Chronic kidney disease

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Globally, the prevalence of chronic kidney disease is estimated to be approximately 850 million cases, with approximately 4 million individuals needing kidney replacement therapy for kidney failure. By 2050, chronic kidney disease is projected to become the fifth leading underlying cause of death worldwide. Despite its numerous causes, chronic kidney disease can be screened for, diagnosed, and staged with simple laboratory tests. Individuals with chronic kidney disease are at increased risk of kidney failure and many other health implications. Risk of premature cardiovascular disease is particularly noteworthy, as most patients with chronic kidney disease develop a disability or die from cardiovascular disease before ever progressing to kidney failure. Since 2019, large randomised trials have identified several effective treatments that both slow progressive kidney function decline and reduce cardiovascular risk, greatly expanding available treatments for chronic kidney disease. The wide range of complications associated with chronic kidney disease means that patients encounter many different specialties. Active engagement in chronic kidney disease identification and timely initiation of cost-effective interventions by all clinicians could now substantially reduce the global burden of complications of chronic kidney disease and kidney failure.

Introduction

Chronic kidney disease is defined as abnormalities of kidney structure or function that are present for a minimum of 3 months and have implications for health.[1] Previous Seminars on chronic kidney disease published in *The Lancet* have each highlighted the latest advances in our understanding of the condition and emerging management strategies (figure 1).[2–5] The definition of chronic kidney disease, which originated in 2002, shifted the focus beyond immediately life-threatening kidney failure requiring dialysis or symptomatic nephrotic syndrome, to include early disease evident on biochemical testing and abnormalities of kidney structure or function.[3]

The 2012 *Lancet* Seminar on chronic kidney disease highlighted the implications for health that justified this broad chronic kidney disease definition. Among the many health implications, increased risk of premature cardiovascular disease is particularly noteworthy, and becomes apparent when glomerular filtration rate (GFR) falls to less than 60 mL/min per 1·73 m² or when urinary albumin-to-creatinine ratio (uACR) increases to higher than 3 mg/mmol (ie, uACR ~30 mg/g or ~30 mg per day; figure 2).[36] Many patients with chronic kidney disease will be affected by disability or die from premature death from cardiovascular disease before ever requiring referral to specialist nephrology services.[3]

The 2017 *Lancet* Seminar on chronic kidney disease described the global burden of chronic kidney disease.[4] At that time, the world population was estimated to be 7·6 billion.[37] Representative samples from 18 high-income and 14 middle-income or low-income countries provided a pragmatic global estimate of chronic kidney disease prevalence of 844 million cases (stages G1–G5), with 3·9 million people receiving kidney replacement therapy for kidney failure (ie, maintenance dialysis or kidney transplantation).[37] At that time, chronic kidney disease trials were low in number compared with other specialties,[38,39] and few interventions were shown to slow chronic kidney disease progression or reduce cardiovascular risk.[40] The 2017 Seminar raised concerns that the widened focus on maintaining kidney health among asymptomatic individuals meant less emphasis on the complex care needs of people with symptomatic kidney failure[41] and the accompanying decline in quality of life and negative socioeconomic impact.[4] By the publication of the 2021 *Lancet* Seminar on chronic kidney disease, however, concerns were abated, as major progress had been made with an evidence base for emergent pharmacotherapies to slow chronic kidney disease progression.[5] The 2021 Seminar also reviewed potential dietary and lifestyle strategies in chronic kidney disease.

In 2025, a new WHO resolution recognised that the global burden of non-communicable diseases can be reduced through promotion of kidney health and by strengthening prevention and control of kidney disease.[35] This 2025 *Lancet* Seminar on chronic kidney disease focuses on recent randomised trials that have established simply implemented treatments to slow progression of chronic kidney disease and reduce cardiovascular risk, which, if used widely, will help meet the WHO resolution objective. These treatments now form the basis of standards of care for patients with chronic kidney

Search strategy and selection criteria

We searched MEDLINE for Kidney Disease: Improving Global Outcomes clinical practice guidelines and controversy conference reports, and for guidelines or reviews from the European Renal Best Practice group and other European Renal Association working groups (appendix pp 2–3). We also searched for chronic kidney disease considerations within European Society of Cardiology and European Association for the Study of Diabetes clinical practice guidelines. For our review of trials and meta-analyses, we selected high-impact trials cited within these guidelines. We highlighted trials that form the foundation of chronic kidney disease management, key studies published in the past 5 years, and reviews of new therapeutic approaches (eg, upcoming drug targets) relevant to chronic kidney disease.

See Online for appendix

disease. To adequately identify and treat the very large numbers of patients with chronic kidney disease in low-income, middle-income, and high-income countries[42,43] will require enormous collaborative effort by care providers across diverse health-care settings and specialties.[44,45] The 2024 major update of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the Evaluation and Management of Chronic Kidney Disease—the first update since its original publication in 2012—encourages such cooperation.[1,46] In this Seminar, we therefore also highlight this guideline's key messages and provide a simple approach to chronic kidney disease diagnosis, staging, and management that can be applied by clinicians in most clinical settings.

Chronic kidney disease nomenclature and staging based on GFR and albuminuria

The mission of KDIGO is to unite the international nephrology community through formulating evidence-based clinical practice guidelines, standardising nomenclature,[47] and resolving scientific controversies. KDIGO recommends what is known as the CGA chronic kidney disease staging system, in which C refers to primary cause, G refers to categories of GFR (G1–G5), and A refers to categories of albuminuria (A1–A3).

