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EDITORIAL

Long-Term Anticoagulation for Patients Receiving Dialysis

Tilting the Benefit-to-Risk Ratio?

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It has been >6 decades since the earliest demonstration of dialysis as a lifesaving therapy for patients with severely impaired kidney function. Globally, an estimated 2 million patients are receiving maintenance dialysis for end-stage renal disease, and between 1990 and 2010, a remarkable 70% growth in patients receiving maintenance dialysis was noted.[1] This unidirectional trend is likely to continue unabated.

Unfortunately, mortality and morbidity remain high in patients on dialysis. Cardiovascular disease is the leading cause of death. There are many reasons for the relentless burden of cardiovascular events in the dialysis population. Biological differences between patients receiving dialysis and those not receiving dialysis may explain the failure to extend the benefits of therapies observed in patients not on dialysis to patients on dialysis. More important, patients on dialysis are often excluded from large cardiovascular-focused randomized controlled trials, which significantly limits the evidence needed to make clinical decisions. As a result, clinicians caring for patients receiving dialysis frequently find themselves extrapolating information on safety and efficacy from nondialysis clinical trials. How confident can they be? As we await trial evidence, careful analyses of data from large observational cohorts can augment our understanding of outcomes, particularly of adverse events.

In the current issue of *Circulation*, Siontis et al[2] examine the outcomes associated with the use of apixaban, an oral factor Xa inhibitor, in patients with nonvalvular atrial fibrillation who are receiving dialysis. Their observational study included >25 000 Medicare beneficiaries (mean age, 68.2 years; male, 54.3%; hemodialysis, 94.6%) from the US Renal Data System, a national data registry funded by the National Institute of Diabetes and Digestive and Kidney Diseases. Overall, 9.2% of patients were prescribed apixaban, and the remaining were treated with warfarin. The authors noted, however, a remarkable increase in the number of new apixaban prescriptions over the study period extending from October 2010 to December 2015, with >1 in 4 new anticoagulation prescriptions in 2015 for apixaban. In a prognosis-based propensity score analysis, there was no difference between apixaban and warfarin in the risk of stroke or systemic embolism. The risk of major bleeding, however, was 28% lower with apixaban (95% CI, 13–41).

In patients with normal kidney function who develop nonvalvular atrial fibrillation, anticoagulation therapy to reduce systemic thromboembolism has been the standard of care based on rigorous data from randomized controlled trials. In a meta-analysis that included 6 trials (n=2900 patients) comparing warfarin with controls, warfarin treatment reduced ischemic stroke by 67% (95% CI, 54–77), all stroke (ischemic and hemorrhagic) by 64% (95% CI, 49–74), and all-

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cause mortality by 26% (95% CI, 3–43).[3] The absolute increase in major extracranial hemorrhage associated with warfarin was less than the absolute reduction in strokes. From these data, the number needed to treat for 1 year to primarily prevent 1 stroke was 37, and the comparable estimate for secondary stroke prevention was 12.

Sadly, to date, there have been no data from a randomized controlled trial that directly compares warfarin and placebo in patients with atrial fibrillation who are receiving dialysis. Some available observational data in patients receiving dialysis have suggested a lack of efficacy[4] and potential increased risk for ischemic stroke[5] with warfarin therapy. Furthermore, the burden of taking warfarin is not trivial for a patient receiving dialysis and includes drug and dietary interactions and the need for additional blood draws for therapy monitoring. This is, of course, in addition to the potential for excess bleeding risk, given that patients receiving dialysis are anticoagu-

Table. Summary of Ongoing Randomized Controlled Trials for Anticoagulation in Dialysis Patients With Atrial Fibrillation

