

chronic kidney disease

Chronic kidney disease and arrhythmias: highlights from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Patients with chronic kidney disease (CKD) are predisposed to heart rhythm disorders, including atrial fibrillation (AF)/flutter, supraventricular tachycardias, ventricular arrhythmias, and sudden cardiac death (SCD). This population is also historically underrepresented in clinical trials of treatment for heart rhythm disorders.¹

Kidney Disease: Improving Global Outcomes (KDIGO) recently convened an international, multidisciplinary Controversies Conference that covered unique issues in the management of AF and the prediction and prevention of SCD in patients with CKD. The conference report was published in the *European Heart Journal* with the goal of increasing the visibility of its proceedings to a broader audience.² Highlights of the conference report are summarized here with a focus on areas of direct relevance to nephrologists.

Atrial fibrillation: oral anticoagulant and antiplatelet therapy

AF is the most common sustained arrhythmia, and patients with CKD have an increased prevalence of AF: estimates range from 16% to 21% in nondialysis CKD patients and from 15% to 40% in those on dialysis. Both CKD and AF are risk factors for stroke, but the multifactorial mechanisms responsible for stroke and thromboembolism in patients with CKD and AF are poorly understood. AF may be a direct cause of cardioembolic stroke, a risk marker for ischemic stroke, and rarely, a consequence of stroke.³ The contribution of AF

as a mediator of stroke in CKD, as well as other outcomes related to AF in this population, requires further research.

The predictive value and calibration of widely used risk scores for the prediction of stroke in dialysis patients are similar to those used in the general population. The CHA₂DS₂-VASC score is the most commonly recommended score for risk stratification in patients with CKD.⁴ Observational data have suggested that a treatment threshold of CHA₂DS₂-VASC ≥ 2 is associated with benefit from oral anticoagulants, even in patients with CKD.⁵ Although the majority of guidelines do not recommend the formal use of bleeding risk scores, the increased bleeding risk in patients with CKD both with and without anticoagulation should also be considered in making treatment decisions.

Pivotal randomized controlled trials (RCTs) have established that direct oral anticoagulants (DOACs) are noninferior to warfarin among patients with Cockcroft-Gault estimated creatinine clearance (eCrCl) of 30 to 50 ml/min (for apixaban, 25–50 ml/min). The safety profile of DOACs is superior to warfarin. In RCTs that compared DOACs with warfarin, DOACs were associated with an approximately 50% reduction in risk of intracranial hemorrhage. Among patients with eCrCl between 25 and 50 ml/min, treatment with apixaban and edoxaban also resulted in significantly fewer major bleeding events.⁶ There is insufficient evidence to recommend any one DOAC in this population,

Table 1 | Therapeutic anticoagulation on the basis of kidney function^{a6–8}

eCrCl, ml/min	Warfarin	Apixaban ^b	Dabigatran	Edoxaban	Rivaroxaban
>95	Adjusted dose (INR 2–3)	5 mg b.i.d.	150 mg b.i.d.	60 mg q.d. ^{c,d}	20 mg q.d.
51–95	Adjusted dose (INR 2–3)	5 mg b.i.d.	150 mg b.i.d.	60 mg q.d. ^c	20 mg q.d.
31–50	Adjusted dose (INR 2–3)	5 mg b.i.d. (eCrCl cutoff 25 ml/min)	150 mg b.i.d. or 110 mg b.i.d. ^e	30 mg q.d. ^c	15 mg q.d.
15–30	Adjusted dose for INR 2–3 should be considered	2.5 mg b.i.d. could be considered	Unknown (75 mg b.i.d.) ^{f,g}	30 mg q.d. could be considered	15 mg q.d. could be considered
<15 on or not on dialysis	Equipose based on observational data and meta-analysis	Unknown (2.5 mg b.i.d.) ^f	Not recommended	Not recommended	Unknown (15 mg q.d.) ^f

b.i.d, twice daily; eCrCl, Cockcroft-Gault estimated creatinine clearance; eGFR, estimated glomerular filtration rate; ENGAGE-AF TIMI, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; INR, international normalized ratio; q.d, daily.

^aIt is important to note that kidney function assessments in all randomized controlled trials published to date were based on eCrCl although eGFR is more commonly used and both measures are not equivalent. Therefore, individualization of dosing based on either method is reasonable.

