High Absolute Risks and Predictors of Venous and Arterial Thromboembolic Events in Patients With Nephrotic Syndrome: Results From a Large Retrospective Cohort Study

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Background—No data are available on the absolute risk of either venous thromboembolism (VTE) or arterial thromboembolism (ATE) in patients with nephrotic syndrome. Reported risks are based on multiple case reports and small studies with mostly short-term follow-up. We assessed the absolute risk of VTE and ATE in a large, single-center, retrospective cohort study and attempted to identify predictive factors in these patients.

Methods and Results—A total of 298 consecutive patients with nephrotic syndrome (59% men; mean age, 42±18 years) were enrolled. Mean follow-up was 10±9 years. Nephrotic syndrome was defined by proteinuria ≥3.5 g/d, and patients were classified according to underlying histological lesions accounting for nephrotic syndrome. Objectively verified symptomatic thromboembolic events were the primary study outcome. Annual incidences of VTE and ATE were 1.02% (95% confidence interval, 0.68 to 1.46) and 1.48% (95% confidence interval, 1.07 to 1.99), respectively. Over the first 6 months of follow-up, these rates were 9.85% and 5.52%, respectively. Proteinuria and serum albumin levels tended to be related to VTE; however, only the predictive value of the ratio of proteinuria to serum albumin was significant (hazard ratio, 5.6; 95% confidence interval, 1.2 to 26.2; P=0.03). In contrast, neither the degree of proteinuria nor serum albumin levels were related to ATE. Sex, age, hypertension, diabetes, smoking, prior ATE, and estimated glomerular filtration rate predicted ATE (P≤0.02).

Conclusions—This study verifies high absolute risks of symptomatic VTE and ATE that were remarkably elevated within the first 6 months. Whereas the ratio of proteinuria to serum albumin predicted VTE, estimated glomerular filtration rate and multiple classic risk factors for atherosclerosis were predictors of ATE. (Circulation. 2008;117:224-230.)

Key Words: cardiovascular diseases ■ nephrotic syndrome ■ proteinuria ■ risk factors ■ thrombosis

The first observations of an increased risk of venous (VTE) and arterial thromboembolism (ATE) in patients with nephrotic syndrome (NS) date back to >50 years ago.1,2 In the ensuing half-century, VTE rates ranging from 2% in children to as high as 42% in adults3–8 and a relative risk of ATE ranging from 1 to 5.5 have been reported in these patients.7,8 Whereas NS resulting from membranous glomerulopathy has been correlated with an exceptionally high risk of VTE, especially renal vein thrombosis,9,10 likewise correlations have not been described for ATE.7,8

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The pathophysiological mechanisms of thromboembolism in patients with NS have yet to be unraveled. Nevertheless, alterations in plasma levels of proteins involved in coagulation and fibrinolysis, enhanced platelet aggregation, low plasma albumin, hyperviscosity, and hyperlipidemia, as well as treatment with corticosteroids and diuretics, are considered predisposing factors for the development of thromboembolic events.5,6,10–16

The reported risks of VTE and ATE in patients with NS are based on numerous case reports and small studies with mostly short-term follow-up and therefore are of limited accuracy. Data on the absolute risk of either VTE or ATE are not available. We conducted a single-center retrospective study to assess the absolute risk of symptomatic VTE and ATE in a large cohort of patients with NS. We also attempted to identify predictive factors.
Methods

Study Patients

Consecutive patients with NS, seen between January 1995 and December 2004 at our outpatient nephrology clinic, were retrospectively identified from computer-stored hospital files. Patients who at time of study entry (February 2005) were >18 years of age, had not been diagnosed with acute life-threatening diseases, and had been followed up for at least 6 months at our center were enrolled. The diagnosis of NS was confirmed by proteinuria of ≥3.5 g/dL derived from a 24-hour urine collection, or a protein-to-creatinine ratio (7 patients) calculated from a single urine sample.17 Hypoalbuminemia (serum albumin <3.4 g/dL), hypercholesterolemia, and hypertriglyceridemia were recorded but were not a requisite for the diagnosis of NS.18 On the basis of histology of a percutaneous renal biopsy or the clinical context, patients were classified as having membranous glomerulopathy, minimal change disease, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, diabetic nephropathy, and NS not otherwise specified.18

