Clinical Kidney Journal, 2025, vol. 18, no. 5, sfaf104

https://doi.org/10.1093/ckj/sfaf104
Advance Access Publication Date: 15 April 2025
Original Article

ORIGINAL ARTICLE

Prophylactic anticoagulation in patients with nephrotic syndrome in the Cure Glomerulonephropathy (CureGN) cohort

Blanca Tarragón[1], Heedeok Han[1], Mariela Navarro-Torres[1], Pietro Canetta[1], Benjamin Wooden[1], Vimal K. Derebail[2], Dorey Glenn[2], Amy Mottl[2], David Massicotte-Azarniouch[2], Bryce Kerlin[3,4], Michelle Hladunewich[5], Gaia Coppock[6], Michelle Rheault[7], Laura H. Mariani[8] and Andrew Bomback[1]

[1]Department of Medicine, Division of Nephrology, Columbia University Irving Medical Center, New York, NY, USA, [2]UNC Kidney Center, Division of Nephrology and Hypertension, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [3]Department of Pediatrics, Ohio State University College of Medicine, Columbus, OH, USA, [4]Center for Clinical and Translational Research, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH, USA, [5]Division of Nephrology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada, [6]Department of Medicine, Renal Electrolyte and Hypertension Division, University of Pennsylvania, Philadelphia, PA, USA, [7]Division of Nephrology, Department of Pediatrics, University of Minnesota Masonic Children's Hospital, MN, USA and [8]Department of Internal Medicine, Division of Nephrology, University of Michigan, Ann Arbor, MI, USA

Correspondence to: Blanca Tarragón; E-mail: blancatarragon@gmail.com

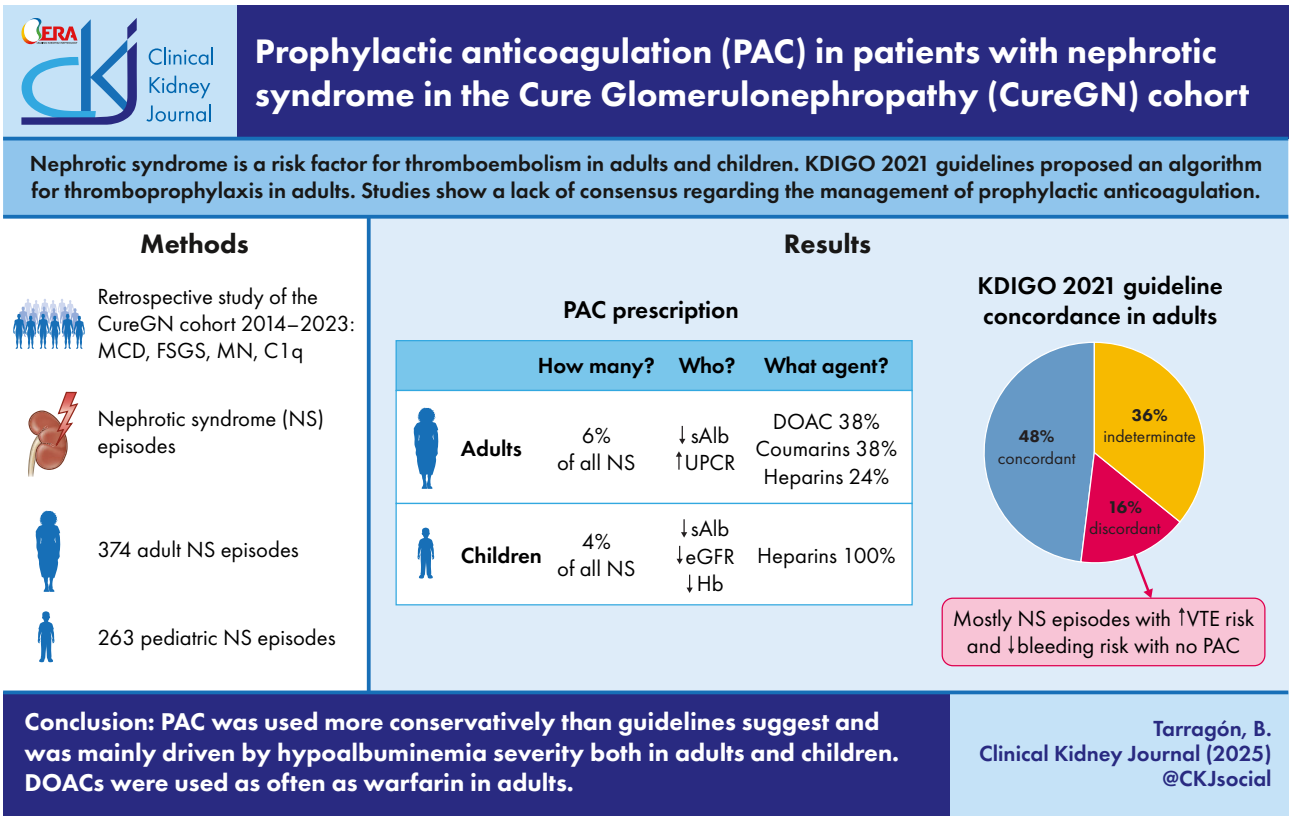
ABSTRACT

Background. Adult and paediatric patients with nephrotic syndrome (NS) due to different glomerular diseases are at a higher risk of thromboembolic events than the general population, but the use of prophylactic anticoagulation (PAC) among them has not been well described. Although the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines offer an algorithm to guide the management of PAC, the degree of implementation in practice is unknown.
Methods. We evaluated thromboprophylaxis management in patients with NS secondary to membranous nephropathy, focal segmental glomerulosclerosis, minimal change disease and C1q nephropathy enrolled in the Cure Glomerulonephropathy (CureGN) cohort study (diagnosed 2010–2023) and assessed the concordance or discordance with the 2021 KDIGO guidelines practice points in adults. We also analysed thrombotic and bleeding events.
Results. Among 374 adult and 263 paediatric NS episodes, PAC was prescribed in 21 (6%) and 11 (4%) episodes, respectively. In adults, PAC prescription was associated with a history of prior thrombosis, lower serum albumin and higher proteinuria, with coumarins and direct oral anticoagulants (DOACs) being equally the most prescribed agents. In adults, anticoagulation management was concordant with guidelines in 180 (48%) episodes, discordant in 59 (16%) and indeterminate in 135 (36%). Most (92%) guideline-discordant episodes were cases with a high thrombotic risk and low bleeding risk where PAC was not prescribed. In children, PAC prescription was associated with lower albuminaemia and worse kidney function, with heparins being the only agent used. Thrombotic events occurred during 5 (1.3%) and 4 (1.5%) of all adult and paediatric NS episodes, respectively.

