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Intersection of Cardiovascular Disease and Kidney Disease: Atrial Fibrillation

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Abstract

Purpose of review—Atrial fibrillation (AF) is the most common sustained arrhythmia in the patients with kidney disease. The purpose of this review is to describe the burden of AF 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 AF and review the treatment options for AF specific to patients with kidney disease.

Recent findings—Recent literature has revealed that the clinical multi-organ impact of AF in patients with CKD and ESRD is substantial. Although novel oral anticoagulants to treat AF 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—AF 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 treatment options specific to this population of high-risk patients.

Keywords

Atrial fibrillation; CKD; ESRD

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in the general population. The burden of AF is even greater in patients with concomitant kidney disease. Published studies in the last few years have highlighted the often under-recognized, yet highly prevalent relation between kidney disease and AF. Furthermore, evidence has suggested that

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the burden of AF will likely rise in this high-risk population, making the intersection of kidney disease and AF 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 AF, typically 2-to-3-fold higher than reported in the general population.[1–5] In participants with moderate to advanced CKD in the Chronic Renal Insufficiency Cohort (CRIC), the prevalence of AF was 18%overall and >25% in participants ≥ 70 years old.[5] Older age, female sex, tobacco use and history of cardiovascular disease, including heart failure, were significantly associated with prevalent AF in that study. Another study of the Medicare 5% sample with CKD found that the two-year *incidence* of AF 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 AF with lower 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 AF is estimated to be 7–20%.[8] An analysis of 63,884 Medicare/Medicaid-eligible dialysis patients found that age >60 years, male sex, white race, overweight/obesity, inability to ambulate, and prior cardiovascular disease were significantly associated with prevalent AF.[7] Furthermore, recent data from the United States Renal System (USRDS) reported that the prevalence of AF continues to increase among patients with ESRD.[8]

While these data are compelling, our estimates of the burden of AF are likely conservative given current methods of ascertainment of AF, and particularly incident AF. 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 AF and the fact that many patients are asymptomatic. Thus, innovative methods are needed to capture prevalent and incident AF more comprehensively and cost-effectively in large studies of patients with kidney disease.

Mechanisms that contribute to increased risk of AF in CKD

Several possible mechanisms may explain the high rate of identified AF among 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 AF;[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 AF 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 risk of AF 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 AF and kidney disease given the disproportionately high burden of disease in this population.

AF associated with increased risk of stroke and death in CKD and ESRD

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

Among patients with CKD, several clinical studies have reported that AF is associated with increased risk of stroke and death. In a study of 132,372 patients with nonvalvular AF, patients with CKD had 49% increased rate of stroke or systemic thromboembolism compared with patients without kidney disease.[29] In a study of nearly 11,000 patients with AF, 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.[30] In the ROCKET AF (Rivaroxaban Once-daily, oral direction factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation), 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.[31] A model that included creatinine clearance improved net reclassification index by 8.2% (95% 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 NRI improved by 17.4%, suggesting that stroke risk stratification in patients with AF should include kidney function.[31] A large study of the 2006 5% Medicare population found that incident AF was associated with a 27% increased rate of death among patients with CKD.[6] A single center study of 387 Japanese patients with AF reported higher death rates in patients with decreased eGFR and high $CHADS_2$ score compared with patients with preserved eGFR and low $CHADS_2$ score.[32] Among patients with eGFR<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 <2 and 6.9-fold (95% CI 3.5–13.5) higher rate of death in patients with $CHADS_2$ score ≥ 2.[32] Furthermore, *change* in kidney function may also be an important predictor of AF complications. A study of 617 AF patients followed over 2 years (with measures of kidney function every 6 months), found that *decline* in eGFR>25% over 6 months was associated with greater than 2-fold increased rate of stroke and death.[33]

Complications associated with AF among ESRD patients on dialysis appear to be even greater.[34,35] In a study of 132,372 patients with nonvalvular AF, patients with ESRD had 83% increased rate compared with patients without kidney disease.[29] In another study of dually eligible Medicare-Medicaid chronic dialysis patients, chronic AF was significant associated with 26% higher rates of ischemic strokes.[36] A similar study of incident dialysis patients found that AF was one of the strongest risk factors for ischemic stroke, even stronger than age or hypertension.[37] Among >17,000 dialysis patients enrolled in the international Dialysis Outcomes and Practice Patterns Study (DOPPS), AF 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).[35] Within the nationally comprehensive U.S. Renal Data System between 1989 and 2006, the adjusted 1-year risk of death was 45% higher in dialysis patients with AF compared with those who did not have documented AF.[8]

These large studies are the first step in elucidating the complex interaction between kidney disease and AF and highlight that AF is far from a “benign” arrhythmia.

