Kidney Medicine

Anticoagulation in CKD: Trials and Tribulations

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Compared with the general population, patients with chronic kidney disease (CKD) are more likely to experience cardiovascular comorbid conditions such as atrial fibrillation (AF).[1] Both CKD and AF independently

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lead to a prothrombotic state, increasing the risk of ischemic stroke.[2] Although stroke risk can be reduced with an anticoagulant in those with AF, patients with CKD are also prone to bleeding,[2] and declining kidney function may cause accumulation of renally cleared anticoagulants. So, in balancing both thromboembolic and bleeding risks, what is the optimal treatment plan for patients with CKD and AF?

Warfarin has long been the anticoagulant of choice for the prevention of stroke in patients with AF and CKD. However, there are many challenges to using warfarin. Interindividual pharmacokinetics, multiple food and drug interactions, and a narrow therapeutic window leading to difficulty maintaining international normalized ratio in a therapeutic range may increase the risk of stroke, bleeding, or death. Warfarin also increases the risk of vascular calcification and, in nondialysis CKD, is associated with anticoagulant-related nephropathy.[3]

In recent years, direct oral anticoagulants (DOACs), including direct inhibitors of factor Xa (apixaban, edoxaban, and rivaroxaban) or of thrombin (dabigatran), have revolutionized treatment for those with AF because of their relative ease of use compared with warfarin. Steady pharmacokinetic parameters and predictable therapeutic effects eliminate the need for continuous monitoring, and DOACs are also associated with fewer drug and food interactions.[3] In addition, studies have pointed to the pleotropic effects of DOACs, including anti-inflammatory and vascular protective properties,[3] which may slow the decline of kidney function in those with CKD.[4]

Although studies showing the relative effectiveness and safety of DOACs in CKD are emerging, there is still much unknown about the use of these agents in advanced CKD and end stage kidney disease. In this issue of Kidney Medicine, Ha et al[3] evaluated rivaroxaban, and its comparative effectiveness and safety with warfarin across varying estimated glomerular filtration rate (eGFR) levels. By using administrative data from various jurisdictions in Canada and Australia, they included 55,568 patients (27,784 rivaroxaban-warfarin user matched pairs) who had a range of kidney function categorized as eGFR >60, 45-59, 30-44, and <30 mL/min/1.73 m^2. This study suggested that rivaroxaban is at least as effective and safe as warfarin across the spectrum of kidney function.

However, it is important to note that, of all the Canadians and Australians included in the study, only 2.4% of patients had an eGFR <30 mL/min/1.73 m^2.[5] Although this small sample may be representative of the population of patients with advanced CKD and AF who were deemed suitable for anticoagulation, it may also suggest a prescribing bias against DOACs in this patient group. This prescribing bias may be the result of several uncertainties surrounding the use of DOACs in advanced CKD.

One of the largest knowledge gaps in DOAC therapy is how their effectiveness and safety stack up to warfarin in those with eGFR <30 mL/min/1.73 m^2. Landmark randomized controlled trials have provided solid evidence on the efficacy and safety of DOACS in patients with mild to moderate CKD through subgroup analyses.[6] However, these trials largely excluded patients with advanced stages of kidney disease; so, robust randomized controlled trial data addressing the safety and efficacy of DOACs in AF and later stages of CKD is lacking. Much of the guidance available for the use of DOACs in this population comes from observational studies that have yielded mixed efficacy and safety signals.[7]

Furthermore, optimal dosing recommendations for DOACs in patients with advanced CKD are unclear. Because all DOACs undergo a degree of kidney elimination (apixaban 27%, rivaroxaban 36%, edoxaban 50%, and dabigatran 80%), we expect drug accumulation and subsequent adverse effects (bleeding) with reduced kidney clearance.[8] Thus, dose adjustments based on kidney function would be reasonable in the advanced CKD population and would depend on estimates of kidney function. Yet, currently, there is not 1 universal measure for estimating kidney function for drug dosing, and different measurements are not numerically equivalent. Although Ha et al[3] used eGFR, a value frequently reported by laboratories and often used in observational trials, creatinine clearance was used in large randomized controlled trials that informed kidney dose adjustments in product monographs.

