Risk of arterial thromboembolism, venous thromboembolism, and bleeding in patients with nephrotic syndrome: A population-based cohort study

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Abstract

Background

While venous thromboembolism (VTE) is a well-known complication of nephrotic syndrome (NS), the long-term absolute and relative risks of VTE, arterial thromboembolism (ATE), and bleeding in adults with NS remain unclarified.

Methods

In this matched cohort study, we identified every adult with first-time recorded NS from admissions, outpatient clinics, or emergency room visits in Denmark during 1995-2018. Each NS patient was matched by age and sex with 10 individuals from the general population. We estimated the 10-year cumulative risks of recorded ATE, VTE, and bleeding accounting for the competing risk of death. Using Cox models, we computed crude and adjusted hazard ratios (HRs) of the outcomes in NS patients versus comparators.

Results

Among 3,967 adults with first-time NS, the 1-year risk of ATE was 4.2% (95% confidence interval [CI] 3.6-4.8), of VTE was 2.8% (95% CI 2.3-3.3), and of bleeding was 5.2% (95% CI 4.5-5.9). The 10-year risk of ATE was 14.0% (95% CI 12.8-15.2), of VTE 7.7% (95% CI 6.8-8.6) and of bleeding 17.0% (95% CI 15.7-18.3), with highest risks of ischemic stroke (8.1%), myocardial infarction (6.0%), and gastrointestinal bleeding (8.2%). During the first year, NS patients had increased rates of both ATE (HR_{adj} = 3.11 [95% CI 2.60-3.73]), VTE (HR_{adj} = 7.11 [5.49-9.19]) and bleeding (HR_{adj} = 4.02 [3.40-4.75]) compared to the general population comparators after adjusting for confounders.

Conclusion

Adults with NS have a high risk of ATE, VTE, and bleeding compared to the general population. The mechanisms and consequences of this needs to be clarified.

Introduction

Nephrotic syndrome (NS) is a kidney disorder characterized by heavy proteinuria, hypoalbuminemia, and edema.[1] Venous thromboembolism (VTE) is considered a common and potentially severe complication of NS,[2] but the risk of arterial thromboembolism (ATE) and bleeding in NS patients has received little attention. Several factors related to NS may contribute to an increased risk of both ATE and VTE,[3] such as hyperlipidemia,[4] an imbalance in pro- and anti-thrombotic factors,[4, 5] impaired thrombolytic activity,[4, 5] treatment with steroids,[6] and underlying cancer or diabetes. [7-10] Other factors common in NS patients are generally associated with increased bleeding risk, including albuminuria,[11, 12] decreased kidney function,[12] underlying cancer,[13] or treatment with steroids or anticoagulants.[14, 15]

Previous studies of NS patients have reported increased risk of VTE,[16, 17] cardiovascular heart disease,[17, 18] and ischemic stroke.[17, 19] The risk of VTE in NS patients has been reported to be 3% during initial hospitalization,[20] and 2-10% during up to 10 years of follow-up.[21-23] Interestingly, higher risk of ATE in NS patients have been reported including a 3-year risk of cardiovascular events of 8%[24] and 10-year risk of ATE of 15%.[23] However, the applicability of these findings to all NS patients is limited by small sample sizes,[18, 21, 23, 24] incomplete follow-up,[17, 18, 20, 22-24] unaddressed competing risks of death,[17, 21-23] and exclusion of patients with comorbidities.[17, 21, 24] Moreover, major bleeding events in patients with NS have been described in case reports,[25-27] but no previous study has examined the risk of bleeding in these patients. Accurate data on the risk of thromboembolism and bleeding in NS are needed to identify patients at high risk of these complications and to optimize preventive strategies.

Using Danish medical registries, the current study intended to examine the absolute risk of thromboembolic or bleeding events in patients with NS, compare the rates in patients with NS to the

rates in individuals without NS, and identify high-risk patients based on prior comorbidity and underlying histopathology.

Methods

Setting

This cohort study was based on data from nationwide population-based registries.[28-31] Data were linked at the individual level using the unique personal identifiers assigned to all Danish citizens at birth or immigration from the Danish Civil Registration System.[32] Denmark has a free tax-supported health care system with universal access to specialized hospital-based care for patients with NS.[33]

Exposure

We identified all adults (age ≥18 years) with first-time hospital-recorded NS (primary or secondary discharge diagnosis from an admission, outpatient clinic visit, or emergency room visit) in Denmark during 1995-2018 from the Danish National Patient Registry covering all Danish hospitals.[28] The date of initiation of the hospital contact was used as the index date. We excluded patients with kidney transplantation recorded before the index date. Codebooks are provided in the Appendix.

Comparison cohort

We established a comparison cohort of up to 10 individuals from the Danish general population for each NS patient matched for calendar time, age in years, and sex.[32] Comparators were sampled with replacement among individuals without prior NS or kidney transplantation,[34] and the matching date was used as the index date.

Outcomes

The primary outcomes were ATE, VTE, and bleeding recorded as primary or secondary diagnoses during an admission, outpatient visit, or emergency room visit in the Danish National Patient Registry after the index date.[28] ATE included myocardial infarction, ischemic stroke, and other ATE; VTE included pulmonary embolism (PE), deep vein thrombosis (DVT), and other VTE; and

bleeding included cerebral bleeding, respiratory tract bleeding, gastrointestinal bleeding, and urinary tract bleeding.