Study Title	Study Methods	Study Inclusion Criteria	Study Outcomes
AXADIA, Compare Apixaban and Vitamin-K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease, NCT02933697	Study arms: apixaban 2.5 mg twice a day for 6 to 24 mo vs phenprocoumon daily adjusted to an International Normalized Ratio (INR) of 2.0–3.0 for 6–24 mo Study design: Phase 3b trial Allocation: randomized Intervention model: parallel assignment Masking: none (open label) Country: Germany Estimated enrollment: 222 Study sponsor: Atrial Fibrillation Network Study collaborators: Bristol-Myers Squibb and Pfizer	End-stage kidney disease with chronic hemodialysis treatment 3 times per week for at least 3 mo Chronic paroxysmal, persistent, or permanent nonvalvular atrial fibrillation documented by standard or Holter ECG on at least 2 separate days before (or apart from) hemodialysis procedures CHA_2DS_2-VASc score of 2 or more Patients with ischemic stroke who meet the above criteria can be included after more than 3 mo if not severely handicapped Males and females, age 18 y or older	Primary: major and clinically relevant, nonmajor bleeding and specific bleedings in dialysis patients Secondary: prevention of thromboembolic events Pharmacokinetic: Blood level of apixaban prior and after hemodialysis
RENAL-AF, Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients with Atrial Fibrillation, NCT02942407	Study arms: apixaban 5 mg twice daily (apixaban 2.5 mg twice daily for selected patients) vs warfarin daily dose adjusted to target INR of 2.0–3.0 for 15 mo Study design: Phase 4 trial Allocation: randomized Intervention model: parallel assignment Masking: none (open label) Country: United States Estimated enrollment: 762 Study sponsor: Duke University Study collaborator: Bristol-Myers Squibb	End-stage kidney disease with chronic hemodialysis treatment Atrial fibrillation on ECG at enrollment or 2 or more reports of atrial fibrillation from separate monitoring events at least 2 wk apart CHA_2DS_2-VASc score of 2 or more Considered by the treating physician(s) to be candidate for oral anticoagulation Males and females, age 18 y or older Patients with moderate or severe mitral stenosis are excluded	Primary: time, measured in days, from randomization to the onset of first major bleeding/clinically relevant nonmajor bleeding event Secondary: stroke or systemic embolism, mortality, adherence to treatment with apixaban or with warfarin, plasma apixaban concentration, apixaban pharmacodynamics, chromogenic factor Xa assay Other: biomarkers—growth/differentiation factor 15, high sensitivity troponin T, B-type natriuretic peptide
AVKDIAL, Oral Anticoagulation in Hemodialysis Patients, NCT02886962	Study arms: no oral anticoagulation, and no monitoring of the INR vs vitamin K antagonist daily with INR target between 2 and 3 for 24 mo Study design: Phase 4 trial Allocation: randomized Intervention model: parallel assignment Masking: none (open label) Country: France Estimated enrollment: 855 Study sponsor: University Hospital, Strasbourg, France Study collaborators: not provided	End-stage kidney disease with chronic hemodialysis treatment for at least 1 mo History of or a new episode of atrial fibrillation (either permanent or paroxysmal) CHA_2DS_2-VASc score of 2 or more High risk of bleeding as defined by (1) HASBLED score ≥3 or (2) HASBLED ≥ CHA_2DS_2-VASc score, or (3) recent history of severe bleeding, particularly cerebral or gastrointestinal, or (4) prior recurrent (>2) history of falls Males and females, age 18 y or older	Cumulative incidence of severe bleeding and thrombosis

lated for dialysis treatments, and the baseline risk for major bleeds, even in the absence of anticoagulation, is significantly higher because of many factors, including platelet dysfunction and higher frequency of falls.[6] Such data swayed members of the Kidney Disease: Improving Global Outcomes Controversies Conference to conclude that there was insufficient high-quality evidence to recommend warfarin for the prevention of stroke in patients with atrial fibrillation and dialysis-dependent chronic kidney disease.[7] This evidence gap was also captured in a survey question administered by the National Kidney Foundation: "Should warfarin be used in patients receiving dialysis with nonvalvular atrial fibrillation?" Approximately 45% of >5000 respondents answered no, and 55% responded yes.[6] Results from the ongoing AVKDIAL trial (Oral Anticoagulation in Hemodialysis Patients; Table) promise to inform this debate by comparing the cumulative incidence of severe bleeding and thrombosis between anticoagulation with a vitamin K antagonist and placebo.

