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A Systematic Review of Prophylactic Anticoagulation in Nephrotic Syndrome

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Introduction: Nephrotic syndrome is associated with an increased risk of venous and arterial thromboembolism, which can be as high as 40% depending on the severity and underlying cause of nephrotic syndrome. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend prophylactic anticoagulation only in idiopathic membranous nephropathy but acknowledge that existing data are limited and of low quality. There is a need for better identification of vulnerable patients in order to balance the risks of anticoagulation.

Methods: We undertook a systematic search of the topic in MEDLINE, EMBASE and COCHRANE databases, for relevant articles between 1990 and 2019.

Results: A total of 2381 articles were screened, with 51 full-text articles reviewed. In all, 28 articles were included in the final review.

Conclusion: We discuss the key questions of whom to anticoagulate, when to anticoagulate, and how to prophylactically anticoagulate adults with nephrotic syndrome. Using available evidence, we expand upon current KDIGO guidelines and construct a clinical algorithm to aid decision making for prophylactic anticoagulation in nephrotic syndrome.

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Nephrotic syndrome (NS) is a manifestation of glomerular disease characterized by >3.5 g/d of proteinuria, hypoalbuminemia, dyslipidemia, and edema. Primary glomerular pathologies frequently associated with NS include, but are not limited to, membranous glomerulonephritis (MGN), minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and membranoproliferative glomerulonephritis (MPGN). Important secondary causes include diabetic nephropathy and amyloid disease. One serious clinical implication of NS is the development of a hypercoagulable state, placing patients at increased risk for venous thromboembolism (VTE) and arterial thromboembolism (ATE).[1] In some instances, thromboembolic disease is the initial presenting symptom, leading to the subsequent discovery of NS.[2–4]

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PATHOPHYSIOLOGY

Hypercoagulability reflects an imbalance in coagulation homeostasis created by urinary losses of antithrombotic factors and increased hepatic synthesis of pro-thrombotic factors. There are reduced levels of the natural anticoagulant antithrombin III, and higher levels of clotting factors V, VIII, and fibrinogen in patients with NS.[5,6] Protein C and S levels may also be reduced, but this is a less consistent finding.[7]

Abnormalities are also found in platelet function. Albumin loss results in increased free arachidonic acid and formation of thromboxane A2, leading to platelet aggregation, which is further accentuated by hypertriglyceridemia, another feature of NS.[8,9] Other contributing factors are the potential pro-coagulopathic role of corticosteroids, a staple of many glomerulonephritis treatment regimens, and volume contraction in NS patients with diuretic use.

In-depth analyses on the mechanisms of hypercoagulability in NS have been extensively covered in the literature and are beyond the scope of our review.

RISK OF THROMBOEMBOLISM

Bellomo and Atkins found venous thromboembolic events to occur in 40% of patients with membranous nephropathy.[10] Deep vein thrombosis is said to develop in approximately 15% of patients with NS, and renal vein thrombosis had been reported to develop in 25% to 30% of patients with NS, with the greatest risk seen in MGN (37%), MPGN (26%), and MCD (24%).[11]

In a retrospective cohort study of 298 patients with NS, Mahmoodi *et al*. examined the rates of objectively verified thromboembolic events and reported an annual incidence of 1% and 1.5% for VTE and ATE in this population, respectively. This study verifies high absolute risks of symptomatic VTE and ATE that were remarkably elevated within the first 6 months of diagnosis.[1] For comparison, the rate of VTE in the general population is estimated to be 1 to 2 per 1000 persons per year.[12]

Similar findings were reported by Kayali *et al*., in a retrospective analysis of patients discharged from U.S. hospitals, identifying those with NS and deep vein thrombosis (DVT), pulmonary embolism (PE), or renal vein thrombosis (RVT). Approximately 1.5% and 0.5% of admitted patients with NS between 1979 and 2005 in this study experienced DVT and PE respectively, with those between 18 and 39 years of age at greatest risk.[13]

The risk of VTE and ATE, however, varies among patients with NS, and these events are associated with high rates of morbidity and mortality, with a 6% and 12% incidence of death at 30 days following DVT and PE, respectively.[14,15] There is therefore a need for accurate identification of those individuals who are most vulnerable, in order to balance the risks of anticoagulation.

AIMS

Unfortunately, firm evidence on the optimal population to treat, and regimen to treat with has remained elusive, as high-quality clinical trials are difficult to carry out. It has been estimated 972 patients are required to adequately power a clinical trial because of the low overall frequency of events.[16] The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend prophylactic anticoagulation in idiopathic membranous glomerulonephritis only, but acknowledge that existing data are limited and of low quality.[17]

In this context, we undertook a systematic review to address the key questions of *who*, *when*, *how*, and for *how long* to prophylactically anticoagulate adult patients with nephrotic syndrome. Using the evidence, we build on the current KDIGO recommendations and construct a clinical algorithm that may aid clinicians in their decision making for prophylactic anticoagulation in a patient with NS.

METHODS

We undertook a systematic search of MEDLINE, EMBASE and COCHRANE databases from the period of 1990 to August 2019.

Search Strategy

We searched within MEDLINE and EMBASE databases using keywords detailed below. Medical Subject Headings (MeSH) were used where available with all subheadings included. Keywords were allocated to group 1 or group 2 for the purposes of the search.

Group 1 search terms were "nephrotic syndrome," "membranous glomerulonephritis," "minimal change glomerulonephritis," "minimal change disease,","lipoid nephrosis," and "focal sclerosing glomerulosclerosis."

