Evaluating the risk of cardiovascular events associated with different immunosuppression treatments for glomerular diseases

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Patients with glomerular disease are at high risk of cardiovascular disease but the contribution of immunosuppression to this risk is unclear. In this retrospective cohort study of 1912 patients (comprised of 759 with IgA nephropathy, 540 with focal segmental glomerulosclerosis, 387 with membranous nephropathy and 226 with minimal change disease) from British Columbia, Canada, we evaluated the association between exposure to specific immunosuppressive medications and a composite outcome including coronary artery, cerebrovascular and peripheral arterial events. Survival models were adjusted for baseline cardiovascular risk factors, type of glomerular disease, estimated glomerular filtration rate (eGFR) and proteinuria over time. During a median follow-up of 6.8 years, 212 patients (11.1%) experienced the primary outcome. Corticosteroid exposure was not significantly associated with the primary outcome after adjusting for cardiovascular risk factors. In fully adjusted models, cumulative calcineurin inhibitor exposure at modest (150-300 defined daily doses [DDD]) and higher (300 or more DDD) doses were associated with a 2-fold higher risk of cardiovascular events (hazard ratio 2.98, 95% confidence interval 1.27-6.95) and (2.78, 1.32-5.84), respectively. A peak daily dose of antimetabolite (azathioprine, mycophenolate mofetil and mycophenolate sodium) of 0.5 or more DDD was associated with higher risk of cardiovascular events after adjustment for baseline risk factors and type of glomerular disease, but not after adjusting for time-varying eGFR and proteinuria (1.70, 0.91-3.20). Each 10 grams of cumulative cyclophosphamide exposure was associated with a 1.5-fold higher risk of cardiovascular events in a fully adjusted model (1.46, 1.22-1.75) Thus, our findings suggest that immunosuppressive therapies used in the treatment of glomerular disease may have different cardiovascular risk profiles, which should be considered when deciding on immunosuppression for individual patients and as a safety endpoint in future clinical trials.

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Lay Summary

Individuals with glomerular disease (immune-mediated types of kidney disease) are at risk of experiencing cardiovascular problems, such as heart attacks and strokes. The immune therapies used to treat glomerular disease are thought to contribute to this risk; however, this has not been adequately studied. In this study of 1912 adult patients with glomerular disease from British Columbia, Canada, we show that exposure to calcineurin inhibitors and cyclophosphamide over time was associated with a higher risk of having a cardiovascular event compared with not being exposed to those drugs. Conversely, we did not find an increased risk of cardiovascular events associated with exposure to corticosteroids or antimetabolites. The findings suggest that commonly used treatments for glomerular disease have different risk profiles for developing cardiovascular disease in the future. If validated in other similar cohorts, this could inform discussions with patients about the risks and benefits of specific treatments for glomerular disease.

Patients with glomerular disease frequently develop cardiovascular risk factors resulting from their underlying disease, including hypertension, dyslipidemia, proteinuria, and decreased kidney function.[1–4] As a result, the 2021 Kidney Disease: Improving Global Outcomes guidelines consider these patients to be at increased risk for

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cardiovascular events and recommend lipid-lowering therapy in patients with nephrotic syndrome to reduce cardiovascular risk.[5] However, there has been limited epidemiologic data to accurately quantify this risk across different types of glomerular disease and determine the contributions of traditional and glomerular disease–specific cardiovascular risk factors.[6–12] Using a population-level cohort, we previously demonstrated that patients with glomerular disease have a high absolute rate of cardiovascular events of 24.7 per 1000 person-years, which includes coronary artery, cerebrovascular, or peripheral vascular events and which is 2.5-fold higher than that seen in the age- and sex-adjusted general population.[13] Proteinuria (including in the subnephrotic range) and estimated glomerular filtration rate (eGFR) at the time of biopsy, along with type of glomerular disease, were shown to be important risk factors for cardiovascular events that, when combined with traditional risk factors, can improve cardiovascular risk stratification in patients with glomerular disease.[13]

Immunosuppression medications used to treat glomerular diseases may have differing effects that not only promote but also potentially reduce cardiovascular risk. Some types of immunosuppression therapies, such as corticosteroids, calcineurin inhibitors, and cyclophosphamide, can cause hypertension, dyslipidemia, and diabetes, or directly result in cardiac toxicity, thereby increasing the risk of cardiovascular events.[14–18] Because eGFR and proteinuria at biopsy are associated with increased cardiovascular risk in patients with glomerular disease,[13] it is possible that immunosuppression therapies that improve glomerular disease control may result in improvements in eGFR and proteinuria over time and, therefore, be associated with a reduction in cardiovascular risk. As such, there is a potentially complex relationship between immunosuppression medications and cardiovascular risk related to the opposing effects of drug toxicity versus improved control of the underlying glomerular disease. To our knowledge, there are no studies that have investigated the risk of cardiovascular events associated with immunosuppression therapies for glomerular disease that account for longitudinal control of disease activity. Improved understanding of the contribution of individual immunosuppression therapies to the development of cardiovascular events would help inform treatment decisions that balance the benefit versus toxicity of treatment, especially in patients with a higher baseline cardiovascular risk profile.

In a population-level cohort of patients with biopsy-proven IgA nephropathy, membranous nephropathy, focal segmental glomerular sclerosis (FSGS), and minimal change disease, we sought to investigate the risk of cardiovascular events associated with longitudinal exposure to immunosuppression therapies while simultaneously adjusting for eGFR and proteinuria over time as markers of disease activity.

METHODS

Study design

This was a retrospective population-level cohort study of adult patients, aged ≥18 years, with glomerular disease diagnosed on a native kidney biopsy between January 1, 2000, and December 31, 2012, in British Columbia (BC), Canada. This cohort was used previously to study cardiovascular risk in patients with glomerular disease.[13] Full details regarding the study design are provided in the Supplementary Methods. In brief, the following glomerular disease types were included: (i) IgA nephropathy, (ii) membranous nephropathy, (iii) FSGS, and (iv) minimal change disease. Patients with lupus nephritis and anti-neutrophil cytoplasmic autoantibody vasculitis were not included because of the substantial literature that already exists regarding cardiovascular risk in these populations. Histologic features and clinical data provided at the time of biopsy were used to exclude patients with an identifiable underlying cause (infection, other glomerular disease, or systemic autoimmune disease); thus, cases were restricted to those with a higher likelihood of immune cause. Additional exclusion criteria included the onset of end-stage kidney disease at or before biopsy, and no follow-up available after biopsy. The date of biopsy was the study baseline, and patients were followed up until December 31, 2014. Approval for this study was granted by the research ethics board of the University of British Columbia with waived individual patient consent.

Data sources

Patients meeting the histology inclusion criteria were identified from a centralized provincial pathology database that captures all patients with biopsy-proven glomerular disease in mainland BC. Individual-level linkage with clinical and administrative databases was conducted using a unique personal health number. Laboratory data were captured from community- and hospital-based laboratories. Dialysis and transplantation events, laboratory data, and comorbidities were ascertained from a province-wide clinical information system for patients with kidney disease. Hospital admissions were captured from the Discharge Abstract Database,[19] physician encounters from the Medical Services Plan,[20] pharmacy-dispensed medications from PharmaNet,[21] and i.v. medications from hospital-based pharmacies. Patient demographics and death events were captured from BC Vital Statistics.[22] Patient-level information was linked through Population Data BC (www.popdata.bc.ca) at the University of British Columbia; all data were deidentified before creation of the analytical data set. Further information regarding each data source is provided in the Supplementary Methods.