Received: 17.9.2024; Editorial decision: 3.3.2025

Conclusions. PAC was used more conservatively than guidelines suggest and was mainly driven by hypoalbuminaemia severity in both adults and children. Although not included in the guidelines practice points, DOACs were used as often as coumarins in adults.

GRAPHICAL ABSTRACT



Keywords: anticoagulation, DOAC, nephrotic syndrome, paediatric, thrombosis

KEY LEARNING POINTS

What was known:

- Nephrotic syndrome is a risk factor for thromboembolic events in both the adult and paediatric population, especially when serum albumin is <2–2.5 g/dl.
- The 2021 Kidney Disease: Improving Global Outcomes (KDIGO) 2021 guidelines proposed a unified thromboprophylaxis algorithm, although acknowledging insufficient evidence to support widespread use among diverse clinical scenarios.
- Current literature shows a lack of consensus regarding prophylactic anticoagulation (PAC) regimens.

This study adds:

- We offer evidence on how PAC is used in real clinical practice in a large, multicentre, international cohort.
- We demonstrate how PAC has been used more conservatively than the 2021 KDIGO guidelines suggest, without a significant impact on thrombotic events.

Potential impact:

- Practice points on thromboprophylaxis in the KDIGO guidelines might need to be updated with modern studies including patients with various glomerulopathies and considering the use of direct oral anticoagulants for prophylaxis in this setting.
- More evidence is needed on thromboprophylaxis management in paediatric nephrotic syndrome.

INTRODUCTION

Patients with nephrotic syndrome (NS) are at higher risk of thromboembolic events than the general population, especially during the first 6 months after diagnosis [1–3]. The main primary glomerulopathies that cause NS are focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN) and minimal change disease (MCD), with MN being associated with the greatest thrombotic risk in adults [2, 4]. Among the identified risk factors for venous thromboembolic events (VTEs) in NS, hypoalbuminaemia is one of the key determinants [2, 5–10]. Although prophylactic anticoagulation (PAC) can be used to reduce the incidence, morbidity and mortality of thrombosis, there is a lack of consensus regarding the criteria for PAC initiation and the agent of choice [3, 8, 11, 12].

The 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines include a practice point with an algorithm for prevention of VTEs in adults with NS, basing the use of PAC on albuminaemia and bleeding risk [13]. There is limited evidence backing these recommendations and studies published prior to and after these guidelines demonstrate how inconsistently thromboprophylaxis management is applied in NS [14–20].

Heparin and coumarin agents have traditionally been used for thromboprophylaxis in NS and are the drugs of choice in KDIGO guidelines. However, recent retrospective studies suggest a role for direct oral anticoagulants (DOACs) in this setting [17–19].

The aim of this study is to describe PAC prescription patterns in adults and children in the Cure Glomerulonephropathy (CureGN) cohort and to assess the concordance with the practice points in the 2021 KDIGO guidelines.

MATERIALS AND METHODS

Study population

We retrospectively analysed data extracted from the CureGN cohort. CureGN is an ongoing observational prospective cohort study of adults and children with MCD, FSGS, immunoglobulin A nephropathy (IgAN) and MN diagnosed by kidney biopsy within the 5 years before study enrolment [21]; it also includes patients with C1q nephropathy, which is considered a variant of MCD and FSGS [22, 23]. Patients were excluded from the CureGN cohort if they had end-stage kidney disease at screening, prior organ or haematopoietic stem cell transplant, malignancy, hepatitis B or C, human immunodeficiency virus infection, diabetes mellitus or systemic lupus erythematosus at biopsy. Clinical data were collected approximately every 4 months at study visits. Demographics, clinical characteristics and treatments were collected at enrolment and prospectively. Institutional review board approval was obtained for each enrolling site in agreement with the Declaration of Helsinki.

All children and adults with a diagnosis of MN, FSGS or MCD (including C1q) enrolled in the CureGN cohort by 13 April 2023 were considered for this analysis of PAC management. We excluded patients without NS during follow-up and those with a pre-enrolment history of stroke, arrhythmia or valvular disease that could justify the use of anticoagulation. We also excluded NS episodes with concurrent anticoagulation at the beginning of the episode, since we could not attribute its use to prophylaxis for NS. The follow-up period refers to time since CureGN enrolment.

Data collection and definitions

NS episode

To temporally attribute PAC prescription to NS, we defined NS episodes as start and stop dates. One patient could have multiple episodes. The start of an NS episode was defined as a visit from up to 90 days before enrolment in CureGN where the urine protein:creatinine ratio (UPCR) was ≥3 g/g and serum albumin (sAlb) was ≤3 g/dl and where no visit in the previous 365 days met those criteria. The end of an NS episode was the first visit with either a UPCR <3 g/g or sAlb >3 g/dl with at least one visit with NS criteria in the previous 365 days. Lab values obtained within a 90-day period could be considered as the same visit (the latest visit). For the paediatric population, the UPCR threshold was 2 g/g, according to the KDIGO guidelines [13].

Medications

Medication start and stop dates were collected at enrolment in CureGN, including those received before enrolment, and the medication list was updated at every study visit. Anticoagulants included unfractionated heparin, enoxaparin, dalteparin, tinzaparin, fondaparinux (grouped as 'heparins'), apixaban, edoxaban, dabigatran, rivaroxaban (grouped as 'DOACs') and warfarin and acenocumarol (grouped as 'coumarins'). Antiplatelet medications included acetylsalicylic acid (ASA), prasugrel, ticagrelor and dipyridamole.

PAC was defined as any prescription of an anticoagulant started during an NS episode and before a thrombotic event if there was one.

VTE and bleeding risk assessment

VTE risk was assessed using the sAlb nadir of each episode and classified as high (sAlb <2 g/dl), intermediate (sAlb 2–2.5 g/dl) or low (sAlb >2.5 g/dl), according to the thresholds applied in the KDIGO guidelines and described in the literature [13, 24].

We applied the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score using parameters at the start of the episode to stratify the bleeding risk into low (<4 points), intermediate (4 points) or high (>4 points) [25]. Items with a missing value were assigned zero points.

Demographic, clinical and laboratory measures

Patients <18 years of age at screening were classified as paediatric. Race, ethnicity and sex were self-reported. Clinical parameters were captured at the beginning of each NS episode. Estimated glomerular filtration rate (eGFR) was calculated using the race-agnostic Chronic Kidney Disease Epidemiology Collaboration formula [26] in patients ≥25 years of age and the U25 formula [27] including age and sex in patients <25 years of age.

Thrombotic events included deep venous thrombosis (DVT), pulmonary embolism (PE), renal vein thrombosis (RVT) and 'other thrombosis', which included arterial thrombotic events. Bleeding episodes refer to gastrointestinal (GI) bleeding requiring hospitalization, the only haemorrhagic event available in our CureGN dataset.