Group 2 search terms were "thromboembolism," "venous thromboembolism," "arterial thromboembolism," "arterial occlusive diseases," "thrombosis," "venous thrombosis," "pulmonary embolism," "deep vein thrombosis," "anticoagulation," "anticoagulants," "warfarin," "apixaban," "rivaroxaban," "dabigatran," "edoxaban," and "heparin."

Group 1 search terms were combined individually with group 2 search terms using the Boolean operator "AND." The subsequent pairings were combined with "OR" operator to generate a single pool of results.

We searched the COCHRANE database for the following combinations: "nephrotic syndrome AND anticoagulation," "nephrotic syndrome AND thrombosis," "nephrotic syndrome AND thromboembolism," "nephrotic syndrome AND warfarin," "nephrotic syndrome AND heparin," "membranous glomerulonephritis AND anticoagulation," "minimal change disease AND anticoagulation," and "focal sclerosing glomerulonephritis AND anticoagulation."

The pooled results from each database were combined and duplicates removed. Articles were then screened for relevance.

Inclusion and Exclusion Criteria

Articles were included if they pertained to the epidemiology of thromboembolic disease in NS, risk factors associated with thromboembolic disease in NS, prophylaxis of thromboembolic disease in NS, or treatment of thromboembolic disease in NS. We included only articles available in English. Articles were excluded if they were clearly related to other subject matter. Articles were also excluded if they were review or opinion articles, did not clearly outline treatment parameters, or did not provide adequate follow-up or

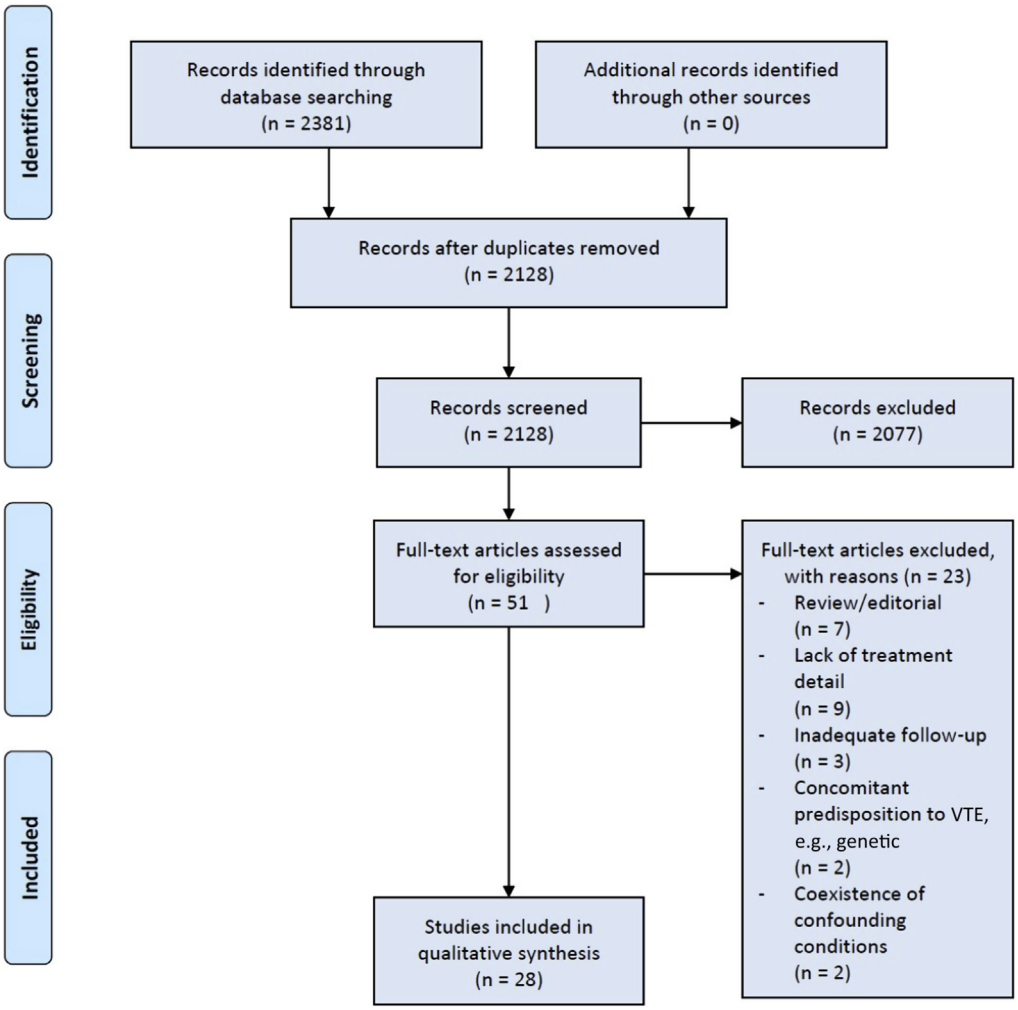

Figure 1. Search strategy and results. VTE, venous thromboembolism.

description of outcomes. We also excluded articles examining only pediatric populations.

Algorithm Formulation

The rationale for our algorithm to approach prophylactic anticoagulation in NS patients can be found in the Discussion.

RESULTS

Our search strategy returned 564 articles on MEDLINE, 1777 articles on EMBASE, and 40 articles on the COCHRANE database. After de-duplication, 2128 articles remained, which were screened. After screening, 51 full-text articles were identified and reviewed as potentially suitable, with 28 articles being included in the final review (Figure 1).

