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COMMENTARY

Stroke prevention in atrial fibrillation with chronic kidney disease: a delicate balance of efficacy and safety considerations

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Oral anticoagulant (OAC) use is the standard of care for stroke prevention in atrial fibrillation (AF). This is based on several randomized and observational studies demonstrating a reduction in stroke/systemic embolism risk and a reduction in mortality. These benefits are considered to outweigh the known potential risk of increased bleeding, as supported by several patient-centered studies examining how patients weigh benefits vs risks of OACs.

Yet, patients with AF and comorbid severe chronic kidney disease (CKD), especially those who require dialysis, are a unique subgroup for whom the typical risk-benefit balance may not favor the use of OAC for stroke prevention [1–3]. This is particularly important because patients with severe CKD are at increased risk of bleeding already due to underlying platelet dysfunction. Increased bleeding is even more problematic for patients with end-stage kidney disease (ESKD) who receive chronic hemodialysis because of the need for intravascular access via 2 large gauge needles thrice weekly, situationally a setup for bleeding to occur [4]. There also remains some question as to the overall efficacy of OAC therapy in general for patients with AF and ESKD. So, the benefits are less clear compared with the bleeding risks.

For all these reasons, managing AF in patients with advanced stages of CKD or ESKD is one of the most challenging clinical scenarios. Deciding if anticoagulation is necessary and beneficial is complicated by limited clinical data. If a decision is made to initiate OAC therapy, selecting the most appropriate agent and dosing adds further complexity [5].

To provide insight into the safety and efficacy of OAC use among patients with AF and advanced CKD, Ballegaard et al. [6] conducted a Danish national cohort study. They identified all patients with incident AF between January 2010 and June 2022 and then estimated the glomerular filtration rate using the 2009 CKD-EPI equation from laboratory data just prior to study inclusion. Patients were determined to have advanced CKD if the estimated glomerular filtration rate was <30 mL/min/1.73 m^3. Among the population, 21% were receiving chronic dialysis.

The study had several key findings. First, only 40% of patients with AF and severe CKD were prescribed OAC therapy for stroke prevention. Among those using a vitamin K antagonist (VKA; 39% of all OAC users), the time in the therapeutic range was low at 50%. Despite the overall poor quality of anticoagulation therapy, use of OAC was still associated with a 25% reduction in the risk of stroke (hazard ratio [HR], 0.75; 95% CI, 0.58-0.97) and a 23% reduction in the risk of death (HR, 0.77; 95% CI, 0.71-0.84). This suggests that OAC therapy is efficacious, even in patients at severe stages of CKD or those who have ESKD. On the other hand, as expected, OAC use was also associated with a 40% increase in the risk of major bleeding (HR, 1.41; 95% CI, 1.18-1.68), and the numerical percent of patients experiencing 1-year major bleeding events was approximately twice those of stroke or systemic embolism (7.6%-10.9% vs 3.6%-4.8%, respectively). When comparing use of direct OACs (DOACs) with VKA therapy, there was no difference in the risk of thromboembolic or bleeding outcomes, but

the risk of death was statistically lower with DOAC therapy (−5.5%; 95% CI, −2.0% to −9.2%).

The study had several important strengths that are worth highlighting. First, many studies of patients with AF and/or those with patients treated with OAC systematically exclude patients with severe CKD—but this study instead focused on this vulnerable population. A second strength is that the study cohort included an older population of patients who are also not typically well-represented in clinical trials. Lastly, the numerous subgroup and sensitivity analyses provided valuable insights into key subgroups, including comparisons of different OAC medications, levels of OAC control, concomitant antiplatelet therapy, and assessing for issues of misclassification.

There are important limitations to consider as well. These include the nature of the study design (retrospective and nonrandomized) and relative lack of diversity in a northern European population. Also, there are potential concerns about unmeasured confounding, particularly where they showed a decreased risk of death but not thromboembolism when comparing use of DOACs with VKA therapy.

Despite these limitations, the results from this nationwide cohort study seem to align with findings in other studies examining patients with AF and ESKD receiving dialysis. Notably, the RENAL-AF [7], AXADIA-AFNET8 [8], and Valkyrie [9] trials each attempted to randomize patients with AF and ESKD to DOAC vs VKA therapy. However, these were limited in scope (97-154 patients per trial) and remain highly underpowered to detect important clinical differences pointing toward difficulty in recruiting patients for such a study. Furthermore, they only compared 2 different OAC regimens and did not assess the important question of if OAC therapy should be offered in the first place.