Anticoagulation management and concordance with KDIGO guidelines

The 2021 KDIGO guidelines for glomerular diseases [13] proposed an algorithm adapted from Hofstra and Wetzels [28],

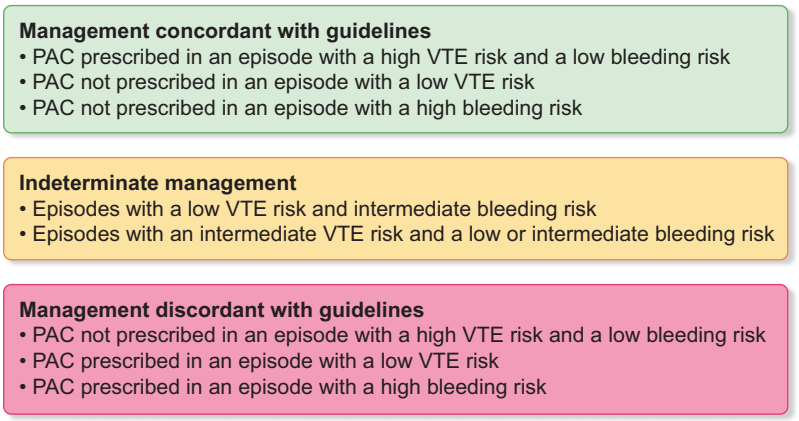


Figure 1: Definitions of anticoagulation management.

conceived for patients with MN, and suggested its use for all adult patients with NS. Patients with sAlb <2–2.5 g/dl are considered as having a high VTE risk and should receive anticoagulants if their bleeding risk is low or ASA if their bleeding risk is high. They use GNTools for thrombosis and bleeding risk assessment [29]; bleeding risk in this tool uses the ATRIA score [25].

In this study, anticoagulation management in adults was considered guideline concordant when PAC was prescribed in an episode with high VTE risk and low bleeding risk, when PAC was not prescribed in an episode with low VTE risk and when PAC was not prescribed in an episode with high bleeding risk. Management was considered guideline discordant when PAC was not prescribed in an episode with high VTE risk and low bleeding risk and when PAC was prescribed in an episode with low VTE risk or high bleeding risk. In the remaining scenarios, management was classified as indeterminate (Fig. 1).

Statistical analysis

Categorical variables were expressed as number and percentage and continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the sample distribution. Fisher's exact test and *t*-test were used to compare categorical and continuous variables, respectively. Missing data are reported individually in each table. Statistical analyses were performed using Stata 14.1 (StataCorp, College Station, TX, USA).

RESULTS

Patient and NS episode characteristics

A total of 295 adults and 204 children were included in this study (Fig. 2, Table 1, Supplementary Table 1). The mean age was 47 ± 17 years and 9 ± 5 years and 55% and 56% were male in the adult and paediatric populations, respectively. Both populations were predominantly White and non-Hispanic and had a mean follow-up period of 52 months for the adults and 60 months for the children.

We identified 374 adult NS episodes. Ninety-three (25%) had a high VTE risk (sAlb nadir of 1.6 ± 0.3 g/dl), 127 (34%) had an intermediate VTE risk (sAlb nadir of 2.3 ± 0.2 g/dl) and 154 (41%) had a low VTE risk (sAlb nadir of 2.8 ± 0.1 g/dl). In the paediatric population, 263 NS episodes were identified, with a sAlb nadir of 2.0 ± 0.6 g/dl.

Anticoagulation prescription

PAC was prescribed in 21 (6%) of the 374 adult episodes (Table 2): 11 (12%) of the high VTE risk episodes, 8 (6%) of the intermediate VTE risk episodes and 2 (1%) of the low VTE risk episodes. The mean time from NS episode start to PAC prescription was 96 ± 121 days. Five (24%) patients were also receiving antiplatelet therapies. PAC prescription was associated with a history of previous thrombosis (33% versus 5%; $P < .001$), lower initial sAlb (1.9 versus 2.4 g/dl; $P < .001$), lower sAlb nadir (1.9 versus 2.4 g/dl; $P < .001$) and higher proteinuria (UPCR 11.0 versus 8.5 g/g; $P = .019$).

Coumarins and DOACs were equally prescribed ($n = 8$), with heparins being less frequently used ($n = 5$). No factors were associated with the prescription of DOACs versus other agents (Supplementary Table 2). The DOACs used were apixaban ($n = 7$) and rivaroxaban ($n = 1$).

PAC was prescribed in 11 of the 263 paediatric episodes (4%) (Supplementary Table 3), at a mean time of 211 ± 110 days since the start of the NS episode. Only heparins were prescribed. PAC use was associated with a lower sAlb nadir (1.6 versus 2.0 g/dl; $P = .028$), worse kidney function (eGFR 75 versus 107 ml/min/1.73 m^2; $P = .028$) and lower haemoglobin (11.3 versus 13.0 g/dl; $P = .005$).

PAC guideline concordance in adult patients

Of the 374 adult NS episodes, anticoagulation management was guideline concordant in 180 (48%), discordant in 59 (16%) and indeterminate in 135 (36%) episodes (Table 3). Most (92%) of the guideline-discordant episodes were cases with high VTE risk and low bleeding risk where PAC was not prescribed (Fig. 3); of note, antiplatelet therapy was more frequently prescribed in the guideline-discordant episodes (12% versus 4%; $P = .048$). Overall, guideline discordance was associated with younger age (39 versus 51 years; $P < .001$), Asian, Black/African American and other races ($P = .002$) and Hispanic ethnicity ($P = .017$). Guideline concordance was associated with higher initial sAlb (2.7 versus 1.8 g/dl; $P < .001$) and sAlb nadir (2.7 versus 1.6 g/dl; $P < .001$), worse kidney function (eGFR 66 versus 83 ml/min/1.73 m^2;