Covariates

Sex and age were obtained from the Civil Registration System.[32] We obtained data on previous kidney diseases, comorbidities, and ATE, VTE or bleeding recorded up to 10 years prior to the index date from the Danish National Patient Registry. Data were also obtained on fracture/trauma or surgery up to 90 days before the index date and concurrent pregnancy.[28]

We obtained information on current use of selected medications from prescriptions filled at community pharmacies during the 90 days before the index date (or 14 days for antivirals and antibiotics) from the Danish National Prescription Registry (Table 1).[29]

Histopathological findings among patients with kidney biopsy from 180 days before to 180 days after the NS index date were obtained from the Danish National Pathology Database.[30] In patients with more than one biopsy, we used the biopsy closest to the NS index date. In the case of concurrent findings in the biopsy, we categorized the patient with the first findings of membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN), other proliferative glomerulonephritis, focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), or "other histopathology".

Finally, plasma creatinine (p-creatinine) test results from general practice or hospital care analyzed at hospital laboratories were obtained from Danish laboratory databases.[31] Before 2014, data were available from the Central or Northern Denmark Region only, but data were available from all Danish Regions from 2014 onwards.[31] After excluding tests from admissions or emergency room visits, we calculated an outpatient eGFR for each patient based on the most recent p-creatinine test taken within one year before the index date using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula without adjusting for race.[35]

Statistical analyses

We constructed contingency tables for the covariates described above including age group (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+ years) and calendar period (1995-1999, 2000-2005, 2006-2011, 2012-2018). We followed patients from the index date until the first outcome event, death, emigration, 31 December 2018, or 10 years of follow-up, whichever came first. Patients who experienced ATE events were censored for subsequent ATE events, but not for subsequent VTE or bleeding events, and vice versa.

We computed cumulative incidence proportions (i.e., risk) for ATE, VTE, and bleeding overall and by type during 0-10 years after the index date considering the competing risk of death.[36] We plotted these risks and tabulated them during different follow-up periods (0-30 days, 0-1 year, 0-5 years, 0-10 years).

Using Cox proportional hazard regression analysis, we computed hazard ratios (HRs) for the outcomes with 95% confidence intervals (CIs) during different follow-up periods in the NS cohort compared to the comparison cohort. The proportionality was confirmed visually in log-log plots and by plotted Schoenfeld residuals. We computed crude and adjusted HRs adjusted for potential confounders (see Table 5).

We tabulated the characteristics of NS patients with a kidney biopsy at the end of the biopsy assessment period (day 180 after the index date). Next, we plotted the risk of ATE, VTE, and bleeding from day 180 to 10 years after the NS index date stratified by the type of histopathology. To address that some patients may have experienced an outcome event before the end of the biopsy assessment period, we estimated the risks during the period from the NS index date to day 180 by type of histopathology. In the main cohorts, we stratified the risk of outcomes by kidney diseases and comorbidities diagnosed prior to the NS index date. Among NS patients with recent eGFR tests, we tabulated the risks of the outcomes stratified by renal function based on the Kidney Disease:

Improving Global Outcomes (KDIGO) CKD G-stages.[37] In a sensitivity analysis, we computed the risks of the outcomes restricted to individuals without a history of hospital-recorded ATE, VTE or bleeding to remove the potential risk of repeated recording of prevalent events.

All analyses were performed in SAS version 9.4 (Cary, NC, USA). Illustrations were created in R version 4.0.4 (www.r-project.org).[38, 39]

Results

Cohort characteristics

We identified 3,967 adults with first-time NS during 1995-2018 and matched them to 39,670 individuals from the general population (Suppl. Figure 1). The NS cohort comprised 43% women, with a median age of 59 years (IQR 43 – 72) (Table 1). The NS cohort and the general population comparison cohort were well-balanced in regards to age and sex (matching factors). Comorbidities and filled prescriptions for select medications were more common in NS patients than in the general population comparators (Table 1). Almost half (n=1,902 [48%]) of the NS patients had a kidney biopsy within 180 days of the NS index date and, among these, MN (24%) and MCD (25%) were the most common histopathological findings (Table 2). During the 10-year follow-up, the proportion of NS patients censored due to death was approximately 2-fold higher than the proportion of comparators (Suppl. Figure 1).

Absolute risk of ATE, VTE, and bleeding

The 1-year risk of ATE after NS was 4.2% (95% CI 3.6-4.8), of VTE was 2.8% (95% CI 2.3-3.3), and of bleeding was 5.2% (95% CI 4.5-5.9; Table 3 and Figure 1). During long-term follow-up, we observed 10-year risk of ATE of 14.0% (95% CI 12.8-15.2; Table 3), VTE of 7.7% (95% CI 6.8-8.6), and bleeding of 17.0% (95% CI 15.7-18.3). During ten years of follow-up the risk was highest of gastrointestinal bleeding (8.2%), ischemic stroke (8.1%) and myocardial infarction (6.0%), and whereas the absolute risks of different types of VTEs were lower (Table 4 and Figure 2).