AF and renal outcomes

While it is generally accepted that CKD increases the risk of developing AF, few studies have evaluated the potential bidirectional relationship between AF and CKD. One cohort study of Japanese participants in the Niigata Preventative 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) and with AF at entry was associated with 80% higher adjusted rate of developing eGFR<60 ml/min/1.73 m^2 and a 116% higher adjusted rate of developing proteinuria that could be detected by urine dipstick testing.[38] We recently extended the work from this study to a large integrated healthcare delivery system in Northern California.[39] In a study of 206,229 adults with confirmed CKD, we identified outpatient and inpatient AF using validated approaches. Our primary outcome was progression to ESRD, defined as the receipt of chronic dialysis or 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 AF compared to those without AF, 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,.[39] In adjusted models stratified by age, gender, race and baseline eGFR level, we found a consistently higher adjusted rate of ESRD associated with incident AF in all of the targeted patient subgroups, except for baseline eGFR <30 ml/min/1.73 m^2. Adjustment of interim hospitalizations for HF and MI only slightly attenuated the association between incident AF and ESRD. While previous literature has shown that CKD is associated with a high incidence and prevalence of AF,[1–5] our novel results support that AF may contribute to an accelerated progression of CKD to ESRD independent of other known risk factors.

Several possible mechanisms may contribute to how AF could increase the risk of ESRD. AF promotes systemic inflammation, [12–16] which has been strongly associated with progression of ESRD in patients with CKD.[40,41] Given that AF can also induce fibrosis within the myocardium,[42] it is possible that this same fibrosis process is activated within the kidney as well, perhaps through a systemic pro-fibrotic tendency (although there is not definitive evidence for this mechanism). AF also contributes to decline of left ventricular systolic and diastolic function over time,[43,44] which may promote progression of CKD through altered hemodynamics, [44,45] venous congestion and activation of the renin-angiotensin-aldosterone system.[24,25] It is also possible that AF may be prothrombotic, leading to renal micro-infarcts, similar to silent cerebral infarcts that have been noted in patients with AF.[46] It is also plausible that some of the medications used to treat AF may contribute to decline in renal function (e.g., diuretics).

AF and kidney transplant

The burden and consequences of AF in kidney transplant recipients remains largely understudied. The USRDS estimates that ~7% of all cardiovascular hospitalizations are

primarily due to AF in the first 2 years after kidney transplantation.[47] Among 304 kidney transplant recipients at a single center in Italy, 6.9% had incident AF in the post-operative period after surgery (median time of 3 days).[48] The cumulative post-operative AF 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 AF after kidney transplant was among kidney transplant recipients who were older, men and white with a higher burden of hypertension and coronary heart disease. Another analysis examined the prevalence of *pre-transplant* AF and associated outcomes after transplant among over 62,000 first kidney transplant recipients.[49] Of those, 6.4% were diagnosed with AF prior to kidney transplant. Over a mean follow-up of 4.9 years, pre-transplant AF was associated with 46% increased rate of death, 41% increase in rate of graft failure and 36% increase in rate of stroke after transplant compared to patients who did not have AF prior to kidney transplant.[49] It seems clear that pre- and post-transplant AF has serious implications on outcomes post transplantation. These studies are a preliminary step to further characterize the burden and consequences of AF in kidney transplant recipients. Further investigations are necessary to fully understand the unique interactions of peri-kidney transplant care and AF

Treatment of AF 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 AF and 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 increased risk for thromboembolism and a paradoxical increased risk of bleeding, making decisions on anticoagulation challenging. A previous analysis identified serum creatinine concentration of >1.5 mg/dL as an independent predictor of major bleeding events.[51] Observational studies and clinical trials have reported 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 AF 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/systemic embolism was reduced by 76% in participants treated with adjusted-dose warfarin compared to participants treated with aspirin/low-dose warfarin.[65] There was no difference in major hemorrhage in the 2 groups.[65] Yet the mean eGFR was 50 ml/min/1.73 m^2 among the CKD participants in this trial; thus, it remains unknown if 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 prevention of stroke in patients with AF.[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. Yet, all have substantial renal clearance with prolonged half-life in patients with CKD (Table 1). Three of these novel anticoagulants have been recently been approved for clinical use (dabigatran, apixaban and rivaroxaban) and have been shown to be non-inferior or superior to adjusted-dose warfarin for stroke prevention, and, in some cases, reduced risk of major hemorrhagic complications. While 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 support 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.