Medical records were reviewed for symptomatic thromboembolic events and exposure to risk factors for VTE and atherosclerosis, respectively. Risk factors for VTE included major surgery, trauma, malignancy, immobilization for >1 week, use of oral contraceptives, hormonal replacement therapy, and pregnancy. Risk factors for atherosclerosis, recorded at baseline (ie, diagnosis of NS), were hypertension, as defined by a systolic blood pressure of ≥140 mm Hg or ≥160 mm Hg in patients ≥60 years of age or a diastolic blood pressure of ≥90 mm Hg measured on at least 2 occasions or the use of antihypertensive drugs; diabetes mellitus;19-20 cigarette smoking; and hyperlipidemia, defined by levels of total cholesterol >6.5 mmol/L (250 mg/dL) or triglycerides >2.5 mmol/L (220 mg/dL) or the use of lipid-lowering drugs. The diagnosis of a multisystem disease was documented. End-stage renal disease was defined by application of regular dialysis.

Diagnosis of Thromboembolic Events

Only objectively verified symptomatic thromboembolic events were considered. Deep vein thrombosis (DVT) was confirmed by compression ultrasound; pulmonary embolism, by ventilation and perfusion lung scanning or spiral computed tomography; renal vein thrombosis, by venography or Doppler ultrasound; and mesenteric vein thrombosis, by computed tomography scanning. Unstable angina pectoris and Q-wave and non–Q-wave myocardial infarction were confirmed by typical ECG features, elevated levels of cardiac enzymes, radionuclide imaging techniques, or coronary angiography. Ischemic stroke was documented by computed tomography scanning or magnetic resonance imaging; peripheral artery disease was documented by intraarterial or magnetic resonance angiography. Cerebral transient ischemic attack required neurological symptoms and signs lasting <24 hours.22 Amenouros fugax was established when sudden monocular blindness lasted <24 hours.

Statistical Analysis

We calculated annual incidences of VTE and ATE by dividing the number of events by the total number of observation years. The observation time for each patient was defined as the period from the diagnosis of NS until the first episode of thromboembolism, a censoring event (end-stage renal disease or death), or end of study. When calculating the incidence rates of VTE, we ignored the occurrence of ATE and vice versa. The 95% confidence intervals (CIs) around the annual incidences were assessed with the Poisson distribution assumption.

Kaplan-Meier23 methods were used for survival plots. To evaluate the effects of baseline characteristics on VTE- and ATE-free survival, we used the Cox proportional-hazards model with a single covariate.24 Results were expressed as hazard ratios with 95% CIs and probability values.

Continuous variables are presented as mean±SD and categorical data as numbers and frequencies. For continuous data, differences were evaluated by the Student t test, Mann-Whitney U test, Kruskal-Wallis test, or univariate ANOVA, depending on the normality of the data and levels of the outcome variable. Categorical variables were compared with χ² or Fisher’s exact test. Statistical significance was considered at a 2-tailed value of P<0.05. Statistical analyses were performed with SAS software, version 9.1 (SAS Institute, Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patients

Table 1 shows the clinical characteristics at diagnosis of NS of the total study population of 298 patients and subgroups according to the underlying nephropathies. Whereas all cases classified as membranous glomerulopathy, minimal change disease, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis were confirmed by renal biopsy; the diagnoses of diabetic nephropathy and NS not otherwise specified were 28% and 46% based on renal biopsy, respectively. NS in the not-otherwise-specified group was due to systemic diseases (19%), infections (8%), heredofamilial diseases (8%), clinically suspected primary glomerular diseases that were not confirmed by biopsy (19%), biopsy-proven cases of IgA nephropathy (17%), and miscellaneous diseases (28%).

Overall, the mean±SD age was 42±18 years; 59% of patients were male; 10% were <18 years of age; 61% had hypertension, 92% had hyperlipidemia, 14% had diabetes, and 10% had a prior thromboembolic event at diagnosis of NS; and 50% reported ever having smoked. For individual patients, the mean observation period was 10±8 years for VTE and 10±9 years for ATE. The observation period differed among subgroups (P<0.001). Compared with patients with non-diabetic nephropathies, patients with diabetic nephropathy were older (P=0.005), had a higher prevalence of hypertension (P<0.001) and prior ATE (P=0.005), and had lower eGFR (P<0.001), less proteinuria (P=0.003), and higher serum albumin levels (P=0.02). Among patients with non-diabetic nephropathies, age, serum cholesterol, serum albumin, proteinuria, and eGFR varied significantly (P<0.003) according to the type of nephropathy.

