EDITORIAL

Korean J Intern Med 2026;41:3-5
https://doi.org/10.3904/kjim.2025.406

Uncertain benefit, certain harm: the anticoagulation paradox in hemodialysis—re-evaluation of stroke prevention and bleeding risk in end-stage kidney disease

Tae-Wan Chung

Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Hospital, Daegu, Korea

See Article on Page 107-117

INTRODUCTION: DUAL AND CONFLICTING HAZARDS IN HEMODIALYSIS PATIENTS

Patients with end-stage kidney disease (ESKD) on maintenance hemodialysis carry a high burden of atrial fibrillation (AF) and thromboembolic risk. Concurrently, this thromboembolic risk is accompanied by an equally substantial bleeding risk. Patients undergoing hemodialysis are prone to bleeding due to platelet dysfunction, uremic endothelial damage, gastrointestinal fragility, and repeated heparin administration during dialysis sessions [1]. This has created a dilemma for clinicians. Anticoagulation strategies that are effective in the general AF population cannot be directly applied to hemodialysis patients, in whom both thrombotic and hemorrhagic risks are markedly elevated.

This commentary examines the study by Yang et al. [2] in the *Korean Journal of Internal Medicine*, which compared three anticoagulation strategies in 933 patients with ESKD and AF. The cohort included patients who received no anticoagulation (n = 604), warfarin (n = 197), or direct oral anticoagulants (DOACs; n = 132). The study addresses a critical and unresolved question: how can thromboembolic prevention be balanced against bleeding risk in this uniquely vulnerable population?

Warfarin has historically been the standard anticoagulant for stroke prevention in patients with AF undergoing hemodialysis, supported by the theoretical advantage of prothrombin time (PT)-guided dose adjustment. However, in practice, PT levels in hemodialysis patients are highly unstable, leading to dangerous fluctuations between under- and over-anticoagulation. The former increases the embolic risk, whereas the latter increases the bleeding risk.

WARFARIN: 45% FEWER STROKES, 170% MORE BLEEDING

This Korean study provides concrete evidence of the paradox of warfarin use in hemodialysis patients. Warfarin reduced ischemic stroke or systemic embolism by 45% (adjusted hazard ratio [aHR] 0.55, 95% confidence interval [CI] 0.31–1.00) compared with no anticoagulation, indicating a statistically significant benefit. However, this benefit came at a steep cost. The risk of major bleeding increased 2.7-fold (aHR 2.69, 95% CI 2.06–3.51), driven by both a 7-fold higher risk of intracranial hemorrhage (aHR 7.18, 95% CI 3.82–13.5) and an 82% increase in gastrointestinal bleeding (aHR 1.82, 95% CI 1.27–2.63).

These findings align with decades of observational studies demonstrating the inconsistent net clinical benefit of warfarin in ESKD [3-5]. The fundamental problem is not the inherent anticoagulant effect of warfarin, but rather the difficulty of maintaining stable anticoagulation in patients undergoing hemodialysis. Fluctuations in nutritional status, drug clearance, and uremic coagulopathy render the traditional view of warfarin as 'monitorable and adjustable' illusory in

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

practice [6].

DOACS: SUPERIOR SAFETY WITH COMPARABLE EFFICACY

This study provides encouraging data on the use of DOACs in patients with ESKD. Compared with no anticoagulation, DOACs reduced ischemic stroke or systemic embolism by 64% (aHR 0.36, 95% CI 0.19–0.69). This represents a greater reduction than that observed with warfarin. In terms of safety, DOACs increased major bleeding risk by 37% (aHR 1.37, 95% CI 1.02–1.84), substantially less than the 169% increase associated with warfarin.

Most importantly, DOACs demonstrated a significantly better safety profile than did warfarin in direct comparisons. The risk of major bleeding was 49% lower with DOACs (aHR 0.51, 95% CI 0.40–0.66). This difference was driven by trends toward lower risks of intracranial hemorrhage (aHR 0.70, $p = 0.081$) and gastrointestinal bleeding (aHR 0.73, $p = 0.083$), although these individual comparisons were not statistically significant.

