Thromboembolic phenomena in patients with nephrotic syndrome: pathophysiology, risk factors, prophylaxis and treatment

Abstract

Thromboembolic events resulting from disturbances in the body's balance of thrombotic and antithrombotic abilities are among the most life-threatening complications of nephrotic syndrome. Certain causes of nephrotic syndrome leave the patient particularly susceptible to thromboembolism. The severity of proteinuria and degree of hypoalbuminaemia are other common predictors of risk. Timely initiation of prophylactic therapy can help prevent morbidity and mortality associated with this complication in patients with nephrotic syndrome. The duration of treatment and choice of therapeutic agent depends on several factors, including the degree of hypoalbuminaemia, risk factors for thrombosis and risk of bleeding. This article reviews current understanding of the pathophysiology and risk factors for thromboembolism associated with nephrotic syndrome, and summarises recommendations and strategies for preventing and treating thromboembolic events in patients with nephrotic syndrome.

Key words: Coagulation; Coagulopathy; Nephrotic syndrome; Thromboembolism; Thrombosis

Submitted: 5 October 2023; accepted following double-blind peer review: 16 October 2023

Samuel SY Wang[1]

Haoming Tang[2]

Hsin-Yueh Ng[2]

Jun Jie Lian[2]

Muhammad M Javaid[1,3,4,5]

Author details can be found at the end of this article

Correspondence to:
Muhammad M Javaid;
mmjavaid@doctors.org.uk

Introduction

Nephrotic syndrome, typically characterised by massive proteinuria (over 3.5 g/day), hypoalbuminaemia, oedema and hyperlipidaemia, is a common presentation of many glomerular diseases (Tian et al, 2023). Underlying causes include primary glomerulopathies (such as membranous nephropathy, minimal change disease and focal segmental glomerulosclerosis), a variety of secondary causes including diabetic nephropathy, systemic lupus erythematosus, malignancy and amyloidosis, medications such as bisphosphonates and non-steroidal anti-inflammatory drugs, and heavy metal poisoning (Hull and Goldsmith, 2008; Mittal et al, 2020).

Thrombosis, including arterial and venous thromboembolism, is associated with nephrotic syndrome. Up to 27% of adults and 3% of children with nephrotic syndrome develop a thrombotic event during the disease course, the majority of which occur within 90 days of the initial diagnosis (Waller et al, 2021). Vestergaard et al (2022) found the 1-year absolute risk of arterial and venous thromboembolism was 4% and 3% respectively, and the 10-year absolute risk was 14% and 8% respectively. Common thromboembolic phenomena reported in patients with nephrotic syndrome include deep vein thrombosis, renal vein thrombosis, pulmonary embolism and, less commonly, arterial embolism in the lower limbs, cerebral and coronary circulation (Singhal and Brimble, 2006). Renal vein thrombosis was estimated to be present in up to 30% of patients with nephrotic syndrome and deep vein thrombosis in up to 15% of patients (Singhal and Brimble, 2006; Welander et al, 2021). Patients with nephrotic syndrome have a higher risk of thromboembolism than cancer-associated venous thromboembolism and venous thromboembolism in hospitalised patients for medical reasons (Waller et al, 2021).

Understanding thromboembolic phenomena associated with nephrotic syndrome is important because the incidence is higher than that of other kidney diseases. These are some of the most severe complications of nephrotic syndrome after infections and lead to significant morbidity. They are associated with cardiovascular collapse and death and often present asymptomatically before becoming haemodynamically significant, such as pulmonary embolism (Kerlin et al, 2012; Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work

OPEN ACCESS

How to cite this article:
Wang SSY, Tang H, Ng H-Y, Lian JJ, Javaid MM. Thromboembolic phenomena in patients with nephrotic syndrome: pathophysiology, risk factors, prophylaxis and treatment. Br J Hosp Med. 2024. https://doi.org/10.12968/hmed.2023.0354

Group, 2021). Appropriate anticoagulation prophylaxis and timely treatment of thromboembolic events are crucial in improving outcomes in patients with nephrotic syndrome.

This article summarises the pathophysiology and risk factors for arterial and venous thromboembolism in patients with nephrotic syndrome and provides prophylactic and therapeutic strategies to assist physicians with evaluation and management.

