Venous thromboembolism in primary nephrotic syndrome – is the risk high enough to justify prophylactic anticoagulation?

Alastair J Rankin – MRCP (Glasgow)
Emily P McQuarrie – MRCP (Glasgow)
Jonathan G Fox – FRCP (Glasgow)
Colin C Geddes – FRCP (Glasgow, Edinburgh)
Bruce Mackinnon – FRCP (Glasgow)
Glasgow Renal and Transplant Unit. On behalf of the Scottish Renal Biopsy Registry.

Running title: VTE in primary nephrotic syndrome
Key words: Nephrotic syndrome, anticoagulation, venous thromboembolism, glomerulonephritis

Corresponding author: Alastair Rankin, Renal Unit, Ward4D, Queen Elizabeth University Hospital, 1345 Govan Rd, Govan, Glasgow G51 4TF, Alastair.rankin@nhs.net, 07792 597 049

Word count (abstract): 325
Word count (main text): 3580
Number of references: 21

ABSTRACT

BACKGROUND: The reported incidence of venous thromboembolism (VTE) in patients with nephrotic syndrome (NS) varies widely, as does the approach to prophylactic anticoagulation. We aimed to assess the incidence of VTE in patients with primary NS in order to inform a sample size calculation to determine if a future clinical trial will ever be feasible.

METHODS: All adults undergoing native renal biopsy for NS between 2008 and 2013 yielding a diagnosis of primary glomerulonephritis were identified. Baseline serum albumin, urine protein:creatinine ratio, estimated glomerular filtration rate, date of biopsy and histological diagnosis were recorded. Episodes of objectively verified VTE were identified using the electronic patient record. Sample size calculations were performed based on 2 independent samples with a dichotomous outcome and to achieve a power of 80% and $p < 0.05$.

RESULTS: 206 patients were included, of which 60% were male and mean age at biopsy was 55 years (standard deviation 19). Median follow-up was 2.9 years (inter-quartile range (IQR) 1.6-4.7). Fourteen (6.8%) patients suffered VTE. Median time to diagnosis of VTE from renal biopsy was 36 days (IQR -22 to 178), with 6 VTEs occurring prior to biopsy and 1 during remission. In a total of 270 patient years of NS there were 7 VTE that could potentially have been avoided if anticoagulation was given for the duration of NS, i.e. 2.6% risk per year of NS; this risk was highest for patients with minimal change nephropathy at 13.3% per year of NS, compared to 0.65% per year of NS for those with idiopathic membranous nephropathy. Assuming a 75% reduction in

the incidence of VTE with prophylactic anticoagulation, 972 participants would be required for a future clinical trial to have 80% power.

CONCLUSIONS: Patients with primary NS are at an increased risk of VTE. The timing of VTE means that only half of episodes would be targeted by prophylactic anticoagulation. Given the low frequency of events, a well-powered clinical trial would be challenging to achieve.

INTRODUCTION

Patients with nephrotic syndrome (NS) due to primary renal diseases are at an increased risk of venous thromboembolism (VTE). However, the reported incidence of VTE in patients with NS varies widely from 7–50%[1]. These figures are often based on historical data, with series that differ in their inclusion criteria and commonly include asymptomatic thrombi[1].The risk is reported to be highest in patients with idiopathic membranous nephropathy (IMN),[2] severe hypoalbuminaemia[3], and early in the course of NS - particularly within the first 6 months from diagnosis[1,4].

In order to reduce the morbidity and mortality of VTE in patients with NS, international guidelines advise consideration of prophylactic anticoagulation for high risk patients for the duration of NS[5]. There are no prospective randomised clinical trials that examine the use of prophylactic anticoagulation in patients with NS. Furthermore, these patients may have a high prevalence of recognised risk factors for bleeding such as chronic kidney disease (CKD) (estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^2), hypertension and anaemia[6,7]. The decision to start anticoagulation is therefore based on clinician judgement, balancing the risk of thrombosis versus the risk of bleeding.

In the absence of trial evidence, an accurate description of the risk of clinically significant VTE in NS is crucial to assist clinicians in their decision-making. Given the advances in radiological tests for diagnosis of VTE and also new

approaches to remission induction, existing data from cohorts that pre-date these developments may not be applicable to the modern clinical era. To date, the practice in our centre has been not to anticoagulate patients with NS routinely, unless there is clinical evidence of symptomatic VTE. We aimed to assess the incidence of symptomatic VTE within our population of patients with NS due to biopsy-proven primary glomerulonephritis, in order to inform a sample size calculation to determine if a future clinical trial will ever be feasible.