Antithrombotic stewardship activities aim to ensure that all patients receive the safest and most efficacious therapy to prevent or treat thrombotic conditions [10]. This is of particular importance for patients with AF and advanced CKD. In the absence of high-quality, randomized trial data in this high-risk population, clinicians are left to apply the best available evidence to make clinical decisions for their patients. That now includes this large observational cohort by Ballegaard et al. [6]. Key stewardship activities that are of particular relevance for this population include (1) ensuring high-quality VKA management when that agent is selected, (2) selecting the appropriate DOAC dose adjusting for renal function and avoiding relevant drug–drug interactions, and (3) reassessing other bleeding risk factors that may alter the risk-benefit balance of anticoagulant therapy.

The promise of anticoagulant therapy that is not renally dependent is on the horizon. Several factor XI and XIa inhibitors are currently being tested in patients with AF, venous thromboembolism, and other thrombotic conditions [11]. Most of these agents, both oral and parenteral, have little-to-no renal clearance. As such, they may be ideal for the population of our patients with CKD or ESKD if they are shown to have efficacy in reducing thrombotic risk. Even so, it will be imperative that antithrombotic stewardship efforts are designed to support patients and clinicians who will face increasing choice and complexity when selecting the best strategy to prevent stroke associated with AF.

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AUTHOR CONTRIBUTIONS

G.D.B. drafted the manuscript. J.A.W.M. provided critical revisions. Both authors approved the final version.

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REFERENCES

[1] Potpara TS, Ferro CJ, Lip GYH. Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction. *Nat Rev Nephrol*. 2018;14:337–51.

[2] Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. *Semin Thromb Hemost*. 2010;36:34–40.

[3] Jones A, Swan D, Lisman T, Barnes GD, Thachil J. Anticoagulation in chronic kidney disease: current status and future perspectives. *J Thromb Haemost*. 2024;22:323–36.

[4] van Eck van der Sluijs A, Abrahams AC, Rookmaaker MB, Verhaar MC, Bos WJW, Blankestijn PJ, et al. Bleeding risk of haemodialysis and peritoneal dialysis patients. *Nephrol Dial Transplant*. 2021;36:170–5.

[5] Tscharre M, Steiner D, Mutschlechner D, Ay C, Gremmel T. Anticoagulation in atrial fibrillation and end-stage kidney disease on hemodialysis: a meta-analysis of randomized trials comparing direct oral anticoagulants with vitamin K antagonists. *Res Pract Thromb Haemost*. 2024;8:102332. https://doi.org/10.1016/j.rpth.2024.102332

[6] Ballegaard ELF, Olesen JB, Kamper AL, Feldt-Rasmussen B, Gislason G, Torp-Pedersen C, et al. Oral anticoagulation for stroke prevention in atrial fibrillation and advanced kidney disease. *Res Pract Thromb Haemost*. 2024;8:102350. https://doi.org/10.1016/j.rpth.2024.102350

[7] Pokorney SD, Chertow GM, Al-Khalidi HR, Gallup D, Dignacco P, Mussina K, et al. Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial. *Circulation*. 2022;146:1735–45.

[8] Reinecke H, Engelbertz C, Bauersachs R, Breithardt G, Echterhoff H-H, Gerß J, et al. A randomized controlled trial comparing apixaban with

the vitamin K antagonist phenprocoumon in patients on chronic hemodialysis: the AXADIA-AFNET 8 Study. *Circulation*. 2023;147:296–309.

[9] de Vriese AS, Caluwé R, van der Meersch H, de Boeck K, de Bacquer D. Safety and efficacy of vitamin K antagonists versus rivaroxaban in hemodialysis patients with atrial fibrillation: a multicenter randomized controlled trial. *J Am Soc Nephrol*. 2021;32:1474–83.

[10] Burnett AE, Barnes GD. A call to action for anticoagulation stewardship. *Res Pract Thromb Haemost*. 2022;6:e12757. https://doi.org/10.1002/rth2.12757

[11] Prakash S, Mares AC, Porres-Aguilar M, Mukherjee D, Barnes GD. Factor XI/XIa inhibitors for the prevention and treatment of venous and arterial thromboembolism: a narrative review. *Vasc Med*. 2024;29:85–92.