Patients with primary membranous nephropathy are at high risk of cardiovascular events

Taewoo Lee[1,2], Vimal K. Derebail[1], Abhijit V. Kshirsagar[1], Yunro Chung[3], Jason P. Fine[3], Shannon Mahoney[1], Caroline J. Poulton[1], Sophia Lionaki[4], Susan L. Hogan[1], Ronald J. Falk[1], Daniel C. Cattran[5], Michelle Hladunewich[5], Heather N. Reich[5,6] and Patrick H. Nachman[1,6]

[1]UNC Kidney Center, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [2]Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, Korea; [3]Biostatistics Department, Gillings School of Global Public Health, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [4]Laiko Hospital, Athens, Greece; and [5]Division of Nephrology, Department of Medicine, University of Toronto, and Toronto Glomerulonephritis Registry, University Health Network, Toronto, Ontario, Canada

Here we conducted a retrospective study to examine the risk of cardiovascular events (CVEs) relative to that of end-stage renal disease (ESRD) in patients with primary membranous nephropathy, in a discovery cohort of 404 patients. The cumulative incidence of CVEs was estimated in the setting of the competing risk of ESRD with risk factors for CVEs assessed by multivariable survival analysis. The observed cumulative incidences of CVEs were 4.4%, 5.4%, 8.2%, and 8.8% at 1, 2, 3, and 5 years respectively in the primary membranous nephropathy cohort. In the first 2 years after diagnosis, the risk for CVEs was similar to that of ESRD in the entire cohort, but exceeded it among patients with preserved renal function. Accounting for traditional risk factors and renal function, the severity of nephrosis at the time of the event (hazard ratio 2.1, 95% confidence interval 1.1 to 4.3) was a significant independent risk factor of CVEs. The incidence and risk factors of CVEs were affirmed in an external validation cohort of 557 patients with primary membranous nephropathy. Thus early in the course of disease, patients with primary membranous nephropathy have an increased risk of CVEs commensurate to, or exceeding that of ESRD. Hence, reduction of CVEs should be considered as a therapeutic outcome measure and focus of intervention in primary membranous nephropathy.

Kidney International (2016) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2015.12.041

KEYWORDS: cardiovascular disease; glomerulonephritis; membranous nephropathy

Correspondence: *Patrick H. Nachman, University of North Carolina at Chapel Hill, 7004 Burnett-Womack CB No. 7155, Chapel Hill, North Carolina 27599-7155, USA. E-mail: patrick_nachman@med.unc.edu or to Heather N. Reich, c/o the Toronto GN Registry 12N-228 200 Elizabeth Street, Toronto, Ontario M5G 2C4.*

[6]These authors contributed equally.

Received 30 September 2014; revised 18 November 2015; accepted 11 December 2015

Primary membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults.[1] The goals of therapy of MN have primarily focused on the prevention of ESRD, an event that generally occurs after several years,[2] whereas other complications of the nephrotic syndrome may occur early in the course of disease. A well-recognized early complication of MN are venous thromboembolic events,[3–7,8] with hypoalbuminemia being the most important independent risk factor.[9] While the increased risk of venous thromboembolic events is well characterized, the risk of arterial thromboembolic events, primarily consisting of CVEs (acute myocardial ischemic events and infarction, ischemic cerebrovascular events, and peripheral artery occlusive disease), has only been described to a limited extent by Mahmoodi *et al.*[10] Small cohort studies[11–13] have reported on the risk of CVEs in primary MN, but the data relative to their incidence, timing, and risk factors are scant. We hypothesized that primary MN is associated with a high risk of CVEs, and that there may be a temporal pattern favoring events early in the course of disease given the thrombophilic state associated with MN. We further hypothesized that, early in the course of disease, the risk of major CVEs is commensurate to or exceeds that of ESRD and represents an important cause of morbidity. If confirmed, the prevention of early CVEs should be considered as part of the early goals of therapy of the nephrotic syndrome of primary MN.