Nevertheless, DOACs are not ideal solutions. The 5-fold increase in intracranial hemorrhage risk compared with no anticoagulation (aHR 5.02, 95% CI 2.66–9.47) remains concerning. Moreover, 79% of patients treated with DOAC in this study received off-label low-dose regimens, and the optimal dose for ESKD remains undefined [7-9]. Current dosing strategies for ESKD remain extrapolative rather than evidence based. Thus, although DOACs may represent a more favorable option, they have not yet been validated as standard therapy for this population.

THE MORTALITY PARADOX: SELECTION BIAS OR REAL BENEFIT?

Both warfarin (aHR 0.53, 95% CI 0.38–0.74) and DOACs (aHR 0.57, 95% CI 0.43–0.78) were associated with approximately 45% lower risk of all-cause mortality compared with no anticoagulation. This finding warrants a cautious interpretation.

In observational studies of ESKD, patients selected for anticoagulation tend to be younger and healthier and have better functional status. These factors are independently associated with survival. Despite propensity score weighting, unmeasured confounders such as frailty, nutritional status, and dialysis adequacy may contribute to this mortality difference. Therefore, the mortality benefit should not be interpreted as causal until confirmed in randomized trials. Potential selection bias and competing risk effects inherent to ESKD populations limit our ability to attribute the observed survival benefit to anticoagulation itself.

CONCLUSION: FROM ROUTINE ANTICOAGULATION TO SHARED DECISION-MAKING

This multicenter Korean study advances our understanding of anticoagulation in ESKD by providing direct three-way comparisons with robust outcome data.

The key insight is not merely that DOACs perform better than warfarin, but rather that anticoagulation in ESKD requires accepting an increased bleeding risk in exchange for stroke prevention.

DOACs appear to offer a more favorable risk–benefit ratio than warfarin, but decisions to administer anticoagulation therapy must be individualized based on patient-specific bleeding risk, stroke risk, and goals of care.

Future research should better define these competing hazards and clarify the net clinical benefit by identifying patients who are most likely to benefit from anticoagulation. Until randomized evidence becomes available, anticoagulation during hemodialysis should be guided by nuanced, shared decision-making that acknowledges both potential benefits and risks.

Although anticoagulation remains the cornerstone of stroke prevention in patients with AF, the era of default anticoagulation for all patients must provide a more thoughtful, patient-centered approach in this uniquely vulnerable population.

REFERENCES

1. Wasse H, Gillen DL, Ball AM, et al. Risk factors for upper gastrointestinal bleeding among end-stage renal disease patients. Kidney Int 2003;64:1455-1461.
2. Yang Y, Lee SH, Hwang W, Jung J, Park JH. Comparative efficacy and safety of warfarin and direct oral anticoagulants in patients with end-stage renal disease and atrial fibrillation.

https://doi.org/10.3904/kjim.2025.406

Korean J Intern Med 2025;41:107-117.
3. Shah M, Avgil Tsadok M, Jackevicius CA, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. Circulation 2014;129:1196-1203.
4. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol 2009;20:2223-2233.
5. Wizemann V, Tong L, Satayathum S, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. Kidney Int 2010;77:1098-106.
6. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. Circulation 2018;138:1519-1529.
7. 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.
8. 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.
9. Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban pharmacokinetics at steady state in hemodialysis patients. J Am Soc Nephrol 2017;28:2241-2248.

Received : December 12, 2025
Accepted : December 18, 2025

Correspondence to
Tae-Wan Chung, M.D.
Department of Cardiology in Internal Medicine, Keimyung University Dongsan Hospital, 56 Dalseong-ro, Jung-gu, Daegu 41931, Korea
Tel: +82-53-258-4623, Fax: +82-53-258-4630
E-mail: jtw.dsmc@gmail.com
https://orcid.org/0000-0002-9887-6398

Conflicts of interest
The author discloses no conflicts.

Funding
None