For more on **KDIGO** see https://kdigo.org

What was known from previous *Lancet* Seminars on chronic kidney disease?	What is new in this *Lancet* Seminar on chronic kidney disease?	What is expected in terms of ongoing trials and development?	What is needed to reduce the global burden of chronic kidney disease?
2005[2] • The global challenge of chronic kidney disease, including growing numbers of patients requiring kidney replacement therapy, was highlighted **2012**[3] • Important health implications of chronic kidney disease beyond the complication of kidney failure were described, with particular recognition of associated cardiovascular risk • Blood-pressure lowering, renin-angiotensin system inhibition, and statin-based regimens were key interventions **2017**[4] • Health-service provision to incentivise early intervention was still evolving in many countries • Inequity in access to services for chronic kidney disease disproportionally affected disadvantaged populations • Interventions targeting specific symptoms, or aimed at supporting educational or lifestyle considerations (which make a positive difference for people with chronic kidney disease), were featured **2021**[5] • The emergence of clinical cardiorenal benefits of SGLT2 inhibitors and nsMRAs from trials mainly studying chronic kidney disease with diabetes were emphasised[6–9] (as well as no effect of DDP4 inhibitors on cardiorenal outcomes[10]) • Potential lifestyle and dietary interventions were reviewed in detail • Controversy on management of specific primary causes of chronic kidney disease, including IgA nephropathy, were highlighted while trials were still ongoing	• The 2024 KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease, its first update since the first version was published in 2012[1] • Use of the kidney failure risk equation to estimate 5-year risk of need for dialysis or transplantation to improve patient counselling and referral to nephrology services when risk >5% is encouraged;[1] we propose using high risk as a method to prioritise a rapid-sequence approach to initiation of risk-modifying treatment • SGLT2 inhibition importantly reduces risk of kidney failure, heart failure hospitalisation, and other cardiovascular risk in a broad range of patients with chronic kidney disease, and, including glomerular diseases[7,11–13] • GLP-1 receptor agonists reduce the risk of kidney failure and major cardiovascular outcomes in patients with chronic kidney disease and diabetes (FLOW trial: chronic kidney disease-specific data using subcutaneous semaglutide in its anti-diabetic dose)[14,15] • Targeting the aldosterone pathway in patients with chronic kidney disease already on SGLT2 inhibition additionally reduces albuminuria,[16–18] encouraging consideration of combined use of core treatments for diabetic kidney disease • Several advances in treatment options in addition to the renin-angiotensin system and SGLT2 inhibition have shown to be effective in IgA nephropathy (eg, ERAs[19–21] and particularly immunosuppression)[22,23]	• New 2026 European Society of Cardiology guidelines on the management of cardiovascular disease in patients with chronic kidney disease in collaboration with the European Renal Association and new American Heart Association–American College of Cardiology cardio–kidney–metabolic syndrome guidelines are expected[24,25] • Chronic kidney disease trials studying nsMRAs and aldosterone synthase inhibitors in non-diabetic chronic kidney disease are ongoing;[26–28] nsMRAs are also being studied in type 1 diabetes[26] • Phase 2 trials of soluble guanylate cyclase activators in patients with diabetes and non-diabetic chronic kidney disease are ongoing[28] • More trials of immunomodulation for specific glomerular diseases are required • Definitive assessment of the clinical cardiovascular and kidney effects of an anti-inflammatory treatment with an IL-6 monoclonal antibody (ZEUS trial) is ongoing in patients with chronic kidney disease (NCT05021835)[28] • Real-time ketone monitors to facilitate the use of SGLT2 inhibitors (off label) in patients with type 1 diabetes and chronic kidney disease are needed[29] • The role of genetics in chronic kidney disease research and clinical practice is increasing[30]	• Implementation of the four core interventions for chronic kidney disease and the three extra interventions for chronic kidney disease in diabetes by all clinicians who encounter such patients is needed to reduce the global burden of chronic kidney disease and its complications • When new targets for final common pathways of chronic kidney disease progression are identified, large, simple trials of promising interventions testing effects in a wide range of patients with chronic kidney disease are preferred[31,32] (pursuing small trials of specific diseases and orphan drug designation for such interventions should be discouraged to avoid their limitations)[33] • Development of primary kidney disease-specific interventions, which are then tested in sufficiently large and long (≥2 year) trials, is required to adequately assess the safety and benefit of important GFR-based outcomes • The concept of active primary prevention of chronic kidney disease should be developed[34] and the provision of kidney replacement therapy should be expanded to implement the 2025 WHO resolution[35] and the KDIGO vision on maintenance of kidney health[34]

Figure 1: **Important progress in understanding chronic kidney disease and its management**
ESC=European Society of Cardiology. ERAs=endothelin receptor antagonists. GFR=glomerular filtration rate. GLP-1=glucagon-like peptide-1. KDIGO=Kidney Disease: Improving Global Outcomes. nsMRAs=non-steroidal mineralocorticoid receptor antagonists.