In this study, we present data on the cumulative incidence rate of CVEs in a large inception cohort of primary MN from the Glomerular Disease Collaborative Network (GDCN cohort) of the University of North Carolina at Chapel Hill.[9] We performed a detailed analysis of risk factors of CVEs with a focus on the severity of nephrotic syndrome. We validated our findings by comparing them to those derived from an external independent cohort of patients with primary MN from the Toronto Glomerulonephritis Registry (TGNR cohort) of the University of Toronto.[14]

RESULTS

Incidence of cardiovascular events in primary MN

A total of 404 patients with primary MN identified from the GDCN registry constituted the study cohort to evaluate

the risk of CVE. Table 1 shows the detailed baseline characteristics of the study and validation cohorts. Patients in the GDCN study cohort (60% men, mean age 55 years) presented with a mean proteinuria of 8.7 ± 6.2 g/d and a mean serum albumin of 2.5 ± 0.8 g/dl. Eighty-eight percent presented with nephrotic syndrome (defined as proteinuria >3.5 g/d and serum albumin <3.2 g/dl), and 62% had an estimated glomerular filtration rate (eGFR) greater than 60 ml/min per 1.73 m^2. During the median follow-up of 24.3 months (interquartile range 9.9–52.7 months), 31 patients had a CVE, 58 progressed to ESRD, and 6 died of causes other than CVEs. Of the 31 CVEs, 22 were acute coronary syndrome, 8 were acute ischemic cerebrovascular events, and 1 was an acute peripheral arterial thromboembolic event. The distribution of CVEs according to times after biopsy and the status of nephrotic syndrome at the time of event is shown in Figure 1. The majority of total CVEs (21 of 31 events) occurred within 2 years after diagnosis, with 57% (12 of 21 events) of them occurring while the patient had severe proteinuria (mean 7.6 ± 4.1 g/d) and hypoalbuminemia (mean 2.5 ± 0.7 g/dl). In contrast, about one-third of total CVEs (10 of 31 events) occurred beyond 2 years after diagnosis. These late CVEs occurred in 7 patients in complete remission and in 3 patients with subnephrotic proteinuria at the time of the event (Figure 1). The proteinuria (2.2 ± 1.5 g/d, $P < 0.001$) and hypoalbuminemia (3.6 ± 0.4 g/dl, $P < 0.001$) at the time of the event in patients with late CVEs were significantly less severe compared to those of patients who experienced CVEs early within 2 years of kidney biopsy (7.6 ± 4.1 g/d and 2.5 ± 0.7 g/dl, respectively) (Table 2).

The cumulative incidence rates of newly diagnosed CVEs in competing risk analysis were 4.4%, 5.4%, and 8.2%, at 1, 2, and 3 years after biopsy, respectively. At the same time points, the cumulative incidence rates of ESRD were 5.6%, 8.9%, and 11.9%, respectively (Figure 2a). Among patients with baseline eGFR ≥ 60 ml/min per 1.73 m^2, the estimated incidence of CVEs exceeded that of ESRD during the first 3 years after diagnosis (cumulative incidence rates of 2.6%, 3.7%, and 6.4% for CVEs vs. 0.5%, 2.5%, and 6.1% for ESRD at 1, 2, and 3 years, respectively) (Figure 2b). In contrast, among patients with eGFR less than 60 ml/min per 1.73 m^2 at baseline, the cumulative incidence of ESRD exceeded that of CVEs beyond the first 6 months after kidney biopsy (cumulative incidence of 7.1%, 8.0%, and

Table 1 | Baseline characteristics of the GDCN study cohort and TGNR validation cohort

