Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN

CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Narrative Review

Canadian Journal of Kidney Health and Disease
Volume 11: 1–12

DOI: 10.1177/20543581241232472
journals.sagepub.com/home/cjk

Sage

Cardiovascular Risk in Patients With Glomerular Disease: A Narrative Review of the Epidemiology, Mechanisms, Management, and Patient Priorities

Robert L. Myette[1,2], Caroline Lamarche[3], Ayodele Odutayo[4], Nancy Verdin[5], and Mark Canney[2,6]

Abstract

Purpose of review: Cardiovascular (CV) disease is a major cause of morbidity and mortality for patients with glomerular disease. Despite the fact that mechanisms underpinning CV disease risk in this population are likely distinct from other forms of kidney disease, treatment and preventive strategies tend to be extrapolated from studies of patients with undifferentiated chronic kidney disease (CKD). There is an unmet need to delineate the pathophysiology of CV disease in patients with glomerular disease, establish unique risk factors, and identify novel therapeutic targets for disease prevention. The aims of this narrative review are to summarize the existing knowledge regarding the epidemiology, molecular mechanisms, and management of CV disease in patients with common glomerular disease, highlight the patient perspective, and propose specific areas for future study.

Sources of information: The literature for this narrative review was accessed using common research search engines, including PubMed, PubMed Central, Medline, and Google Scholar. Information for the patient perspective section was collected through iterative discussions with a patient partner.

Methods: We reviewed the epidemiology, molecular mechanisms of disease, management approaches, and the patient perspective in relation to CV disease in patients with glomerulopathies. Throughout, we have highlighted the current knowledge and have discussed future research approaches, both clinical and translational, while integrating the patient perspective.

Key findings: Patients with glomerular disease have significant CV disease risk driven by multifactorial, molecular mechanisms originating from their glomerular disease but complicated by existing comorbidities, kidney disease, and medication side effects. The current approach to risk stratification and treatment relies heavily on existing data from CKD patients, but this may not always be appropriate given the unique pathophysiology and mechanisms associated with CV disease risk in patients with glomerular disease. We highlight the need for ongoing glomerular disease-focused studies aimed to better delineate CV disease risk, while integrating the patient perspective.

Limitations: This is a narrative review and does not represent a comprehensive and systematic review of the literature.

Abrege

Motif de la revue: Les maladies cardiovasculaires sont une cause majeure de morbidité et de mortalité chez les patients atteints d'une maladie glomérulaire. Bien que les mécanismes qui sous-tendent le risque de maladie cardiovasculaire dans cette population sont probablement distincts des autres formes de néphropathies, le traitement et les stratégies

[1]Division of Nephrology, Children's Hospital of Eastern Ontario, Ottawa, Canada
[2]The Ottawa Hospital Research Institute, Ottawa, ON, Canada
[3]Hôpital Maisonneuve-Rosemont Research Center, Department of Medicine, Division of Nephrology, Université de Montréal, ON, Canada
[4]Division of Nephrology, University Health Network, Toronto, ON, Canada
[5]University of Calgary, AB, Canada
[6]Department of Medicine, The Ottawa Hospital Research Institute, University of Ottawa, ON, Canada

Corresponding Author:
Mark Canney, Department of Medicine, The Ottawa Hospital Research Institute, University of Ottawa, 1967 Riverside Drive, Ottawa, ON K1H 7W9, Canada.
Email: mcanney@toh.ca

préventives ont tendance à être extrapolés à partir d'études portant sur des patients atteints d'insuffisance rénale chronique indifférenciée. Il existe ainsi un besoin de délimiter la physiopathologie des maladies cardiovasculaires chez les patients atteints d'une maladie glomérulaire, d'établir les facteurs de risque propres à la maladie glomérulaire et d'identifier de nouvelles cibles thérapeutiques pour la prévenir. Les objectifs de cette revue narrative sont de résumer les connaissances existantes concernant l'épidémiologie, les mécanismes moléculaires et la prise en charge des maladies cardiovasculaires chez les patients atteints d'une maladie glomérulaire commune, de mettre en évidence le point de vue des patients et de proposer des domaines précis pour de futures études.

Sources de l'information: La documentation a été consultée par le biais des moteurs de recherche courants, notamment PubMed, PubMed Central, Medline et Google Scholar. Les points de vue des patients ont été recueillis au moyen de discussions itératives avec un patient partenaire.

Méthodologie: Nous avons examiné l'épidémiologie et les mécanismes moléculaires de la maladie, les approches de prise en charge et la perspective des patients en lien avec les maladies cardiovasculaires chez les patients atteints d'une maladie glomérulaire. Nous avons fait état des connaissances actuelles et discuté des approches à envisager pour les recherches futures, tant cliniques que translationnelles, tout en intégrant la perspective du patient.

Principales observations: Les patients atteints d'une maladie glomérulaire présentent un risque significatif de maladie cardiovasculaire associé à des mécanismes moléculaires multifactoriels provenant de la maladie glomérulaire elle-même. Ce risque est compliqué par les comorbidités existantes, la néphropathie et les effets secondaires des médicaments. L'approche actuelle de stratification du risque et de traitement repose en grande partie sur les données existantes pour les patients atteints d'insuffisance rénale chronique; cette approche pourrait ne pas toujours convenir, compte tenu de la physiopathologie unique et des mécanismes associés au risque de maladie cardiovasculaire chez les patients atteints d'une maladie glomérulaire. Nos résultats mettent en lumière le besoin d'études continues, axées sur les maladies glomérulaires, qui visent à mieux cerner le risque de maladies cardiovasculaires chez ces patients, tout en intègrant leur point de vue.

Limites: Il s'agit d'une revue narrative; cette étude ne constitue pas une revue exhaustive et systématique de la littérature.

Keywords

glomerular disease, cardiovascular disease, molecular mechanisms, patient perspective, research priorities

Received July 6, 2023. Accepted for publication January 9, 2024.

Introduction

It is well-established that patients with chronic kidney disease (CKD) have a disproportionately high burden of cardiovascular (CV) disease.[1] Large-scale population studies in individuals with CKD have convincingly shown that the risk of major adverse CV events increases with both a reduction in estimated glomerular filtration rate (eGFR) and an increase in albuminuria.[2-4] Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest that lipid-lowering therapy be used for primary prevention in patients with a 10-year risk of a CV event of more than 10%, and in all patients with CKD over the age of 50 years.[5] To date, studies of CV risk in patients with kidney disease have been dominated by older patients with undifferentiated CKD and a high burden of traditional risk factors, such as diabetes, long-standing hypertension, and atherosclerosis. In contrast, there has been a paucity of studies examining the risk of CV events in patients with specific forms of kidney disease, such as glomerulonephritis (GN). It is unclear if the CKD guidelines should similarly apply to individuals with GN, who might be younger and have a different risk factor profile compared with those with undifferentiated CKD.

