Longitudinal Analysis of Prophylactic Anticoagulation in Primary Nephrotic Syndrome: Low Incidence of Thromboembolic Complications

Thomas McDonnell[a]   John Hartemink[a]   Omar Ragy[a]   Katherine Parker[b]

Meshaal Shukkur[a]   Jecko Thachil[b]   Durga Kanigicherla[a, c]

[a]Manchester Institute of Nephrology and Transplantation, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester, UK; [b]Department of Hematology, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester, UK; [c]Division of Cardiovascular Sciences, University of Manchester, Manchester, UK

Abstract

Introduction: Thromboembolic events (TEEs) are a serious and potentially fatal complication of nephrotic syndrome (NS). Despite this, there is a lack of evidence examining the benefits of prophylactic anticoagulation (PAC) in NS. It was our objective to review the risk factors, rates of TEEs, and patterns of PAC in patients with primary NS, with the aim to provide a pragmatic approach to PAC in primary NS. ***Methods:*** This is a retrospective longitudinal cohort study of adult patients with primary NS. Included were as follows: biopsy-proven minimal change disease and focal segmental glomerulosclerosis (described as a combined podocytopathy cohort) plus membranous nephropathy (MN) over an 8-year period from a single centre. Anticoagulation practice, TEEs, and longer term outcomes were recorded. ***Results:*** Fifty-four patients with MN and 48 patients with podocytopathies were included. Baseline demographics and severity of NS were compa- rable. Those with MN were more likely to develop TEE 12 (22%) versus 4 (8%) (*p* = 0.027) though this difference was predominantly seen at index diagnosis. Only 2 patients developed TEEs during active incident NS. Rates of PAC were similar when comparing MN (53%) and podocyto- pathies (58%). Those with a serum albumin <20 g/L and HAS-BLED score <3 were most likely to receive PAC (22/30, 73% in MN vs. 21/30, 70% in podocytopathy). Warfarin was the most common agent used in MN cohort 18/26 (69%) versus prophylactic dose low-molecular-weight heparin in the podocytopathy cohort 12/28 (43%). ***Discussion/ Conclusion:*** PAC practices applied in this cohort of patients were pragmatic and effective, with low TEE rates during active NS.

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Introduction

Thromboembolic events (TEEs) are a serious and potentially fatal complication in nephrotic syndrome (NS). Primary glomerulonephritis is the commonest cause of NS and can be categorised based on histology.

Correspondence to:
Durga Kanigicherla, durga.kanigicherla@manchester.ac.uk
Thomas McDonnell, Thomas.mcdonnell@srft.nhs.uk

Membranous nephropathy (MN) and podocytopathies, which are divided into minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS), are the leading causes of primary NS [1]. TEEs can be separated into both venous (VTE) and arterial events (ATE), and both are associated with primary glomerulonephritis [2]. Risk of TEEs differs with the primary cause of NS, with the greatest risk in MN. There are reports of up to 36% of patients with MN experiencing VTE on screening studies [3, 4]. Recent studies in MCD reported an incidence rate of VTE at 4–12% compared to about 24% in older studies [5–7]. In FSGS, VTE has been noted in 3–10% of patients, although this also includes studies where patients underwent prospective radiological screening [2, 5, 8]. In contrast to VTE, there is limited literature relating to ATE and risk factors.

Clinical markers of severity of NS are linked to the development of TEEs beyond the underlying cause. Risk for deep vein thrombosis (DVT) and/or renal vein thrombosis (RVT) seems to be higher when the serum albumin (sAlb) concentration is less than 20–25 g/L [9]. Traditional risk factors such as sex, age, hypertension, diabetes, smoking, prior ATE, and eGFR were significantly associated with ATE in a study of patients with NS undertaken by Mahmoodi et al. [7], but there was no association between ATE events with degree of proteinuria or sAlb. In contrast, a larger study by Lee et al. [10] of two large cohorts of patients with MN, one as a validation cohort, found that early cardiovascular events within the first 2 years had a correlation with proteinuria and hypoalbuminemia. However, after 2 years, events were not related to the nephrotic state.