Thromboembolic Events

Twenty-nine patients had at least 1 episode of VTE during the observation period, corresponding to an annual incidence of 1.02% (95% CI, 0.68 to 1.46) (Table 2). The median observation period until VTE was 0.9 years (interquartile range, 17.3 years). The most commonly encountered first VTE was pulmonary embolism (38%), followed by DVT (34%), combined pulmonary embolism and DVT (10%), combined pulmonary embolism and renal vein thrombosis (10%), renal vein thrombosis (3%), and mesenteric vein thrombosis (3%). None of these patients had VTE before they received a diagnosis of NS. No fatal VTE was observed. 

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Variable | Total | MG | MCD | FSGS | MPGN | DN | NOS
---|---|---|---|---|---|---|---
Prior VTE, n (%) | 3 (1) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (2)
Prior ATE, n (%) | 28 (9) | 9 (13) | 2 (4) | 2 (6) | 0 (0) | 8 (25) | 7 (8)
Ever smoked, n (%)* | 116 (50) | 33 (98) | 47 (100) | 29 (97) | 20 (95) | 21 (91) | 40 (73)
MSD, n (%) | 28 (9) | 2 (3) | 2 (4) | 0 (0) | 5 (19) | 0 (0) | 19 (23)

Laboratory measurements†

Proteinuria, g/d | 8.1±5.2 | 9.7±6.5 | 9.2±5.4 | 10.2±5.9 | 6.5±2.6 | 6.0±2.5 | 6.4±3.6

eGFR, mL·min⁻¹·1.73m⁻² | 59±28 | 71±23 | 78±32 | 58±23 | 70±27 | 36±18 | 46±25

Albumin, g/L | 28±8 | 26±7 | 24±7 | 29±10 | 28±9 | 33±8 | 31±9

Cholesterol, mmol/L | 9.0±3.5 | 9.9±3.0 | 10.6±4.0 | 9.3±2.9 | 8.4±2.9 | 7.4±2.8 | 7.4±3.5

Triglycerides, mmol/L | 3.0±2.1 | 3.3±2.3 | 2.3±1.3 | 3.1±1.8 | 2.4±1.4 | 4.1±4.1 | 3.0±1.2

Follow-up

VTE observation period, y | 10±8 | 10±8 | 13±11 | 10±7 | 15±10 | 5±5 | 7±6

ATE observation period, y | 10±9 | 11±8 | 13±11 | 11±7 | 15±10 | 5±4 | 7±7

ESRD, n (%) | 39 (13) | 5 (7) | 1 (2) | 7 (19) | 6 (23) | 6 (19) | 14 (17)

Death, n (%) | 15 (5) | 4 (6) | 2 (4) | 2 (6) | 0 (0) | 3 (9) | 4 (5)

Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>MG</th>
<th>MCD</th>
<th>FSGS</th>
<th>MPGN</th>
<th>DN</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior VTE, n (%)</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Prior ATE, n (%)</td>
<td>28 (9)</td>
<td>9 (13)</td>
<td>2 (4)</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td>8 (25)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Ever smoked, n (%)*</td>
<td>116 (50)</td>
<td>33 (98)</td>
<td>47 (100)</td>
<td>29 (97)</td>
<td>20 (95)</td>
<td>21 (91)</td>
<td>40 (73)</td>
</tr>
<tr>
<td>MSD, n (%)</td>
<td>28 (9)</td>
<td>2 (3)</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>5 (19)</td>
<td>0 (0)</td>
<td>19 (23)</td>
</tr>
</tbody>
</table>

Laboratory measurements†

Proteinuria, g/d | 8.1±5.2 | 9.7±6.5 | 9.2±5.4 | 10.2±5.9 | 6.5±2.6 | 6.0±2.5 | 6.4±3.6

eGFR, mL·min⁻¹·1.73m⁻² | 59±28 | 71±23 | 78±32 | 58±23 | 70±27 | 36±18 | 46±25

Albumin, g/L | 28±8 | 26±7 | 24±7 | 29±10 | 28±9 | 33±8 | 31±9

Cholesterol, mmol/L | 9.0±3.5 | 9.9±3.0 | 10.6±4.0 | 9.3±2.9 | 8.4±2.9 | 7.4±2.8 | 7.4±3.5