METHODS

All adult patients undergoing native renal biopsy for the primary indication of NS between 2008 and 2013 in the Glasgow Renal & Transplant Unit were identified. This unit serves a defined population of 1.6 million, with the predominant ethnic group being white.

Baseline serum albumin (sAlb), urine protein:creatinine ratio (uPCR), eGFR (calculated by Modified Diet in Renal Disease (MDRD4) formula[8]), date of biopsy and histological diagnosis were recorded. We excluded patients who did not have a diagnosis of primary glomerulonephritis. Patients with membranous nephropathy were excluded if it was secondary to an established causative factor – patients are routinely screened for viral hepatitis and systemic lupus erythematosus at presentation and undergo full clinical examination, chest x-ray and other investigations to exclude secondary causes as appropriate.

Data were also collected regarding aspirin, anticoagulation and immunosuppressive therapy during follow-up. Bleeding complications were recorded.

Using the electronic patient record, which includes automated downloads of all radiological reports and clinical correspondence, incidence of objectively confirmed VTE at any site was determined. VTE were diagnosed by Doppler ultrasound, computed tomography with contrast, ventilation-perfusion imaging or post-mortem pathological examination. Patients were not prospectively screened for VTE but investigated on the basis of clinical suspicion. VTE occurring more than1 year prior to biopsy and episodes of arterial thrombosis were not included. Incidence of renal replacement therapy (RRT) and cause of death were also recorded.

Follow-up was deemed as the latest date of contact with renal services in a setting that would allow identification of significant VTE (mostly out-patient clinic review). Patients who suffered VTE were censored from the date that VTE was confirmed. Patients who required RRT were not censored from follow-up, but were censored for the purposes of calculating duration of NS. If no information was available regarding cause of death, the patients were censored at the time of last renal review.

Total time in NS was calculated for each patient based on partial remissions and relapses during follow-up. Time to first partial remission was calculated based on the date of the 2nd consecutive uPCR<300mg/mmol and

sAlb>30g/L. Relapse was defined as the first date after remission on which the patient had a 2nd consecutive uPCR >300mg/mmol and sAlb <30g/L, or the date on which the patient began treatment for a clinical diagnosis of relapse of NS.

Ethics

Data were accessed via the West of Scotland Electronic Renal Patient Record, which is the primary clinical record for all patients attending secondary care renal services in our centre. As an evaluation of current clinical practice using routinely collected patient data, ethical approval was not required.

Data analysis

Baseline demographics were compared using Student t-test, Mann-Whitney U-test, and $\chi 2$ test as appropriate, with mean values and standard deviation reported for normally distributed data, and median plus inter-quartile range for non-parametric data. Relative risk (RR) was calculated using binary logistic regression. Reported RR and the associated 95% confidence intervals (95% CIs) express the risk of death based on the achievement of remission. Analyses were undertaken using IBM SPSS (version 22, New York) with additional tables and figures created using Microsoft Excel 2011 Software (Microsoft, USA). Sample size calculations were performed based on 2 independent samples with a dichotomous outcome and to achieve a power of 80% and $p < 0.05$.[9]

RESULTS

Demographics

A total of 1178 patients underwent first renal biopsy between 2008 and 2013, for which NS was the primary indication in 291. In 85 patients, NS was secondary to systemic disease (diabetes, lupus, secondary membranous or amyloidosis) and these patients were excluded from further analyses. Of the remaining 206 patients with NS secondary to biopsy-proven primary glomerular disease, 60% were male, mean age at biopsy was 55 (SD 19) years, mean eGFR 72 (SD 40) ml/min/1.73m^2, median uPCR 812 mg/mmol (IQR 535-1200) and mean sAlb 19.1g/l (SD 7.1) (*table 1*). Histological diagnoses made were idiopathic membranous nephropathy (IMN) (38%), minimal change nephropathy (MCN) (26%), focal segmental glomerulosclerosis (FSGS) (18%), IgA nephropathy (IgAN) (11%) and mesangiocapillary glomerulonephritis (MCGN) (7%).

