

Review Article

Anticoagulation in Older Adults With Advanced Chronic Kidney Disease and Atrial Fibrillation: Comparative Safety of Apixaban, Rivaroxaban, and Warfarin

MOHAMED ABDELLATIF¹

¹ DEPARTMENT OF PHARMACY, FRASER HEALTH, BRITISH COLUMBIA, CANADA

² DEPARTMENT OF PHARMACY, BURJEEL MEDICAL CITY, ABU DHABI, UNITED ARAB EMIRATES

CORRESPONDENCE

MOHAMED ABDELLATIF, BSC, PHARMD, BCPS
DEPARTMENT OF PHARMACY
FRASER HEALTH, BRITISH COLUMBIA, CANADA
BURJEEL MEDICAL CITY, ABU DHABI, UNITED ARAB EMIRATES
Email: Mohamed_abdellatif@outlook.com
ORCID: 0009-0004-8823-5185

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Abstract

Background: Older adults with atrial fibrillation (AF) and chronic kidney disease (CKD) stage 4–5 have simultaneously high risks of ischemic stroke and anticoagulant-related bleeding. Evidence guiding drug selection is limited because pivotal direct oral anticoagulant (DOAC) trials largely excluded patients with severe renal impairment.

Objective: To review contemporary comparative evidence for apixaban, rivaroxaban, and warfarin in older adults with advanced CKD, with emphasis on major bleeding, thromboembolism, renal function, dose selection, and the distinction between non-dialysis CKD and kidney failure requiring dialysis.

Summary: Observational data consistently suggest that apixaban is associated with less major bleeding than warfarin or rivaroxaban in non-dialysis CKD stage 4–5, while stroke rates appear broadly similar but are less precisely estimated. A 2024 nationwide US cohort found major bleeding to be higher with warfarin and rivaroxaban than with apixaban. A separate cohort of patients with severe CKD, mean age 78.5 years, similarly found lower major bleeding with apixaban than with warfarin or rivaroxaban. Recent 2026 analyses continue to

support a favorable apixaban safety signal, but certainty remains limited by confounding and sparse randomized evidence. In dialysis, small randomized trials have not established clear superiority of apixaban or vitamin K antagonists.

Conclusion: In older adults with AF and non-dialysis advanced CKD who require anticoagulation, apixaban currently has the most consistent observational safety signal. Warfarin remains appropriate in selected patients, particularly when DOACs are unsuitable. Anticoagulation in kidney failure requiring dialysis should remain individualized because the net clinical benefit is uncertain.

Keywords: atrial fibrillation; chronic kidney disease; apixaban; rivaroxaban; warfarin; elderly; bleeding; anticoagulation

1. Introduction

Atrial fibrillation and CKD frequently coexist in older adults. Declining kidney function increases both thromboembolic and bleeding risk, creating one of the most difficult anticoagulation decisions in routine practice. CKD also alters drug clearance, platelet function, vascular integrity, and exposure to interacting medications. In advanced CKD, these factors are amplified by frailty, anemia, fluctuating renal function, falls, polypharmacy, and invasive procedures.

The evidence gap is important. Most pivotal DOAC trials excluded patients with creatinine clearance below approximately 25–30 mL/min. Consequently, treatment decisions in CKD stage 4–5 rely heavily on pharmacokinetic data, post-hoc analyses, observational cohorts, and small randomized studies. The central question is therefore not simply whether anticoagulation reduces stroke, but which agent offers the best balance between thromboembolic prevention and bleeding in an elderly high-risk population.

2. Why Advanced CKD Changes the Risk–Benefit Balance

Older adults with advanced CKD may have high CHA₂DS₂-VASc scores because of age, hypertension, diabetes, vascular disease, and heart failure. At the same time, uremic platelet dysfunction, anemia, antiplatelet therapy, gastrointestinal pathology, falls, and impaired drug elimination increase bleeding risk. Renal function may also change rapidly during infection, heart failure, dehydration, or acute kidney injury, making a previously appropriate dose unsafe.

Bleeding scores should therefore be used to identify modifiable risk factors rather than as automatic reasons to withhold anticoagulation. Important targets include unnecessary aspirin or nonsteroidal anti-inflammatory drugs, uncontrolled hypertension, excessive alcohol, poorly controlled warfarin therapy, drug interactions, and inappropriate DOAC dosing.