Relative risk of ATE, VTE, and bleeding

NS patients had a markedly higher risk of ATE, VTE, and bleeding than the general population comparators throughout the follow-up (Figure 1, Table 3), and a similar pattern was observed for every subtype of outcomes (Figure 2). When comparing NS patients to the general population, the 1-year rate of VTE (HR_{adj} of 7.11 (95% CI 5.49-9.19) was higher than that of ATE (HR_{adj} of 3.11 (95% CI 2.60-3.73) and bleeding (HR_{adj} of 4.02 (95% CI 3.40-4.75) after adjustment for confounders (Table 5). This increased rate was attenuated when the follow-up was extended up to 10 years (Table 5).

Subgroup analyses

Among patients with a kidney biopsy, patients with MCD were younger; had a lower prevalence of diabetes, cancer, recent surgery, and SLE; lower eGFR; and fewer filled prescriptions of anticoagulants than those with MN, MPGN, FSGS, and ”other histopathology” (Suppl. Table 1).

Patients with MN, MPGN, FSGS and “other histopathology” had the highest risk of ATE, those with MN, MPGN, “other proliferative glomerulonephritis” and “other histopathology” had the highest risk of VTE, and those with MPGN, FSGS and “other histopathology” had the highest risk of bleeding (Figure 3). The group with MCD had lower risk of both ATE, VTE, and bleeding than other groups. We observed too few outcomes during the first 180 days after NS to report the risk in most groups (Suppl. Table 2).

Among NS patients with kidney disease or comorbidity diagnosed prior to the index date, we observed the highest 10-year risk of ATE in those with cystic kidney disease and diabetes; of VTE in those with SLE, connective tissue disease, cancer or coagulation defects; and of bleeding in those with peptic ulcer, acute kidney injury or chronic kidney disease, coagulation defects or diabetes (Suppl. Table 3).

Interestingly, the risk of ATE in NS patients increased markedly with lower eGFR, with 3-fold higher risk of ATE in patients with CKD stage 5 (29.0%) compared to those with CKD stage 1-2 (8.8%), while the risk of VTE and bleeding increased less with lower eGFR (Suppl. Table 4).

Sensitivity analyses

The findings were robust after restricting the analyses to individuals without any history of thromboembolic or bleeding events. The absolute risk of ATE, VTE, and bleeding was slightly lower in these analyses than in our main analyses in both cohorts (Suppl. Figure 2).

Discussion

In this nationwide matched cohort study, we found that the short-term risk of ATE, VTE and bleeding events was high in NS patients. The risk remained high 10 years after presenting with NS. Compared to the general population, NS patients have a 2- to 4-fold higher long-term risk of ATE, VTE and bleeding. In NS patients, the risk of ischemic stroke and myocardial infarction is higher than the risk of other types of ATE or VTE, and the risk of gastrointestinal bleeding is higher than the risk of other types of bleeding. The results also indicate that NS patients with histopathological findings of MPGN and "other histopathology" have a high risk of ATE, VTE and bleeding, while those with MN have a particularly high risk of ATE and VTE, and those with FSGS of ATE and bleeding. Finally, lower kidney function was especially associated with ATE, than with VTE and bleeding.

The magnitudes of the long-term HRs for VTE in the current study are in line with the reported odds ratio of 2.89 for VTE in patients with hospital-diagnosed NS patients in Denmark,[16] and the HR of 2.56 for VTE in 907 patients with primary NS in USA.[17] A study including 206 NS patients in Scotland reported a 3-year risk of VTE in NS patients of 6.8% after 3 years,[21] which is similar to the 5-year risk of VTE in our study. A lower 10-year risk of VTE (2.25%) was reported among 7,037 military veterans with NS,[22] but the different setting and loss to follow-up may explain this

difference. Compared to the 30-day risk in the current study, a higher prevalence of VTE (3.0%) was found among 7,473 NS patients in Japan during the initial hospitalization, potentially due to differences in the study population and setting.[20] Furthermore, a much higher prevalence of VTE (10%-36%) has been reported in China when screening NS patients for VTE by radiological examination.[41-43] A study of 289 NS patients in the Netherlands reported an average annual risk of 1.0% for VTE and 1.5% for ATE during a median 10-years of follow-up,[23] but they did not consider the competing risk of death, and thus likely overestimated the risks of the outcomes.[36] A considerable proportion of NS patients died during our follow-up, underlining the importance of considering the competing risk of death.[36, 40] Acute coronary syndrome and myocardial infarction accounted for most ATE events in previous studies,[17, 23, 24] and an increased risk of ischemic stroke and myocardial infarction has been reported in patients with NS.[17-19] While previous reviews have stated that ATE is a rare complication of NS,[1, 44] we observed high absolute and relative risk of ATE in NS similarly to other studies.[17-19, 23, 24]

Interestingly, the VTE risk has been considered highest in NS patients with MN, MPGN, or MCD based on historical data.[4, 5, 45] We detected high risks of VTE in patients with MN and MPGN, and a somewhat lower risk in patients with MCD. This may be explained, in part, by differences in factors associated with the outcomes, as patients with MCD were younger and had fewer comorbidities than the other groups. Whether differences in antithrombotic prevention or the prothrombotic mechanisms associated with different glomerulopathies also contribute to the different risks of ATE, VTE, and bleeding need to be clarified.