Conclusions

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

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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.

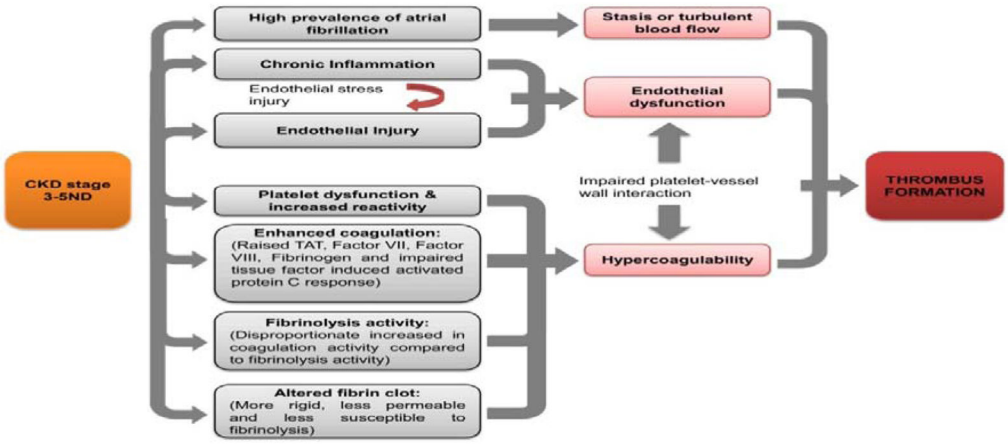

Figure 1.

Potential mechanisms of increased thromboembolic risk in patients with chronic kidney disease stages 3–5 nondialysis (CKD 3-5ND). Factors known to be associated with CKD lead to abnormalities in all 3 factors in Virchow's triad, enhancing the risk of thrombus formation.

(Adapated from Ng et al, Am J Kidney Dis. 2013 Sep;62(3):615–32. doi: 10.1053/j.ajkd.2013.02.381. Epub 2013 Jun 5)

Table 1

Key pharmacological characteristics of novel oral anticoagulants

Feature	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*	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

*For patients with atrial fibrillation. Abbreviation: ESRD, end-stage renal disease. Adapted with permission from Wolters Kluwer Health © Eikelboom, J. W. & Weitz, J. I. New anticoagulants. *Circulation* **121** (13), 1523–1532 (2010).

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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]	Dabigat ran 150 mg 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 haemorrhage 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] (5,599)	Apixaban 5 mg twice daily vs. aspirin	Double- blind; restricted to those deemed unsuitable for warfarin	Serum creatinine >221 umol/L or eCrCr<25 ml/min	2.5 mg twice daily if serum creatinine ≥ 133 umol/L plus 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 haemorrhage and intracranial bleeding comparable with both agents; no significant difference in cardiovascular or total mortality
ROCKET AF[69] (14, 264)	Rivaroxaban 20 mg per day vs. warfarin	Double- blind; restricted to those at high risk of stroke	eCrCl<30 ml/min	15 mg per day if CrCl<50 ml/min	21% eCrCl 30–49 ml/min	55%	Rivaroxaban noninferior to warfarin for stroke and non-CNS embolism; major haemorrhage 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 umol/L or eCrCl<25 ml/min	2.5 mg twice daily if serum creatinine ≥ 133 umol/L plus age ≥ 80 years or weight ≤ 60 kg	15% eCrCl 30–50 ml/min	62%	Stroke, non-CNS embolism, major haemorrhage, intracranial bleeding and total mortality reduced by apixaban vs. warfarin; no significant difference in cardiovascular mortality

Abbreviations: CKD=chronic kidney disease; CNS=central nervous system; eCrCl=estimated creatinine clearance; INR=international normalized ratio; NA=not available

Hart, R. G. (2012) Anticoagulants in atrial fibrillation patients with chronic kidney disease *et al. Nat. Rev. Nephrol.* doi:10.1038/nrneph.2012.160