Triglycerides, mmol/L | 3.0±2.1 | 3.3±2.3 | 2.3±1.3 | 3.1±1.8 | 2.4±1.4 | 4.1±4.1 | 3.0±1.2

Follow-up

VTE observation period, y | 10±8 | 10±8 | 13±11 | 10±7 | 15±10 | 5±5 | 7±6

ATE observation period, y | 10±9 | 11±8 | 13±11 | 11±7 | 15±10 | 5±4 | 7±7

ESRD, n (%) | 39 (13) | 5 (7) | 1 (2) | 7 (19) | 6 (23) | 6 (19) | 14 (17)

Death, n (%) | 15 (5) | 4 (6) | 2 (4) | 2 (6) | 0 (0) | 3 (9) | 4 (5)

Table 2. Risk of Thromboembolism by Type of Nephropathies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=298)</th>
<th>MG (n=72)</th>
<th>MCD (n=49)</th>
<th>FSGS (n=36)</th>
<th>MPGN (n=26)</th>
<th>DN (n=32)</th>
<th>NOS (n=83)</th>
</tr>
</thead>
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<tr>
<td>VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, n</td>
<td>29</td>
<td>10</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Observation period, y</td>
<td>2857</td>
<td>716</td>
<td>645</td>
<td>362</td>
<td>378</td>
<td>171</td>
<td>585</td>
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<tr>
<td>Annual incidence</td>
<td>1.02</td>
<td>1.40</td>
<td>0.62</td>
<td>1.38</td>
<td>1.32</td>
<td>0.58</td>
<td>0.68</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.68–1.46</td>
<td>0.67–2.57</td>
<td>0.17–1.59</td>
<td>0.45–3.22</td>
<td>0.43–3.09</td>
<td>0.01–3.26</td>
<td>0.19–1.75</td>
</tr>
<tr>
<td>ATE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, n</td>
<td>43</td>
<td>10</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Observation period, y</td>
<td>2904</td>
<td>762</td>
<td>656</td>
<td>390</td>
<td>396</td>
<td>148</td>
<td>551</td>
</tr>
<tr>
<td>Annual incidence</td>
<td>1.48</td>
<td>1.31</td>
<td>0.30</td>
<td>1.54</td>
<td>0.51</td>
<td>7.43</td>
<td>2.18</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.07–1.99</td>
<td>0.63–2.41</td>
<td>0.04–1.10</td>
<td>0.56–3.35</td>
<td>0.06–1.82</td>
<td>3.71–13.30</td>
<td>1.13–3.80</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

The onset of VTE, only 6 patients (21%) were exposed to another risk factor for VTE (immobilization, n=2; malignancy, n=2; surgery, n=1; and use of oral contraceptives, n=1). The annual incidence of VTE, calculated over the first 6 months of observation time, was 9.85% (95% CI, 5.38 to 16.52).

Forty-three patients had ≥1 ATE during the observation period, resulting in an annual incidence of 1.48% (95% CI, 1.07 to 1.99) (Table 2). The median observation period until ATE was 3.5 years (interquartile range, 7.3 years). The most commonly observed first ATE was myocardial infarction (44%), followed by unstable angina pectoris (14%), peripheral artery disease (14%), ischemic stroke (11.5%), cerebral transient ischemic attack (11.5%), amaurosis fugax (2%), and aorta thrombosis (2%). Three of these events (7%) were fatal. Fifteen of the 43 patients (35%) had already experienced
DVT study for VTE and the Framingham study for ATE).25,26

dotted lines represent the estimated age- and sex-weighted annual incidences in the general population (ie, Worcester DVT study for VTE and the Framingham study for ATE).25,26 PE indicates pulmonary embolism; RVT, renal vein thrombosis; CAD, coronary artery disease (unstable angina pectoris or myocardial infarction); CVD, cerebrovascular disease (ischemic stroke or transient ischemic attack); and PAD, peripheral artery disease. *Annual incidence in the general population is not shown). In contrast, neither the degree of proteinuria nor the level of serum albumin predicted ATE. Sex, age, hypertension, diabetes, smoking, prior ATE, and eGFR were significantly associated with ATE.