The pathophysiology of CV disease in individuals with GN is complex and multifactorial, involving a range of molecular and cellular processes. It includes both traditional and non-traditional risk factors, some of which might be unique to the underlying GN. Glomerular disease activity tends to wax and wane over time, as patients experience periods of relapse and remission. When the disease is active, patients are at risk of complications, such as systemic inflammation or vascular thrombosis in the setting of nephrotic syndrome. The treatment of GN could itself contribute to the risk of CV events, for example, related to toxicity of immunosuppression, such as corticosteroids[6] or calcineurin inhibitors. Because patients with GN are often diagnosed at a young age, one must also consider the cumulative burden of both their kidney disease and the scope for complications, such as CV disease from a life-course perspective (Figure 1).

The objectives of this narrative review are to describe the epidemiology and the pathophysiology of CV disease in patients with GN, identify potential treatment strategies to reduce CV risk, and discuss priorities and challenges of such strategies from the perspective of a patient with GN. The case is hypothetical but reflects real-life experiences that have been shared by patients with kidney disease. We specifically focus on arterial CV events, although we acknowledge that hypercoagulability and venous thrombotic events are an important source of morbidity in people with GN. Throughout, we highlight knowledge gaps and opportunities for future research (Table 1; Box 1–3).

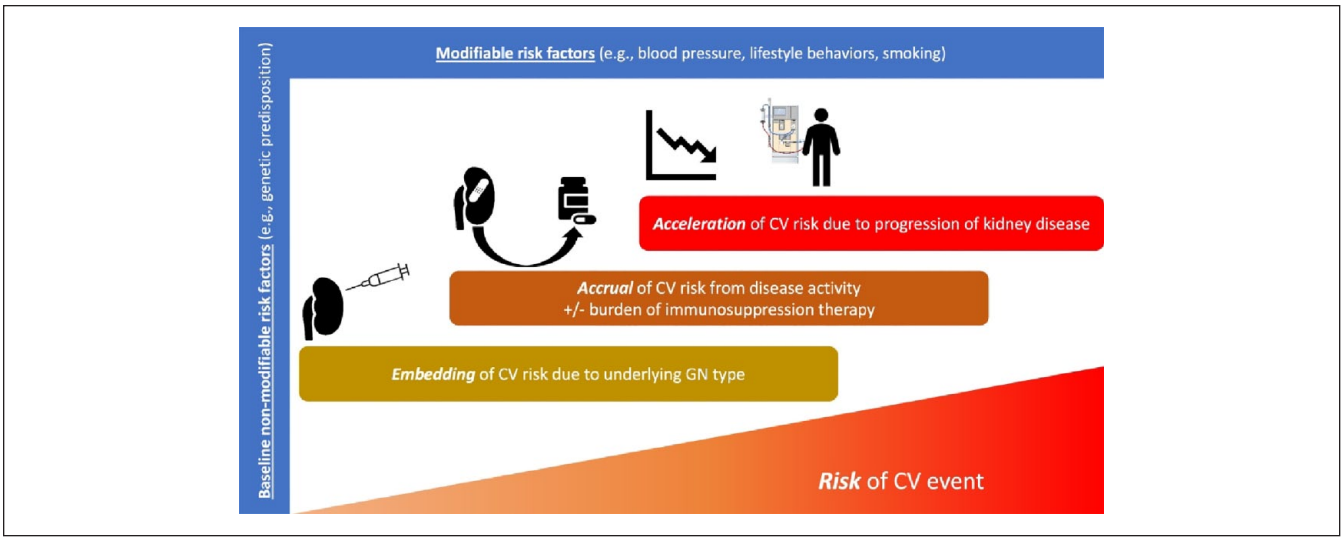

Figure 1. Conceptual framework for the development of cardiovascular risk in patients with glomerulonephritis across the life course.
Note. CV = cardiovascular; GN = glomerulonephritis.

Table 1. Knowledge Gaps and Opportunities to Reduce the Burden of Cardiovascular Disease in Patients With GN.

Issues	Basic science/translational initiatives	Clinical/epidemiological initiatives	Challenges/gaps for future research
Understanding the CV disease risk in patients with GN	• Fundamental basic science research directed at elucidating molecular mechanisms of CV disease in GN and identification of novel therapeutic targets • Development and validation of urine and serum biomarkers	• Collaborative, multicenter cohort studies to evaluate CV disease risk and inform the design of future clinical trials • Better CV risk stratification through incorporation of GN-specific factors	• Harmonization of data collection across centers • Effective engagement of patients with GN to ensure that studies are acceptable and feasible from a patient perspective
Optimizing pharmacological and non-pharmacologic interventions at the patient level	• Using serum and urine biomarkers to better understand non-pharmacological interventions	• Awareness and identification of modifiable CV risk factors (weight loss, smoking cessation, exercise) • Clinical studies to refine the roles of lipid-lowering therapies and SGLT2i in CV risk reduction	• Financial burden of taking medications for extended duration. • Adherence to lifestyle interventions and preventative therapies • Funding for dedicated clinical trials of CV medications in GN
Conscious and appropriate medication selection	• *In vitro* and *in vivo* studies aimed at investigating cardiovascular effects of immune therapies at the cellular level	• Evaluation of differential CV effects of specific immune therapies • Incorporation of CV disease endpoints alongside kidney outcomes in therapeutic clinical trials	• Paucity of large registries with longitudinal granular information about immunosuppression exposure • Low CV event rate during short follow-up in clinical trials
Effective communication with patients	• Embracing patient partnerships to inform research priorities that can be addressed with bench-to-bedside approaches • Communication of research findings to patients in an understandable way	• Early and authentic engagement of patient partners and those with lived experience in clinical studies • Empowering patients to take ownership of factors within their control • Multidisciplinary care • On-line resources	• The complexity of GN and its study can be difficult to explain • Physical/emotional/psychological burden associated with GN may restrict patients from taking control of certain aspects of their care

Note. GN = glomerulonephritis; CV = cardiovascular; SGLT2i = sodium glucose co-transporter 2 inhibitors.

Box 1. Clinical Vignette.

Debbie is a 45-year-old lady who was diagnosed with IgA nephropathy 3 years ago. Her biopsy showed evidence of longstanding injury that is reflected in her laboratory tests that demonstrate reduced kidney function (eGFR of 45 mL/min) and proteinuria. Debbie has a full-time job and is a mother to 2 school-age children. Here, she tells us about how she adapted to being diagnosed with kidney disease

Patient narrative

"I was diagnosed with high blood pressure at age 36 when I was pregnant with my second daughter. I found a way to do regular BP testing at home and keep those records for my appointments with my family doctor. We added that to our family routine. About 3 years ago, I began to experience profound fatigue that made it hard to get through busy days at work and at home. I had discoloration and foaming in my urine and generally felt unwell. I saw my family doctor who tested my blood and urine. I was referred to a kidney doctor who diagnosed me with glomerulonephritis. I wondered if I would have to quit my job. I loved my job. Losing my income meant that we would have a harder time traveling and doing other things we enjoyed as a family. More importantly, I was tired all the time. How was I supposed to do household stuff? I felt helpless. What else could I be doing to slow this disease?"