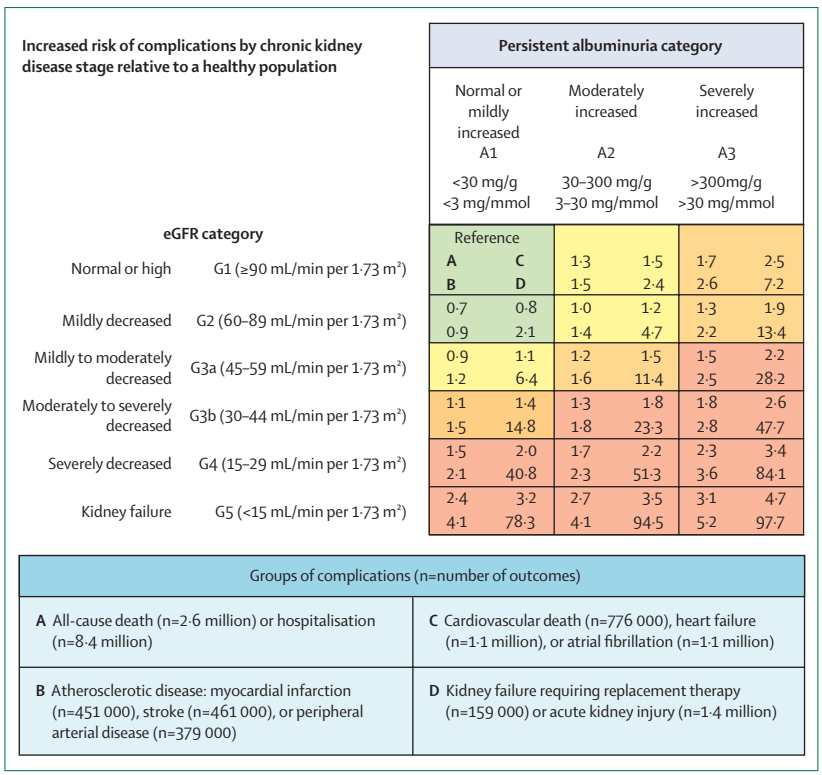


Figure 2: **KDIGO chronic kidney disease staging nomenclature and system**
Classification according to body surface area-indexed glomerular filtration rate and albuminuria categories, and associations with a selection of its complications. The numbers in each shaded box represents the hazard ratios for each category versus the reference group, after adjustment for age, sex, smoking status, systolic blood pressure, lipid measurements, anthropometry, previous disease, and medication use. Green corresponds to no chronic kidney disease, yellow corresponds to moderate risk, orange corresponds to high risk, and red corresponds to very high risk of kidney failure relative to a healthy population. Chronic kidney disease is defined as abnormalities in kidney structure or function present for a minimum of 3 months, with implications for health. Chronic kidney disease is classified on the basis of cause, glomerular filtration rate category (G1–G5), and albuminuria category (A1–A3). Plot adapted from the 2024 KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease.[1] This figure uses data from studies contributing to the Chronic Kidney Disease Prognosis Consortium: Estimated Glomerular Filtration Rate, Albuminuria, and Adverse Outcomes.[36] To formally convert albumin-to-creatinine values from mg/g to mg/mmol, division by 8·84 is required. eGFR=estimated glomerular filtration rate. Adapted with permission from the Chronic Kidney Disease Prognosis Consortium. © Chronic Kidney Disease Prognosis Consortium.

GFR and uACR are strong independent predictors of kidney failure (ie, GFR <15 mL/min per 1·73 m²), irrespective of the cause of chronic kidney disease. Both markers should be measured to ensure complete chronic kidney disease staging.[48] The stage is then used to categorise patients into moderate, high, and very high risk of kidney failure relative to a healthy population (figure 2).

GFR is the total volume of filtrate produced per minute by an individual's glomeruli. GFR is generally indexed to 1·73 square metres of body surface area to enable standardised comparison across individuals with different body sizes. GFR can be estimated from validated formulas by use of blood biomarkers, most commonly serum creatinine.[49–51] Creatinine is a metabolite produced by muscle cells and can be measured with simple, low-cost assays, but can be inaccurate at extremes of muscle mass.[52,53] Thus, when a precise estimate of GFR is required, KDIGO recommends measuring an additional biomarker, cystatin C. Cystatin C is produced by all nucleated cells and minimises confounding by muscle mass. Use of combined serum creatinine and cystatin C estimated GFR (eGFR) equations is the most accurate method to estimate GFR in most clinical settings.[1] Directly measured GFR by use of clearance methods or exogenous filtration markers is time consuming and costly, and hence reserved for when particular accuracy is required (eg, GFR assessment of potential living kidney donors).[54,55]

Albuminuria serves as a key marker of kidney disease. Increased albuminuria can result from primary glomerular diseases (eg, glomerulonephritis) or from elevated intraglomerular pressure with hyperfiltration (eg, in people with obesity, diabetes, or low nephron number).[56] As the development of albuminuria often precedes decline in GFR, albuminuria screening is recommended for individuals at very high risk of chronic kidney disease, which can include those older than 60 years and those with obesity, diabetes, high blood pressure, cardiovascular disease, structural kidney abnormalities, a family history of chronic kidney disease, or incidental haematuria.[1]

Urine dipstick tests are a simple and rapid albuminuria detection method. Spot uACR tests should be used for albuminuria diagnosis and quantification.[1,57] Although the classification of albuminuria into categories (A1–A3) does generally reflect dipstick detection thresholds (figure 2), a log–log linear relationship exists between uACR and the risk of kidney failure.[58] Albuminuria of approximately 1 g per day or more (ie, a uACR roughly >100 mg/mmol or >1000 mg/g) reflects particularly elevated risk of kidney failure, even when eGFR is preserved.[36] Within-individual variation in uACRs is substantial. First-morning void samples are preferred for uACR assessment, as they correlate most closely with 24-h timed urine albumin measurements, but random spot samples still provide a reasonably reliable estimate and are more practical.[59] Proteinuria is less specific than albuminuria as it includes both albumin and non-albumin proteins, and has traditionally been used to assess non-diabetic glomerular diseases (and especially nephrotic syndrome).