3. Guideline Position

KDIGO 2024 recommends non-vitamin K antagonist oral anticoagulants in preference to warfarin for AF in CKD stages G1–G4, while emphasizing dose adjustment and greater caution in G4–G5. For stage 5 CKD and dialysis, evidence is substantially less certain. Contemporary AF guidance similarly accepts labeled DOAC dosing or warfarin in stage 4 CKD, but treats kidney failure and dialysis as an area requiring individualized decision-making rather than a routine extension of general-population evidence.

4. Comparative Evidence in Non-Dialysis CKD Stage 4–5

The strongest head-to-head evidence comes from large real-world cohorts. Fu and colleagues used Medicare and Optum claims to compare new users of warfarin or rivaroxaban with apixaban among patients with AF and non-dialysis CKD stage 4–5. After propensity matching, warfarin was associated with substantially more major bleeding than apixaban (hazard ratio [HR] 1.85), including more gastrointestinal and intracranial bleeding. Rivaroxaban was also associated with more major bleeding than apixaban (HR 1.69). Ischemic stroke differences were not statistically significant, although event numbers were limited.[1]

A separate 2024 cohort of 6,794 patients with severe CKD had a mean age of 78.5 years and a mean estimated glomerular filtration rate of 24.7 mL/min/1.73 m². Major bleeding occurred at 1.5 versus 2.9 events per 100 person-years with apixaban and warfarin, respectively; apixaban was associated with a 47% relative reduction in major bleeding. Rivaroxaban was associated with more bleeding than warfarin, and apixaban was safer than rivaroxaban.[2]

The direction of these findings is consistent across several observational datasets and meta-analyses: apixaban generally demonstrates the most favorable bleeding profile in advanced CKD. However, observational evidence can be affected by treatment selection, frailty, unmeasured renal trajectory, and dose-selection bias. These data support a clinical preference, not proof of superiority equivalent to a large randomized trial.

5. What Has Changed in 2026?

Recent evidence has strengthened, but not eliminated, the uncertainty. A 2026 systematic review and meta-analysis including 21 studies and more than 184,000 patients with advanced CKD found DOACs were associated with lower risks of stroke or systemic embolism and major bleeding than vitamin K antagonists, although bleeding heterogeneity was substantial and agent-specific effects favored apixaban.[3]

A September 2026 cohort of patients with AF and advanced CKD not requiring dialysis compared apixaban, warfarin, and no anticoagulation. Apixaban was associated with lower ischemic stroke risk than no anticoagulation but with more major bleeding; warfarin increased major bleeding without a statistically significant stroke reduction. Directly compared with warfarin, apixaban showed a more favorable overall balance.[4] These findings are clinically important because they address not only which anticoagulant to use, but whether anticoagulation itself provides sufficient net benefit in advanced CKD.

6. Dialysis Is a Different Population

Evidence in dialysis should not be merged with non-dialysis CKD stage 4–5. The competing risks of stroke, cardiovascular death, and bleeding are extreme, warfarin time in therapeutic range is often poor, and calciphylaxis is an additional concern with vitamin K antagonists. The RENAL-AF and AXADIA-AFNET 8 trials were small and underpowered; neither established clear superiority of apixaban over a vitamin K antagonist. Bleeding events were more frequent than ischemic events in these trials.[5,6]

Recent meta-analyses suggest lower bleeding with factor Xa inhibitors than with warfarin in dialysis, but results are driven largely by observational data and remain heterogeneous. Therefore, the apparent apixaban advantage in non-dialysis stage 4–5 CKD should not be assumed to apply with the same certainty to dialysis patients.

7. Practical Comparison

Agent	Potential advantages	Major limitations in advanced CKD
Apixaban	Lowest renal clearance among commonly used factor Xa inhibitors; strongest observational safety signal in advanced CKD.	Dose reduction must follow approved criteria rather than renal impairment alone; evidence in dialysis remains limited.
Rivaroxaban	Once-daily administration; labeled renal dose available for AF in severe renal impairment in some jurisdictions.	Consistently more major bleeding than apixaban in advanced CKD cohorts; gastrointestinal bleeding is a concern.
Warfarin	Usable across the full spectrum of renal function; measurable anticoagulant effect; preferred for mechanical valves and moderate–severe rheumatic mitral stenosis.	Labile INR, drug/food interactions, poor time in therapeutic range in severe CKD, higher intracranial/GI bleeding in several cohorts, calciphylaxis concern.

8. Dose Selection and Monitoring

Dose selection should use the renal function measure specified in the product label and supporting evidence, often Cockcroft–Gault creatinine clearance rather than automatically substituting eGFR. In frail older adults, serum creatinine may overestimate kidney function because of low muscle mass. Renal function should be reassessed after acute illness and periodically during stable therapy.

