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Editorial Comment

EDITORIAL COMMENT

Same rhythm, different song—approaches to atrial fibrillation management by cardiologists and nephrologists

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ABSTRACT

Atrial fibrillation (AF) is common in patients with chronic kidney disease (CKD), affecting 10–25% of patients requiring dialysis. Compared with the general population, patients requiring dialysis are also at increased risk of stroke, the major thromboembolic complication of AF. The evidence base for management strategies of AF specific to patients with advanced CKD is limited and not informed by randomized controlled trials. These gaps in evidence encompass rate and rhythm control strategies as well as a paucity of data informing which patients should receive anticoagulation. The European Renal Association–European Dialysis and Transplant Association and European Heart Rhythm Association undertook a survey of nephrologists and cardiologists exploring management strategies in patients with AF and CKD. We review the results of this survey, highlighting the differences in clinical approaches from cardiologists and nephrologists to these conditions. Closer collaboration between these specialties should lead to improved outcomes for patients with advanced CKD and AF. Specific issues that will need to be addressed may include healthcare burden to patients, location of clinics compared with dialysis sites and awareness of complications of treatments specific to CKD, such as calciphylaxis associated with vitamin K antagonism.

Keywords: anticoagulation, atrial fibrillation, dialysis, stroke, warfarin

BACKGROUND

The prevalence of atrial fibrillation (AF) increases with declining kidney function to the point where ~10–25% of patients with end-stage renal disease (ESRD) requiring dialysis or transplantation will have symptomatic AF [1–3]. AF and chronic kidney disease (CKD) have several shared risk factors, including diabetes, advancing age and prior ischaemic heart disease. Inflammation may also have a contributory role in atrial structural remodelling and AF inducibility. Moreover, ESRD presents specific scenarios that exacerbate the risk of AF, such as variability in serum potassium and other electrolytes throughout

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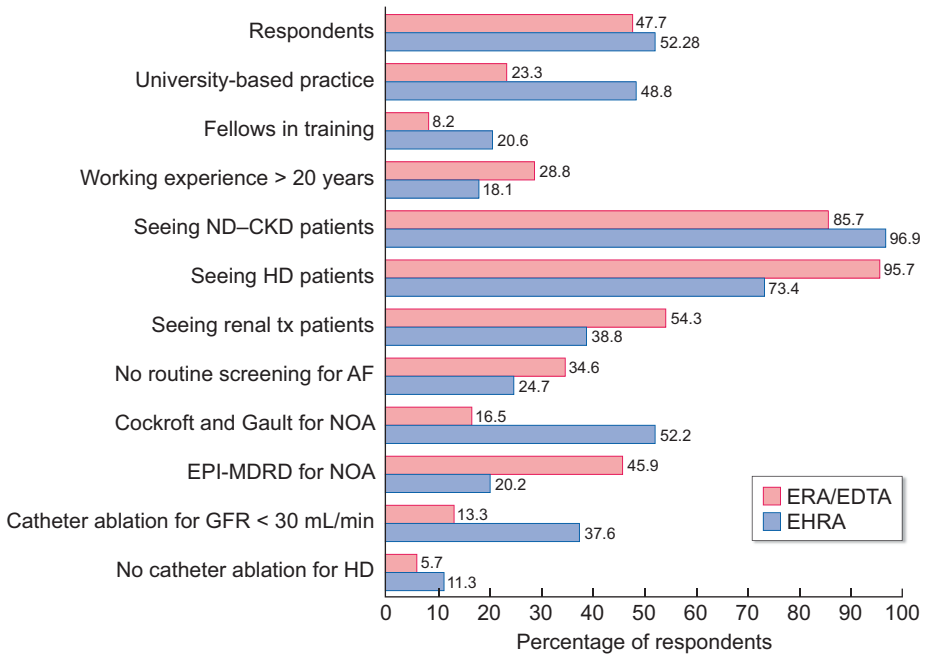

FIGURE 1: Main differences between cardiologists and nephrologists who answered the joint survey of the EHRA and ERA/EDTA [14]. Data are expressed as the percentage of respondents of both associations. ND-CKD, non-dialysis CKD.

the dialysis cycle. Patients with ESRD have a high prevalence of structural cardiac disease that may augment the propensity to develop AF, such as left atrial enlargement, left ventricular hypertrophy and associated cardiac filling disorders and myocardial fibrosis, which may affect cardiac conduction [4–6].