Variable definitions

Proteinuria was from 24-hour urine collections; when these were not available, daily urinary protein excretion was estimated from spot urine protein or albumin to creatinine ratios based on established methods, as done previously.[23,24] Glomerular filtration rate was estimated from provincially

standardized creatinine measurements using the Chronic Kidney Disease Epidemiology Collaboration formula.[25,26] Laboratory data at baseline were taken as the closest value within 6 months of biopsy. End-stage kidney disease was defined as per the Canadian Organ Replacement Register as the first occurrence of permanent dialysis or kidney transplantation.[27] Sex was defined as the biological sex at birth and was categorized as male or female. Comorbidities before the biopsy date included the presence of hypertension, diabetes, dyslipidemia, smoking, and prior cardiovascular disease. The primary outcome was the occurrence of any major adverse cardiovascular event after biopsy. This included acute ischemic events and revascularization procedures for coronary artery, cerebrovascular, and peripheral vascular disease, and death due to myocardial infarction or stroke. This is similar to the outcome definitions used in major cardiovascular clinical trials.[28–32] All comorbidity and outcome variables were based on definitions validated for use in administrative data (see Supplementary Table S1 for further details).

Primary exposure of interest: immunosuppression

Immunosuppressive medications were categorized using defined daily doses (DDDs), which allows drugs from the same class to be grouped together.[33] Calcineurin inhibitors included tacrolimus and cyclosporine (DDD of 5 and 250 mg, respectively). Antimetabolites included azathioprine, mycophenolate mofetil, and mycophenolate sodium (DDD of 150, 2000, and 1440 mg, respectively). Oral and i.v. corticosteroids were converted into equivalent prednisone doses. Cyclophosphamide included oral and i.v. versions. Immunosuppression treatment episodes over time were constructed using medication dispensing data, allowing gaps and overlaps of 14 days.[34,35] The dispensed total dose was averaged across the duration of the treatment episode to generate a daily dose. Further details are provided in the Supplementary Methods.

Statistical analysis

Time from kidney biopsy to the first occurrence of the primary outcome, censored at death, date of last follow-up, or the end of the study period (December 31, 2014), was modeled using extended Cox proportional hazards regression to allow for time-varying variables. In this type of analysis, the value for each time-varying variable was dynamically updated at each event time in the cohort to estimate the hazard function. Given the potential for a long lag time between drug exposure and the onset of cardiovascular risk, all cardiovascular outcome events during follow-up were considered, including those before and after end-stage kidney disease. eGFR (ml/min per 1.73 m^2) over time was categorized as >90, 60 to 90, 30 to 60, <30, and end-stage kidney disease to capture the onset of dialysis or transplantation as a separate category along a continuum of kidney function decline. Proteinuria over time had a nonlinear functional form; as such, it was modeled using 2 separate linear relationships, one for values ≤4 g/d and a second for values >4 g/d. Proteinuria and eGFR over time were evaluated in separate univariable models and together in multivariable models that sequentially included type of glomerular disease and traditional cardiovascular risk factors at baseline (age, sex, hypertension, diabetes, dyslipidemia, smoking, and prior cardiovascular disease). The purpose of this analysis was to understand the time-varying association between markers of disease activity and cardiovascular events before evaluating immunosuppression exposure.

The association between immunosuppression exposure over time and the risk of cardiovascular events was evaluated separately for each type of immunosuppression medication (with the reference group being time unexposed to that same treatment). Immunosuppression exposure was set as unexposed at the time of kidney transplantation or 6 months after the initiation of dialysis (because immunosuppression prescribed after kidney transplantation or >6 months after starting dialysis was less likely to be prescribed for treatment of glomerular disease). The optimal lag time for each drug category (based on model fit) was found to be 30 months for corticosteroids, 24 months for antimetabolites, 18 months for cyclophosphamide, and 0 months for calcineurin inhibitors (i.e., no lag time). These lag times account for the time delay between drug exposure and the onset of cardiovascular risk and were used for all subsequent models. For each category of immunosuppression medication, the following time-varying metrics of drug exposure were considered: daily exposure (yes/no), daily dose, cumulative dose in a prior window period, and peak daily dose in a prior window period. Various window periods were considered, ranging from 6 months to 6 years. The optimal parameterization and window period for each category of immunosuppression medication was chosen on the basis of model fit with the lowest Akaike information criterion from univariable models. The association between each category of immunosuppression medication and the risk of the primary outcome was evaluated in multivariable models that sequentially included traditional cardiovascular risk factors at baseline (as above), type of glomerular disease, and eGFR and proteinuria over time. The proportional hazards assumption was checked using Schoenfeld residuals plots, and there was no violation of the assumption. The time-varying Cox regression model estimates the direct effect of immunosuppression drug exposure on the risk of cardiovascular events after adjusting for eGFR and proteinuria over time as measures of glomerular disease activity. This approach is distinct from estimating both the direct effect and any indirect effect mediated through changes in eGFR and proteinuria. Further details on the interpretation of these results, along with a causal diagram, are provided in the Supplementary Methods.

Four sensitivity analyses were conducted. First, the lag times chosen for each category of immunosuppression medication were varied to determine consistency of results. Second, alternative metrics of each immunosuppression

exposure were evaluated. Third, common combinations of immunosuppression medications were included together in multivariable models to determine independent associations with cardiovascular risk. Fourth, the primary analysis was repeated after excluding patients with minimal change disease.

Finally, the association between time-varying immunosuppression drug exposure and noncardiovascular death was examined in a cause-specific hazards model using the same exposure window periods and lag times as in the primary analysis.

RESULTS

The analytic cohort comprised 1912 patients, including 759 with IgA nephropathy, 540 with FSGS, 387 with membranous nephropathy, and 226 with minimal change disease (Supplementary Figure S1). Patient characteristics are shown in Table 1.

