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Atrial Fibrillation: More Than a Subclinical Problem in Patients on Hemodialysis

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The incidence of atrial fibrillation (AF) is increased in individuals with chronic kidney disease with the highest risk in those with end-stage kidney disease (ESKD).[1] This relationship is unsurprising given shared risk factors for AF and chronic kidney disease, including older age, hypertension, and vascular disease. Current data almost certainly underestimate the true prevalence of AF in the hemodialysis population. Asymptomatic, "subclinical," short-duration AF lasting >6 minutes has been recognized as a risk factor for stroke in the general population. Continuous cardiac monitoring devices, such as implantable loop recorders (ILRs), increase the identification of asymptomatic and subclinical AF, and in the general population, there is considerable interest in whether or not the universal application of anticoagulation to such patients is of overall benefit.[2] Less is known on the prevalence and risk factors for subclinical AF in the hemodialysis population. Patients with ESKD on hemodialysis (ESKD-HD) represent the "perfect storm" for arrhythmogenesis with a myriad of contributing factors, including underlying structural heart disease (left ventricular hypertrophy, myocardial fibrosis, and coronary artery disease), inflammation, autonomic imbalance, electrolyte disorders, hemodynamic stress, and fluid balance fluctuations.

The management of AF in patients with ESKD is problematic. Nephrologists need to navigate the competing risks of oral anticoagulation and inherent bleeding risk with the risk of AF-related ischemic stroke in ESKD. Observational studies and subsequent meta-analyses in ESKD have not identified the compelling benefits of warfarin anticoagulation in AF in reducing stroke risk as was found in the general population.[3] The direct oral anticoagulant apixaban can be used for AF stroke prevention in ESKD; however, meta-analysis data provide no evidence that it improves outcomes,[4] and the Renal Haemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation (NCT02942407) study was stopped early owing to slow recruitment and withdrawal of funding. In the absence of high-quality data and guidelines, clinicians try to identify a subgroup of "high-risk" patients with ESKD wherein oral anticoagulation may reduce stroke risk and mortality without excessive bleeding risk.

In this issue of the *KI Reports*, Koplan *et al.*[5] shed important additional light on the patterns of AF in an ESKD maintenance hemodialysis cohort. This elegant substudy of the multicenter Monitoring in Dialysis Study reported on a total of 66 patients in whom an ILR was implanted. Patients were monitored for a median of 177 days. The mean age of the cohort was 56 years with the study participants having a high prevalence of diabetes mellitus (64%), hypertension (85%), and obesity. Most of the study participants had a normal left ventricular ejection fraction. There was no documented history of previous AF or atrial flutter in 89% of the patients.

During the monitoring period, ILR-detected AF was recorded in 41% of all patients. Although most of the AF episodes were short-lived and self-limiting (<1 hour), a new diagnosis of AF (defined as ≥6 minutes in duration) was detected in 31% of the patients. The AF burden was significant with AF detected on 20% of monitored days in 22% of the patients. This finding is unambiguously significant and confirms previous observations in an Australian cohort.[6]

Risk stratification approaches in patients with chronic kidney disease have relied on the CHA_2DS_2-VASc and HAS-BLED scoring

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criteria to inform the prescription and safety of anticoagulation. Patients with ESKD-HD were largely excluded from validation of both these scores. In the general population, Kaplan *et al.*[7] identified an interaction between AF burden and stroke risk in non-anticoagulated patients, with increasing AF duration and CHA_2DS_2-VASc score found to be associated with annualized stroke risk. Stroke risk crossed an actionable threshold of >1% per year in patients with a CHA_2DS_2-VASc score of 2 with >23.5 hours of maximum daily AF duration and those with CHA_2DS_2-VASc score of 3 to 4 with >6 minutes of AF.[7] The study by Koplan *et al.*[5] adds important data to our understanding of subclinical AF in an ESKD-HD cohort with a high CHA_2DS_2-VASc score. It remains unclear whether the stroke risk is equal across the spectrum from single short-lived episodes of AF to those who remain in chronic AF. This relationship has not been previously explored in an ESKD-HD population, and an actionable threshold for AF burden has not been identified. Such data would be profoundly useful for clinicians to individualize risk-benefit discussions with patients.

In combination with the original results reported in the Monitoring in Dialysis Study,[8] the association between arrhythmias, and in particular AF, with the dialytic cycle is clear. A temporal pattern was observed in ILR-detected episodes, with highest risk of AF during each dialysis session and then decreasing slowly in the subsequent 24 to 36 hours.[8] It therefore follows that changes in dialysis prescription may modulate AF and stroke risk. Nephrologists may consider individualizing the dialysis prescription when considering the management of AF, from electrolyte prescription to ultrafiltration rates and dialysis hours. Further studies are warranted to understand potential modifiable risk factors to ameliorate the AF risk in patients on ESKD-HD and whether this leads to beneficial clinical outcomes.

Meanwhile, randomized trials in ESKD comparing warfarin, apixaban, and no anticoagulation (SAFE-D [Strategies for the Management of Atrial Fibrillation in patiEnts receiving Dialysis], NCT03987711; AXADIA [Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease], NCT02933697) are ongoing, with these results eagerly anticipated. The left atrial appendage occlusion device also merits consideration. Although these devices have not undergone randomized study in ESKD, they seem to be non-inferior to anticoagulation in the general population and may be a suitable alternative in selected patients, weighing up the risk and benefits based on available safety data.[9]

Many questions remain: Do subclinical AF episodes occurring peridialysis have the same significance as interdialytic AF episodes? Should all patients with ESKD-HD receive an ILR? What is the role of other wearable technologies, such as external patches or smart watches, for AF monitoring? Should we look for AF in patients in whom the clinician has already decided on clinical grounds would not be an anticoagulation candidate? Can antiplatelet and anticoagulant drugs be safely combined in this population?

At some stage in their early medical career, it is inevitable that every young doctor will face chastisement from a wise senior colleague for ordering a seemingly unnecessary investigation. "Do not order a test if the result will not change your patient's management!" espouses the wise older clinician. Many of us remember these poignant defining moments and years after hear themselves uttering the same advice to younger colleagues. Simplistically viewed, unnecessary medical investigations add to health care costs, but complexity always arises when the results of such tests are abnormal. Importantly, the argument proposed by the wise physician is not that an abnormal finding of the "unnecessary" investigation would not be intrinsically interesting or thought provoking but that it would not change the therapeutic management plan for the particular individual. Is this old style of thinking still relevant in the sophisticated evidence-based health care environment of the 21st century? Koplan *et al.*[5] present fascinating data concerning the detection of asymptomatic AF in an ESKD-HD cohort. The prism through which readers view these findings will be equally fascinating.

DISCLOSURE

All the authors declared no competing interests.

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