The major thromboembolic complication of AF is stroke. In patients without major renal dysfunction, anticoagulation with vitamin K antagonists (VKAs) or non-vitamin K oral anticoagulants (NOACs) has been shown to be an effective treatment to reduce the risk of stroke in patients with AF, considered to be at increased risk of stroke using a risk score such as CHA_2DS_2-VASc [7]. The major complication of anticoagulation is bleeding, and bleeding risk can be assessed prior to commencement of anticoagulant therapy using bleeding risk scores such as the HAS-BLED score [8].

Unfortunately, patients with advanced CKD, including dialysis patients, have been excluded from randomized clinical trials of anticoagulation for stroke prevention in AF [9, 10]. ESRD is a risk factor for stroke, with a much higher incidence of stroke in patients with ESRD compared with the general population, both in patients with and without AF [1, 11]. Similarly, patients with advanced CKD are at increased risk of bleeding compared with the general population, even prior to commencing anticoagulation and after commencing anticoagulation [12, 13].

Therefore the risk:benefit ratio for commencement of anticoagulation in patients with advanced CKD, including patients requiring dialysis, is complex and not informed by randomized controlled trials (RCTs). In addition to this, the optimal methods for monitoring and adjusting VKA doses are far from being established in advanced CKD, making the time within the therapeutic international normalized ratio range more unstable and less predictable compared with patients without CKD. Warfarin dosing algorithms are underused in nephrological practice. These aspects may further foster either the bleeding or thrombotic risk of advanced CKD patients.

Nevertheless, in the face of a high prevalence of AF and elevated risk of stroke, clinicians are required to make therapeutic decisions to mitigate stroke risk informed by a limited evidence base. Recently the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) and European Heart Rhythm Association (EHRA) undertook a survey of both nephrologists and cardiologists, exploring attitudes and therapeutic decision making in patients with AF and advanced CKD [14]. The results highlight heterogeneous approaches to management in these patients, perhaps reflecting the gap in evidence to inform clinical practice. It appears that although the cardiac rhythm of AF is the same, cardiologists and nephrologists do appear to be literally singing different lyrics. We discuss the survey and highlight the major areas of divergence of opinion and what evidence is required to better inform future therapeutic decisions.

The EHRA and ERA-EDTA survey of attitudes of physicians in the treatment of AF in patients with CKD

The EHRA and ERA-EDTA jointly conducted a physician-based survey examining nephrologists and cardiologists approaches to AF in patients with CKD [14]. In total, 306 physicians responded to the survey, with approximately an even split between cardiologists and nephrologists, with 160 EHRA-affiliated physicians (52.3%) and 146 respondents affiliated with ERA-EDTA (47.7%). The respondents to the survey were primarily based in university-based public hospitals; as expected, the majority of them responded from Europe. The main characteristics of the respondents are summarized in Figure 1. More EHRA respondents were fellows in training, while the majority of the ERA-EDTA respondents had been in practice for >10 years. While, as expected, >90% of ERA-EDTA participants had experience managing AF in patients requiring haemodialysis (HD), the majority of EHRA respondents had extensive experience of AF in CKD, with 73.8% having seen HD patients with AF.

The survey addressed a number of key issues in the management of patients with advanced CKD and AF, including the need for multidisciplinary teams of cardiologists and nephrologists,

measurement of renal function in patients with AF, screening for AF, stroke prevention strategies, use of specific anticoagulation drugs and strategies for rate and rhythm control in patients with AF and CKD. Before delving into the results of this survey, it is worth remembering that there are fairly limited data to support any particular management strategy for AF in advanced CKD. A Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference in 2016 highlighted that patients with CKD have frequently being excluded from clinical trials of anticoagulation and arrhythmia strategies and that there are major gaps in the evidence used to inform the best management of these patients [15].