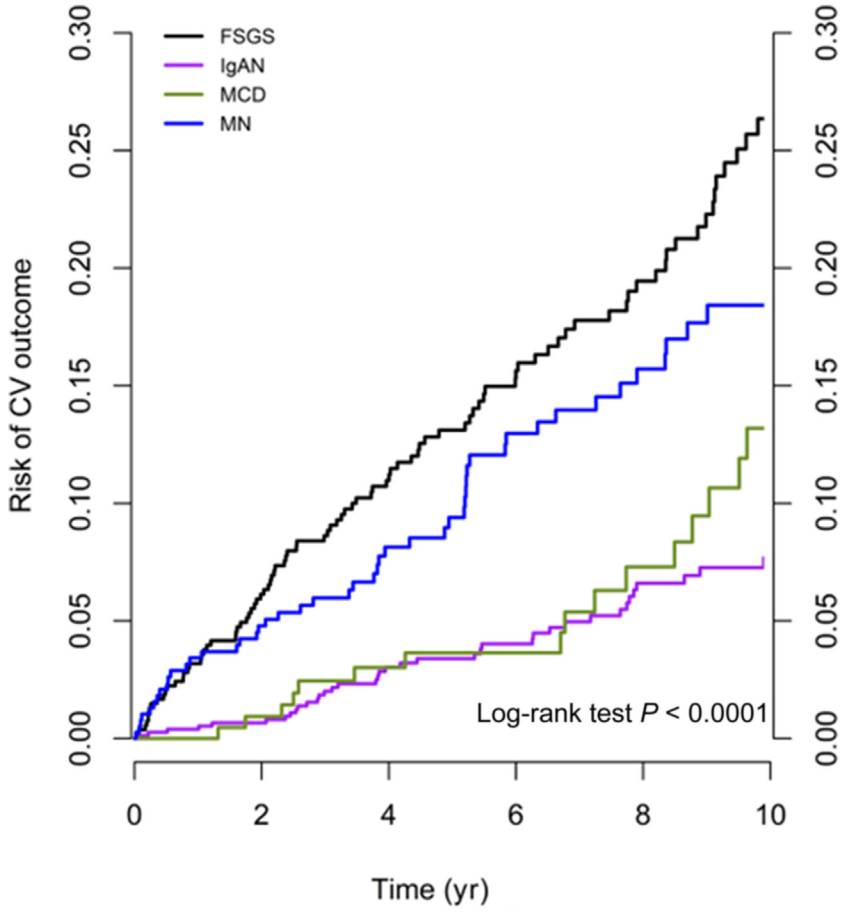
Absolute risk of cardiovascular events

Over a median (interquartile range [IQR]) follow-up of 6.8 years (3.6–10.5 years), 212 patients (11.1%) experienced the primary cardiovascular outcome, which comprised acute ischemic events or revascularization procedures for coronary artery disease (n = 115 [6.0%]), cerebrovascular disease (n = 46 [2.4%]), and peripheral vascular disease (n = 51 [2.7%]). Considering time to first event, the absolute risk of the primary cardiovascular outcome is shown in Figure 1 and the individual components of the outcome in Supplementary Figure S2. In the overall cohort, the 10-year

Table 1 | Characteristics of the cohort overall and by glomerular disease type

Characteristic	Overall (n = 1912)	IgAN (n = 759)	MN (n = 387)	FSGS (n = 540)	MCD (n = 226)
Duration of follow-up, yr	6.8 (3.6–10.5)	7.2 (3.8–10.8)	6.4 (3.2–9.9)	6.4 (3.5–10.1)	6.9 (3.6–10.9)
Age, yr	50.6 (16.8)	44.8 (14.4)	57.0 (15.4)	54.5 (17.2)	49.4 (18.8)
Male sex	1137 (59.5)	466 (61.4)	222 (57.4)	326 (60.4)	123 (54.4)
Creatinine, μmol/l	115 (83–184)	119 (91–180)	89 (73–121)	149 (97–223)	97 (74–153)
eGFR, ml/min per 1.73 m^2	57.7 (31.8–86.2)	57.5 (34.2–81.3)	76.3 (49.0–93.6)	40.9 (22.3– 74.5)	67.5 (39.1–98.3)
Proteinuria, g/d	2.6 (1.2–5.7)	1.5 (0.8–2.8)	5.9 (3.3–9.0)	2.6 (1.4–5.0)	5.7 (1.8–8.5)
Proteinuria category, g/d					
<1	358 (18.7)	225 (29.6)	18 (4.7)	81 (15.0)	34 (15)
1–4	730 (38.2)	353 (46.5)	91 (23.5)	245 (45.4)	41 (18.1)
4–8	383 (20.0)	87 (11.5)	123 (31.8)	109 (20.2)	64 (28.3)
≥8	243 (12.7)	16 (2.1)	120 (31.0)	50 (9.3)	57 (25.2)
Albumin, g/l	36 (26–41)	39 (35–42)	25 (19–31)	38 (32–42)	22 (16–31)
MAP, mm Hg	100 (90–110)	100 (92–110)	97 (87–107)	102 (93–111)	94 (85–107)
Comorbidities at the time of biopsy					
Hypertension	1309 (68.5)	510 (67.2)	258 (66.7)	432 (80.0)	109 (48.2)
Diabetes	315 (16.5)	72 (9.5)	75 (19.4)	137 (25.4)	31 (13.7)
Dyslipidemia	810 (42.4)	202 (26.6)	221 (57.1)	285 (52.8)	102 (45.1)
Smoking	71 (3.7)	25 (3.3)	11 (2.8)	29 (5.4)	6 (2.7)
Any prior CV disease	385 (20.1)	89 (11.7)	102 (26.4)	150 (27.8)	44 (19.5)
Prior coronary artery disease	339 (17.7)	80 (10.5)	90 (23.3)	133 (24.6)	36 (15.9)
Prior cerebrovascular disease	70 (3.7)	15 (2.0)	20 (5.2)	25 (4.6)	10 (4.4)
Prior peripheral vascular disease	22 (1.2)	4 (0.5)	2 (0.5)	14 (2.6)	2 (0.9)
Immunosuppression use during follow-up					
Any immunsuppression	1191 (62.3)	372 (49.0)	277 (71.6)	340 (63.0)	202 (89.4)
Corticosteroids	1144 (59.8)	357 (47.0)	258 (66.7)	333 (61.7)	196 (86.7)
Calcineurin inhibitors[a]	382 (20.0)	102 (13.4)	102 (26.4)	122 (22.6)	56 (24.8)
Cyclophosphamide	247 (12.9)	28 (3.7)	129 (33.3)	36 (6.7)	54 (23.9)
Antimetabolites[b]	334 (17.5)	133 (17.5)	56 (14.5)	109 (20.2)	36 (15.9)
Experienced ESKD during follow-up	442 (23.1)	191 (25.2)	48 (12.4)	188 (34.8)	15 (6.6)
Experienced the primary CV outcome event					
Composite CV outcome	212 (11.1)	44 (5.8)	51 (13.2)	100 (18.5)	17 (7.5)
Coronary artery disease	115 (6.0)	30 (4.0)	25 (6.5)	49 (9.1)	11 (4.9)
Cerebrovascular disease	46 (2.4)	7 (0.9)	17 (4.4)	18 (3.3)	4 (1.8)
Peripheral vascular disease	51 (2.7)	7 (0.9)	9 (2.3)	33 (6.1)	2 (0.9)

CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FSGS, focal segmental glomerular sclerosis; IgAN, IgA nephropathy; MAP, mean arterial pressure; MCD, minimal change disease; MN, membranous nephropathy.
[a]Calcineurin inhibitors included cyclosporine and tacrolimus.
[b]Antimetabolite medications included mycophenolate mofetil, mycophenolic acid, and azathioprine.
Data are presented as mean (SD), median (interquartile range), or n (%).



No. at risk:

FSGS:	540	471	351	252	183	111
IgAN:	759	723	540	436	324	221
MCD:	226	209	157	122	90	62
MN:	387	345	239	186	139	84

Figure 1 | The risk of the primary cardiovascular (CV) outcome for each type of glomerular disease. FSGS, focal segmental glomerular sclerosis; IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy.

risk of a cardiovascular event was 16.0% (95% confidence interval [CI], 13.8%–18.3%). This risk differed significantly across types of glomerular disease, being highest in those with FSGS and membranous nephropathy and lower in those with IgA nephropathy and minimal change disease (log-rank $P < 0.001$; Figure 1).

Cardiovascular risk associated with proteinuria and eGFR and over time

Proteinuria and eGFR measurements over time were considered metrics of glomerular disease activity. During the follow-up period, the median (IQR) number of proteinuria and eGFR measurements per patient were 11 (3–22) and 17 (6–34), respectively. The median (IQR) frequency of proteinuria measurements was 1 every 5.5 months (2.9–10.9), and the median (IQR) frequency of eGFR measurements was 1 every 3.1 months (1.6–6.0).

