

Chronic kidney disease

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Chronic kidney disease is a progressive disease with no cure and high morbidity and mortality that occurs commonly in the general adult population, especially in people with diabetes and hypertension. Preservation of kidney function can improve outcomes and can be achieved through non-pharmacological strategies (eg, dietary and lifestyle adjustments) and chronic kidney disease-targeted and kidney disease-specific pharmacological interventions. A plant-dominant, low-protein, and low-salt diet might help to mitigate glomerular hyperfiltration and preserve renal function for longer, possibly while also leading to favourable alterations in acid-base homeostasis and in the gut microbiome. Pharmacotherapies that alter intrarenal haemodynamics (eg, renin–angiotensin–aldosterone pathway modulators and SGLT2 [SLC5A2] inhibitors) can preserve kidney function by reducing intraglomerular pressure independently of blood pressure and glucose control, whereas other novel agents (eg, non-steroidal mineralocorticoid receptor antagonists) might protect the kidney through anti-inflammatory or antifibrotic mechanisms. Some glomerular and cystic kidney diseases might benefit from disease-specific therapies. Managing chronic kidney disease-associated cardiovascular risk, minimising the risk of infection, and preventing acute kidney injury are crucial interventions for these patients, given the high burden of complications, associated morbidity and mortality, and the role of non-conventional risk factors in chronic kidney disease. When renal replacement therapy becomes inevitable, an incremental transition to dialysis can be considered and has been proposed to possibly preserve residual kidney function longer. There are similarities and distinctions between kidney-preserving care and supportive care. Additional studies of dietary and pharmacological interventions and development of innovative strategies are necessary to ensure optimal kidney-preserving care and to achieve greater longevity and better health-related quality of life for these patients.

Introduction

Chronic kidney disease is a progressive condition characterised by structural and functional changes to the kidney due to various causes. Chronic kidney disease is typically defined as a reduction in kidney function, an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m², or markers of kidney damage, such as albuminuria, haematuria, or abnormalities detected through laboratory testing or imaging and that are present for at least 3 months (appendix p 5).¹ The global burden of chronic kidney disease is substantial and growing: approximately 10% of adults worldwide are affected by some form of chronic kidney disease, which results in 1.2 million deaths and 28.0 million years of life lost each year.^{2,3} By 2040, chronic kidney disease is estimated to 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 of chronic kidney disease varies considerably by region. There are many causes of chronic kidney disease, including those that are common and well researched, such as diabetes, glomerulonephritis, and cystic kidney diseases, but causation in chronic kidney disease is not yet fully understood. For instance, despite a close association between chronic kidney disease and hypertension, whether hypertension is a cause or a consequence of chronic kidney disease is controversial.⁵ As another example, chronic kidney disease of unknown aetiology and for which there is no known treatment is found in some agricultural communities in south Asia and central America; recurrent volume depletion has been speculated to be a cause, especially with the increasing frequency of climate change-related heat waves.⁶ This possible cause of chronic kidney disease

of unknown aetiology highlights the potential role of adequate hydration as a kidney-preserving strategy. The global burden of chronic kidney disease has also been attributed to air pollution, and is disproportionately borne by some world regions.⁷ Chronic kidney disease severity also varies from kidney damage with normal function to kidney failure (or end-stage renal disease), which typically occurs when eGFR decreases to less than 15 mL/min per 1.73 m². In general, the prevalence of chronic kidney disease increases with age and, in high-income countries, is more common in people with obesity, diabetes, and hypertension.^{8,9}

Chronic kidney disease is usually insidious, and most affected individuals are asymptomatic until the disease becomes advanced (ie, eGFR of less than 30 mL/min per 1.73 m²). The rate of loss of kidney function varies by aetiology, exposures, and interventions but, in most cases,

Search strategy and selection criteria

We reviewed biomedical literature to identify all studies in which the effects of diet and lifestyle modifications and pharmacotherapeutic interventions were examined for conservative or preservative management of chronic kidney disease. Both the PubMed and Google Scholar databases were searched for studies published in English or with an English abstract between Jan 1, 1970, and Feb 1, 2021, using the terms “chronic kidney disease”, “kidney-preserving therapy”, “conservative management”, “diet”, “lifestyle modifications”, “pharmacological strategies”, and “renal hyperfiltration”. Full-text articles deemed pertinent were selected and the reference lists of the identified reports and articles were searched for further material.

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See Online for appendix

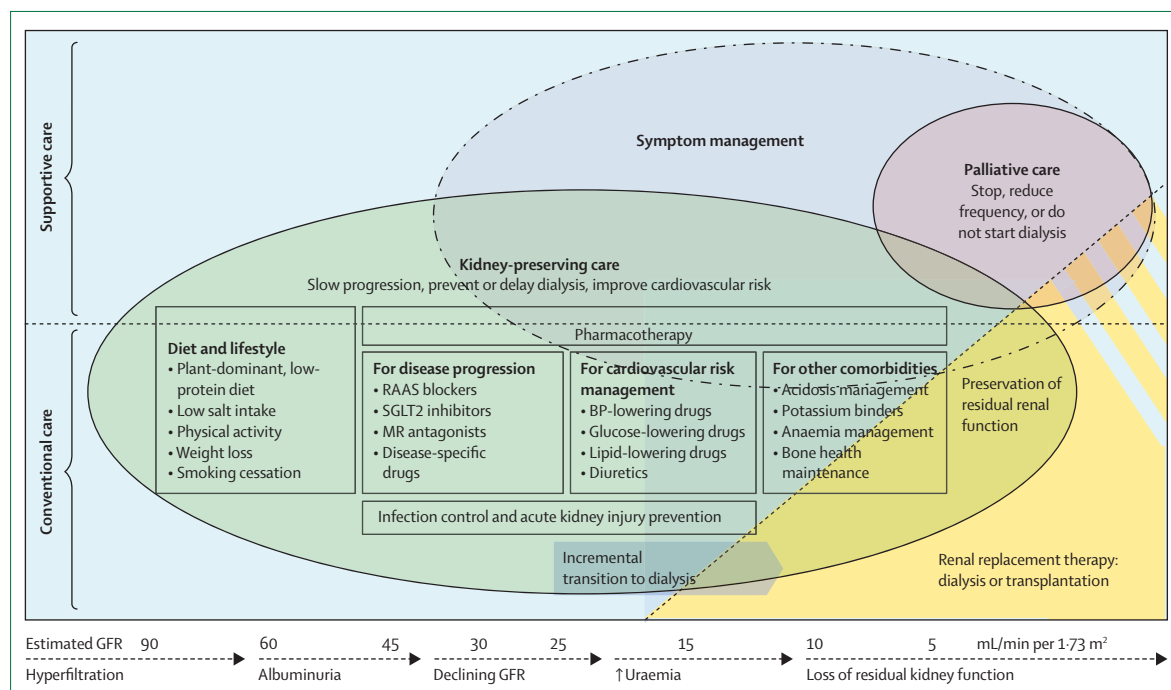


Figure 1: Conservative and preservative management of chronic kidney disease without dialysis or renal transplantation

This chart highlights the role of preservative management and its goals (green domain) within the overall conservative management of chronic kidney disease without dialysis (blue zone), juxtaposing renal replacement therapy including dialysis and kidney transplantation (yellow zone). The X axis (showing chronic kidney disease progression) should be read exclusively from left to right. The bottom half of the chart represents conventional (life-prolonging and kidney-prolonging) strategies, whereas the top half represents supportive care, including palliative and hospice care, in which dialysis is often avoided or withdrawn (violet domain).¹⁷ The oblique dotted line between the two main zones (conservative management vs renal replacement therapy) suggests that there is variability in transitioning to dialysis therapy (moving from bottom left to top right), including timing (early vs late vs never), level of care (life-prolonging vs supportive care), and type of dialysis (conventional vs incremental). The symptom management (purple) domain provides wide ranges of interventions to encompass the goals of care under both kidney preserving care and palliative and hospice care. Preservative management can preserve residual kidney function for longer, especially after incremental transition to dialysis. See appendix p 6 for an overview of these strategies over the course of chronic kidney disease progression. BP=blood pressure. GFR=glomerular filtration rate. MR=mineralocorticoid receptor. RAAS=renin-angiotensin-aldosterone system.

progression to kidney failure typically takes between months and decades to develop. Signs and symptoms of kidney failure result from progressive uraemia, anaemia, volume overload, electrolyte abnormalities, mineral and bone disorders, and acidaemia, and inevitably lead to death if left untreated.¹⁰

Renal replacement therapy, either in the form of chronic dialysis or kidney transplantation, is a life-sustaining treatment for people with kidney failure. Because of the shortage of kidney donors and of the comorbidities that develop with age and often preclude kidney transplantation,^{11,12} dialysis remains the prevailing treatment option for most people with kidney failure.¹³ Kidney failure requiring dialysis is often associated with substantially reduced quality of life and high mortality rates,¹⁴ especially in the first year after transition to dialysis,¹⁵ underscoring the importance of preserving kidney function in people with, or at high risk of, chronic kidney disease.

