MAYO CLINIC

End-Stage Renal Disease, Nonvalvular Atrial Fibrillation, and the Warfarin Dilemma

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There are more than 660,000 Americans with kidney failure and nearly 470,000 on dialysis.[1] Of these, estimates of nonvalvular atrial fibrillation (NVAF) approach 20%.[2] Atrial fibrillation nearly doubles the anticipated mortality and increases the stroke risk by approximately six-fold in these patients. The intersection between end-stage renal disease (ESRD) and NVAF is complicated and not easily parsed. Atrial fibrillation likely increases the rate of progression to ESRD in patients with underlying chronic kidney disease (CKD). By increasing filling pressures and wall tension, CKD may increase the propensity for atrial fibrillation. Both diseases share common risk factors including hypertension, diabetes mellitus, vascular disease, and advancing age which contribute to interstitial fibrosis, oxidative stress, and electrolyte imbalances.

Strategies for stroke prevention in NVAF begin with shared decision-making to balance the risks and benefits. Patient specific risk is estimated using scoring tools for thromboembolism (CHA_2DS_2-VASc score) and major bleeding (HAS-BLED score). Both tools share a number of variables common to both diseases. Therefore, it is not surprising that patients with ESRD and NVAF are simultaneously at increased risk for both thrombotic and hemorrhagic outcomes.

Warfarin has long been the mainstay anticoagulant for patients with ESRD due to metabolism limitations of other drugs. The use of warfarin for primary prevention of stroke in this setting has been controversial largely due to a lack of randomized controlled trial data to inform decision-making. Severe renal impairment (creatinine clearance $<$ 25-30 mL/min) has been an exclusion criterion for participation in recent anticoagulation trials comparing direct oral anticoagulant to warfarin in NVAF. Most prior studies of warfarin for these patients have been observational, retrospective in design, and with mixed results. Some studies have shown improved outcomes for patients with ESRD on warfarin,[3,4] whereas others have not.[5,6] Adverse effects of warfarin include both an excess of major bleeding as well as increased stroke rates. Factors that may vitiate whatever beneficial effects warfarin may have include accelerated vascular calcification, impaired hemostasis, and poor time in the therapeutic range as potential reasons.[7,8] In a recent meta-analysis of 15 studies and 47,480 patients with NVAF in ESRD, outcomes were compared between 10,445 patients provided warfarin versus 37,035 not anticoagulated.[9] There was no difference in the ischemic stroke rates (7.7% vs 7.1%; hazard ratio, 0.96; 95% CI, 0.82-1.13). However, the hemorrhagic stroke rate was significantly higher among warfarin-treated patients (2.4% vs 1.9%; hazard ratio, 1.46; 95% CI, 1.05-2.04). Major bleeding rates were borderline higher in the warfarin treated patients (16.1% vs 15%) and mortality rates did not defer by treatment. These data largely substantiate several prior meta-analyses on this topic.

In light of these combined data, recent guidelines have softened their enthusiasm for warfarin in this setting. For example, the American Heart Association guidelines have noted "for patients with NVAF and CHA_2DS_2-VASc score $\geq$ 2 (men) or $\geq$ 3 (women) who have end-stage CKD, it might be reasonable to prescribe warfarin or apixaban for oral anticoagulation" (Class IIb[10]). In contrast, the Kidney Disease: Improving Global Outcomes guidelines recommend against the routine anticoagulation of CKD stage 5D patients with atrial fibrillation for primary prevention of stroke.[11] In keeping with these guidelines, in an observational study of 12,284 patients with CKD and

newly diagnosis NVAF, only 15% were started on warfarin therapy.[12] At 1 year, nearly 70% of these patients had discontinued the use of this medication.

In the current issue of *Mayo Clinic Proceedings*, Niznik and colleagues assessed anticoagulation quality using time in therapeutic range surrogate among 151 dialysis patients receiving warfarin.[13] The time in range was low at 44% despite meticulous attention to management by an on-site dedicated pharmacy team devoted to anticoagulation management using point-of-care testing and a validated management protocol. This team then implemented a strategy of dietary review and education by registered dietician nutritionists to improve the consistency of vitamin K intake among 15 of these patients. Despite an aggressive educational effort, the median time in therapeutic range did not differ before or after the intervention. These combined data underscore the complexity of ESRD and the challenges of warfarin management.

What does the future hold? In an observational study of more than 20,000 Medicare beneficiaries with NVAF receiving dialysis, the efficacy and safety of apixaban (n=2351) was compared with warfarin (n=23,172). In sensitivity analysis, apixaban 5 mg twice daily was associated with lower thromboembolism, major bleeding, and death rates compared with warfarin.[14] A randomized trial comparing apixaban with vitamin K antagonists in this setting is ongoing.[15] Other possibilities could include the use of atrial appendage closure devices. This may be particularly attractive for patients who have already suffered a hemorrhagic complication.

In the meantime, it is important to differentiate primary from secondary prevention for these patients. For ESRD patients who have already suffered a stroke/transient ischemic attack (TIA) or peripheral embolism in the setting of NVAF, anticoagulation is warranted. Clearly further information is needed, especially data derived from randomized controlled trials. The data from the current study by Niznik and colleagues[13] clearly show that despite the dedicated efforts at a major medical center — efforts that involved both close pharmacologic monitoring and dietary review — the time in the therapeutic range for dialysis patients on warfarin was remarkably low. The study by Niznik and colleagues[13] thus stimulates the following question: Is this the basis for the apparent lack of benefit and the adverse effects of warfarin in this patient population? Is the low time in the therapeutic range still potentially remediable by other yet-to-be-tried strategies, or is it an intrinsic and intractable aspect of the use of warfarin in this patient population? And, finally, is the prudent therapeutic approach founded on the use of apixaban rather than warfarin? Answers to this last question, hopefully, will soon be provided by an ongoing randomized trial.

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