Pathophysiology

Various acquired changes (Figure 1) involving prothrombotic proteins, antithrombotic factors and thrombolytic activity have been implicated in increased susceptibility to thromboembolism in patients with nephrotic syndrome (Waller et al, 2021; Kelddal et al, 2022). Damage to the glomerular filtration barrier increases permeability to endogenous substances (Mirrakhimov et al, 2014). Urinary loss of homeostatic proteins, such as antithrombin III and free protein S, and a concomitant marked increase in hepatic synthesis of prothrombotic proteins such as fibrinogen, factor V, factor VII and alpha-2 macroglobulin lead to a prothrombotic state and increased risk of thromboembolism (Loscalzo, 2013). Furthermore, impaired fibrinolytic activity caused by elevated levels of plasminogen activator inhibitor-1, decreased levels of plasminogen and clots that are relatively resistant to fibrinolysis further favours the prothrombotic environment (Glassock, 2007; Loscalzo, 2013).

Nephrotic syndrome also causes impaired platelet function. The loss of albumin leads to increased formation of thromboxane A2 and the release of free arachidonic acid, coupled with decreased flexibility of red cell membranes and increased levels of von Willebrand factor, leading to platelet aggregation, adhesion and hyperactivity (Zwaginga et al, 1994; Colle et al, 1999). This effect is further amplified by dysregulated lipid metabolism in patients with nephrotic syndrome, increasing the risk of arterial thrombosis (Lin et al, 2020; Tian et al, 2023). Thrombophilic causes beyond coagulation proteins include patients' existing comorbidities, volume depletion with concomitant diuretic use and resultant haemoconcentration, steroid therapy for nephrotic syndrome or other associated conditions, prolonged immobilisation, genetic susceptibilities associated with thrombophilia (eg factor V Leiden), extracellular vesicles in blood coagulation, and immune complex activation of the clotting cascade (Kerlin et al, 2012; Tian et al, 2023). These shift the homeostatic balance of the system towards a more prothrombotic state.

Risk factors for thromboembolism

Factors associated with increased risk of thromboembolism in nephrotic syndrome (Table 1) are discussed in more detail below.

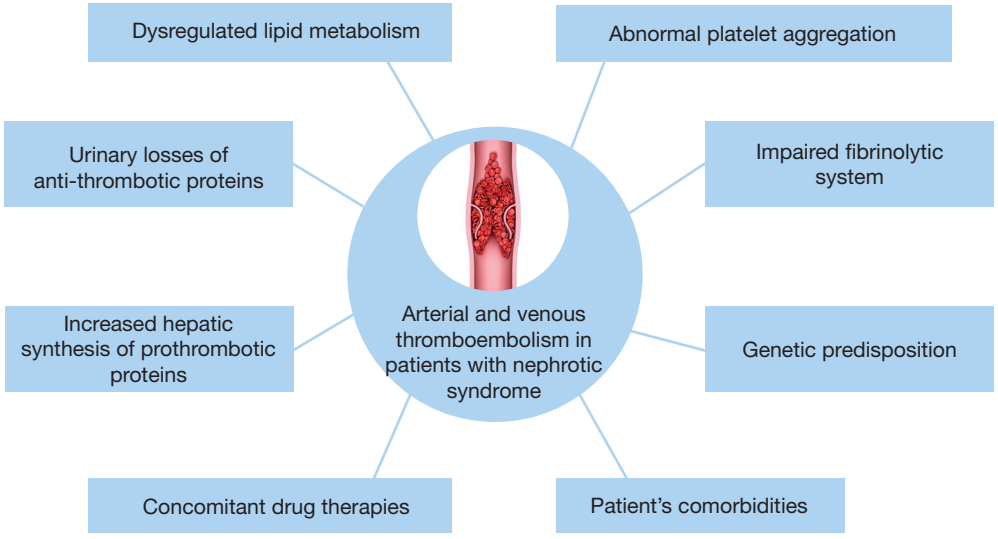

Figure 1. Pathophysiological contributors to thromboembolism in patients with nephrotic syndrome. Image of clot © Maurizio De Angelis/Science Photo Library.