Geographical variation and temporal trends in chronic kidney disease prevalence

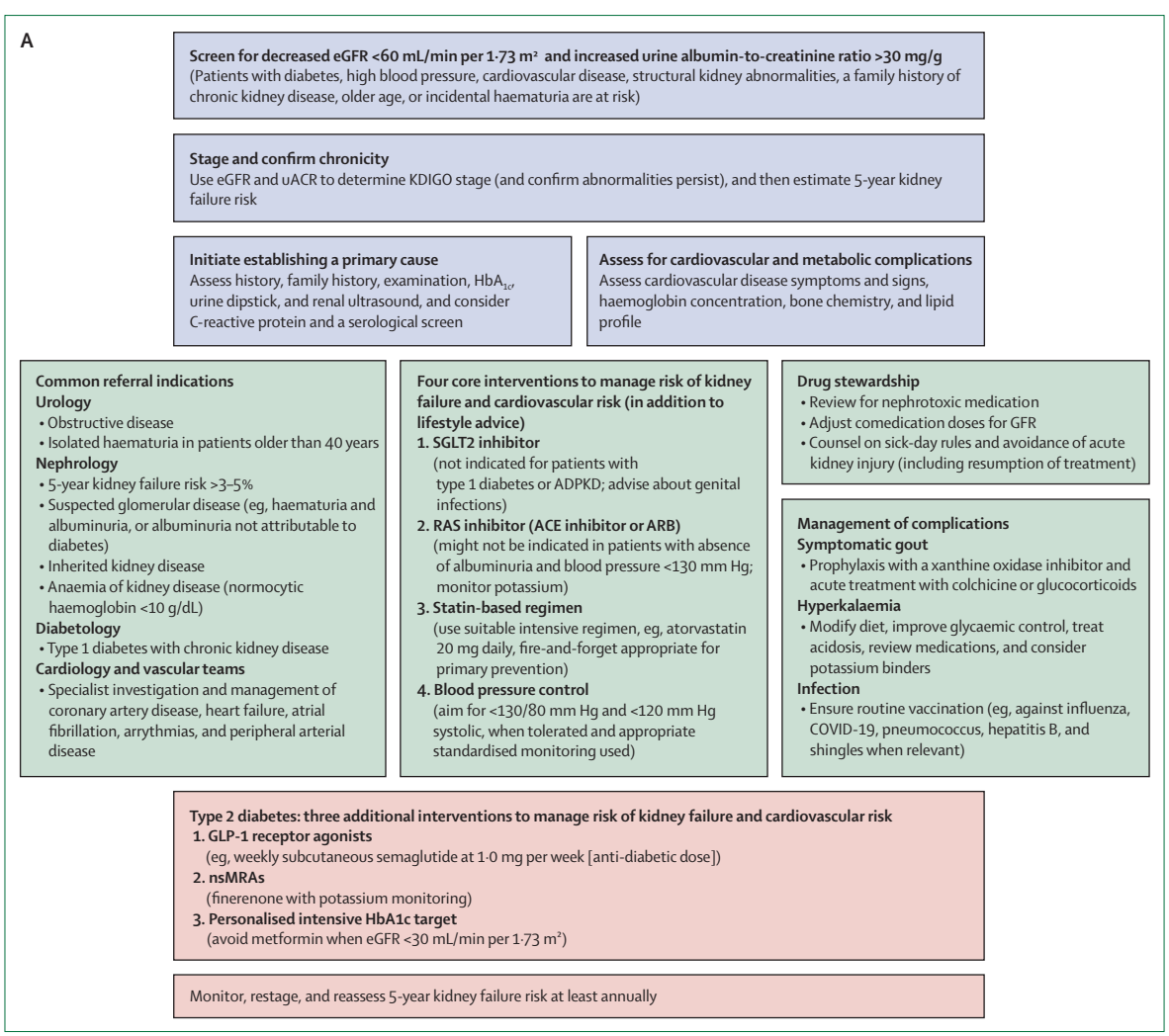
Based on the KDIGO chronic kidney disease definitions, the Global Burden of Disease Chronic Kidney Disease Collaboration estimated the prevalence of chronic kidney disease in 2017 to be approximately 9·1%.[60] Chronic kidney disease stages G1 and G2 accounted for 5·0% of the prevalence, stage G3 for 3·9%, stage G4 for 0·16%, and stage G5 for 0·07% (including 0·04% on dialysis and 0·01% with a kidney transplant).[60] This estimation represented a 29% increase in prevalence of chronic kidney disease since 1990, which is largely explained by population ageing. Age-standardised prevalence of chronic kidney disease is 1·3 times higher in female individuals than in male individuals.[61] Once chronic kidney disease develops, however, eGFR declines faster

in male individuals than in female individuals,[61] and age-standardised incidence of dialysis or transplantation is approximately 1·5-times higher in male individuals.[60,62]

Chronic kidney disease affects countries of all income levels.[42,43] Data from national and regional kidney failure replacement therapy registries illustrate the wide geographical variation in numbers of patients with chronic kidney disease and of patients receiving kidney replacement therapy.[63] Approximately 90% of the global population receiving kidney replacement therapy is estimated to reside in upper-middle-income or high-income countries, yet such countries contain only about half of the global population.[64] Provision of kidney replacement therapy is particularly low in Africa and in low-income parts of Asia.[43,65] An estimated 1·2 million people died with chronic kidney disease as the underlying cause in 2017.[60] The Global Burden of Disease study projects that by 2050, chronic kidney disease will become the fifth most common underlying cause of death worldwide. Chronic kidney disease mortality might rank even higher in populations with long life expectancy.[66] Chronic kidney disease represents the second fastest predicted increase among major causes of death, after Alzheimer's disease.[67]