Median follow-up was 2.9 years (IQR 1.6-4.7). The median duration of NS was 0.79 years (IQR 0.3-2.0) years; however, this varied for different histological diagnoses (*table 2*). 22 (10.7%) patients developed end-stage renal failure requiring long-term RRT. Median time to RRT from biopsy in these patients was 1.5 years (IQR 0.3-2.2).

Incidence of VTE

Fourteen (6.8%) patients had VTE, of whom 7 had IMN, 5 MCN, 1 IgAN and 1 FSGS. 65% were male and, at time of diagnosis of VTE, mean age was 53.6

(SD 14) years, mean eGFR 61.2 (SD 32) ml/min/1.73m^2, median uPCR 750 (IQR 404-1453) mg/mmol and mean serum albumin 22.8 (SD 10.8) g/l. There was no significant difference in the mean age (p=0.67), sAlb at biopsy (p=0.5) or median uPCR at biopsy (p=0.9) between those who suffered a VTE and those who did not. Nine VTEs occurred in the 123 patients with a sAlb <20 at biopsy (7.3%) and 5 VTEs occurred in 83 patients with a sAlb ≥20 at biopsy (6.0%) (p=0.7).

Site and timing of VTE

The sites of VTE were pulmonary (n=8), leg deep vein (n=3), renal vein (n=2) and portal vein (n=1). Median time to diagnosis of VTE from renal biopsy was 36 days (IQR -41 to 178). Six patients had a diagnosis of VTE before biopsy, with only 1 of these 6 patients being known to renal services at time of VTE. Excluding VTE pre-biopsy (n=6), median time to VTE was 177 days (99-223 days) with 7 of the 8 VTEs occurring within the first year after biopsy. In total, 270 patient years of NS post-biopsy were observed, during which time there were 8 VTEs; this equated to a 3.0% risk of VTE per year of NS post-biopsy. One of the 8 patients suffered a VTE (PE) 17 days after achieving remission from MCN. The incidence of VTE that could potentially be avoided by routine anticoagulation during periods of NS is therefore 2.6% per year of NS (*figure 1*).

VTE by histological diagnosis

The incidence of VTE varied with histological diagnosis. 7 of the 79 patients with IMN had VTE over a cumulative 155 years of NS, equating to 4.5% risk

per year of NS. However, this fell to 0.65% when pre-biopsy VTE were excluded. Patients with MCN had a higher risk, with 5 VTE in 54 patients over 30 years of NS leading to a 16.7% risk per year of NS. The rate of VTE in patients with MCN that could potentially be prevented by prophylactic anticoagulation during NS was 13.3% per year of NS. Patients with histological diagnoses that were neither IMN nor MCN, had an overall risk of 2.4% for each year of NS.

Medications

Fifteen patients in the non-VTE group were prescribed oral anticoagulation (7 atrial fibrillation (AF), 3 historical VTE, 2 left ventricular mural thrombus post-myocardial infarction, 1 for arterio-venous graft patency, 1 femoral artery thrombosis, and 1 brachial artery thrombosis). Eight patients were on anticoagulation prior to biopsy and continued this during follow-up, 7 were started during follow-up, of whom 6 were already in remission from NS. No patients were prescribed anticoagulation as primary prophylaxis of VTE due to NS. During follow-up, 70 patients were prescribed aspirin of which 3 (4.3%) developed VTE. There was no difference in the incidence of VTE between patients who were prescribed aspirin or not (p=0.3). 124 patients (60%) received immunosuppressive medications during follow-up. 58 of these patients received steroid monotherapy and 48 received steroids in conjunction with a calcineurin inhibitor. In addition, 26 patients received cyclophosphamide. VTE rates were higher in those who were prescribed immunosuppression compared to those who were not (p=0.04).

Bleeding complications

No patient who was anticoagulated for a VTE suffered a bleeding complication. Of the remaining patients, 7 (3.4%) experienced episodes of major bleeding, 6 of which were gastrointestinal bleeding.