Approaches to preserving kidney function

There has been growing recognition that conservative management without dialysis is a viable, patient-centred

treatment option for a substantial proportion of patients with chronic kidney disease.¹⁶ Within conservative management strategies, there are several overlapping intervention domains, with similarities and differences, that can be offered to patients with chronic kidney disease (figure 1).¹⁷ Kidney-preserving care is a life-sustaining conservative management therapy with the primary goal of slowing chronic kidney disease progression and preserving kidney function to avoid dialysis for as long as possible or, ideally, altogether. This approach strives to achieve the greatest possible survival, improved cardiovascular health, and superior health-related quality of life through effective treatment of renal and non-renal comorbidities and their associated symptoms.^{18,19}

Given that conservative management is defined as chronic kidney disease care without dialysis or kidney transplantation,²⁰ misconceptions of dialysis-free management as so-called no care, or misguided conflation with hospice care might have contributed to an underuse of the full spectrum of kidney-preserving management.^{12,18} Notwithstanding heterogeneity in definitions, provision of (or access to) care, and patient demographics or socioeconomic status across different domains of the

	Advantages and rationale	Disadvantages	Additional comments
Diet and lifestyle			
Plant-dominant, low-protein diets*	Patient-centred, inexpensive, improves metabolic markers, and mitigates acidosis; might slow disease progression and attenuate uraemia	Risk of muscle loss and frailty; risk of diet-induced hyperkalaemia	Effects on patient-level kidney outcomes not yet confirmed in randomised controlled trials
Nutrient-focused dietary interventions (low sodium, low phosphate, and low potassium)*†	Experience in clinical practice	Uncertain effectiveness of single-nutrient approaches (eg, strict phosphate control) on patient-level outcomes	Potassium-restricted diets might cause more harm than no intervention by limiting intake of potassium-rich, healthy fruits and vegetables
Increasing physical activity, weight reduction, and smoking cessation*†	Numerous clear health benefits	Sustained goals can be challenging to achieve	See table 2 for more details
Pharmacological agents to slow chronic kidney disease progression			
Renin-angiotensin-aldosterone system blockade (ACEi, ARB)‡	Proven benefit in preventing kidney failure in randomised trials in people with diabetes	Risk of AKI and of hyperkalaemia	Uncertain benefits for non-diabetic kidney disease with proteinuria <0.5 g/day
SGLT2 inhibitors‡	Clear reductions in patient-level adverse cardiovascular and renal outcomes in people with type 2 diabetes	Risk of mycotic genital infections, volume depletion, and euglycaemic ketoacidosis; reported increased risk of limb amputation not substantiated	Less data for initiation at eGFR <30 mL/min per 1.73 m ² ; emerging evidence of benefit in people with non-diabetic kidney disease
Non-steroidal mineralocorticoid receptor antagonists†‡	Reduction in adverse cardiovascular and renal outcomes in people with type 2 diabetes; potential anti-inflammatory and antifibrotic effects	Risk of hyperkalaemia	Uncertain effects of steroidal mineralocorticoid receptor antagonists (eg, spironolactone) on patient-level kidney outcomes; non-steroidal mineralocorticoid receptor antagonists have not yet been evaluated in non-diabetic kidney disease
Tolvaptan for polycystic kidney disease*†	Slowed decline in glomerular filtration rate	Risk of polydipsia or polyuria and deranged liver function	Tolvaptan might delay the predicted onset of kidney failure
Rituximab for primary membranous nephropathy*†	Increased likelihood of long-term remission compared with ciclosporin	Little data from randomised controlled trials directly comparing with alkylating agents	Effect of combination therapies to be determined
Steroids for IgA nephropathy*†	Experience in clinical practice	Mixed results in clinical trials; increased risk of adverse events, especially serious infection	Additional trial ongoing (NCT01560052)
Pharmacological strategies to reduce cardiovascular risk			
Lipid-lowering treatments‡	Reduction in adverse cardiovascular events in people with chronic kidney disease; well tolerated	No clear benefit for initiating treatment in people requiring dialysis	Few data on new lipid-lowering therapies in chronic kidney disease
Blood pressure-lowering treatments‡	Reduction in adverse cardiovascular and potentially renal outcomes	Possibly greater risk of adverse events as kidney function declines	Addressing volume overload is a crucial aspect of blood pressure-lowering in advanced chronic kidney disease
Glucose-lowering drugs‡	SGLT2 inhibitors and GLP-1 receptor agonists reduce adverse cardiovascular events in people with type 2 diabetes	Risk of hypoglycaemia and other treatment-related adverse events with intensive glucose reduction	Inconsistent benefits for cardiovascular and kidney outcomes with intensive glucose control; cardiovascular and renal benefits vary with class of glucose-lowering drug
Pharmacological and other strategies to slow progression and manage uraemia and associated symptoms			
Sodium bicarbonate and veverimer for acidosis management*†	Sodium bicarbonate improves acidosis, might slow progression of chronic kidney disease	Effect on long-term outcomes uncertain; sodium bicarbonate might worsen sodium and fluid retention	Veverimer might improve acidosis without causing sodium retention; randomised trial ongoing (NCT03710291)
Potassium binders (sodium polystyrene, zirconium, and patiomer)*†	Reduced risk of hyperkalaemia; enables use of ACEi and ARB	No data on patient-level outcomes or progression of kidney disease	Randomised trial ongoing (NCT0388066)
Sodium and volume management (sodium restriction, loop diuretics, and thiazide diuretics)*†	Experience in clinical practice	Uncertain effect on chronic kidney disease progression	Few data from randomised controlled trials
Symptom management (eg, for pruritus, pain, fatigue, and sleep disorders)*†	Important priority for patients with unpleasant symptoms	Unlikely to influence need for renal replacement therapy or to affect risk of chronic kidney disease progression	Few data from randomised controlled trials
Prevention of AKI*	AKI might increase future risk of chronic kidney disease	Effect of sick day advice (ie, temporary discontinuation of ACEi or ARBs) on incidence of AKI not yet evaluated in randomised trials	Some drug combinations (eg, ACEi and ARB) increase risk of AKI
Prevention of infection (eg, hepatitis C and COVID-19)*	Many infectious events might cause AKI, chronic kidney disease, or both	Direct kidney involvement unknown	Effect of infection prevention strategies not clear
Footnotes indicate the strength of the evidence for intervention efficacy (two footnotes signify that the evidence ranges between the two levels). For the potential roles of these measures in secondary and tertiary prevention of chronic kidney disease see appendix p 7. ACEi=ACE inhibitors. AKI=acute kidney injury. ARB=angiotensin receptor blockers. eGFR=estimated glomerular filtration rate. *Supported by biological or observational data but little or no evidence from randomised controlled trials. †Some evidence from small randomised trials or trials evaluating effects on surrogate outcomes. ‡Supported by data from large randomised trials assessing effects on patient-level outcomes.			
Table 1: Intervention strategies to preserve kidney function in people with chronic kidney disease			

	Effect on chronic kidney disease progression	Effect on cardiovascular disease and mortality	Comments	Recommendations
Physical activity	Slower decline in kidney function	Lower risk of adverse cardiovascular outcomes and mortality	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 chronic kidney disease not receiving dialysis; small trials in patients receiving dialysis show improvements in physical function and health-related quality of life	Target of 150 min/week of moderate intensity physical activity for patients with chronic kidney disease; exercise should be individualised for patients according to comorbidities and functional status (mixed data in dialysis-dependent patients)
Smoking cessation or avoidance	Smoking is associated with a greater risk of incident chronic kidney disease	Smoking is associated with increased risk of all-cause mortality, including vascular causes and cancer, in people with chronic kidney disease	Smoking cessation should be prioritised in all individuals for numerous recognised health benefits	Smoking cessation for all patients with behavioural counselling and pharmacological therapies as required, with appropriate dose adjustment for patients with chronic kidney disease
Dietary sodium restriction	Reduced albuminuria and improved fluid status in people with and without chronic kidney disease	Reduces blood pressure and improves arterial stiffness in people with and without chronic kidney disease	People with chronic kidney disease are more likely to have salt-sensitive hypertension	Limit sodium intake to a maximum of 2·3 g/day (<100 mmol) according to the American Heart Association
Higher proportion of plant-based protein in diet	Higher proportion of plant-based protein and fibre intake might improve acidosis, mitigate inflammation, reduce phosphorus burden, slow progression of chronic kidney disease, and create less uraemic toxins	Higher red meat intake might be associated with atherosclerosis due to higher carnitine generation via gut microbiota	Reducing dietary protein intake can increase the risk of muscle mass loss and frailty; protein intake recommendations vary depending on chronic kidney disease stage, acute kidney injury, and need for dialysis	Higher intake of complex carbohydrates and fresh fruits and vegetables as opposed to processed carbohydrates
Weight reduction	Improved cardiometabolic health; potentially slower decline in kidney function and improved albuminuria	Improves blood pressure	Little evidence from randomised controlled trials to guide the dietetic management of people with overweight and obesity and chronic kidney disease	Multidisciplinary approach to weight loss in overweight and obese individuals with chronic kidney disease with involvement of a renal dietitian; mixed data in dialysis patients related to the obesity paradox

See also appendix p 6 for schematic depictions of these strategies over the course of chronic kidney disease progression.