The risk of the primary cardiovascular outcome associated with proteinuria and eGFR over time, both modeled as time-varying covariates in extended Cox proportional hazards regression models, is shown in Table 2. In a multivariable model that adjusted for type of glomerular disease and traditional cardiovascular risk factors at baseline (age, sex, hypertension, diabetes, dyslipidemia, smoking, and prior cardiovascular disease), there was a significant association between both proteinuria and eGFR over time and cardiovascular risk. Each 1-g/d increase in proteinuria up to a maximum of 4 g/d was associated with a 16% relative increase in the risk of cardiovascular events (hazard ratio [HR], 1.16; 95% CI, 1.04–1.30; $P = 0.007$); however, this risk reached a

Table 2 | Univariable, bivariable, and multivariable models for the risk of the primary CV outcome associated with proteinuria and eGFR over time

	Univariable models		Bivariable model		Multivariable model: CV risk factors		Multivariable model: CV risk factors + GN type	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Proteinuria over time								
Per g/d increase up to 4 g/d	1.48 (1.34–1.63)	<0.001	1.21 (1.08–1.35)	<0.001	1.18 (1.06–1.32)	0.003	1.16 (1.04–1.30)	0.007
Per g/d increase above 4 g/d	1.01 (0.97–1.05)	0.68	1.02 (0.98–1.06)	0.31	1.02 (0.98–1.07)	0.35	1.02 (0.97–1.06)	0.52
eGFR over time								
>90 ml/min per 1.73 m^2	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
60–90 ml/min per 1.73 m^2	2.59 (1.16–5.80)	0.02	2.65 (1.18–5.92)	0.02	1.24 (0.55–2.82)	0.60	1.36 (0.60–3.10)	0.46
30–60 ml/min per 1.73 m^2	5.80 (2.74–12.26)	<0.001	5.72 (2.71–12.11)	<0.001	2.01 (0.93–4.37)	0.08	2.33 (1.05–5.13)	0.04
<30 ml/min per 1.73 m^2	11.01 (5.20–23.31)	<0.001	9.74 (4.59–20.68)	<0.001	2.49 (1.13–5.52)	0.02	2.83 (1.25–6.40)	0.01
ESKD	20.42 (9.86–42.30)	<0.001	14.61 (6.92–30.86)	<0.001	5.37 (2.46–11.72)	<0.001	6.40 (2.84–14.39)	<0.001

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GN, glomerulonephritis; HR, hazard ratio; Ref, reference group.
All models are extended Cox proportional hazards regression models that allow for time-varying variables. The univariable models include only 1 of proteinuria or eGFR over time. The bivariable model includes both proteinuria and eGFR over time. The multivariable models include both proteinuria and eGFR over time and adjust for cardiovascular risk factors at baseline (age, sex, hypertension, diabetes, dyslipidemia, smoking, and prior cardiovascular disease), with or without type of glomerular disease (focal segmental glomerular sclerosis, membranous nephropathy, minimal change disease, and IgA nephropathy).

plateau such that any additional increase in proteinuria above 4 g/d was not associated with a further increase in cardiovascular risk (HR, 1.02; 95% CI, 0.97–1.06; $P = 0.52$) (Figure 2). Compared with eGFR >90 ml/min per 1.73 m^2, lower eGFR over time was associated with an increased risk of cardiovascular events, including a moderately low eGFR between 30 and 60 ml/min per 1.73 m^2 (HR, 2.33; 95% CI, 1.05–5.13; $P = 0.04$). More preserved eGFR between 60 and 90 ml/min per 1.73 m^2 was not significantly associated with cardiovascular risk (HR, 1.36; 95% CI, 0.60–3.10; $P = 0.46$).

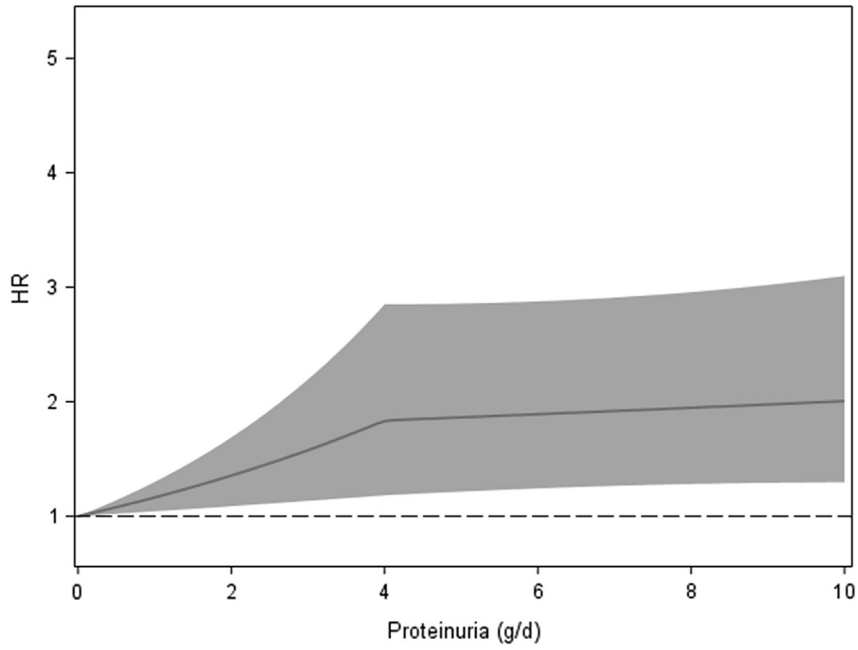


Figure 2 | The relationship between proteinuria over time and the risk of the primary cardiovascular outcome. Each 1-g/d increase in proteinuria up to a maximum of 4 g/d was associated with a 16% relative increase in the risk of cardiovascular events (hazard ratio [HR], 1.16; 95% confidence interval [CI], 1.04–1.30; $P = 0.007$); however, this risk reached a plateau such that any additional increase in proteinuria above 4 g/d was not associated with a further increase in cardiovascular risk (HR, 1.02; 95% CI, 0.97–1.06; $P = 0.52$).