Survival

Thirty-nine (19%) patients died during follow-up. Two patients had PE listed on their death certificate and were included in analyses as having experienced a VTE. Of the remaining patients, 9 died from infective causes (of which 5 were bronchopneumonia), 8 died from CKD [5 declined/withdrew from RRT, 1 pulmonary oedema despite RRT in the context of acute kidney injury and an acutely ischaemic limb, 1 refractory nephrotic syndrome with recurrent infections, 1 details unknown], 5 from metastatic malignancy, 3 chronic lung disease, 1 heart failure, 1 stroke, 1 sigmoid volvulus, 1 acute intestinal pneumonitis, 1 neurological complications of action myoclonus renal syndrome and 1 patient suffered sudden cardiac death (no post-mortem). A further 2 patients had incomplete information regarding their cause of death but are documented as having acute respiratory symptoms prior to their death, 1 of whom had definitive imaging to exclude VTE. For 4 patients, there was no information available about cause of death; all were still nephrotic at time of death. Failure to reach remission was an indicator of poor prognosis, with a five fold increase in the risk of death compared to patients who achieved at least partial remission (RR 5.23; 95% CI 2.89-9.45).]

Sample size required for a randomised trial

If a 75% reduction in the incidence of VTE with prophylactic anticoagulation is predicted, a randomised trial would require 972 patients to have 80% power and alpha 0.05. The 200 eligible patients in this study (6 patients had VTE before biopsy and would have been excluded from a trial) were recruited from a population of 1.6 million over 6 years, indicating an annual incidence of 2.1 new cases per 100,000 patients. Accounting for an exclusion rate of 20%, it would require 10 large centres (serving populations >1.6 million) to recruit patients over 3 years, with subsequent follow-up for 3 years, to achieve this power, assuming a similar ratio of histological diagnoses and remission rates as observed in our cohort. If, however, anticoagulation were estimated only to reduce VTE rate by 50% then a trial would require a sample size of 2618 to have the same power. If the 4 patients who died of unknown cause of death are counted as having had a VTE and the estimated reduction in VTE rate is maintained at 75%, a trial would require 610 participants to have 80% power and alpha 0.05

DISCUSSION

This is the largest series investigating the incidence of VTE in patients with NS due to biopsy-proven primary glomerulonephritis in the modern clinical era. The overall incidence of clinically significant VTE is 6.8%, with the risk highest early in the course of NS. However, we highlight that almost half of these VTE could not have been prevented with prophylactic anticoagulation as they occurred prior to achieving a renal diagnosis. Furthermore, by analysing risk according to duration of NS, we have identified a previously

unrecognised higher risk of VTE in patients with MCN, than IMN, during the period(s) of NS. Overall, the low incidence of events in a population of patients with the relatively rare condition of NS due to primary glomerulonephritis means that a definitive clinical trial is unlikely to be performed.

Incidence of VTE

The incidence of VTE in our study is consistent with the two largest reported cohorts, in which the rate of clinically significant VTE was found to be 7% and 7.9%, respectively[2,3]. However, both these studies included historical data for patients from the same registry that dated back to 1974, with *Lionaki et al* also using patients from as far back as 1969. NS was not an inclusion criterion in these studies, which may explain the association between the severity of hypoalbuminaemia and the risk of VTE that was observed in these patients but not identified in our study. Interestingly, in our cohort, the incidence of post-biopsy VTE that anticoagulation may prevent was 2.6% per year of NS, but if anticoagulation were stopped at normalisation of serum albumin (as is recommended in the KDIGO guidelines[5]), rather than at remission, the incidence would be 1.85% with a further 1 VTE per 100 patients occurring off treatment. One patient was diagnosed with PE 17 days following complete remission from MCN. It is possible that this could have been prevented by prophylactic anticoagulation if the patient actually developed a DVT during NS (which later emoblised).

The incidence of VTE within the general population and in patients with CKD without NS is already established,[12–14] and allows comparison of risk with these results. Patients with CKD 3 or 4 have been shown to have an incidence of VTE of 4.5 per 1000 patient years, which is approximately twice that of the general population.[13] 46% of patients in our study had an eGFR <60ml/min/1.73m^2 at time of biopsy but the overall incidence of VTE in our cohort was still higher at 12.4 VTE per 1000 patient years.

Timing of VTE

We found the risk of VTE to be highest early in the course of NS with a median time to VTE of 37 days from renal biopsy (177 days if VTEs prior to renal diagnosis are excluded). This may be partly explained by a reduction in thrombotic risk in patients who enter remission - 72% of our cohort achieved at least transient remission. 33% of those who had VTE experienced it as part of their NS presentation highlighting the importance of checking for NS in patients who present with VTE[10].