Table 2: Lifestyle modification strategies to slow the progression of chronic kidney disease and preventing adverse cardiovascular outcomes

conservative management of chronic kidney disease, the use of conservative management is rising, with a greater focus on kidney-preserving strategies.^{21–33}

The focus of efforts to slow the loss of kidney function varies depending on the severity of chronic kidney disease and underlying causes, encompassing a range of pharmacological and non-pharmacological approaches (figure 1; appendix pp 6–7), given that these measures are consistent with the secondary and tertiary prevention of chronic kidney disease³⁴ (table 1). In patients with chronic kidney disease (as in the general population), lifestyle and dietary modifications (table 2) should be prioritised because these can improve cardiometabolic health and are likely to have favourable long-term effects on the kidney. The focus of care in primary prevention is to achieve optimal control of risk factors for chronic kidney disease by addressing physical inactivity and obesity, smoking, high blood pressure, and high blood glucose.³⁵ Addressing these risk factors is important across the spectrum of kidney function. Although the cost-effectiveness of population-wide screening for chronic kidney disease is controversial, targeted screening of individuals with risk factors (eg, obesity, hypertension, and diabetes) through

regular assessments of eGFR and albuminuria is recommended.³⁶

For individuals with established chronic kidney disease, addressing complications and associated comorbidities and managing symptoms in addition to protecting kidney function are important steps. Slowing the progression of chronic kidney disease 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, and renin–angiotensin–aldosterone system blockade (appendix pp 6–7). For specific aetiologies, such as primary glomerulonephritis and autosomal dominant polycystic kidney disease, newer targeted therapies also have an important role. Because cardiovascular disease is a more common cause of death than kidney failure in patients with chronic kidney disease, reducing cardiovascular risk is a fundamental aspect of care for this population.³⁷

Large-scale, collaborative meta-analyses have shown 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 be used to inform prognosis and direct care priorities for people with chronic kidney disease.³⁸⁻⁴²

The Kidney Disease: Improving Global Outcomes (KDIGO) classification of chronic kidney disease incorporates eGFR and the urine albumin-to-creatinine ratio 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 for chronic kidney disease (appendix p 5).⁴³ Other tools, such as the Kidney Failure Risk Equation⁴⁴ to estimate the risk of kidney failure, and the Dialysis Transition Mortality Prediction Score,⁴⁵ to estimate mortality in the first year of dialysis, can also be used to inform discussion, facilitate specialist referral, and contribute to shared decision making. After progression to advanced chronic kidney disease, when uraemia cannot be controlled without renal replacement therapy, incremental transition to peritoneal or haemodialysis therapy might be a preferred approach with the goal of preserving residual kidney function while reducing the frequency of dialysis, although clinical trials are needed to examine this and other alternative dialysis transition strategies.⁴⁶

Physical activity, obesity, and weight loss

Obesity is the hallmark of metabolic syndrome and associated with chronic kidney disease.⁴⁷ Evidence suggests that increased adiposity measures (eg, body-mass index and waist circumference) are independently associated with a decline in glomerular filtration rate.⁴⁸ This association might result from systemic and intraglomerular hypertension, the effect of prediabetes concentrations of blood glucose on podocyte stress, and other unrecognised factors.^{49,50} Physical activity is the core component of lifestyle modification strategies to manage weight for a positive effect on chronic kidney disease progression.

The Look AHEAD trial,⁵¹ in which 5145 people with obesity and type 2 diabetes were randomly assigned to intensive lifestyle intervention or diabetes support and education, showed that intensive lifestyle intervention reduced weight by an average of 4 kg and resulted in a relative risk reduction of onset of very high-risk chronic kidney disease (according to the KDIGO classification system) of approximately 30% compared with control ($p=0.0016$).

A range of weight loss interventions can be recommended to people with chronic kidney disease. Caloric restriction, in conjunction with a plant-dominant, low-protein diet, can lead to gradual weight loss in most people with obesity and chronic kidney disease.^{52,53} Efforts to identify pharmacological agents that can reduce bodyweight and improve clinical outcomes have yielded few or modest results.⁵⁴ The role of bariatric surgery in mitigating the risk of chronic kidney disease is also uncertain.⁵⁵ Observational studies have suggested that bariatric surgery is associated with a lower risk of patient-

level kidney outcomes.⁵⁶ Gastric bypass surgery increases remission of albuminuria in people with type 2 diabetes, obesity, and microalbuminuria when compared with optimal medical treatment, and might represent an important treatment option for selected individuals.⁵⁷

In more advanced chronic kidney disease, prolonged survival has been paradoxically reported with larger body-mass index, a phenomenon that is known as the obesity paradox or reverse epidemiology.⁵⁸ Conversely, weight loss can contribute to poorer outcomes, whereas effective nutritional interventions to gain weight including muscle mass might improve longevity.⁵⁹ Any unintentional weight loss warrants prompt investigation and dietary interventions, and unnecessary weight loss in advanced chronic kidney disease should be avoided, unless absolutely required (eg, as a strict requirement for imminent kidney transplantation or other life-saving procedures that require a lower weight).⁶⁰

Plant-dominant, low-protein diet

In many causes of chronic kidney disease, afferent arterioles are relatively dilated and efferent arterioles are relatively contracted as a compensatory mechanism to maintain glomerular filtration rate in the short term—a process known as glomerular hyperfiltration or intraglomerular hypertension. This interaction is partly regulated via tubuloglomerular feedback.⁴⁹ In the long term, glomerular hyperfiltration can cause further damage to the kidney through mechanisms such as mechanical stress and activation of inflammatory mediators that promote interstitial fibrosis.^{61,62} Dietary protein restriction, by enhancing the afferent arteriole tone, might alleviate intraglomerular hypertension, mitigate renal interstitial fibrosis,^{61,62} and slow the progression of chronic kidney disease (figure 2). This effect acts in parallel and is complementary to the postglomerular effect of renin-angiotensin-aldosterone pathway modulators, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, which reduce intraglomerular pressure by promoting efferent arteriolar vasodilatation.⁶³

Evidence from randomised controlled trials supporting the beneficial effect of dietary protein restriction comes from the Modification of Diet in Renal Disease study, which randomly assigned 585 participants with non-diabetic kidney disease to assess the effect of typical (1.3 g/kg per day) versus low-protein diets (0.58 g/kg per day) on eGFR decline. Although the primary results of this trial were inconclusive, they did not take into account the acute effect of dietary protein restriction, which reduces short-term glomerular filtration rate through afferent arteriolar constriction, similarly to what is observed with initiation of ACE inhibitors or angiotensin receptor (AGTR1) blockade therapy. Subsequent analyses of the Modification of Diet in Renal Disease study data excluding the acute effect of the dietary intervention on glomerular filtration rate suggested that there was a benefit of dietary

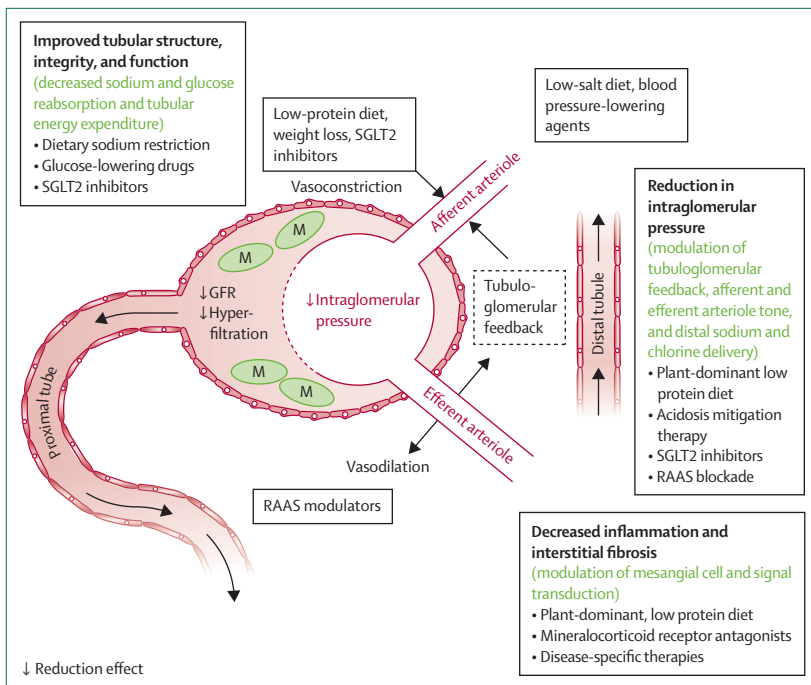


Figure 2: Effects of dietary protein and sodium intake and pharmacological therapies on afferent and efferent arteriolar tone, intraglomerular pressure, and glomerular structures and functions

Dietary protein restriction results in contraction of the afferent arterioles leading to reduced intraglomerular pressure, reducing damage to glomerular structure and function in the long term. The kidney-protective effects of a plant-dominant, low protein diet act in parallel and might be complementary to the effect of SGLT2 inhibitors, RAAS blockade, mineralocorticoid receptor antagonism, and other blood pressure-lowering agents, thereby more effectively reducing intraglomerular pressure and mitigating interstitial fibrosis. GFR=glomerular filtration rate. M=mesangial cells. RAAS=renin-angiotensin-aldosterone system.

protein restriction (appendix p 2).⁶⁴ Additional analyses also showed that dietary protein restriction might reduce blood pressure and proteinuria.⁶⁵ The findings from this study are supported by meta-analyses that show a reduced risk of progression to kidney failure and improvements in proteinuria and other favourable biochemical outcomes, such as higher serum concentrations of bicarbonate, lower azotaemia, and lower serum concentrations of 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 frailer people or older than 80 years.⁷⁰ Therefore, current guidelines recommend a conservatively low range of 0.6–0.8 g/kg per day of dietary protein in people with substantial albuminuria (more than 300 mg/g) to ensure safety and adequate nutritional intake (appendix p 2).⁷¹