Patient perspective

In this anecdote, Debbie shares a number of worries and fears that are experienced by patients living with GN. In focus groups conducted by the Standardized Outcomes in Nephrology (SONG) Initiative Study,[7] factors deemed most important by patients and their caregivers were life participation, fatigue, the ability to work, and the impact of kidney disease on one's family.[8] In qualitative analyses, the key themes that underpinned these prioritized outcomes were "constraining day-to-day existence", "impaired agency and control", and "threats to future health". Outcomes were ranked higher if they involved a lack of control over one's future health or if they increased uncertainty from unpredictable events

Epidemiology of CV Disease in Patients With GN

What Is the Incidence of CV Events?

Because GN is a rare condition, obtaining accurate population-level estimates of CV disease in people with GN is challenging. O'Shaughnessy and colleagues[9] used the United States Renal Data System to evaluate the risk of major CV events (myocardial infarction, ischemic stroke, or CV death) among 658 168 patients with different causes of kidney failure who initiated dialysis between 1997 and 2014. As expected, the event rate was highest in patients with diabetic nephropathy (14.34 events per 100 person-years). Compared with immunoglobulin A (IgA) nephropathy, after adjusting for potential confounding variables, the risk of a CV event was higher in patients with focal segmental glomerulosclerosis (FSGS, hazard ratio [HR] = 1.65, 95% confidence interval (CI) = 1.53-1.78), membranous nephropathy (HR = 1.67, 95% CI = 1.52-1.83), lupus nephritis (HR = 1.86, 95% CI = 1.71-2.03), and vasculitis (HR = 1.55, 95% CI = 1.41-1.71). This study was the largest to demonstrate heterogeneity in CV risk among specific forms of GN but had some limitations, including potential misclassification of GN based on physician reporting as opposed to a biopsy, and lack of information about risk factors, such as dyslipidemia or hypertension. Most importantly, the index date only started after initiation of dialysis, whereas one would ideally want to identify high-risk patients much earlier in the course of their kidney disease.

Few studies have evaluated the risk of CV events from the time of kidney biopsy in patients with GN. A study from 2 centers in the United States and Canada examined the incidence of CV events from the time of biopsy in patients with membranous nephropathy, with kidney failure treated as a competing risk.[10] The cumulative incidence of CV events was 4.4% at year 1 and 8.8% at year 5. In the first 2 years after diagnosis, the risk of a CV event exceeded the risk of kidney failure among patients with preserved kidney function at baseline. A population-based study from British Columbia (BC), Canada, expanded on this study to include other forms of primary GN.[11] The investigators employed administrative data linkages to estimate the absolute risk of major CV events in 1912 adult patients with IgA nephropathy (n = 759), FSGS (n = 540), membranous nephropathy (n = 387), and minimal change disease (MCD, n = 226). During a median follow-up time of 6.8 years, 212 patients experienced a CV event, representing an incidence rate of 24.7 per 1000 person-years, some 2.5 times as high as the age- and sex-matched general adult population. The 10-year risk of CV events was 16% (95% CI = 13.8-18.3) and differed by GN type, being highest in FSGS (27%) and lowest in IgA nephropathy (7.7%). Notably, each type of GN had an incidence rate that exceeded 10 events per 1000 person-years, the threshold suggested by KDIGO to initiate lipid-lowering therapy for primary prevention of CV disease. Although this study provided population-level estimates of absolute CV risk, the lack of a control population with other forms of CKD, such as diabetic kidney disease precluded an assessment of relative risk across different causes of CKD at similar levels of eGFR and albuminuria. This, and other limitations from prior studies are summarized in Table 2.

What Are the Risk Factors for CV Disease?

There are limited data available in the literature, which describe specific risk factors for CV events in this population. A single-center study of 298 consecutive patients with nephrotic syndrome showed that traditional risk factors, such

Table 2. Summary of Studies Examining the Incidence of and Risk Factors for Cardiovascular Events in Patients With Glomerular Disease.

Author	Study population	Key findings	Limitations
Mahmoodi et al[12]	• Consecutive adult patients with nephrotic syndrome (n = 298) who attended an outpatient nephrology clinic at a single center in the Netherlands • Followed for a mean of 10 years	• Annual incidence of CV events was 1.48% (95% CI = 1.07-1.99) • Male sex, older age, diabetes, hypertension, smoking, prior CV event, and lower eGFR were associated with higher risk of CV events	• Small sample size from a single center • Most events were experienced by patients with non-GN causes of nephrotic syndrome (diabetic nephropathy or unspecified cause)
Lee et al[10]	• Adult patients with biopsy-proven membranous nephropathy from 2 centers in the US (n = 483) and Canada (n = 557)	• Cumulative incidence of CV events at 3 years was 8.2% in the US cohort and 2.5% in the Canadian cohort • Using both cohorts, age (per 10 years) at biopsy (HR = 1.6, 95% CI = 1.3-1.9), prior history of CV disease (HR = 4.5, 95% CI = 2.2-9.0), and severity of nephrotic syndrome (HR = 2.4, 95% CI = 1.4-4.0) were independently associated with the CV outcome	• Restricted to patients with membranous nephropathy • Risk estimates and risk factors differed substantially in the 2 cohorts suggesting heterogeneity in outcome definitions or capture of events
O'Shaughnessy et al[9]	• Adult patients in the United States who started dialysis between 1997 and 2014 and whose kidney failure was attributed to IgAN (n = 9828), FSGS (n = 27029), MN (n = 5660), MPGN (n = 3718), lupus nephritis (n = 12398), vasculitis (n = 5023), diabetic nephropathy (n = 567778), or ADPKD (n = 26734) • Followed for 5 years after dialysis initiation	• Patients with diabetic nephropathy had the highest rate of CV events • Compared with IgAN, FSGS (HR = 1.65, 95% CI = 1.53-1.78), MN (HR = 1.67, 95% CI = 1.52-1.83), and MPGN (HR = 1.55, 95% CI = 1.40-1.73) were each independently associated with higher CV risk • Similar risk estimates were observed for lupus nephritis (HR = 1.86, 95% CI = 1.71-2.03) and vasculitis (HR = 1.55, 95% CI = 1.41-1.71)	• Time at risk started on day 91 after dialysis initiation • Potential misclassification of GN type based on physician reporting as opposed to biopsy • The majority (86%) of the study population had diabetic nephropathy
Canney et al[11]	• Population-level cohort of 1912 adult patients with biopsy-proven IgAN, FSGS, MCD, and MN in British Columbia, Canada • Followed for a median of 6.8 years from time of kidney biopsy	• Ten-year CV risk of 14.7% (95% CI = 12.8-16.8). • Incidence 2.5 times higher than the age-matched and sex-matched general population • GN type, proteinuria, and eGFR were associated with higher CV risk	• No CKD control group • Outcomes were ascertained from administrative data