	GDCN (n = 404)	TGNR (n = 557)
Age (years)[a]	51.4 ± 15.5	46.7 ± 16.7
Male gender (%)	60	65
Race,[a] white (%)	71	73
Black	20	7
Asian/Others	9	20
Diabetes (%)[a]	9	3
Smoking		
Ever (%)	33	31
Current (%)	21	NA
Previous history of CVE (%)	12	13
Serum creatinine (mg/dl)[a]	1.5 ± 1.3	1.1 ± 0.7
eGFR (ml/min/1.73 m^2)[a]	68.9 ± 33.5	78.9 ± 36.7
eGFR >60 (%)	62	72
eGFR 45–60 (%)	16	15
eGFR <45 (%)[a]	22	13
Proteinuria (g/d)[a]	8.7 ± 6.2	7.7 ± 6.6
Serum albumin (g/dl)	2.5 ± 0.8	2.5 ± 0.7
Serum total cholesterol (mg/dl)[b]	337.9 ± 107.7	326.9 ± 100
<200 (%)	7	9
200–300 (%)	33	34
≥300 (%)	60	57
Nephrotic syndrome (%)[a]	88	74
Medication use[c]		
Aspirin (%)	21	17
Corticosteroids (%)[a]	76	50
CNI (%)	7	10
Cyclophosphamide (%)	22	15
Statin (%)	40	22
Follow-up duration (months)[a]	24.3 (9.9–52.7)	52 (21.3–96.2)

Data presented as mean ± SD or median (interquartile range) for continuous variables and as percentages for categorical variables.
CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate by modified MDRD equation; GDCN, Glomerular Disease Collaborative Network; MN, membranous nephropathy; TGNR, Toronto Glomerulonephritis Registry.
[a]Significant difference with P value <0.05 by t-test for continuous variables and χ^2 test for categorical variables.
[b]Number of patients with valid laboratory values was limited: GDCN, 270 of 404 (67%); TGNR, 341 of 557(61%).
[c]Number of patients with valid information was limited in TGNR cohort: aspirin and statin use, 352 of 557 (63%).

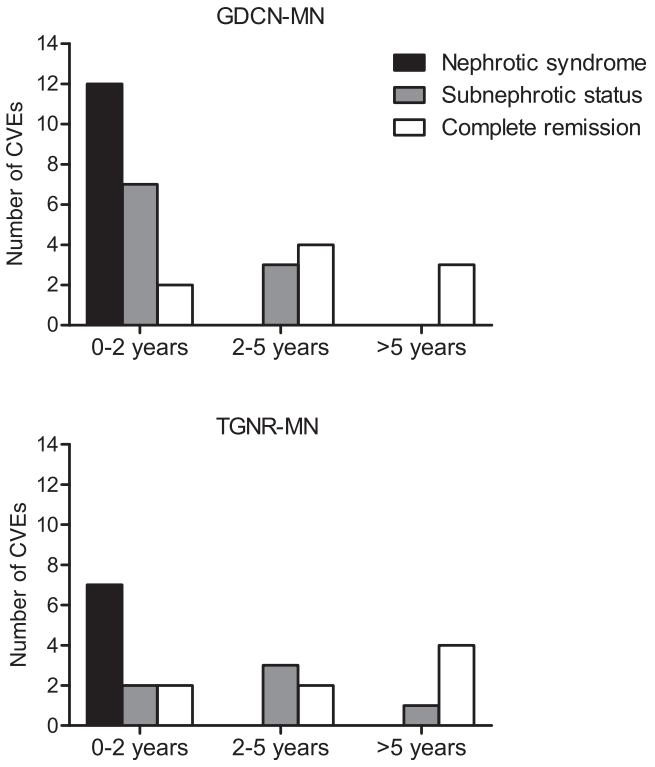

Figure 1 | Number of cardiovascular events observed according to the duration of follow-up and the status of nephrotic syndrome in primary MN cohorts. CVE, cardiovascular event; GDCN, Glomerular Disease Collaborative Network; MN, membranous nephropathy; TGNR, Toronto Glomerulonephritis Registry.