More recent data suggest salutary effects of plant-dominant, low-protein diets,⁵² in which more than 50% of ingested protein is derived from non-animal sources (ie, fruits, vegetables, nuts, legumes, and seeds). There are different types of plant-dominant diets, listed here with increasing amounts of foods from plant sources:⁷² vegan or strict vegetarian diets that not only exclude meat, poultry, and seafood but also eggs and dairy products; lacto-vegetarian, ovo-vegetarian, or lacto-ovo-vegetarian

diets that can include dairy products and eggs; and pescatarian or pesco-vegetarian diets that include a vegetarian diet combined with occasional intake of some or all types of seafoods, mostly fish.⁷² Although some, but not all studies have shown that plant-dominant diets are associated with a lower risk of chronic kidney disease and glomerular filtration rate decline, less proteinuria, amelioration of acidosis, and better cardiovascular profile,⁷³ and although experimental data also suggest that such diets can reduce uraemic toxin generation and exert favourable effects on cardiovascular health in people with kidney failure,^{52,53,74,75} these effects have not yet been definitively shown in randomised controlled trials.⁷⁶

There is growing interest in the role of the gut microbiome in chronic kidney disease, although the role of any microbiome-related interventions is not yet proven.⁷⁶ The gut microbiome in chronic kidney disease might be altered by uraemia, natural intake of probiotics,⁷⁷ and the type of diet (including plant-origin vs animal-origin foods).⁷⁸ A plant-dominant, fibre-rich, low-protein diet can lead to favourable alterations in the gut microbiome, which might modulate uraemic toxin generation.⁵² Several gut-derived uraemic toxins, including indoxyl sulfate, indole-3 acetic acid, p-cresyl sulfate, trimethylamine N-oxide, and phenylacetylglutamine, are associated with cardiovascular disease and mortality in chronic kidney disease.⁷⁹ Circulating p-cresyl sulfate and indoxyl sulfate (protein-bound uraemic retention solutes) and other catabolic by-products of protein metabolism can exert harmful effects on several organs and homeostatic pathways, such as inflammation, oxidative stress, endothelial dysfunction, muscle wasting, renal interstitial fibrosis, worsening proteinuria, accelerated chronic kidney disease progression, and insulin resistance.^{80–82} Therefore, a high-fibre, plant-dominant, low-protein diet has been proposed, but not yet proven in clinical trials, to favourably modulate microbiome, reduce uraemic toxin generation, and help to control uraemia without dialysis, potentially while enhancing cardiovascular health, which is consistent with the goals of the conservative and preservative management of chronic kidney disease.⁸³

Intravascular volume and acid-base and electrolyte homeostasis

Subclinical volume overload is highly prevalent in people with chronic kidney disease and perturbations in systemic haemodynamics are strongly associated with risk of poor cardiovascular and kidney outcomes.^{84–86} Optimisation of intravascular volume is, therefore, an important focus of care, particularly as kidney function declines, and can be achieved through dietary sodium restriction and diuretics. Many patients with chronic kidney disease exhibit a tendency for salt-sensitive hypertension.⁸⁷ Although loop diuretics are the mainstay pharmacological therapy for the management of excess fluid, emerging data from randomised controlled trials suggest that distal thiazide diuretics can reduce blood pressure and extracellular

volume even at lower eGFRs,⁸⁸ with additional trials ongoing.⁸⁹

The prevalence of hyperkalaemia increases as kidney function declines, and epidemiological data show a U-shaped association between serum potassium and adverse outcomes.⁹⁰ Commonly used treatments such as ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists increase the risk of hyperkalaemia. Although dietary potassium restriction is traditionally recommended for people with advanced chronic kidney disease, there are concerns that such diets might limit the consumption of healthy plant proteins, fruit, and vegetables.⁹¹ Traditional and newer potassium binders might allow more effective control of hyperkalaemia, and trials are underway to test the effect of newer potassium binders on clinical outcomes.^{92,93}

Metabolic acidosis in chronic kidney disease results from the inability of the kidney to excrete endogenous acid, and has been shown to be associated with loss of kidney function and unfavourable effects on muscle mass and bone health.⁹⁴ Small trials have collectively suggested that correction of metabolic acidosis with bicarbonate might slow progression of chronic kidney disease.⁹⁵ In 2019, everimer (a novel binder of hydrochloric acid in the gastrointestinal tract) was shown to increase serum bicarbonate concentrations in people with chronic kidney disease, with an ongoing trial to test the effect of this agent on clinical outcomes, including progression of kidney disease or kidney failure requiring dialysis.⁹⁶

Traditional and emerging pharmacotherapies

Renin–angiotensin–aldosterone system inhibition, mineralocorticoid receptor antagonism, and other blood pressure-lowering therapies

Renin–angiotensin–aldosterone pathway modulators, specifically ACE inhibitors or angiotensin receptor blockers, have been the cornerstone of kidney-preserving pharmacological therapies for several decades. The evidence is strongest in people with type 2 diabetes and albuminuric chronic kidney disease, for whom the angiotensin receptor blockers losartan (RENAAL trial) and irbesartan (IDNT trial) have been shown to reduce the risk of kidney failure, doubling of creatinine, or death (appendix p 8).^{97,98} Importantly, several studies^{99–101} have shown an increased risk of adverse outcomes and no clear benefits with multi-agent renin–angiotensin–aldosterone system blockade, for which reason angiotensin-converting enzyme inhibitors and angiotensin receptor blockade combination therapy is strongly discouraged.

The FIDELIO-DKD trial of the non-steroidal mineralocorticoid receptor antagonist finerenone in diabetic kidney disease showed a significant reduction in the risk of the primary kidney outcome (sustained 40% reduction in eGFR, kidney failure, or kidney death) and cardiovascular outcome (myocardial infarction, stroke, heart failure, or cardiovascular death).¹⁰² Several

studies have suggested that the older steroidal mineralocorticoid receptor antagonist spironolactone reduces proteinuria in diabetic kidney disease,¹⁰³ but clear data regarding its effects on hard outcomes such as kidney disease progression or need to start dialysis are not currently available. Renin–angiotensin–aldosterone pathway modulation with angiotensin-converting enzyme inhibitors or angiotensin receptor blockade therapy is also generally recommended for people with type 1 diabetes and kidney disease⁹⁸ and for those without diabetes but with significant proteinuria;¹⁰⁴ the effects in people with little or no proteinuria are uncertain.

Although blood pressure reduction per se probably reduces the risk of kidney failure,^{105,106} the haemodynamic effect of intensive blood pressure lowering might paradoxically induce a more rapid decline in kidney function.^{107–110} Notwithstanding such mixed data, the KDIGO guidelines recommend a systolic blood pressure target of less than 120 mm Hg in people with chronic kidney disease not on dialysis to reduce the risk of cardiovascular events and mortality. However, individualisation of blood pressure targets is crucial and should take into account comorbidities, frailty, and patient preferences, given the ongoing uncertainty about the risk–benefit profile of intensive blood pressure targets in patients with moderate-to-advanced chronic kidney disease.¹⁰⁷

Glucose-lowering therapies

Glucose-lowering therapies could potentially reverse the fundamental metabolic abnormality pathognomonic of diabetes.¹¹¹ Although post-hoc analyses of the ADVANCE trial¹¹² suggested that the risk of kidney failure might be smaller in people treated to lower targets of haemoglobin A_{1c}, meta-analyses of more intensive versus less intensive glucose reduction did not show clear effects on the risk of kidney failure.¹¹³ Subsequent studies have further shown clear differences between different classes of glucose-lowering therapies.

SGLT2 inhibitors

SGLT2 (SLC5A2) inhibitors were developed to reduce blood glucose in people with diabetes by blocking proximal tubular glucose reabsorption, thus inducing glycosuria (figure 2). Early studies in type 2 diabetes identified that these drugs significantly reduce proteinuria and have a clear beneficial effect on kidney haemodynamics. This is manifest clinically as an acute reduction in eGFR (approximately 3–5 mL/min per 1.73 m²) followed by stabilisation of kidney function compared with either placebo or sulfonylurea therapy, benefits that are observed on top of renin–angiotensin–aldosterone system blockade. (appendix p 8).¹¹⁴ Several cardiovascular safety studies mandated by regulatory authorities have successively shown reductions in composite outcomes based on reductions in eGFR or doubling of creatinine, kidney failure, and death due to

kidney disease.^{115–117} However, these trials were done in people at high risk of cardiovascular disease, less than 25% of whom had kidney disease.

The first primary kidney trial of SGLT2 inhibitors assessing efficacy on major clinical outcomes was the CREDENCE study.¹¹⁸ A total of 4401 participants with albuminuric diabetic kidney disease (albuminuria 300–5000 mg/g, eGFR 30–90 mL/min per 1.73 m²) were randomly assigned to receive canagliflozin or placebo (appendix p 8). The trial was stopped early for efficacy after the primary outcome (doubling of serum creatinine, kidney failure, or death due to cardiovascular or kidney disease) was reduced by 30%, with similar reductions in a range of renal outcomes, including kidney failure and the need for dialysis or kidney transplantation.¹¹⁸ Major cardiovascular events (myocardial infarction, stroke, or cardiovascular death) and hospitalisations for heart failure were also significantly reduced. On the basis of these findings, major treatment guidelines worldwide have now been updated to recommend SGLT2 inhibitors for people with diabetic kidney disease.