Note. CV = cardiovascular; CI = confidence interval; eGFR = estimated glomerular filtration rate; GN = glomerulonephritis; HR = hazard ratio; IgAN = IgA nephropathy; FSGS = focal segmental glomerulosclerosis; MN = membranous nephropathy; MPGN = membranoproliferative glomerulonephritis; ADPKD = autosomal dominant polycystic kidney disease; MCD = minimal change disease; CKD = chronic kidney disease.

as male sex, older age, diabetes, smoking, and hypertension were associated with arterial thromboembolic events.[12] Proteinuria and serum albumin levels were predictors of venous but not arterial thromboembolic events. This analysis was likely underpowered due to small sample size and low event rate. In the 2 aforementioned studies from Canada, older age, the presence of diabetes, and a prior history of CV disease were all independently associated with higher risk of a CV event during follow-up.[10,11] In the BC cohort, a multivariable model that incorporated traditional risk factors had a C-statistic of 0.82 (95% CI = 0.79-0.85). Adding type of GN, magnitude of proteinuria and level of kidney function at the time of biopsy to the model led to improvements in model fit, discrimination (C-statistic 0.84, 95% CI = 0.81-0.87) and reclassification, suggesting that the inclusion of GN-specific variables can improve CV risk stratification.[11] Consistent with this finding, the severity of nephrotic syndrome over time was identified as an independent risk factor for CV events among patients with membranous nephropathy (HR = 2.2, 95% CI = 1.1-4.3).[10] Although identification of CV risk factors can refine an individual patient's risk profile, they do not necessarily tell us what is driving the risk in patients with GN. In the next section, we explore potential mechanisms of CV disease in this population.

Box 2. Clinical Vignette.

At her next clinic visit, Debbie's nephrologist raises an additional concern of future cardiovascular disease and recommends that she start taking a statin along with more medications to optimize her blood pressure control. This is how Debbie felt about the encounter

Patient narrative

"My nephrologist is worried about my high blood pressure and how my kidney disease puts me at higher risk of heart problems in the future. They want to put me on a drug to lower my cholesterol. I don't even have high cholesterol. I don't smoke and I try to do all the right things. I know from commercials and information from my family doctor that high blood pressure could cause heart attacks and strokes, but I had no idea that kidney disease could as well. I had a lot to learn. It was frustrating to be given so little information and to have to rely on medication and wait for results. I strongly believe that eating well plays a large role in maintaining good health, as does activity and exercise. What could I do to slow down the kidney problems and reduce my risk? It was really hard to figure out how to tell my children that I have yet another health issue. How could I be a part of their activities? And mine? It was devastating. When my husband and I sat down to talk about this, the subject of how this would affect us financially came up—time off work to go to appointments, hospital parking, and then taking medication for the rest of my life. It was all so discouraging. How do other people with GN manage?"

Patient perspective

These impressions from Debbie highlight the importance of effective communication around the discussion of cardiovascular risk with patients. In the SONG Initiative Study, patients with GN felt scared about "silent surprises" that could complicate their kidney disease, which compounded their anxiety. In the context of a silent or seemingly invisible risk, such as future cardiovascular disease, it is understandable that Debbie would feel unsure about the prospect of taking medication indefinitely. In the same study, patients prioritized outcomes that "nourished" them, such as sleep and physical strength. Similarly, Debbie is looking for ways to take back control over her health, beyond taking medications, and this should be encouraged and incorporated into her management plan. Finally, we must be cognizant of the hidden financial costs of living with a chronic disease

Mechanisms of CV Disease in GN

Mechanisms of CV disease in GN can be broadly classified as traditional and non-traditional. Traditional risk factors for CV diseases are highly prevalent in patients with GN. They include hypertension, diabetes mellitus, obesity, and dyslipidemia. However, non-traditional risk factors, such as inflammation,[13-16] endothelial dysfunction,[17-25] oxidative stress,[13,26-28] and vascular calcification[29] also contribute to the increased CV disease risk (Table 3). Most of these risk factors are also implicated in CKD pathophysiology; however, some are disease or treatment specific. As an example, immunosuppressive drugs, such as prednisone, calcineurin inhibitors and antimetabolites, can contribute to the development of CV disease through the promotion of cardiac hypertrophy and fibrosis, mitochondrial dysfunction, arrhythmia, hypertension, vascular remodeling, and dyslipidemia development.[30] Importantly, relevant studies on how the pathophysiology of CV disease in GN patients compares with CKD have not been done.

The extent to which the factors discussed in Table 3, alone or in combination, contribute to development of CV disease in patients with GN requires further interrogation. Compared with patients with undifferentiated CKD who often present quite late in the disease course, individuals with GN usually have a defined time of disease onset at the time of kidney biopsy. This can help to disentangle the contribution of GN to subsequent CV risk over and above the development of reduced kidney function from chronic injury. For example, a window of opportunity for advanced study in GN patients is through careful analysis of histopathological findings from their kidney biopsy. It is not uncommon for patients with GN to undergo several biopsies throughout their life. This would allow for correlation of biopsy findings at presentation, as well as subsequent changes on biopsy (vascular, tubulointerstitial, or glomerular), with subsequent CV risk. A comprehensive approach that encompasses histopathology data, biomarkers, and vascular studies could provide fundamental insights into disease pathogenesis.

Clinical Targets to Treat and Prevent CV Diseases in GN Patients

Whereas the inflammatory component of GN is likely addressed through immunosuppressive treatments that achieve disease remission, the management of traditional CV risk factors requires a separate CV risk assessment to inform the use of adjunctive cardioprotective medications.

Lifestyle Modification

Lifestyle modification should be considered for all people with GN and with risk factors for CV disease. This includes adherence to a heart healthy diet, increasing physical activity, weight loss, and smoking cessation. There are no dedicated clinical trials of lifestyle modification in people with GN but it is reasonable to anticipate that the relative benefits of lifestyle modification for reducing CV risk in the general population are generalizable to people with GN. Importantly, given that children and young adults with GN are generally at low CV risk in the absence of a family history of premature heart disease, lifestyle modifications should be considered the first-line treatment.

Table 3. Non-Traditional Mechanisms of CV Disease in GN.