Histological subtype

Membranous nephropathy is the histological subtype of nephrotic syndrome consistently associated with the highest thromboembolic risk (Lionaki et al, 2012). In 1313 patients with idiopathic nephrotic syndrome, the incidence of venous thromboembolism was highest in those with membranous nephropathy (7.9%), followed by those with focal segmental glomerulosclerosis (3%), while only 0.4% of cases with immunoglobulin A nephropathy developed venous thromboembolism. After adjusting for variables, including the degree of proteinuria, serum albumin level, gender and cancer history, the adjusted hazard ratio for venous thromboembolism was 10.8 for membranous nephropathy and 5.9 for focal segmental glomerulosclerosis compared to immunoglobulin A nephropathy (Barbour et al, 2012; Gordon-Cappitelli and Choi, 2020).

In paediatric nephrotic syndrome, although the incidence of thromboembolic events is generally lower, the incidence of membranous nephropathy-associated thromboembolism can approach that of adults (Mahan et al, 1984; Kerlin et al, 2009).

Besides membranous nephropathy and focal segmental glomerulosclerosis, an increased risk of thromboembolism has been reported with minimal change disease, membranoproliferative glomerulonephritis and renal amyloidosis (Chugh et al, 1981; Gyamlani et al, 2017).

Hypoalbuminaemia and proteinuria

Degree of hypoalbuminaemia and proteinuria are substantial risk factors for thromboembolic events in nephrotic syndrome. The Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group (2021) clinical practice guideline recommends that prophylactic anticoagulation be considered for patients with nephrotic syndrome who have serum albumin levels <20–25 g/litre. The severity of hypoalbuminaemia is deemed a surrogate marker of the degree of imbalance between prothrombotic and antithrombotic factors in patients with nephrotic syndrome and of ultimate thrombotic risk to patients (Lin et al, 2020, Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group, 2021). Patients with an albumin level <25 g/litre are at highest risk, with a thromboembolic event

Table 1. Risk factors for thromboembolism in patients with nephrotic syndrome

Histological subtype (membranous nephropathy, focal segmental glomerulosclerosis)
Severe hypoalbuminaemia (<25 g/litre)
Degree of proteinuria
Time from diagnosis (<6–12 months)
Advancing age (especially >60 years)
Prior thromboembolic events
Genetic predispositions for thromboembolism (eg factor V Leiden)
Recent abdominal or orthopaedic surgery
Prolonged immobilisation
Pregnancy
Corticosteroid and/or diuretic use
Antiphospholipid antibodies
Malignancy
Heart failure with New York Heart Association class III or IV
Obesity
Atherosclerotic risk factors (age, male sex, hypertension, smoking, diabetes, low estimated glomerular filtration rate)

rate of 8.5 per 1000 patient-years (Lin et al, 2020). Each 10 g/litre decrease in serum albumin levels resulted in a 2.13-fold elevated risk of venous thromboembolism (Lionaki et al, 2012; Gordon-Cappitelli and Choi, 2020). The proteinuria:serum albumin ratio is more sensitive and specific than either serum albumin level or proteinuria alone in predicting occurrence of venous thromboembolism (Mahmoodi et al, 2008).

Advancing age

Adults have a substantially higher predisposition to thrombogenesis than children, with approximately a 7–8-fold increase in the incidence of events (Al-Azzawi et al, 2016; Waller et al, 2021). After the first year of age, when congenital nephrotic syndrome presenting in infancy becomes the less common reason for thrombogenesis, the risk of thromboembolism appears to correlate well with increasing age. Consequently, compared to children under the age of 12 years, the risk of nephrotic syndrome-associated thromboembolism is significantly higher in children over 12 years of age (Kerlin et al, 2009, 2012). In adults, age more than 60 years is an independent predictor for venous thromboembolism in patients with nephrotic syndrome (Zhang et al, 2014; Al-Azzawi et al, 2016). Therefore, advancing age is a risk factor for thromboembolic events in both children and adults with nephrotic syndrome.

Time since diagnosis

The time since diagnosis helps clinicians assess patients' thromboembolic risks and guides therapeutic management, as thromboembolism usually happens early in the disease in children and adults (Kerlin et al, 2012). In children with nephrotic syndrome and thromboembolism, the median time to presentation of the first thromboembolic event was 70.5 days, and 61% of thromboembolic events presented within the first 3 months of the diagnosis of nephrotic syndrome (Andrew and Brooker, 1996; Kerlin et al, 2009). A similar trend has been observed in adults, with most thromboembolic events occurring within the first 6 months of diagnosis of nephrotic syndrome (Mahmoodi et al, 2008).

