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Anticoagulation for the Prevention of Thrombotic Events in Nephrotic Syndrome

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INTRODUCTION

Nephrotic syndrome (NS) predisposes to venous thromboembolic events with membranous nephropathy carrying the highest risk.[1] Clinicians caring for patients with NS must balance the benefits of anticoagulation against potential harms, primarily bleeding. The management of venous thromboembolic events risk is complicated by little quality data examining anticoagulation for thromboprophylaxis in NS. A well-conducted, randomized controlled trial could inform which patients might benefit most from anticoagulation and the optimal agents. The design of such a trial would require investment from patients and treating providers because there would need to be extensive collaboration and multicenter enrolment given the rarity of NS and thrombosis events in NS.

We conducted a multinational survey of nephrologists to evaluate the current landscape of real-world practice of thrombosis prevention in NS and identify areas of clinical equipoise. Our results could inform future clinical trial design examining safety and efficacy of anticoagulation for thromboprophylaxis in NS. The final survey, email script, and survey methods are described in Supplementary Material.

RESULTS

The majority of our 380 respondents were adult nephrologists (87%) and had hospital-based academic practices (71%). Respondents were largely from the United States (43%) or Canada (31%), and most respondents had >10 years of experience in clinical practice (Table 1). The decision to prescribe anticoagulants was based on clinical factors for 87% of respondents, including NS type, degree of hypoalbuminemia, and bleeding risk. Of the respondents, 64% felt confident about prescribing anticoagulants for a patient with NS (Supplementary Table S1). When presented with a hypothetical NS case with low-bleeding risk, 13% stated they would never use anticoagulation agents. Most respondents

Table 1. Demographic characteristics of survey respondents

Characteristics	*N* = 380 (%)
Primary patient population of practice	
Adult	331 (87.1)
Pediatric	49 (12.9)
Primary location of clinical practice	
Hospital, academic tertiary care, university-affiliated	268 (70.5)
Hospital, non-university affiliated	52 (13.7)
Community clinic private practice	51 (13.4)
Other	9 (2.4)
Country of practice	
United States	163 (42.9)
Canada	116 (30.5)
Australia	44 (11.6)
Other[a]	56 (14.7)
Years since independent practice	
Still in training	23 (6.1)
<5 yr	69 (18.2)
5–10 yr	55 (14.5)
>10–20 yr	113 (29.7)
>20 yr	120 (31.6)
Number of patients seen with nephrotic syndrome in last 12 mo	
<10	161 (42.4)
10–20	140 (36.8)
>20	79 (20.8)
Number of times considered starting anticoagulation for nephrotic syndrome in last 5 yr	
<5	171 (45.0)
5–10	116 (30.5)
>10	93 (24.5)

[a]Includes the following as noted by respondents: Africa (2), Albania (2), Argentina (2), Austria (2), Belgium (1), Brazil (1), Chile (1), Europe (4), Ghana (1), Honduras (1), India (4), Iran (1), Ireland (1), Israel (2), Italy (1), Kenya (3), Middle-East (1), Morocco (1), Nepal (1), Nigeria (1), Oman (1), Pakistan (3), Panama (1), Philippines (2), Punjab (1), Qatar (1), Romania (1), Saudi Arabia (2), South Korea (1), Spain (4), Taiwan (1), United Arab Emirates (2), Ukraine (1).

(70%) based their decision on clinical factors, 7% always prescribed a usual anticoagulant, and 9% would use aspirin. Among the 70% using clinical factors for decision-making, 66% would consider anticoagulation for primary glomerular diseases other than membranous nephropathy. The mean (SD) level of hypoalbuminemia below which anticoagulation would be recommended was 22 (3.5) g/l. The level of proteinuria was considered by 43% of respondents when deciding to prescribe anticoagulants. The mean (SD) level of proteinuria prompting recommendation of anticoagulation was 7.4 (3.2) g/d (Supplementary Table S2). Among anticoagulants, direct oral anticoagulants (DOACs) were most selected (49% of respondents: 30% prophylactic dose, 19% therapeutic dose), followed by warfarin (25% of respondents: 20% INR target 2–3, 5% INR target 1.5–2.5), then low-molecular weight heparin (12% of respondents: 9% prophylactic dose and 3% therapeutic dose) (Figure 1). DOACs were most frequently chosen among the 27 respondents who would choose anticoagulation irrespective of clinical factors and among the 237 respondents who received anticoagulants based on clinical factors (Supplementary Figure S1). The majority of respondents agreed that a randomized controlled trial is needed to address efficacy and safety of anticoagulation in NS (Supplementary Table S3).