^bApixaban dose modification from 5 mg b.i.d. to 2.5 mg b.i.d. if patient has any 2 of the following: serum creatinine ≥ 1.5 mg/dl, age 80 years or older, or body weight ≤ 60 kg.

^cIn the ENGAGE-AF TIMI 48 study, the dose was halved if any of the following were present: eCrCl of 30 to 50 ml/min, body weight ≤ 60 kg, or concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors).

^dThis dose has not been approved for use by the US Food and Drug Administration in this category of kidney function.

^eIn countries where 110 mg b.i.d. is approved, clinicians may prefer this dose after clinical assessment of thromboembolic versus bleeding risk. This dose has not been approved for use by the US Food and Drug Administration.

^fDirect oral anticoagulants doses listed in parenthesis are doses that do not currently have any clinical safety or efficacy data. The doses of direct oral anticoagulants apixaban 5 mg b.i.d.^b, rivaroxaban 15 mg q.d., and dabigatran 75 mg b.i.d. are included in the US Food and Drug Administration approved labelling based on limited dose pharmacokinetic and pharmacodynamics data with no clinical safety data. We suggest consideration of the lower dose of apixaban 2.5 mg oral b.i.d. in chronic kidney disease GFR category G5 or G5D (on dialysis therapy) [G5/G5D] to reduce bleeding risk until clinical safety data are available.

^gDabigatran 75 mg available only in the United States.

Adapted with permission from Turakhia *et al.*²

because no head-to-head trials have directly compared individual DOACs (Table 1).

There are no RCTs that examined the efficacy and safety of anticoagulation in CKD patients with eCrCl < 30 ml/min, and there is insufficient high-quality evidence to recommend warfarin for the prevention of stroke in patients with AF and dialysis-dependent CKD. To reduce bleeding risk, lower dose apixaban (2.5 mg orally twice daily) or rivaroxaban (15 mg daily) may be considered in this population until clinical safety data are available. For all patients with CKD and AF, team-based, multidisciplinary participation in decisions regarding oral anticoagulation is recommended, together with annual re-evaluation of treatment goals and risk–benefit assessment in CKD patients on anticoagulant therapy.

There is insufficient evidence to recommend single or dual antiplatelet therapy for prevention of stroke/thromboembolism in AF among patients with CKD GFR category G4 to G5D (on dialysis therapy) [G4–G5D], even when oral anticoagulation therapy is considered undesirable. Similarly, these patients should not receive concomitant antiplatelet therapy while taking anticoagulants, unless specifically indicated. In patients who recently received a coronary stent, the duration of concomitant antiplatelet therapy should be minimized and individualized based on clinical factors and the type of stent used.

Atrial fibrillation: rate versus rhythm control

Indications for a rhythm control strategy in CKD patients mirror those in the general population (Supplementary Figure S1). Patients without clear indications for rhythm control should default to rate control. Regardless of which strategy is pursued, anticoagulation should be continued based on stroke risk, unless otherwise contraindicated. Special considerations in more advanced CKD include alterations in symptomatology and an increased propensity to develop tachycardia-mediated cardiomyopathy in patients with structural heart disease.

If a rate control strategy is pursued, the pharmacokinetics and dialyzability of the rate control agents should be considered. Atrioventricular nodal ablation and pacemaker implantation are options when pharmacological therapies alone are insufficient; however, the high rates of complications associated with transvenous devices in hemodialysis patients should be considered before pacemaker implantation in patients with advanced CKD.

Direct current cardioversion is the most commonly used method of rhythm restoration in patients with persistent AF. Cardioversion alone is generally insufficient to maintain normal sinus rhythm, and long-term antiarrhythmic drugs or catheter ablation are

necessary for rhythm control. The use of antiarrhythmic drugs is complicated in patients with CKD because of reduced renal clearance, as well as proarrhythmic potential in individuals with structural heart disease. Catheter ablation is more effective than antiarrhythmic drugs alone for maintenance of sinus rhythm. In patients with CKD and atrial flutter, radiofrequency ablation is considered a firstline therapy because of its high success and low complication rates.

Sudden cardiac death

The annual risk of SCD is higher in hemodialysis patients compared with other patient populations, accounting for up to 35% of all-cause mortality in patients initiating dialysis. Evidence is limited regarding the electrical and hemodynamic mechanisms underlying SCD. Risk factors predisposing to SCD in patients on dialysis have been identified, but more research is needed to identify targets for intervention.