Other factors

Estimated glomerular filtration rate and risk factors for atherosclerosis, including age, male sex, hypertension, diabetes and prior arterial thromboembolism, are strong predictors for arterial thromboembolism (Mahmoodi et al, 2008). Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group (2021) recommend using the Framingham risk score to calculate the risk of arterial thromboembolism and decide on the need for prophylactic therapy. This considers age, sex, smoking, serum cholesterol level and blood pressure, with the added risk of low estimated glomerular filtration rate or higher levels of proteinuria in adults with a serum albumin level <32 g/litre.

Some medical conditions, physiological states and medical therapies exacerbate thrombogenesis. Conditions such as the presence of antiphospholipid antibodies, prior thromboembolic events, obesity, genetic susceptibilities, pregnancy, existing malignancy and New York Heart Association class III or IV heart failure predispose patients to thrombosis (Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group, 2021). Prolonged immobilisation and recent major abdominal or orthopaedic surgeries increase the risk of a thromboembolic event. Treatment with diuretics and corticosteroids (especially intravenous corticosteroids) in patients with nephrotic syndrome increases the risk of thromboembolic events (Glassock, 2007; Tian et al, 2023). Some of these factors were reflected in the Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group (2021) guideline as considerations for thromboprophylaxis for patients with nephrotic syndrome.

Recommendations for prevention and treatment of thromboembolic events

When to start prophylactic treatment

Prophylactic anticoagulation has been suggested as a preventive strategy to address the prothrombotic state in patients with nephrotic syndrome (Gordon-Cappitelli and Choi, 2020;

Lin et al, 2020). Early initiation of anticoagulation is highly recommended for high-risk patients, such as patients with low serum albumin levels or patients with a diagnosis of membranous nephropathy, provided the benefit-to-bleeding risk ratio is high.

Hypoalbuminaemia is associated with a higher risk of thromboembolic events. Each 1.0 g/dl decrease in serum albumin levels is associated with a 2.13-fold increase in risk of thromboembolic events (Gordon-Cappitelli and Choi, 2020). Kelddal et al (2019) found a 3-fold increase in risk when serum albumin levels fall below 25 g/litre, Lee et al (2014) found a 6-fold increase in risk when serum albumin levels fall below 22 g/litre, and Welander et al (2021) found a 21.7-fold increase in risk when serum albumin levels fall below 20 g/litre. The Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Groups (2021) guideline proposes the initiation of anticoagulation when serum albumin levels fall below 20–25 g/litre for patients with nephrotic syndrome who have any other risk factors for thromboembolism (eg proteinuria >10 g/day, body mass index >35 kg/m^2, a genetic predisposition, heart failure of New York Heart Association class III or IV, recent abdominal or orthopaedic surgery, or prolonged immobilisation). This is supported by multiple studies suggesting that anticoagulation should be started when serum albumin levels are between 20 and 30 g/litre (Lin et al, 2020; Welander et al, 2021). On the other hand, some experts advocate starting prophylactic anticoagulation on diagnosis of nephrotic syndrome, regardless of serum albumin levels (Kelddal et al, 2019).

Histological diagnosis of membranous nephropathy carries a higher risk of thromboembolic events than other causes of nephrotic syndrome. The threshold to begin prophylactic anticoagulation may be lower for patients with membranous nephropathy (Lee et al, 2014; Gordon-Cappitelli and Choi, 2020; Lin et al, 2020). Lin et al (2020) developed an algorithm for treating patients with membranous nephropathy, which suggested starting prophylaxis for patients with low-bleeding risk and serum albumin levels <30 g/litre and for patients with moderate-bleeding risk and serum albumin levels <25 g/litre or between 25 and 30 g/litre with at least one additional thromboembolic risk factor. In contrast, for those with non-membranous nephropathy nephrotic syndromes, Lin et al (2020) proposed initiating prophylaxis for patients with low-bleeding risk and serum albumin levels <25 g/litre and patients with moderate-bleeding risk and serum albumin levels <20 g/litre or between 20 and 25 g/litre with at least one additional thromboembolic risk factor. However, the clinical significance of earlier prophylactic anticoagulation for membranous nephropathy has not been studied.