Clinical management of patients with CKD and AF

There are some divergences in practices and areas where general care might be improved. Less than 10% of respondents to the EHRA/ERA-EDTA survey used multidisciplinary teams for managing patients with CKD and AF [14]. Only 12.5% of cardiologists were of the opinion that there was no collaboration between the cardiology and nephrology team, while 37.9% of nephrologists suggested that there was a lack of collaboration. There are multiple reasons for this, but it typically reflects the experience that nephrologists caring for patients requiring dialysis often are required to function autonomously and undertake several non-nephrological aspects of patient management simply to minimize the healthcare burden. The cardiologists may simply be unaware of dialysis patients with AF who are either not referred to cardiology or patients may prefer to have management undertaken by their renal team, with whom they are familiar.

Some areas of care are fairly uncontroversial. Similar proportions of clinicians would screen for AF and a single electrocardiogram would be the preferred means of screening for >80% of both cardiologists and nephrologists. However, it should be noted that previously undocumented AF is commonly detected in up to 41% of dialysis patients in studies using implantable loop recorders [16, 17].

Whether and how to offer anticoagulation?

One of the major tenets of management of AF is the use of thromboprophylaxis with oral anticoagulation to reduce the risk of stroke. The most commonly used risk score for predicting stroke risk is the CHA_2DS_2-VASc, with anticoagulation typically offered to patients with CHA_2DS_2-VASc scores $\geq$2 in females and $\geq$1 in males [7]. The risk of bleeding typically estimated with the HAS-BLED score may further inform which patients may be less likely to benefit from anticoagulation due to excess risk of bleeding [8]. Despite patients with ESRD being at a considerably higher risk (~3–6 times higher) of stroke than patients with normal kidney function [11], there are no data to support the use of risk scores for offering anticoagulation in ESRD. Furthermore, as kidney function is a component of the HAS-BLED score, its utility in advanced CKD is likely to be confounded. In the EHRA/EDTA-ERA survey, a number of scenarios based on CHA_2DS_2-VASc and HAS-BLED risk scores were presented in the survey to test the opinion of cardiologists and nephrologists on when to offer anticoagulation. Both specialties seemed to weight shared decision making with patients as important, but cardiologists seemed much more enthusiastic to use CHA_2DS_2-VASc to guide decision making than nephrologists when considering when to offer anticoagulation.

This highlights that familiarity with a risk score or equation may be a greater driver than clinical appropriateness for selection of a methodology used for treatment decisions. While cardiologists expressed enthusiasm for using CHA_2DS_2-VASc in patients with advanced CKD with limited data to support this approach, nephrologists preferred to use the Chronic Kidney Disease Epidemiology Collaboration equation to assess renal function for informing anticoagulant dosing. This is despite the current European Medicines Agency licensing recommendations that NOACs are prescribed by Cockcroft–Gault creatinine clearance rather than estimated glomerular filtration rate (eGFR) [15].

Although rare, the association of VKA with calciphylaxis is an additional concern when prescribing these agents in patients requiring dialysis, particularly in patients with other risk factors for calciphylaxis, such as obesity, severe CKD–mineral bone disorder (CKD-MBD) or diabetes [18]. Many cardiologists may not be aware of the association between VKA and calciphylaxis, and even if they are aware of this condition, they are unlikely to be the physician who makes the diagnosis or provides inpatient care for this condition. Even though it is rare, the severe pain, secondary infection and poor survival associated with calciphylaxis are likely to further temper nephrologists' enthusiasm for prescribing VKA to patients requiring dialysis.

Do nephrologists consider rate or rhythm control in AF?

It appears that nephrologists are more comfortable with aiming for rate control versus rhythm control (where the goal is reversion to sinus rhythm) in patients with advanced CKD. This is possibly due in part to the experience nephrologists have in managing β-blockers as antihypertensive drugs. In contrast, cardiologists seem more enthusiastic to offer therapies that might restore patients to sinus rhythm either using catheter ablation techniques or with antiarrhythmic drugs that would be considered more specialized, such as propafenone, dronedarone or flecanide. Some of these preferences are likely to be influenced by familiarity with procedures or drugs, but they may also reflect access to follow-up monitoring, which would be required to assess both efficacy and safety. The evidence base is unclear, as there are limited or no data from RCTs to inform practice with these in patients requiring dialysis. Therefore, despite patients with ESRD having a high prevalence of AF and being at risk of paroxysmal AF due to fluid and electrolyte shifts, it is possible that some patients with ESRD do not access antiarrhythmic therapies with some clinical benefit. This may be due to a combination of limited clinical data to support their use combined with the unfamiliarity of nephrologists with some specialized antiarrhythmic strategies. As an example, despite the higher haemorrhagic risk of HD patients when receiving oral anticoagulation, catheter ablation is probably underutilized.(RCTs)

