Both chronic kidney disease (CKD) and atrial fibrillation (AF) are emerging health epidemics worldwide. AF is the most common heart rhythm disorder, and the burden of this dysrhythmia is expected to increase as the population ages. Similarly, CKD is a disease of the elderly that is expected to affect 40% to 50% of US adults >65 years of age in the near future. This is likely attributable to manifestations of common risk factors and pathology that eventually lead to high cardiovascular and stroke risk in patients with CKD, especially patients with AF and CKD. Unfortunately, the few observational studies that are available provide conflicting reports on the impact of therapies aimed at stroke prevention in patients with AF and CKD, leading some to question the incremental influence of AF on stroke risk and others to question whether any antplatelet or anticoagulation therapy reduces stroke risk in patients with AF. The result is significant uncertainty and variation in the management of patients with AF and CKD.

It is in this setting that Shih et al present a nationwide cohort analysis from Taiwan focused on patients with AF undergoing hemodialysis in this issue of Circulation. To better understand cardiovascular outcomes in patients with concomitant AF and end-stage renal disease (ESRD), the authors used administrative claims data to compare the risks of cardiovascular events in patients with ESRD with newly diagnosed nonvalvular AF compared with matched patients without AF. They found that AF was associated with increased risks of ischemic stroke, cardiovascular death, hospitalization for heart failure, and all-cause mortality. The authors then conducted a separate analysis accounting for the competing risk of in-hospital death. In this subsequent analysis, the authors demonstrated that AF was no longer associated with an increased risk of ischemic stroke. The authors conclude that the risk of stroke is modestly higher in patients undergoing hemodialysis with new-onset AF than in those without AF and that this risk becomes insignificant after accounting for the competing risk of in-hospital death.

The authors should be congratulated for studying and attempting to better understand the relationship between CKD, AF, and stroke risk. However, there are some key points for clinicians to consider when interpreting the study, particularly in regard to the competing-risks assessment. Death is a competing risk, but cardiovascular death, including stroke, makes up the majority of death in patients with EDRD. Thus, when one accounts for all-cause mortality (especially in a claims database), many fatal stroke events, particularly those that lead to out-of-hospital death, may be misclassified and thus underrepresent all-cause stroke. This limitation has significant implications on the generalizability of the findings for treatment considerations.

Moreover, interpreting the findings in this study is complicated by the potential for competing “benefits” of possible therapies. Specifically, the stroke risk attributable to AF or non-AF causes may not be as clinically important if possible therapies have clinical effect across many disease states, for example, prevention of stroke, coronary events, and venous thromboembolism. Anticoagulants have been noted to have possible benefits across several cardiovascular indications. So despite the valiant effort to characterize the competing risks in patients on hemodialysis and AF, it is hard to make clinical treatment decisions without measurement of the complete benefits of therapies such as warfarin in patients with ESRD. Moreover, the risks from the therapy have to be measured in the context of both the frequency and severity of the outcomes we are trying to prevent.

Despite the frequency of CKD and the availability of several new agents on the market for AF, we have a dearth of any high-quality evidence on the treatment of AF in patients with severe/advanced CKD, in particular those with ESRD on renal replacement therapy. Treatment guidelines differ with regard to recommendations for oral anticoagulation in patients with AF and ESRD. Some data demonstrate an association between oral anticoagulation and improved outcomes in patients with AF and ESRD. The recent trials with the novel oral anticoagulants studied these agents compared with warfarin in patients with a creatinine clearance as low as 25 mL/min. The use of these agents in patients with ESRD and dialysis is untested and thus would seem contraindicated, particularly given their partial renal clearance, yet there are reports of increasing off-label use in dialysis patients. It should also be noted that warfarin clearly has limitations in the ESRD population, a population of patients getting frequent arterial graft access 3 times a week for dialysis. Aside from
from the inherent bleeding risks with therapy, there is documented difficulty in keeping patients within therapeutic range with warfarin.\textsuperscript{15} Hence, each potential therapy has multiple possible risks and benefits.

So how do we move forward? It seems the only rational way is to conduct a randomized study in patients with advanced CKD/ESRD and AF. Such trials can be conducted with the help of systems that can facilitate trial conduct and enrollment. These systems should use learning healthcare delivery systems and ideally involve partnerships among cardiovascular physicians, nephrology specialists, and patient groups. Given the large dialysis unit systems across the United States and Europe, there is likely an opportunity to harness the patient populations and healthcare systems to apply large simple trial concepts. These include attempting to enroll all eligible patients with few exclusions. Enrollment should be possible for most patients with AF and stroke risk except those with current bleeding and prior intracranial hemorrhage. Additionally, open-label trials should be feasible given the well-known management challenges with these drugs and the opportunity for central blinded end-point assessment. Finally, national coverage for standard of care for ESRD patients enrolled in clinical trials should be assured as mandated by the Affordable Care Act. Figuring out the optimal treatment strategy to improve cardiovascular outcomes in patients with AF and ESRD is critically important for both our patients and our health systems.

Importantly, as highlighted by data presented by Shih et al.,\textsuperscript{12} evaluation of ESRD patients with AF will also require an assessment of the net clinical effect of any stroke prevention therapy. Ideally, this assessment would involve measurement of clinical outcomes associated with irreversible harm such as stroke, cardiovascular death, and major bleeding associated with significant patient risk (eg, intracranial bleeding or bleeding requiring hospitalization). Given the overall high risk for death in all patients with ESRD, one might imagine the need for evaluation of all-cause mortality as part of the net effect. Unlike other AF patient populations in whom efficacy and safety of oral anticoagulation are evaluated separately, clinical trials in patients with ESRD and AF will require net-effect analysis given the competing risks, possible competing benefits of therapies, and high mortality risk of the population. Standardized data elements for dialysis care and follow-up will greatly aid in the conduct of pragmatic trials and informing best practice. Randomized trials with systematic analysis of cardiovascular outcomes are needed to help move clinicians and regulatory groups away from the current blueprint of dosing and treatment decision based solely on pharmacokinetics and pharmacodynamics.\textsuperscript{16} Randomized studies are the standard for drug approval in the overall population and should not differ in patients with ESRD, in whom treatment decisions are even more complex.

In conclusion, we must consider it our mandate as we move into the next phase of healthcare delivery to build and to expect systems that help us both care for our patients and answer real-time relevant clinical questions. The management of AF in patients with ESRD is indeed an important clinical question situated at the intersection of two common clinical problems but a question with a paucity of meaningful clinical information. In the meantime, clinicians will need to struggle with the available conflicting evidence and the limitations inherent to observational studies. Only clinical trials aimed at understanding the net clinical effect will determine best practice for our patients with end-stage kidney disease and AF.

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**References**


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