Discussion

This study shows a high risk of VTE and ATE in patients with NS. Absolute risks of VTE (1.02% per year) and ATE (1.48% per year) were each ~8 times higher in these patients than the estimated age- and sex-weighted annual incidences in the general population (the Worcester DVT study, 0.12%; and the Framingham study, 0.18%, respectively).25,26 Risks of both VTE and ATE were particularly high within the first 6 months of NS (annual incidences, 9.85% and 5.52%, respectively). Survival analysis showed that over 25 years of observation, the probability of a thromboembolic event was 48%, with the risk of VTE being approximately equal to the risk of ATE. Whereas the risk of VTE was roughly similar among the different groups of NS, the risk of ATE was remarkably high in patients with diabetic nephropathy compared with patients with nondiabetic nephropathies. For the first time, we report that the ratio of proteinuria to serum albumin predicts VTE and that multiple classic risk factors for atherosclerosis are associated with ATE in patients with NS, including sex, age, hypertension, diabetes, smoking, prior ATE, and eGFR.

Our finding of the increased risk of VTE is in agreement with previous reports. In our study, 10% of patients experienced symptomatic VTE, confirmed by objective techniques, during a total observation period of 2857 years. Annual incidences were not provided in previous studies. Not considering the observation period, the incidence rate of VTE in adults with NS ranged from 8% to 42%, with an overall incidence of 23%.5 However, risk estimates in those studies were based on small numbers of patients and asymptomatic cases of renal vein thrombosis in particular; it often was not clear whether thrombosis at other sites was objectively verified and whether consecutive patients were evaluated.4,5,27,28 Renal vein thrombosis especially has received attention with an overall incidence rate of 28%, ranging from

![Figure 1. Annual incidences per types of thromboembolism among the total cohort. Some patients are listed in 2 or 3 categories; therefore, the total of these categories exceeds the number of patients. Solid circles denote annual incidences of VTE (black) and ATE risk (red), with the corresponding 95% CIs represented by the vertical bars. Dotted lines represent the estimated age- and sex-weighted annual incidences in the general population (ie, Worcester DVT study for VTE and the Framingham study for ATE).25,26](attachment:image1.png)

![Figure 2. Kaplan-Meier estimates of the probability of VTE-, ATE-, and any (VTE, ATE, or both) event-free survival.](attachment:image2.png)
22% to 42%. However, the high rates of renal vein thrombosis in previous reports reflect the vigor of the investigators; 90% of renal vein thromboses were demonstrated in clinically asymptomatic patients. Whereas the ratio of pulmonary embolism to DVT in the general population is 1:2, it was 1.3:1 in our study. Our finding of the high risk of pulmonary embolism could be explained by an apparently large proportion of asymptomatic renal vein thrombosis.

Although there has been controversy in the past about the association of NS and ATE, an increased risk of coronary events has been documented in a retrospective, controlled study in 142 patients with NS. After adjustment for age, sex, hypertension, and smoking, the relative risk of myocardial infarction in these patients was 5.5, and its annual incidence was 1.49%. Our absolute risk estimates were lower when we confined our analysis to nondiabetic patients without prior ATE (0.82% versus 1.49%), as Ordonez et al did. This difference might reflect our longer follow-up because annual incidences of ATE over a comparable follow-up were 2.71% in the total cohort and 1.20% in nondiabetic patients without prior ATE in our study. The somewhat lower risk in our patients could be ascribed to application of statins (51% patients) and renin-angiotensin system inhibitors (81% patients) because these drugs were not available during the period in which patients in the study of Ordonez et al were followed up. The beneficial effect of these drugs is supported by a 3-fold-lower annual incidence of end-stage renal disease (1.4% versus 4.3%). Furthermore, our patients were on average 6 years younger (38 versus 44 years). Given that the risk estimates by Ordonez et al were based on only 11 episodes of myocardial infarction, their study size was less than half of ours, and the fact that they documented only coronary events, we presume that our estimates reflect a more accurate assessment of the absolute ATE risk conferred by NS. In addition, we established that compared with the general population, the risks of cerebrovascular events and