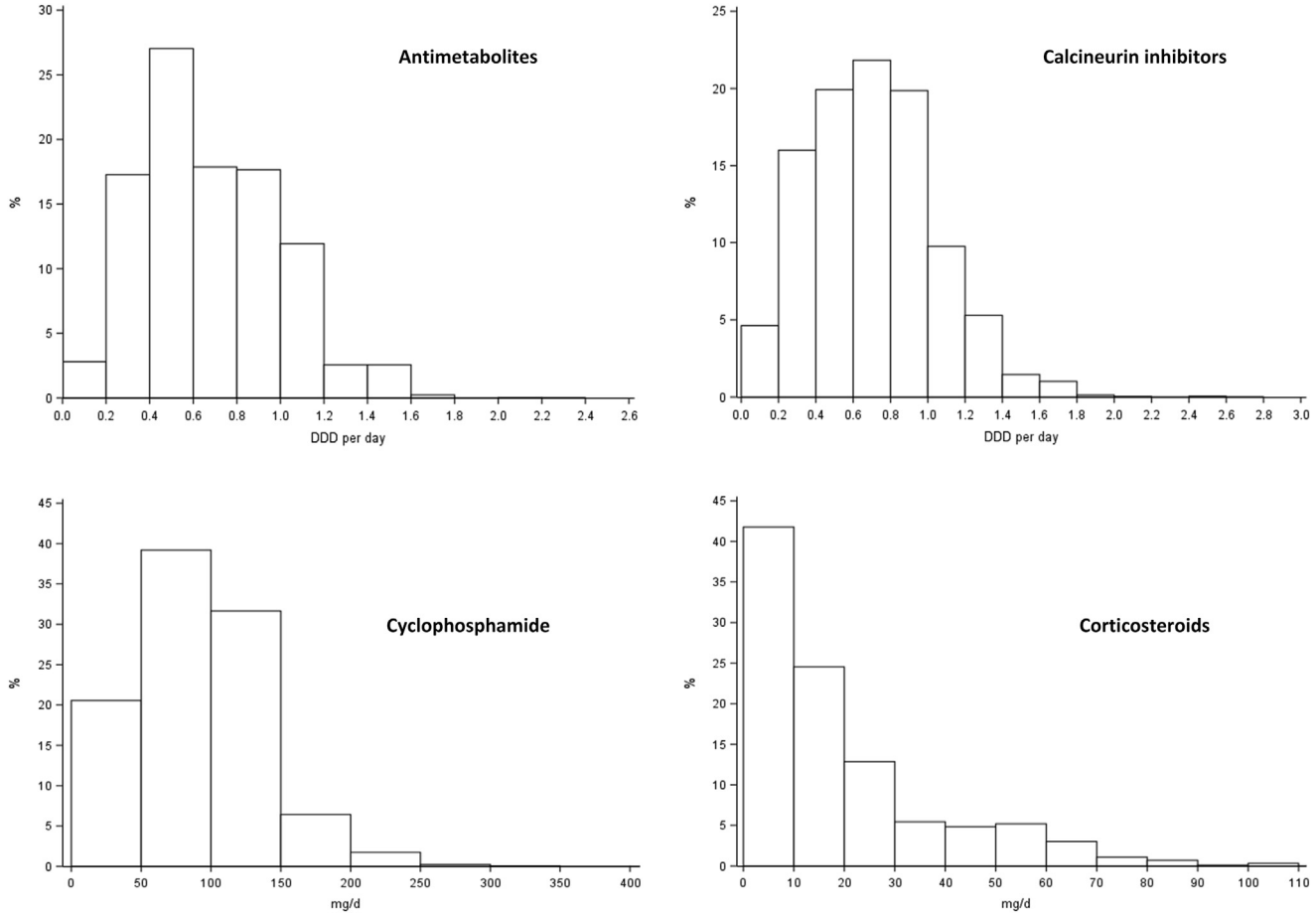


Figure 3 | The distribution of the daily dose for each type of immunosuppression medication used in the analytic cohort. The distributions were analyzed among patients exposed to each type of immunosuppression medication. Corticosteroids were converted to equivalent prednisone doses. One defined daily dose (DDD) is as follows: cyclosporine, 250 mg; tacrolimus, 5 mg; mycophenolate mofetil, 2000 mg; mycophenolate sodium, 1440 mg; and azathioprine, 150 mg. The *y* axis represents the proportion of person-time (days) with nonzero drug exposure.

Cardiovascular risk associated with immunosuppression exposure

During follow-up, 62.3% of the cohort was exposed to immunosuppression, including 59.8% to corticosteroids, 20% to calcineurin inhibitors, 12.9% to cyclophosphamide, and 17.5% to antimetabolites (Table 1). The distributions of the daily dose used in the cohort for each type of immunosuppression medication are shown in Figure 3. The median (IQR) daily dose of each class of drug was as follows: prednisone, 11.5 (5–25) mg/d; calcineurin inhibitors, 0.67 (0.4–0.8) DDD; antimetabolites, 0.65 (0.44–0.88) DDD; and cyclophosphamide, 86.5 (50–102) mg/d.

Different metrics for immunosuppression drug exposure over time were considered, including daily exposure (yes/no), daily dose, and cumulative dose or peak daily dose in various window periods. For each type of immunosuppression medication, the metric of drug exposure with the lowest Akaike information criterion in univariable models was selected for use in subsequent analyses (Supplementary Table S2). For prednisone, calcineurin inhibitors, and cyclophosphamide, this was the cumulative dose in a prior 6-, 4-, and 2-year window period, respectively; and for antimetabolites, this was the peak daily dose in a prior 6-year window period.

The risk of the primary cardiovascular outcome associated with prednisone, calcineurin inhibitor, antimetabolite, and cyclophosphamide exposures over time is shown in Table 3. This was evaluated in sequential multivariable models that first adjusted for baseline cardiovascular risk factors and type of glomerulonephritis, and then additionally adjusted for eGFR and proteinuria over time. Cumulative prednisone exposure was not significantly associated with the risk of cardiovascular disease in either of the multivariable models. Cumulative calcineurin inhibitor exposure at modest (150–300 DDD) and higher (≥300 DDD) doses were both associated with a >2-fold higher risk of cardiovascular disease after adjustment for baseline cardiovascular risk factors and type of glomerulonephritis, an effect that was unchanged after additional adjustment for eGFR and proteinuria over time (HR, 2.98; 95% CI, 1.27–6.95; $P = 0.01$; and HR, 2.78; 95% CI, 1.32–5.84; $P = 0.007$). Peak doses of antimetabolites ≥0.5 DDD/

Table 3 | Univariable and multivariable models for the risk of the primary CV outcome associated with immunosuppression exposure over time

	Univariable models		Multivariable model: CV risk factors + GN type		Multivariable model: CV risk factors + GN type + eGFR/proteinuria	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Prednisone exposure over time: cumulative dose in prior 6-yr window period						
None	Ref	Ref	Ref	Ref	Ref	Ref
≤2 g	1.97 (1.40–2.79)	<0.001	1.33 (0.94–1.89)	0.11	1.34 (0.95–1.91)	0.10
2–6 g	1.38 (0.85–2.25)	0.20	1.16 (0.70–1.91)	0.56	1.21 (0.74–1.99)	0.45
≥6 g	1.00 (0.61–1.64)	0.99	0.95 (0.57–1.60)	0.85	1.22 (0.73–2.04)	0.45
Calcineurin inhibitor exposure over time: cumulative dose in prior 4-yr window period						
None	Ref	Ref	Ref	Ref	Ref	Ref
≤150 DDD	0.43 (0.11–1.73)	0.23	0.45 (0.11–1.83)	0.25	0.42 (0.10–1.73)	0.23
150–300 DDD	2.00 (0.88–4.54)	0.10	2.52 (1.10–5.81)	0.03	2.98 (1.27–6.95)	0.01
≥300 DDD	1.45 (0.71–2.95)	0.31	2.34 (1.12–4.88)	0.02	2.78 (1.32–5.84)	0.007
Antimetabolite exposure over time: peak daily dose in prior 6-yr window period						
None	Ref	Ref	Ref	Ref	Ref	Ref
<0.5 DDD	0.69 (0.17–2.80)	0.61	0.79 (0.20–3.21)	0.74	0.54 (0.13–2.20)	0.39
≥0.5 DDD	1.97 (1.01–3.63)	0.03	1.98 (1.06–3.70)	0.03	1.70 (0.91–3.20)	0.10
Cyclophosphamide exposure over time: cumulative dose in prior 2-yr window period						
Per 10 g	1.42 (1.20–1.67)	<0.001	1.39 (1.16–1.67)	<0.001	1.46 (1.22–1.75)	<0.001