Risk of VTE by type of glomerulonephritis

We found a greater risk of VTE in patients with IMN and MCN when compared to other histological types. NS remission rates were highest in MCN (89%) and lowest in IMN (63%). While the thrombotic risk of IMN has been reported previously,[1,2,11] the risk associated with MCN is under-recognised. The proportion of VTE that could potentially be prevented with prophylactic anticoagulation was higher in MCN compared to IMN, presumably due to the more insidious onset of IMN allowing VTE to occur prior to renal diagnosis. In

fact, per year of NS patients with IMN had the lowest rate of VTE that would be targeted by prophylactic anticoagulation. The combination of high thrombotic risk and short duration of NS means that patients with MCN arguably have the most to benefit from anticoagulation, in that the frequent relapse rate means these patients could be anticoagulated for short durations (reducing their cumulative bleeding risk on anticoagulant) but still covering the periods of greatest thrombotic risk (i.e. early in the course of NS). However, this would require anticoagulation to be started shortly after renal biopsy, and also re-started during relapses (1 patient suffered first VTE during 4th relapse). The MCN sub-group in our cohort is relatively small and therefore this observation should be validated in other cohorts to confirm it.

Prophylactic anticoagulation – sample size calculation for randomised controlled trial

There are no randomised controlled trials to support the use of prophylactic anticoagulation in patients with NS. One prospective study gave prophylactic-dose low molecular weight heparin (Enoxaparin 40mg) to 30 patients with NS, and after a median follow-up of 13 months no thrombi were identified.[15] A further retrospective study from a centre in which routine practice is to offer VTE prophylaxis in the form of aspirin if sAlb 20-30g/L, and prophylactic dose LMWH or low dose warfarin if sAlb <20g/L, found no VTE in 143 patients established on therapy for >1 week with a median follow-up of 2.9 years.[16] There were 2 episodes of VTE occurring within the first week of treatment and there were 3 episodes of haemorrhage requiring treatment. They also found a

high incidence of VTE (7.5% of all patients) occurring before diagnosis. In our cohort, aspirin alone is not associated with a lower risk.

The true reduction in VTE risk that can be expected in patients with NS undergoing anticoagulation is not known. The estimation of a 75% reduction in VTE risk with prophylactic anticoagulation used in our sample size calculation is likely to be optimistic. Despite this, and accepting 80% power, the required sample size would still be challenging to recruit, especially given the relative rarity of the condition and the expected high prevalence of exclusion criteria (e.g. bleeding tendency). The risk of VTE in NS is similar to the risk of VTE in patients with some active cancers,[17] in whom routine anticoagulation is not currently recommended.[18] In contrast, it is also similar to the risk of stroke in patients with atrial fibrillation (a CHA_2DS_2-VASc score of 2 carries a risk of stroke of 2.2% per year[19]) in whom anticoagulation is recommended.[20] It is unknown if patients with nephrotic syndrome would be at an increased risk of bleeding. Independent risk factors for bleeding on anticoagulation include renal disease[6,7], hypertension[6,7] and anaemia[6], all of which may be more prevalent in a population with CKD, but were not common in our cohort with only 13% having an eGFR < 30 ml/min/1.73$m^2$and an overall mean haemoglobin of 13 g/dL.

Nephrotic syndrome and mortality rate

Overall, the mortality rate was high in this study, with 19% of the cohort having died at a median follow-up of 3 years. Two deaths were directly attributed to PE. This is the first study to report deaths in this context and the mortality rate

associated with NS is not widely acknowledged. Our data demonstrate that achieving even partial remission is associated with a reduced risk of death. We cannot exclude the possibility that an unrecognised burden of VTE might have contributed to mortality.