Despite the demonstrated association between NS and TEEs, there is paucity of evidence examining benefits of prophylactic anticoagulation (PAC) and when and in whom initiation could be considered. Few single-centre series are available showing benefit of PAC, with efficacy in prophylaxis group and low incidence of bleeding. However, randomised control trials are lacking and there is in fact only one prospective study, designed merely to assess the safety of low-molecular-weight heparin (LMWH) in a small number of patients [10]. Resulting review articles and KDIGO guidance propose consideration of PAC in those with sAlb less than a threshold of 20–25 g/L, if bleeding risk is not elevated. However, it is well acknowledged that this is not rooted in robust evidence [9, 11].

Given the lack of clarity and heterogeneity of practice, it was our objective to review the patterns of prophylaxis for TEEs as well as the risk factors and rates of TEEs in patients with primary NS in our centre. We studied these with the aim to add further evidence to this sparsely investigated area in NS.

Methods

This is a retrospective longitudinal cohort study of adult patients with primary NS. This is a service evaluation project that received approval from the Clinical Audit department at the Manchester Royal Infirmary; anonymised data were approved for analysis and publication of results as part of service evaluation project.

Study Population
All patients presenting to Manchester University NHS Foundation Trust with NS related to biopsy-proven MN, MCD, and FSGS (combined to podocytopathy cohort), from August 2013 to February 2021, were considered eligible for inclusion. Date of biopsy was considered "time-zero." Date at last follow-up was at censoring or at death.

Patients were excluded if they did not exhibit NS. NS was defined as sAlb <30 g/L and urinary protein creatinine ratio (uPCR) >300 mg/mmol. sAlb was measured via anionic dye bromocresol purple (BCP) method. The bromocresol green assay is known to overestimate sAlb measurements in comparison to BCP (used in this study); KDIGO 2021 management of glomerular diseases guidelines section 39 reflects this, suggesting that a value of 20 g/L should be used when BCP or immunoassays for sAlb levels are used in comparison to 25 g/L when bromocresol green assay is used (when referencing PAC initiation in MN). Only patients with primary NS were included in the study, as in thromboembolism associated with secondary NS, an increase in risk of TE could be contributed by primary cause (such as cancer or autoimmune disease). Standard treatment of primary kidney disease (MN/podocytopathy) was followed as per KDIGO 2012 guidance.

Patients already receiving anticoagulation at presentation were excluded, though 6 patients were already on antiplatelet agents. Antiplatelet agents were not used as prophylaxis of TEE in the study. Demographics, baseline clinical variables (serum creatinine, eGFR, sAlb, and uPCR at presentation) were recorded. Bleeding risk was estimated using the HAS-BLED (hypertension = 1, age >65 = 2, stroke history = 1, renal disease = 1, liver disease = 1, labile INR = 1, ethanol = 1, drugs = 1) score if patients were to receive anticoagulation [12].

Outcome
Outcomes of interest during follow-up included TEEs. These were defined a TEE as any arterial or venous thrombosis documented during the follow-up period (DVT, pulmonary embolism (PE), RVT, and arterial thrombosis in the form of ischaemic event). No routine imaging was undertaken; clinically appropriate imaging was undertaken as per patient symptoms: Doppler ultrasound for DVT, CT pulmonary angiogram for PE, and CT abdomen pelvis for RVT. Time taken for sAlb to increase above 20 g/L during follow-up was measured; type and duration of anticoagulation if used were noted. KDIGO glomerulonephritis guidelines were published in 2012 and used as reference for clinical

practice. Guidance suggested: Consideration of PAC if sAlb drops below 20–25 g/L (20 g/L was used given BCP assay use) with one or more of the following: proteinuria >10 g/d; body mass index> 35 kg/m^2; family history of thromboembolism with documented genetic predisposition; New York Heart Association class III or IV congestive heart failure; recent abdominal or orthopaedic surgery; or prolonged immobilization. Either warfarin or LMWH could be used; decision was left to the treating clinician in combination with patient preference. Complete remission (CR), this was defined as a uPCR <30 mg/mmol, stable serum creatinine, and sAlb >35 g/L, mortality, and related bleeding events. Any bleeding event that occurred within the time frame of a patient being on PAC for NS was included.