The 2025 WHO kidney disease resolution encourages member states to invest in health systems and policies aimed at prevention, early detection, and management of kidney disease, with particular focus on equitable access. Expanded access to kidney replacement therapy will reduce premature mortality from kidney disease in resource-limited areas of the world. Prioritising kidney transplantation over dialysis is cost-effective and results in improved quality of life. As a modality, kidney transplantation is less susceptible to disruption during pandemics and humanitarian crises.[35,68]

Poor access to kidney replacement therapy also represents a crucial missed opportunity to reduce mortality associated with acute kidney injury. Globally, a large proportion of



(Figure 3 continues on next page)

B

	Summarised indications for use in chronic kidney disease from US labels	Summarised 2024 KDIGO guideline update recommendation[1] and practice points (and FLOW trial details)[14]
Angiotensin-II receptor blocker (oral losartan or irbesartan)	Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension (or similar such wording)	Use is recommended in patients with chronic kidney disease and diabetes at stage A2–A3 albuminuria or in patients at stage A3 albuminuria without diabetes (limit to G1–G4); use is suggested in patients with A2 albuminuria without diabetes; consider starting people with chronic kidney disease and A1 albuminuria for specific indications (eg, to treat high blood pressure or heart failure)
SGLT2 inhibitor (oral dapagliflozin or empagliflozin 10 mg once daily)	To reduce the risk of sustained decline in eGFR, end-stage kidney disease, cardiovascular death, and hospitalisation (for heart failure*) in adults with chronic kidney disease at risk of progression	Recommend use in patients with type 2 diabetes and chronic kidney disease; in absence of diabetes, use in patients with uACR ≥200 mg/g and suggest use in patients with eGFR 20–45 mL/min per 1·73 m² when uACR <200 mg/g; generally, start when eGFR ≥20 mL/min per 1·73 m² and continue to dialysis as studies have shown continued safety and efficacy at low GFRs
Oral canagliflozin 100–300 mg daily once daily	To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalisation for heart failure in adults with type 2 diabetes and diabetic nephropathy with albuminuria	
Non-steroidal mineralocorticoid receptor antagonist (Oral finerenone 10–20 mg)	To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalisation for heart failure in adult patients with chronic kidney disease associated with type 2 diabetes	Suggest use in patients with type 2 diabetes when eGFR >25 mL/min per 1·73 m², serum potassium concentration is normal, and uACR >30 mg/g despite maximum tolerated dose of RAS inhibitor
GLP-1 receptor agonist (subcutaneous semaglutide 1·0 mg weekly after 8-week titration phase)	To reduce the risk of worsening kidney disease, kidney failure, and death due to cardiovascular disease in adults with type 2 diabetes and chronic kidney disease (other indications exist for weight management with higher dosing)	Trial reported after publication of the 2024 KDIGO guideline update; FLOW trial eGFR and uACR inclusion criteria were eGFR 50–75 mL/min per 1·73 m² plus uACR 300–5000 mg/g, or eGFR 25–50 mL/min per 1·73 m² plus uACR 100–5000 mg/g[14,78]

Figure 3: **Evaluation and management of chronic kidney disease**
(A) Basic evaluation and management information for all clinicians. (B) Additional detail on four pharmacological indications for use and guideline recommendations statements for core chronic kidney disease treatments. For more details see 2024 KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease.[1] ACE=angiotensin-converting enzyme. eGFR=estimated glomerular filtration rate. GFR=glomerular filtration rate. GLP-1=glucagon-like peptide-1. HbA_{1c}=glycated haemoglobin. nsMRA=non-steroidal mineralocorticoid receptor antagonist. PAD=peripheral arterial disease. RAS=renin-angiotensin system. uACR=urine albumin-to-creatinine ratio. *Dapagliflozin indication is specifically for hospitalisation for heart failure, whereas empagliflozin is indicated to prevent all-cause hospitalisation.

deaths due to acute kidney injury occur in low-income and lower-middle-income countries.[69] In these regions, the majority of acute kidney injury cases are community-acquired and frequently arise from infections, exposure to toxins, or complications related to pregnancy.[70] Much of the diagnosed acute kidney injury in middle-income and high-income countries occurs during hospitalisations.[69]

Primary causes of chronic kidney disease

For a given eGFR and uACR, the risk of kidney failure appears to be independent of the primary cause of chronic kidney disease (with the exception of autosomal-dominant polycystic kidney disease [ADPKD]).[71] Key interventions target final common pathways of GFR loss irrespective of chronic kidney disease cause (eg, renin-angiotensin system [RAS] inhibitors[72–75] and SGLT2 inhibitors[11,12]).[76] Nevertheless, identifying a primary cause is required to direct specific treatment strategies, such as immunosuppression for vasculitis or lupus nephritis.[1,77]

Initial investigations for patients with newly diagnosed chronic kidney disease (and acute kidney injury) include a urine dipstick test and quantification of albuminuria, measurements of blood pressure and glycated haemoglobin, and renal ultrasound. Urine dipstick testing can detect non-visible haematuria and aid the identification of glomerulonephritis. Ultrasound scanning evaluates kidney size and symmetry, and screens for urinary tract obstruction and ADPKD (figure 3).[79] When diagnosis is unclear, other diagnostic investigations include screening for paraproteins, serological profiling, detailed renal artery imaging, genetic testing,[80] and kidney biopsy[77] (figure 4).

