

Title:

Preserving Kidney Function in People with Chronic Kidney Disease

(Running Head: **Kidney Preserving Care**)

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ABSTRACT (250 words)

Chronic kidney disease (CKD) is a progressive disease with no cure and high morbidity and mortality. It occurs commonly in people with diabetes and hypertension. Preservation of kidney function can improve outcomes and may be achieved by use of non-pharmacologic strategies, including dietary adjustments, and CKD-targeted and kidney disease specific pharmacologic interventions. Plant-dominant low-protein and low-salt diet may help mitigate glomerular hyperfiltration and preserve kidney function, while also possibly leading to favorable alterations in acid-base homeostasis and the gut microbiome. Pharmacotherapies that alter intrarenal hemodynamics including angiotensin pathway modulators and sodium glucose cotransporter-2 inhibitors can help preserve kidney function by mechanisms in addition to improving blood pressure and glucose control such as by reducing intraglomerular pressure, while novel agents such as nonsteroidal mineralocorticoid receptor antagonists may protect the kidney through anti-inflammatory or anti-fibrotic mechanisms. Some glomerular and cystic kidney diseases may benefit from disease specific therapies. Managing CKD associated cardiovascular risk, infection control and prevention of acute kidney injury are crucial given the high burden of these complications and associated morbidity and mortality and role of non-conventional risk factors in CKD. When kidney replacement therapy becomes inevitable, an incremental transition to dialysis may be considered and has been proposed to possibly preserve residual kidney function longer. There are similarities and distinctions between kidney preserving and supportive care. To ensure optimal kidney preserving care and to achieve greater longevity along with superior health-related quality of life, additional studies on preexisting interventions and development of innovative strategies are warranted as reviewed here.

Keywords:

Kidney preservation, dialysis freedom, plant-dominant low-protein diet, angiotensin pathway modulators, sodium glucose cotransporter-2 inhibitors, supportive care, palliative and hospice medicine

1. Chronic Kidney Disease

Chronic kidney disease (CKD) is a progressive condition characterized by structural and functional changes to the kidney, which occur due to a wide variety of etiologies. It is typically defined as a reduction in kidney function, estimated glomerular filtration rate [eGFR] <60 ml/min/1.73m², or markers of kidney damage, such as albuminuria, hematuria or abnormalities detected on imaging, present for at least 3 months (supplemental **Figure S1** in online appendix).¹ The global burden of CKD is substantial and growing; approximately 10% of adults worldwide are affected by some form of CKD, resulting in 1.2 million deaths and 28 million years-lost-of-life each year.²⁻³ By 2040, it is estimated that CKD will become the fifth leading cause of death globally, one of the largest projected increases of any major cause of death.⁴

The prevalence of different aetiologies varies considerably by region. There are many causes of CKD, including those that more common and well-researched such as diabetes, glomerulonephritis and cystic kidney diseases; however, causation in CKD is not fully understood. For instance, despite close association of CKD with hypertension, it remains controversial as to whether hypertension is a cause or consequence of CKD.⁵ As another example, in some agricultural societies in South Asia and Central America there exists CKD of unknown aetiology (CKDu) for which there is no known treatment while recurrent volume depletion has been speculated as a cause of CKDu especially under the climate change with more heat waves.⁶ The global burden of CKD has also been attributable to air pollution and disproportionally borne by certain regions of the world.⁷ CKD severity also varies from kidney damage with normal function, through to *kidney failure* (or end-stage kidney disease), which typically occurs when eGFR falls below 15 mL/min/1.73m². In general, the prevalence of CKD increases with age, and in high-income countries is more common in those with obesity, diabetes mellitus and hypertension.^{8,9}

Symptoms of CKD are usually insidious and most affected individuals are asymptomatic until the disease becomes advanced, i.e., eGFR <30 ml/min/1.73m². The rate of loss of kidney function varies by etiology, exposures and interventions, but in most cases progression to kidney failure typically takes months to decades to develop. Signs and symptoms of kidney failure result from progressive uremia, anemia, volume overload, electrolyte abnormalities, mineral and bone disorders, and acidemia, and inevitably lead to death if left untreated.¹⁰

Renal (kidney) replacement therapy – either in the form of chronic dialysis or kidney transplantation – are life-sustaining treatments for people with kidney failure. Because of a shortage of donor kidneys, as well as comorbidities which develop with increased age and often preclude kidney transplantation,^{11,12} dialysis remains the prevailing treatment option globally for most people with kidney failure.¹³ Kidney failure requiring dialysis is also associated with substantially reduced quality of life and high mortality rates¹⁴ especially in the first year upon transition to dialysis,¹⁵ underscoring the importance of preserving kidney function in people with or at high risk of CKD.

2. Approach to preserving kidney function

There has been growing recognition that conservative management without dialysis is a viable patient-centered treatment option for a substantial proportion persons with CKD.¹⁶ As shown in **Figure 1**, within conservative management strategies there are several mostly overlapping intervention domains with similarities and distinctions that can be offered to patients with CKD.¹⁷ Kidney preserving care is a life-sustaining type of conservative management with the primary goal of slowing CKD progression and preserving kidney function to prolong dialysis-free time for as long as possible, or ideally avoid it altogether. This approach strives to achieve the greatest survival including improved cardiovascular

health and superior health-related quality of life with effective treatment of renal and non-renal comorbidities and their associated symptoms.^{18,19}

Given that conservative management is defined as CKD care without dialysis or a kidney transplantation,²⁰ misconceptions of dialysis-free management as “no care” or conflation with hospice care may have contributed to underutilization of the kidney-preserving management of CKD across its full spectrum.^{12,18} Notwithstanding heterogeneity in definitions, provision of or access to care, and patient demographics or socioeconomic status across these different domains under the conservative management of CKD, evidence suggests that there is a rising utilization of conservative management with more focus on kidney preserving strategies.²¹⁻³³

The focus of efforts to slow the loss of kidney function vary depending on the severity of CKD and underlying etiology, encompassing a range of pharmacological and non-pharmacological approaches as shown in **Figure 1** and supplemental **Figures S2 and S3** under online appendix, given that these measures are consistent with the secondary and tertiary prevention of CKD,³⁴ and also summarized in **Table 1**. In the general population, lifestyle and dietary modifications should be prioritized as these can improve cardiometabolic health with likely favorable long-term effects on the kidney. The focus of care in primary prevention remains achieving optimal control of risk factors for CKD by addressing physical inactivity and obesity, smoking, as well as elevated blood pressure and blood glucose.³⁵ Addressing these risk factors remains important across the whole spectrum of kidney function. Whereas the cost-effectiveness of population wide screening for CKD remains controversial, it is recommended that targeted screening is performed in individuals with risk factors (e.g. obesity, hypertension and diabetes mellitus) by regular assessment of eGFR and albuminuria.³⁶

For individuals with established CKD, in addition to protecting kidney function, addressing complications and associated comorbidities, and managing symptoms are also important. Slowing the progression of CKD can be achieved through a range of lifestyle, dietary and pharmacological strategies, which include weight loss, moderate dietary protein restriction, blood pressure and glucose control, as well as renin-angiotensin system blockade (supplemental **Figures S2 and S3**). For specific disease etiologies such as primary glomerulonephritis and autosomal dominant polycystic kidney disease, newer targeted therapies also have an important role (see below). As many more individuals with CKD die due to cardiovascular disease than progress to kidney failure, reducing cardiovascular risk is a fundamental aspect of the care in this population.³⁷

Large-scale collaborative meta-analyses have demonstrated that eGFR and albuminuria are strongly and independently associated with risk of a range of adverse outcomes including progression to kidney failure, cardiovascular events, and death, and both kidney markers should therefore be used to inform prognosis and direct care priorities for people with CKD.³⁸⁻⁴² The Kidney Disease Improving Global Outcomes (KDIGO) classification of CKD incorporates eGFR and UACR into a two-dimensional framework to stratify individuals' risk, focus management priorities and guide referral to specialist care, and is perhaps the most widely used staging system (supplemental **Figure S1**).⁴³ Other tools such as the Kidney Failure Risk Equation,⁴⁴ or the Dialysis Transition Mortality Prediction Score⁴⁵ are also available and can be used to estimate risk of kidney failure and first year dialysis mortality, respectively, and thus inform discussion, facilitate specialist referral and contribute to shared decision making. Upon progression to advanced CKD where uremia cannot be controlled without renal replacement therapy, incremental transition to peritoneal or hemodialysis therapy may be a preferred approach with the goal to preserve residual

kidney function while receiving less than usual dialysis, although clinical trials are needed to examine this and other alternative dialysis transition strategies.⁴⁶

3. Physical activity, obesity and weight loss

Obesity is the hallmark of metabolic syndrome and associated with CKD.⁴⁷ Large-scale collaborative meta-analyses have demonstrated that increased adiposity measures (e.g. body mass index and waist circumference) are strongly independently associated with decline in GFR.⁴⁸ The precise mechanism by which obesity may contribute to risk of CKD is uncertain but may include systemic and intraglomerular hypertension, the effect of pre-diabetes levels of blood glucose on podocyte stress, as well as other unrecognized factors.^{49,50}

Physical activity is the core component of lifestyle modification strategies to manage weight for impact on CKD progression. The effect of weight reduction on risk of CKD has been demonstrated in the post-hoc analysis of Look-AHEAD trial, where 5,145 obese individuals with type 2 diabetes were randomized to intensive lifestyle intervention or diabetes support and education.⁵¹ The trial demonstrated that intensive lifestyle intervention reduced weight by 4 kg on average and reduced the onset of very high risk CKD according to the KDIGO classification system by approximately 30%.