Limitations and strengths

This study has a number of limitations. Primarily, the small number of events limits the conclusions that can be drawn. It is a cohort from a single-centre, albeit one which serves a population of 1.6 million. Follow-up was relatively short; however, in light of the increased frequency of thrombotic events early in the course of NS, it is likely to be sufficient and is in line with previous studies. The data have been collected retrospectively via a comprehensive, prospectively compiled regional electronic patient record that contains laboratory results, radiology reports, clinical correspondence and medication records. We are therefore confident that there is a low likelihood that we have missed episodes of clinically significant VTE. We did not assess the incidence of arterial thrombus and this has previously been reported to be increased in patients with NS and may benefit from prophylactic anticoagulation[4,21]. Our study focused on patients with a histological diagnosis of a primary glomerulonephritis in whom the main indication for biopsy was NS. Therefore, our results are not applicable to patients with NS secondary to systemic diseases, patients with NS for whom a histological diagnosis is not being pursued and patients who had a different primary indication for biopsy.

The study has strengths. It is a cohort of patients exclusively with histologically-confirmed primary glomerulonephritis. It is set within the modern clinical era and, as patient inclusion was limited to patients with biopsies performed in 2008 or after, the results are reflective of a contemporary approach to the diagnosis and management of NS and VTE. None of our patients were on anticoagulation for primary prophylaxis of VTE due to NS. These data therefore illustrate the natural history of VTE risk in patients with NS in the contemporary clinical era.

Conclusions

Our data confirm that patients with primary NS are at increased risk of VTE compared with the general population and those with CKD. The timing of VTE means that only half of episodes would be targeted by prophylactic anticoagulation, greatly reducing any extrapolated benefit. Contrary to existing guidelines, our data suggest that patients with MCN, rather than IMN, have the greatest potential benefit to gain from prophylactic anticoagulation. There remains equipoise regarding the clinical benefit of prophylactic anticoagulation but the low incidence of events in a population of patients with a relatively rare condition means that a definitive clinical trial is unlikely to be performed.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

References

1. Kerlin BA, Ayoob R, Smoyer WE: Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. Clin J Am Soc Nephrol 2012;7:513–520.

2. Barbour SJ, Greenwald A, Djurdjev O, Levin A, Hladunewich MA, Nachman PH, Hogan SL, Cattran DC, Reich HN: Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis. Kidney Int 2012;81:190–195.

3. Lionaki S, Derebail VK, Hogan SL, Barbour S, Lee T, Hladunewich M, Greenwald a., Hu Y, Jennette CE, Jennette JC, Falk RJ, Cattran DC, Nachman PH, Reich HN: Venous Thromboembolism in Patients with Membranous Nephropathy. Clin J Am Soc Nephrol 2012;7:43–51.

4. Mahmoodi BK, Ten Kate MK, Waanders F, Veeger NJGM, Brouwer JLP, Vogt L, Navis G, Van Der Meer J: High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: Results from a large retrospective cohort study. Circulation 2008;117:224–230.

5. Group KW: KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl 2012;2:1–274.

6. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE: A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol 2011;58:395–401.

7. Pisters R, Lane D a., Nieuwlaat R, De Vos CB, Crijns HJGM, Lip GYH:

A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The euro heart survey. Chest 2010;138:1093–1100.

8. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F: Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–54.

9. Chow, SC, Shao, J, Wang H: Sample Size Calculation in Clinical Research. ed 2nd New York, Chapman & Hall/CRC Biostatistics Series, 2008.

10. Htike N, Superdock K, Thiruveedi S, Surkis W, Teehan G: Evaluating proteinuria and nephrotic syndrome in patients with venous thromboembolism. Am J Med Sci 2012;343:124–6.

11. Llach F, Papper S, Massry SG: The clinical spectrum of renal vein thrombosis: acute and chronic. Amm J Med 1980;69(6):819-27

12. Anderson FA, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE: A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991;151:933–938.

13. Wattanakit K, Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR: Chronic kidney disease increases risk for venous thromboembolism. J Am Soc Nephrol 2008;19:135–140.

14. Christiansen CF, Schmidt M, Lamberg AL, Horvath-Puho E, Baron JA,

Jespersen B, Sorensen HT: Kidney disease and risk of venous thromboembolism: a nationwide population-based case-control study. J Thromb Haemost 2014;12:1449–1454.

15. Rostoker G, Durand-Zaleski I, Petit-Phar M, Ben Maadi A, Jazaerli N, Radier C, Rahmouni A, Mathieu D, Vasile N, Rosso J: Prevention of thrombotic complications of the nephrotic syndrome by the low-molecular-weight heparin enoxaparin. Nephron 1995;69(1):20-8

14. Medjeral-Thomas N, Ziaj S, Condon M, Galliford J, Levy J, Cairns T, Griffith M: Retrospective Analysis of a Novel Regimen for the Prevention of Venous Thromboembolism in Nephrotic Syndrome. Cjasn 2013;9:1–6.