Diabetes and hypertension are now the most commonly attributed causes of chronic kidney disease in most regions, with diabetes predominating.[60,85–87] In 2011 in China (where in 2017, an estimated 132 million people had chronic kidney disease),[60] diabetic kidney disease became more common than glomerulonephritis, mirroring profound societal changes.[85] In 2017 in India, the prevalence of chronic kidney disease was approximately 115 million cases, with diabetes representing approximately a quarter of all cases.[88] Chronic kidney disease is particularly common in some regions of Africa, where diabetes, hypertension, and

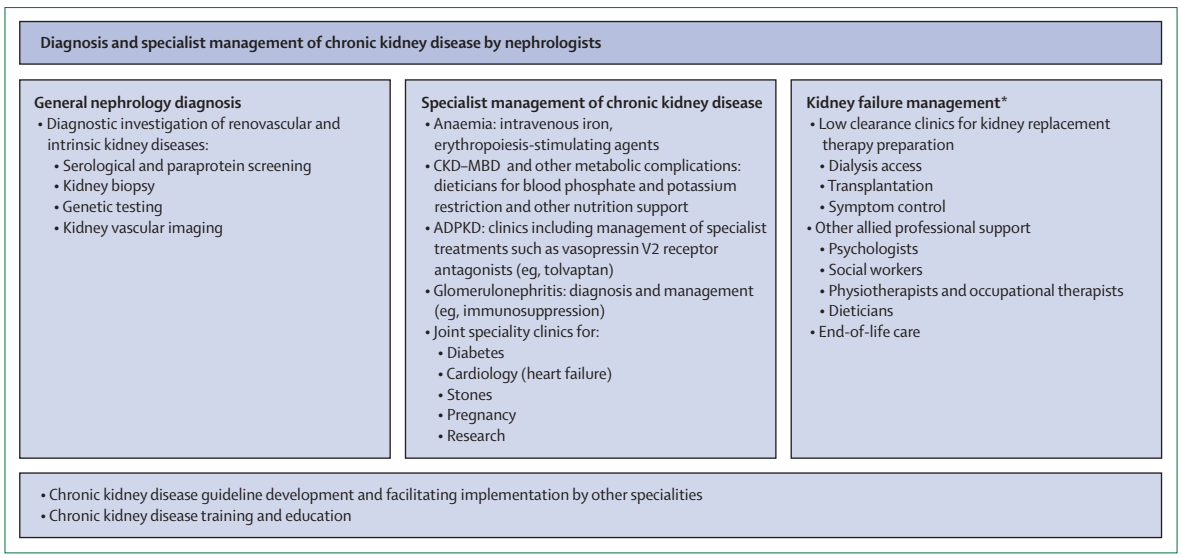


Figure 4: **Specialist nephrology management of chronic kidney disease**
For more detailed information, see Kidney Disease: Improving Global Outcomes reports, such as guidelines and conference reports covering chronic kidney disease diagnosis and management,[1] including specialist management of glomerular disease,[77] ADPKD,[81] CKD–MBD,[82,83] anaemia,[84] and other areas of practice. ADPKD=autosomal-dominant polycystic kidney disease. CKD–MBD=chronic kidney disease mineral bone disorder. ESA=erythropoiesis-stimulating agent. *Nephrologists are recommended to use 2-year kidney failure risk exceeding 40% as a trigger to begin counselling for kidney replacement therapy.

HIV-associated nephropathies are the main causes.[89] *APOL1* risk variants are key contributors to chronic kidney disease burden in west Africa.[90]

The term diabetic nephropathy is typically used to refer to classic histological features of kidney involvement from diabetes.[91,92] However, biopsy studies show a myriad of pathological findings in patients with diabetes, and chronic kidney disease progression can occur even when little albuminuria is present (ie, stage A1 or A2), which prompts the term diabetic kidney disease as a broader designation.[93,94] Clinically, the diagnosis of diabetic kidney disease is usually based on clinical suspicion and informed by the duration of diabetes, the presence of other microvascular complications, and exclusion of alternative causes of chronic kidney disease. Alternative causes should be suspected when the patient has a short history of hyperglycaemia and in the presence of other systemic diseases affecting the kidneys, microscopic haematuria, large or abrupt changes in eGFR or albuminuria, or abnormal serology.[94]

Hypertensive nephropathy is a commonly presumed cause of chronic kidney disease.[12,71] Prolonged high blood pressure results in scarring of glomeruli and vessel wall thickening, but is usually not associated with A3 albuminuria. The bidirectional relationship between blood pressure and chronic kidney disease[95] means that unidentified causes, which could be genetic,[30,96,97] might be erroneously ascribed to hypertension that is secondary to chronic kidney disease.

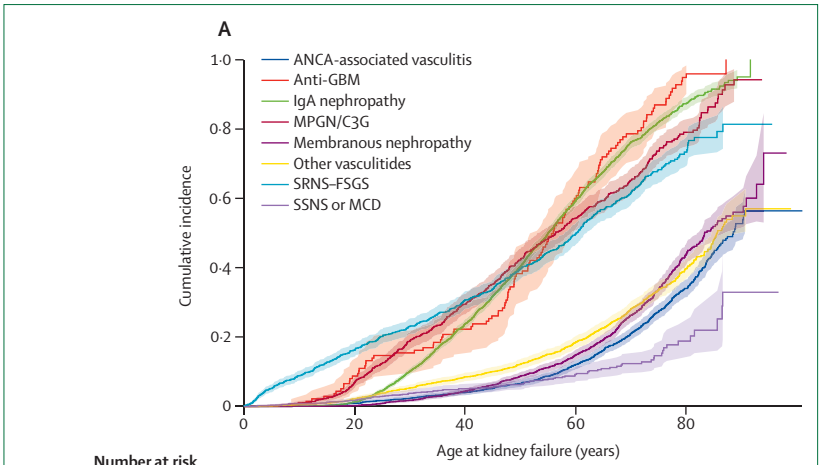
A group of rarer causes represent approximately 5–10% of the total chronic kidney disease burden,[98] but roughly 25% of cases of kidney failure.[99] The UK National Registry of Rare Kidney Diseases has recorded 28 such diseases and the median age at onset of kidney failure (figure 5).[99] Of these 28 diseases, a group of glomerular diseases account for nearly half, with the most common being IgA nephropathy, membranous nephropathy, and vasculitis. Rarer glomerular diseases include C3 glomerulopathy and anti-glomerular basement membrane disease.[99]