	Risk factor	Mechanism
Inflammation[13-16]	• Risk factor for, and a consequence of, reduced kidney function and is highly associated with CV disease	• Induces a type of premature aging that is associated with vascular disease (vascular senescence), atherosclerosis, insulin resistance, microvascular, and immune dysfunction • Many factors are involved in promoting this inflammatory state, such as an increase in pro-inflammatory cytokine production, uremic toxin accumulation, oxidative stress, acidosis, infections, adipose tissue metabolism, and gut microbiota dysbiosis • Autoimmune causes of GN directly contribute to the inflammation burden
Endothelial dysfunction[17-25]	• The endothelium plays a critical role in regulating vascular tone and blood flow, and dysfunction of this layer can lead to hypertension, atherosclerosis, and other complications	• The release of pro-inflammatory cytokines, oxidative stress, and other factors that impair production and release of NO, a key mediator of endothelial function. • A reduction in NO bioavailability can lead to vasoconstriction, increases in platelet activation and adhesion, and impaired angiogenesis and tissue repair • Endothelial dysfunction is a hallmark of CV disease and is seen in CKD. However, endothelial dysfunction has also been shown in patients with GN in the absence of CKD • Mackinnon and colleagues showed endothelial dysfunction, specifically in patients with GN and proteinuria, independent of kidney function • Endothelial dysfunction was also demonstrated in ANCA-associated vasculitis, FSGS, diabetic nephropathy, and IgA nephropathy
Oxidative stress[13,26-28]	• Oxidative stress is another important factor in the development of CV disease in glomerulonephritis and contributes to all-cause mortality in CKD	• ROS are produced by various cells in response to inflammation and cellular stress, and they can cause damage to the endothelial cells • ROS can promote the activation of pro-inflammatory pathways, further exacerbating the inflammatory response and contributing to the development of CV diseases • ROS was shown to be involved in pathogenic processes in numerous mouse models of GN • ROS are also important mediators of the immune system, and as such may play protective roles in some forms of autoimmune GN, including lupus
Vascular calcifications[29]	• Vascular calcifications are important predictors of CV disease, and they develop in GN patients as they progress to CKD	• Vascular calcifications are caused by VSMC apoptosis and vesicle release, dysregulation between inhibitors and promoters of calcification • VSMC differentiation from a contractile to an osteochondrogenic phenotype (pathologic) is favored by elevated serum phosphate, inflammation, and uremia

Note. CV = cardiovascular; GN = glomerulonephritis; NO = nitric oxide; CKD = chronic kidney disease; ANCA = antineutrophilic cytoplasmic antibody; FSGS = focal segmental glomerulosclerosis; IgA = immunoglobulin A; ROS = reactive oxygen species; VSMC = vascular smooth muscle cells.

Hypertension

Chronic hypertension is common among people with GN. In a case series of 708 people with biopsy-proven, primary GN, the prevalence of hypertension at the time of diagnosis ranged from 44% in adults with mesangioproliferative GN to 81% in people with membranoproliferative GN.[31] In the few studies that have leveraged 24-hour ambulatory blood pressure monitors in people with GN, up to 15% of people with GN have masked hypertension and 25% of people with GN have isolated nighttime hypertension.[32] While the variability in hypertension prevalence may reflect differences in age and clinical comorbidities at the time of GN diagnosis, the pathogenesis of hypertension in GN is likely similar across etiologies and includes sodium and water retention in the context of glomerular and tubulointerstitial damage, renin-angiotensin system (RAS) upregulation due to renal ischemia and increased sympathetic system activity arising from the kidney.[33] Hypertension may also be a consequence of immunosuppressive treatments employed in the management of GN, including corticosteroids and calcineurin inhibitors, which can make management of hypertension in GN particularly challenging.

Given that people with GN are at high absolute risk for a CV event, all individuals should be considered for non-pharmacologic and pharmacologic strategies for managing hypertension. Non-pharmacologic treatments include restricting dietary sodium, increasing exercise, weight loss, and smoking cessation. Pharmacologic treatment involves the initiation of blood pressure lowering medications, among which RAS blockade with angiotensin-converting enzyme

(ACE) inhibitors and angiotensin receptor blockers (ARBs) are first-line treatments due to their proteinuria lowering effects. These medications should be titrated to their maximally tolerated dose and adjunctive medications, such as diuretics should be used to mitigate side effects of RAS blockade, such as hyperkalemia.

With respect to blood pressure treatment targets, currently, the guideline recommended systolic blood pressure target for adults with CKD is < 120 mmHg, which is based on the SPRINT (Systolic Blood Pressure Intervention Trial).[34] Compared with a systolic blood pressure target of < 140 mmHg, intensive systolic blood pressure lowering to a target of < 120 mmHg was associated with lower rates of the primary composite outcomes of myocardial infarction, non-myocardial infarction acute coronary syndrome, acute decompensated heart failure, stroke, and death from CV disease causes (HR = 0.81, 95% CI = 0.63-1.05). Importantly, the SPRINT study excluded people with proteinuria 1 g per day or more and people with GN on immunosuppression. However, people with GN that were not on immunosuppression were included. Although an intensive versus liberal systolic blood pressure target has yet to be formally examined in a dedicated randomized controlled trial (RCT), multiple meta-analyses have demonstrated a consistent benefit-risk profile of blood pressure lowering, regardless of baseline proteinuria.[35,36] While the benefits of treating hypertension and blood pressure lowering are consistent, irrespective of the etiology of CKD or the degree of proteinuria, there is limited information regarding the impact of intensive blood pressure lowering in young adults. In children, there is even less information regarding the treatment of hypertension and the guideline recommended target is a 24-hour mean arterial pressure that is less than the 50th percentile for age, sex, and height using a 24-hour ambulatory blood pressure monitor.[37] Therefore, blood pressure lowering medication in children and young adults should be initiated after a shared decision-making process.

Hyperlipidemia

Similar to hypertension, hyperlipidemia may also be a complication of GN itself and is indeed a diagnostic criterion for nephrotic syndrome. Hyperlipidemia may also be secondary to immunosuppressive medications, such as calcineurin inhibitors or glucocorticoids. The underlying principles for the management of hyperlipidemia are also similar to hypertension. Lifestyle modification should be considered for all people with GN and with persistent hyperlipidemia. Some adults with GN may be at high absolute risk for CV disease, and statins should be considered as first-line treatment for hyperlipidemia in appropriate people, with the target dose determined based on the predicted absolute risk of CV disease. In the absence of established risk prediction tools for people with GN, the KDIGO guidelines recommend a CV risk assessment based on the totality of CV risk factors, such as lipid parameters, chronic inflammatory conditions, genetic ancestry, and sex-specific risk factors, such as pre-eclampsia and menopause.[38] Non-statin treatments, such as ezetimibe, can also be added in people intolerant of statin or who are at high CV risk and fail to achieve a reduction in their low-density lipoprotein (LDL) cholesterol by ≥50% or to normal limits, despite a statin. However, such recommendations are extrapolated data from CKD patients in general, and the benefits to control lipids to treat and prevent CV diseases were never prospectively tested in GN patients.