CI, confidence interval; CV, cardiovascular; DDD, defined daily dose (equivalent to tacrolimus, 5 mg; cyclosporine, 250 mg; mycophenolate mofetil, 2000 mg; mycophenolate sodium, 1440 mg; and azathioprine, 150 mg); eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; HR, hazard ratio; Ref, reference group.
Results are presented for univariable and multivariable extended Cox proportional hazards regression models that include the metric of drug exposure as a time-varying variable. The multivariable models adjust for cardiovascular risk factors at baseline (age, sex, hypertension, diabetes, dyslipidemia, smoking, and prior cardiovascular disease), type of glomerular disease (focal segmental glomerular sclerosis, membranous nephropathy, minimal change disease, and IgA nephropathy) with or without both proteinuria and eGFR over time.

day were associated with an increased risk of cardiovascular disease after adjustment for baseline cardiovascular risk factors and type of glomerulonephritis, but after further adjustment for eGFR and proteinuria over time, this effect was attenuated (HR, 1.70; 95% CI, 0.91–3.20; $P = 0.10$). Cumulative exposure to cyclophosphamide over 2 years was associated with increased cardiovascular risk in both multivariable models. In the fully adjusted model, each 10 g of cumulative cyclophosphamide exposure was associated with a 1.5-fold higher risk of cardiovascular disease (HR, 1.46; 95% CI, 1.22–1.75; $P < 0.001$). Importantly, in all the fully adjusted multivariable models that are presented in Table 3, proteinuria and eGFR over time were significantly associated with cardiovascular risk and, as shown in Table 4, the point estimates were similar irrespective of the type of immunosuppression medication included in the model.

Sensitivity and ancillary analyses

First, the lag times that were used in the primary analysis were varied longer or shorter by 6 months, with no substantial change to the point estimates for each immunosuppression drug exposure (Supplementary Table S3). Second, the multivariable models were repeated using the alternative metrics of peak or cumulative dose immunosuppression exposure within a prior window period (presented in Supplementary Table S2). The pattern of results was consistent with the primary analysis (Supplementary Table S4). Third, multivariable models were created that included 2 immunosuppression medication exposures over time modeled as separate variables and based on medication patterns commonly observed in clinical practice. There was no substantial change to the point estimates for each drug exposure compared with the primary analysis where each drug was considered separately (Supplementary Table S5). Fourth, the primary analysis was repeated after excluding patients with minimal change disease (n = 226). The results were similar to the primary analysis (Supplementary Table S6). Finally, the association between immunosuppression exposures and noncardiovascular death was examined in a cause-specific hazards model. Exposure to antimetabolites, calcineurin inhibitors, or cyclophosphamide was not consistently associated with a higher (or lower) risk of noncardiovascular death before experiencing a cardiovascular event (Supplementary Table S7). Exposure to corticosteroids was associated with a higher risk of noncardiovascular death before a cardiovascular event. For example, the adjusted HR (95% CI) for a cumulative dose of ≤2 g in a prior 6-year window period (compared with no exposure) was 1.58 (1.11–2.25).

Table 4 | The association between proteinuria and eGFR over time with the risk of the primary cardiovascular outcome in fully adjusted multivariable models that include different types of immunosuppression exposure over time

	Multivariable model: prednisone		Multivariable model: calcineurin inhibitors		Multivariable model: antimetabolites		Multivariable model: cyclophosphamide	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Proteinuria over time								
Per g/d increase up to 4 g/d	1.18 (1.05–1.31)	0.004	1.16 (1.04–1.30)	0.007	1.16 (1.04–1.30)	0.008	1.17 (1.05–1.31)	0.005
Per g/d increase above 4 g/d	1.01 (0.97–1.06)	0.69	1.02 (0.97–1.07)	0.43	1.02 (0.97–1.06)	0.49	1.02 (0.97–1.06)	0.52
eGFR over time:								
>90 ml/min per 1.73 m^2	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
60–90 ml/min per 1.73 m^2	1.35 (0.59–3.07)	0.48	1.37 (0.60–3.11)	0.46	1.35 (0.59–3.07)	0.48	1.44 (0.63–3.30)	0.39
30–60 ml/min per 1.73 m^2	2.29 (1.04–5.06)	0.04	2.18 (0.99–4.82)	0.05	2.26 (1.02–4.99)	0.04	2.53 (1.14–5.62)	0.02
<30 ml/min per 1.73 m^2	2.77 (1.22–6.28)	0.01	2.77 (1.22–6.26)	0.01	2.76 (1.22–6.25)	0.01	3.11 (1.36–7.11)	0.007
ESKD	6.26 (2.78–14.10)	<0.001	6.47 (2.87–14.56)	<0.001	6.30 (2.80–14.19)	<0.001	7.18 (3.15–16.33)	<0.001

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; Ref, reference group.
Results are for the same multivariable extended Cox proportional hazards regression models as presented in Table 3 that include the metric of drug exposure as a time-varying variable, cardiovascular risk factors at baseline (age, sex, hypertension, diabetes, dyslipidemia, smoking, and prior cardiovascular disease), type of glomerular disease (focal segmental glomerular sclerosis, membranous nephropathy, minimal change disease, and IgA nephropathy), and both proteinuria and eGFR over time. Prednisone was modeled as the cumulative dose in a prior 6-year window period (0, ≤2, 2–6, or ≥6 grams), calcineurin inhibitors were modeled as the cumulative dose in a prior 4-year window period (0, ≤150, 150–300, or ≥300 defined daily dose), antimetabolites were modeled as the peak daily dose in a prior 6-year window period (0, <0.5, or ≥0.5 defined daily dose/day), and cyclophosphamide was modeled as the cumulative dose in a prior 2-year window period (per 10 grams).

DISCUSSION

This is the first study to investigate the longitudinal relationship between individual immunosuppression therapies and the risk of cardiovascular events in individuals with glomerular disease, while also accounting for longitudinal measures of disease activity. Both lower eGFR and higher proteinuria over time were independently associated with higher risk of cardiovascular events, and these risk associations were consistent irrespective of the type of immunosuppression used during follow-up. After adjusting for baseline traditional cardiovascular risk factors and any potential impact of immunosuppression treatment on eGFR and proteinuria over time, higher cumulative exposure to calcineurin inhibitors within the prior 4 years and cumulative cyclophosphamide exposure within the prior 2 years were both associated with a significantly higher risk of cardiovascular events. Conversely, neither corticosteroid nor antimetabolite exposure was found to be consistently associated with higher cardiovascular risk.