ADPKD is the most common monogenic disease.[99] Globally, ADPKD is the fourth most common primary kidney disease among patients on kidney replacement therapy, with median age of onset of kidney failure between 50–60 years.[81] Some unique forms of chronic kidney disease are specific to individual regions (eg, Mesoamerican nephropathy).[100,101]

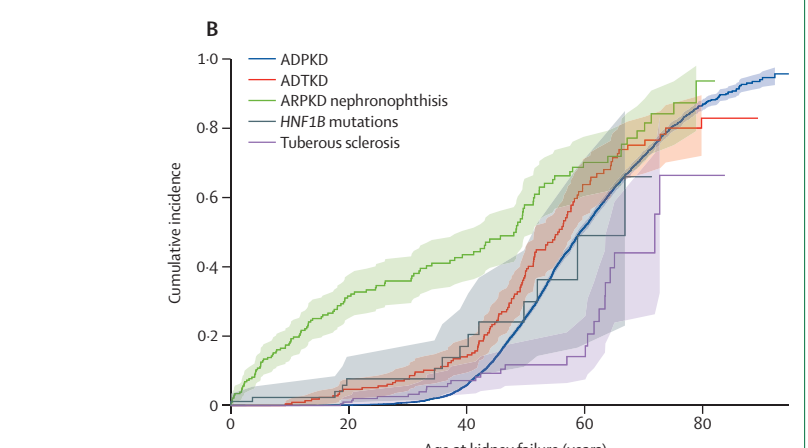
Estimating risk of kidney failure

The KDIGO heat map (figure 2) provides categories of an individual's increased risk of kidney failure relative to a corresponding reference general population without chronic kidney disease. Absolute risk within each chronic kidney disease stage category can vary substantially, so calculating absolute risk of kidney failure requiring replacement therapy using a validated prediction formula is recommended for individuals with chronic kidney disease stage G3–G5.[1] A simple-to-use and widely generalisable formula is the kidney failure risk equation, which, in its 4-variable form, only requires age, sex, eGFR, and uACR.[102] This simplicity means kidney failure risk over 2 years or 5 years can be routinely reported by laboratories into electronic records when recent eGFR and uACR values are both available.[102,103] In addition to supporting patient counselling, knowledge of risk facilitates identification of patients at high risk who might benefit from closer GFR monitoring and

For more on the **kidney failure risk equation** see https://www.kidneyfailurerisk.com



Number at risk (number censored)					
ANCA-associated vasculitis	2375 (0)	2344 (10)	2183 (98)	1697 (413)	425 (1390)
Anti-GBM	137 (0)	125 (0)	102 (5)	51 (7)	4 (13)
IgA nephropathy	4147 (0)	4043 (51)	2741 (481)	959 (1193)	79 (1619)
MPGN–C3G	1089 (0)	933 (85)	585 (228)	293 (332)	36 (481)
Membranous nephropathy	2439 (0)	2425 (8)	2209 (126)	1535 (582)	281 (1514)
Other vasculitides	2331 (0)	2062 (221)	1750 (405)	1286 (694)	319 (1427)
SRNS–FSGS	1536 (0)	1094 (203)	727 (403)	364 (598)	40 (809)
SSNS or MCD	1705 (0)	1092 (588)	715 (933)	373 (1252)	60 (1546)



Number at risk (number censored)					
ADPKD	7797 (0)	7632 (152)	6128 (1264)	1887 (3136)	117 (4018)
ADTKD	215 (0)	201 (4)	152 (35)	36 (80)	4 (98)
ARPKD nephronophthisis	233 (0)	123 (42)	67 (81)	21 (101)	1 (112)
HNF1B mutations	86 (0)	49 (32)	24 (54)	4 (69)	0 (72)
Tuberous sclerosis	249 (0)	195 (52)	99 (139)	29 (204)	2 (221)

Figure 5: **Kaplan–Meier estimates of cumulative incidence of kidney failure for glomerular (A) and cystic kidney diseases (B) in the UK**
Data are censored for death. ADPKD=autosomal dominant polycystic kidney disease. ADTKD=autosomal dominant tubulointerstitial kidney disease. ANCA=antineutrophil cytoplasmic antibody. eGFR=estimated glomerular filtration rate. MPGN–C3G=membranoproliferative glomerulonephritis and C3 glomerulopathy. SRNS–FSGS=steroid resistant nephrotic syndrome, congenital nephrotic syndrome, or focal segmental glomerulosclerosis. SSNS–MCD=steroid sensitive nephrotic syndrome or minimal change disease. Reproduced from Wong et al.[99]

For **examples of risk-prediction tools** see https://ckdpcrisk.org/ckdpatchscore2/ and https://professional.heart.org/en/guidelines-and-statements/prevent-calculator

accelerated intensification of risk-modifying therapy. Referral to nephrology is recommended when 5-year kidney failure risk exceeds 3–5%.[1] Establishing a primary diagnosis is important. Referral for investigation and early treatment of an intrinsic cause (eg, glomerulonephritis), or for complex management of chronic kidney disease-specific complications, is also important (figure 3, 4).