To avoid any missed events, patient records were reviewed using multiple sources, including the patients' coded diagnoses, hospital correspondence, discharge notifications, imaging, blood results, and primary care records. The database was reviewed by two independent clinicians to ensure accuracy.

Statistical Analysis

Descriptive statistics were used to summarise clinical and laboratory data. Continuous data were expressed as mean (95% CI) or median (interquartile range). Groups were compared using Student's *t* test for normally distributed data or Wilcoxon rank sum test for non-parametric data. Events were presented as absolute values and percentages and were compared using a proportion test. Kaplan-Meier survival plots with log-rank test were used for survival analysis, when examining TEEs. These were generated based on primary diagnosis (MN vs. iNS) and sAlb at presentation (<20 vs. ≥20 g/L). A *p* value smaller than 0.05 was considered statistically significant. Statistical analysis was performed using Stata software package (version 14.2; StataCorp).

Results

During the study period, 109 patients were identified as having histology consistent with MN or MCD and FSGS (combined as a podocytopathy cohort). Seven patients were excluded as they did not meet the definition of NS; all 7 had a sAlb >30 g/L at presentation. There were 54 patients with MN and 48 with podocytopathies. Within the podocytopathy group, 25 had histology consistent with FSGS and 23 with MCD. There were no statistically significant differences in baseline characteristics between the two groups (Table 1). Pre-existing diabetes was noted in 13% in MN versus 10% in the podocytopathy cohort and HAS-BLED scores were 1 versus 1.1, respectively. Median eGFR was 55.5 versus 63.1 mL/min/1.73 m^2, median sAlb 17 versus 15.5 g/L, and median uPCR 965 versus 815.5 mg/mmol in MN versus podocytopathies groups. The number who presented with sAlb <20 g/L at presentation was 70% for MN versus 67% for podocytopathies. Mean follow-up in the MN group was 2,057 days versus 1,390 days in podocytopathies.

Sixteen TEEs were noted in total. An increased number of TEEs occurred within the MN group versus the podocytopathy group at 12 versus 4 events (*p* = 0.027). Five of the 16 TEEs occurred at index presentation: 1 with PE, 1 with DVT, and 3 with combined RVT and PEs. All of these were in the MN group (*p* = 0.031). Five of the 11 events noted during follow-up were in venous beds: 3 DVTs, 1 cerebral venous sinus thrombus, and 1 PE. There were a total of 6 ATE including 4 cerebrovascular strokes, 1 myocardial infarction, and 1 femoral artery thrombus (Table 2). There was no statistically significant difference in mortality between the MN group versus podocytopathy group at 15% versus 23%, with none of these being related to TEEs.

When reviewing PAC practices, the 5 patients who suffered TEEs at index presentation were excluded (all from the MN group) as anticoagulation for proven thrombosis is standard of care and not considered PAC. PAC was used in 53% of MN patients and 58% in podocytopathies, which was not statistically significant. There was no difference between the proportion of patients anticoagulated with a HAS-BLED score <3 and sAlb <20 g/L: 73% in MN versus 70% in the podocytopathy cohort. Most common agent used for PAC in MN was warfarin at 69%, while prophylactic dose of LMWH was the commonly used agent for PAC in the podocytopathies at 43%, which was statistically significant.