Sodium Glucose Co-Transporter 2 Inhibitors

Beyond targeting CV risk factors, sodium glucose co-transporter 2 inhibitors (SGLT2i) are novel reno-protective medications that have generated interest regarding the potential for CV benefits in people with GN. SGLT2i confer consistent relative risk reductions across the full spectrum of CV risk and irrespective of traditional CV risk factors, such as blood pressure,[39] glycemic control,[40] and body weight.[41] SGLT2i work by inhibiting glucose and sodium reabsorption in the proximal tubule that increases the sodium concentration within the filtrate and results in tubuloglomerular feedback at the juxtaglomerular apparatus triggering afferent arteriolar vasoconstriction.[42] This results in an initial decline in intraglomerular pressure, an elevation in creatinine and decrease in GFR. However, over the long term, there is glomerular hemodynamic adaptation and the decrease in intraglomerular pressure reduces the rate of GFR decline. Importantly, SGLT2i have been proven beneficial in people with CKD,[43] including reducing the incidence of all-cause mortality (HR = 0.87, 95% CI = 0.78-0.97), CV death or heart failure (HR = 0.74, 95% CI = 0.66-0.82), and progression of CKD (HR = 0.60, 95% CI = 0.53-0.68) as compared with placebo, without evidence of effect modification based on diabetes status.[43] SGLT2i confer particularly large reductions in the incidence of heart failure (HR = 0.68, 95% CI = 0.61-0.76).[44] They also have a small but nonetheless important effect on atherosclerotic CV disease and reduce the incidence of the composite of CV death, myocardial infarction, and stroke by 10% (HR = 0.90, 95% CI = 0.85-0.95), particularly in people with established CV disease.[44]

While the benefits of SGLT2i for kidney progression have been clearly demonstrated in people with GN, the effects on CV outcomes have not been directly examined. Although people with GN were included in the kidney outcome RCTs and a pre-specified subgroup analysis in IgA nephropathy demonstrated compelling evidence of renal benefit,[45] there were too few participants to specifically study CV outcomes. Nonetheless, SGLT2i may be readily used in people with GN who have an alternate indication for the medication, such as concomitant type 2 diabetes. Likewise, the utility for SGLT2i for reducing CKD progression may also be a pathway to car-

dioprotective benefits, given that advanced CKD in-and-of-itself contributes to CV disease.

However, the use of SGLT2i for primary prevention of CV disease in people with an isolated diagnosis of GN will require further study, including consideration for potential differences in efficacy related to the pathophysiology of GN. For instance, in a small mechanistic study of people with FSGS, use of SGLT2i did not alter renal hemodynamic function or reduce proteinuria, possibly due to decreased SGLT2 receptor expression in FSGS.[46] Herein also lies an important barrier to ultimately preventing CV disease in people with GN. Despite knowledge of the clinical factors contributing to CV disease in GN, the overarching challenge continues to be the lack of risk prediction models to identify people with GN who would benefit from cardioprotective medications and the lack of direct evidence regarding the CV efficacy of treatments targeting traditional and non-traditional risk factors. This lack of evidence is further compounded by methodological challenges related to conducting RCTs in GN, including the relative rarity of GN compared with other causes of CKD, the slow but progressive nature of GN and the relative underfunding of research in GN.[38] This means that the benefit/risk profile of initiating new medications to prevent CV disease in people with GN remains unclear and will likely require multinational collaborative efforts to advance this clinically important question.

Antiplatelet Treatment

Although antiplatelet therapies are indicated in the secondary prevention of CV disease, there is little evidence to support their use for the primary prevention of CV disease, in large part because any cardioprotective benefit from antiplatelets are largely counterbalanced by an increased risk of bleeding.[47] Although people with specific subtypes of GN may have more risk for hypercoagulability, there have been no dedicated studies of antiplatelet treatment in people with GN for CV disease prevention. Given the risks of bleeding, empirical use of antiplatelets for primary prevention cannot be recommended in the absence of dedicated clinical trials.

Emerging Treatments for CV Disease

Beyond SGLT2i, other novel treatments, such as glucagon-like peptide 1 (GLP-1) receptor agonists are emerging as important adjunctive cardioprotective medications in people with CKD. Endogenous GLP1 is an incretin hormone that is produced in the intestinal L cells via receptors in pancreatic beta cells in response to food intake, and results in an insulinotropic response.[48] Due to the presence of GLP1 receptors in extra-pancreatic tissues such as the brain, heart, kidneys, and vasculature, GLP1 receptor agonists have been shown to have other beneficial effects. Specific to CV disease, GLP1 receptor agonists reduce the incidence of the composite of CV death, myocardial infarction, or stroke, versus placebo, with consistent effects in people with and without diabetes.[49,50] GLP1 receptor agonists are recommended in people with diabetes at high CV risk, including people with CKD.[51] Guidelines have yet to be updated to include the more recent evidence in people without diabetes. There is little evidence regarding the effects of GLP1 receptor agonists in people with GN and there are no forthcoming clinical trials. Given their favorable benefit-risk profile, these medications may be considered for high-risk patients.

Non-steroidal mineralocorticoid receptor antagonists (nsMRAs), namely, finerenone, have also emerged as important adjunctive treatments for preventing CV disease in people with CKD and diabetes.[52] Non-steroidal mineralocorticoid receptor antagonist has a distinct chemical structure compared with steroidal mineralocorticoid receptor antagonists (sMRAs), such as spironolactone, thereby resulting in nsMRAs having more selectivity for the mineralocorticoid receptor and less side effects.[53] The role of nsMRAs in people with non-diabetic CKD and in people with GN remains to be clarified.

Glomerular Disease and CV Risk in Children

Glomerulopathies present both acute and chronic complications in children. Initial considerations are around the degree of renal involvement with subsequent determination of glomerular filtration rate, as well as managing hyperkalemia, and fluid overload. Longer-term complications include chronicity associated with relapsing disease, as well as medication side effects. Furthermore, these children affected by glomerulopathies may have traditional risk factors for CV disease, while others have both traditional and non-traditional risk factors.[54] Traditional risk factors for CV disease in children include obesity, metabolic syndrome, dyslipidemia, as well as pre-existing hypertension. Non-traditional CV disease risk is often associated with proteinuria, or degree of renal involvement, exposure to second-hand smoking, or first-hand exposure, as well as prematurity that is associated with lower nephron mass.[54]

In a Cure Glomerulonephritis (CureGN) study by Ashoor et al,[54] 761 children with glomerulopathies (283 with MCD, 177 with FSGS, 36 with MN, and 265 with IgA) were enrolled at median 16 months from glomerular disease origin and assessed for traditional and non-traditional CV disease risk factors. Importantly, several traditional CV disease risk factors were identified in this patient population, including, 21% of children having hypertension, 51% being overweight or obese, and 71% having dyslipidemia. Non-traditional risk factors included exposure to second-hand smoke, which was observed in 24% of children enrolled. Furthermore, 12% were born premature (as defined by $<$ 37 weeks of gestation at delivery).