Finally, we observed a considerably higher risk of bleeding in NS patients than age- and sex-matched individuals from the general population, and the association persisted after adjusting for confounders. The mechanisms and consequences of the increased bleeding risk in NS, including the role of prophylactic antithrombotic treatment, should be addressed in future studies.

Certain limitations need to be considered when interpreting our findings. First, we relied on recorded diagnoses to identify first-time NS, potentially overlooking NS patients without a diagnosis code specific to NS.[46] Furthermore, less severe events of VTE may have been diagnosed and recorded in NS patients than in the general population, which would lead to overestimating the association between NS and VTE. However, guidelines do not recommend screening asymptomatic NS patients for VTE by radiological examination.[47] In addition, ATE and bleeding have not previously been described as common complications of NS.[41-43] Therefore, we do not expect that surveillance bias alone can explain our findings.

We lacked data on lifestyle factors (obesity, smoking, alcohol use, eating habits, etc.) and clinical variables (e.g., blood pressure), but we adjusted the HRs for a wide range of lifestyle-related hospital diagnoses and prescribed medications. To estimate whether the adjusted 1-year HR for ATE could be explained by confounding, we calculated an E-value based on the point estimate and CI.[48] With an E-value of 5.7, a confounder had to be 5.7-times more prevalent in the NS cohort, and itself increase the risk of ATE 5.7-fold to explain the association, which is unlikely.

Notably, the eGFR levels may have been slightly underestimated before the year 2010, as not all Danish laboratories had standardized p-creatinine assays at that time.[49] This may have led to a minor overestimation of the risk of the outcomes in lower CKD stages.

In summary, our study showed that patients with NS have higher short- and long-term risks for both ATE, VTE, and bleeding complications compared to the general population. The absolute risk of ischemic stroke and myocardial infarction was higher than the risk of other types of ATE or VTE, and gastrointestinal bleeding was the most common type of bleeding. We showed that eGFR level, history of kidney disease or comorbidity, and histopathological findings are useful to identify different subgroups of patients in particularly high risk of ATE, VTE, and bleeding among patients

with NS. Though VTE is a well-known complication of NS, the mechanisms and consequences of the high risk of ATEs and bleeding events observed in the current study need to be clarified.

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Disclosures

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Tables

Table 1. Characteristics of the nephrotic syndrome cohort and the general population comparison cohort at the index date

Characteristics	Nephrotic syndrome cohort (n=3,967)	General population comparison cohort (n=39,670)
Female sex	1,721 (43%)	17,210 (43%)
Age in years, median [IQR]	59 [43 - 72]	59 [43 - 72]
Calendar period		
1995-1999	666 (17%)	6,660 (17%)
2000-2005	973 (25%)	9,730 (25%)
2006-2011	985 (25%)	9,850 (25%)
2012-2018	1,343 (34%)	13,430 (34%)
Kidney disease diagnosed in hospital up to 10 years before index date		
Glomerulonephritis (excl. nephrotic syndrome)	529 (13%)	71 (0%)
Renal tubulointerstitial diseases	181 (5%)	314 (1%)
Acute kidney injury or chronic kidney disease	594 (15%)	297 (1%)
Cystic kidney disease	14 (0%)	31 (0%)
Hypertension with nephropathy	86 (2%)	30 (0%)
Diabetic nephropathy	216 (5%)	81 (0%)
Comorbidity diagnosed in hospital up to 10 years before index date		
Diabetes	616 (16%)	1,554 (4%)
Any connective tissue disease	248 (6%)	612 (2%)
Systemic lupus erythematosus (SLE)	51 (1%)	23 (0%)
Sicca syndrome (Sjögren)	< 5 (-)	6 (0%)
Amyloidosis	33 (1%)	5 (0%)
Heart failure	337 (8%)	943 (2%)
Chronic pulmonary disease	358 (9%)	1,709 (4%)
Ulcer disease	142 (4%)	725 (2%)
Liver disease	87 (2%)	247 (1%)
Non-hematological cancer	261 (7%)	1,784 (4%)
Hematological cancer	130 (3%)	256 (1%)
Coagulation defect	72 (2%)	142 (0%)
Ongoing pregnancy	114 (3%)	810 (2%)
Recent fracture/trauma	164 (4%)	937 (2%)
Recent surgery	513 (13%)	1,455 (4%)
Most recent eGFR		
Median eGFR ml/min/1.73 m^2 [IQR]	64 [38 - 90]	80 [65 - 92]
Missing eGFR*	3,092 (78%)	35,186 (89%)
History of thromboembolic or bleeding events up to 10 years before index date		
Prior arterial thromboembolism	401 (10%)	2,141 (5%)
Prior venous thromboembolism	196 (5%)	628 (2%)
Prior bleeding requiring hospital contact	519 (13%)	2,304 (6%)
Current use of medication at index date		
Proton pump inhibitors**	598 (15%)	2,459 (6%)
Antidiabetics**	511 (13%)	1,852 (5%)
Any anticoagulant drugs**	833 (21%)	5,032 (13%)
Aspirin**	554 (14%)	3,589 (9%)