During total follow-up, 8 patients who initially received PAC, suffered a bleeding episode. However, only 1 patient (2%) experienced a bleeding episode while anticoagulated for NS, suffering a retroperitoneal haemorrhage while on warfarin. The other 7 either occurred distant to or unrelated to incident NS and PAC. Two received anticoagulation for other reasons and 5 were not receiving anticoagulation during the bleeding episode.

Time taken for sAlb to increase above 20 g/L in MN versus the podocytopathy group was almost three times as long at 146.2 days versus 54.7 days (*p* < 0.01). Mean duration of anticoagulation was 497 versus 156 days in the MN versus the podocytopathy group, respectively (*p* < 0.05). Survival curve of time to TEEs (Fig. 1) shows that there was no difference in risk for patients with MN compared to those with podocytopathies (log rank 0.29) or for patients presenting with sAlb of <20 g/L to those >20 g/L (Fig. 2) (log rank 0.780).

Table 2 separates patients into causes of NS (MN vs. podocytopathies) excluding those who presented with a TEE. Groups are subdivided based on sAlb above/below 20 g/L at presentation, and further subdivided based on whether PAC was initiated or not. Each patient who suffered a TEE post presentation has been placed in one

Table 1. Baseline demographics and results for the cohort, split into membranous nephropathy (MN) and a podocytopathy (combined FSGS/MCD)

	Membranous	Podocytopathy (FSGS/MCD)	*p* value
Baseline characteristics			
Number	54	48	
Age (IQR)	63.2 (18.3)	63.8 (36.1)	0.668
Proportion male, %	39	25	0.036
Diagnosis	–	25 FSGS 23 MCD	
Diabetes, *n* (%)	7 (13)	5 (10)	0.810
HAS-BLED (mean)	1	1.1	0.612
eGFR (IQR)	55.5 (42)	63.1 (56.2)	0.995
sAlb (IQR)	17 (8)	15.5 (9.5)	0.120
Patients with sAlb <20 g/L, *n* (%)	38 (70)	32 (67)	0.129
uPCR, mg/mmol (IQR)	965 (623)	815.5 (630)	0.301
Results			
Mean follow-up, days (95% CI)	2,057 (1,885–2,229)	1,390 (1,249–1,531)	<0.001
Mortality, *n* (%)	8 (15)	11 (23)	0.294
TEEs, *n* (%)	12 (22)	4 (8)	0.027
VTEs, *n* (%)	8 (15)	2 (4)	0.071
ATEs, *n* (%)	4 (7)	2 (4)	0.487
TEEs at presentation, *n* (%)	5 (9)	0	0.031
TEEs post diagnosis, *n* (%)	7 (13)	4 (8)	0.452
Numbers (excluding index TEEs)	49	48	
Time to TEE, days (95% CI)	1,018 (380–1,658)	285 (−83.6–655)	0.037
Total PAC, *n* (%)	26 (53)	28 (58)	0.620
Duration of PAC, days (95% CI)	497 (265–728)	156 (52.3–259)	0.042
Warfarin, *n* (%)	18 (69)	8 (29)	0.026
Therapeutic dose: LMHW, *n* (%)	1 (4)	2 (7)	0.545
Prophylactic dose: LMHW, *n* (%)	2 (8)	12 (43)	0.002
DOAC, *n* (%)	1 (4)	0	0.178
Mixed, *n* (%)	4 (15)	6 (21)	0.598
Number anticoagulated with HAS-BLED <3 and sAlb <20 g/L, *n* (%)	22/30 (73)	21/30 (70)	0.633
Bleeding events related to PAC	1 (4)	0	
Time to sAlb increase to >20 g/L, days	146.2 (104–188)	45.7 (29–62.3)	<0.01

of these categories. Detailed description of the type and time of TEE, in addition to if TEE was during active NS is described. PAC is more common when sAlb is <20 g/L, as in podocytopathy group this was 76% versus 65% in the MN group.