Anticoagulation confers a risk of bleeding that can be minor or major. Patients' bleeding risk can be stratified using the ATRIA or the HAS-BLED scoring systems. Using the ATRIA system, scores below 3, 3–5, or above 5 classify patients into low, moderate or high-risk bleeding respectively. Using the HAS-BLED system, scores of 0–1, 2, or above 3 can be used to stratify patients into low, moderate or high-risk bleeding respectively (Lee et al, 2014; Lin et al, 2020). However, both systems were validated for patients with atrial fibrillation, and scores should be interpreted cautiously to evaluate bleeding risks in patients with nephrotic syndrome. The Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Groups (2021) guideline and multiple studies have proposed that patients with nephrotic syndrome should be anticoagulated when the risk of thromboembolic events outweighs the patient-specific risks of an anticoagulation-induced bleeding event. Lee et al (2014) developed a Markov decision model that guides decision making for initiating prophylactic anticoagulants based on bleeding risk and serum albumin levels. Starting prophylaxis has the greatest benefit for patients with low bleeding risk and serum albumin levels <30 g/litre, whereas patients with high bleeding risk should not have anticoagulation started regardless of serum albumin level.

Owing to the multiple causes of nephrotic syndrome, prophylactic anticoagulation for venous thromboembolism should be individualised. Patients with other risk factors for venous thromboembolism, such as a family history of thrombophilia, prolonged immobilisation or morbid obesity, might benefit more from prophylactic anticoagulation, so it is essential to discuss the need for anticoagulation with the patient. Prophylactic anticoagulation is contraindicated in patients with bleeding diathesis, CNS lesions prone to haemorrhage, genetic mutations affecting warfarin metabolism or efficacy, frailty or prior gastrointestinal bleeding (Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group, 2021).

Choice of prophylactic agent

Table 2 discusses recommended agents for prophylaxis of thromboembolism in patients with nephrotic syndrome (Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group, 2021). Low molecular weight heparin is usually used before conversion to warfarin for long-term maintenance anticoagulation, with a target international normalised ratio of 2–3 (Lin et al, 2020; Welander et al, 2021). According to the Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group (2021), heparin or its derivatives or warfarin are preferred for prophylaxis. However, no studies to date have compared the effectiveness of heparin and warfarin.

Direct oral anticoagulants are currently not recommended for prophylaxis because there are limited studies evaluating their effectiveness and a lack of definite indications. Direct oral anticoagulants are mainly albumin-bound, so hypoalbuminaemia could significantly affect their dosing and half-lives in patients with nephrotic syndrome, limiting their role as first-line prophylactic agents (Gordon-Cappitelli and Choi, 2020; Lin et al, 2020). Kelddal et al (2022) treated 21 patients with nephrotic syndrome with apixaban (n=10) or rivaroxaban (n=11) and showed that direct oral anticoagulant treatment effectively prevented and treated thromboembolism, with only five patients reporting minor bleeds. However, the small number of cases means that no definitive conclusions can be drawn, and larger studies are required to settle this question. Direct oral anticoagulants might be an alternative to warfarin and low molecular weight heparin in exceptional circumstances in the event of the failure or intolerability of these agents (Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group, 2021).

The role of aspirin prophylaxis is unclear and is considered to reduce cardiovascular events in patients with membranous nephropathy (Gordon-Cappitelli and Choi, 2020). The Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group (2021) guideline proposes prophylaxis with aspirin monotherapy in patients with membranous nephropathy who have serum albumin levels between 25 and 32 g/litre and a high arterial thromboembolism risk of over 20/1000 patient years. Aspirin monotherapy can also be considered for patients with high bleeding risk and serum albumin levels <25 g/litre.