DISCUSSION

This survey of nephrologists provides real-world insights into anticoagulation practices for thromboprophylaxis in NS patients. Most respondents consider anticoagulation, with two-thirds feeling confident in their decision making. DOACs are the most frequently chosen anticoagulants. Patient clinical factors play an important role in clinicians' decisions. The overwhelming majority of respondents agreed that a trial is needed.

Our survey indicates hypoalbuminemia as an important factor guiding anticoagulation decisions, and this is consistent with the observed thrombotic risk with hypoalbuminemia demonstrated in large cohort studies.[2,3] The serum albumin threshold for recommending anticoagulation in a low-bleeding risk setting (mean 22 g/l) was lower than the risk level suggested by observational patient registries (28 g/l)[3] and by 2021 Kidney Disease Improving Global Outcomes guidelines (25 g/l).[4] This lower threshold may reflect greater uncertainty among respondents on the risk-benefit ratio of anticoagulation, requiring higher perceived thrombotic risk.

DOACs were the most popular anticoagulants among nephrologists, chosen twice as commonly as warfarin. This is the preference despite Kidney Disease Improving Global Outcomes guidelines suggesting warfarin or low-molecular weight heparin be used for thrombosis prevention in NS, noting further studies of DOACs are needed to support their use for this indication.[4] The choice of DOACs probably reflects growing comfort over warfarin in patients with kidney disease. DOACs for atrial fibrillation in patients with more advanced chronic kidney disease and even in end-stage kidney disease has been shown to be largely safe and effective.[S1–S5] The lack of needed therapeutic monitoring, fewer drug interactions, and importance placed on patient preferences seen in our survey may also account for DOAC preference. We cannot be certain of these drivers for DOAC preference because we did not ask specific justifications for anticoagulant choice in our survey.

The efficacy and safety of DOACs in patients with NS remains clinically uncertain due to physiologic alterations that occur in NS. Rivaroxaban and apixaban are highly protein-bound in circulation. With hypoalbuminemia and urinary protein losses, possible altered pharmacokinetics and pharmacodynamics must

