Balancing the Benefits and Harms of Oral Anticoagulation in Chronic Kidney Disease: What Does Available Evidence Tell Us?

The risks for venous thromboembolism (VTE) and atrial fibrillation (AF) are 2 to 3 times and 10 to 20 times greater in patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD), respectively, than in the general population (1, 2). In patients with ESKD, VTE is associated with an increased risk for death and AF is associated with increased risks for stroke and death (1, 2). Older age, hypertension, diabetes mellitus, and congestive heart failure are highly prevalent in patients with CKD and ESKD, such that, on the basis of guidelines developed for the general population, most require VTE prophylaxis during hospitalization and/or anticoagulation for their AF (3, 4). However, compared with the general population, patients with CKD and ESKD have a significantly increased risk for bleeding when treated with warfarin anticoagulation (5). Warfarin has also been associated with an increased risk for valvular calcification and calcific uremic arteriolopathy in this patient population (2, 6). The balance of benefit and harm of warfarin therapy is uncertain in patients with CKD and ESKD, as this patient population was largely excluded from available trials. The tremendous variability in warfarin use for AF in patients with ESKD reflects this uncertainty (7). With emerging evidence of increased efficacy and safety of non–vitamin K oral anticoagulants (NOACs) in the general population, there is a renewed interest in defining the role of anticoagulant therapy to prevent stroke and VTE in patients with CKD and ESKD.

In their article, Badve and colleagues reported an ambitious systematic evidence review to evaluate the benefits and harms of oral anticoagulant therapy for a range of clinical indications in patients with CKD stages 3 to 5, including those receiving dialysis (8). Although they identified 45 trials with a total of 34 082 participants, only 8 included patients with ESKD (n = 685). Seven of the trials that included patients with ESKD evaluated vitamin K antagonists (VKAs) for the prevention of access thrombosis. The remaining trial evaluated the effect of VKAs on hemostatic factors. The results that Badve and colleagues report for patients with CKD who did not receive dialysis are from CKD subgroup analyses of larger trials, with most being from studies of AF (n = 16 787), cardiovascular diseases other than AF (n = 9727), thromboprophylaxis (n = 3908), and treatment of acute VTE (n = 2975).

As in the general population, compared with VKAs, NOACs reduced the risk for stroke or systemic embolism and hemorrhagic stroke but without a significantly reduced risk for bleeding in patients with early CKD (that is, creatinine clearance >25 mL/min) and AF. Compared with VKAs for preventing recurrent VTE, VTE-related death, or risk for major bleeding, the effects of NOACs were uncertain because all CIs were wide and crossed 1. There was no difference in the risk for VTE or VTE-related death between NOAC and placebo for thromboprophylaxis. For patients with advanced CKD and ESKD, no randomized controlled trial data are available that evaluate the effects of VKAs or NOACs on the prevention of stroke or systemic embolism in AF or on VTE and VTE-related death. In the vascular access trials, in ESKD, compared with placebo, adjusted-dose warfarin did reduce the risk for access thrombosis or catheter malfunction, with an uncertain effect on bleeding (risk ratio, 2.66 [95% CI, 0.39 to 18.19]). None of these trials evaluated NOACs. When all trials were combined, compared with VKAs, high-dose NOACs were not associated with a significantly reduced risk for major bleeding.

Despite the tremendous burden of disease in patients with advanced CKD and ESKD, they have historically been excluded from trials of VKAs and NOACs for prevention and treatment of VTE as well as for prevention of stroke and systemic embolism in AF. In this systematic review, NOACs had similar effectiveness to VKAs for prevention of recurrent VTE and VTE-related death and similar efficacy to placebo for thromboprophylaxis in early CKD. However, it does support the superior benefit profile of NOACs without additional risks compared with VKAs for patients with early CKD and AF. Assuming this result reflects the truth and recognizing the limitations of subgroup analysis, is there a level of renal dysfunction for which clinicians should apply greater caution in extrapolating these findings? In observational studies, warfarin use in patients who have ESKD with AF has not been shown to reduce the risk for embolic stroke, but it has been associated with a 2-fold greater risk for hemorrhagic stroke (9). The reduced risk observed for hemorrhagic stroke with NOACs compared with VKAs in the general population and now in patients with early CKD suggests a potential benefit in ESKD. However, a recent retrospective cohort study of patients who have ESKD with AF observed no difference in the risks for stroke or systemic embolism between the NOAC (apixaban) or the VKA (warfarin), raising concerns that these medications might be all risk and no benefit, at least for prophylaxis (10). Two highly anticipated ongoing studies in patients with AF and ESKD, RENAL-AF (RENal Hemodialysis Patients ALlocated Apixaban Versus Warfarin in Atrial Fibrillation) (Clinical Trials.gov: NCT02942407) and AXADIA (ClinicalTrials.gov: NCT02933697), are required to prove efficacy. Until the results of these trials become available, the decision to use anticoagulant therapy in patients with ESKD will continue to require an individualized approach that balances potential benefits and harms.

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