Vitamin K antagonists**	166 (4%)	822 (2%)
NOACs/DOACs**	40 (1%)	222 (1%)
Thiazides/loop diuretics**	792 (20%)	3,830 (10%)
Beta-blockers**	689 (17%)	3,249 (8%)
Calcium channel blockers**	721 (18%)	2,565 (6%)
ACE-inhibitors**	821 (21%)	3,095 (8%)
Angiotensin-II receptor antagonists**	443 (11%)	2,165 (5%)
Other antihypertensives	100 (3%)	261 (1%)
Statins**	754 (19%)	3,819 (10%)
Glucocorticoids**	348 (9%)	835 (2%)
Antibiotics***	318 (8%)	955 (2%)
Antivirals***	9 (0%)	42 (0%)
Immunosuppressants**	64 (2%)	163 (0%)
NSAIDs**	511 (13%)	3,135 (8%)
Opioids**	478 (12%)	2,211 (6%)
Antipsychotics**	117 (3%)	787 (2%)
Antidepressants**	340 (9%)	2,524 (6%)

Values are given as n (%) unless otherwise noted. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NOAC, novel oral anticoagulant; DOAC, direct oral anticoagulant; ACE, angiotensin converting enzyme; NSAID, non-steroidal anti-inflammatory drug

* Missing eGFR may be due to incomplete coverage, as complete nationwide coverage of laboratory data was not achieved before 2014.

** Prescriptions filled during the 90 days before the index date.

*** Prescriptions filled during the 14 days before the index date.

Table 2. Histopathological findings in 1,902 patients identified with first-time hospital-recorded nephrotic syndrome (NS) and kidney biopsies ± 180 days from the index date.

	Patients with a kidney biopsy in the context of hospital-recorded NS
Type of glomerulonephritis*	
Membranous nephropathy (MN)	455 (24%)
Membranoproliferative glomerulonephritis (MPGN)	108 (6%)
Other proliferative glomerulonephritis	303 (16%)
Focal segmental glomerulosclerosis (FSGS)	163 (9%)
Minimal change disease (MCD)	468 (25%)
Other histopathology	405 (21%)

Values are given as n (%).

*Each person was categorized with a maximum of one type of histopathological finding. In case of several biopsies in the same patient, the biopsy closest to the NS admission date was used, and in the case of several findings in the same biopsy, the patient was categorized according to the finding listed first from the top (see codebook 6).

Table 3. Risk of arterial thromboembolism, venous thromboembolism and bleeding in patients with nephrotic syndrome (NS) and individuals from the general population (matched for age and sex) stratified by follow-up period

	0-30 days		0-1 year		0-5 years		0-10 years	
	No. events	**Risk, % (95% CI)**	**No. events**	**Risk, % (95% CI)**	**No. events**	**Risk, % (95% CI)**	**No. events**	**Risk, % (95% CI)**
Arterial thromboembolism								
NS cohort	42	1.1 (0.8 - 1.4)	164	4.2 (3.6 - 4.8)	368	10.1 (9.1 - 11.1)	468	14.0 (12.8 - 15.2)
General population	35	0.1 (0.1 - 0.1)	463	1.2 (1.1 - 1.3)	1820	5.1 (4.9 - 5.4)	2704	8.6 (8.3 - 8.9)
Venous thromboembolism								
NS cohort	26	0.7 (0.4 - 0.9)	110	2.8 (2.3 - 3.3)	211	5.7 (5.0 - 6.5)	261	7.7 (6.8 - 8.6)
General population	11	0.0 (0.0 - 0.0)	139	0.4 (0.3 - 0.4)	580	1.6 (1.5 - 1.8)	910	2.9 (2.7 - 3.1)
Bleeding								
NS cohort	53	1.3 (1.0 - 1.7)	203	5.2 (4.5 - 5.9)	448	12.2 (11.2 - 13.3)	570	17.0 (15.7 - 18.3)
General population	30	0.1 (0.1 - 0.1)	478	1.2 (1.1 - 1.3)	1874	5.3 (5.1 - 5.5)	2941	9.5 (9.2 - 9.8)

Abbreviations: CI, confidence interval; NS, nephrotic syndrome;

Table 4. Risk of subtypes of arterial thromboembolism, venous thromboembolism, and bleeding among patients with nephrotic syndrome stratified by follow-up period.