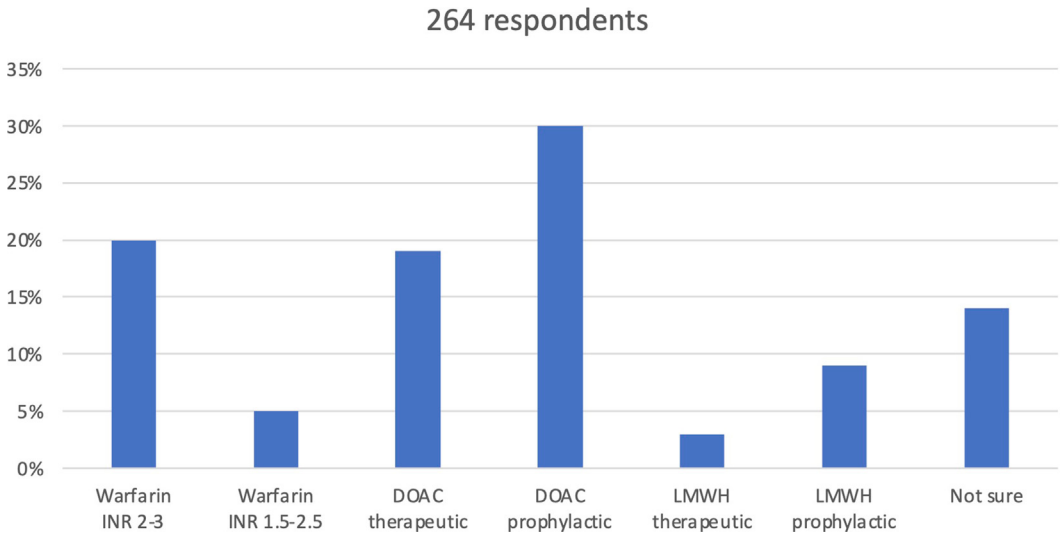

Figure 1. Choice of anticoagulant and dose in nephrotic syndrome, when a decision is made to anticoagulate. DOAC, direct oral anticoagulant; LMWH, low-molecular weight heparin.

be considered. Greater bleeding risk could occur due to excess free circulating DOAC secondary to hypoalbuminemia. Conversely, patients could experience decreased therapeutic effect due to increased renal excretion of protein-bound DOAC. In a phase 1a study of 8 patients with NS, greater free apixaban exposure, higher clearance of total apixaban and slower clearance of free apixaban was observed after a single 10 mg dose of apixaban compared to healthy controls.[5] These changes were more pronounced in patients with more severe NS. Whether this would translate to greater bleeding risk in patients with NS treated with apixaban is still unclear. Pharmacokinetic and pharmacodynamic multidose studies of apixaban in NS are awaited to help inform its use in NS (NCT04278729, ACTRN1261900 1193167p).

A randomized controlled trial examining thrombosis prevention in NS is fraught with many challenges. NS is rare, and thrombosis in NS is even rarer. Venous thromboembolic events may present before or coincident with the diagnosis of NS such that $<$10% of patients develop incident clinically evident thrombosis that is potentially preventable.[6,7] Most survey respondents demonstrated interest in a potential trial. Nearly 40% of the respondents stated that they were not confident whether to prescribe anticoagulants, demonstrating uncertainty within the community. Given responses to our survey and the Kidney Disease Improving Global Outcomes recommendations, nephrologists may be reluctant to enroll patients with more severe levels of hypoalbuminemia (i.e., $<$20–25 g/l) into a placebo-controlled trial. A trial would also need to consider the popularity and convenience of DOACs and patient preferences. Study designs could utilize treatment arms based on albumin level; however, complexity and sample size may be greater, thus reducing feasibility. A study assessing bleeding risks while examining circulating thrombotic biomarkers as surrogates of anticoagulant efficacy may be more realistic but would require validation.

Our survey results have limitations. The overall response rate to our survey is unknown. Although it was intended for nephrology clinical providers, survey distribution occurred via email lists of Nephrology Societies that included nonclinicians. Our survey sought opinions on anticoagulation solely in a low-bleeding risk setting as was specified in the clinical vignette. This was done to reflect current guidelines, which generally recommend prophylactic anticoagulation only in these patients.[4,8] We do not address bleeding risk assessment nor clinicians' perceptions of bleeding risk in patients with NS. Regarding additional clinical factors that might influence the choice to prescribe anticoagulants, we did not ask specific questions about age, obesity, immobility, or smoking history, because it is unclear whether these factors influence venous thromboembolic event risk in NS.[3,9] The respondents were dominated by nephrologists from Canada and the United States, limiting generalizability because anticoagulant availability may vary globally. Finally, the survey was based on a fictional clinical vignette and participants' responses may not reflect their real-life practice.

Clinical factors, particularly severity of hypoalbuminemia, play a major role in nephrologists' decisions to offer anticoagulation for thromboprophylaxis in NS. There is variability in anticoagulant preference; however, DOACs are popular despite little published data confirming their efficacy and safety in NS. Studies examining pharmacokinetics and pharmacodynamics of DOACs in NS are still warranted, given their protein-

binding characteristics. Substantial uncertainty exists around decision-making for thromboprophylaxis in NS, creating similar uncertainty for clinical equipoise about appropriate control arms for clinical trials. Although a randomized controlled trial to examine safety and efficacy of thromboprophylaxis in NS would be beneficial, conducting this would likely require a large, multicenter, international, concerted effort and remain challenging to power sufficiently. Identifying surrogate markers of clinical efficacy may offer alternative approaches to address these issues.