The kidney-protective effects of SGLT2 inhibition have also been observed in people with non-diabetic kidney disease. The DAPA-CKD trial¹¹⁹ showed 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 chronic kidney disease (eGFR 25–75 mL/min per 1.73 m², urine albumin-to-creatinine ratio 200–5000 mg/g), with clear and independent benefits irrespective of diabetes status or aetiology of chronic kidney disease.¹²⁰ The trial also showed that dapagliflozin substantially reduced the risk of hospitalisation for heart failure or cardiovascular death and all-cause mortality, irrespective of diabetes status. On the basis of these findings, SGLT2 inhibitors are anticipated to be routinely offered to people with albuminuric chronic kidney disease, regardless of the presence of diabetes. A trial of empagliflozin in non-diabetic kidney disease that includes people with low or normal albuminuria is ongoing.¹²¹ The mechanisms underpinning the cardiovascular and kidney benefits of SGLT2 inhibition are an area of active investigation, but are probably multifactorial, including reductions in intraglomerular pressure, favourable effects on the extracellular fluid compartment, and multiple direct effects on cellular and metabolic functions.¹²²

DPP4 inhibitors

DPP4 inhibitors are widely used to improve glycaemic control in people with type 2 diabetes. The effects on hard kidney outcomes, such as progression of kidney disease and end-stage renal disease, were formally assessed in the CARMELINA trial,¹²³ in which almost 7000 participants with type 2 diabetes enriched for either or both cardiovascular disease and kidney disease (reduced glomerular filtration rate, increased albuminuria, or both) were randomly assigned to linagliptin or placebo. The trial

showed 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-related endpoints being observed in the trial. Therefore, the available data suggest that DPP4 inhibitors do not meaningfully reduce the risk of kidney disease progression in patients with type 2 diabetes.

GLP-1 receptor agonists

There have not yet been any outcome studies sufficiently powered to detect effects on clinically important kidney outcomes with the use of GLP-1 receptor agonists, another class of drugs developed in the past 10 years to improve glucose control in type 2 diabetes. GLP-1 receptor agonists have been shown to reduce the risk of cardiovascular events in meta-analyses of completed cardiovascular outcome trials.¹²⁴ Similar meta-analyses of these trials suggest that the risk of a composite kidney outcome (including progression of albuminuria, substantial losses of renal function [40% or 57% reductions in eGFR], renal failure, or kidney-related death) is significantly reduced by GLP-1 receptor agonists. However, this reduction appears to be primarily driven by effects on albuminuria; no other clear benefit was observed on kidney outcomes.¹²⁴ A dedicated kidney outcome study (FLOW, NCT03819153) is currently underway, specifically recruiting people with chronic kidney disease and comparing the effects of semaglutide versus 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 optimising blood pressure control with ACE inhibitors or angiotensin receptor blockers, along with lifestyle modifications, such as salt and protein restriction and weight loss.¹²⁵ The role of corticosteroids in managing IgA nephropathy is controversial because of the conflicting evidence from randomised trials that yielded both negative and positive data.^{126,127} 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.^{128,129}

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,^{130–132} many of these patients will develop spontaneous remission; as with other causes of proteinuric chronic kidney disease, optimal supportive care should include the maximum tolerated ACE inhibitor or angiotensin receptor blockade therapy.¹³³ For patients with more severe proteinuria, at high risk of disease

progression, or both, other treatments are recommended, including alkylating agents such as cyclophosphamide,¹³⁴ calcineurin inhibitors,^{135,136} rituximab,¹³⁷ or a combination of these agents.¹³⁸ For other primary glomerular diseases, there is a paucity of evidence from randomised controlled trials.¹³⁹ Autosomal dominant polycystic kidney disease is another non-glomerular disease common worldwide and for which tolvaptan, a vasopressin receptor antagonist, has shown an effect in slowing the rate of kidney growth and glomerular filtration rate decline¹⁴⁰ in early and late stages.¹⁴¹

These traditional and emerging pharmacotherapies strategies are summarised in table 1 and in figure 1 (see also appendix pp 3–4).

Addressing cardiovascular risk during chronic kidney disease progression

Cardiovascular disease is a leading cause of death in patients with chronic kidney disease, and is therefore a major focus of preservative care in this population.¹⁴² Lower eGFR and higher albuminuria are independently associated with a higher risk of cardiovascular events (in addition to the risk conferred by traditional risk factors such as blood pressure, high cholesterol, and lifestyle) (figure 3).^{42,143}

Whereas the traditional shared risk factors such as overweight, hypertension, diabetes, dyslipidaemia, and smoking are associated with cardiovascular disease in patients with earlier chronic kidney disease stages, a host of non-traditional risk factors magnify the risk of cardiovascular disease, especially in patients with advanced chronic kidney disease. Some of these so-called kidney-specific factors include inflammation with or without protein-energy wasting, mineral and bone disorders, and endothelial dysfunction.^{144–151}

The management of cardiovascular disease in chronic kidney disease is challenging (appendix p 9).¹⁵² These challenges include interpretation of cardiac biomarkers that are used to diagnose myocardial infarction, the exclusion of individuals with more advanced chronic kidney disease from cardiovascular outcome trials, and the absence of a clear benefit of revascularisation for individuals with chronic kidney disease and stable coronary artery disease.^{153–156} The mainstays of cardiovascular risk reduction in chronic kidney disease include lifestyle modification (table 2), blood pressure reduction with renin–angiotensin–aldosterone pathway modulators, lipid reduction with statins, and specific glucose-lowering drugs that have been shown to reduce cardiovascular outcomes in people with type 2 diabetes (appendix pp 3–4).^{124,157} Evidence suggests that in people with non-dialysis-dependent chronic kidney disease, higher physical activity is associated with slower disease progression,¹⁵⁸ lower risk of cardiovascular events and mortality,^{159,160} and some improvements in kidney function and blood pressure;¹⁶¹ in patients receiving dialysis, improvements in physical function and health-related

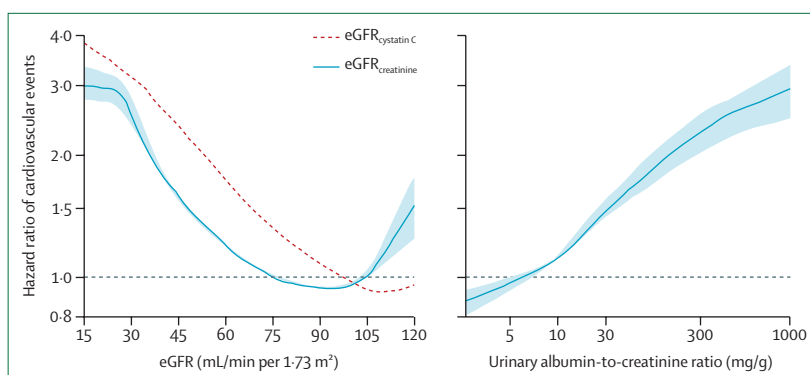


Figure 3: Association of eGFR and albuminuria with hazard ratio of cardiovascular events

Association of eGFR (creatinine-based eGFR presented with cystatin C-based eGFR for comparison) and albuminuria with hazard ratio of cardiovascular events after adjustment for traditional cardiovascular risk factors. Data from the Chronic Kidney Disease Prognosis Consortium of 637 315 individuals from 24 cohorts (ie, general population, high risk of chronic kidney disease, and established chronic kidney disease), followed up for a mean of 8.9 years, during which time 10 605 cardiovascular deaths, 6283 coronary heart disease events, 180 stroke events, and 2066 heart failure events occurred. Cystatin C-based eGFR data from a meta-analysis of ten general population cohorts with 64 010 participants, of whom 3193 died from cardiovascular causes during follow-up. eGFR=estimated glomerular filtration rate. The blue shaded area around the line represents the 95% CI. Adapted from Matsushita and colleagues⁴² by permission of Elsevier and from Shlipak and colleagues.¹⁴³

quality of life are also observed.¹⁶² Smoking is associated a greater risk of incident chronic kidney disease¹⁶³ and increased risk of all-cause mortality in people with chronic kidney disease.¹⁶⁴ Dietary sodium restriction improves albuminuria, hypertension, fluid status, and arterial stiffness in people with and without chronic kidney disease,^{165–167} which is also more likely to harbour salt-sensitive hypertension.¹⁶⁸ Higher plant-based sources of protein and dietary fibres may have salutary effects,⁵² whereas higher red meat intake may be deleterious to patients with chronic kidney disease.¹⁶⁹ Protein intake recommendations vary depending on the stage of the disease, acute kidney injury events, and need for dialysis.⁷⁰ Weight reduction improves blood pressure in chronic kidney disease,^{170,171} notwithstanding the obesity paradox in patients requiring dialysis.⁵⁹

However, there is insufficient evidence to support commencing lipid-lowering therapy for primary prevention of cardiovascular disease in most people with advanced chronic kidney disease requiring dialysis, especially in the absence of high concentrations of serum LDLs.¹⁷² In people with type 2 diabetes, guidelines recommend that SGLT2 inhibitors and GLP-1 receptor agonists be prioritised in people with chronic kidney disease.^{173,174} Although antiplatelets are often offered for secondary cardiovascular prevention, the relative benefits and harms for primary prevention are unknown,¹⁷⁵ as is the role of anticoagulation with warfarin versus direct acting oral anticoagulants in advanced chronic kidney disease.¹⁷⁶ In a randomised controlled trial of patients with a history of acute coronary syndrome in the previous 3 months, type 2 diabetes, and low concentrations of HDLs, apabetalone (a novel epigenetic modulator) added to standard therapy resulted in a 52% reduction in the risk of major adverse cardiovascular events among subgroups