Our findings have implications for the management of immunosuppression in patients with glomerular disease because they suggest that an individual's cardiovascular risk should be incorporated into shared decision-making about treatment. By controlling for eGFR and proteinuria over time, our results indicate that if the available immunosuppression options for a patient are equally effective at treating their glomerular disease, one treatment may be preferable over another by being associated with lower cardiovascular risk. For example, chronic cumulative exposure to calcineurin inhibitors over a 4-year period was associated with a >2-fold higher risk of cardiovascular disease. An increase in cardiovascular risk was observed with even modest exposures above 150 DDD, which can be reached using tacrolimus doses above 0.5 mg/d or cyclosporine doses above 25 mg/d over a 4-year period. This underscores the potential negative impact on cardiovascular health that can result from chronic low-dose calcineurin inhibitor use, which is commonly used in the management of patients with glomerular disease. Each 10 g of cumulative cyclophosphamide exposure over a 2-year period was associated with a 50% increase in cardiovascular risk. This dosing pattern is consistent with the clinical use of cyclophosphamide, which is often prescribed for shorter periods of more intense treatment. For example, a single 6-month course of cyclophosphamide according to the Ponticelli regimen for a 70-kg patient with membranous nephropathy results in a cumulative exposure of 15.8 g and, therefore, may be associated with a significant increase in cardiovascular risk.[5,36] The lag times used in the survival models account for the time delay between drug exposure and the onset of cardiovascular risk. In the case of calcineurin inhibitors, the risk of cardiovascular events slowly increased after drug initiation based on increasing cumulative drug exposure during a 4-year window period. In the case of cyclophosphamide, there was an 18-month delay between the cumulative exposure during any 2-year window period and the onset of higher cardiovascular risk.

This study demonstrates the importance of proteinuria and kidney function over time as potentially modifiable risk factors for cardiovascular disease. Risk estimates for proteinuria and eGFR were remarkably consistent across all models, including after adjustment for each type of

immunosuppression medication. This suggests that better control of glomerular disease using any therapy that results in better kidney function and proteinuria could contribute to lower cardiovascular risk. There may, therefore, be a trade-off between effective control of the underlying glomerular disease, which contributes to a lower risk of cardiovascular events, and the increased cardiovascular risk associated with specific therapeutic agents used to achieve disease control. This likely explains the negative confounding observed with calcineurin inhibitors and cyclophosphamide. In both cases, the HR point estimates associated with treatment ***increased*** after adjusting for the beneficial effects of improved control of the underlying glomerular disease, as measured by eGFR and proteinuria over time (Table 3). Our results also demonstrate that cardiovascular risk increases with worsening proteinuria in the subnephrotic range up to 4 g/d, at which point it reaches a plateau and does not increase further with proteinuria values above 4 g/d (Figure 2). This is in contradiction to the 2021 Kidney Disease: Improving Global Outcomes guidelines that predominantly emphasize managing cardiovascular risk in patients with overt nephrotic syndrome and is consistent with data in the general population and in cohorts with chronic kidney disease in which cardiovascular risk is associated with lower levels of proteinuria.[1,2,5,37] Similar to other studies, our results demonstrate the >2-fold higher risk of cardiovascular disease associated with an even modest reduction in kidney function with eGFR <60 ml/min per 1.73 m^2 (Table 2).[1,2,38] This emphasizes the importance of treating glomerular disease early before irreversible kidney function decline not only to reduce progression to end-stage kidney disease but also to lower the risk of complications, such as cardiovascular disease.

There are several nuances to our cohort and study design that need to be considered when interpreting the results. Our research question focused on evaluating the direct effect of immunosuppression treatment on cardiovascular risk, so that the results could be used to compare 2 treatment options that might be expected to have similar impact on disease control but possible differing cardiovascular risk. In clinical practice, the observed risk of a cardiovascular event may be lower if an effective immunosuppression therapy improves proteinuria and/or eGFR, and if this in turn lowers an individual's cardiovascular risk. This, along with other factors to consider in the interpretation of our findings, is discussed in detail in the Supplementary Methods. Antimetabolites were not associated with cardiovascular events, but there was a wide CI with less certainty around the magnitude of risk (HR, 1.70; 95% CI, 0.91–3.20 for peak daily dose ≥0.5 DDD). Because only 17.5% of patients were treated with antimetabolites, a larger cohort is needed for better precision around this potential degree of modestly increased risk. For both calcineurin inhibitors and antimetabolites, the low-dose categories had point estimates <1 with wide CIs (0.42; 95% CI, 0.10–1.73; and 0.54; 95% CI, 1.13–2.20, respectively). This may also indicate the need for a larger cohort to generate more precise risk estimates, in addition to the potential heterogeneity introduced by using a reference group that was unexposed to antimetabolites but have been treated with other therapies, which was compared with a group specifically selected because they were maintained on low doses of treatment for prolonged periods of time. Although corticosteroid exposure was associated with increased cardiovascular risk in a univariable model, this was substantially attenuated and no longer significant after adjusting for baseline cardiovascular risk factors and type of glomerulonephritis. This is surprising given that corticosteroids can result in hypertension, dyslipidemia, and diabetes, which are known cardiovascular risk factors.[14] It is possible that the lack of association between corticosteroids and cardiovascular events could in part be due to competing events given that exposure to corticosteroids was associated with a higher risk of death before experiencing a cardiovascular event. However, the existing evidence linking corticosteroids with hard cardiovascular outcomes is limited. Clinical trials have not shown any reduction in cardiovascular events associated with early corticosteroid withdrawal in kidney transplantation or with lower doses of corticosteroids in anti-neutrophil cytoplasmic autoantibody vasculitis.[14,39] Observational studies have shown no association between corticosteroids and cardiovascular events in membranous nephropathy, and conflicting association with subclinical atherosclerotic disease in systemic lupus erythematosus.[8,40] Our results underscore the need to appropriately adjust for preexisting traditional risk factors when evaluating the association between corticosteroids and cardiovascular disease.

Strengths of this study include a large sample of patients with biopsy-confirmed glomerular disease in a population-level cohort, availability of longitudinal measures of kidney function and proteinuria, granular data for prescribed immunosuppression treatments, and a relatively long follow-up duration for ascertainment of cardiovascular events. Our findings should be interpreted in the context of the study's limitations. Although we used multiple data sources to exclude secondary glomerular diseases (e.g., due to infection or a systemic disease), it is still possible that some cases were misclassified. This is particularly challenging in differentiating immune-mediated FSGS from secondary disease, although we excluded cases of FSGS if there was an identifiable secondary cause on biopsy, such as diabetes or another glomerular disease. Several cardiovascular risk factors were not available, including family history and body mass index, which may have contributed to unmeasured confounding. Although having a high specificity, definitions of other traditional risk factors from administrative data sources have lower sensitivity, which may also contribute to residual confounding. It is possible that factors, such as hypertension, diabetes, and dyslipidemia, are on the causal pathway between exposure to specific immunosuppression therapies and future cardiovascular events. To conduct a valid mediation analysis, one would need to consider both time-varying mediators and variables that potentially confound the relationship between the mediator and the outcome (e.g., time-varying medication exposure, such as statin therapy). Our data set does not

contain sufficient data elements suitable for this purpose. For immunosuppression exposures, the choice of optimal dosing thresholds, lag times, and window periods were data driven and thus susceptible to overfitting. In sensitivity analyses using different metrics of drug exposure and lag times, the findings were consistent with the primary results. Nonetheless, these definitions require validation and should thus be considered as identifying approximate patterns of drug exposure and likely time frames over which the risk of cardiovascular disease ought to be considered in clinical practice. Finally, our study is not able to determine mechanisms of drug-induced cardiovascular disease. Further research is needed to investigate mechanisms of cardiovascular diseases caused by immunosuppression therapies and methods to mitigate this risk in patients who otherwise require treatment.