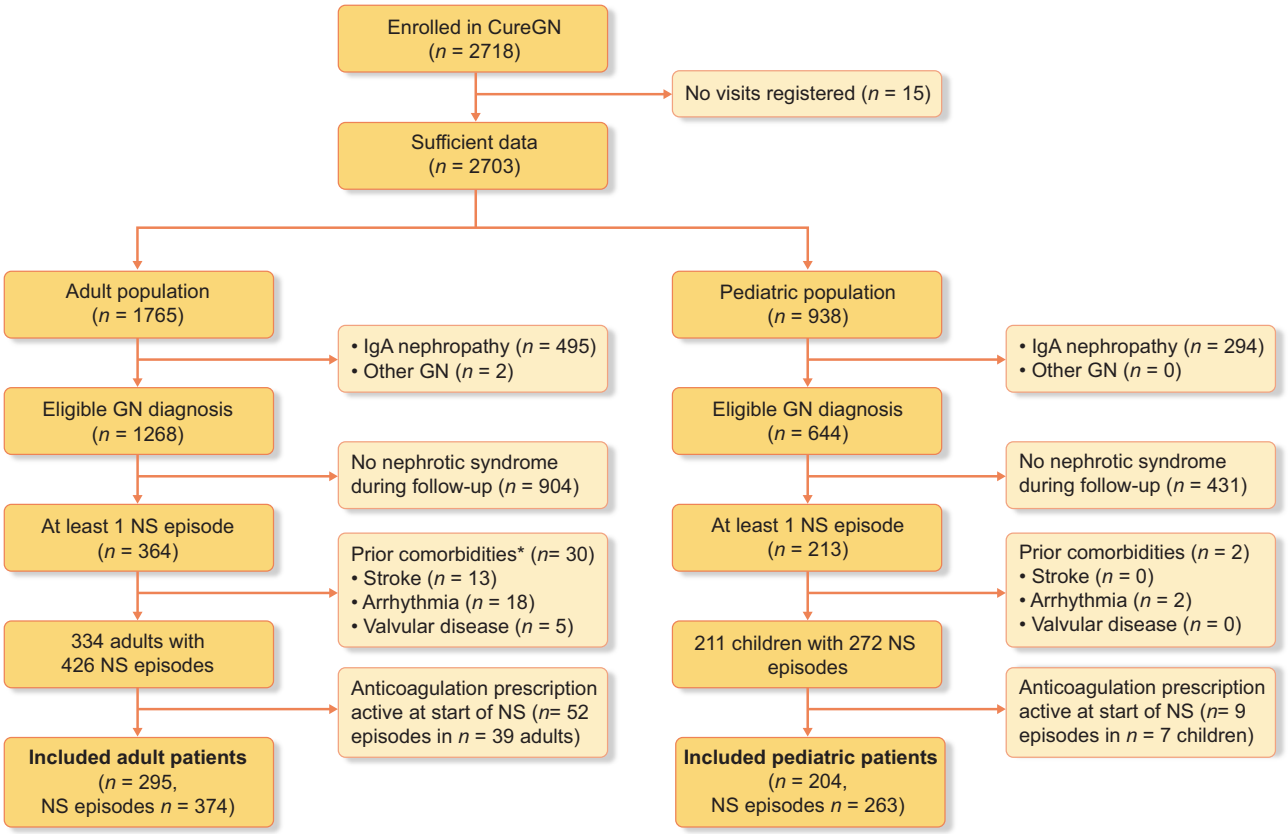


Figure 2: Patient inclusion. *Some patients had more than one comorbidity.

Table 1: Adult patient characteristics.

Parameters	All ($n = 295$)	MN ($n = 148$)	FSGS ($n = 81$)	MCD ($n = 66$)
Age (years), mean ± SD	47 ± 17	51 ± 15	44 ± 16	42 ± 19
Sex, *n* (%)				
Female	133 (45)	55 (37)	38 (47)	40 (60)
Male	162 (55)	93 (63)	43 (53)	26 (40)
Race, *n* (%)				
Asian	21 (7)	15 (10)	1 (1)	5 (8)
Black or African American	52 (18)	27 (18)	12 (15)	13 (19)
White	197 (67)	99 (67)	55 (68)	43 (65)
Other	25 (8)	7 (5)	13 (16)	5 (8)
Ethnicity, *n* (%)				
Hispanic	44 (15)	20 (14)	15 (19)	9 (14)
Non-Hispanic	250 (85)	128 (86)	65 (80)	57 (86)
Not reported	1 (<1)	0	1 (1)	0
Follow-up (months), mean ± SD	52 ± 27	55 ± 26	48 ± 28	53 ± 28
Study visits, *n* (%)	13 (6)	13 (5)	12 (6)	13 (6)
NS episodes, *n*	374	177	108	89
NS episode duration (days), median (IQR)	269 (118–383)	267 (115–365)	239 (119–374)	301 (129–441)

$P < .001$), lower haemoglobin (12.3 versus 13.5; $P < .001$) and hypertension (61% versus 34%; $P < .001$).

Of the 93 episodes with high VTE risk, 62 had low bleeding risk (Fig. 3). Among those, management was mostly guideline discordant, since only 8 (13%) received thromboprophylaxis. PAC prescription was numerically more frequent among patients with a history of previous thrombosis and higher serum creatinine (Supplementary Table 4). Among the 24 patients in this group with MN, only 4 (17%) received PAC, despite 13 of them having additional risk factors for VTE (Supplementary Table 5).

Table 2: Prophylactic anticoagulation prescription in NS episodes in adults (N = 374).

Parameters	PAC (n = 21)	No PAC (n = 353)	P-value
Age (years), mean ± SD	46 ± 15	47 ± 16	.607
Sex, n (%)			.368
Female	7 (33)	160 (45)	
Male	14 (67)	193 (55)	
Race, n (%)			.158
Asian	0	24 (7)	
Black or African American	4 (19)	59 (17)	
White	13 (62)	245 (69)	
Other	4 (19)	25 (7)	
Ethnicity, n (%)			.148
Hispanic	6 (29)	47 (13)	
Non-Hispanic	15 (71)	305 (86)	
Not reported	0	1 (<1)	
Glomerular diagnosis, n (%)			.100
MN	15 (71)	162 (46)	
FSGS	3 (14)	105 (30)	
MCD	3 (14)	86 (24)	
Hypertension, n (%)	9 (43)	201 (57)	.259
Body mass index, mean ± SD	30.0 ± 5.3 (n = 9)	29.6 ± 7.0 (n = 213)	.871
Active smoking, n (%)	2 (22) (n = 9)	45 (16) (n = 290)	.636
Previous thrombosis, n (%)	7 (33)	19 (5)	<.001*
Family clotting disorder, n (%)	2 (10)	36 (10)	1.000
Previous GI bleeding episodes, n (%)	1 (5)	6 (2)	.335
Labs at start of NS			
Serum albumin (g/dl), mean ± SD	1.9 ± 0.5	2.4 ± 0.5	<.001*
Serum albumin nadir (g/dl), mean ± SD	1.9 ± 0.5	2.4 ± 0.5	<.001*
Serum creatinine (mg/dl), mean ± SD	1.5 ± 0.8	1.5 ± 1	.959
eGFR (ml/min/1.73 m^2) , mean ± SD	70 ± 31	70 ± 33	.980
CKD stages 3–5, n (%)	9 (43)	146 (42)	1.000
UPCR (g/g), mean ± SD	11.0 ± 4.9	8.5 ± 4.9	.023*
Haemoglobin (g/dl), mean ± SD	12.8 ± 2.1	12.5 ± 2.1	.568
VTE risk, n (%)			.001*
Low	2 (10)	152 (43)	
Intermediate	8 (38)	119 (34)	
High	11 (52)	82 (23)	
ATRIA score, n (%)			.483
Low	15 (71)	225 (64)	
Intermediate	3 (14)	90 (25)	
High	3 (14)	38 (11)	
Anticoagulation agent[a], n (%)			
Coumarin	8 (38)	–	–
DOAC	8 (38)	–	–
Heparin	5 (24)	–	–
Days from NS to anticoagulation, mean ± SD	96 (121)	–	–
Antiplatelet therapy, n (%)	7 (34)	61 (18)	.079
Active at start of NS	5 (24)	45 (13)	.178
Prescribed during NS	2 (10)	17 (5)	.289
Corticosteroids prescribed during NS, n (%)	11 (52)	113 (32)	.060

[a]One patient was switched from coumarin to DOAC.
*Statistical significance.