A range of interventions may be employed for weight loss in people with CKD. Caloric restriction such as in a plant-dominant, low-protein diet can lead to gradual weight loss in most obese persons with CKD.^{52,53} Efforts to identify pharmacological agents which can lower body weight and improve clinical outcomes have yielded limited or modest results.⁵⁴ The role of bariatric surgery to mitigate the risk of CKD also remains uncertain.⁵⁵ Observational studies have suggested that bariatric surgery is associated with lower risk of patient-level kidney outcomes.⁵⁶ Although these effects have not been clearly demonstrated in trials, there is randomized evidence that gastric bypass surgery increases remission of

albuminuria in people with type 2 diabetes, obesity and microalbuminuria when compared to optimal medical treatment, and may represent an important treatment option in select individuals.⁵⁷

In more advanced CKD, prolonged survival has been paradoxically reported with larger body mass index, a phenomenon that is known as the obesity paradox or reverse epidemiology, while lower BMI may reflect poorer nutritional status or weight loss due to sarcopenia or multimorbidity.⁵⁸ Alternatively, weight loss may contribute to poorer outcomes while effective nutritional interventions to gain weight including muscle mass may improve longevity.⁵⁹ Any unintentional weight loss warrants timely work-up and dietary interventions, and unnecessary weight loss in advanced CKD should be avoided, unless absolutely required, e.g., for a strict requirement of an imminent kidney transplantation that stipulates lower weight or other life-saving procedures.⁶⁰

4. Plant-Dominant Low-Protein Diet

For many causes of CKD including diabetic kidney disease, afferent and efferent arterioles tend to be relatively dilated and contracted, respectively, as a compensatory mechanism partially regulated via tubuloglomerular feedback to maintain GFR in the short-term – a process known as glomerular hyperfiltration or intraglomerular hypertension.⁴⁹ In the long-term this can cause further damage to the kidney through mechanisms including mechanical stress and activation of inflammatory mediators which promote interstitial fibrosis.^{61,62} Dietary protein restriction, by enhancing afferent arteriole tone, may alleviate intraglomerular hypertension, mitigate renal interstitial fibrosis^{61,62} and slow the progression of CKD (**Figure 2**). The pre-glomerular effect of dietary protein restriction acts in parallel and is complementary to the post-glomerular effect of angiotensin pathway modulators including angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers

(ARBs), which lower intraglomerular pressure by promoting efferent arteriolar vasodilatation.⁶³

Key randomized evidence supporting the beneficial effect of dietary protein restriction comes from the *Modification of Diet in Renal Diseases* (MDRD) study, which randomized 585 participants with non-diabetic kidney disease to assess the effect of usual vs. low protein diets (1.3g vs 0.58g per kg/day) on eGFR decline. While the primary results of this trial were inconclusive, these did not take into account the acute effect of dietary protein restriction, which lowers GFR in the short-term due to afferent arteriolar constriction, similar to what is observed with initiating ACE inhibitors or ARB therapy. Subsequent analyses of the MDRD data which excluded the acute effect on GFR suggested benefit with dietary protein restriction (see supplemental **Figure S4** in online appendix).⁶⁴ Additional analyses also showed that dietary protein restriction may lower blood pressure and proteinuria.⁶⁵ The findings from the MDRD study are supported by meta-analyses that demonstrate reduced risk of progression to kidney failure and improvements in proteinuria and other favorable biochemical outcomes such as higher bicarbonate and lower azotemia and phosphorus.⁶⁶⁻⁶⁹ The benefits of dietary protein restriction need to be considered in the context of potential risks to protein-energy wasting and loss of muscle mass and strength, particularly in the elderly.⁷⁰ Hence current guidelines recommend a conservatively low range of 0.6-0.8 g/kg/day of dietary protein in people with significant albuminuria (>300 mg/g) to ensure safety and adequate nutritional intake (see **Table 3**).⁷¹

More recent data suggest salutary effects of plant-dominant low protein diets,⁵² in which >50% of the source of protein is derived from non-animal-based sources that include not only fruits and vegetables, but also nuts, legumes, and seeds. There are different types of plant-dominant diets with proportionately higher choice of foods from plant sources:⁷² (1) Vegan or strict vegetarian diets that not only exclude meat, poultry, and seafood but also eggs

and dairy products; (2) Lacto- and/or ovo-vegetarian diets that may include dairy products and/or eggs; and (3) pescatarian or pesco-vegetarian diets that include a vegetarian diet combined with occasional intake of some or all types of seafoods, mostly fish.⁷² While some but not all studies have shown that plant-dominant diets are associated with lower risk of CKD and GFR decline, less proteinuria, amelioration of acidosis, and better cardiovascular profile,⁷³ these effects remain to be definitively demonstrated in randomised trials.⁷⁴ Experimental data also suggests such diets may lower uremic toxin generation and exert favourable effects on cardiovascular health in people with kidney failure;^{52,53,75,76} however randomized trials assessing effects on clinical outcomes are needed to confirm or refute these observations.

There is growing interest in the role of the gut microbiome in CKD, although the role of any microbiome related interventions remains to be proven.⁷⁴ The gut microbiome in CKD may be altered by uremia, natural intake of probiotics,⁷⁷ and the type of food including plant versus animal origin.⁷⁸ A plant-dominant, fiber-rich, low-protein diet may lead to favorable alterations in the gut microbiome, which may modulate uremic toxin generation.⁵² Uremic plasma impairs barrier function and depletes the tight junction protein constituents of intestinal epithelium.⁷⁹ The influx of retained uremic solutes from the bloodstream induces changes in the microbial population along with gut wall inflammation and breakdown of epithelial junctions.⁸⁰⁻⁹¹ Bacterial-derived toxins then translocate back across the leaky gut barrier into the systemic circulation and promote inflammation and multi-organ dysfunction.^{80,92} Several gut-derived uremic toxins are associated with cardiovascular disease and mortality in CKD including indoxyl sulfate, indole-3 acetic acid, p-cresyl sulfate, TMAO, and phenylacetylglutamine.⁹² The circulating *p-cresyl-sulfate* and *indoxyl-sulfate*, which are protein-bound uremic retention solutes, and other catabolic by-products of protein metabolism can exert harmful effects including inflammation, oxidative stress, endothelial

dysfunction, muscle wasting, renal interstitial fibrosis, worsening proteinuria and accelerated CKD progression, as well as insulin resistance.⁹³⁻⁹⁵ Hence, it has been proposed, but not yet proven in clinical trials, that a high-fiber, plant-dominant, low-protein diet, by modulating microbiome favorably might lower uremic toxin generation and help control uremia without dialysis, while cardiovascular health may be enhanced, consistent with the goals of the conservative management of CKD.⁹⁶

5. Intravascular volume and electrolyte homeostasis

Subclinical volume overload is highly prevalent in people with CKD and perturbations in systemic hemodynamics are strongly associated with risk of cardiovascular and kidney outcomes.⁹⁷⁻⁹⁹ Optimization of intravascular volume is therefore an important focus of care, particularly as kidney function declines, and can be achieved by dietary sodium restriction and the use of loop and non-loop diuretics. Dietary salt restriction can be particularly effective for blood pressure and volume control as many patients with CKD exhibit a tendency for salt-sensitive hypertension.¹⁰⁰ Loop diuretics are the mainstay pharmacological therapy for controlling intravascular volume, especially as kidney function declines. However there is emerging randomized evidence to suggest that distal thiazide diuretics can reduce blood pressure and extracellular volume even at lower eGFR,¹⁰¹ with additional trials ongoing.¹⁰² It has also been widely hypothesized that the beneficial effect of SGLT2 inhibitors on cardiovascular and kidney outcomes may also be partly explain by favorable effects on the extracellular fluid compartment without depleting intravascular volume thus avoiding activation of neurohormonal pathways.¹⁰³

The prevalence of hyperkalemia increases as kidney function declines and epidemiological data demonstrates a U-shaped association between serum potassium and adverse outcomes, such that both high and low potassium levels are associated with poor

outcomes.¹⁰⁴ Commonly used treatments such as ACE inhibitor, ARBs and mineralocorticoid receptor antagonists increase the risk of hyperkalemia. While dietary potassium restriction is generally recommended in people with advanced CKD, concerns have been expressed that such diets may limit the consumption of healthy plant proteins, fruit and vegetables.¹⁰⁵ Traditional and newer potassium binders may allow more effective control of hyperkalemia, enabling potentially beneficial dietary regimens and more effective use of renin angiotensin aldosterone system blockade, and trials are underway to test the effect of newer potassium binders on clinical outcomes.^{106,107}

Metabolic acidosis in CKD results from the inability of the kidney to excrete endogenous acid and has been shown to be associated with loss of kidney function and unfavorable effects on muscle mass and bone health.¹⁰⁸ Small trials have collectively suggested that correction of metabolic acidosis with bicarbonate may slow progression of CKD.¹⁰⁹ Most recently veverimer, a novel binder of hydrochloric acid in the gastrointestinal tract, has been shown to increase serum bicarbonate concentrations in people with CKD, with an ongoing trial to test the effect of this agent agents on a hard kidney outcome.¹¹⁰

6. Traditional and Emerging Pharmacotherapies

These strategies have been summarized in **Table 1** and **Figure 1** as well as supplemental Figure S2 and discussed below.

RAAS inhibition, mineralocorticoid receptor antagonism and other BP lowering therapies

The cornerstone of kidney-preserving pharmacologic therapies over recent decades has been angiotensin pathway modulators that block the renin-angiotensin-aldosterone system, specifically ACE inhibitors or ARBs. The evidence is strongest in people with type 2 diabetes and albuminuric CKD, in whom the *RENAAL* and *IDNT* trials demonstrated that the

respective ARBs losartan and irbesartan reduced the risk of a kidney failure, doubling of creatinine or death.^{111,112} In the *RENAAL* study, the risk of kidney failure was separately significantly reduced (see Supplemental [Figure S4](#)).¹¹¹ These agents have thus been considered standard-of-care for people with type 2 diabetes and diabetic kidney disease (DKD) for the best part of two decades. Importantly, several studies¹¹³⁻¹¹⁵ have demonstrated an increased risk of adverse outcomes with multi-agent RAAS blockade without clear benefits, so combination ACEI and ARB therapy is strongly discouraged.

More recently, the FIDELIO trial of the non-steroidal mineralocorticoid receptor antagonist finerenone in DKD showed a significant reduction in the risk of the primary kidney (sustained 40% reduction in eGFR, kidney failure or kidney death) and cardiovascular (myocardial infarction, stroke, heart failure or CV death) outcomes.¹¹⁶ Several studies have suggested that the older aldosterone antagonist spironolactone reduces proteinuria in DKD,¹¹⁷ but clear data regarding effects on hard outcomes are not currently available.

RAS blockade with ACEI or ARB are also generally recommended for people with type 1 diabetes and kidney disease.¹¹² They are also widely recommended for other types of kidney disease largely based on smaller studies and meta-analyses. In non-diabetic kidney disease, the available data from a meta-analysis suggest that the kidney protective effects are clearest in people with significant proteinuria,¹¹⁸ with uncertainty about effects in people with little or no proteinuria.

While BP lowering *per se* likely reduces the risk of kidney failure overall,^{119,120} this remains somewhat controversial as intensive BP lowering (systolic target <120mmHg) may be associated with more rapid decline in kidney function. Available data suggests this may reflect drug induced hemodynamic effects with no deleterious impact on the long-term risk of kidney failure.¹²¹ Based largely on results from the SPRINT study, in people with CKD who do not have diabetes, intensive BP lowering reduces the risk of cardiovascular events and

death and recently updated KDIGO guidelines therefore recommend a systolic BP target of less than 120 in people with CKD based on these effects. However, individualization of BP targets is crucial, taking into account comorbidities, frailty and patient preferences, given ongoing uncertainty about the risk-benefit profile of intensive BP targets in patients with moderate-to-advanced CKD.¹²² For kidney diseases not associated with high blood pressure or diabetes (as for example CKDu) it is unknown whether ACEI/ARB are beneficial.

Glucose lowering therapies.

Glucose lowering therapies in people with diabetes could potentially reverse the fundamental metabolic abnormality pathognomonic of the disease.¹²³ While post-hoc analyses of the ADVANCE trial suggested the risk of kidney failure might be lower in people treated to lower hemoglobin A1c targets,¹²⁴ analyses of eGFR loss over time showed no difference, and meta-analyses of more vs less intensive glucose lowering did not demonstrate clear effects on the risk of kidney failure.¹²⁵ Subsequent studies have further demonstrated clear differences between different classes of glucose lowering therapies.