Another important study by Shah et al,[55] looked at associations between obesity and CV disease risk factors. They used the Nephrotic Syndrome Study Network (NEPTUNE) cohort and prospectively analyzed 541 patients. The prevalence of obesity in the pediatric arm of this cohort was 38%, and obesity over time was associated with higher systolic blood pressure index and hypertension. Furthermore, obesity was associated with a lower likelihood of achieving complete remission of proteinuria.[55] Thus, it is apparent that increased focus must be placed on targeting weight management in children with glomerular disease as hypertension and proteinuria are both independent risk factors for CV disease.

The above important studies also revealed that children with glomerular disease, particularly MCD, had infrequent monitoring for dyslipidemia and were less likely to be offered lipid-lowering treatment.[54] In addition, a recent study in children with IgA nephropathy showed that those with dyslipidemia may have a lower probability of renal survival,[56] highlighting the urgent need for diagnosis and management of these common sequelae associated with glomerular disease. In the Ashoor study, another important factor noted was that up to 14% of children with hypertension were not being treated,[54] thus contributing further to their CV disease risk burden.

A recent area of intense research interest is on legacy effects of pediatric disease and CV disease risk factors on adult CV disease outcomes.[57-59] In a study by Jacobs et al,[57] the HR for fatal CV events was elevated in those participants who smoked as a youth (HR = 1.61, 95% CI = 1.21-2.13), who were obese as a youth (HR = 1.44, 95% CI = 1.33-1.57), who had elevated cholesterol (HR = 1.30, 95% CI = 1.14-1.47) or triglycerides (HR = 1.50, 95% CI = 1.33-1.70), and for those with elevated systolic blood pressure (HR = 1.34, 95% CI = 1.19-1.50). In addition, children with glomerulopathies are exposed, in most cases, to high-dose steroids, which lead to obesity, dyslipidemia, glucose intolerance, and frank diabetes, as well as hypertension.

These studies reveal an unmet need in pediatric glomerular disease. An increased focus needs to be on identifying children with glomerulopathy who have modifiable risk factors for CV disease and intervening early and effectively. Importantly, the first choice for intervention would be lifestyle modification, including increased exercise and dietary counseling. Pharmacological intervention must only be initiated after careful shared decision-making with the child or youth and their caregivers while weighing the risks versus the benefits. In certain instances, particularly patients with proteinuria refractory to therapy, renin-angiotensin-aldosterone (RAS) blockade and statins are cautiously employed. However, there is evidence to suggest they may be underprescribed in dyslipidemic children with GN.[54] It is therefore clear that large, collaborative studies are paramount to address these key issues for children with glomerular disease.

Conclusion

It is clear that CV disease risk is elevated in patients with GN; however, there are few studies directly investigating GN patients and their CV disease risk. Much of our practice is an extrapolation from patients with CKD. Dedicated epidemiological, basic science, and translational studies with multicenter collaboration will be needed to address the evidence gaps in the prevention and targeted management of CV disease in people with different forms of GN across the age spectrum. Of equal importance is effective engagement with patient partners and those with lived experience to prioritize research questions, inform the feasibility of study designs and ensure that the needs of patients with GN are being met.[60]

Box 3. Clinical Vignette.

Debbie arranges a follow-up appointment with her nephrologist and allied health staff to tackle these issues and focus on strategies to overcome them

Patient narrative

"That's how it started. Since then, we built a strong family and support network. As a family we all share household chores to save my energy for daily exercise and family activities. My kids and husband learned to cook, they rotate through cleaning the house, and laundry was a shared adventure. With the support of the kidney social worker, we were connected to another family living with GN. It was so good for everyone. We learned that all expenses related to my appointments could be deducted as part of our taxes. We also adjusted our vacation plans so I could work part-time. The struggles aren't over, and we are adapting as we go"

Patient perspective

It is clear that GN has a major impact not only on the CV health of patients, but also on their wellbeing as a whole. An important message is revealed when engaging patient partners and those with lived experience. They are able to remind clinicians caring for people with GN that the impact of the disease does not stop when they leave the clinic

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

All authors provided consent for publication.

Availability of Data and Materials

Not applicable.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Robert L. Myette https://orcid.org/0000-0002-6441-8612
Mark Canney https://orcid.org/0000-0002-4308-3083

References

1. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet*. 2013;382:339-352.
2. Chronic Kidney Disease Prognosis Consortium; Matsushita K, van der Velde M, Astor BC, 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.
3. Matsushita K, Ballew SH, Coresh J, et al. Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2017;5(9):718-728.
4. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2015;3(7):514-525.
5. KDIGO. KDIGO 2013 clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int*. 2013;3:259-305.
6. Pujades-Rodriguez M, Morgan AW, Cubbon RM, et al. Dose-dependent oral glucocorticoid cardiovascular risks in people with immune-mediated inflammatory diseases: a population-based cohort study. *PLoS Med*. 2020;17(12):e1003432.
7. Tong A, Manns B, Wang AYM, et al. Implementing core outcomes in kidney disease: report of the standardized outcomes in nephrology (SONG) implementation workshop. *Kidney Int*. 2018;94(6):1053-1068.
8. Carter SA, Gutman T, Gutman T, et al. Identifying outcomes important to patients with glomerular disease and their caregivers. *Clin J Am Soc Nephrol*. 2020;15:673-684.
9. 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.
10. Lee T, Derebail VK, Kshirsagar AV, et al. Patients with primary membranous nephropathy are at high risk of cardiovascular events. *Kidney Int*. 2016;89(5):1111-1118.
11. 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(6):740-750.
12. 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. *Circulation*. 2008;117:224-230.
13. Carracedo J, Alique M, Vida C, et al. Mechanisms of cardiovascular disorders in patients with chronic kidney disease: a process related to accelerated senescence. *Front Cell Dev Biol*. 2020;8:185.
14. Guzik TJ, Cosentino F. Epigenetics and immunometabolism in diabetes and aging. *Antioxid Redox Signal*. 2018;29:257-274.
15. Mihai S, Codrici E, Popescu ID, et al. Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. *J Immunol Res*. 2018;2018:2180373.
16. Angeletti A, Bruschi M, Kajana X, et al. Mechanisms limiting renal tissue protection and repair in glomerulonephritis. *Int J Mol Sci*. 2023;24:8318.
17. Carracedo J, Buendía P, Merino A, et al. Cellular senescence determines endothelial cell damage induced by uremia. *Exp Gerontol*. 2013;48(8):766-773.
18. da Cunha RS, Santos AF, Barreto FC, et al. How do uremic toxins affect the endothelium? *Toxins*. 2020;12:412.
19. Morris ST, McMurray JJ, Rodger RS, et al. Impaired endothelium-dependent vasodilatation in uraemia. *Nephrol Dial Transplant*. 2000;15(8):1194-1200.
20. Mackinnon B, Deighan CJ, Ferrell WR, et al. Endothelial function in patients with proteinuric primary glomerulonephritis. *Nephron Clin Pract*. 2008;109(1):c40-c47.
21. Farrah TE, Melville V, Czopek A, et al. Arterial stiffness, endothelial dysfunction and impaired fibrinolysis are pathogenic mechanisms contributing to cardiovascular risk in ANCA-associated vasculitis. *Kidney Int*. 2022;102(5):1115-1126.
22. Zhang Q, Zeng C, Fu Y, et al. Biomarkers of endothelial dysfunction in patients with primary focal segmental glomerulosclerosis. *Nephrology*. 2012;17(4):338-345.
23. Avogaro A, Albiero M, Menegazzo L, et al. Endothelial dysfunction in diabetes: the role of reparatory mechanisms. *Diabetes Care*. 2011;34(suppl 2):S285-S290.
24. Bertaglia G, Ossi E, Casonato A, et al. Von Willebrand factor abnormalities in IgA nephropathy. *Nephrol Dial Transplant*. 1997;12(3):474-479.
25. Hernández E, Toledo T, Alamo C, et al. Elevation of von Willebrand factor levels in patients with IgA nephropathy: effect of ACE inhibition. *Am J Kidney Dis*. 1997;30(3):397-403.
26. De la Fuente M, Miquel J. An update of the oxidation-inflammation theory of aging: the involvement of the immune system in oxi-inflamm-aging. *Curr Pharm Des*. 2009;15(26):3003-3026.
27. Gwinner W, Gröne HJ. Role of reactive oxygen species in glomerulonephritis. *Nephrol Dial Transplant*. 2000;15(8):1127-1132.