Evidence base for therapeutic decisions for patients with ESRD and AF

There is a high prevalence of AF and increased risk of stroke in ESRD. There are limited data from appropriately conducted RCTs of anticoagulation strategies in AF in ESRD to inform practice. Observational data from dialysis patients with AF in the USA, where apixaban, dabigatran and rivaroxaban are licensed in patients requiring dialysis, demonstrate no difference in risk of stroke/systemic embolism between apixaban and warfarin {hazard ratio [HR] 0.88 [95% confidence interval (CI) 0.69–1.12]},

but apixaban has been associated with a significantly lower risk of major bleeding [HR 0.72 (95% CI 0.59–0.87)] [19]. A recent meta-analysis examining randomized trials of anticoagulation in patients with CKD and AF demonstrated that, compared with VKAs, NOACs reduced the risk of stroke or systemic embolism [risk ratio (RR) 0.79 (95% CI 0.66–0.93)] and haemorrhagic stroke [RR 0.48 (95% CI 0.30–0.76)]. However, none of these 11 trials included patients with ESRD [20]. The major trials of NOACs, such as ARISTOLTE and ROCKET-AF, excluded patients with a creatinine clearance <25 mL/min and 30 mL/min, respectively [9, 10]. The RENal Haemodialysis Patients ALlocated Apixaban Versus Warfarin in AF trial (ClinicalTrials.gov: NCT02942407) has completed but not yet reported and AXADIA is ongoing (ClinicalTrials.gov: NCT02933697). Both trials compare apixaban with VKAs in participants with AF requiring HD. Another ongoing trial [AVKDIAL (ClinicalTrials.gov: NCT02886962)] is comparing VKAs with no oral anticoagulation in patients with ESRD and AF. While one hopes that these trials will help inform anticoagulation strategies for patients with AF requiring dialysis, it is unlikely that these trials will be of sufficient size to demonstrate both definitive efficacy and safety benefits to conclusively inform clinical practice. Furthermore, there remains a lack of high-quality data to inform the use of anticoagulation in patients not requiring dialysis but with creatinine clearance <25 mL/min.

What are the potential opportunities to improve care?

The EHRA/EDTA-ERA survey highlighted that cardiologists and nephrologists may have different approaches, but both groups of clinicians are applying treatment strategies with the clear goals of optimizing outcomes in patients with AF and advanced CKD by reducing stroke risk and maintaining appropriate cardiac rate and rhythm by applying the existing evidence base, which is limited, to the individual patient. It is highly likely that there are mutual learning opportunities to further tailor care. Until recently, the obvious ways to allow both specialties to further educate the other would be with a multidisciplinary meeting, combined clinics and continuing medical education meetings between both cardiology and nephrology. However, amidst the current coronavirus disease 2019 pandemic, we are learning new ways of practising medicine and interacting with our patients while reducing unnecessary contacts. This may permit more efficacious use of time and allow telemedicine clinics whereby patients will have joint consultations with several clinicians without the need for the clinicians and patients to be in the same place. This should permit true shared decision making, as the patient with ESRD may benefit from specialist input from cardiology while guided by their nephrologist around what impact anticoagulation or antiarrhythmics might have on dialysis or transplant listing. The spectacular upscaling of educational webinars during the pandemic will lend itself to multispecialty education, without the need to commit to attending a conference outside one's main specialty.