	0-30 days		0-1 year		0-5 years		0-10 years	
	No. events	**Risk, % (95% CI)**	**No. events**	**Risk, % (95% CI)**	**No. events**	**Risk, % (95% CI)**	**No. events**	**Risk, % (95% CI)**
Type of arterial thromboembolism								
Myocardial infarction	13	0.3 (0.2 - 0.6)	58	1.5 (1.1 - 1.9)	154	4.2 (3.6 - 4.9)	198	6.0 (5.2 - 6.8)
Ischemic stroke	26	0.7 (0.4 - 0.9)	97	2.5 (2.0 - 3.0)	213	5.8 (5.1 - 6.6)	272	8.1 (7.2 - 9.1)
Other arterial thromboembolism (ATE)	7	0.2 (0.1 - 0.4)	16	0.4 (0.2 - 0.6)	29	0.8 (0.5 - 1.1)	39	1.2 (0.9 - 1.6)
Type of venous thromboembolism								
Pulmonary embolism (PE)	13	0.3 (0.2 - 0.6)	56	1.4 (1.1 - 1.8)	93	2.5 (2.0 - 3.0)	117	3.4 (2.8 - 4.0)
Deep vein thrombosis (DVT)	12	0.3 (0.2 - 0.5)	43	1.1 (0.8 - 1.5)	87	2.4 (1.9 - 2.9)	105	3.1 (2.5 - 3.7)
Other venous thromboembolism (VTE)	5	0.1 (0.0 - 0.3)	23	0.6 (0.4 - 0.9)	58	1.6 (1.2 - 2.1)	74	2.3 (1.8 - 2.8)
Type of bleeding								
Cerebral bleeding	5	0.1 (0.0 - 0.3)	23	0.6 (0.4 - 0.9)	57	1.6 (1.2 - 2.0)	69	2.0 (1.6 - 2.6)
Respiratory tract bleeding	8	0.2 (0.1 - 0.4)	42	1.1 (0.8 - 1.4)	100	2.8 (2.3 - 3.3)	133	4.1 (3.4 - 4.8)
Gastrointestinal bleeding	14	0.4 (0.2 - 0.6)	86	2.2 (1.8 - 2.7)	201	5.5 (4.8 - 6.2)	271	8.2 (7.3 - 9.2)
Urinary tract bleeding	28	0.7 (0.5 - 1.0)	67	1.7 (1.3 - 2.1)	143	3.9 (3.3 - 4.6)	177	5.2 (4.5 - 6.0)

Abbreviations: CI, confidence interval;

Table 5. Relative risk of arterial thromboembolism, venous thromboembolism, and bleeding in patients with nephrotic syndrome compared to individuals from the general population.

	Crude*	Adjusted**
Arterial thromboembolism		
0-30 days	12.21 (7.80–19.12)	9.60 (6.10–15.11)
0-1 year	3.85 (3.22–4.60)	3.11 (2.60–3.73)
0-5 years	2.44 (2.18–2.73)	2.17 (1.93–2.43)
0-10 years	2.20 (1.99–2.42)	2.08 (1.88–2.29)
Venous thromboembolism		
0-30 days	24.05 (11.88–48.67)	17.97 (8.76–36.86)
0-1 year	8.62 (6.71–11.07)	7.11 (5.49–9.19)
0-5 years	4.39 (3.75–5.14)	4.03 (3.43–4.74)
0-10 years	3.67 (3.20–4.21)	3.51 (3.04–4.04)
Bleeding		
0-30 days	18.02 (11.52–28.20)	14.24 (9.05–22.41)
0-1 year	4.67 (3.96–5.50)	4.02 (3.40–4.75)
0-5 years	2.93 (2.64–3.24)	2.70 (2.43–3.00)
0-10 years	2.51 (2.30–2.75)	2.43 (2.21–2.66)

Values are presented as hazard ratio (95% confidence interval).

*Cohorts matched for age and sex, not adjusted.

**Adjusted for age, sex, calendar year, diabetes, prior thromboembolic events, prior bleeding events, cancer, amyloidosis, systemic lupus erythematosus, history of recent trauma/fracture, recent surgery, and use of medication at index date (including any anticoagulant drugs, statins, beta-blockers, calcium channel blockers, thiazides/loop diuretics, ACE-inhibitors, angiotensin-II receptor antagonists, NSAIDs, other antihypertensives, proton pump inhibitors, antidiabetics, glucocorticoids, antidepressants).