Duration of prophylactic treatment

Anticoagulation prophylaxis should be continued based on the severity of hypoalbuminaemia, thromboembolic risk factors and bleeding risk stratification (Gordon-Cappitelli and Choi, 2020). The Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases

Table 2. Prophylactic anticoagulation recommendations for patients with nephrotic syndrome

Antithrombotic agents	Points to consider
Low molecular weight heparin	Dose reduction advised in patients with creatinine clearance <30 ml/min
	Contraindicated in patients with renal failure
Warfarin	Preferred anticoagulant
	Aim for target international normalised ratio of 2–3
	Close monitoring of international normalised ratio as a result of fluctuating free drug level caused by changing serum albumin level
Aspirin	Recommended for prophylaxis of arterial thromboembolism in high-risk patients with serum albumin levels between 25 and 32 g/litre
	May be used as alternative to warfarin in patients with serum albumin levels <25 g/litre who have a high bleeding risk
Heparin	Unfractionated heparin 5000 U subcutaneous twice per day can be considered
Factor Xa inhibitors (apixaban, rivaroxaban)	Not currently recommended for routine use in patients with nephrotic syndrome because of a lack of safety and efficacy data
Direct thrombin inhibitors (dabigatran)	Not currently recommended for routine use in patients with nephrotic syndrome because of a lack of safety and efficacy data

From Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group (2021)

Work Group (2021) guideline recommends continuing prophylaxis while the patient remains nephrotic (serum albumin levels <30 g/litre). Regular follow ups are needed because of the changes in a patient's risk of thromboembolic events and bleeding. Regular follow up is also recommended to monitor international normalised ratio, serum albumin levels and the effectiveness of prophylaxis. Adherence to strict international normalised ratio targets is needed to avoid preventable bleeding episodes (Kelddal et al, 2019).

Treatment of established thromboembolism

Treating overt thromboembolic events in patients with nephrotic syndrome is relatively straightforward, via anticoagulation with sequential unfractionated or low molecular weight heparin and oral warfarin. The Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group (2021) guideline outlined that for thromboembolic events (venous or arterial thromboembolism), full-dose anticoagulation is required for 6–12 months and should not be stopped while the patient has nephrotic syndrome.

Therapeutic options

Subcutaneous low molecular weight heparin is preferred, especially when bridging to warfarin and when the oral route is not viable (eg because of vomiting or malabsorption). Dosing is based on weight and renal impairment because of its primary renal clearance. Tinzaparin does not accumulate in patients with a creatinine clearance of at least 20 ml/min and might be a better choice for patients with poor renal function (Helfer et al, 2020). Thrombosis Canada (2023) recommends using low molecular weight heparin with warfarin for 5 days initially and until the international normalised ratio rises to at least 2.0 for two consecutive days (Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group, 2021).

Low molecular weight heparin is generally the agent of choice for treatment and prevention of venous thromboembolism during pregnancy. Vitamin K antagonists, factor Xa inhibitors and direct thrombin inhibitors are not recommended.

Fondaparinux can be used for patients with a history or diagnosis of heparin-induced thrombocytopenia (Bates et al, 2016). There are some crucial considerations in the prescription of heparin. In bridging warfarin with intravenous heparin, the effectiveness of heparin is reduced because there are low levels of antithrombin III. Additionally, hypoalbuminaemia in patients with nephrotic syndrome contributes to a raised free fraction of warfarin, resulting in a shorter drug half-life (Ducloux, 2011).

Factor Xa and direct thrombin inhibitors

Not enough is known about the safety and efficacy of factor Xa and direct thrombin inhibitors to consider them as first-line treatment for thromboembolism in patients with nephrotic syndrome. Factor Xa and direct thrombin inhibitors are heavily and moderately bound to albumin respectively, affecting their half-lives. Given the hypoalbuminaemic state of patients with nephrotic syndrome, there is an absence of pharmacokinetic studies or dose-adjusted nomograms (Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group, 2021). A pilot study of 16 patients with venous thromboembolism compared the effectiveness of thrombus dissolution using rivaroxaban and low molecular weight heparin and found a potential benefit of rivaroxaban over low molecular weight heparin. However, further larger studies are needed before recommending routine use of rivaroxaban in patients with nephrotic syndrome (Zhang et al, 2018). The American Society of Hematology recommended against checking anti-factor Xa activity and proposed dose adjustments based on specific product labelling or using a substitute anticoagulant (Schünemann et al, 2018).