SGLT2 inhibitors

Sodium glucose cotransporter 2 inhibitors (SGLT2i) were developed to lower blood glucose in people with diabetes by blocking proximal tubular glucose reabsorption thus inducing glycosuria. Early studies in type 2 diabetes identified that these agents significantly lower proteinuria and have a clear effect on kidney hemodynamics. This manifests as an acute reduction in eGFR of approximately 3-5 ml/min/1.73m² followed by stabilization of kidney function compared to either placebo or sulfonylurea therapy, a benefit that was in addition to that conferred by ACEi/ARB therapy.¹²⁶

A number of cardiovascular safety studies mandated by regulatory authorities successively demonstrated reductions in composite outcomes based on reductions in eGFR or doubling of creatinine, kidney failure and death due to kidney disease.¹²⁷⁻¹²⁹ However, these trials were done in people at high cardiovascular risk, a minority of whom had kidney disease.

The first primary kidney trial of SGLT2i assessing efficacy on major clinical outcomes was the CREDENCE trial, where 4401 participants with albuminuric DKD (albuminuria 300-5000 mg/g, eGFR 30-90 mL/min/1.73m²) were randomized to canagliflozin or placebo¹³⁰ (see Supplemental [Figure S4](#)). The trial was stopped early for efficacy, as the primary outcome was reduced by 30%, with similar reductions in a range of kidney outcomes including kidney failure alone, and the need for dialysis or kidney transplantation. Major cardiovascular events (myocardial infarction, stroke or cardiovascular death) and hospitalizations for heart failure were also significantly reduced. Major treatment guidelines around the world have now been updated to recommend SGLT2i in people with DKD based on these findings.

The kidney protective effects of SGLT2 inhibition have also been demonstrated in people with non-diabetic kidney disease. The DAPA-CKD trial¹³¹ demonstrated that dapagliflozin reduces the risk of sustained 50% decline in eGFR, kidney failure or death due to cardiovascular or kidney disease by 44% in people with CKD (eGFR 25-75 mL/min/1.73m² and UACR 200 to 5,000 mg/g), with clear, separate benefits irrespective of diabetes status or etiology of CKD.¹³² The trial also demonstrated a substantial reduction in hospitalization for heart failure or cardiovascular death as well as all-cause death. Based on these findings, it is anticipated that SGLT2 inhibitors are likely be routinely offered to people with albuminuric CKD regardless of the presence of diabetes. A trial of empagliflozin in non-

diabetic kidney disease, which includes people with low or normal albuminuria, is ongoing.¹³³

DPP4 inhibitors

The Dipeptidyl Peptidase-4 (DPP4) inhibitors are widely used to improve glycemic control in people with type 2 diabetes. The effects on hard kidney outcomes were formally assessed in the CARMELINA trial, where almost 7000 participants with type 2 diabetes enriched for kidney disease (reduced GFR, increased albuminuria, or both) and/or cardiovascular disease were randomized to linagliptin or placebo.¹³⁴ The trial demonstrated that linagliptin did not increase the risk of cardiovascular events, but also did not reduce the risk of a composite renal outcome of 40% eGFR decline, kidney failure or renal death, despite over 600 kidney endpoints being observed in the trial. The available data therefore suggest that this class of agents does not meaningfully reduce the risk of kidney disease progression in type 2 diabetes.

GLP 1 agonists

There have not yet been any outcome studies powered to detect effects on clinically important kidney outcomes with the glucagon-like peptide 1 (GLP1) receptor agonists, another class of agents recently developed to improve glucose control in type 2 diabetes. These agents have been shown to reduce the risk of cardiovascular events in meta-analyses of completed cardiovascular outcome trials.¹³⁵ Similar meta-analyses of these trials suggest that the risk of a composite kidney outcome (including progression of albuminuria, substantial losses of kidney function (40% or 57% reductions in eGFR), kidney failure or kidney related death) is significantly reduced by the GLP1 receptor agonists; however, this appears to be primarily driven by effects on albuminuria as no clear benefit observed on kidney outcomes

excluding progression of albuminuria.¹³⁵ A dedicated kidney outcome study (FLOW, NCT03819153) is currently underway, specifically recruiting people with CKD and comparing the effects of semaglutide vs placebo on the risk of major kidney and cardiovascular outcomes.

Examples of treatment of primary glomerulonephritides and cystic disorders

IgA nephropathy, the most common idiopathic glomerulonephritis worldwide, is currently treated by optimizing blood pressure control with ACE inhibitors or ARBs, along with lifestyle modifications including salt and protein restriction and weight loss,¹³⁶ while the role of corticosteroids remains controversial with conflicting evidence from randomized trials including both negative^{137,138} and positive data.^{137,138} New therapeutic strategies for IgA nephropathy are an area of active investigation, and several agents are currently being tested, including combined angiotensin and endothelin receptor blockade and drugs targeting complement pathways.^{139,140} Primary membranous nephropathy is another globally prevalent glomerulonephritis. Although the discovery that it is an autoimmune condition has led to substantial changes in the diagnosis, treatment and monitoring of this disease,¹⁴¹⁻¹⁴³ many of these patients will develop spontaneous remission; as with other etiologies of proteinuric CKD, optimal supportive care should include maximum tolerated ACE inhibitor or ARB.¹⁴⁴ For those with more severe proteinuria and/or at high risk of disease progression other treatments are recommended including alkylating agents such as cyclophosphamide,¹⁴⁵ calcineurin inhibitors,^{146,147} rituximab,¹⁴⁸ or a combination of these agents.¹⁴⁹ For other primary glomerular diseases, there is a paucity of randomized evidence.¹⁵⁰ Autosomal dominant polycystic kidney disease (ADPKD) is a common non-glomerular disease worldwide. In recent years, disease modifying therapy, specifically the vasopressin-receptor antagonist tolvaptan has shown slowed rate of kidney growth and GFR decline¹⁵¹ in early and later stage disease.¹⁵²

7. Addressing cardiovascular risk during CKD progression

Cardiovascular disease (CVD) is a leading cause of death in patients with CKD and is therefore a major focus of care in this population.¹⁵³ Lower eGFR and higher albuminuria are independently and positively associated with cardiovascular outcomes beyond traditional risk factors in all ages (**Figure 3**).^{42,154} Whereas the traditional “shared” risk factors including overweight hypertension, diabetes, dyslipidemia, and smoking are associated with CVD in patients with CKD, a host of non-traditional risk factors magnify the risk of CVD especially in advanced CKD. Some of these “kidney specific” factors include increased activity of renin-angiotensin system, neurohormonal activation, water and sodium retention, anemia, inflammation with or without protein-energy wasting, mineral and bone disorders (including calcium and phosphorus dysregulation, increased parathyroid hormone and FGF-23 and alpha klotho deficiency), and endothelial dysfunction.¹⁵⁵⁻¹⁶²

Management of cardiovascular disease in CKD remains challenging (**Figure S5** under online Appendix).¹⁶³ These challenges include interpretation of cardiac biomarkers which are used to diagnose myocardial infarction, the exclusion of individuals with CKD from cardiovascular outcome trials (particularly those receiving dialysis), and higher proportion of non-atherosclerotic cardiovascular events as kidney function declines with no clear benefit for revascularization for individuals with CKD and stable coronary artery disease.¹⁶⁴⁻¹⁶⁷ The mainstays of cardiovascular risk reduction in CKD include blood pressure lowering with renin-angiotensin aldosterone system blockade, lipid lowering with statins, and specific glucose lowering agents that have been shown to reduce cardiovascular outcomes in people with type 2 diabetes.^{135,168} While lipid lowering with statin therapy improves cardiovascular outcomes in people with CKD not on dialysis, there is insufficient evidence to support commencing lipid-lowering therapy for primary prevention of CVD in most people

with kidney failure requiring dialysis, especially in the absence of high serum LDL-cholesterol levels.¹⁶⁹ In people with type 2 diabetes, guidelines recommend that SGLT2 inhibitors and GLP-1 receptor agonists be prioritized in people with CKD.^{170,171} While antiplatelets should be routinely offered for secondary cardiovascular prevention, relative benefits and harms for primary prevention remain uncertain due to increased bleeding risk.¹⁷² The role of anticoagulation with warfarin versus direct acting oral anticoagulants in advanced CKD also remains uncertain and is subject to ongoing evaluation in randomized trials.¹⁷³

A recent randomized control trial showed that among patients with recent acute coronary syndrome, type 2 diabetes, and low high-density lipoprotein cholesterol levels, the selective bromodomain and extra-terminal protein inhibitor apabetalone, a novel epigenetic modulator, added to standard therapy did not significantly reduce the risk of major adverse cardiovascular events;¹⁷⁴ however, in the subgroup analysis, there was 50% reduction in CVD events among participants with preexisting CKD stage 3.¹⁷⁵ Future cardiovascular outcome trials should focus on enrolling substantial proportions of patients with CKD and ideally prespecify the assessment of treatment effects according to eGFR and albuminuria. Additionally, patient-reported outcomes including health related quality of life should be considered a key outcome for holistic assessment of interventions in all cardiovascular outcome trials involving patients with CKD.¹⁷⁶ It is equally important to integrate and measure quality of life and other patient-related outcomes into routine clinical measurement for continuous quality improvement in health systems and optimization of patient-centered care.¹⁷⁶

8. Acute Kidney Injury

Patients with CKD, especially in more advanced stages (eGFR <30 ml/min/1.73m²) often do not exhibit linear progression of disease, which may be related to superimposed episodes of acute kidney injury (AKI), as well as other factors.¹⁷⁷ Some but not all studies

suggest that each AKI event may accelerate progression of CKD.^{178,179} Hence, preventing AKI is an important components of the management of CKD. This involves avoiding AKI-associated drug combinations e.g., ACE inhibitors or ARBs in conjunction with loop diuretics and non-steroidal anti-inflammatory drugs,¹⁸⁰ as well as preventing infections which can precipitate hypotension or septic shock necessitating the use of potentially nephrotoxic antimicrobials. Other contributors to AKI include cardiovascular events, particularly decompensated heart failure leading to venous congestion and impaired kidney blood flow, or coronary artery bypass and other major surgery with possible intra-operative hypotensive episodes.^{181,182}

9. Role of supportive care and palliative and hospice medicine

People with advanced CKD, particularly those with kidney failure, often experience a high burden of symptoms, which impacts substantially on health-related quality of life.¹⁸³ While randomized evidence is limited, observational studies suggest that chronic dialysis may not be associated with improved survival in some older patients with a high burden of comorbidities, and that at least some of these elderly people might regret their decision to commence dialysis in view of treatment related complications, high symptom burden and poor quality of life.^{184,185} These factors have led to increased recognition of the importance of supportive care of kidney failure with focus on palliative care and hospice medicine (**Figure 1**).

There are similarities and distinctions between the kidney preserving management and supportive care, which includes palliative care and hospice medicine, as shown in **Table 3**. Both strategies are expected to minimize risk of adverse events or complications including AKI as CKD progresses, although the kidney-preserving management is more strongly focused on kidney function longevity. Whereas palliative care strategies are often considered

for those with advanced age or more severe comorbidities such as terminal cancer,^{21-24,26-33} kidney-preserving management is a kidney and life sustaining strategy for all individuals and at any stage of CKD.