28. Scherlinger M, Tsokos GC. Reactive oxygen species: the Yin and Yang in (auto-)immunity. *Autoimmun Rev*. 2021;20(8):102869.
29. Jablonski KL, Chonchol M. Vascular calcification in end-stage renal disease. *Hemodial Int*. 2013;17:S17-S21.
30. Elezaby A, Dexheimer R, Sallam K. Cardiovascular effects of immunosuppression agents. *Front Cardiovasc Med*. 2022;9:981838.
31. Gellineo L, Bulimbašić S, Ćorić M, et al. Hypertension in primary glomerulonephritis–report from the Croatian referral centre for glomerular diseases. *J Hypertens*. 2018;36:e274.
32. Wen RW, Chen Xq, Zhu Y, et al. Ambulatory blood pressure is better associated with target organ damage than clinic blood pressure in patients with primary glomerular disease. *BMC Nephrol*. 2020;21:541.
33. Ihm CG. Hypertension in chronic glomerulonephritis. *Electrolyte Blood Press*. 2015;13:41-45.
34. SPRINT Research Group; Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103-2116.
35. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *CMAJ*. 2013;185:949-957.
36. Ku E, McCulloch CE, Inker LA, et al. Intensive BP control in patients with CKD and risk for adverse outcomes. *J Am Soc Nephrol*. 2023;34:385-393.
37. ESCAPE Trial Group; Wühl E, Trivelli A, Picca S., et al. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med*. 2018;361:1639-1650.
38. 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:S1-S276.
39. Furtado RHM, Raz I, Erica L, et al. Efficacy and safety of dapagliflozin in type 2 diabetes according to baseline blood pressure: observations from DECLARE-TIMI 58 trial. *Circulation*. 2022;145:1581-1591.
40. Inzucchi SE, Kosiborod M, Fitchett D, et al. Improvement in cardiovascular outcomes with empagliflozin is independent of glycemic control. *Circulation*. 2018;138:1904-1907.
41. Ji Q, Ji L, Mu Y, et al. Effect of empagliflozin on cardiorenal outcomes and mortality according to body mass index: a subgroup analysis of the EMPA-REG OUTCOME trial with a focus on Asia. *Diabetes Obes Metab*. 2021;23(8):1886-1891.
42. Cherney DZ, Odutayo A, Aronson R, et al. Sodium glucose cotransporter-2 inhibition and cardiorenal protection: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74:2511-2524.
43. Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet*. 2022;400:1788-1801.
44. McGuire D, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol*. 2021;6:148-158.
45. Wheeler DC, Toto RD, Stefánsson BV, et al. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney Int*. 2021;100(1):215-224.
46. Rajasekeran H, Reich HN, Hladunewich MA, et al. Dapagliflozin in focal segmental glomerulosclerosis: a combined human-rodent pilot study. *Am J Physiol Renal Physiol*. 2018;314:F412-F422.
47. ASCEND Study Collaborative Group; Bowman L, Mafham M, Wallendszus K, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med*. 2018;379:1529-1539.
48. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132(6):2131-2157.
49. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389:2221-2232.
50. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021;9(10):653-662.
51. Marx N, Federici M, Schütt K, et al. 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J*. 2023;44:4043-4140.
52. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med*. 2021;385:2252-2263.
53. Agarwal R, Kolkhof P, Bakris G, et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur Heart J*. 2021;42:152-161.
54. Ashoor IF, Mansfield SA, O'Shaughnessy MM, et al. Prevalence of cardiovascular disease risk factors in childhood glomerular diseases. *J Am Heart Assoc*. 2019;8:e012143.
55. Shah PP, Brady TM, Meyers KEC, et al. Association of obesity with cardiovascular risk factors and kidney disease outcomes in primary proteinuric glomerulopathies. *Nephron*. 2021;145(3):245-255.
56. Zhuang H, Lin Z, Zeng S, et al. Dyslipidemia may be a risk factor for progression in children with IgA nephropathy. *Pediatr Nephrol*. 2022;37(12):3147-3156.
57. Jacobs DR Jr, Woo JG, Sinaiko AR, et al. Childhood cardiovascular risk factors and adult cardiovascular events. *N Engl J Med*. 2022;386:1877-1888. doi:10.1056/NEJMoa2109191.
58. Lechner BL, Bockenhauer D, Iragorri S, et al. The risk of cardiovascular disease in adults who have had childhood nephrotic syndrome. *Pediatr Nephrol*. 2004;19(7):744-748.
59. Magnussen CG, Smith KJ. Pediatric blood pressure and adult preclinical markers of cardiovascular disease. *Clin Med Insights Blood Disord*. 2016;9:1-8.
60. Elliott MJ, McCarron TL, Schick-Makaroff K, et al. The dynamic nature of patient engagement within a Canadian patient-oriented kidney health research network: perspectives of researchers and patient partners. *Health Expect*. 2023;26(2):905-918. doi:10.1111/hex.13716.