Among the 127 episodes with intermediate VTE risk, 79 had low bleeding risk. In this subgroup (Supplementary Table 4), PAC was used in 5 (6%) episodes and was associated with a lower sAlb nadir (2.1 versus 2.3; P = .014) and higher UPCR (13.0 versus 8.0 g/g; P = .017).

Thromboembolic and bleeding events

Thrombotic events occurred during 5 of the 374 adult NS episodes (1.3%) at a median of 70 days (IQR 49–146) since the start of the episode (Supplementary Table 6): 1 RVT, 1 PE, 2 DVTs and 1 episode with both PE and DVT. All were men; 3 with MN and 2 with FSGS. Four had high VTE risk, representing an incidence of 4.3% in that group, and one had intermediate VTE risk. None received PAC despite a low calculated bleeding risk. Another 10 thrombotic events happened outside of an NS episode, at a median of 834 days (IQR 559–959) from the beginning of the episode.

Among the 263 paediatric NS episodes, thromboembolic events were diagnosed in 4 (1.5%) (Supplementary Table 6), all with FSGS, at a median of 21 days (IQR 9–152) after the beginning of the episode: 1 DVT, 1 arterial thrombotic event and 2 episodes with both a PE and a DVT. The median age was 14 years (IQR 11–15), median sAlb nadir was 1.6 g/dl (IQR 0.9–2.2) and

Table 3: Guideline-concordant versus discordant anticoagulation management in adult NS episodes.

Parameters	Guideline concordant ($n = 180$)	Guideline discordant ($n = 59$)	*P*-value
Age (years), mean ± SD	51 ± 17	39 ± 15	<.001*
Sex, *n* (%)			1.000
Female	84 (47)	28 (47)	
Male	96 (53)	31 (53)	
Race, *n* (%)			.002*
Asian	9 (5)	6 (10)	
Black or African American	24 (13)	14 (24)	
White	139 (77)	31 (53)	
Other	8 (5)	8 (13)	
Ethnicity, *n* (%)			.033*
Hispanic	17 (9)	13 (22)	
Non-Hispanic	162 (90)	46 (78)	
Not reported	1 (1)	0 (0)	
Diagnosis, *n* (%)			.157
MN	82 (46)	25 (42)	
FSGS	56 (31)	13 (22)	
MCD	42 (23)	21 (36)	
Hypertension, *n* (%)	109 (61)	20 (34)	<.001*
Body mass index, mean ± SD	28.2 ± 6.4 ($n = 103$)	30.0 ± 7.3 ($n = 33$)	.192
Active smoking, *n* (%)	26 (17) ($n = 153$)	4 (11) ($n = 37$)	.456
Previous thrombosis, *n* (%)	11 (6)	5 (8)	.552
Family clotting disorder, *n* (%)	14 (8) ($n = 179$)	5 (9) ($n = 56$)	.782
Liver cirrhosis, *n* (%)	1 (1)	0	1.000
Previous GI bleeding episodes, *n* (%)	6 (3)	1 (2)	1.000
Labs at start of NS			
Serum albumin (g/dl), mean ± SD	2.7 ± 0.4	1.8 ± 0.5	<.001*
Serum albumin nadir (g/dl), mean ± SD	2.7 ± 0.4	1.6 ± 0.4	<.001*
Serum creatinine (mg/dl), mean ± SD	1.6 ± 1.2	1.1 ± 0.6	.004*
eGFR (ml/min/1.73 m^2), mean ± SD	66 ± 34	83 ± 30	<.001*
CKD stages 3–5, *n* (%)	77 (42)	13 (23)	.008*
UPCR (g/g), mean ± SD	8.0 ± 5.1	10.2 ± 4.7	.006*
Haemoglobin (g/dl), mean ± SD	12.3 ± 2.0	13.5 ± 2.3	<.001*
VTE risk, *n* (%)			<.001*
Low	152 (85)	2 (3)	
Intermediate	13 (7)	2 (3)	
High	15 (8)	55 (94)	
ATRIA score, *n* (%)			<.001*
Low	105 (58)	56 (95)	
Intermediate	37 (21)	0	
High	38 (21)	3 (5)	
Anticoagulation prescribed during NS, *n* (%)			
Yes	8 (4)	5 (8)	
No	172 (96)	54 (92)	
Antiplatelet therapy, *n* (%)			
Active at start of NS	28 (16)	7 (12)	.671
Prescribed during NS	7 (4)	7 (12)	.048*

*Statistical significance.

median UPCR was 11.6 g/g (IQR 8.4–17.0). None of the patients had received PAC. Only two other thrombotic events occurred outside of an NS episode, 655 and 751 days after the start of an NS episode.

GI bleeding episodes were reported in two adult NS episodes and none in the paediatric population. One was in an episode with low bleeding risk after 194 days of coumarins treatment for a DVT. The other was an episode with high bleeding risk after 16 days of PAC with apixaban with concomitant ASA.

DISCUSSION

Our retrospective analysis of a large, multicentre, international cohort showed that thromboprophylaxis management in adults with NS was often not aligned with current guidelines (Fig. 3). This was most frequent among NS episodes with a high VTE risk, where 59% of cases did not follow the practice point. The 2021 KDIGO guidelines suggest a unified algorithm for all patients with NS; as these guidelines are based on data from patients only with MN [8, 10], the authors acknowledge the unknown value for patients with a different glomerulopathy [13]. Furthermore, the proposed bleeding risk assessment tool uses the ATRIA score, only validated for adult patients with atrial fibrillation receiving warfarin; although there are alternative tools, none of them have been validated in the setting of NS [30–32]. Hence this algorithm offers limited applicability to patients with glomerulopathies other than MN, those using other anticoagulants such as heparins or DOACs

