributes to the decline of left ventricular systolic and diastolic function over time [44,45], which may promote progression of CKD through altered hemodynamics [45,46], venous congestion [2,17–23] and activation of the renin–angiotensin–aldosterone system [24,25]. It is also possible that atrial fibrillation may be prothrombotic, leading to renal microinfarcts, similar to silent cerebral infarcts that have been noted in patients with atrial fibrillation [47]. It is also plausible that some of the medications used to treat atrial fibrillation may contribute to a decline in renal function (e.g., diuretics).

## ATRIAL FIBRILLATION AND KIDNEY TRANSPLANT

The burden and consequences of atrial fibrillation in kidney transplant recipients remains largely understudied. The USRDS estimates that approximately 7% of all cardiovascular hospitalizations are primarily because of atrial fibrillation in the first 2 years after kidney transplantation (http://www.usrds.org). Among 304 kidney transplant recipients at a single center in Italy, 6.9% had incident atrial fibrillation in the postoperative period after surgery (median time of 3 days) [48]. The cumulative postoperative atrial fibrillation risk was highest on the day of surgery (2.5%), increased steeply up to day 3 (5.3%) and reached 9.5% on the 19th day of admission [48]. The highest risk of incident atrial fibrillation after kidney transplant was among kidney transplant recipients who were older, male and white with a higher burden of hypertension and coronary heart disease. Another analysis examined the prevalence of pretransplant atrial fibrillation and associated outcomes after transplant among over 62 000 first kidney transplant recipients [49▪]. Of those, 6.4% were diagnosed with atrial fibrillation prior to kidney transplant. Over a mean

**Table 1.** Key pharmacological characteristics of novel oral anticoagulants

| Features | Drug | | | |
|---|---|---|---|---|
| | Dabigatran etexilate | Apixaban | Rivaroxaban | Edoxaban |
| Coagulation target | Thrombin | Factor Xa | Factor Xa | Factor Xa |
| Prodrug | Yes | No | No | No |
| Bioavailability (%) | 6 | 70 | 80 | Not known |
| Protein binding (%) | 35 | 90 | 90 | 55 |
| Dosing frequency[a] | Twice-daily | Twice-daily | Once-daily | Once-daily |
| Half-life (h) | 12–14 | 12 | 7–11 | 8–10 |
| Renal clearance (%) | 80 | 25 | 35 | 40 |
| Routine monitoring | No | No | No | No |
| Drug interactions | P-glycoprotein | CYP3A4 and P-glycoprotein | CYP3A4 and P-glycoprotein | CYP3A4 and P-glycoprotein |
| Approved for ESRD | No | No | No | No |

ESRD, end-stage renal disease. Adapted with permission [70].
[a]For patients with atrial fibrillation.



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**Table 2.** Overview of phase III randomized trials of new oral anticoagulants

| Study (*n*) | Agents | Design features | Exclusion criteria related to CKD | Dose adjustment related to CKD | Stage 3 CKD (%) | Mean time in therapeutic range (INR 2–3) | Main results |
|---|---|---|---|---|---|---|---|
| RE-LY [68] | Dabigatran 150 or 110 mg twice-daily vs. warfarin | Warfarin given open-label | eCrCl <30 ml/min | None | 10% eCrCl 30–49 ml/min | 64% | Stroke, non-CNS embolism and cardiovascular mortality reduced by dabigatran 150 mg vs. warfarin; major hemorrhage reduced by dabigatran 110 mg vs. warfarin; intracranial bleeding reduced by both doses of dabigatran vs. warfarin; no significant differences in total mortality |
| AVERROES [67] (5599) | Apixaban 5 mg twice-daily vs. aspirin | Double-blind; restricted to those deemed unsuitable for warfarin | Serum creatinine >221 μmol/l or eCrCl <25 ml/min | 2.5 mg twice-daily if serum creatinine ≥133 μmol/l and age ≥80 years or weight ≤60 kg | 30% eCrCl 30–59 ml/min | NA | Stroke and non-CNS embolism reduced by apixaban vs. aspirin; major hemorrhage and intracranial bleeding comparable with both agents; no significant difference in cardiovascular or total mortality |
| ROCKET AF [69] (14 264) | Rivaroxaban 20 mg/day vs. warfarin | Double-blind; restricted to those at high risk of stroke | eCrCl <30 ml/min | 15 mg/day if CrCl <50 ml/min | 21% eCrCl 30–49 ml/min | 55% | Rivaroxaban noninferior to warfarin for stroke and non-CNS embolism; major hemorrhage comparable with both agents; intracranial bleeding reduced by rivaroxaban vs. warfarin; no significant difference in cardiovascular or total mortality |
| ARISTOTLE [55] | Apixaban 5 mg twice-daily vs. warfarin | Double-blind | Serum creatinine >221 μmol/l or eCrCl <25 ml/min | 2.5 mg Twice-daily if serum creatinine ≥133 μmol/l and age ≥80 years or weight ≤60 kg | 15% eCrCl 30–50 ml/min | 62% | Stroke, non-CNS embolism, major hemorrhage, intracranial bleeding and total mortality reduced by apixaban vs. warfarin; no significant difference in cardiovascular mortality |

CKD, chronic kidney disease; CNS, central nervous system; eCrCl, estimated creatinine clearance; INR, international normalized ratio; NA, not available. Data from Hart *et al.* [71].