Articles pertaining to epidemiology and risk factors for thromboembolism in NS are summarized in Table 1,[13,18–29] and articles examining prophylaxis or treatment of thromboembolism in NS are summarized in Table 2[30–34] and Table 3.[35–43]

DISCUSSION

The "Who"

Histological Subtype of Nephrotic Syndrome

The histological subtype of NS is an important factor in assessing the risk of thromboembolism. Membranous glomerulonephritis appears to confer an especially high risk of thrombosis among the causes of NS. Barbour *et al*. analyzed patients from the Toronto Glomerulonephritis Registry, identifying 1313 patients with MGN, FSGS, and IgA nephropathy (IgAN). After adjustment for key variables including malignancy, histological subtype was observed to be an independent predictor for VTE, with MGN carrying a hazard ratio of 10.8 when compared against IgAN.[18]

Other studies have yielded similar findings: MGN was reported to be the most common histological subtype associated with PE in a prospective study of 512 consecutive NS patients,[21,28] whereas others have simply reported very high rates of thromboembolic events in patients with MGN-related NS, with one series finding that 36% of patients with MGN experienced a VTE.[22,23,25,29]

Table 1. Studies assessing epidemiology and risk factors for ATE and VTE in nephrotic syndrome

Authors	Year	Modality	Sample size	Histology	Primary outcome(s)	Results and key observations
Barbour *et al.*[18]	2012	Retrospective cohort study	1313	MGN (30.1%) FSGS (28.2%) IgAN (41.7%)	VTE (DVT, PE, RVT, other)	44 Patients (3.4%) experienced VTE Histologic subtype, particularly MGN, was independent risk factor for VTE
Fenton *et al.*[19]	2018	Retrospective cohort study	78	MCD	VTE	9 Patients (12%) developed VTE
Gyamlani *et al.*[20]	2017	Retrospective cohort study	7037	MCD, FSGS, MPGN, MGN Diabetic nephropathy Unclassified	VTE (DVT, PE, RVT)	158 VTEs over follow-up period 3.17 Events per 1000 patient years Proportionate increase in event rate with declining SA SA threshold as high as 40 g/l
Harza *et al.*[21]	2013	Prospective cohort study	191	MGN (29%) FSGS (25%) IgAN (18%) MPGN (15%) MCD (13%)	VTE (DVT, PE, RVT)	23 Patients (12%) developed VTEs Most VTEs occurred in first 6 months (65.2%) MGN + MPGN highest risk subtypes
Kayali *et al.*[13]	2008	Retrospective cohort study	925,000	Unspecified	VTE (DVT, PE, RVT)	1.5% Had DVT, 0.5% had PE, RVT less common Relative risk of DVT in NS was 6.81 in age group 18–39 yr
Kumar *et al.*[22]	2012	Retrospective cohort study	101	MGN (77% primary, 23% secondary)	VTE (DVT, PE), stroke, ATE	15 Patients (19.2%) with primary MGN experienced VTE Risk was highest in first 6 mo Risk factors: severe hypoalbuminemia, hypercholesterolemia, and proteinuria
Li *et al.*[23]	2012	Prospective study	100	MGN	VTE (PE, RVT)	36 Patients (36%) experienced VTE
Li *et al.*[24]	2016	Prospective cohort study	120	FSGS	VTE	12 Patients (10%) experienced VTE
Lionaki *et al.*[25]	2012	Retrospective cohort study	898	MGN	VTE	65 Patients (7%) experienced VTE Hypoalbuminemia (SA <28 g/l) most significant risk factor for VTE risk
Maas *et al.*[26]	2017	Retrospective cohort study	125	MCD	VTE, ATE	11 Patients (9%) experienced VTE or ATE
Mahmoodi *et al.*[1]	2008	Retrospective cohort study	298	MGN (24%) MCD (16%) FSGS (12%) MPGN (9%) Diabetic nephropathy (11%)	VTE, ATE	Annual incidence of VTE/ATE was 1.02%/1.48% respectively in patients with NS Risk was highest in first 6 mo
Waldman *et al.*[27]	2007	Retrospective cohort study	95	MCD	VTE, ATE	4 Patients (4.2%) developed thrombosis in follow-up period
Zhang *et al.*[28]	2014	Prospective cohort study	512	MGN (35.7%) FSGS (7%) SLE (11.5%) MPGN (2.9%) MCD (2.2%) IgAN (4.9%) Not specified (17.4%)	PE, RVT	180 Patients (35%) had PE and/or RVT MGN and increasing age were independent predictors of PE and/or RVT
Zou *et al.*[29]	2018	Retrospective cohort study	766	MGN	VTE (DVT, RVT, PE) ATE (stroke, PVD)	53 Patients (6.9%) experienced VTE 71 Patients (9.3%) experienced ATE Low SA was independent risk factor Risk highest in first 6 mo

ATE, arterial thromboembolic event; DVT, deep vein thrombosis, FSGS, focal sclerosing glomerulosclerosis; IgAN, IgA nephropathy; MCD, minimal change disease; MGN, membranous glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; PE, pulmonary embolism; PVD, peripheral vascular disease; RVT, renal vein thrombosis; SA, serum albumin; SLE, systemic lupus erythematosus; VTE, venous thromboembolic event.
Histological subtypes are included where available and important study outcomes are listed.