Conclusions

Various pathophysiological factors, including imbalance between prothrombotic and antithrombotic factors and an impaired thrombolytic system, increase the risk of thromboembolism in patients with nephrotic syndrome. Thromboembolic events can cause significant morbidity and mortality in patients with nephrotic syndrome. Recognition of patients at increased risk and initiating appropriate prophylaxis is imperative to prevent such events and associated complications. Treatment of established thromboembolic

Key points

- Nephrotic syndrome is associated with venous and arterial thromboembolism, leading to significant morbidity and mortality.
- Thromboembolic phenomena in patients with nephrotic syndrome are mainly the result of an imbalance of prothrombotic factors and antithrombotic proteins as well as impaired thrombolytic activity.
- Risk factors for thromboembolism in patients with nephrotic syndrome include certain histological subtypes, severe hypoalbuminaemia, massive proteinuria, advancing age, duration since diagnosis, and other comorbidities and medications.
- Early initiation of prophylactic anticoagulation is recommended in patients with hypoalbuminaemia, membranous nephropathy or a high benefit-to-bleeding risk ratio.
- Treatment of established thromboembolic events should be individualised based on risk factors and comorbidities.

events should be based on the patient's comorbidities and risk factors for complications associated with particular anticoagulants. Low molecular weight heparin and warfarin are the agents of choice for prophylaxis and treatment. The use of direct oral anticoagulants is not recommended because of a lack of knowledge of pharmacokinetics and appropriate dose in the context of hypoalbuminaemia in patients with nephrotic syndrome.

Author details

[1]Department of Renal Medicine, Tan Tock Seng Hospital, Singapore

[2]Duke-NUS Medical School, Singapore

[3]Monash Rural Health Mildura, Monash University, Victoria, Australia

[4]Department of Renal Medicine, Woodlands Health, Singapore

[5]School of Medicine, Deakin University, Victoria, Australia

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

Al-Azzawi HF, Obi OC, Safi J, Song M. Nephrotic syndrome-induced thromboembolism in adults. Int J Crit Illn Inj Sci. 2016;6(2):85–88. https://doi.org/10.4103/2229-5151.183019

Andrew M, Brooker LA. Hemostatic complications in renal disorders of the young. Pediatr Nephrol. 1996;10(1):88–99. https://doi.org/10.1007/BF00863459

Barbour SJ, Greenwald A, Djurdjev O et al. Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis. Kidney Int. 2012;81(2):190–195. https://doi.org/10.1038/ki.2011.312

Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):92–128. https://doi.org/10.1007/s11239-015-1309-0

Chugh KS, Malik N, Uberoi HS et al. Renal vein thrombosis in nephrotic syndrome–a prospective study and review. Postgrad Med J. 1981;57(671):566–570. https://doi.org/10.1136/pgmj.57.671.566

Colle JP, Mishal Z, Lesty C et al. Abnormal fibrin clot architecture in nephrotic patients is related to hypofibrinolysis: influence of plasma biochemical modifications: a possible mechanism for the high thrombotic tendency? Thromb Haemost. 1999;82(11):1482–1489. https://doi.org/10.1055/s-0037-1614859

Ducloux D. Physiopathologie et traitement des complications du syndrome néphrotique [Physiopathology and treatment of nephrotic syndrome complications]. Nephrol Ther. 2011;7(1):52–57. https://doi.org/10.1016/j.nephro.2010.03.003

Glassock RJ. Prophylactic anticoagulation in nephrotic syndrome: a clinical conundrum. J Am Soc Nephrol. 2007;18(8):2221–2225. https://doi.org/10.1681/ASN.2006111300

Gordon-Cappitelli J, Choi MJ. Prophylactic anticoagulation in adult patients with nephrotic syndrome. Clin J Am Soc Nephrol. 2020;15(1):123–125. https://doi.org/10.2215/CJN.05250419

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(1):157–164. https://doi.org/10.1093/ndt/gfw227

Helfer H, Siguret V, Mahé I. Tinzaparin sodium pharmacokinetics in patients with chronic kidney disease: practical implications. Am J Cardiovasc Drugs. 2020;20(3):223–228. https://doi.org/10.1007/s40256-019-00382-0

Hull RP, Goldsmith DJ. Nephrotic syndrome in adults. BMJ. 2008;336(7654):1185–1189. https://doi.org/10.1136/bmj.39576.709711.80

Kelddal S, Nykjær KM, Gregersen JW et al. Prophylactic anticoagulation in nephrotic syndrome prevents thromboembolic complications. BMC Nephrol. 2019;20(1):139. https://doi.org/10.1186/s12882-019-1336-8

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):305. https://doi.org/10.1186/s12882-022-02929-x