The goal of supportive care including palliative and hospice medicine is to help individuals maximize the benefits of treatment and to improve symptoms and quality of life by delivering effective symptom-focused treatment through a multidisciplinary approach that incorporates shared decision making, detailed communication with patients and their caregivers, advanced care planning, and psychological and social support.^{186,187} Standardized tools to identify those who may benefit most from supportive care are not widely validated, and thus treatment decisions must be individualized. People who may benefit from supportive care with more focus on palliative and hospice medicine engagement include those with advanced kidney disease who have exhausted preservative management of their kidney disease and who do not wish to commence chronic dialysis due to very advanced age, complex comorbidities with a short life expectancy or other life limiting illnesses and those who decide to reduce dialysis dose and frequency to minimum such as fluid management, the so-called decremental dialysis, or to withdraw completely from renal replacement therapy.¹⁸⁸ Novel prediction tools have been developed to identify those individuals who would have the highest mortality in the first year upon transitioning to dialysis and who may therefore benefit from palliative care;⁴⁵ however, these tools need to be more widely validated in different populations and thus individualized approach based on the preference of the patient and his/her care-partner remains key. The decision must be according to free choice of the patient without pressure by family members and care-partners or health care professionals, nor should it be influenced by rationing dialysis care such as during COVID-19 pandemic surges or other resource constrains.¹⁷ Importantly, preservation of kidney function and supportive care are entirely complementary and should be considered as parts of the full spectrum of

conservative management of kidney disease depending on the severity of CKD and goals of the individual, rather than mutually exclusive choices (see [Figure 1](#) and [Table 3](#)).

10. Infection Control and Management of CKD in the COVID-19 Pandemic

Evidence suggests that uremia is associated with worse immunologic response, as exemplified by diminished antibody response to hepatitis B vaccination or higher risk of infections as kidney function worsens not explained otherwise by concurrent comorbidities, as well as the historical observation that autoimmune diseases such as systemic lupus erythematosus are less aggressive once patients are uremic.¹⁸⁹ Similarly, some infection such as hepatitis C virus may cause CKD if remain untreated, or may lead to CKD,^{190,191} or with pre-existing CKD may lead to faster disease progression and greater mortality.¹⁹² Conversely, it is possible that treatment of hepatitis C can have a salutary effect in preserving kidney function.¹⁹³ Patients with CKD have a two-fold higher risk of death after respiratory infections,¹⁹⁴ hence, influenza and pneumococcal vaccination may be an indirect way to prevent AKI and avoid CKD progression although this has not been assessed in clinical trials.¹⁹⁵

During the COVID-19 pandemic, data suggest a two-fold increase of mortality from COVID in the presence of CKD.¹⁹⁶ Despite screening and isolation of affected patients, outbreaks cannot always be prevented, given cases with long incubation period or asymptomatic carrier status.¹⁹⁶ In order to maintain staffing levels and to protect patients, outpatient CKD care has undergone a radical transformation by using telemedicine, remote care and minimising blood testing to those tests that guide dietary and therapeutic decisions.¹⁹⁷ Advance care planning and ensuring completion of renal replacement therapy modality plans are of even higher importance, as COVID-19 can cause AKI, which could be due to septic shock and cytokine release or from direct renal tropism of the virus.^{198,199} The

disproportionately high incidence of AKI requiring frequent or continuous renal replacement therapy in critically sick patients with COVID-19 may have implications for long-term kidney longevity in COVID-19 survivors, Ongoing and future trials are expected to address these questions including as to whether ACE-receptor modulators or other modulators of kidney function can avert COVID involvement in AKI and CKD progression.²⁰⁰

11. Global and Regional Disparities in Preserving Kidney Care

Preserving kidney function in people with CKD is confounded by regional and global health inequalities, disparities in healthcare models, pharmaceutical industry policies, and geopolitical and fiscal correlations.²⁰¹ Income disparities including poverty and social disadvantage have a dominant impact on risk on incident CKD and its progression.^{202,203} Many people at risk of CKD in low- and middle-income countries (LMIC) are not provided with appropriate infrastructure for screening and identification of CKD. The awareness of CKD is relatively poor, and opportunities for updating knowledge and education on preserving kidney health are limited.²⁰⁴

In LMICs, diet and lifestyle modification may offer an inexpensive approach for secondary and tertiary prevention of CKD notwithstanding limited scientific evidence to justify population-based programs with lower sodium and higher plant-based diet intake. Whereas pharmacotherapy and dialysis treatment are almost universally accessible in high-income countries, many people in LMICs are unable to access these options.²⁰⁵ The out-of-pocket expenditure for CKD preserving pharmacotherapy is high relative to income; for instance, in India, the high costs for SGLT2 inhibitors or renal replacement therapy are more likely than communicable diseases to push people into poverty range.²⁰⁶

In some affluent nations including the USA there are racial disparities in CKD care.²⁰⁷ Black Americans are by far more likely to develop CKD and exhibit faster disease

progression than Caucasians.²⁰⁸ This disparity may be related to socioeconomic factors exposing many US Blacks to higher CKD risks notwithstanding high prevalence of APOL1-gene allele with higher ESKD likelihood, which may confound kidney preserving therapies.²⁰⁹ The current creatinine based eGFR equations have a race index for Blacks, which inflates the eGFR value by as high as 16% compared to non-Blacks with the same serum creatinine level.²¹⁰ In an effort to reduce racial disparities in CKD care, race indices has been suggested to be removed from eGFR equations to enable more commensurate approach to burden of CKD²¹¹ and instead, race-free measurements such as serum Cystatin C derived eGFR equations could be used, also given their more linear associations with clinical outcomes as shown in [Figure 3](#).^{154,211}

12. Conclusion remarks and future steps

The primary goal of kidney preserving care is to slow CKD progression and preserve kidney function to prolong dialysis-free time while striving to achieve the greatest quality of life and survival. These strategies also include effective treatment of renal and non-renal comorbidities and their associated symptoms.¹⁸ There are similarities and distinctions between kidney preserving management and supportive care in CKD. Dietary interventions using plant-dominant low-protein diet and pharmacotherapies including angiotensin pathway modulators and SGLT2 inhibitors as well as newer non-steroidal mineralocorticoid receptor antagonists should be leveraged. In kidney preserving care, the choice of blood pressure lowering medication is guided by factors beyond hypertension therapy, and similarly, the choice of glucose lowering agents should be driven by their kidney protective efficacy beyond glycemic control. When dialysis therapy is necessary and kidney transplantation cannot be offered, transition to dialysis treatment may be able to be commenced gradually and incrementally with the goal to preserve residual kidney function longer. Some patients may benefit from sporadic dialysis such as peritoneal or hemodialysis for ultrafiltration as a

prelude to incremental transition to dialysis.²¹² Other strategies for future studies in lieu of (or to compliment) dialysis may include – but not limited to –intestinal dialysis models^{213,214} and diaphoresis therapy for control of uremia and management of fluid and electrolytes,^{215,216} given relevant animal models.²¹⁷ Because transition to dialysis may be associated with adverse consequences and burdens of therapy while survival may not be much improved in certain persons irrespective of age, future studies are needed to refine current interventions and to examine novel models and strategies to prolong kidney and patient survival without dialysis if possible and to live long and well with kidney disease. ■

AUTHORS' CONTRIBUTIONS:

Drs. KKZ, THJ, DN, BN, and VP have equally substantially contributed to the conception and design of the article and interpreting the relevant literature, drafted the article and revised it critically for important intellectual content.

AUTHORS' DISCLOSURES:

See posted authors disclosures.

TABLES

Table 3. Similarities and distinctions between the kidney preserving management and supportive and palliative care.

Table 1. Strategies to preserve kidney function in people with CKD.

Table 3. Lifestyle Strategies for Prevention of Progressive CKD and Cardiovascular Disease in Patients with CKD.

Additional tables under Online Appendix

Supplemental Table S1. Recommendations for dietary protein intake to preserve kidney function in people with CKD.

Supplemental Table S2. Pharmacologic Strategies for Prevention of Progressive CKD and Cardiovascular Disease in Patients with CKD

Table 1. Strategies to preserve kidney function in people with CKD. Numeric ranks (i, ii, and iii) in the first column indicate level of strength of the evidence for intervention efficacy: (i) supported by established randomized controlled trials, (ii) supported by biological basis but limited or no controlled trial evidence, and (iii) weak to moderate biological basis. See also [Figure S3](#) under online Appendix for the potential roles of these measures under secondary and tertiary prevention of CKD.

* See [Table 2](#) for additional lifestyle strategies including reduced salt intake, weight reduction and smoking cessation.

Interventions	Advantages and rationale	Disadvantages	Additional comments
Diet and lifestyle*			
Plant-dominant low-protein diets (ii)	Patient-centered, inexpensive, improves metabolic parameters, mitigates acidosis. May slow progression and attenuate uremia	Concerns expressed about risk of muscle loss and frailty. Concerns about hyperkalemia with more plant-based diet.	Effect of plant-based diets on patient-level kidney outcomes remains to be definitively demonstrated in randomized trials
Nutrient focused dietary interventions (ii to iii) (Low Na, low PO ₄ , low K)*	Traditional familiarity in clinical practice	Effectiveness of single-nutrient approaches (e.g., strict phosphate control) on patient-level outcomes remains uncertain	Restricted K diet may cause more harm by limiting healthy K-rich fruits and vegetables.
Higher physical activity, weight reduction, smoking cessation (ii to iii)	Numerous clear health benefits (see Table 2)	Can be challenging to achieve sustained goals.	See Table 2 for more details.
Pharmacological agents to slow CKD progression			
Renin-angiotensin system blockade (ACEi/ARBs) (i)	Proven benefit for preventing kidney failure in randomized trials in people with diabetes	Risk of AKI and hyperkalemia	Kidney benefits in non-diabetic kidney disease with proteinuria <0.5g/day uncertain
SGLT2 inhibitors (i)	Clear reductions in patient-level cardiovascular and kidney outcomes in people with type 2 diabetes	Risk of mycotic genital infections, volume depletion, diabetic ketoacidosis, and limb amputation.	Less data for initiation at eGFR <30ml/min/1.73m ² Emerging evidence of benefit in people with nondiabetic kidney disease
Mineralocorticoid receptor antagonists (MRAs) (I to ii)	May slow CKD progression and reduce albuminuria. Potential anti-inflammatory and anti-fibrotic effects	Risk of hyperkalemia.	Studies are needed to compare traditional vs. newer MRAs
Tolvaptan for polycystic kidney disease (i to ii)	Slows decline in GFR	Risk of polydipsia/polyuria and deranged liver function	Data on long-term outcomes data needed
Rituximab for primary membranous nephropathy (i to ii)	Increases likelihood of long-term remission compared to ciclosporin	Little randomized data compared with alkylating agents	Effect of combination therapies less clear
Steroids for IgA nephropathy (ii to iii)	Extensive clinical experience	Mixed results in clinical trials, increased risk of adverse events, especially serious infection	Large trial ongoing
Pharmacologic strategies to reduce cardiovascular risk			