Regardless of whether we use eGFR or creatinine clearance to measure kidney function, there is generally a lack of guidance on the optimal DOAC dosing in patients with AF and eGFR <30 mL/min. Although product monographs for each DOAC list recommendations for kidney dose adjustments down to eGFR 15 mL/min, this is largely based on data from clinical pharmacology studies comparing serum drug concentrations in those with varying degrees of kidney impairment with those with normal kidney function. However, data from these studies are inconsistent. Some studies evaluating the effects of

impaired kidney function on single dose of rivaroxaban suggest that it is likely to accumulate in patients with CKD and patients receiving hemodialysis, even at lesser doses.[9] However, a different study of rivaroxaban in participants receiving dialysis found no significant accumulation after multiple doses.[9] Further, single dose studies report modest increases in apixaban exposure in patients with advanced CKD, including those receiving dialysis, whereas another study found supratherapeutic levels in patients receiving hemodialysis and recommended dose adjustments.[9] Similarly, varying dosing regimens have been suggested to offset the increased dabigatran and edoxaban exposure observed in patients with severe kidney impairment.[9-11]

The dosing of DOACs is further complicated by interpatient variability, which has been observed in patients with variable stages of kidney disease.[12] This may be owing to factors such as body size and composition, gastrointestinal physiology, additional comorbid conditions, pharmacogenetic factors, and drug interactions.[12,13] Thus, generalizing the benefits of DOACS reliably and safely across the spectrum of kidney function becomes difficult because the extent of pharmacokinetic and subsequent pharmacodynamic alterations in various stages of kidney impairment is uncertain.

Faced with this clinical conundrum, clinicians may turn to evidence-based guidelines to offer insight on best practices. However, the American Guidelines American Heart Association/American College of Cardiology/Heart Rhythm Society,[14] the European Society of Cardiology,[15] the Kidney Disease Improving Global Outcomes,[16] and the Canadian Cardiovascular Society[17] are not aligned with one another when it comes to the recommended anticoagulant in those with eGFR <30 mL/min/1.73 m^2. For example, the 2019 American guidelines on AF provide a class IIb recommendation for the use of either apixaban or warfarin in patients with AF and end stage kidney disease or receiving hemodialysis.[14] Conversely, the European and Canadian guidelines caution DOAC use in patients with eGFR between 15-30 mL/min/1.73 m^2 and contraindicate use in eGFR <15 mL/min/1.73 m^2 and those undergoing dialysis.[15,17] This is not surprising, given the lack of robust randomized controlled trial data, and the conflicting observational and pharmacokinetic data in this population. So, the question still exists, can we effectively use DOACs in patients with AF who have eGFR <30 mL/min/1.73 m^2.

Certainly, concerns about accumulation of renally cleared DOACs and safety implications of increased risk of bleeding remain a top priority. Nevertheless, understanding the efficacy implications of kidney dose adjustments is an equally important piece of this puzzle, especially in with eGFR <15 mL/min/1.73 m^2 and those dependent on dialysis. In a study comparing effectiveness and safety of apixaban versus warfarin among dialysis patients, there was no difference overall in rates of stroke or embolism.[18] Yet, the 5 mg apixaban group showed significantly lesser rates of stroke compared with warfarin versus the group that received 2.5 mg apixaban. Such findings highlight the need for outcome-based studies evaluating the most effective dose of each DOAC in patients with advanced CKD, receiving dialysis.

As the quest for the optimal anticoagulation strategy for those with AF and advanced CKD continues, it is important to emphasize the practical aspects of the different agents. Although warfarin presents the challenge of maintaining in-target international normalized ratios, there is comfort in measuring international normalized ratio to determine a patient's coagulation state. Importantly, the availability of a cost effective reversal agent such as vitamin K is reassuring given the risk of bleeding. DOACs on the other hand have much steadier and predictable pharmacokinetics and less risk of major bleeding compared with warfarin in the general population, yet only dabigatran has a direct-acting reversal agent.[19] Reversal of rivaroxaban and apixaban involves using inactive human factor Xa to combat the direct inhibitory effects of these DOACs on endogenous factor Xa.[18] These agents are very costly, and there is no guidance on their post reversal effects on hypercoagulation. In addition, DOACs are not completely free of drug interactions. Permeability glycoprotein (P-gp) inhibitors like ketoconazole and inducers like rifampin may increase or decrease levels of DOACs, respectively, and CYP3A4 inducers like valproic acid may reduce levels of apixaban and rivaroxaban.[20]

Considering the existing evidence on anticoagulant use in those with advanced CKD, it is clear that 1 agent is not the magic potion above all others. Still, Ha et al[3] were able to add to a limited body of real-world evidence showing effectiveness and safety of rivaroxaban in those with eGFR <30 mL/min/1.73 m^2. More robust studies are needed to demystify the role of DOACs across the spectrum of kidney function. Whether 1 anticoagulant is a greater poison to those with advanced CKD, including those dependent on dialysis, is a tantalizing question that remains to be answered.

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