Data regarding secondary prevention of SCD with implantable cardioverter-defibrillator (ICD) therapy indicate some benefits, but further studies are needed to assess longer term risk–benefit. ICD placement for primary prevention is indicated in patients with left ventricular ejection fractions (LVEFs) of $\leq 35\%$, but no data exist on the utility of ICD in dialysis patients with LVEFs of $>35\%$. Available data suggest that the benefit of ICDs decreases with declining kidney function. Subcutaneous defibrillators might be associated with fewer and less severe complications, but further research is needed to evaluate this approach, as well as wearable cardioverter defibrillators and pacing devices (including leadless pacemakers).

Potassium and fluid homeostasis

Both hyperkalemia and hypokalemia have been associated with higher risk of all-cause and cardiovascular mortality in patients on chronic dialysis. Abrupt fluctuations in serum potassium in hemodialysis patients may contribute to higher mortality and hospitalization rates. In contrast, hypokalemia is more common in patients on peritoneal dialysis and has been associated with an increased risk of all-cause, cardiovascular, and infectious mortality.

For patients undergoing hemodialysis, both the dialysate potassium concentration and the schedule of hemodialysis treatments affect the risk of SCD. Studies have indicated that low potassium dialysate (< 2 mEq/l) is associated with a higher incidence of sudden death.²

Rapid correction of acidemia, low serum or dialysate calcium, and high ultrafiltration rates may contribute to the arrhythmogenic potential of low potassium dialysate.

Ultrafiltration rates >10 ml/hour per kilogram have been associated with intradialytic hypotension and increased mortality. Hemodynamic stress during hemodialysis is associated with cardiac stunning, which may promote regional fixed systolic dysfunction. It is possible that personalizing dialysis parameters for individual patients could reduce the risk of SCD and nonfatal arrhythmias, but this approach is untested and would be logistically complicated to implement.

Given the high burden of arrhythmias and the paucity of relevant studies in individuals with CKD, nephrologists and cardiologists should forge closer partnerships in coordinating their care of such patients. A major conclusion of the conference was the need for future RCTs to include participants with CKD to better inform management strategies in this population.

DISCLOSURE

CW declared having received consultancy fees from Boehringer Ingelheim, GlaxoSmithKline, and Sanofi Genzyme; speaker honorarium from Boehringer Ingelheim, Merck Sharpe & Dohme, and Sanofi Genzyme; and research support from Sanofi Genzyme. CAH declared having received consultancy fees from AbbVie, FibroGen, KBP Biosciences, OxThera, and Relypsa; equity ownership/stock options on Boston Scientific, Bristol-Myers Squibb, General Electric, Johnson & Johnson, and Merck; and research support from Amgen, National Institutes of Health, Relypsa, and Zoll. CAH also expects future consultancy roles from AstraZeneca, Boehringer Ingelheim, Corvidia, and Sanifit. MPT declared having received consultancy fees from Abbott, iBeat, iRhythm, Medtronic, and Precision Health Economics; equity ownership/stock options on AliveCor and iBeat; speaker honorarium from Abbott and Medtronic; and research support from American Heart Association, Apple, Cardiva Medical, and Veterans Health Administration.

SUPPLEMENTARY MATERIAL

Figure S1. Algorithm for decision-making about rate control versus rhythm control in chronic kidney disease (CKD).

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

REFERENCES

1. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. *Kidney Int.* 2006;70:2021–2030.

2. Turakhia MP, Blankestijn PJ, Carrero J-J, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Eur Heart J*. 2018. <https://doi.org/10.1093/eurheartj/ehy060>.
3. Kamel H, Okin PM, Elkind MS, et al. Atrial fibrillation and mechanisms of stroke: time for a new model. *Stroke*. 2016;47:895–900.
4. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
5. Bonde AN, Lip GY, Kamper AL, et al. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. *J Am Coll Cardiol*. 2014;64:2471–2482.
6. Qamar A, Bhatt DL. Anticoagulation therapy: balancing the risks of stroke and bleeding in CKD. *Nat Rev Nephrol*. 2015;11:200–202.
7. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;17:1467–1507.
8. Lau YC, Proietti M, Guiducci E, et al. Atrial fibrillation and thromboembolism in patients with chronic kidney disease. *J Am Coll Cardiol*. 2016;68:1452–1464.