Lipid lowering (ii to iii)	Reduces vascular events in people with CKD, well tolerated	No clear benefit for initiating treatment in people on dialysis	Data on new lipid lowering therapies in CKD limited
Blood pressure lowering (i to ii)	Reduces cardiovascular and may reduce kidney outcomes	Greater risk of adverse events as kidney function declines	Addressing volume overload crucial aspect of blood pressure lowering in advanced CKD
Hypoglycemic agents (ii to iii)	SGLT2- and GLP-1 receptor agonists reduce adverse cardiovascular events in type 2 diabetes	Risk of hypoglycemia and other treatment related adverse events with intensive glucose lowering	Inconsistent benefits for cardiovascular and kidney outcomes with intensive glucose control
Pharmacologic and other strategies to slow progression and manage uremia			
Acidosis management pharmacological strategies (sodium bicarbonate [NaHCO ₃] and veverimer) (ii to iii)	NaHCO ₃ improves acidosis, may slow progression of CKD	Effect on long-term outcomes uncertain. NaHCO ₃ administration may worsen sodium and fluid retention	Veverimer may improve acidosis without causing sodium retention. Randomized trials ongoing
Potassium binders (Sodium polystyrene, zirconium and patiromer) (i to ii)	Reduces risk of hyperkalemia, enables use of ACE inhibitors and ARBs	No data on patient-level outcomes or progression of kidney disease	Randomized trials ongoing
Sodium and volume management (Sodium restriction, loop and thiazide diuretics) (ii to iii)	Well established clinical experience	Effect on CKD progression uncertain	Limited randomized data
Symptom management e.g. for pruritus, pain, fatigue, sleep disorders, etc. (ii to iii)	Important priority for patients with more unpleasant symptoms	Unlikely to affect risk of CKD progression or less likely on need for dialysis	Limited randomized data
AKI prevention of and infections (ii to iii)	AKI may increase future risk of CKD	Impact of sick day advice uncertain,	Some drug combinations, e.g. ACEi and ARB increase risk of AKI
Infection prevention e.g. hepatitis C and COVID-19 (ii to iii)	Many infectious events may cause AKI and/or CKD	Direct kidney involvement not certain such as in COVID-19.	Impact of infection prevention strategies not clear

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; DPP-4i: dipeptidyl peptidase-4 inhibitors, eGFR, estimated glomerular filtration rate; GLP-1r: glucagon-like peptide-1 receptor agonists, FSGS: focal segmental glomerulosclerosis, IgA: immunoglobulin A, K: potassium, MBD: mineral and bone disorder, Na: Sodium, P: phosphorus, PKD: polycystic kidney disease, SGLT2i: sodium glucose cotransporter 2 inhibitors, UTI: urinary tract infection,

Table 2. Lifestyle modification strategies for slowing the progression of kidney disease and preventing cardiovascular outcomes. See also supplemental [Figure S2](#) for schematic depictions of these strategies over the course of CKD progression.

Strategies	Effect on kidney disease progression	Effect on cardiovascular disease and mortality	Comments	Recommendations
Physical Activity	Higher physical activity is associated with slower decline in kidney function in people with CKD ²¹⁸	Higher physical activity is associated with lower risk of cardiovascular and mortality outcomes ^{219,220}	Evidence on physical activity and progression of kidney disease and cardiovascular outcomes is largely based on observational studies. Small trials of physical activity show improvements in kidney function and blood pressure in people with CKD not on dialysis. ²²¹ Small trials in patients receiving dialysis demonstrate improvements in physical function and health-related quality of life. ²²²	For patients with CKD, target 150 minute/week of moderate-intensity physical activity. Exercise should be individualized for patients according to co-morbidities and functional status. Mixed data in dialysis dependent patients, unknown benefit of intra-dialytic exercise.
Smoking cessation	Current and former smoking associated greater risk of incident CKD ²²³	Smoking is associated with increased risk of all-cause mortality including from vascular and nonvascular (cancer) etiologies in people with CKD ²²⁴	Smoking cessation should be prioritized in all individuals based on numerous recognized health benefits	Smoking cessation for all patients with behavioral counselling and pharmacologic therapies as required and appropriate dosing adjustment for patients with CKD
Dietary sodium restriction	Sodium restriction lowers albuminuria and improves fluid status in people with and without CKD ^{225,226}	Sodium restriction lowers blood pressure and improves arterial stiffness in people with and without CKD ^{225,227}	People with CKD are more likely to have ‘salt-sensitive’ hypertension ²²⁸	Limit sodium intake to < 2.3g/day (<100 mmol) according to American Heart Association
Higher plant-based proportion of protein intake	Higher plant-based sources of protein and dietary fibers may improve acidosis, mitigate inflammation, lower phosphorus burden, and slow progression of CKD and create less uremic toxins. ⁵²	Higher red meat intake may be associated with atherosclerosis by higher carnitine generation via microbiota. ²²⁹	Lowering dietary protein intake may increase risk of muscle mass loss and frailty. Protein intake recommendations vary depending on CKD stage, AKI events and need for dialysis ⁷⁰	Higher intake of complex carbohydrates and fresh-fruits and vegetables is recommended as opposed to processed carbohydrates.
Weight reduction	Improves cardiometabolic health. May slow decline in kidney function and improve albuminuria	Improves blood pressure ²³⁰	Limited randomized evidence to guide the dietetic management of overweight and obese individuals with CKD	Multidisciplinary approach to weight loss in overweight and obese individuals with CKD with involvement of a kidney dietitian ²³¹ Mixed data in dialysis patients related to obesity paradox. ⁸⁹

Table 3. Similarities and distinctions between kidney preserving care, also known as preservative management of kidney disease, and supportive care including palliative care and hospice medicine. See also [Figure 1](#) for schematic representations of the domains within the CKD management chart.

	Kidney Preserving Care	Supportive Care*	Comments
Slowing CKD progression	+++	+ / ++	Important goal across both domains of care but not the primary goal of supportive care
Preventing or delaying dialysis	+++	+++	Both domains aim to prevent or delay initiation of dialysis
Symptom management	+ / ++	+++	Addressing symptoms is one of the key priorities of supportive care but should also have an important role under preservative management
Health related quality of life and patient reported outcomes	++ / +++	+++	Each domain aims to improve quality of life through different approaches. Kidney preserving care prioritizes aggressive treatments to restore/protect health and quality of life, whereas supportive care places greater focus maintaining quality of life by minimizing invasive interventions
Prioritizing overall survival with life- and kidney-prolonging care	+++	- / +	Preventing complications, addressing comorbidities and prolonging survival is among the highest priorities with kidney preserving care, while alleviating symptoms is prioritized over prolonging survival with supportive care
Cardiovascular health	+++	- / +	Reducing cardiovascular risk is a fundamental aspect of kidney preserving care, and less a priority with supportive care
Minimizing risk of AKI and infection	+++	+ / ++	Minimizing risk of AKI is an important aspect of both domains
Diet and lifestyle modifications	+++	+	Dietary strategies such as plant-dominant low-protein diet are an important component of kidney preserving care, whereas dietary approaches can be more flexible with supportive care focusing on quality of life and comfort care
CKD pharmacotherapy	+++	+	Targeted and non-targeted pharmacotherapies aimed and preserving kidney function are less a priority with supportive care, where pharmacotherapy is mostly for symptom management
Treating uremia and complications of CKD	+++	+ / ++	Priorities in the management of CKD related complications are primarily to avoid unpleasant symptoms with supportive care

Preserving residual kidney function after transition to dialysis and less frequent dialysis	+++	+	Kidney preserving care places greater emphasis on protecting residual kidney function such as incremental transition to dialysis, while palliative dialysis can be infrequent as well including decremental dialysis regimens
Shared decision making and advance care planning	+ / +++	+++	This is a fundamental concept in the care of all people with kidney disease which is often more clearly highlighted under supportive care including palliative care and hospice medicine

Supplemental Table S1. Target ranges of dietary protein intake for the management of kidney disease

Dietary Protein Intake Range	Daily grams of protein intake per kg body weight (g/kg/day)*	Comment
Lower protein diet	0.55-0.6	Recommended by KDOQI 2020 guidelines* for CKD patients without diabetes.
Low-protein diet	0.6-0.8 g/kg/day	More consistently recommended for moderate to advanced CKD (eGFR<45 ml/min/1.73m ² or substantial proteinuria) regardless of etiology. This range is also recommended by KDOQI 2020 guidelines* for CKD patients with diabetes, as well as for PLADO meal plans with >50% plant source of the protein**
Moderately low-protein intake	0.8-1.0 g/kg/day	Recommended for adults without CKD but at high risk of CKD including those with a solitary kidney, diabetes mellitus, hypertension, and polycystic kidneys.
Moderate protein intake	1-1.2 g/kg/day	Recommended for metabolically stable patients on maintenance dialysis.
Moderately high-protein diet	1.2-1.5 g/kg/day	Represents the average protein intake of non-vegan adults without CKD in many regions of the world.

*Kidney Disease Outcome Quality Initiatives (KDOQI) clinical practice guidelines in nutrition in kidney disease 2020²³²

**Protein-dominant low protein (PLADO) diet consists of 0.6-0.8 g/kg/day of protein with at least 50% from plant-based sources²³²

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDOQI: Kidney Disease Outcome Quality Initiative; PLADO: plant-dominant low-protein diet.

Supplemental Table S2. Pharmacologic strategies for slowing the progression of kidney disease and preventing cardiovascular outcomes

Strategies	Effect on kidney disease Progression	Effect on Prevention of CVD Events and/or Mortality	Comments	Recommendations
Blood lowering and BP targets	No clear benefit of BP lowering on risk of kidney failure overall, ^{233,234} although benefits may be present in those with albuminuria ²³⁵	Intensive BP lowering (<120 mm Hg) reduces cardiovascular events and mortality in people without diabetes, with consistent benefits in people with and without CKD. ²³⁶ Mortality benefits are likely to be similar in people diabetic and non-diabetic kidney disease. ²³⁷	Measure BP using standardized office technique with multiple consecutive readings using automated oscillometric BP devices ²³⁸ Ambulatory BP monitoring is considered the reference standard for out-of-office BP assessment, with home BP monitoring being an acceptable alternative. ²³⁸	For patients with CKD, consider a systolic BP of <120 mmHg based on standardized office BP measurement. Individualization of BP target is critically important and needs holistic consideration of functional status, comorbidities, frailty and patient preferences.
Renin-angiotensin system blockade	Reduce the risk of progression to kidney failure in people with diabetic and non-diabetic kidney disease with clearest benefit in people with substantial albuminuria (UACR>300mg/g). ^{118,239}	Reduces cardiovascular outcomes in people with CKD. ²⁴⁰	Can cause an acute rise in serum creatinine due to their effect on intraglomerular pressure, however the benefits of treatment are not modified by acute changes in serum creatinine. ²⁴¹	Treatment should be prioritized in all patients with diabetes and albuminuria (>30mg/g) and in those with non-diabetic kidney disease and high levels of albuminuria (>300 mg/g). Treatment with combination of ACEI and ARB is not recommended due to the high risk of hyperkalemia and acute kidney injury.
Lipid lowering	Likely neutral effect on kidney disease progression. ²⁴²	Combination of simvastatin and ezetimibe significantly reduces risk of major vascular events in people with CKD. ²⁴³ Icosapent ethyl and PCSK9 inhibitors can reduce the risk of cardiovascular outcomes in people atherosclerotic cardiovascular disease, although these trials enrolled relatively few people with CKD. ²⁴⁴⁻²⁴⁶	The benefit of lipid lowering attenuates with decline kidney function. ²⁴⁷ The smaller relative benefit of statins at lower eGFR maybe due to a lower proportion of atherosclerotic compared to non-atherosclerotic cardiovascular events.	Statins alone or in combination with CKD should be initiated in most adult patients with CKD not on dialysis. Icosapent ethyl or PCSK9 could be considered in very high-risk patients such as those with persistently elevated LDL or triglyceride levels.
Glucose lowering	Intensive glucose control reduces progression of kidney disease ²⁴⁸	Uncertainty with regards to effects on macrovascular outcomes with no clear effect on mortality. ²⁴⁹	Clear differences between different glucose lowering agents and their effect on clinical outcomes	Individualization of glycemic targets based on goals of care, comorbidities and patient preferences is key, with more frail patients having more lenient targets to avoid hypoglycemia.

