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Prophylactic and Therapeutic Anticoagulation in Nephrotic Syndrome Using Direct Acting Oral Anticoagulants

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In this issue of *KI Reports*, Arches *et al.*[1] describe one of the most comprehensive cohort studies to date, evaluating the use of direct acting oral anticoagulants (DOACs) for both prophylactic and therapeutic anticoagulation in Nephrotic Syndrome (NS). NS is characterized by proteinuria > 3.5 g/24-h, hypoalbuminemia (< 3 g/dl), and edema, which associates with a significantly elevated risk of venous and arterial thromboembolic events.[2] The pathophysiology of this thrombotic diathesis is complex and includes the urinary losses of regulatory proteins with additional contributions from other hemostatic abnormalities unique to this disorder.[2,3]

Although the decision to commence therapeutic dose anticoagulation in the setting of clinically evident thrombosis is relatively evident, the decision to commence prophylactic anticoagulation is heterogeneous and varies somewhat by individual nephrologist. Physician preferences and practices regarding prophylactic anticoagulation in NS relate to experience, attitudes toward the complications of thromboembolism, and perceived likelihood of thrombosis and bleeding.[2] Commonly proposed decision algorithms relate to the subtype of glomerulopathy, in particular membranous glomerulonephritis and the degree of hypoalbuminemia.[3] Some authors have proposed calculators to aid in decision making on prophylactic anticoagulation[4]; however, these models are unlikely to have undergone extensive evaluations of generalizability, calibration, discrimination, and net benefit.[4] Nonetheless, once a decision is made to commence prophylactic or therapeutic anticoagulation in NS, the subsequent dilemma entails choosing between a DOAC or vitamin K antagonists (VKA) preceded by heparin (VKA/heparin).

The first reports of DOAC use for therapeutic anticoagulation in NS began to emerge in 2014[5,6] and those of prophylactic DOAC use in 2018.[2] Arches *et al.*[1] now report a cohort study including 144 patients with NS from 10 centers across France who were prescribed a DOAC or VKA/heparin either as a prophylactic or a therapeutic anticoagulation strategy.[1] The cohort appears to be appropriately representative of NS with a median (interquartile range) serum albumin of 1.5 (1.2–1.8) g/dl and urine protein-to-creatinine ratio of 8.8 (5.5–12.3) g/g, with membranous glomerulopathy comprising 45.8% of cases and prophylactic anticoagulation constituting the majority of cases.[1]

Because this was not a randomized study, although thromboembolic risk factors and immunosuppression regimes appear relatively balanced between groups,[1] residual confounding cannot be excluded. In particular, any treatment indication biases that lead to one anticoagulation regime being chosen over another cannot be excluded and primary outcome ascertainment cannot be fully assured outside of a prospective study. The authors included some patients who were taking anticoagulation before NS occurrence,[1] and whether these patients had a separate indication for anticoagulation before NS development could influence anticoagulant choice. In addition, international normalized ratio indices in patients taking VKA or antithrombin III levels in those receiving heparin were not presented. In the DOAC group, there was some variation in the choice of drug, but apixaban formed the majority at the 5 mg twice daily dosage, even for prophylaxis.[1,2]