Examining the 4 TEEs that occurred in the podocytopathic group, all 4 occurred in those whose sAlb <20 g/L and PAC were initiated. However, all these events occurred distant to index episode and after achieving CR. The use of PAC during active NS would not have been expected to have a bearing on these events. Patient 1 suffered a CSVT on day 243 during a relapse (not the index episode when PAC was used), patient 2 a femoral artery thrombosis on day 96 with a relapse (not the index episode when PAC was used), patient 3 experienced multiple cerebral infarcts

while in CR with NS on day 621, and patient 4 developed a DVT on day 182 also after achieving CR.

Examining the 7 TEEs that occurred post diagnosis in the MN group, patient 1 suffered a DVT at day 469 after achieving partial remission; at presentation, their sAlb was >20 g/L and they received PAC. Patient 2 suffered a PE at day 415 with active NS; at presentation, his sAlb was >20 g/L and the subject did not receive PAC (HAS-BLED 3). Both patients 3 and 4 had sAlb <20 and received PAC at presentation. Patient 3 suffered 2 DVTs at day 1,126 and 1,379, both times while in CR. Patient 4 suffered a thrombotic cerebrovascular accident (CVA) at day 587 with active NS. Lastly, patients 5, 6, and 7 with sAlb <20 did not receive PAC. Patient 5 suffered a thrombotic CVA at day 1,062 while in CR (HAS-BLED

Table 2. Patients were categorised based on their diagnosis: membranous nephropathy (MN) and podocytopathy (a combination of FSGS/MCD)

	Podocytopathy (FSGS/MCD), n = 48				MN, n = 49			
	Alb ≥20, n = 15		Alb <20, n = 33		Alb ≥20, n = 15		Alb <20, n = 34	
	PAC (+), n = 3	PAC (−), n = 12	PAC (+), n = 25	PAC (−), n = 8	PAC (+), n = 4	PAC (−), n = 11	PAC (+), n = 22	PAC (−), n = 12
TEs during incident NS	0	0	0	0	0	1	1	0
Details						• PE at day 415 while in NS	• CVA at day 587 while in NS	
TEEs after CR of NS	0	0	4	0	1	0	1	3
Details			• CSVT at day 243 during relapse • Femoral artery thrombus at day 96 during relapse • Multiple cerebral infarcts at day 621 while in remission • DVT at day 182 while in remission		• DVT at day 469 while in remission		• DVT at day 1,126 while in remission	• CVA at day 1,062 while in remission • MI at 1,040 while in remission • CVA at day 2,432 while in remission

Each category was further stratified by serum albumin levels (sAlb ≥20 g/L or <20 g/L at initial presentation) and PAC therapy was administered. This resulted in four distinct subgroups for each pathological diagnosis. The occurrence of thromboembolic events (TEEs) was recorded for each subgroup, detailing whether events happened during the initial episode of nephrotic syndrome or after achieving complete remission.
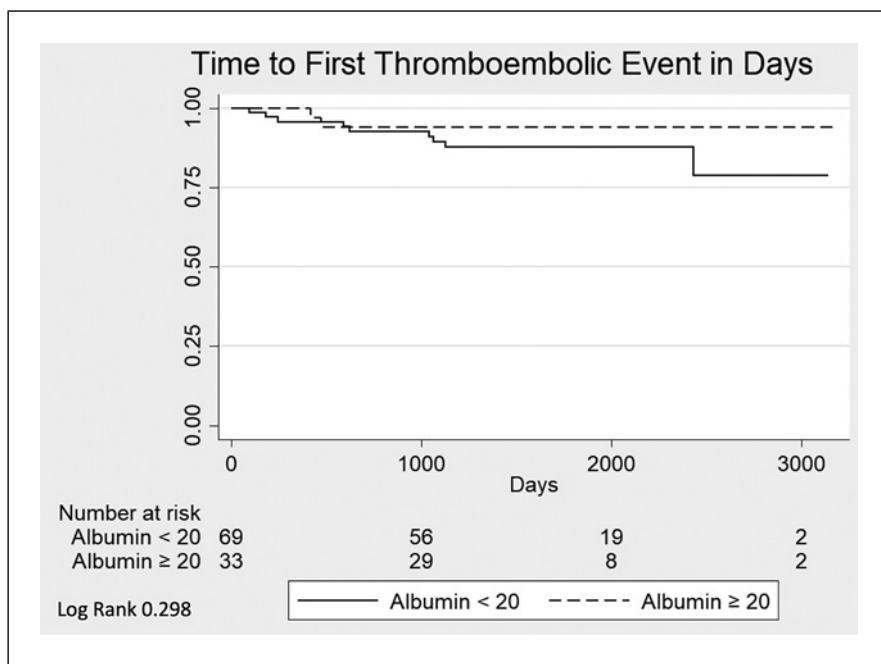