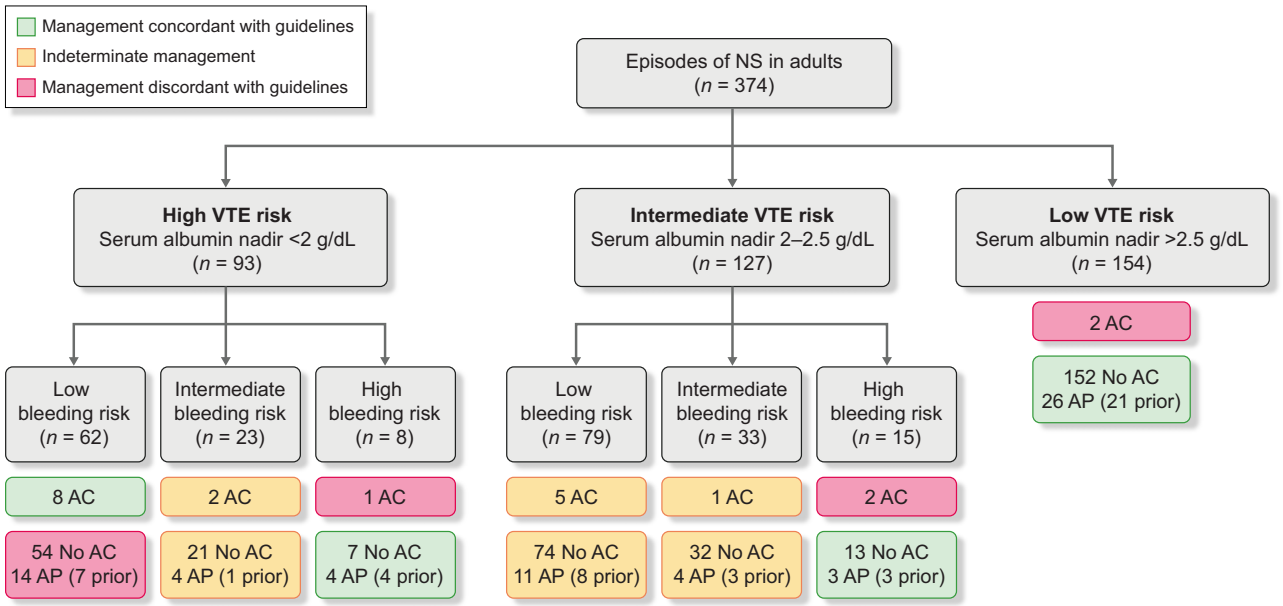


Figure 3: Anticoagulation management in adult NS episodes. AC: anticoagulation; AP: antiplatelet therapy.

and the paediatric population. In accordance with our observations, recent surveys and retrospective studies analysing PAC in this population showcase a heterogenous approach across the globe [14–16, 18–20, 33].

In our study, the majority of guideline-discordant episodes were cases with a high VTE risk and a low bleeding risk where anticoagulants were not prescribed (Fig. 3). Guideline discordance was associated with a younger age, Asian, Black/African American and Other races and Hispanic ethnicity (Table 3). Younger patients being undertreated might be explained by an exaggerated sense of lower thrombotic risk, possibly derived from evidence showing a higher risk in patients >60 years of age [34]. However, race and ethnicity have not been defined as risk factors for thrombosis in NS in the largest available cohorts [2, 8, 12]. The prescription of antiplatelet agents was more frequent among guideline-discordant episodes, possibly demonstrating a preference towards mitigating bleeding risk when managing thromboprophylaxis in patients with NS.

Overall, PAC was only prescribed in 5.6% of the adult NS episodes (Table 2). A lower sAlb and higher UPCR were associated with PAC prescription. This is consistent with a survey report where 93% of healthcare professionals would use sAlb as a determinant for prescribing PAC and 61% would also use the degree of proteinuria [33]. Hypoalbuminaemia has consistently been described as a VTE risk factor in adults, in terms of both severity [3, 8, 12, 35] and duration [11], with a threshold of 2.5–2.8 g/dl in MN and 2–2.5 g/dl in other glomerulopathies [11, 12]. In our cohort, patients receiving PAC had a mean sAlb of 1.9 g/dl, versus a mean sAlb of 2.4 g/dl in those who did not, reflecting the values used in the KDIGO algorithm for categorizing a high VTE risk. Recent publications propose a threshold of sAlb <2.5 g/dl for prescribing PAC in patients with MN and sAlb <2 g/dl for other underlying entities [11, 18, 19].

Proteinuria has also been found as a risk factor in nephrotic patients with VTE, although only in those with MN [35, 36], and both the 2012 and 2021 KDIGO guidelines consider proteinuria >10 g/day as an added factor favouring PAC [13, 37]. Aligned with this, we found that patients receiving PAC had a mean UPCR of 11.0 g/g, significantly higher than those not receiving it (8.5 g/g; $P = .023$).

MN has persistently been identified as the glomerulopathy with the highest thrombotic risk [2, 3, 34], especially those with a positive anti-PLA2R antibody [13, 38–40]. Surprisingly, neither PAC prescription nor guideline concordance were significantly associated with a histology of MN in our study. Specifically, in patients with MN and a low bleeding risk, PAC was only prescribed in 7 of 55 (13%) patients with a sAlb nadir <2.5 g/dl and in 4 of 24 (17%) patients with a sAlb nadir <2.0 g/dl, despite the presence of additional VTE risk factors already described in the 2012 KDIGO guidelines as conditions for considering PAC (Supplementary Table 5).

In our adult cohort, coumarins and DOACs were equally prescribed. In the KDIGO guidelines, DOACs were not recommended, given the paucity of evidence at the time of publication [13]. Since then, retrospective studies of DOACs used as prophylaxis in collectively >70 adult patients with NS of various origins have favourably demonstrated their efficacy and safety, including when compared with warfarin [11, 17–19]. DOACs have already been proven to be safer in terms of bleeding events and all-cause mortality in patients with CKD [41].

Despite the proportion of episodes that did not adhere to guidelines, we observed a VTE rate of only 1.3% in all adult NS episodes, while previous studies have reported rates of 6–36% in MN and 2–12% in other entities, including MCD or FSGS [11, 15, 16, 24]. In our high VTE risk group, the thrombosis rate was 4.3%, resembling that of published studies. Worldwide, thrombosis in NS seems to have diminished over time [24], possibly due to improvements in patient care; this could be accentuated in our cohort, where patients were treated at academic medical centres with access to state-of-the-art care. In any case, an incidence of 4.3% in patients with sAlb <2.5 g/dl could justify PAC, since it parallels the baseline VTE risk of major orthopaedic surgery (4.3%) [42] and high-risk hospitalized medical patients (3.5%) [42], where PAC is recommended.

In our paediatric cohort, PAC was prescribed in 4.2% of NS episodes. Current KDIGO guidelines do not include this

population in the algorithm and suggest consulting haematology for thrombosis and bleeding risk evaluation [13]. In this study, we found that PAC prescription in children was associated with hypoalbuminaemia, worse kidney function and lower haemoglobin, possibly reflecting a selection of cases with more aggressive kidney disease, although none of these have been identified as VTE risk factors in this population [43, 44]. Conversely, previously reported risk factors like proteinuria, age ≥12 years or corticosteroid resistance were not associated with PAC prescription in our population. Heparins were the agent prescribed in all cases of paediatric PAC. DOACs were approved for the treatment and prophylaxis of thrombosis in the paediatric population in 2021, although no studies included children with NS [45, 46].