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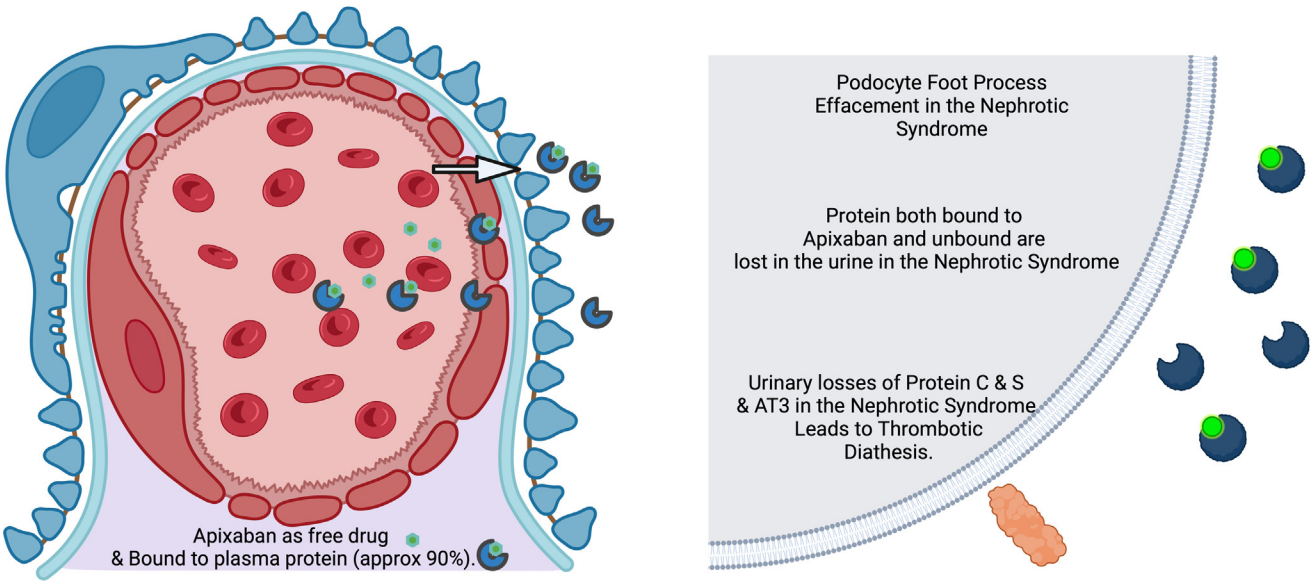

Figure 1. Apixaban is highly protein-bound, and pilot data suggest that urinary loss of protein-bound drug occurs in nephrotic syndrome. In addition, losses of urinary protein unbound to apixaban may increase the free fraction of circulating apixaban. The implications of these peculiarities on bleeding risk and the risk of treatment failure for anticoagulation in nephrotic syndrome are unclear at present. Warfarin as an alternative to apixaban is also highly protein-bound; however, the dose is adjusted to achieve a certain INR value. Perhaps in future, direct testing for free drug fraction and for degree of urinary losses of apixaban-bound protein losses will allow for personalized approach to DOAC dosing in nephrotic syndrome. Created in BioRender. S, D. (2025) https://BioRender.com/h32v104. DOAC, direct acting oral anticoagulant; INR, international normalized ratio.

The primary outcomes in this study were bleeding and thromboembolism.[1] The median duration of exposure to anticoagulation was 91 days (DOAC) versus 73 days (VKA/heparin), with some individuals having much longer exposure, which likely reflects a failure to achieve NS remission in these patients. Of 72 patients, 3 patients in the DOAC group and none in the VKA/heparin group experienced thromboembolic events (Table 3). One of these 3 patients was taking apixaban and had genetic thrombophilia, whereas the other 2 patients were on rivaroxaban. Although the infrequency perturbs any meaningful statistical analysis, it may raise questions about the possibility of treatment failure of DOACs in some patients with NS. Cases of VKA/heparin failure subsequently successfully treated with DOACs and the converse have previously been reported.[2]

Apixaban appears to be a favorable choice among DOACs in NS because of the established safety profile in patients with reduced glomerular filtration rate in conditions other than NS.[2] It remains unclear whether NS leads to increased urinary losses of protein-bound DOAC with reduced therapeutic effect in steady state, whether the urinary loss of albumin paradoxically leads to higher free drug levels, or perhaps a combination of both scenarios (Figure 1).[2] The clinical impact of these peculiarities on thrombotic and bleeding risk merits further investigation.[2,7] A thoroughly conducted study evaluated this issue in 11 patients with NS after a single dose of 10 mg apixaban.[7] In this study, C_{max} value for free apixaban as a percentage of the total circulating apixaban was lower in controls and highest for those with the most severe NS, suggesting possibly greater free fraction exposure in NS because of urinary albumin losses.[7] However, those with severe NS also experienced higher apparent drug clearance, in particular the protein bound drug, suggesting that urinary loses may be contributing.[7] Further research is needed into the steady state pharmacokinetics and pharmacodynamics of DOACs in large NS cohorts. This could possibly provide a better understanding of free drug exposure and urinary drug losses as specific metrics in individual patients, which could add a personalized bespoke approach to DOAC dosing if readily available and economically viable.[2,7,8]