<table>
<thead>
<tr>
<th>Variable</th>
<th>no. patients/no. studied</th>
<th>VTE HR (95% CI) P value</th>
<th>ATE HR (95% CI) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>177/298</td>
<td>1.2 (0.6 - 2.6) 0.64</td>
<td>2.2 (1.1 - 4.5) 0.02</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35</td>
<td>117/298</td>
<td>1.0, reference</td>
<td>1.0, reference</td>
</tr>
<tr>
<td>35 - 54</td>
<td>102/298</td>
<td>1.3 (0.5 - 3.0)</td>
<td>7.9 (2.7 - 23.5)</td>
</tr>
<tr>
<td>≥ 55</td>
<td>79/298</td>
<td>1.1 (0.4 - 3.1)</td>
<td>14.2 (4.7 - 42.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>182/298</td>
<td>1.1 (0.5 - 2.4) 0.82</td>
<td>2.5 (1.2 - 5.1) 0.01</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>221/241</td>
<td>1.7 (0.2 - 12.6) 0.61</td>
<td>0.6 (0.2 - 1.7) 0.34</td>
</tr>
<tr>
<td>Diabetes</td>
<td>42/298</td>
<td>0.8 (0.2 - 3.3) 0.72</td>
<td>4.8 (2.4 - 9.5) &lt; 0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>116/234</td>
<td>2.0 (0.9 - 4.7) 0.10</td>
<td>2.8 (1.4 - 5.5) 0.003</td>
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<td>Prior ATE</td>
<td>28/298</td>
<td>0.6 (0.1 - 4.2) 0.57</td>
<td>11.8 (6.0 - 23.3) &lt; 0.001</td>
</tr>
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<td>Prior VTE</td>
<td>3/298</td>
<td>NE</td>
<td>5.3 (0.7 - 39.5) 0.10</td>
</tr>
<tr>
<td>MSD</td>
<td>28/298</td>
<td>1.1 (0.3 - 3.6) 0.90</td>
<td>0.7 (0.2 - 2.1) 0.47</td>
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<td>Proteinuria, g/d</td>
<td></td>
<td>0.08</td>
<td>0.79</td>
</tr>
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<td>3.5 - 4.8</td>
<td>92/272</td>
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<td>4.9 - 8.1</td>
<td>91/272</td>
<td>3.1 (0.6 - 15.0)</td>
<td>0.8 (0.4 - 1.7)</td>
</tr>
<tr>
<td>≥ 8.2</td>
<td>89/272</td>
<td>5.2 (1.1 - 23.0)</td>
<td>0.8 (0.4 - 1.8)</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>0.96</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
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<td>≥ 60</td>
<td>127/251</td>
<td>1.0, reference</td>
<td>1.0, reference</td>
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<td>30 - 59</td>
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<td>≤ 29</td>
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<td>1.0 (0.2 - 4.9)</td>
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<td>Serum albumin, g/dl</td>
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<td>0.25</td>
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</tr>
<tr>
<td>3.3 - 2.5</td>
<td>67/184</td>
<td>1.6 (0.3 - 8.2)</td>
<td>0.5 (0.2 - 1.4)</td>
</tr>
<tr>
<td>≤ 2.4</td>
<td>67/184</td>
<td>2.6 (0.5 - 12.4)</td>
<td>0.5 (0.2 - 1.2)</td>
</tr>
<tr>
<td>P/A ratio</td>
<td>157/298</td>
<td>5.6 (1.2 - 26.2) 0.03</td>
<td>1.7 (0.4 - 6.5) 0.46</td>
</tr>
</tbody>
</table>

Figure 3. Proportional-hazards analysis of association with the time to the first VTE and ATE among the total cohort. Solid squares denote the hazard ratios of VTE (black) and ATE (red), with the corresponding 95% CIs represented by the horizontal bars. HR indicates hazard ratio; MSD, multisystem disease; NE, not estimatable; and P/A ratio, ratio of proteinuria to serum albumin.
Peripheral artery disease were elevated about the same extent as the risk of coronary artery disease in these patients.