The other histological subtypes of NS also share the risk of thrombosis, although the risk does not appear to be as pronounced. Studies on the clinical outcomes of patients with MCD and FSGS have demonstrated high thrombotic rates during follow-up,[19,24,26,27] whereas others have found high risks of VTE and ATE in NS across a range of histological subtypes.[1,44] One study found the risk of thrombosis in MCD to be higher than MGN in their analysis.[16]

The observation of greater thrombotic risk in MGN compared to other subtypes, even after correcting for serum albumin and proteinuria, is not well understood. One hypothesis is a dissimilarity in the way in which MGN affects the coagulation cascade compared to other subtypes. Huang *et al*. conducted a comparison of coagulation parameters using blood tests and thromboelastography in 101 MGN patients, 61 MCD patients, and 20 healthy controls. They observed that the R value, which is the time taken for the first evidence of clot to be observed, was significantly lower in MGN patients compared with MCD patients and controls.[45] An association between MGN and genetic predispositions to thromboembolism, such as Factor V Leiden, have also been postulated.[46,47]

Table 2. Studies assessing use of warfarin or heparin as prophylaxis or treatment of thromboembolism in nephrotic syndrome

Authors	Year	Modality	Sample size	Histology	Intervention	Prophylaxis versus treatment	Results and key observations
Kelddal *et al.*[30]	2019	Retrospective cohort study	79	MCD (44.3%) MGN (24.1%) FSGS (8.9%) Other (22.8%)	Warfarin alone, warfarin with bridging LMWH, high/low-dose LMWH versus none	Prophylaxis	More thromboembolism events in nonprophylaxis group. Prophylaxis may increase bleeding risk, particularly if concurrent aspirin.
Medjeral-Thomas *et al.*[31]	2014	Retrospective cohort study	143	MGN (40.6%) MCD (31.4%) FSGS (28.0)	SA <20 g/l: LMWH 20 mg or warfarin (INR, 1.5–2.5) SA 20–30g /l: aspirin 75 mg	Prophylaxis	No VTEs in patients with established prophylaxis >1 wk 2 VTEs occurred in patients within 1 wk of commencing prophylaxis
Rostoker *et al.*[32]	1995	Prospective pilot study	55	MGN (29%) MCD (27%) FSGS (23.6%) SLE (3.6%) Other (16.4%)	LMWH 40 mg	Prophylaxis	LMWH was effective and safe with low incidence of bleeding
Wang *et al.*[33]	2011	Case report	1	MCD	LMWH	Treatment	Successful treatment of mesenteric vein thrombosis and portal vein thrombosis
Yang *et al.*[34]	2002	Case report	1	MCD	LMWH	Treatment	Successful treatment of renal vein thrombosis

FSGS, focal sclerosing glomerulosclerosis; INR, international normalized ratio; LMWH, low–molecular-weight heparin; MCD, minimal change disease; MGN, membranous glomerulonephritis; SA, serum albumin; SLE, systemic lupus erythematosus; VTE, venous thromboembolic event.
Histological subtypes are included where available, and important study outcomes are listed.

Summary

The presence of NS, regardless of histological subtype, appears to confer a clinically relevant potential for thrombotic complications, occurring at a significantly higher rate than in the general population. The risk appears to be accentuated if the underlying disease is MGN, although the pathophysiology behind this observation is not entirely clear. Current KDIGO guidelines suggest anticoagulation only for idiopathic MGN; however, available evidence suggests that perhaps anticoagulation can be considered in all patients with NS.

The "When"

Serum Albumin

Serum albumin has been observed to be a strong predictor of VTE in NS.[20,25,27,48,49] The KDIGO guidelines reflect this in their recommendation for anticoagulation in patients with MGN when serum albumin falls to less than 25 g/l in the presence of other thrombotic risk factors.[17]

The severity of hypoalbuminemia is thought to be a surrogate marker for the degree of imbalance in prothrombotic and anti-thrombotic factors, translating into elevated thrombotic risk. Lionaki *et al*. reported a serum albumin threshold of 28 g/l, below which there was a 3.9-fold increase in VTE risk, rising to 5.8-fold when serum albumin was less than 22 g/l in MGN patients.[25] Gyamlani *et al*., in a retrospective analysis of 7,037 U.S. veterans, found that thrombotic risk rose proportionately with declining serum albumin, and even mild reductions in serum albumin (30–39.9 g/l) conferred increased risk. The highest-risk group were those with serum albumin less than 25 g/l, with an event rate of 8.5 per 1000 patient years.[20]

One limitation of the current data, however, is the uncertainty as to whether serum albumin thresholds established in these studies are applicable across all histological subtypes of NS. The available studies have either included MGN patients only, or were unable to analyze the subgroups of NS separately when looking at serum albumin thresholds (Table 1).

Summary

Most forms of NS appear to carry some clinically significant risk of thrombosis, and anticoagulation should be considered in the setting of hypoalbuminemia. The serum albumin threshold below which to commence anticoagulation is not clearly established, although most studies concur that the level is between 20 and 30 g/l. This will need to be balanced with the patient's risk of bleeding. If proceeding with anticoagulation, it should be commenced as soon as it is safe, as the risk of thrombosis has consistently been found to be highest in the first 6 months of diagnosis.[1,21,29]

Risk of Bleeding

The decision to prescribe anticoagulation cannot occur without a simultaneous assessment of the patient's risk of bleeding. As randomized trials with sufficient power are difficult to perform, much of our risk assessment strategies are derived from the non-NS population.