	Kidney-preserving care level of relevance	Supportive care level of relevance	Comments
Slowing chronic kidney disease progression	Strongly relevant	Possibly relevant to moderately relevant	Important goal across both domains of care, but not the primary goal of supportive care
Preventing or delaying dialysis	Strongly relevant	Strongly relevant	Both domains aim to prevent or delay initiation of dialysis
Symptom management	Possibly relevant to moderately relevant	Strongly relevant	Addressing symptoms is one of the key priorities of supportive care, but should also have an important role in preservative management
Health-related quality of life and patient-reported outcomes	Moderately relevant to strongly relevant	Strongly relevant	Each domain aims to improve quality of life through different approaches: kidney-preserving care prioritises aggressive treatments to restore and protect health and quality of life, whereas supportive care places a greater focus on maintaining quality of life by minimising invasive interventions
Prioritising overall survival with life-prolonging and kidney-prolonging care	Strongly relevant	Not relevant to possibly relevant	Preventing complications, addressing comorbidities, and prolonging survival are among the highest priorities of kidney-preserving care, whereas alleviating symptoms is prioritised over prolonging survival with supportive care
Cardiovascular health	Strongly relevant	Not relevant to possibly relevant	Reducing cardiovascular risk is a fundamental aspect of kidney-preserving care, and less of a priority with supportive care
Minimising risk of acute kidney injury and infection	Strongly relevant	Possibly relevant to moderately relevant	Important aspect of both domains
Diet and lifestyle modifications	Strongly relevant	Possibly relevant	Dietary strategies (eg, 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
Chronic kidney disease pharmacotherapy	Strongly relevant	Possibly relevant	Targeted and non-targeted pharmacotherapies aimed at preserving kidney function are less of a priority with supportive care, in which pharmacotherapy is mostly for symptom management
Treating uraemia and complications of chronic kidney disease	Strongly relevant	Possibly relevant to moderately relevant	Priorities in the management of chronic kidney disease-related complications are primarily to avoid unpleasant symptoms with supportive care
Preserving residual kidney function after transition to dialysis and less frequent dialysis	Strongly relevant	Possibly relevant	Kidney-preserving care places a greater emphasis on protecting residual kidney function (eg, incremental transition to dialysis), whereas palliative dialysis can be infrequent as well as include decremental dialysis regimens
Shared decision making and advance care planning	Moderately relevant	Strongly relevant	Fundamental concept in the care of all people with kidney disease and that is often more clearly highlighted under supportive care, including palliative care and hospice medicine

See also figure 1 for schematic representations of the domains within the chronic kidney disease management chart.

Table 3: Similarities and distinctions between kidney-preserving management and supportive and palliative care

of participants with pre-existing, stage 3 chronic kidney disease.^{177,178} Patient-reported outcomes, including health-related quality of life, should be considered a key outcome for a holistic assessment of interventions in all cardiovascular outcome trials involving patients with chronic kidney disease.^{19,179}

Acute kidney injury

Patients with chronic kidney disease, especially in more advanced stages (eGFR of less than 30 mL/min per 1.73 m²) often do not exhibit linear progression of disease, which might be related to superimposed episodes of acute kidney injury or other factors.¹⁸⁰ Some (but not all) studies suggest that each acute kidney injury event might accelerate progression of chronic kidney disease.^{181,182} Therefore, preventing acute kidney injury is an important component of the management of chronic kidney disease. This prevention involves avoiding acute kidney injury-associated drug combinations (eg, ACE inhibitors or angiotensin receptor blockers in conjunction with loop diuretics and non-steroidal anti-inflammatory drugs)¹⁸³ and preventing infections that can precipitate hypotension or septic shock necessitating the use of potentially nephrotoxic antimicrobials. Other contributors to acute kidney injury include cardiovascular events, particularly

decompensated heart failure leading to venous congestion and impaired kidney blood flow, or coronary artery bypass and other major surgeries with possible intraoperative hypotensive episodes.^{184,185}

Role of supportive care and of palliative and hospice medicine

People with advanced chronic kidney disease, particularly those with kidney failure, often have a high symptom burden that substantially affects their health-related quality of life.¹⁸⁶ Although there is little evidence from randomised controlled trials, observational studies suggest that chronic dialysis might not be associated with improved survival in some patients older than 80 years with a high burden of comorbidities, and that at least some of these patients might regret their decision to commence dialysis in view of treatment-related complications, high symptom burden, and poor quality of life.^{187,188} These factors have led to an increased recognition of the importance of supportive care of kidney failure (figure 1).

There are similarities and distinctions between kidney-preserving management and supportive care, including palliative care and hospice medicine (table 3). Both strategies are expected to minimise the risk of adverse events or complications, such as acute kidney injury, as chronic kidney disease progresses, although

kidney-preserving management is more strongly focused on kidney function longevity. Whereas palliative care strategies are often considered for those with advanced age (ie, older than 80 years) or more severe comorbidities, such as terminal cancer,^{21–24,26–33} kidney-preserving management is a kidney-sustaining and life-sustaining strategy for all individuals and at any stage of chronic kidney disease.

The goal of supportive care is to improve symptoms and quality of life through a multidisciplinary approach that incorporates shared decision making, detailed communication with patients and their care partners, advanced care planning, and psychological and social support.^{189,190} Standardised tools to identify those who might benefit the most from supportive care are not widely validated, and thus treatment decisions, such as fluid management, must be individualised—including for those who decide to reduce dialysis dose and frequency to a minimum (the so-called decremental or palliative dialysis), or to withdraw completely from renal replacement therapy (figure 1).¹⁹¹ Novel prediction tools have been developed to identify individuals who would have the highest mortality in the first year after transitioning to dialysis and who might therefore benefit from palliative care,⁴⁵ but these tools need to be more widely validated. The decision must be according to the free choice of the patient, without pressure by family members and care partners or health-care professionals, and it should not be influenced by rationing dialysis care such as during COVID-19 pandemic surges or other resource constraints.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 chronic kidney disease, depending on the severity of the disease and on the goals of the individual (figure 1; table 3).

Infection control and management of chronic kidney disease in the COVID-19 pandemic

Evidence suggests that uraemia is associated with worse immune response, as exemplified by the diminished antibody response to hepatitis B vaccination or by the higher risk of infections as kidney function worsens, not otherwise explained by concurrent comorbidities, and by the historical observation that autoimmune diseases such as systemic lupus erythematosus are less aggressive once patients have uraemia.¹⁹² Similarly, some infections, such as hepatitis C, might cause chronic kidney disease if untreated,^{193,194} or can lead to faster disease progression and greater mortality in the case of pre-existing chronic kidney disease.¹⁹⁵ Conversely, treatment of hepatitis C might possibly have a salutary effect in preserving kidney function.¹⁹⁶ Patients with chronic kidney disease have a two times higher risk of death after respiratory infections;¹⁹⁷ therefore, influenza and pneumococcal vaccinations might be an indirect way to prevent acute kidney injury and avoid chronic kidney disease

progression, although this approach has not been assessed in clinical trials.¹⁹⁸

During the COVID-19 pandemic, data suggest a two times increase in mortality from COVID-19 in the presence of chronic kidney disease.¹⁹⁹ Despite screening and isolation of affected patients, outbreaks cannot always be prevented because some infected individuals can have long incubation periods or be asymptomatic carriers.¹⁹⁹ To maintain adequate staffing and to protect patients, outpatient chronic kidney disease care has undergone a radical transformation with the use of telemedicine and remote care to guide dietary and therapeutic decisions.²⁰⁰ Advance care planning and ensuring completion of renal replacement therapy plans are of even higher importance because COVID-19 can cause acute kidney injury through septic shock, cytokine release, or direct renal tropism of the virus.^{201,202} Ongoing and future trials are expected to examine whether ACE receptor modulators or other modulators of kidney function can avert COVID-19 involvement in acute kidney injury and chronic kidney disease progression.^{201–203}

Global and regional disparities in preserving kidney care

Preserving kidney function in people with chronic kidney disease is confounded by regional and global health inequalities, disparities in health-care models, pharmaceutical industry policies, and geopolitical and fiscal complexities.²⁰⁴ Income disparities, poverty, and social disadvantages have a dominant effect on the risk of incident chronic kidney disease and its progression.^{205,206} Many people at risk of chronic kidney disease in low-income and middle-income countries are not provided with appropriate infrastructure for screening and identification of chronic kidney disease. The awareness of chronic kidney disease is relatively poor, and opportunities for updating knowledge and education on preserving kidney health are scarce.²⁰⁷

In low-income and middle-income countries, diet and lifestyle modification might offer an inexpensive approach for primary, secondary, and tertiary prevention of chronic kidney disease, notwithstanding the little scientific evidence to justify population-based programmes for lower sodium intake, promotion of plant-based diets, and adequate hydration. Whereas pharmacotherapy and dialysis treatment are almost universally accessible in high-income countries, many people in low-income and middle-income countries are unable to access these options.²⁰⁸ The out-of-pocket expenditure for chronic kidney disease preserving pharmacotherapy is high relative to income; for instance, in India, the high costs of SGLT2 inhibitors or renal replacement therapy are more likely to push people into the poverty range than communicable diseases.²⁰⁹

In some high-income nations, such as the USA, there are racial disparities in chronic kidney disease care.²¹⁰

Black Americans are far more likely to develop chronic kidney disease and exhibit faster disease progression than White Americans.²¹¹ This disparity might be related to socioeconomic factors such as access to care, exposing many Black Americans to higher chronic kidney disease risks; furthermore the higher prevalence of a pathogenic *APOL1* allele in Black Americans might partly explain the high burden of chronic kidney disease in this population.²¹² The current creatinine-based eGFR equations have a race index for Black Americans, which inflates the eGFR value by as high as 16% compared with non-Black Americans with the same serum creatinine concentration.²¹³ In an effort to reduce racial disparities in chronic kidney disease care, race indices have been suggested to be removed from eGFR equations to enable a more commensurate approach to the burden of chronic kidney disease.²¹⁴ Race-free measurements, such as serum cystatin C-derived eGFR equations, could be used instead, especially given their more linear associations with clinical outcomes (figure 3).^{143,214}

Conclusion remarks and future steps

The primary goal of the conservative management of chronic kidney disease through kidney-preserving care is to slow chronic kidney disease progression 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 chronic kidney disease. Dietary interventions, such as low-salt and plant-dominant, low-protein diets, and pharmacotherapies, such as renin-angiotensin-aldosterone pathway modulators, SGLT2 inhibitors, and newer non-steroidal mineralocorticoid receptor antagonists should be used to the best possible extent. Adequately powered, randomised trials to evaluate the effects of new pharmacotherapies to slow the progression of chronic kidney disease and prevent its complications, especially in early-stage disease, should be prioritised. When dialysis therapy is necessary and kidney transplantation cannot be offered, a gradual and incremental transition to dialysis might preserve residual kidney function for longer. Some patients might benefit from palliative dialysis for ultrafiltration to manage fluid overload and its associated symptoms.²¹⁵ Future studies of strategies to replace or complement dialysis should include, but not be limited to, intestinal dialysis,^{216,217} diaphoresis therapy for control of uraemia, and management of fluid and electrolytes,^{218,219} on the basis of the results from studies in relevant animal models.²²⁰ 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 help patients to live longer and well with chronic kidney disease.¹⁹

Contributors

All authors contributed equally to the conception, interpretation of the relevant literature, writing, and critical revision of this Seminar.