SGLT2 inhibitors	Reduces the risk of kidney failure in people with type 2 diabetes. ²⁵⁰	Reduces the risk of a range of cardiovascular outcomes, particularly heart failure and cardiovascular death as well as all-cause mortality	Emerging evidence of heart and kidney failure benefits irrespective of the presence of diabetes. Limited evidence for initiation at eGFR <30mL/min/1.73m ²	Recommended in people with severely increased albuminuria (UACR >300mg/g) irrespective of the presence of diabetes to reduce the risk of kidney failure, cardiovascular events, or both
GLP-1 receptor agonists	Reduces the risk of albuminuria based composite kidney outcomes, but effects on patient-level kidney outcomes uncertain	Reduces cardiovascular events with similar relative benefit across different levels of kidney function	Heterogeneity of relative benefit observed across different agents within the class	
Antiplatelet therapy	No effect on kidney disease progression	Antiplatelet therapy (mostly aspirin) can reduce myocardial infarction	Antiplatelet therapy increases the risk of major bleeding	Decision to use antiplatelets for primary cardiovascular prevention in CKD needs to take into account the individual's cardiovascular risk as well as bleeding risk, and preferences

FIGURES

Figure 1. Chronic kidney disease (CKD) management chart.

Figure 2. Effects of dietary protein intake and pharmacological therapies on afferent and efferent arteriolar tone, intra-glomerular pressure and glomerular structures and functions.

Figure 3. Association of estimated glomerular filtration rate (based on creatinine based eGFR along with a Cystatin-C based eGFR for comparison) and albuminuria with risk of cardiovascular outcomes, after adjustment for traditional cardiovascular risk factors

Additional Supplemental Figures under Online Appendix

Supplement Figure S1. KDIGO classification of chronic kidney disease (CKD)

Supplement Figure S2: Primary, secondary and tertiary prevention of chronic kidney disease.

Supplement Figure S4. Comparing acute and chronic GFR effects of dietary protein restriction versus kidney protective drugs.

Supplement Figure S1. Combined pharmacological and non-pharmacological approaches to the management of CKD across all levels of kidney function.

Supplement Figure S5. The conceptual framework of the challenges of CVD management in CKD

Figure 1. Chronic kidney disease (CKD) management chart. This chart highlights the role of “preservative management” and its goals (green domain) within the overall “conservative management” of CKD without dialysis (grey zone), juxtaposing the “renal (kidney) replacement therapy” including dialysis and kidney transplantation (yellow zone). On the X axis, the direction is inherently left to right given CKD progression, while on the Y axis, the patient and his/her care-partner(s) as well as providers can move in different directions as they choose based on the goals of care. The lower area of the chart represents conventional or life-prolonging strategies, whereas the in the upper area, supportive care prevails including the “palliative and hospice care” where dialysis is often avoided or withdrawn (red domain). The obliquely run dotted line between the two main zones suggests that there is variability in transitioning to kidney replacement therapy as moving from lower left to upper right including timing (early vs. late vs. never), level of care (life prolonging vs. supportive care), and modality (conventional vs. incremental). The symptom management (blue domain) provides wide ranges of interventions to encompass the goals of care under both the preservative management and palliative and hospice care and can continue after the patient transitions to kidney replacement therapy. The preservative management can continue to preserve the residual kidney function longer especially upon incremental transition to dialysis. See also [Table 3](#) for additional comparisons between preservative and supportive care and supplemental Figure S2 under online appendix for overview of these strategies over the course of CKD progression. (asterisk * under uremia management represents pharmacotherapies for the management of acidosis, anemia and bone disease).

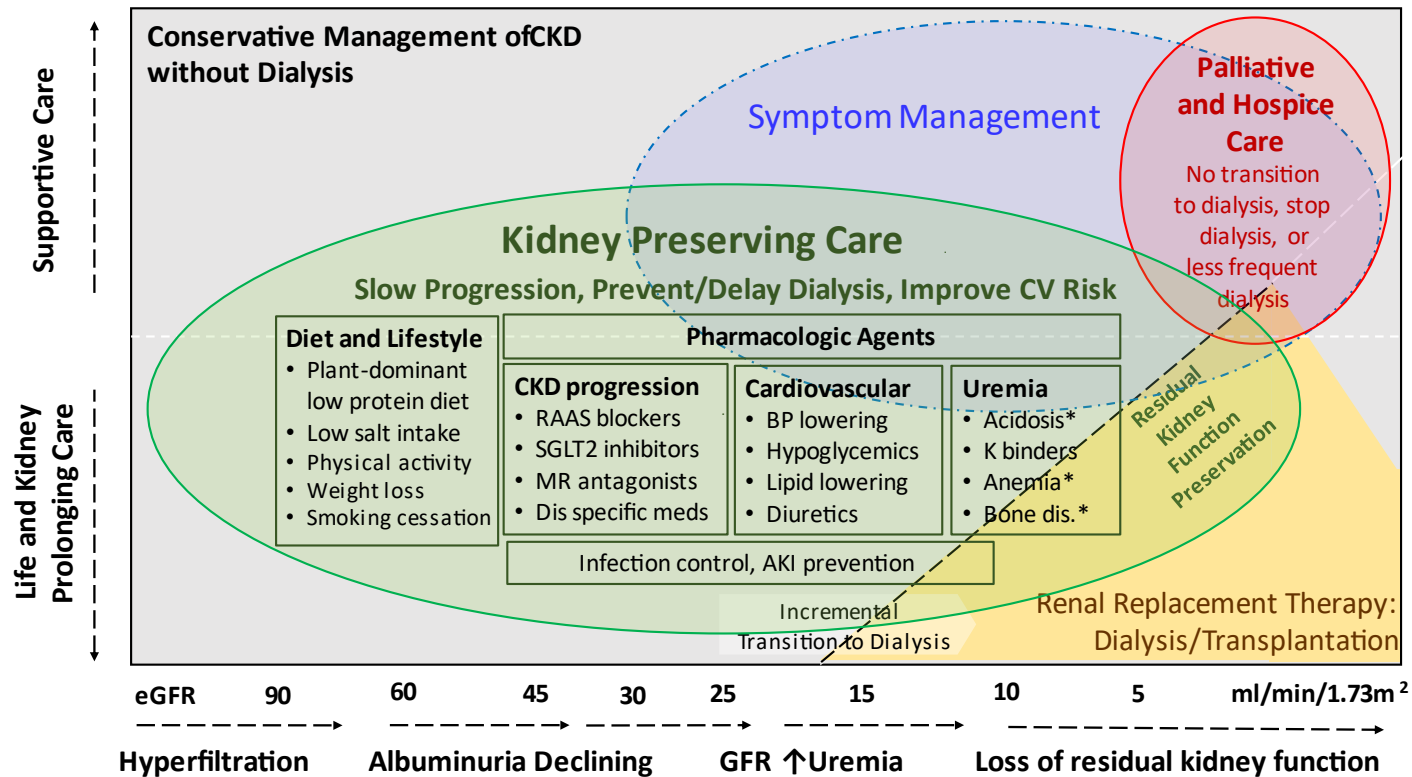


Figure 2. Effects of lower dietary sodium and protein intake with higher proportion of plant-based protein sources and pharmacological therapies on afferent and efferent arteriolar tone and intra-glomerular pressure as well as tubuloglomerular feedback and interstitial fibrosis. Dietary protein restriction results in contraction of the afferent arterioles leading to reduced intra-glomerular pressure. This can lead to less damage to glomerular structure and function in long-term. The kidney protective effects of plant-dominant low protein diet acts in parallel and may be complementary to the effect of SGLT2 inhibitors, renin-angiotensin system blockade, mineralocorticoid receptor antagonism, and other blood pressure lowering agents, thereby more effectively reducing intraglomerular pressure and mitigating interstitial fibrosis.