The closest we have to a decision-making framework currently is a clinical tool derived from a study published in 2014. Lee *et al*. used a Markov decision process to quantify the benefits of anticoagulation versus the risk of major bleeding in patients with idiopathic

Table 3. Studies assessing use of direct-acting anticoagulants as prophylaxis or treatment of thromboembolism in nephrotic syndrome

Authors	Year	Modality	Sample size	Histology	Intervention	Prophylaxis versus treatment	Results and key observations
Basu *et al.*[35]	2015	Case report	1	SLE-related NS	Rivaroxaban	Treatment and prophylaxis	Failure of rivaroxaban in prophylaxis New splenic infarcts
Dupree *et al.*[36]	2014	Case report	1	Not specified	Rivaroxaban	Treatment	Recurrent VTE while on warfarin Successful use of rivaroxaban for 6 mo without recurrent VTE
Han *et al.*[37]	2017	Case report	1	MGN	Rivaroxaban	Treatment	New-onset renal vein thrombosis on rivaroxaban for pulmonary embolism Successful treatment with warfarin
Li *et al.*[38]	2019	Case report	1	Not specified	Rivaroxaban	Treatment	Poor response to rivaroxaban Good response to warfarin with bridging heparin
Reynolds *et al.*[39]	2019	Case report	1	MGN	Apixaban	Treatment	Recurrent VTE despite therapeutic apixaban
Sasaki *et al.*[40]	2014	Case report	1	MGN	Dabigatran	Treatment	Successful treatment of carotid thromboembolism with dabigatran
Sexton *et al.*[41]	2018	Case report	2	MCD MGN	Apixaban	Prophylaxis	No thrombosis in follow-up periods of 8 wk and 3 mo
Shimada *et al.*[42]	2017	Case report	1	Not specified	Edoxaban	Treatment	Recurrence of PE on warfarin Edoxaban used to good efficacy
Zhang *et al.*[43]	2018	Randomized trial	16	MCD (43.8%) MGN (25%) FSGS (12.5%) Other (12.5%) LN (6.25%)	LMWH vs. rivaroxaban	Treatment	7 of 8 Patients achieved thrombus dissolution Rivaroxaban a safe and effective single-agent treatment option

FSGS, focal sclerosing glomerulosclerosis; LMWH, low–molecular-weight heparin; LN, lupus nephritis; MCD, minimal change disease; MGN, membranous glomerulonephritis; SLE, systemic lupus erythematosus; VTE, venous thromboembolic event.
Histological subtypes are included where available and important study outcomes listed.

MGN.[50] The study population was taken from the 2012 study of 898 patients by Lionaki *et al.*,[25] and bleeding risk was represented by the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score. The authors concluded that patients derive variable benefit from prophylactic anticoagulation, depending on their risk of bleeding and serum albumin level. For instance, if the patient was at low risk for bleeding, there was a reasonable risk–benefit ratio from anticoagulation even at serum albumin thresholds as high as 30 g/l. Conversely, for those at high risk for bleeding, the risk–benefit ratio does not become favorable at any serum albumin level. Their clinical tool (https://www.med.unc.edu/gntools/) is currently available on the webpage hosted by the University of North Carolina School of Medicine.[51]

There are, however, limitations to the clinical tool developed by Lee *et al*. The most obvious is that it is applicable only to patients with MGN, and so the risk–benefit ratio of anticoagulation in patients with other forms of NS remains unclear. The ATRIA score may also not be the best predictor of bleeding. The HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [> 65 years], Drugs/alcohol concomitantly) scoring system[52] has repeatedly been found to be a better predictor of bleeding compared to other scoring systems, including ATRIA, across multiple comparisons.[53–58]

Perhaps most important is the uncertainty of the application of any of these bleeding risk assessment tools to a NS patient. The physiology of anticoagulation in nephrotic syndrome is complex and not fully elucidated. A recent study by Kawai *et al*. found that serum albumin levels of less than 36 g/l were associated with more major bleeding events and a trend toward supratherapeutic international normalized ratio (INR), although the study was not targeted to the specific mechanism of hypoalbuminemia encountered in NS.[59]

Summary

Anticoagulation does not appear to be beneficial for patients with high bleeding risk scores, regardless of serum albumin. There are no validation studies for bleeding risk assessment scores in the NS population. Acknowledging this, the HAS-BLED scoring system has better correlation with bleeding risk in the general population compared to other tools. Clinicians should be mindful that the risk of bleeding estimated by these scoring systems may not be accurate, particularly in severe hypoalbuminemia, thus mandating close clinical follow-up.

The "How"

Warfarin and Heparin

Warfarin, a vitamin K antagonist and staple anticoagulant across many indications, is the recommended agent in the KDIGO 2012 guidelines for VTE *prophylaxis* in MGN-related NS. Low-molecular-weight heparin (LMWH) is given as an alternative for prophylaxis, but uncertainty exists in dosing, as heparin's target of action, antithrombin III, is actively lost in urine in NS, potentially conferring heparin

resistance.[60] For *treatment* of documented arterial or venous thromboembolism, the guidelines suggest full-dose anticoagulation with either LMWH or warfarin.[17]

Unfortunately, there is little evidence available in the literature on the optimal prophylactic agent or its dosing, owing to a lack of randomized trials. The available evidence consists primarily of case studies or retrospective cohort studies that represent local treatment practices and protocols rather than a universally agreed-upon treatment strategy (Table 2).

Rostoker *et al*., in 1995, presented a prospective pilot study in 55 patients with various NS subtypes. Patients were given LMWH (enoxaparin) at 40 mg for variable time periods, and this was found to be safe, well tolerated, and effective for thrombosis prevention.[32] Medjeral-Thomas *et al*. carried out a single-center retrospective analysis in 143 patients with NS between 2006 and 2011. Those with serum albumin <20 g/l received enoxaparin 20 mg (or low-dose warfarin; INR, 1.5−2.5) and those with serum albumin 20 to 30 g/l received daily aspirin 75 mg. There were no VTEs in patients who had received prophylaxis for at least 1 week, and the 2 VTEs that were observed occurred within the first week of treatment.[31] The authors concluded that a regimen of prophylactic antiplatelet or anticoagulant therapy appears to be effective in preventing VTE in nephrotic syndrome, with relatively few hemorrhagic complications.