17. Lee AYY, Levine MN: Venous thromboembolism and cancer: Risks and outcomes. Circulation 2003;107(23 Suppl 1):I17-21

18. Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, Clarke JM, Flowers CR, Francis CW, Gates LE, Kakkar AK, Key NS, Levine MN, Liebman HA, Tempero MA, Wong SL, Somerfield MR, Falanga A: Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol 2015;33:654–656.

19. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM: Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on atrial fibrillation. Chest 2010;137:263–272.

17. Aguilar MI, Hart R, Pearce LA: Oral anticoagulants versus antiplatelet

therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database Syst Rev 2007;CD006186.

21. Lee T, Derebail VK, Kshirsagar A V, Chung Y, Fine JP, Mahoney S, Poulton CJ, Lionaki S, Hogan SL, Falk RJ, Cattran DC, Hladunewich M, Reich HN, Nachman PH: Patients with primary membranous nephropathy are at high risk of cardiovascular events. Kidney Int 2016;89:1111–1118.

TABLES

Table 1.Baseline demographics and outcomes in all patients and those who did and did not suffer venous thromboembolism.

Demographics	All patients	VTE	Non-VTE	p-value
N=	206	14 (6.8%)	192 (93.2%)	
Male N (%)	60%	65%	60%	0.79
Mean age at biopsy (SD), years	55 (19)	53 (14)	55 (19)	0.7
Mean eGFR at biopsy (SD), ml/min/1.73m^2	72 (40)	61 (32)	62 (40)	0.5
Median uPCR at biopsy (IQR), mmol/mol	812 (535-1200)	750 (404-1453)	812 (496-1197)	0.91
Mean sAlb at biopsy (SD), g/l	19.1 (7.1)	22.8 (10.8)	18 (7.0)	0.5
Partial remission N (%)	149 (72%)	9 (64%)	140 (73%)	0.54
Immunosuppression N (%)	124 (60%)	12 (86%)	112 (58%)	0.04
RRT N (%)	22 (10.7%)	1 (7.1%)	21 (10.9%)	0.54
Mortality N (%)	39 (19%)	3 (21%)	36 (19%)	0.73

Abbreviations: VTE, venous thromboembolism; eGFR, estimated glomerular filtration rate; uPCR, urinary protein:creatinine ratio; sAlb, serum albumin; RRT, renal replacement therapy.

Data are presented as number (n) +percentage, mean+standard deviation (SD), or median+interquartile range (IQR). Comparison between VTE and non-VTE groups was made using T-test and Mann-Whitney test as appropriate, with significance threshold of p=<0.05

530 Table 2. Outcomes by histological diagnosis

	IMN	MCN	FSGS	IgA	MPGN
N, (% of total)	79 (38.3%)	54 (26.2%)	37 (18%)	22 (10.7%)	14 (6.8%)
Partial remission achieved, n (%)	50 (63%)	48 (89%)	24 (65%)	19 (86%)	9 (64%)
Median duration of NS, years, (IQR)	1.76 (0.79-2.66)	0.32 (0.15-0.54)	0.79 (0.46-1.84)	0.57 (0.24-1.84)	0.54 (0.19-1.65)
VTE, n (%)	7 (8.9%)	5 (9.3%)	1 (2.7%)	1 (4.5%)	0
Proportion of VTE which prophylactic anticoagulation may prevent	1/7	4/5	1/1	1/1	-
Survival, n (%)	59 (75%)	51 (94%)	29 (78%)	16 (735)	12 (85%)

531

532 Abbreviations: IMN, idiopathic membranous nephropathy; MCN, minimal
533 change nephropathy; FSGS, focal segmental glomerulosclerosis; IgA, IgA
534 nephropathy; MCGN, mesangiocapillary glomerulonephritis; VTE, venous
535 thromboembolism;
536
537 Data are presented as number (n) and percentage of total or
538 median+interquartile range (IQR).
539

FIGURES

Figure 1. Summary of the timing of VTE episodes in patients with nephrotic syndrome, highlighting the limitations of prophylactic anticoagulation.