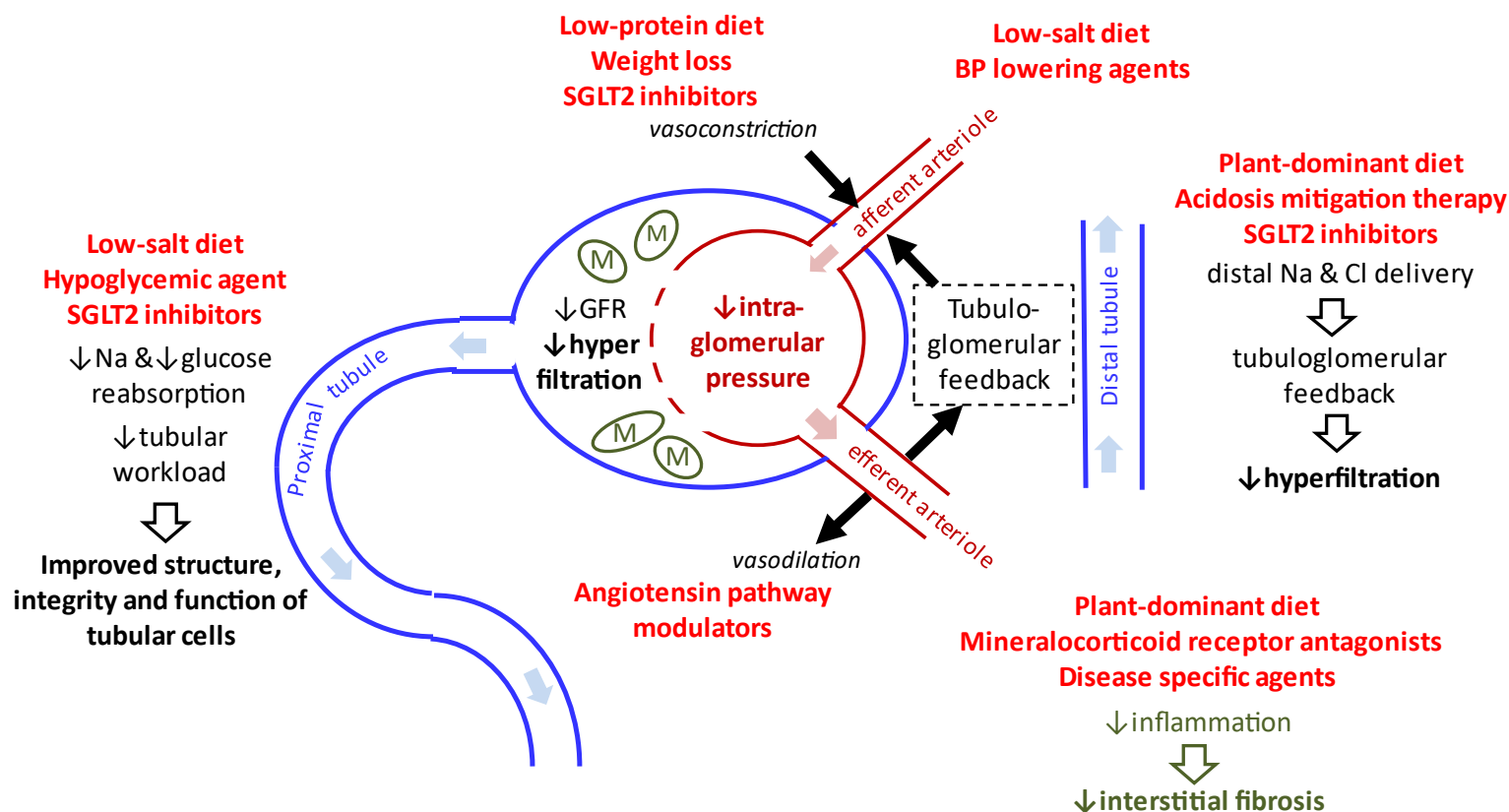
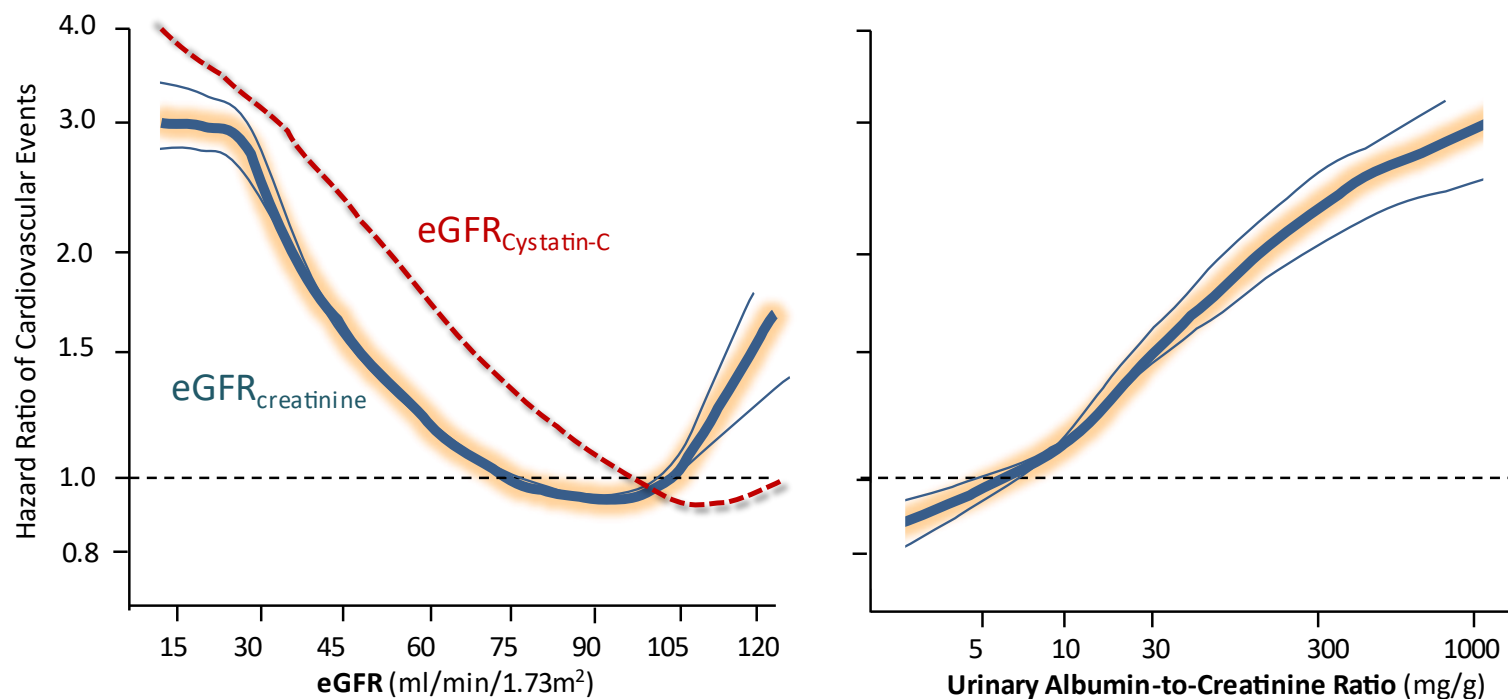


Figure 3. Association of estimated glomerular filtration (eGFR) rate and albuminuria with risk of cardiovascular outcomes, after adjustment for traditional cardiovascular risk factors. Data are from the CKD Prognosis Consortium of 637,315 individuals from 24 cohorts i.e., general population, high risk, and established CKD, followed up for a mean of 8,9 years during which time 10,605 cardiovascular deaths, 6,283 coronary heart disease events, 180 stroke events, and 2,066 heart failure events occurred. Cystatin C eGFR data are from meta-analysis of 10 general-population cohorts with 64,010 participants, of whom 3193 died from cardiovascular causes during follow-up (recreated with modification based on figures in Matsushita et al, *Lancet Diab Endo* 2015⁴² and Shlipak et al, *N Engl J Med* 2013¹⁵⁴)



Online Appendix

Supplemental Figures S1-S5

Title:

Preservative Management of Chronic Kidney Disease to Prevent Kidney Failure

Authors:

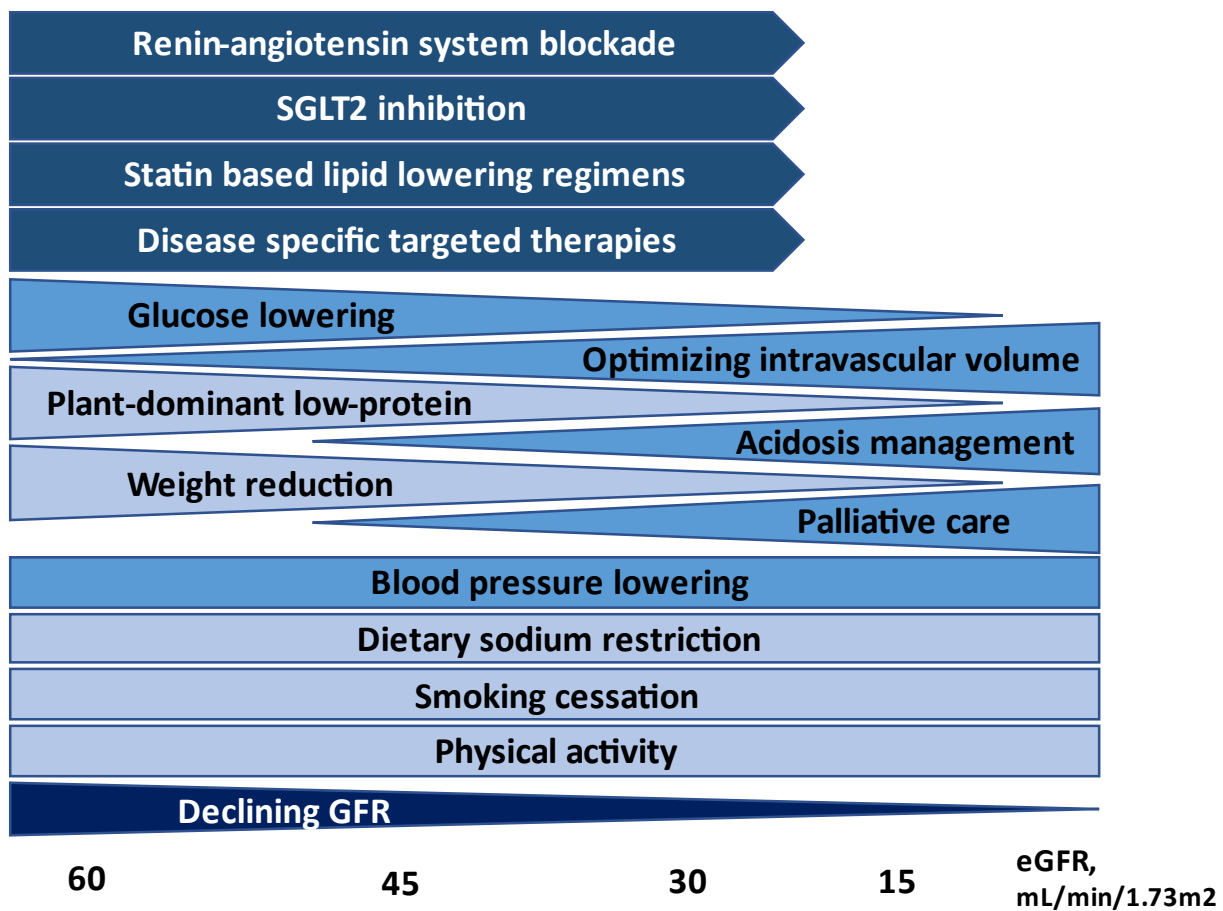
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Supplemental Figure S1. KDIGO classification of chronic kidney disease (CKD). Adapted from the 2012 KDIGO classification of CKD. The colors reflect the ranking of absolute risk of kidney failure: low (green), moderate (yellow), high (orange), and very high (red). Numbers in each cell represent the adjusted relative risk (RR) of kidney failure for the general population assessing albuminuria using either UACR or urine dipstick.(recreated with modification from Gansevoort et al, Kidney Int 2011.²⁵⁷)

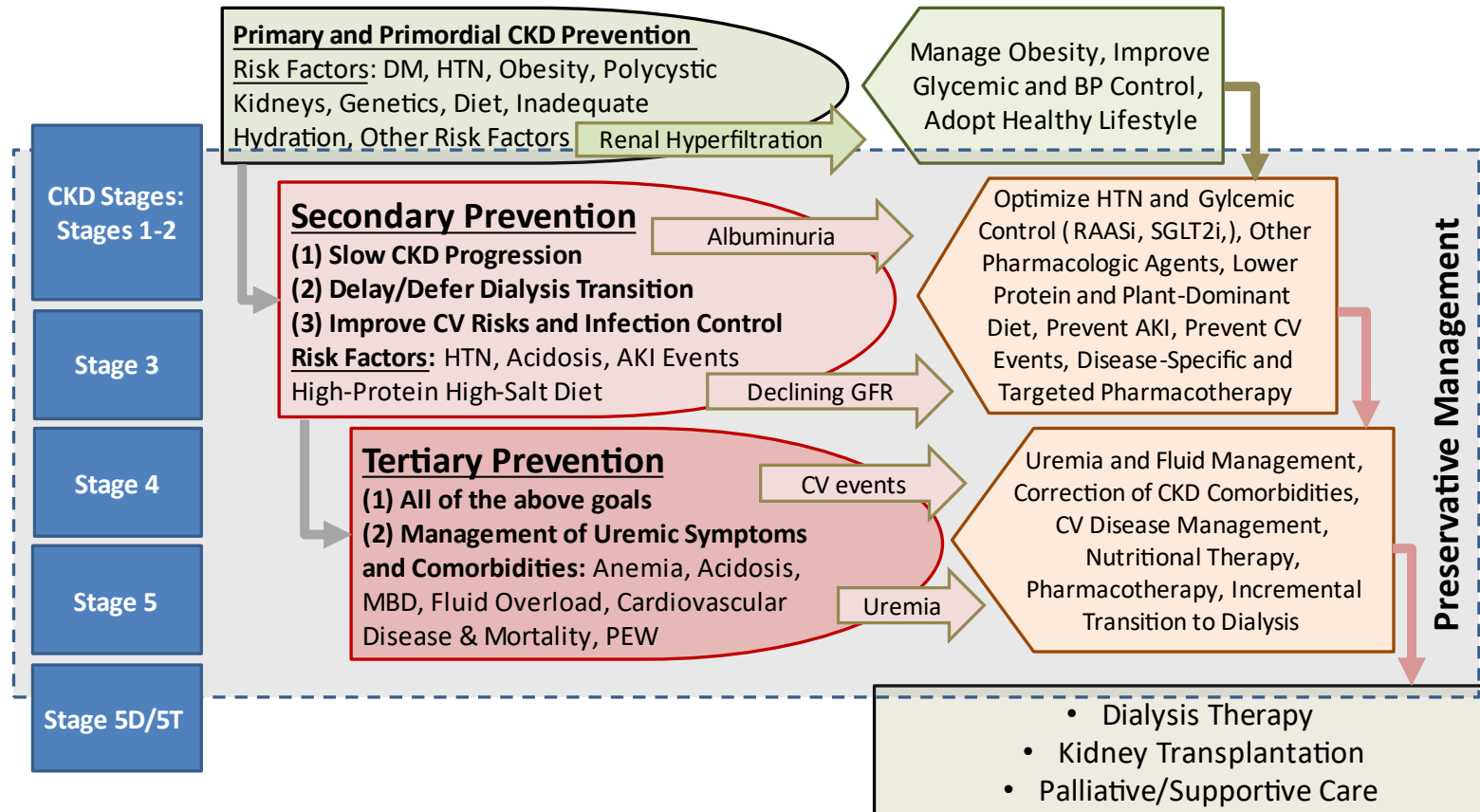
KDIGO: Kidney Disease Improving Global Outcomes; eGFR: estimated glomerular filtration rate; UACR: urinary albumin/creatinine ratio; ESKD: end-stage kidney disease.