Declaration of interests

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed.
We post it as supplied by the authors.

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Appendix

Title:

Chronic Kidney Disease

Authors:

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Vlado Perkovic.

Content: 2 tables, 5 figures. 24 references

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

FIGURES

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

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

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

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 2020¹

**Protein-dominant low protein (PLADO) diet consists of 0.6-0.8 g/kg/day of protein with at least 50% from plant-based sources¹

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, ^{2,3} although benefits may be present in those with albuminuria ⁴	Intensive BP lowering (<120 mm Hg) reduces cardiovascular events and mortality in people without diabetes, with consistent benefits in people with and without CKD. ⁵ Mortality benefits are likely to be similar in people diabetic and non-diabetic kidney disease. ⁶	Measure BP using standardized office technique with multiple consecutive readings using automated oscillometric BP devices ⁷ Ambulatory BP monitoring is considered the reference standard for out-of-office BP assessment, with home BP monitoring being an acceptable alternative. ⁷	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). ^{8,9}	Reduces cardiovascular outcomes in people with CKD. ¹⁰	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. ¹¹	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. ¹²	Combination of simvastatin and ezetimibe significantly reduces risk of major vascular events in people with CKD. ¹³ 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. ¹⁴⁻¹⁶	The benefit of lipid lowering attenuates with decline kidney function. ¹⁷ 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 ¹⁸	Uncertainty with regards to effects on macrovascular outcomes with no clear effect on mortality ¹⁹	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.

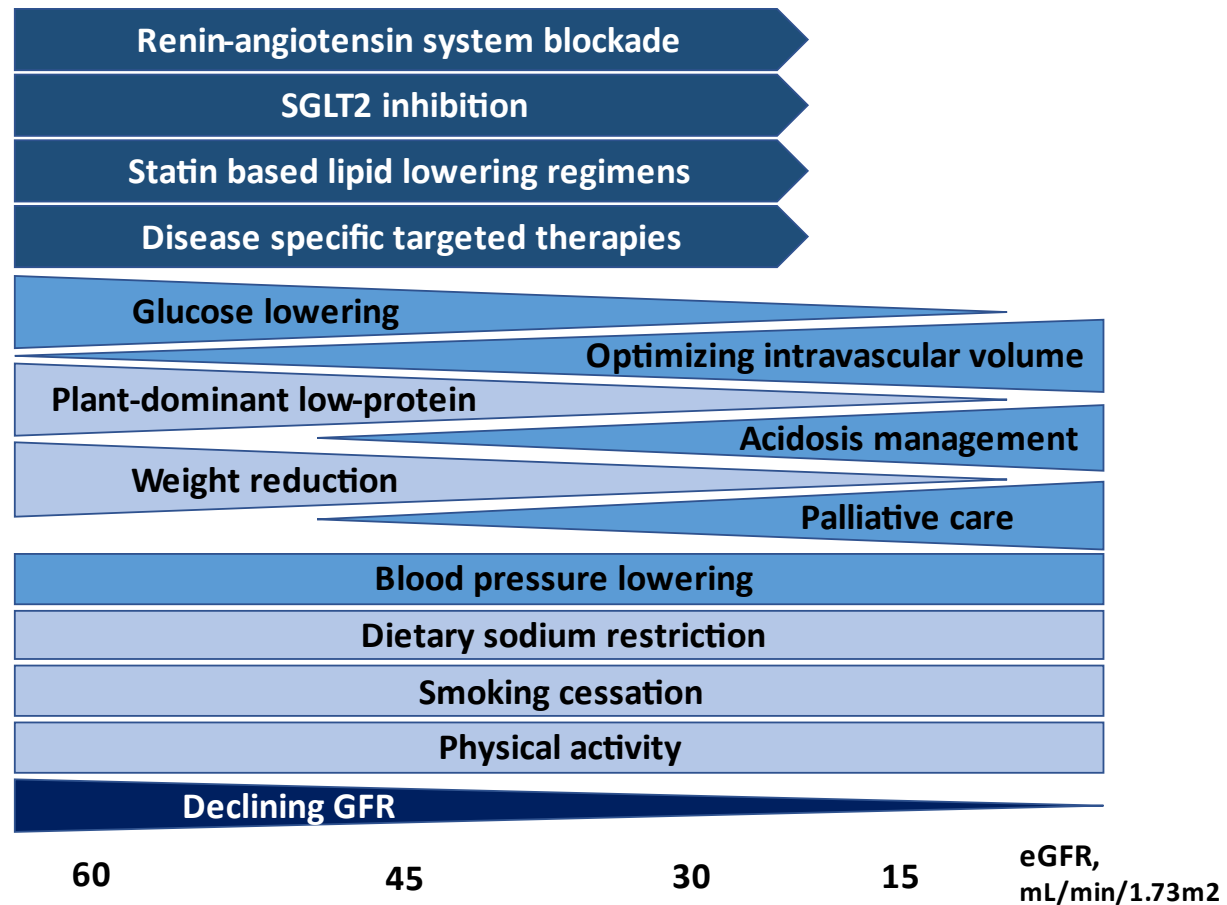
SGLT2 inhibitors	Reduces the risk of kidney failure in people with type 2 diabetes. ²⁰	Reduces the risk of a range of cardiovascular outcomes, particularly heart failure and cardiovascular death as well as all-cause mortality	Emerging evidence of heart and kidney failure benefits irrespective of the 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

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 2011.²¹)

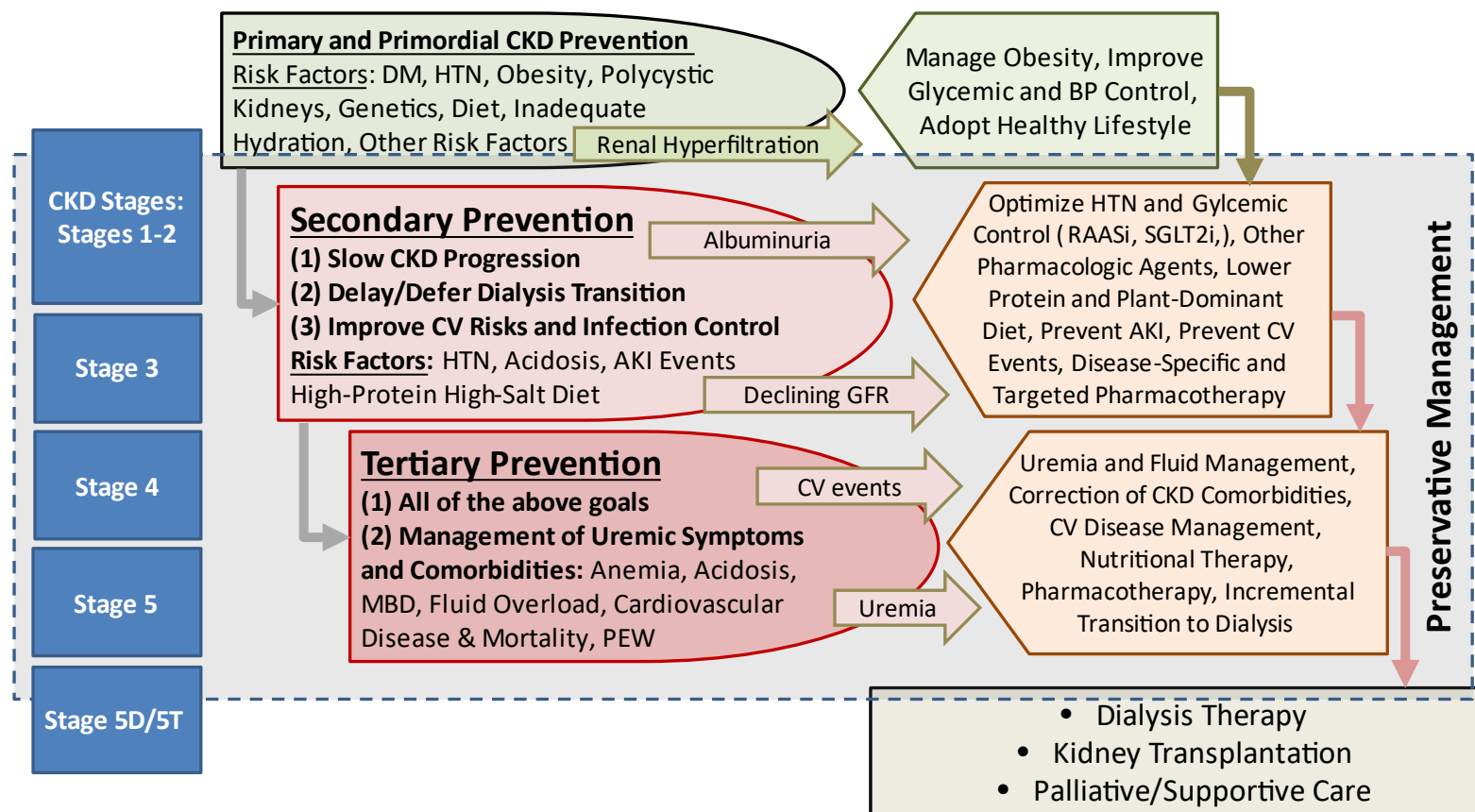
KDIGO: Kidney Disease Improving Global Outcomes; eGFR: estimated glomerular filtration rate; UACR: urinary albumin/creatinine ratio; ESKD: end-stage kidney disease.