Figures

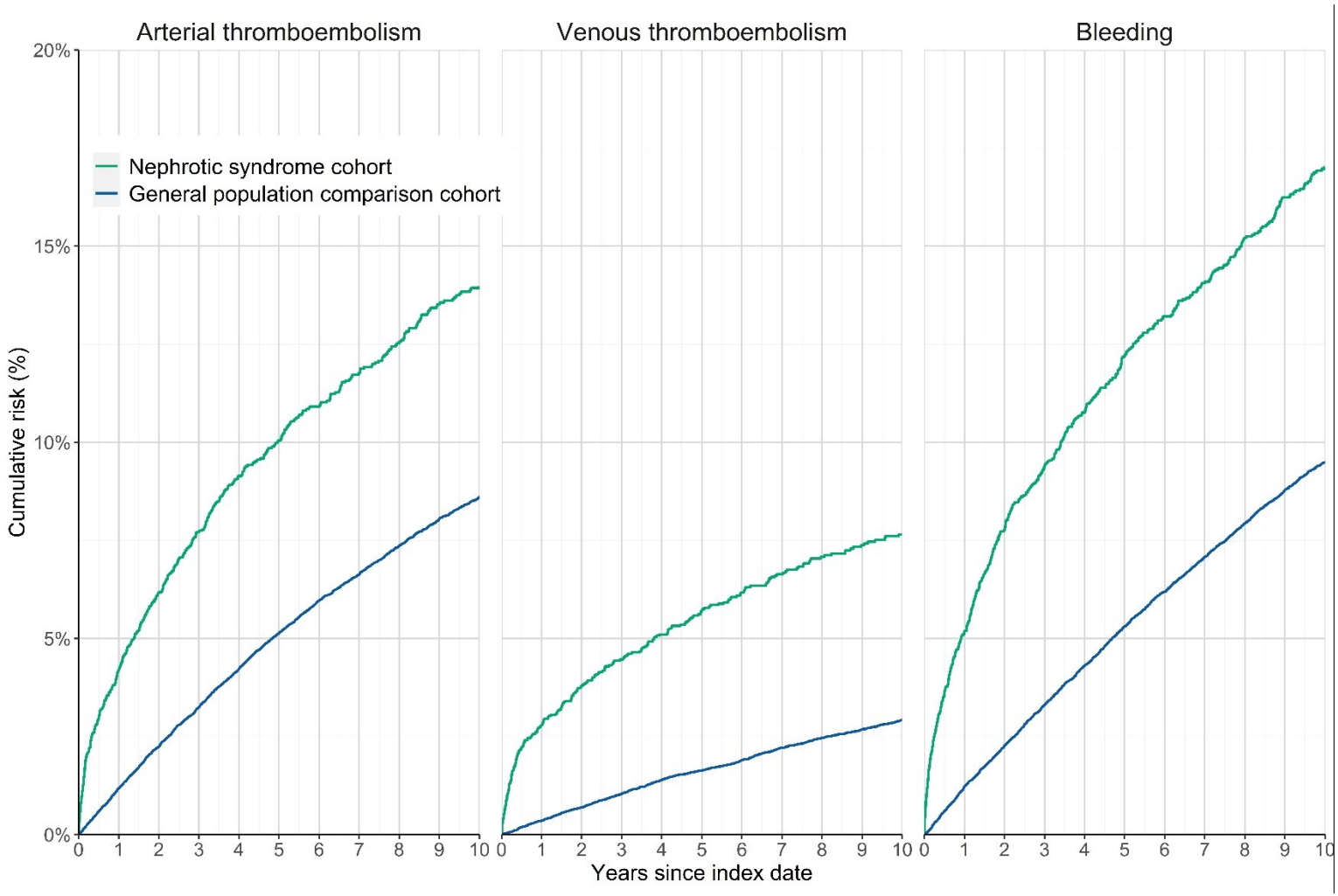

Figure 1. Risk of arterial thromboembolism (left), venous thromboembolism (center) and bleeding (right) in patients with nephrotic syndrome and individuals from the general population (matched for age and sex) during the first 10 years of follow-up.