		UACR (mg/g)				
		A1		A2	A4	
		<30		30-300	>300	
Grade	Range	<10	10-29			
eGFR (mL/min/1.73m ²)	G1	≥90	Reference		8	18
	G2	60-89	Reference		11	20
	G3a	45-59	5	22	40	147
	G3b	30-44	56	74	294	763
	G4	15-29	433	1,044	1,056	2,286
	G5	<15	Kidney failure			

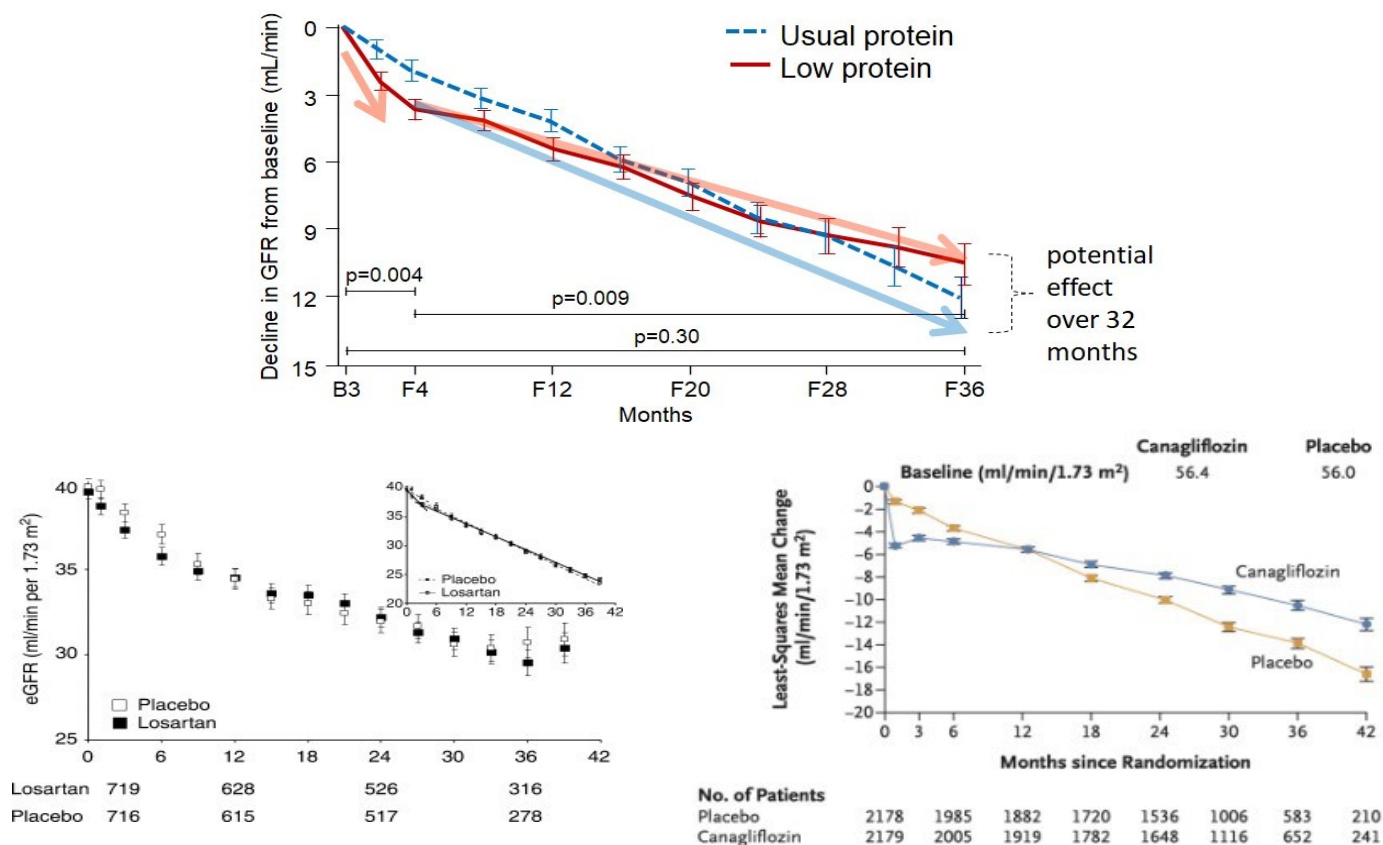
Supplement Figure S2. Combined pharmacological and non-pharmacological approaches to the management of CKD across all levels of kidney function.



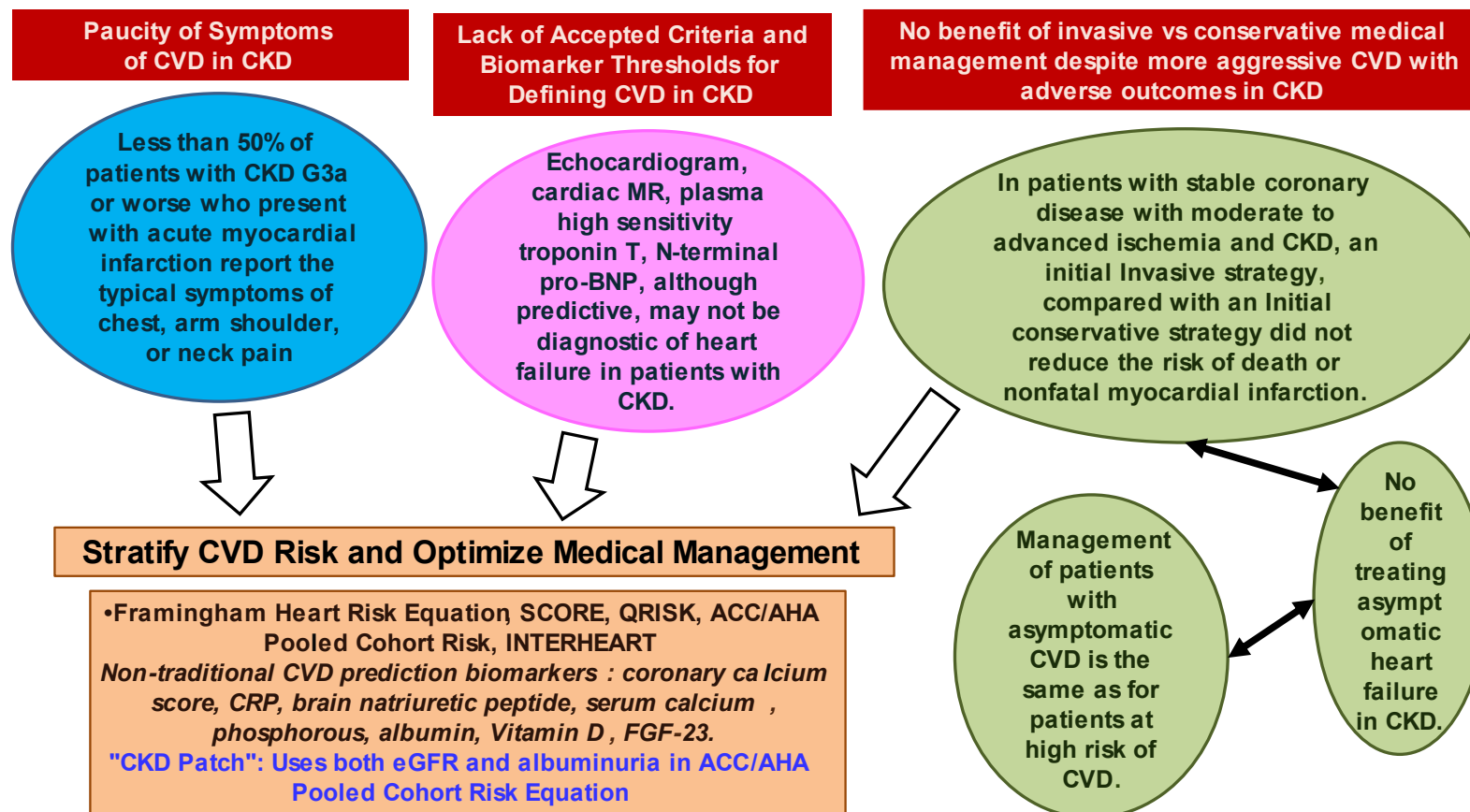
Supplement Figure S3: Primary, secondary and tertiary prevention of chronic kidney disease. Highlighting similarities and distinctions pertaining to primary, secondary, and tertiary preventive measures and their intended goals. The “preservative management” of CKD is consistent with the secondary and tertiary prevention goals and approaches (recreated with modifications from Li et al, *Kidney Int* 2020).³⁴ See also [Tables 2, 3 and 4](#) for detailed strategies.



Supplement Figure S4. Acute and chronic GFR effects of dietary protein restriction and kidney protective drugs. Many interventions that are kidney protective have short-term effects on GFR that differ from their long-term effects. Dietary protein restriction, renin angiotensin system blockade and SGLT2 inhibition all lower intraglomerular pressure, which is reflected clinically by an acute reduction in GFR followed by long-term preservation of GFR. This is demonstrated in the panels below: (Upper Panel) Dietary protein restriction in the MDRD trial, (Right Lower Panel) SGLT2 inhibition with canagliflozin in the CREDENCE trial and (Left Lower Panel) RAS blockade with losartan in the RENAAL trial.



Supplement Figure 5. The conceptual framework of the challenges of CVD management in CKD



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