			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			

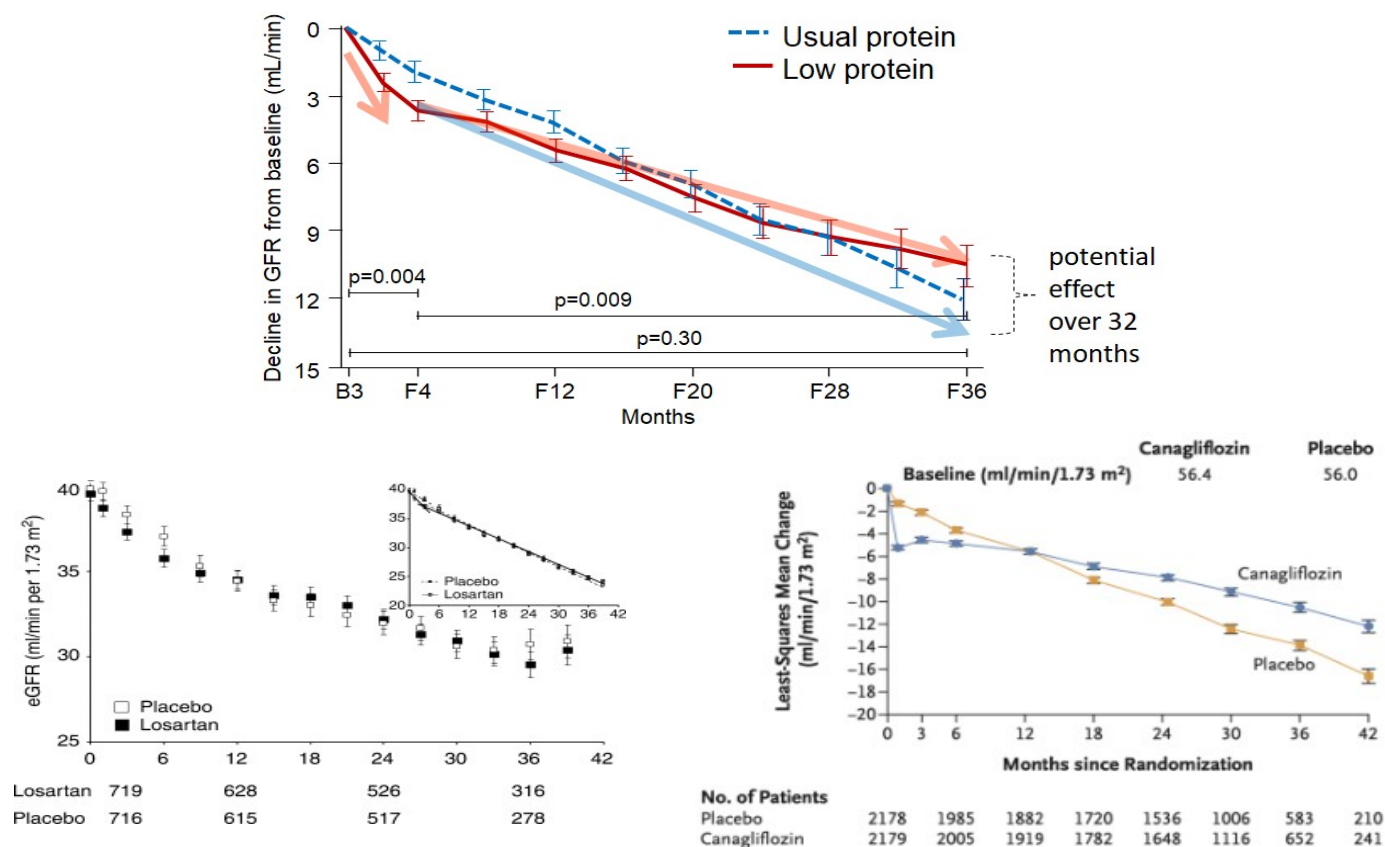
Supplemental Figure S2. Combined pharmacological and non-pharmacological approaches to the management of CKD across all levels of kidney function.

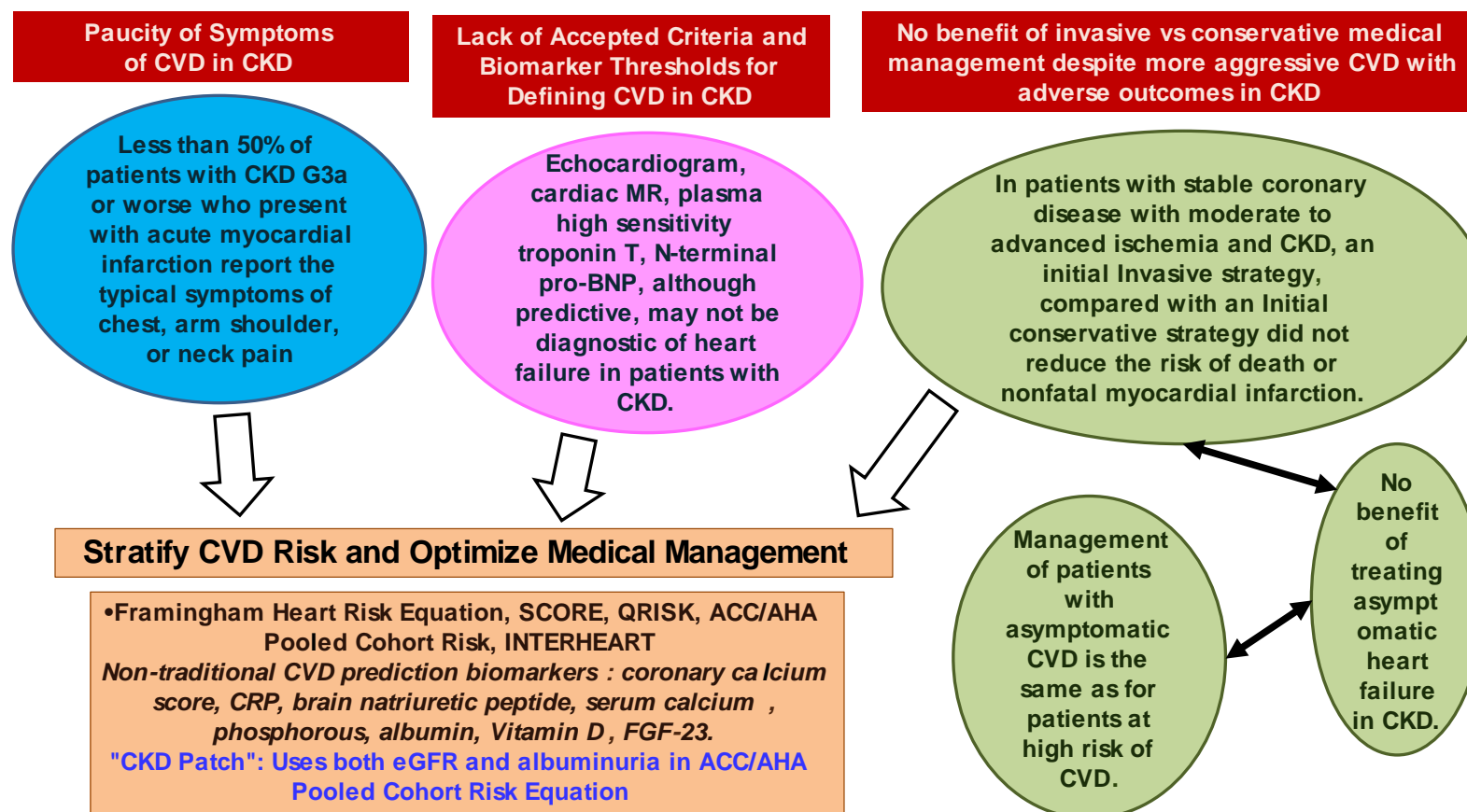


Supplemental Figure S3: Primary, secondary and tertiary prevention of chronic kidney disease. Highlighting similarities and distinctions pertaining to primary, secondary, and tertiary preventive measures and their intended goals. The “preservative management” of CKD is consistent with the secondary and tertiary prevention goals and approaches (recreated with modifications from Li et al, *Kidney Int* 2020).²² See also [Tables 2, 3 and 4](#) for detailed strategies.



Supplemental 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 trial³ (Right Lower Panel) SGLT2 inhibition with canagliflozin in the CREDENCE trial and (Left Lower Panel)²³ RAS blockade with losartan in the RENAAL trial.²⁴



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

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