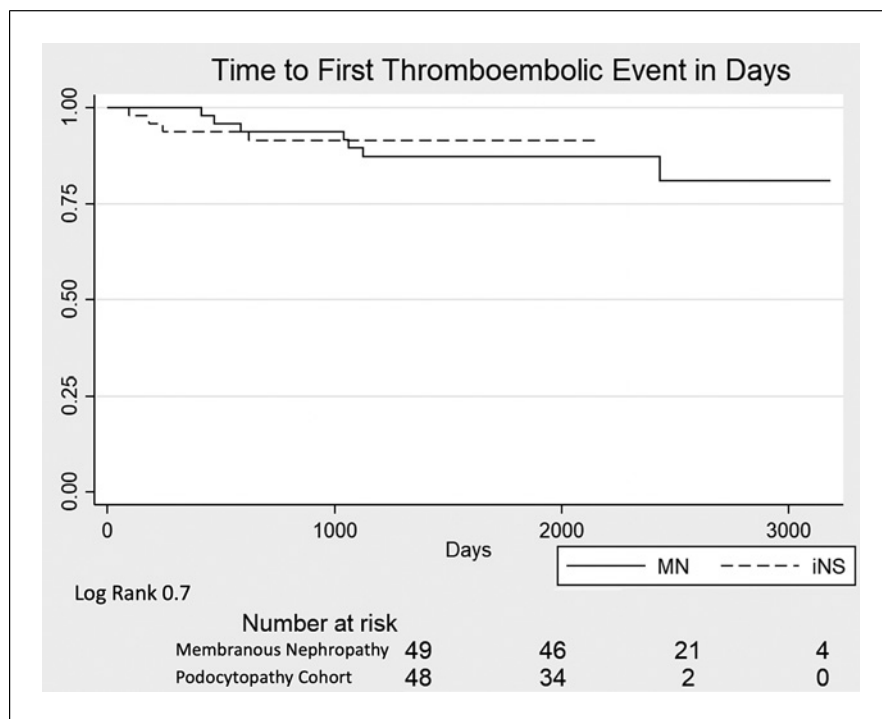**Fig. 1.** Kaplan-Meier curve: time to first TEEs (days); sAlb <20 g/L versus ≥20 g/L.

Fig. 2. Kaplan-Meier curve: time to first TEE (days); MN versus idiopathic NS.

4), patient 6 suffered an MI at day 1,040 while in CR (HAS-BLED 3), and patient 7 suffered a thrombotic CVA at day 2,432 while in CR (HAS-BLED score 3).

Discussion

Use of PAC in patients with pNS remains a poorly understood area owing to lack of studies examining the potential benefits versus risks of PAC, when to anticoagulate and with what agent. In this series of 102 consecutive patients with NS from MN or a podocytopathy, 16 patients developed TEEs during follow-up. However, five experienced TEE at presentation and thus were not eligible for PAC. Of the remaining 97, only 2 patients developed TEEs during active incident NS (2%), with 1 patient on PAC and the other not on PAC, and only one bleeding event (2% of those on PAC) attributed to anticoagulation. The remaining 9 TEEs included 2 during relapses of NS after CR, and 7 after achieving partial or CR of NS. For these 9 patients, PAC during incident NS alone would not have prevented the event. Rates of TEEs during incident NS are low (2%) with the PAC practices employed in this study. This is lower when compared to previous published literature, and certainly no higher even when you include those events associated with relapse or while in remission [5, 13].