More recently, Kelddal *et al*. retrospectively examined 79 patients with NS, 44 of whom received some form of prophylactic anticoagulation, compared with 35 who did not. The prophylaxis regimens varied, from warfarin alone, warfarin with bridging LMWH, or low/high-dose LMWH alone. The authors observed that there were significantly more thromboembolic events in the nontreated group, and that major bleeding only occurred in those who had concurrent aspirin treatment for other reasons.[30]

With regard to dosing, the American College of Chest Physicians Clinical Guidelines for Prevention of Thrombosis advise that the optimal INR range for prevention of thrombosis is 2.0 to 3.0.[61] Although it is worth noting that this INR recommendation was not developed for an NS population, in the absence of contrary evidence or validation studies, it is a reasonable target for warfarin dosing. LMWH dosing is less certain, as there is the choice between prophylactic or therapeutic dosing. The majority of studies using heparin as prophylaxis have opted for prophylactic over therapeutic dosing.

Overall, it is difficult to draw conclusions as to whether these varied prophylactic regimens were truly effective. First, the studies were limited by their observational design. In addition, the number of patients in each study were relatively few, meaning that thrombotic events may simply have not occurred in the intervention groups purely by chance. It can also be difficult to account for changes in thrombotic risk during follow-up; for instance, as patients enter remission with treatment, their risk may naturally decline.

Summary

Available studies suggest that prophylactic anticoagulation is beneficial for thrombosis prevention in at-risk NS patients, although major caveats apply, including the lack of randomized controlled trials. The efficacy of warfarin versus heparin has not been compared directly by any study. Heparin, despite the theoretical possibility of resistance from antithrombin III loss, has been used successfully for both prophylaxis and treatment.[33,34] Low-dose aspirin was used for low-risk patients in one study.[31] If proceeding with prophylaxis, the choice of agent should be guided by patient and clinical factors, such as ease of use and access, patient preference, and feasibility of monitoring requirements.

Direct Oral Anticoagulants

Direct oral anticoagulants (DOACs) were first introduced in 2008, and work by directly inhibiting factor Xa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran, argatroban) in the coagulation cascade. Clinical applications for these agents are widening, and they are first-line options for conditions such as nonvalvular atrial fibrillation, DVT, and PE.[62] DOACs are increasingly favored over warfarin for their rapid onset of activity, lack of monitoring requirement, and reduced bleeding profile; however, their role in NS is not well defined.

The evidence for use of DOACs in NS is extremely limited, consisting mainly of case reports and one small randomized trial, with the majority of studies focused on treatment rather than prophylaxis of thrombosis. We include studies using DOACs for treatment of thrombosis in our discussion, as it illustrates the complexities and our lack of understanding of the coagulation system in NS.

The use of DOACs for treatment of thromboembolism have produced mixed results. Some authors have reported failure of DOACs,[35,37–39] requiring subsequent reversion to traditional agents, whereas others have reported success where traditional anticoagulants have fallen short or were poorly tolerated.[36,40,42] The only randomized trial data are those from a small pilot study by Zhang *et al*., in which 16 patients were allocated to receive either rivaroxaban

Table 4. Pharmacokinetics of currently available anticoagulants

Pharmacological property	Warfarin[65]	Low–molecular-weight heparin[64,66–69]	Rivaroxaban[64,70]	Apixaban[64]	Dabigatran[71]
Mechanism of action	Vitamin K antagonist	Potentiation of antithrombin III	Direct Xa inhibitor	Direct Xa inhibitor	Direct thrombin (factor II) inhibitor
Site of action	Factors II, VII, IX, X inhibition	Factors IIa, IXa, Xa, XIa, XIIa inhibition	Factor Xa inhibition	Factor Xa inhibition	Thrombin, prothrombin inhibition
Bioavailability (oral)	99%–100%	90% (subcutaneous)	80%–100%	66%	6%–7%
Protein binding	99%	Variable[a]	95%	87%	35%
Volume of distribution[b]	10 L	7 L	50 L	21 L	60–70 L
Renal clearance	Very low	Primarily renal clearance	33% (66% via liver metabolism)	27%	85%

[a]Protein binding of heparin is variable and dependent on molecular chain length. Increased protein binding reduces efficacy.
[b]Volume of distribution based on 70-kg man with 42 L total body water. Volume of distribution <10 L implies restriction of drug to intravascular fluid. Volume of distribution >42 L implies distribution to tissues in the body.

or LMWH for treatment of VTE. Nearly all patients achieved the endpoint of thrombus dissolution, and the authors concluded that rivaroxaban was an effective alternative option for treatment of NS-related thrombosis.[43]

Evidence for DOACs as prophylaxis is limited to only one case report detailing the successful use of apixaban as prophylaxis in 2 patients with MGN and MCD[41] (Table 3).

The other major consideration for use of DOACs is safety. DOACs are currently not approved for use in patients with significant renal impairment (creatinine clearance <30 mL/min per 1.73 m^2), although there is mounting evidence to suggest that these agents can be safe in the renal impairment population, so their use may gradually become more widespread.[63,64]

Summary

Evidence for the prophylactic use of DOACs in the setting of NS is extremely limited, and the majority of evidence pertains to treatment of VTE rather than prophylaxis. Overall results are mixed. Given that much of the pharmacokinetics and pharmacodynamics of these agents in NS remain uncertain, the use of DOACs as first-line agents for prophylaxis and treatment of ATE/VTE in NS should be carefully considered. DOACs may be reasonable alternatives to warfarin and LMWH in the event of the failure or intolerability of these agents, allowing for renal function.

Why Does Anticoagulation Fail?