Meanwhile, it is important that we continue to generate better quality data to inform treatment strategies. This should include larger-scale registry data from patients with ESRD and AF that includes antiarrhythmic therapy, anticoagulation data and time in the therapeutic range in patients on VKA. More large-scale RCTs of antithrombotic strategies are required to address both stroke and bleeding risk in patients with ESRD and advanced non-dialysis-dependent CKD. Additionally, it is vital that patients with advanced CKD and AF, who are at an elevated risk for both stroke and bleeding, are included in future RCTs of novel agents to reduce risk of thromboembolic stroke such as factor XI and XII inhibition [21]. Taken together, when it comes to the rhythm of AF, a more coordinated approach between nephrology and cardiology may lead to a more harmonious outcome for patients with advanced CKD.

CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Findlay MD, Thomson PC, Fulton RL *et al.* Risk factors of Ischemic stroke and subsequent outcome in patients receiving hemodialysis. *Stroke* 2015; 46: 2477–2481
2. Wetmore JB, Phadnis MA, Ellerbeck EF *et al.* Relationship between stroke and mortality in dialysis patients. *Clin J Am Soc Nephrol* 2015; 10: 80–89
3. Konigsbrugge O, Posch F, Antlanger M *et al.* Prevalence of atrial fibrillation and antithrombotic therapy in hemodialysis patients: cross-sectional results of the Vienna investigation of AtriaL fibrillation and thromboembolism in patients on hemodialysis (VIVALDI). *PLoS One* 2017; 12: e0169400
4. Rutherford E, Talle MA, Mangion K *et al.* Defining myocardial tissue abnormalities in end-stage renal failure with cardiac magnetic resonance imaging using native T1 mapping. *Kidney Int* 2016; 90: 845–852
5. Paoletti E, De Nicola L, Gabbai FB *et al.* Associations of left ventricular hypertrophy and geometry with adverse outcomes in patients with CKD and hypertension. *Clin J Am Soc Nephrol* 2016; 11: 271–279
6. Patel RK, Jardine AG, Mark PB *et al.* Association of left atrial volume with mortality among ESRD patients with left ventricular hypertrophy referred for kidney transplantation. *Am J Kidney Dis* 2010; 55: 1088–1096
7. Lip GY, Lane DA. Stroke prevention in atrial fibrillation: a systematic review. *JAMA* 2015; 313: 1950–1962
8. Pisters R, Lane DA, Nieuwlaat R *et al.* A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; 138: 1093–1100
9. Granger CB, Alexander JH, McMurray JJ *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365: 981–992
10. Patel MR, Mahaffey KW, Garg J, *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365: 883–891
11. Olesen JB, Lip GY, Kamper AL *et al.* Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012; 367: 625–635
12. Molnar AO, Bota SE, Garg AX *et al.* The risk of major hemorrhage with CKD. *J Am Soc Nephrol* 2016; 27: 2825–2832
13. Shah M, Avgil Tsadok M, Jackevicius CA *et al.* Warfarin use and the risk for stroke and bleeding in patients with atrial

fibrillation undergoing dialysis. *Circulation* 2014; 129: 1196–1203
14. Potpara TS, Ferro C, Lip GYH *et al.* Management of atrial fibrillation in patients with chronic kidney disease in clinical practice: a joint European Heart Rhythm Association (EHRA) and European Renal Association/European Dialysis and Transplantation Association (ERA/EDTA) physician-based survey. *Europace* 2020; 22: 496–505
15. Turakhia MP, Blankestijn PJ, Carrero JJ *et al.* Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Eur Heart J* 2018; 39: 2314–2325
16. Sacher F, Jesel L, Borni-Duval C *et al.* Cardiac rhythm disturbances in hemodialysis patients: early detection using an implantable loop recorder and correlation with biological and dialysis parameters. *JACC Clin Electrophysiol* 2018; 4: 397–408
17. Roy-Chaudhury P, Tumlin JA, Koplan BA *et al.* Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. *Kidney Int* 2018; 93: 941–951
18. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med* 2018; 378: 1704–1714
19. Siontis KC, Zhang X, Eckard A *et al.* Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. Circulation 2018; 138: 1519–1529
20. Ha JT, Neuen BL, Cheng LP *et al.* Benefits and harms of oral anticoagulant therapy in chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2019; 171: 181–189
21. Weitz JI, Fredenburgh JC. Factors XI and XII as targets for new anticoagulants. *Front Med (Lausanne)* 2017; 4: 19