There is significant heterogeneity of practice when it comes to PAC in NS. A survey presented by Prof. Wetzel et al. [unpubl. data] at the 2nd Annual ERKNET Meeting in 2018 highlights the dilemma. Eleven renal centres in the ERKNET group were surveyed with regards to practices around PAC. Eight centres responded with regular use of PAC, with 9 centres using a sAlb threshold as a marker. At sAlb of 17 g/L, all 11 centres would initiate PAC. There was no clear agreement with which agent, although warfarin was the most common choice in the survey. Another recent survey of 117 combined UK nephrologists, renal pharmacists, and haematologists reported that over 80% use a combination of sAlb and bleeding risk when considering initiation of PAC. The most frequent anticoagulants used were warfarin or therapeutic LMWH when sAlb was <20 g/dL, and surprisingly, 25% reported using a direct oral anticoagulant (DOAC) [14].

In our study, there was a trend towards use of PAC in those with sAlb <20 g/L and HAS-BLED score <3. With this approach, rates of TEEs and bleeding were low and similar in patients with MN or a podocytopathy. Warfarin was the most common agent used in MN compared to prophylactic dose of LMWH in the podocytopathy group. The anticoagulation practices applied in this cohort of patients are aligned with prior studies on PAC in NS. In a prospective study, Rosteker et al. [15] established the safety of LMWH in NS. Medjeral-Thomas et al. [16]

showed safety and effectiveness of both warfarin and LMWH for all patients with pNS and a sAlb <20 g/L, however neither study incorporated a bleeding risk assessment tool.

In our study, event rates were higher in NS related to MN compared to the podocytopathy cohort (22 vs. 8%). However, when those who presented with a TEE at index presentation were excluded (n = 5), there was no statistically significant difference between the groups. This is important to note, as the decision to use anticoagulation in patients who present with TEEs at index presentation is already clear. Thus, this evidence suggests that both MN or a podocytopathy diagnosis may confer similar risk post index diagnosis, however this needs validation with larger studies. Survival curves highlighted a trend towards greater risk of developing TEEs in those with sAlb <20 g/L compared to sAlb ≥20 g/L but this did not reach statistical significance, likely relating to the low number of events. The use of PAC in higher risk groups with sAlb <20 g/L is likely to have impacted on the overall number of TEEs (Fig. 1).

Though TEE rates post diagnosis may be similar, as in Figure 2, patients with MN seemed to carry some risk for TEE much longer into their disease course, though again this did not meet statistical significance. Given the nature of the disease characteristics, they also remained nephrotic for much longer, at an average of 146 compared to 54 days, and also received anticoagulation for much longer. When examining the 11 TEEs that occurred post diagnosis, 6 occurred in patients who were in CR and 2 were associated with relapse. In both of these situations, anticoagulation was withheld once CR was achieved and therefore thrombotic events can be considered either unrelated to the incident episode (when PAC would have been used) or unpredictable as in the relapse group. Two of these patients received anticoagulation and the patient who did not receive PAC had a sAlb >20 g/L and a HAS-BLED score of 3 – both of which may be considered as deterrents to PAC.

It is well documented that primary MN carries a greater TEE risk compared to podocytopathy and other forms of NS, which is also seen in our study [16]. Despite the modest size of the cohort in this study, it is still noteworthy that the proteinuria, eGFRs, sAlb, and baseline characteristics are statistically similar between MN and iNS. Therefore, it raises the question of whether there is a unique biological mechanism for the increased thrombosis risk noted in primary MN compared to podocytopathies which cannot be predicted using surrogate markers such as severity of NS.