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follow-up of 4.9 years, pretransplant atrial fibrillation was associated with 46% increased rate of death, 41% increase in the rate of graft failure and 36% increase in the rate of stroke after transplant compared with those who did not have atrial fibrillation prior to kidney transplant [49▪]. It appears that pretransplant and posttransplant atrial fibrillation has serious implications on the outcomes after transplantation. These studies are a preliminary step to further characterize the burden and consequences of atrial fibrillation in kidney transplant recipients. Further investigations are necessary to fully understand the unique interactions of peri-transplant kidney care and atrial fibrillation.

## TREATMENT OF ATRIAL FIBRILLATION IN KIDNEY DISEASE

There are clear and evidence-based guidelines for the use of anticoagulation in the prevention of thromboembolic stroke in the general population [50]. Yet, despite the tremendous burden of atrial fibrillation and the associated adverse consequences in patients with CKD and ESRD, the role of anticoagulation in patients with kidney disease is less defined. Patients with kidney disease uniquely have an increased risk for thromboembolism and a paradoxical increased risk of bleeding, making decisions on anticoagulation challenging. A previous analysis identified serum creatinine concentrations of greater than 1.5 mg/dl as an independent predictor of major bleeding events [51]. Observational studies and clinical trials have reported a heightened risk of hemorrhagic stroke and other bleeding events in patients with reduced kidney function [52–55]. Reduced kidney function is also associated with larger hematoma volumes [56] and poorer survival after intracerebral hemorrhage [57]. Impaired platelet adhesion, decreased storage and section of platelet-activating mediators, disturbances in platelet aggregation and presence of uremic toxins are just a few of the postulated mechanisms to explain the increased bleeding risk in patients with CKD and ESRD [58,59].

Clinical trials of anticoagulation in patients with atrial fibrillation have largely excluded patients with advanced CKD or ESRD [60]. In the ESRD population, observational studies of anticoagulation have yielded conflicting results, with some noting better [61] and others worse [62–64] outcomes with the use of warfarin. In the CKD population, there are limited data on the safety of warfarin. However, the few studies in this area have suggested that warfarin use is associated with lower risk of stroke [65,66]. Among 516 stage 3 CKD patients in the Stroke Prevention in Atrial Fibrillation 3 trial, rates of ischemic stroke and systemic embolism were reduced by 76% in participants treated with adjusted-dose warfarin compared to those treated with aspirin and low-dose warfarin [65]. There was no difference in major hemorrhage in the two groups [65]. However, the mean eGFR was 50 ml/min/1.73 $m^2$ among the CKD participants in this trial and it therefore remains unknown whether the same conclusions can be made at more advanced stages of CKD.

Over the last several years, several novel oral anticoagulants have been tested in large randomized trials for the prevention of stroke in patients with atrial fibrillation [55,67–69]. These novel anticoagulants include two direct thrombin inhibitors (ximelagatran and dabigatran) and two factor Xa inhibitors (apixaban and rivaroxaban), and have the benefit of not requiring regular anticoagulation monitoring and frequent dose adjustments but all have substantial renal clearance with prolonged half-life in patients with CKD (Table 1). Three of these novel anticoagulants have been recently approved for clinical use (dabigatran, apixaban and rivaroxaban) and have been shown to be noninferior or superior to adjusted-dose warfarin for stroke prevention, and, in some cases, reduced the risk of major hemorrhagic complications. Whereas major clinical trials of these agents have excluded patients with advanced CKD, many have included patients with moderate CKD (Table 2). Overall, evidence from these trials supports the use of these novel agents in patients with moderate CKD (Table 2). There remains a paucity of data on the efficacy and safety of these agents in more advanced stages of CKD and ESRD.

## CONCLUSION

The burden of atrial fibrillation in patients with kidney disease is disproportionately high and continues to rise. Atrial fibrillation afflicts patients with all stages of kidney disease, including advanced stages of CKD, ESRD and kidney transplant recipients. Recent work has highlighted that atrial fibrillation and kidney disease synergistically lead to serious complications. Additional studies are necessary to understand the distinct kidney-specific pathophysiological pathways that contribute to the development of atrial fibrillation as well as the unique considerations in preventing and treating atrial fibrillation specific to patients with a broad range of kidney disease.

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## Conflicts of interest

*There are no conflicts of interest.*

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