COMMENTS

Risks of anticoagulation in patients with chronic kidney disease and atrial fibrillation: More than just bleeding?

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Individuals with kidney disease and their healthcare providers can be excused for having a love-hate relationship with anticoagulation. Chronic kidney disease (CKD) heightens the risk of conditions that normally require anticoagulation (deep venous thrombosis, atrial fibrillation), but it also greatly increases the risk of anticoagulation-related complications, most notably major bleeding. This complicates the assessment of the risk/benefit ratio for initiating anticoagulation in individuals with CKD—particularly those with end-stage kidney disease and atrial fibrillation, for whom there is weak evidence supporting a clinical benefit from anticoagulation but a clear signal for excess risk of death and major bleeding. As a result, current recommendations for initiating anticoagulation in patients with end-stage kidney disease and atrial fibrillation at high risk for thromboembolism are equivocal, with most guidelines leaving it up to clinical judgement (and many clinicians in turn deciding to forego anticoagulation). There is much stronger evidence for a net clinical benefit of anticoagulation in CKD patients not yet on dialysis who have atrial fibrillation and are at high risk for thromboembolism, supporting the use of anticoagulation in these patients despite their excess risk of major bleeding.

The findings of Posch and colleagues in Research and Practice in Thrombosis and Haemostasis suggest that estimating the net clinical benefit of anticoagulation with vitamin K antagonists may require consideration of risks beyond just bleeding—specifically, potentially deleterious long-term effects on kidney function. Using data from the IMS Disease Analyzer Germany study—a longitudinal health record database from ~1300 primary care physicians in Germany—Posch and colleagues identified 37 476 individuals with stage 3 or 4 CKD and atrial fibrillation (captured via ICD-10 codes) between January 1, 2009 and August 31, 2015. After excluding individuals diagnosed with atrial fibrillation or CKD prior to January 1, 2008; missing at least one follow-up eGFR measurement or having implausible eGFR values; having a prescription for a direct-acting oral anticoagulant (inhibiting factor Xa or thrombin); or missing baseline data to calculate the CHA2DS2-VASc score, a total of 14 432 individuals were included in the final analytic sample. Of this group, 7409 had a prescription for a vitamin K antagonist as compared to 7023 who did not.

The baseline characteristics of the two groups were fairly comparable except for age (median 78 years for those treated with vitamin K antagonists vs 79 for those who were not), sex (45% female in the vitamin K antagonist group vs 52% in the comparison group), and concurrent use of aspirin (21% in the vitamin K antagonist group vs 44% in the comparison group) at baseline. Importantly, there were no significant differences in median eGFR at baseline (48 mL/min/1.73 m² in the vitamin K antagonist group vs 47 mL/min/1.73 m² in the comparison group). In a linear mixed effect model that adjusted for baseline differences in age and CHA2DS2-VASc score, individuals exposed to vitamin K antagonists had a greater mean annualized eGFR decline than those not exposed to vitamin K antagonists (mean difference 0.29 mL/min/1.73 m²/year, 95% CI 0.06, 0.53). The results were similar in propensity score adjusted analyses which used inverse-probability-of-treatment weights to try to account for differences in baseline characteristics of the two groups (confounding by indication), and when using a 30% decline in eGFR as an alternate outcome (adjusted hazard ratio compared vitamin K antagonist exposure vs non-exposure, 1.20, 95% CI 1.11, 1.30).

The results of this study support the findings from a post-hoc analysis of the Randomized Evaluation of Long Term Anticoagulation Therapy trial that showed a faster decline in mean eGFR in individuals with atrial fibrillation randomized to warfarin as compared to dabigatran. Reasons for these findings are unclear. Posch and colleagues speculate that vitamin K antagonism may accelerate the development of vascular calcification in the kidney, leading to faster decline in eGFR. There is reasonable experimental data to support such speculation, though data directly linking exposure to vitamin...
K antagonists with clinical or histopathologic evidence of vascular calcification in the kidney in humans are lacking. Another possible explanation is the increasingly recognized entity of anticoagulant-related nephropathy. Experimental and clinical data have shown that exposure to warfarin can result in acute kidney injury from glomerular hemorrhage, almost always in the setting of excessively high INR values (INR > 3). Importantly, individuals with CKD are at highest risk of excess anticoagulation from vitamin K antagonists due to the adverse impact of reduced kidney function on the clearance and metabolism of warfarin. Thus, individuals with CKD prescribed vitamin K antagonists may be susceptible to repeated episodes of clinical or subclinical glomerular hemorrhage, resulting in faster decline in eGFR over time. Similar findings have been demonstrated with dabigatran, though there is some evidence that direct-acting oral anticoagulants result in a lower risk of bleeding complications than vitamin K antagonists in CKD patients. Unfortunately, Posch and colleagues excluded individuals treated with direct-acting oral anticoagulants, precluding them from examining whether the change in eGFR over time in this group differed as compared to those treated with vitamin K antagonists. Finally, despite the use of inverse probability of treatment weighting to try to account for baseline differences in covariates, it is difficult to completely exclude the possibility that the results of the current study could be explained by confounding by indication—that is to say, individuals treated with vitamin K antagonists represented a sicker subset of individuals more prone to kidney function decline than those who were not prescribed vitamin K antagonists.

How might these findings impact clinical care of individuals with CKD and atrial fibrillation? At the moment, there are no randomized controlled trials that have specifically examined the effects of vitamin K antagonists versus other oral anticoagulants with respect to kidney disease outcomes, and it is unlikely that any such trials will be forthcoming. However, given the potential adverse effects of vitamin K antagonists on vascular calcification and glomerular hemorrhage, the results of the current study support the notion that kidney function should be routinely monitored in individuals with CKD and atrial fibrillation requiring vitamin K antagonists. In addition, it may be prudent to add the potential adverse effects of vitamin K antagonists on kidney function to the risks associated with initiation of this therapy in select cases (such as individuals with advanced kidney disease). That being said, it is important to note that the median age of the population studied was 78 years old and that the annualized difference in eGFR decline between those exposed to vitamin K antagonists versus those who were not was rather small. The long-term benefit of vitamin K antagonism with respect to avoiding significant comorbidity related to stroke or other thromboembolic events may outweigh a slightly faster rate of kidney function decline for many older patients. Shared decision-making that encompasses the priorities, values and goals of each patient is incumbent when making decisions on starting anticoagulation in CKD patients.

Posch and colleagues have provided a valuable contribution to our understanding of a potential risk associated with vitamin K antagonists in CKD patients. Whether this risk can be mitigated by using direct-acting oral anticoagulants would be of substantial clinical interest in selecting the best agent to reduce the risk of thromboembolic events while minimizing other potential risks such as loss of kidney function.

**RELATIONSHIP DISCLOSURE**

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