Over the recent past there has been a paradigm shift in our understanding of the aetiology of idiopathic MN. Its concept as an autoimmune process was solidified in 2009 following the discovery of the M-type phospholipase A2 receptor as the target antigen, with several newer antigens being discovered in recent years [17, 18]. We speculate that the increased TEE rates seen in idiopathic MN could be associated with an autoimmune process, with either a known, or yet unknown autoantibody affecting the clotting cascade. Even prior to the discovery of phospholipase A2 receptor, it was postulated that there may be a unique autoimmune mechanism responsible for the increased TEE rate in MN. It was proposed at the time that the increased circulating anti-enolase seen in MN could inhibit fibrinolysis and contribute to the exaggerated TEE rates seen [6]. Given the significant advances in our understanding of the immunology of idiopathic MN over the last decade, a dedicated study examining this would be useful.

Use of DOACs only occurred in 1 patient for PAC. Their use has become widespread in general population for both treatment and prophylaxis of VTE, owing to their ease of administration without the requirement for monitoring. They are highly protein-bound (90–95%) which makes their pharmacokinetics predictable [19]. However, for this reason, clinicians have been hesitant to use DOACs for PAC in NS due to the unknown effect of hypoalbuminemia on the drug's efficacy. There have only been a few published case reports and two small retrospective reviews detailing the use of DOACs in NS [20–23]. But looking forward, trials currently underway examining the pharmacokinetics of apixaban in NS would hopefully provide insights into some of these uncertainties [24].

We acknowledge the limitations of this study, given that this was a retrospective review of real-world practice. However, KDIGO 2012 glomerular disease guidelines were used as reference, although some of the variations could have been related to individual clinical preference and patient choice. This may have led to potential alterations in decisions regarding the use of anticoagulation on a patient-by-patient basis. Although the number of patients in the study appears small, this remains one of the largest reported series of patients with PAC, and all eligible patients over an 8-year period were included.

Additionally, no screening imaging was undertaken to investigate asymptomatic TEEs, potentially leading to an underestimation of their occurrence, particularly RVT; however, it is debatable if screening for asymptomatic events would alter the outcomes and is not routinely recommended. The study exclusively focused on patients with primary NS attributed to MN, FSGS, and MCD. It is important to acknowledge that these entities represent "patterns of injury" rather than distinct diseases and may encompass heterogeneity in terms of aetiology and pathogenesis. However, notably, in all cases, efforts were

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undertaken to exclude all known secondary causes of the included primary NSs.

In conclusion, it is evident that the anticoagulation practices applied in this cohort of patients were pragmatic and effective, with low TEE and bleeding rates during active NS, and were certainly no higher than what had been previously observed [5, 13]. Initiating PAC in patients with a sAlb <20 g/L and a HAS-BLED score <3 would appear to be a safe and practical approach until further evidence accumulates from prospective studies or randomised trials. We suggest considering warfarin for PAC in patients with MN and prophylactic dose of LMWH in patients with a podocytopathy due to the prolonged time the sAlb remains under 20 g/L, posing longer duration of risk for TEE in the MN group.

Statement of Ethics

This study protocol was reviewed and approved by the Clinical Audit department at the Manchester Royal Infirmary. The study was a retrospective observational study and fully anonymised secondary data were used. It complied with the Declaration of Helsinki, therefore not requiring review by a Research Ethics Committee. The Clinical Audit department at the Manchester Royal Infirmary waived the need for individual patient consent.

Conflict of Interest Statement

There is no conflict of interest to declare.

Funding Sources

No funding was received for the project.

Author Contributions

Thomas McDonnell was involved with data collection and interpretation, concept, and writing of the manuscript. John Hartemink was involved with statistical analysis. Omar Ragy, Katherine Parker, and Jecko Thachil were involved with concept and editing. Meshaal Shukkur was involved with data collection. Durga Kanigicherla was involved with concept, writing, and editing of the manuscript and supervision.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author, where anonymized data will be made available upon reasonable request.

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