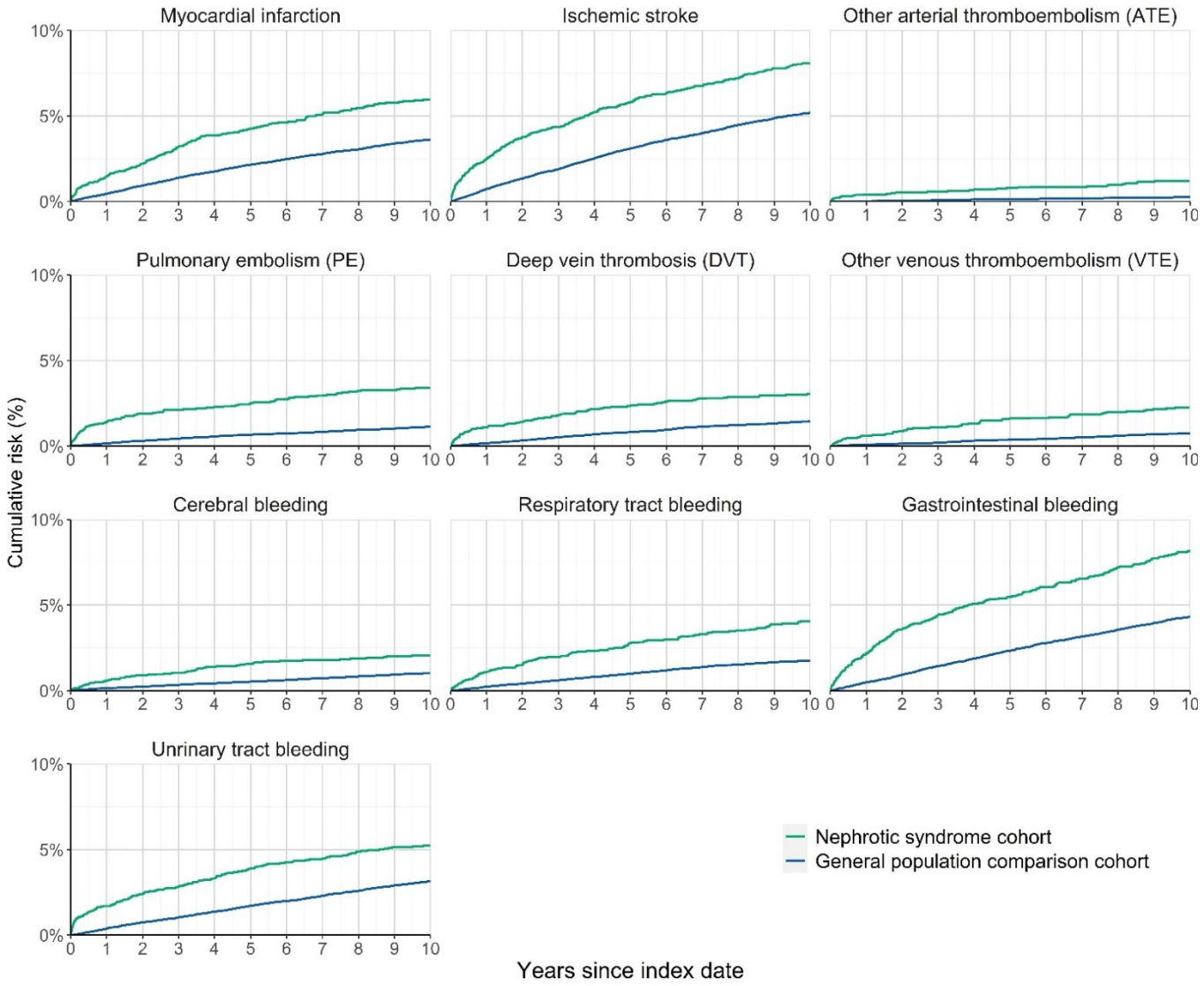

Figure 2. Risk of subtypes of arterial thromboembolism, venous thromboembolism and bleeding in patients with nephrotic syndrome and individuals from the general population (matched for age and sex) during the first 10 years of follow-up.

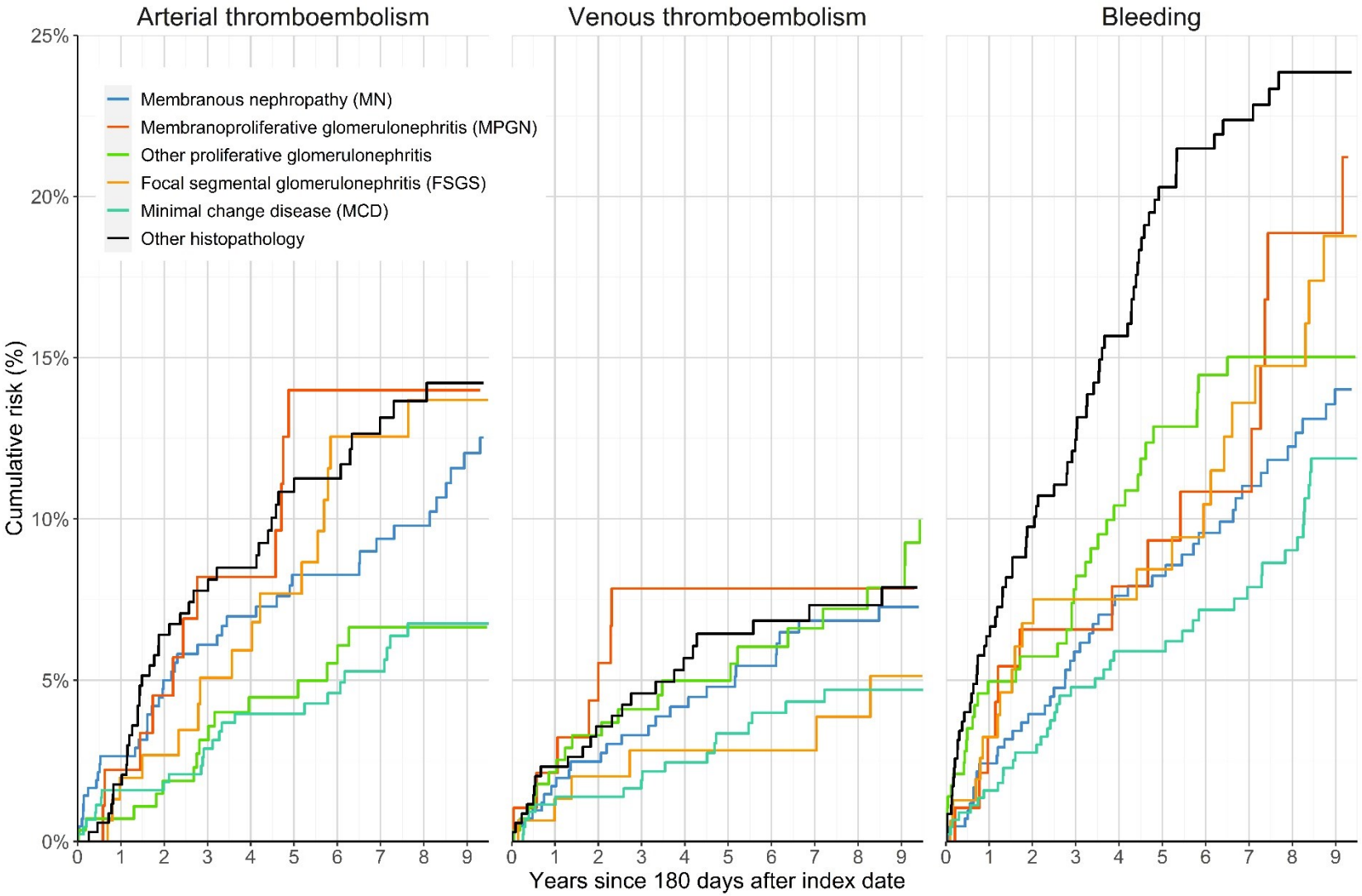

Figure 3. Risk of arterial thromboembolism (left), venous thromboembolism (center) and bleeding (right) in patients with nephrotic syndrome (NS) and kidney biopsy ± 180 days from the NS index date stratified by histopathological findings in the biopsy