Kerlin BA, Blatt NB, Fuh B et al. Epidemiology and risk factors for thromboembolic complications of childhood nephrotic syndrome: a Midwest Pediatric Nephrology Consortium (MWPNC) study. J Pediatr. 2009;155(1):105–110.e1. https://doi.org/10.1016/j.jpeds.2009.01.070

Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. Clin J Am Soc Nephrol. 2012;7(3):513–520. https://doi.org/10.2215/CJN.10131011

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int. 2021;100(4S):S1–S276. https://doi.org/10.1016/j.kint.2021.05.021

Lee T, Biddle AK, Lionaki S et al. Personalised prophylactic anticoagulation decision analysis in patients with membranous nephropathy. Kidney Int. 2014;85(6):1412–1420. https://doi.org/10.1038/ki.2013.476

Lin R, McDonald G, Jolly T et al. Systematic review of prophylactic anticoagulation in nephrotic syndrome. Kidney Int Rep. 2020;5(4):435–447. https://doi.org/10.1016/j.ekir.2019.12.001

Lionaki S, Derebail VK, Hogan SL et al. Venous thromboembolism in patients with membranous nephropathy. Clin J Am Soc Nephrol. 2012;7(1):43–51. https://doi.org/10.2215/CJN.04250511

Loscalzo J. Venous thrombosis in the nephrotic syndrome. N Engl J Med. 2013;368(10):956–958. https://doi.org/10.1056/NEJMcibr1209459

Mahan JD, Mauer SM, Sibley RK et al. Congenital nephrotic syndrome: evolution of medical management and results of renal transplantation. J Pediatr. 1984;105(4):549–557. https://doi.org/10.1016/S0022-3476(84)80418-7

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. Circulation. 2008;117(2):224–230. https://doi.org/10.1161/CIRCULATIONAHA.107.716951

Mirrakhimov AE, Ali AM, Barbaryan A et al. Primary nephrotic syndrome in adults as a risk factor for pulmonary embolism: an up-to-date review of the literature. Int J Nephrol. 2014;2014:1–9. https://doi.org/10.1155/2014/916760

Mittal P, Agarwal SK, Singh G et al. Spectrum of biopsy-proven renal disease in northern India: a single-centre study. Nephrology (Carlton). 2020;25(1):55–62. https://doi.org/10.1111/nep.13582

Schünemann HJ, Cushman M, Burnett AE et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalised and nonhospitalised medical patients. Blood Adv. 2018;2(22):3198–3225. https://doi.org/10.1182/bloodadvances.2018022954

Singhal R, Brimble KS. Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management. Thromb Res. 2006;118(3):397–407. https://doi.org/10.1016/j.thromres.2005.03.030

Thrombosis Canada. Pulmonary embolism (PE): treatment. 2023. https://thrombosiscanada.ca/hcp/practice/clinical_guides?language=en-ca&guideID=44 (accessed 12 January 2024)

Tian Y, Sun B, Sun G. Research progress of nephrotic syndrome accompanied by thromboembolism. Int Urol Nephrol. 2023;55(7):1735–1745. https://doi.org/10.1007/s11255-023-03474-8

Vestergaard SV, Birn H, Darvalics B et al. Risk of arterial thromboembolism, venous thromboembolism, and bleeding in patients with nephrotic syndrome: a population-based cohort study. Am J Med. 2022;135(5):615–625.e9. https://doi.org/10.1016/j.amjmed.2021.11.018

Waller AP, Troost JP, Parikh SV et al. Nephrotic syndrome disease activity is proportional to its associated hypercoagulopathy. Thrombosis Res. 2021;201:50–59. https://doi.org/10.1016/j.thromres.2021.02.007

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(7):e0255009. https://doi.org/ 10.1371/journal.pone.0255009

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(3):897–906. https://doi.org/10.1148/radiol.14140121

Zhang L, Zhang H, Zhang J et al. Rivaroxaban for the treatment of venous thromboembolism in patients with nephrotic syndrome and low AT-III: a pilot study. Exp Ther Med. 2018;15(1):739–744

Zwaginga JJ, Koomans HA, Sixma JJ et al. Thrombus formation and platelet-vessel wall interaction in the nephrotic syndrome under flow conditions. J Clin Invest. 1994;93(1):204–211. https://doi.org/10.1172/JCI116947