DISCLOSURE

MC reports grants from BMS, Leo Pharma, and Pfizer; and personal fees from BMS, Leo Pharma, Bayer, Pfizer, Servier, Valeo, and Sanofi. BB has received honorarium from Servier and AstraZeneca. DWJ has received consultancy fees, research grants, speaker's honoraria, and travel sponsorships from Baxter Healthcare and Fresenius Medical Care; consultancy fees from Astra Zeneca, Bayer, and AWAK; speaker's honoraria from ONO and Boehringer Ingelheim & Lilly; and travel sponsorships from Ono and Amgen. He is a current recipient of an Australian National Health and Medical Research Council Leadership Investigator Grant. VJ has received grant funding consultancy fees and honoraria from Bayer, AstraZeneca, Boehringer Ingelheim, NephroPlus, Biocryst, Vera, Visterra, Otsuka, Chinook, and Zydus Cadilla. PHN has received consultancy fees from GSK, Q32, and Novartis. VKD has received personal fees from Amgen, Travere Therapeutics, Pfizer, Bayer, Forma Therapeutics, and royalties from UpToDate. All the other authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

DMA and VKD designed the first survey iteration. All authors edited the survey and contributed to the final version. DMA performed statistical analyses. DMA and VKD interpreted the findings and DMA wrote the first manuscript draft. All the authors revised the manuscript critically for important intellectual content and approved the final version submitted for publication.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Reference.

Supplementary Methods.

Figure S1. Choice of anticoagulant in nephrotic syndrome, when a decision is made to anticoagulated.

Table S1. Uncertainty of decision to use anticoagulants for thrombosis prophylaxis in nephrotic syndrome.

Table S2. Prophylactic anticoagulation management in nephrotic syndrome.

Table S3. Need for a clinical trial of prophylactic anticoagulation in nephrotic syndrome.

Final survey and invitation email script.

REFERENCES

1. Barbour SJ, Greenwald A, Djurdjev O, et al. Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis. *Kidney Int*. 2012;81:190–195. https://doi.org/10.1038/ki.2011.312
2. Gyamlani G, Molnar MZ, Lu JL, Sumida K, Kalantar-Zadeh K, Kovesdy CP. Association of serum albumin level and venous thromboembolic events in a large cohort of patients with nephrotic syndrome. *Nephrol Dial Transplant*. 2017;32:157–164. https://doi.org/10.1093/NDT/GFW227
3. Lionaki S, Derebail VK, Hogan SL, et al. Venous thromboembolism in patients with membranous nephropathy. *Clin J Am Soc Nephrol*. 2012;7:43–51. https://doi.org/10.2215/CJN.04250511
4. Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100:S1–S276. https://doi.org/10.1016/J.KINT.2021.05.021
5. 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
6. Rankin AJ, McQuarrie EP, Fox JG, Geddes CC, MacKinnon B, Scottish Renal Biopsy Registry. Venous thromboembolism in primary nephrotic syndrome - is the risk high enough to justify prophylactic anticoagulation? *Nephron*. 2017;135:39–45. https://doi.org/10.1159/000448628
7. Kumar S, Chapagain A, Nitsch D, Yaqoob MM. Proteinuria and hypoalbuminemia are risk factors for thromboembolic events in patients with idiopathic membranous nephropathy: an observational study. *BMC Nephrol*. 2012;13:107. https://doi.org/10.1186/1471-2369-13-107
8. Lee T, Biddle AK, Lionaki S, et al. Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy. *Kidney Int*. 2014;85:1412–1420. https://doi.org/10.1038/KI.2013.476
9. Mahmoodi BK, Ten Kate MK, Waanders F, et al. High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study. *Circulation*. 2008;117:224–230. https://doi.org/10.1161/CIRCULATIONAHA.107.716951