The association between serum albumin levels and VTE has previously been suggested, although others failed to confirm this finding. We demonstrated that the ratio of proteinuria to serum albumin was a stronger predictor because it is a probably better reflector of the severity of NS than serum albumin levels or the magnitude of proteinuria alone. It is remarkable that ATE was not shown to be related to either proteinuria or serum albumin because an almost linear association with the occurrence of ATE has been established for nonnephrotic range proteinuria (<3.5 g/d) and even microalbuminuria. Our finding could be ascribed to the imbalance of multiple other risk factors for ATE among different nephropathies. Whereas the incidence of ATE was shown to be higher in patients with diabetic nephropathy or not otherwise specified NS compared with other nephropathies, these patients had less proteinuria and higher serum albumin. However, they were older; had higher prevalence of hypertension, prior ATE, and diabetes; and had lower eGFR. On the other hand, minimal change disease is considered a relatively mild disorder because it reacts more promptly to treatment. Al- though the extent of proteinuria at presentation of this disorder was high, other risk factors were less prevalent.

The historical dichotomy of venous and arterial diseases as 2 different pathophysiological entities with distinct risk factors has recently been challenged because an increased risk of ATE was observed in patients with VTE. Our data do not support such a relationship between VTE and ATE. Moreover, the findings that VTE was related to proteinuria and serum albumin (ie, ratio of proteinuria to serum albumin) and that ATE but not VTE was associated with eGFR and multiple classic risk factors for atherosclerosis might indicate different pathophysiological mechanisms of VTE and ATE in these patients.

Over the first 6 months of observation time, we demonstrated a markedly elevated risk of ~140 times for VTE (annual incidence, 9.85%) and 50 times for ATE (annual incidence, 5.52%) compared with the general population (age- and sex-weighted annual incidences of 0.07% and 0.11%, respectively). Therefore, one might consider primary thromboprophylaxis during this period. Further prospective studies are warranted to assess whether the decline in risk of thromboembolism during follow-up is related to the treatment of NS.

The main limitation of this study is its retrospective design. Consequently, baseline laboratory data were not available in all patients. It could be argued that asymptomatic VTE especially may have been missed because patients were not routinely screened and clinical diagnosis of VTE is unreliable. This would have resulted in an underestimated risk of VTE. However, the clinical relevance of asymptomatic VTE is a matter of debate. Referral bias may have been introduced by the setting of a university hospital. Selection bias seems less likely because consecutive patients were analyzed. Although our study is the largest evaluating thromboembolic events in patients with NS, CIs around the risk ratios were wide, indicating a limited power. We considered multivari- able analysis for ATE. However, because of the large number of predictive factors and small number of events, the multivariable model was overfitted and the power was severely limited to detect moderate effects. Consequently, these data were not included.

In summary, this study delineates high absolute risks of symptomatic VTE and ATE that were excessively elevated within the first 6 months. Whereas the magnitude of proteinuria and serum albumin levels were related to VTE, eGFR and multiple classic risk factors for atherosclerosis predicted ATE.

Disclosures

None.

References

The association between the nephrotic syndrome and thromboembolic events has been known for decades; however, no data are available on the absolute risk of either venous (VTE) or arterial thromboembolism (ATE). The reported risks of thromboembolism in patients with nephrotic syndrome are based on case reports and small studies, most with limited follow-up. Previous assessments of VTE risk have been based largely on asymptomatic cases of renal vein thrombosis, the clinical relevance of which is not clear. Moreover, predictive factors of both VTE and ATE in these patients have yet to be determined. In this study, the absolute risks of symptomatic VTE and ATE were assessed. Thromboembolism was many times higher than the estimated age- and sex-weighted absolute risks in the general population. The risk of thromboembolism was excessively high in the first 6 months of observation. Whereas the risk of VTE was related to the severity of nephrotic syndrome, the risk of ATE was related to estimated glomerular filtration rate and classic risk factors for atherosclerosis. These findings highlight the need for prospective randomized trials to evaluate the effect of current antiproteinuric treatment on the risk of thromboembolism and the benefits of primary thromboprophylaxis. These findings also suggest that primary thromboprophylaxis could be beneficial, particularly during the first 6 months, for patients at highest risk, and further studies are needed to demonstrate clinical utility in this setting.
High Absolute Risks and Predictors of Venous and Arterial Thromboembolic Events in Patients With Nephrotic Syndrome: Results From a Large Retrospective Cohort Study
Bakhtawar K. Mahmoodi, Min Ki ten Kate, Femke Waanders, Nic J.G.M. Veeger, Jan-Leendert P. Brouwer, Liffert Vogt, Gerjan Navis and Jan van der Meer

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