Using a population-level cohort of patients with biopsy-proven glomerular diseases, we demonstrate a significantly higher risk of cardiovascular events associated with a cumulative exposure over several years to calcineurin inhibitors and cyclophosphamide, which was independent of treatment effects on disease activity. Irrespective of the type of immunosuppression therapy, both a reduced eGFR and increasing levels of proteinuria were consistently associated with higher cardiovascular risk, underscoring the importance of achieving optimal control of the underlying glomerular disease to preserve both kidney and cardiovascular health in the long-term. Although these findings require independent validation, they provide a rationale for considering cardiovascular risk in the shared decision-making process about treatment options for glomerular disease, as well as the potential incorporation of cardiovascular events as a safety end point in future clinical trials.

DISCLOSURE

All the authors declared no competing interests. All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the Data Stewards.

DATA STATEMENT

The data sources for this study are all housed within the Secure Research Environment (SRE) provided by Population Data BC under approval from the University of British Columbia (UBC) research ethics board. Data are not accessible outside the SRE or to external researchers. Anyone wishing to collaborate on the data should contact the study investigators, noting that the data can be accessed directly only by members of the project team who have been approved by both Population Data BC and the UBC research ethics board. Further details can be found here: https://www.popdata.bc.ca/secure_data/sre.

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AUTHOR CONTRIBUTIONS

SJB and MC designed the study and developed the analytic plan; YZ, DI, and LE performed all analyses; all authors reviewed the results. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Supplementary material is available online at www.kidney-international.org.

REFERENCES

1. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073–2081.
2. van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality: a collaborative meta-analysis of high-risk population cohorts. *Kidney Int*. 2011;79:1341–1352.
3. Wheeler DC, Bernard DB. Lipid abnormalities in the nephrotic syndrome: causes, consequences, and treatment. *Am J Kidney Dis*. 1994;23:331–346.
4. Radhakrishnan J, Appel AS, Valeri A, Appel GB. The nephrotic syndrome, lipids, and risk factors for cardiovascular disease. *Am J Kidney Dis*. 1993;22:135–142.
5. Kidney Disease. Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4S):S1–S276.
6. Myllymaki J, Syrjanen J, Helin H, et al. Vascular diseases and their risk factors in IgA nephropathy. *Nephrol Dial Transplant*. 2006;21:1876–1882.
7. Mahmoodi BK, ten Kate MK, Waanders F, et al. 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.
8. Lee T, Derebail VK, Kshirsagar AV, et al. Patients with primary membranous nephropathy are at high risk of cardiovascular events. *Kidney Int*. 2016;89:1111–1118.
9. Ordonez JD, Hiatt RA, Killebrew EJ, Fireman BH. The increased risk of coronary heart disease associated with nephrotic syndrome. *Kidney Int*. 1993;44:638–642.
10. Heaf J, Løkkegaard H, Larsen S. The epidemiology and prognosis of glomerulonephritis in Denmark 1985-1997. *Nephrol Dial Transplant*. 1999;14:1889–1897.
11. Hutton HH, Levin A, Gill JS, et al. Cardiovascular risk is similar in patients with glomerulonephritis compared to other types of chronic kidney disease: a matched cohort study. *BMC Nephrol*. 2017;18:95.
12. O'Shaughnessy MM, Liu S, Montez-Rath ME, et al. Cause of kidney disease and cardiovascular events in a national cohort of US patients with end-stage renal disease on dialysis: a retrospective analysis. *Eur Heart J*. 2019;40:887–898.
13. Canney M, Gunning HM, Zheng Y, et al. The risk of cardiovascular events in individuals with primary glomerular diseases. *Am J Kidney Dis*. 2022;80:740–750.
14. Chakkera HA, Sharif A, Kaplan B. Negative cardiovascular consequences of small molecule immunosuppressants. *Clin Pharmacol Ther*. 2017;102:269–276.
15. Iqubal A, Iqubal MK, Sharma S, et al. Molecular mechanism involved in cyclophosphamide-induced cardiotoxicity: old drug with a new vision. *Life Sci*. 2019;218:112–131.
16. Karp I, Abrahamowicz M, Fortin PR, et al. Recent corticosteroid use and recent disease activity: independent determinants of coronary heart disease risk factors in systemic lupus erythematosus? *Arthritis Rheum*. 2008;59:169–175.
17. Zeier M, Van Der Giet M. Calcineurin inhibitor sparing regimens using m-target of rapamycin inhibitors: an opportunity to improve cardiovascular risk following kidney transplantation? *Transpl Int*. 2011;24:30–42.

18. Wall N, Harper L. Complications of long-term therapy for ANCA-associated systemic vasculitis. *Nat Rev Nephrol*. 2012;8:523–532.
19. Canadian Institute for Health Information. Discharge Abstract Database (Hospital Separations). V2. Population Data BC. Data Extract. MOH; 2016. Accessed September 16, 2021. http://www.popdata.bc.ca/data
20. British Columbia Ministry of Health. Medical Services Plan (MSP) Payment Information File. Population Data BC. Data available. MOH; 2016. Accessed September 16, 2021. http://www.popdata.bc.ca/data
21. BC Ministry of Health. PharmaNet. V2. BC Ministry of Health. Data Extract. Data Stewardship Committee; 2011. Accessed September 16, 2021. http://www.popdata.bc.ca/data
22. BC Vital Statistics Agency. Vital Statistics Births. Population Data BC. Data Extract. BC Vital Statistics Agency. 2016. http://www.popdata.bc.ca/data
23. Canney M, Induruwage D, Sahota A, et al. Socioeconomic position and incidence of glomerular diseases. *Clin J Am Soc Nephrol*. 2020;15:367–374.
24. Hogan MC, Reich HN, Nelson PJ, et al. The relatively poor correlation between random and 24-hour urine protein excretion in patients with biopsy-proven glomerular diseases. *Kidney Int*. 2016;90:1080–1089.
25. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
26. Komenda P, Beaulieu M, Seccombe D, Levin A. Regional implementation of creatinine measurement standardization. *J Am Soc Nephrol*. 2008;19:164–169.
27. Canadian Institute for Health Information. *Treatment of End-Stage Organ Failure in Canada, Canadian Organ Replacement Register, 2009 to 2018: End-Stage Kidney Disease and Kidney Transplants — Data Tables*. CIHI; 2019.
28. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192.
29. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322.
30. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834–1844.
31. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657.
32. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
33. WHO Collaborating Centre for Drug Statistics Methodology WHOCC—ATC/DDD Index. Accessed September 16, 2021. https://www.whocc.no/atc_ddd_index/
34. Gardarsdottir H, Egberts TC, Heerdink ER. The association between patient-reported drug taking and gaps and overlaps in antidepressant drug dispensing. *Ann Pharmacother*. 2010;44:1755–1761.
35. Nielsen LH, Løkkegaard E, Andreasen AH, Keiding N. Using prescription registries to define continuous drug use: how to fill gaps between prescriptions. *Pharmacoepidemiol Drug Saf*. 2008;17:384–388.
36. Jha V, Ganguli A, Saha TK, et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy: randomized controlled trial. *J Am Soc Nephrol*. 2007;18:1899–1904.
37. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation*. 2004;110:32–35.
38. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
39. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med*. 2020;382:622–631.
40. Westerweel PE, Luyten RK, Koomans HA, et al. Premature atherosclerotic cardiovascular disease in systemic lupus erythematosus. *Arthritis Rheum*. 2007;56:1384–1396.