The literature demonstrates both success and failure with contemporary anticoagulants, particularly DOACs, but the reasons for failure are poorly understood. Beyond common reasons for medication failure such as medication nonadherence, potential contributors in the setting of NS are alterations in the pharmacokinetics of anticoagulation agents, our clinical expertise with adjusting anticoagulation dose, and the heterogeneity of changes to the coagulation system.

Pharmacokinetics of Anticoagulants

Some authors have hypothesized that the pharmacokinetics and pharmacodynamics of anticoagulants are altered by hypoalbuminemia,[35,39] which merits discussion. The mechanisms of action, bioavailability, volume of distribution, and degree of renal clearance for warfarin, heparin, rivaroxaban, apixaban, and dabigatran are summarized in Table 4.[64–71]

Warfarin, apixaban, and rivaroxaban are highly protein bound. The implications are whether high urinary protein loss translates to excess free drug and increased bleeding risk, or, conversely, whether protein-bound drug is rapidly lost in urine, reducing efficacy. Alternatively, NS may not affect the performance of the drug at all, as suggested by Gugler *et al*. in a pharmacokinetic study of 3 drugs with varying levels of protein binding. In the highly protein-bound drug (diphenylhydantoin), the percentage of free drug doubled in NS patients because of lower serum protein; however, this was counterbalanced by a lower steady-state concentration due to increased clearance, resulting in no overall net difference.[72] Keller *et al*. supported this observation and suggested that in NS and other renal disease, *free*-drug concentration is a more reliable measure of drug efficacy than total plasma concentration.[73]

In 1986, Ganeval *et al*. reported on the pharmacokinetics of warfarin in 11 NS patients compared with 11 normal controls. Warfarin levels in urine were undetectable in the majority of patients, despite being protein bound; and although the blood concentration of free-drug doubled, the overall plasma clearance increased 3-fold, leading to a significantly shorter half-life.[74] These results suggest the effect of NS on the pharmacokinetics of warfarin and other protein-bound anticoagulants, may not be readily

predictable, particularly if other factors such as oral bioavailability, changes in volume of distribution, and drug−drug interactions are taken into consideration.

Clinical Experience and Scope in Anticoagulation Dosing

Perhaps the greater success in the literature for the use warfarin and heparin in NS compared with DOACs is due to our ability to readily measure their efficacy (INR and anti-Xa activity) and make appropriate adjustments to dose, thus avoiding toxicity and maintaining efficacy.

Drug levels or measures of efficacy are performed far less often for DOACs, as one of their key strengths is their predictable pharmacokinetic profile. This creates the potential for subtherapeutic or supratherapeutic drug activity to go undetected. This concept is illustrated in a case report of a patient with MCD who required much higher doses of apixaban (10−15 mg twice a day) to maintain therapeutic drug levels,[75] yet these doses are not routinely prescribed in practice for fear of toxicity and bleeding. This is further compounded by the reduced scope for adjusting the dose of DOACs because of lack of clinical experience and rigid dosing regimens.

The ongoing study of the pharmacokinetics of apixaban in NS, measuring anti-Xa activity at numerous time points, will hopefully further our understanding of this area and allow greater insights into how to dose these agents (ClinicalTrials.gov ID: NCT0259532).

Heterogeneity of Changes in the Coagulation System

There is potentially considerable heterogeneity within alterations to the coagulation system, creating different risk profiles within each individual patient that cannot be readily accounted for. Kerlin *et al*., collating observations from other studies, demonstrated that changes in pro-coagulant, anti-coagulant, and fibrinolytic factors in NS can range from being increased, to unchanged, to decreased.[76] Although some of the discrepancies in observations can likely be attributed to varying study methodologies, it should be acknowledged that the precise mechanism by which NS interacts with these factors is unknown, and is not simply a function of molecular size.

Summary

Much work is needed to understand the complex pharmacokinetics and pharmacodynamics of anticoagulants in the setting of NS. Although there is deep clinical experience in the monitoring and dose adjustment of warfarin and heparin, the same experience is lacking in DOACs, as they are relatively new and have rigid dosing regimens in place. The predictable pharmacokinetic profile of DOACs in the general population, which usually allows for no regular drug monitoring, may need to be reconsidered in the NS. Should DOACs be incorporated into future guidelines for anticoagulation in NS, some form of drug efficacy and toxicity monitoring may be required.

Duration of Treatment

Optimal duration of treatment is poorly established. The KDIGO guidelines suggest continuation of prophylaxis while the patient remains nephrotic (serum albumin <30 g/l), presumably as the pathophysiological processes predisposing to thrombus risk theoretically remain. To date, there are no studies specifically addressing this question, which is not surprising, given the overall level of data available.

In addition to the challenges posed by low event rates and patient numbers, any prospective study hoping to answer this question will need to address the issue of how to account for relapses in the underlying condition. For instance, in the event of thrombotic events occurring after cessation of anticoagulation, the question will arise as to whether this was due to a relapse of NS, or whether the anticoagulation was ceased "too early."

Algorithm: Individualized Approach to Prophylactic Anticoagulation in Nephrotic Syndrome

Using available evidence in combination with existing KDIGO guidelines, we present an algorithm to aid decision making on VTE prophylaxis in NS (Figure 2). We suggest considering the following 3 key patient parameters when making this decision.

Histology

The first distinction is the presence of MGN as opposed to other histological subtypes. The literature suggests that MGN generally confers a higher risk of thrombosis and thus lowers our threshold to commence prophylaxis.