Inappropriate empirical dose reduction is not benign. Underdosing may reduce stroke protection without eliminating bleeding risk. For apixaban in AF, dose reduction should follow approved criteria, including age, weight, and serum creatinine requirements where applicable. Concomitant strong CYP3A4 or P-glycoprotein inhibitors or inducers, antiplatelets, and NSAIDs should be reviewed carefully.

9. When Warfarin May Still Be the Better Choice

Warfarin remains appropriate when a DOAC is contraindicated, unaffordable, or unsuitable because of major interacting drugs. It remains the standard oral anticoagulant for mechanical heart valves and is generally preferred in moderate-to-severe rheumatic mitral stenosis. Warfarin may also be reasonable when clinicians require measurable anticoagulant intensity and reliable INR follow-up is available.

If warfarin is used, quality matters. Poor time in therapeutic range can erase potential benefit and magnify bleeding risk. Medication reconciliation, dietary consistency, antimicrobial interaction review, and structured anticoagulation-clinic follow-up are particularly important in advanced CKD.

10. A Practical Approach for the Older Adult

- Confirm the indication for anticoagulation and exclude mechanical valves or moderate-to-severe rheumatic mitral stenosis.
- Estimate stroke risk, but separately identify modifiable bleeding risks and frailty factors.
- Distinguish non-dialysis stage 4–5 CKD from kidney failure requiring dialysis.
- If anticoagulation is indicated in non-dialysis advanced CKD, consider apixaban preferentially when appropriate because current comparative data show the most consistent bleeding advantage.
- Use labeled dosing criteria and reassess renal function after acute illness or meaningful clinical change.
- Avoid unnecessary concomitant antiplatelet therapy and NSAIDs.
- Reassess the decision periodically as renal function, falls, frailty, goals of care, and competing mortality risk evolve.

11. Conclusion

Anticoagulation in older adults with AF and CKD stage 4–5 requires individualized assessment because both stroke and bleeding risks are high. Current evidence does not support treating all DOACs as interchangeable in advanced CKD. Across multiple large observational studies, apixaban has shown a more favorable major-bleeding profile than warfarin and rivaroxaban, with no clear loss of stroke protection. This makes apixaban a

practical first consideration for many patients with non-dialysis advanced CKD when anticoagulation is indicated and dosing criteria are satisfied.

The evidence is less definitive in dialysis. Small randomized trials have not demonstrated clear superiority of apixaban or vitamin K antagonists, and the net benefit of anticoagulation itself remains uncertain in some patients. The safest approach is therefore phenotype-specific: use the best-supported agent in non-dialysis advanced CKD, but apply shared decision-making and greater caution as kidney function approaches failure and dialysis.

Declarations

Ethics Approval and Consent to Participate

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Consent for Publication

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Author Contributions

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References

1. Fu EL, Desai RJ, Paik JM, et al. Comparative safety and effectiveness of warfarin or rivaroxaban versus apixaban in patients with advanced CKD and atrial fibrillation: nationwide US cohort study. *Am J Kidney Dis.* 2024;83(3):293-305.e1. doi:10.1053/j.ajkd.2023.08.017.
2. Wetmore JB, et al. Risk of major bleeding, stroke/systemic embolism, and death associated with different oral anticoagulants in patients with atrial fibrillation and severe chronic kidney disease. *J Am Heart Assoc.* 2024. PMID:39119973.
3. Metwaly AS, Alqurain AA, Alghanim FF, et al. Direct oral anticoagulants versus warfarin in atrial fibrillation with advanced chronic kidney disease: a systematic review and meta-analysis. *Cureus.* 2026;18(3):e106043. doi:10.7759/cureus.106043.
4. Chen Q, Singer DE, Fu EL, et al. Oral anticoagulants in patients with atrial fibrillation and advanced CKD not requiring dialysis. *JAMA Netw Open.* 2026;9(9):e2632225. doi:10.1001/jamanetworkopen.2026.32225.
5. Reinecke H, Engelbertz C, Bauersachs R, 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.
6. Pokorney SD, Chertow GM, Al-Khalidi HR, et al. Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial. *Circulation.* 2022;146:1735-1745.
7. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.* 2024;105(Suppl 4S):S117-S314.
8. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation. *Circulation.* 2024;149:e1-e156. doi:10.1161/CIR.0000