Direct oral anticoagulant agents were developed in the general population to overcome the limitations of warfarin and were successfully demonstrated in well-designed and adequately powered randomized controlled trials to have noninferior efficacy and better safety compared with warfarin therapy.[8–11] Two comparable dialysis-focused trials, AXADIA (Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease) and RENAL-AF (Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients With Atrial Fibrillation), are ongoing for apixaban (Table). The superior bleeding risk profile of direct-acting oral anticoagulants is attractive for the dialysis population and makes the "real-world" experience highlighted by Siontis et al[2] particularly relevant. Unlike apixaban (27% renal clearance), dabigatran (80% renal clearance) and rivaroxaban (36% renal clearance) have been associated with increased risk of major bleeding in patients receiving hemodialysis.[12] A look at the combined data from Chan et al[12] and Siontis et al[2] suggests that the risk of major bleeding in patients receiving hemodialysis approximates to 20 events per 100 patient-years with apixaban, 23 to 36 per 100 patient-years with warfarin, 68 per 100 patient-years for rivaroxaban, and 83 per 100 patient-years for dabigatran, suggesting that the risks of major bleeding from rivaroxaban and dabigatran are unlikely to outweigh any potential benefit of reducing systemic embolism in patients receiving dialysis. It is interesting that the reduction in the risk of major bleeding observed by Siontis et al[2] in patients receiving dialysis is comparable to results from the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), which excluded patients receiving dialysis altogether (hazard ratio for major bleeding, 0.69; 95% CI, 0.60–0.80).[8] However, for relevant efficacy and safety outcomes, we need to await results from the AXADIA and RENAL-AF trials. Future trials are needed to investigate the outcomes in patients receiving peritoneal dialysis because the current ongoing trials exclude those patients.

Beyond the potential reduction in the risk of conventional bleeding, direct oral anticoagulants should be compared with warfarin for other complications linked to warfarin therapy such as anticoagulant nephropathy (particularly relevant to patients with end-stage renal disease with residual renal function),[13] vascular calcification, and calciphylaxis.[14] As opposed to the US Food and Drug Administration label that suggests reduced dose (2.5 mg twice a day) for patients with renal impairment who meet at least 1 additional criterion (body weight ≤60 kg or age ≥80 years), experts suggest a reduced dose for all patients receiving dialysis to attenuate bleeding risk.[7] Pharmacokinetic data on apixaban are limited, and a recent multiple-dose administration study of apixaban noted that 5 mg twice a day dosing resulted in supratherapeutic drug concentrations in patients receiving hemodialysis.[15] Of particular importance, Siontis et al[2] noted no difference between the 2 doses for major bleeding, gastrointestinal bleeding, and intracranial bleeding but observed lower risks of incident stroke and systemic embolism and death with 5 mg twice a day dosing, emphasizing an urgent need to test different dosing strategies for apixaban in patients receiving dialysis. Finally, improved insights into a mechanistic link between atrial fibrillation and stroke and better knowledge of competing risks for stroke outside of atrial fibrillation in patients receiving dialysis are much awaited. In the meantime, clinicians should make decisions about anticoagulation for nonvalvular atrial fibrillation in patients receiving dialysis in a collaborative fashion (cardiologist, nephrologist, primary care physician, pharmacist) and only after a discussion of the benefits and risks with patients and with clear understanding of logistics of monitoring. There should also be an explicit plan to reassess therapy on a periodic basis, a practice that can be forgotten in a busy clinical care setting.

ARTICLE INFORMATION

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