Our study has several limitations. Many of the included episodes may have preceded the publication of the 2012 KDIGO guidelines, which we used to establish concordant versus discordant management; undisclosed dates of NS episodes precluded us from observing and analysing trends in PAC prescription over time. Our data were not obtained directly from medical records, but from CureGN study visits records, which offered limited data points for defining NS episodes, and interpretation of anticoagulation and antiplatelet prescriptions was based solely on time relative to those episodes. The exclusion of patients receiving anticoagulation at what we defined as the start of the NS may have underestimated the proportion of patients receiving it as prophylaxis. Finally, bleeding events and risk may have been underestimated due to limited availability of haemorrhagic events data.

In conclusion, we found that PAC was used more conservatively than guidelines suggest and was mainly driven by hypoalbuminaemia severity both in adults and children. Anticoagulation also diverged from guidelines in terms of the agent of choice, with DOACs being used as often as coumarins in adults. We also found a lower rate of thrombosis than in previous reports, although still high enough to routinely consider PAC using risk assessment algorithms. Updated, high-quality studies are needed to determine the real thrombotic risk in patients with different causes of NS with the current standard of care and to evaluate the safety and efficacy of PAC, including DOACs, to create evidence-based thromboprophylaxis management algorithms.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

FUNDING

Funding for the CureGN consortium is provided by UM1DK100845, UM1DK100846, UM1DK100876, UM1DK100866 and UM1DK100867 from the National Institute of Diabetes and Digestive and Kidney Disease. Patient recruitment is supported by NephCure. B.T. was supported by the Fundación Alfonso Martín Escudero.

AUTHORS' CONTRIBUTIONS

B.T. was responsible for study conception and design, data collection, analysis and interpretation of results and manuscript preparation. H.H. was responsible for study conception and design, data collection and manuscript preparation. M.N.-T. was responsible for analysis and interpretation of results and manuscript preparation. P.C., B.W., V.K.D., D.G., A.M., D.M.-A., B.K., M.H., G.C., M.R. and L.H.M. were responsible for study conception and design and manuscript preparation. A.B. was responsible for study conception and design, analysis and interpretation of results and manuscript preparation.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

A.B. reports consulting honoraria from Alexion, Apellis, Catalyst, Amgen, Novartis, Silence, Visterra and Q32. M.H. reports involvement in active studies by Chinook Therapeutics and Ionis Pharmaceuticals. V.K.D. reports consulting honoraria for Novartis, Travere, Bayer, Forma Therapeutics (Novo Nordisk), Merck, Amgen and iCell Gene Therapeutics and royalties from UpToDate.

REFERENCES

1. Lee T, Derebail VK, Kshirsagar AV *et al*. Patients with primary membranous nephropathy are at high risk of cardiovascular events. *Kidney Int* 2016;**89**:1111–8. https://doi.org/10.1016/j.kint.2015.12.041
2. Barbour SJ, Greenwald A, Djurdjev O *et al*. Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis. *Kidney Int* 2012;**81**:190–5. https://doi.org/10.1038/ki.2011.312
3. 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**:224–30. https://doi.org/10.1161/CIRCULATIONAHA.107.716951
4. Politano SA, Colbert GB, Hamiduzzaman N. Nephrotic syndrome. *Prim Care* 2020;**47**:597–613. https://doi.org/10.1016/j.pop.2020.08.002
5. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *Clin J Am Soc Nephrol* 2012;**7**:513–20. https://doi.org/10.2215/CJN.10131011
6. Bellomo R, Atkins RC. Membranous nephropathy and thromboembolism: is prophylactic anticoagulation warranted? *Nephron* 1993;**63**:249–54. https://doi.org/10.1159/000187205
7. Bellomo R, Wood C, Wagner I *et al*. Idiopathic membranous nephropathy in an Australian population: the incidence of thromboembolism and its impact on the natural history. *Nephron* 1993;**63**:240–1. https://doi.org/10.1159/000187197
8. 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
9. Waller AP, Troost JP, Parikh SV *et al*. Nephrotic syndrome disease activity is proportional to its associated hypercoagulopathy. *Thromb Res* 2021;**201**:50–9. https://doi.org/10.1016/j.thromres.2021.02.007
10. Lee T, Biddle AK, Lionaki S *et al*. Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy. *Kidney Int* 2014;**85**:1412–20. https://doi.org/10.1038/ki.2013.476