Risk of Bleeding

We use the HAS-BLED scoring system to stratify patients into low-, moderate-, or high-risk bleeding groups (Supplementary Table S1). Drawing from the work of Lee *et al*., anticoagulation should not be pursued in patients at highest risk for bleeding (HAS-BLED score of ≥3) regardless of histological subtype or serum albumin level.[50]

Serum Albumin

For MGN, if bleeding risk is low, we selected a higher serum albumin threshold of 30 g/l below which to consider anticoagulation, based on the results of Lionaki *et al*. and Gyamlani *et al*.[20,25] If the patient is at moderate risk for bleeding (HAS-BLED score of 2), we suggest that

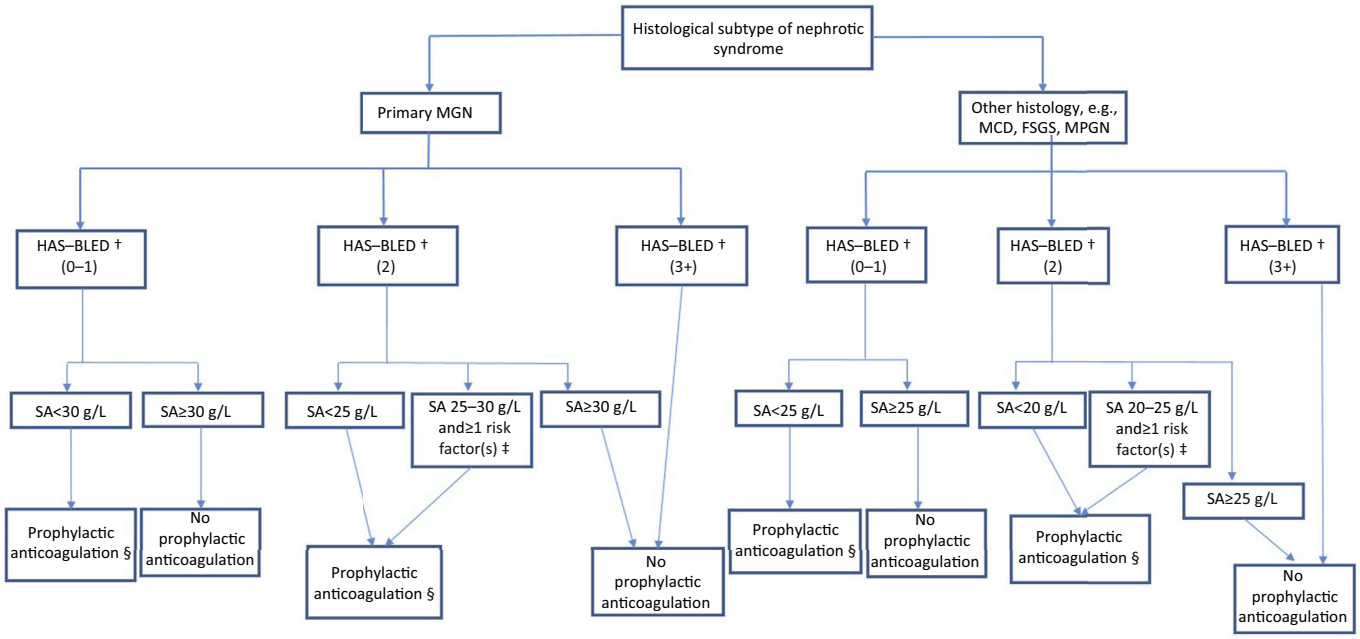

Figure 2. Algorithm for suggested approach to thromboembolism prophylaxis in nephrotic syndrome patients. †HAS-BLED scores for bleeding risk: 0–1, low risk; 2, moderate risk; 3–5, high risk; 5+, very high risk (see Supplementary Table S1). ‡Additional risk factors: proteinuria >10 g/d, body mass index >35 kg/m^2, documented genetic predisposition to venous thromboembolism (VTE), prolonged immobilization, recent abdominal or orthopedic surgery, New York Heart Association Class III to IV congestive heart failure. §Prophylactic anticoagulation first-line therapy: warfarin (international normalized ratio [INR], 2.0–3.0) or enoxaparin 40 mg daily. FSGS, focal segmental glomerulosclerosis; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly); MCD, minimal change disease; MGN, membranous glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; SA, serum albumin.

the serum albumin threshold be reduced to <25 g/l, which is in line with current KDIGO guidelines. Patients with a serum albumin level between 25 and 30 g/l should be considered for anticoagulation if there are one or more additional risk factors of heavy proteinuria >10 g/d, high personal or genetic risk of VTE, morbid obesity, advanced heart failure, immobilization, or recent abdominal/orthopedic surgery.

For non-MGN subtypes, the algorithm is similar, but the serum albumin below which anticoagulation should be considered is lower (25 g/l for patients with low bleeding risk and 20 g/l for those with moderate bleeding risk), reflecting the lower risk of thrombosis in NS associated with non-MGN subtypes.

CONCLUSIONS

Many uncertainties remain regarding anticoagulation in NS. Available evidence suggests that patients with MGN have the highest rates of thrombosis, although other NS subtypes also carry clinically significant risk. Limiting anticoagulation prophylaxis to only those patients with MGN may therefore need to be reconsidered.

Susceptibility to thrombosis escalates with declining serum albumin levels, but bleeding is the main consideration against initiating anticoagulation. A combination of all 3 aspects, which we have incorporated into a suggested algorithm, should inform clinical decision making.

Clinical trials to definitively answer these questions are difficult to perform, and we are likely to be dependent on meta-analyses and systematic reviews for future guidance. For this reason, further studies in this area should strive to maintain uniform treatment regimens to allow gradual accumulation of data, and we hope that our algorithm can contribute to this goal. Pharmacokinetic and pharmacodynamic studies on the actions of anticoagulants in NS will further our understanding.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary Material

Supplementary File (PDF)

Table S1. HAS-BLED system for risk of bleeding with anticoagulation.

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