The rate of thromboembolic events in this study was lower than reported in some other studies.[7] This could relate to an era effect with improvements in the induction of remission in NS in the contemporary era, because of more widespread effective treatments negating the need for anticoagulation for many patients or shortening the duration of exposure. Nonetheless, the morbidity and mortality of thromboembolic events in NS in the short-term can be life altering and even fatal, and despite effective contemporary treatments, residual treatment resistance and delays with remission induction still exist.[9] This

is evident in this study, where a minority of patients in both groups required lengthy periods of exposure to anticoagulation.[1]

The overall bleeding rate in this study was approximately 10% and mostly mucosal in nature. Although the event rate was too low to allow robust statistical comparisons between groups, the rate was 6.9 % in the DOAC group and 13.9% in the VKA/heparin group.[1] Major bleeding occurred in 2 patients in the DOAC group and 3 in the warfarin group. Female sex, age > 75 years, and duration of exposure to anticoagulation appeared to be significant predictors of bleeding; and a more detailed description of the bleeding episodes is presented in the supplementary tables accompanying the article. Arches *et al.*[1] used the HAS BLED score,[1] and though this can be useful to describe the bleeding risk profile of the cohort, tools such as this should be used with caution in relation to deciding on anticoagulation in NS because the predictive model was developed in a patient population that differs significantly from that of NS.

Clinical equipoise exists about the optimal therapeutic strategy for anticoagulation in NS and though an adequately powered multicenter pragmatic randomized trial is desired by the community, it may not be achieved. Until such a study is undertaken, multicenter retrospective cohort studies from densely populated regions such as reported by Arches *et al.*[1] in this issue of *KI Reports*[1] are likely to the best available evidence. In the absence of aspirational randomized evidence, Arches *et al.*[1] adds further cautious optimism for the safety and efficacy of DOACs in NS and contributes significantly to this field.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Arches C, Jalal-Eddine A, Titeca-Beauport D, et al. Safety and efficacy of oral direct factor Xa inhibitors in patients with nephrotic syndrome: results from a national retrospective study. *Kidney Int Rep*. 2025;10:1188–1195.
2. Sexton DJ, de Freitas DG, Little MA, et al. Direct-acting oral anticoagulants as prophylaxis against thromboembolism in the nephrotic syndrome. *Kidney Int Rep*. 2018;3:784–793. https://doi.org/10.1016/j.ekir.2018.02.010
3. Gordon-Cappitelli J, Choi MJ. Prophylactic anticoagulation in adult patients with nephrotic syndrome. *Clin J Am Soc Nephrol*. 2020;15:123–125. https://doi.org/10.2215/CJN.05250419
4. UNC School of Medicine. Prophylactic anticoagulation in patients with membranous nephropathy: a decision analysis. Accessed March 13, 2025. https://www.med.unc.edu/gntools/bleedrisk.html
5. Dupree LH, Reddy P. Use of Rivaroxaban in a patient with history of nephrotic syndrome and hypercoagulability. *Ann Pharmacother*. 2014;48:1655–1658. https://doi.org/10.1177/1060028014549349
6. Sasaki Y, Raita Y, Uehara G, Higa Y, Miyasato H. Carotid thromboembolism associated with nephrotic syndrome treated with dabigatran. *Case Rep Nephrol Urol*. 2014;4:42–52. https://doi.org/10.1159/000362162
7. Derebail VK, Zhu J, Crawford ML, et al. Pharmacokinetics and pharmacodynamics of Apixaban in nephrotic syndrome: findings from a Phase 1a trial. *Am J Kidney Dis*. 2023;81:373–376. https://doi.org/10.1053/j.ajkd.2022.09.011
8. Zhang L, Zhang H, Zhang J, Tian H, Liang J, Liu Z. Rivaroxaban for the treatment of venous thromboembolism in patients with nephrotic syndrome and low AT-III: a pilot study. *Exp Ther Med*. 2018;15:739–744. https://doi.org/10.3892/etm.2017.5471
9. Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med*. 2019;381:36–46. https://doi.org/10.1056/NEJMoa1814427