11. Welander F, Holmberg H, Dimény E *et al*. Prophylactic anticoagulants to prevent venous thromboembolism in patients with nephrotic syndrome—a retrospective observational study. *PLoS One* 2021;**16**:e0255009. https://doi.org/10.1371/journal.pone.0255009
12. Gyamlani G, Molnar MZ, Lu JL *et al*. Association of serum albumin level and venous thromboembolic events in a large cohort of patients with nephrotic syndrome. *Nephrol Dial Transplant* 2017;**32**:157–64. https://doi.org/10.1093/ndt/gfw227
13. Rovin BH, Adler SG, Barratt J *et al*. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int* 2021;**100**(4 Suppl):S1–276. https://doi.org/10.1016/j.kint.2021.05.021
14. Medjeral-Thomas N, Ziaj S, Condon M *et al*. Retrospective analysis of a novel regimen for the prevention of venous thromboembolism in nephrotic syndrome. *Clin J Am Soc Nephrol* 2014;**9**:478–83. https://doi.org/10.2215/CJN.07190713
15. Kelddal S, Nykjaer KM, Gregersen JW *et al*. Prophylactic anticoagulation in nephrotic syndrome prevents thromboembolic complications. *BMC Nephrol* 2019;**20**:139. https://doi.org/10.1186/s12882-019-1336-8
16. Matyjek A, Rymarz A, Nowicka Z *et al*. Anti-Xa activity of enoxaparin for prevention of venous thromboembolism in severe nephrotic syndrome—a single center prospective study. *J Clin Med* 2021;**10**:5709. https://doi.org/10.3390/jcm10235709
17. Tijani A, Coons EM, Mizuki B *et al*. Direct oral anticoagulants versus warfarin for venous thromboembolism prophylaxis in patients with nephrotic syndrome: a retrospective cohort study. *Ann Pharmacother* 2022;**57**:787–94. https://doi.org/10.1177/10600280221129348
18. Van Meerhaeghe T, Cez A, Dahan K *et al*. Apixaban prophylactic anticoagulation in patients with nephrotic syndrome. *TH Open* 2022;**6**:e299–303. https://doi.org/10.1055/a-1920-6224
19. Kelddal S, Hvas AM, Grove EL *et al*. Safety and effectiveness of direct oral anticoagulants in patients with nephrotic syndrome: a report of 21 cases. *BMC Nephrol* 2022;**23**:1. https://doi.org/10.1186/s12882-022-02929-x
20. McDonnell T, Hartemink J, Ragy O *et al*. Longitudinal analysis of prophylactic anticoagulation in primary nephrotic syndrome: low incidence of thromboembolic complications. *Glomerular Dis* 2023;**3**:266–74. https://doi.org/10.1159/000534652
21. Mariani LH, Bomback AS, Canetta PA *et al*. CureGN study rationale, design, and methods: establishing a large prospective observational study of glomerular disease. *Am J Kidney Dis* 2019;**73**:218–29. https://doi.org/10.1053/j.ajkd.2018.07.020
22. Devasahayam J, Erode-Singaravelu G, Bhat Z *et al*. C1q nephropathy: the unique underrecognized pathological entity. *Anal Cell Pathol (Amst)* 2015;**2015**:490413. https://doi.org/10.1155/2015/490413
23. Abu-Shahin N, Al-Khader A, Qattan D *et al*. C1q nephropathy among children with nephrotic syndrome: ten-year experience from a pediatric nephrology unit. *Turk J Pediatr* 2018;**60**:14–21. https://doi.org/10.24953/turkjped.2018.01.003
24. Parker K, Ragy O, Hamilton P *et al*. Thromboembolism in nephrotic syndrome: controversies and uncertainties. *Res Pract Thromb Haemost* 2023;**7**:102162. https://doi.org/10.1016/j.rpth.2023.102162
25. Fang MC, Go AS, Chang Y *et al*. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study. *J Am Coll Cardiol* 2011;**58**:395–401. https://doi.org/10.1016/j.jacc.2011.03.031
26. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis* 2010;**55**:622–7. https://doi.org/10.1053/j.ajkd.2010.02.337
27. Pierce CB, Muñoz A, Ng DK *et al*. Age- and sex-dependent clinical equations to estimate glomerular filtration rates in children and young adults with chronic kidney disease. *Kidney Int* 2021;**99**:948–56.
28. Hofstra JM, Wetzels JFM. Should aspirin be used for primary prevention of thrombotic events in patients with membranous nephropathy? *Kidney Int* 2016;**89**:981–3. https://doi.org/10.1016/j.kint.2016.01.019
29. Lee T, Biddle A, Lionaki S *et al*. GNTools. https://www.med.unc.edu/gntools/index.html (9 April 2024, date last accessed).
30. Pisters R, Lane DA, Nieuwlaat R *et al*. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;**138**:1093–100. https://doi.org/10.1378/chest.10-0134
31. Gage BF, Yan Y, Milligan PE *et al*. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J* 2006;**151**:713–9. https://doi.org/10.1016/j.ahj.2005.04.017
32. Aggarwal R, Ruff CT, Virdone S *et al*. Development and validation of the DOAC score: a novel bleeding risk prediction tool for patients with atrial fibrillation on direct-acting oral anticoagulants. *Circulation* 2023;**148**:936–46. https://doi.org/10.1161/CIRCULATIONAHA.123.064556
33. Parker K, Choudhuri S, Lewis P *et al*. UK prescribing practice of anticoagulants in patients with chronic kidney disease: a nephrology and haematology-based survey. *BMC Nephrol* 2023;**24**:9. https://doi.org/10.1186/s12882-022-03041-w
34. Zhang LJ, Zhang Z, Li SJ *et al*. Pulmonary embolism and renal vein thrombosis in patients with nephrotic syndrome: prospective evaluation of prevalence and risk factors with CT. *Radiology* 2014;**273**:897–906. https://doi.org/10.1148/radiol.14140121
35. Kumar S, Chapagain A, Nitsch D *et al*. 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
36. Li SJ, Guo JZ, Zuo K *et al*. Thromboembolic complications in membranous nephropathy patients with nephrotic syndrome–a prospective study. *Thromb Res* 2012;**130**:501–5. https://doi.org/10.1016/j.thromres.2012.04.015
37. Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl (2011)* 2012;**2**:139–274. http://www.kidney-international.org
38. Zhu H, Xu L, Liu X *et al*. Anti-PLA2R antibody measured by ELISA predicts the risk of vein thrombosis in patients with primary membranous nephropathy. *Ren Fail* 2022;**44**:594–600. https://doi.org/10.1080/0886022X.2022.2057861
39. Li J, Wang X, Jiang S *et al*. Serum PLA2R antibody as a predictive biomarker for venous thromboembolism risk in primary membranous nephropathy. *Med Clin (Barc)* 2023;**161**:417–21. https://doi.org/10.1016/j.medcli.2023.06.007
40. Jeyalan V, Stauss M, Liew Kang S *et al*. POS-469 A retrospective analysis of venous thromboembolism incidence amongst patients with membranous nephropathy: a sin-

gle centre experience. Is anti-PLA2R an accessory or an accomplice? *Kidney Int Rep* 2022;**7**(2 Suppl):S209. https://doi.org/10.1016/j.ekir.2022.01.499

41. Makani A, Saba S, Jain SK *et al*. Safety and efficacy of direct oral anticoagulants versus warfarin in patients with chronic kidney disease and atrial fibrillation. *Am J Cardiol* 2020;**125**:210–4. https://doi.org/10.1016/j.amjcard.2019.10.033
42. Nendaz M, Spirk D, Kucher N *et al*. Multicentre validation of the Geneva Risk Score for hospitalised medical patients at risk of venous thromboembolism. Explicit ASsessment of thromboembolic RIsk and prophylaxis for medical PATients in SwitzErland (ESTIMATE). *Thromb Haemost* 2014;**111**:531–8. https://doi.org/10.1160/TH13-05-0427
43. Kerlin BA, Haworth K, Smoyer WE. Venous thromboembolism in pediatric nephrotic syndrome. *Pediatr Nephrol* 2014;**29**:989–97. https://doi.org/10.1007/s00467-013-2525-5
44. Dadgar K, Xue Y, Chung J *et al*. Childhood nephrotic syndrome and the clinical profile of thromboembolism: a systematic review and meta-analysis. *Pediatr Res* 2023;**93**:1463–9. https://doi.org/10.1038/s41390-022-02302-6
45. Halton J, Brandão LR, Luciani M *et al*. Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY): a randomised, controlled, open-label, phase 2b/3, non-inferiority trial. *Lancet Haematol* 2021;**8**:e22–33. https://doi.org/10.1016/S2352-3026(20)30368-9
46. Male C, Lensing AWA, Palumbo JS *et al*. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. *Lancet Haematol* 2020;**7**:e18–27. https://doi.org/10.1016/S2352-3026(19)30219-4

Received: 17.9.2024; Editorial decision: 3.3.2025