Chronic kidney disease and cardiovascular diseases

An eGFR of less than 60 mL/min per 1·73 m² and A2–A3 albuminuria are independently associated with higher risks of both atherosclerotic cardiovascular disease (ie, myocardial infarction, stroke, and peripheral arterial disease) and predominately non-atherosclerotic cardiovascular disease (ie, heart failure, atrial fibrillation, and sudden cardiac death).[36,104–108] These associations replicate the pattern in the KDIGO heatmap (figure 2).[36] Clinical assessment for the presence of symptoms and signs of these cardiovascular diseases should be part of a holistic approach to managing chronic kidney disease (figure 3).

Associations between chronic kidney disease and cardiovascular diseases are generally similar by age, sex, race, and diabetes status, which calls for a uniform cardiovascular risk-management approach in patients with chronic kidney disease.[36,109,110] If calculating an individual's absolute risk of atherosclerotic cardiovascular disease and cardiovascular mortality is required, validated risk prediction tools exist that incorporate eGFR and albuminuria.[111] The PREVENT risk scores were developed using data from the USA but add predictions for a wider range of cardiovascular diseases.[112]

Approaches to management of cardiovascular risk in chronic kidney disease

Lifestyle modification (including smoking cessation, weight loss, and increased physical activity), intensive blood-pressure lowering, glycaemic control, and statin-based regimens are core strategies to reduce cardiovascular risk in patients with chronic kidney disease.[1] Intentional weight loss has been shown to improve blood pressure and lipid profiles in patients with chronic kidney disease,[113] and to decrease risk of worsening of chronic kidney disease stage, which in turn should reduce cardiovascular risk in the long term.[114]

A blood pressure of less than 130/80 mm Hg is recommended to reduce cardiovascular risk in patients with chronic kidney disease, with some guidelines encouraging a target blood pressure of less than 120 mm Hg systolic, when tolerated.[115–117] The latter target is supported by SPRINT trial data, in which standardised blood pressure measurements were largely unattended.[115–118] Evidence from trials of intensive blood pressure lowering show clear reductions in the risk of major adverse cardiovascular outcomes compared with standard blood pressure targets.[119,120] Whether intensive blood-pressure regimens reduce kidney failure risk remains unclear.[119,120] Sodium restriction to less than 5 g sodium chloride intake daily is encouraged,[1] as trials of dietary reduction suggest this strategy lowers blood pressure and albuminuria.[121]

Dyslipidaemia is common in patients with chronic kidney disease and appears to become more atherogenic as

GFR declines. Dyslipidaemia is characterised by low concentrations of high-density lipoprotein cholesterol, high triglycerides, and an increased proportion of atherogenic, low-density lipoprotein particles, which are small and dense.[122–124] Generally, large trials have shown reductions in cardiovascular risk caused by statin-based regimens are directly proportional to the absolute decrease in low-density lipoprotein cholesterol caused by these regimens, but effects begin to attenuate as eGFR declines to less than 30 mL/min per 1·73 m² (and uncertainty exists about initiation in patients on dialysis).[125] Therefore, early initiation of intensive statin-based regimens in patients with chronic kidney disease is essential to maximise long-term benefits.[1,125,126] Chronic kidney disease is a lifelong condition, and statin-based regimens are shown to be safe and low cost. Therefore, to maximise lifetime benefits, KDIGO guidelines recommend treating all patients with chronic kidney disease who are 50 years or older, as well as younger adults who are at increased cardiovascular risk due to diabetes or previous cardiovascular disease or who exceed 10% estimated 10-year cardiovascular risk.[127] A so-called fire-and-forget primary prevention strategy, by which appropriately intensive statin-based regimens are initiated without follow-up lipid measurements, is recommended.[128] This approach facilitates cost-effective and equitable implementation for the millions of patients with chronic kidney disease who would benefit from such treatment, as many are undertreated. Estimates from 2013–19 suggest approximately one-half of patients with chronic kidney disease stage G3–G5 in high-income European countries are not prescribed statins (with suitably intensive regimens also underused).[129]

Trials in populations without chronic kidney disease have shown the potential for plant-based, Mediterranean-style diets to reduce risk of atherosclerotic cardiovascular disease.[130–132] Patients with chronic kidney disease might consider this diet in addition—but not as an alternative—to statin-based regimens to reduce cardiovascular risk.[1]

Reducing kidney failure risk in patients with chronic kidney disease, including with anti-diabetic treatments

KDIGO guidelines encourage daily intake of roughly 0·8 g protein per kilogram bodyweight for patients with chronic kidney disease,[1] as high protein intake can contribute to increased intraglomerular pressure and balances against the risk of protein-energy wasting.[133]

RAS inhibition with a single-agent angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker is recommended for many patients with chronic kidney disease.[1] Trials show that risk of kidney failure is reduced in patients with diabetes and A3 albuminuria by up to approximately 25%, and that early treatment prevents worsening of albuminuria.[134–138] Less evidence is available in patients with chronic kidney disease without diabetes, but data from trials and a meta-analysis in patients with proteinuric, non-diabetic chronic kidney disease support the use of RAS inhibitors.[72–75] The benefits of RAS inhibition in patients with normal or low blood pressure and low albuminuria (ie, A1–A2) are still uncertain.[139] Combining two RAS inhibitors is not recommended, as trials have shown this strategy does not improve outcomes and increases the risk of acute kidney injury and hyperkalaemia.[140]

Large trials have shown the efficacy and safety of SGLT2 inhibitors, which reduce the risk of kidney failure by approximately one-third, and the risk of heart failure by approximately two-fifths, in patients with chronic kidney disease.[11] Benefits of SGLT2 inhibitors on kidney disease progression occur regardless of diabetes status or primary cause of kidney disease,[11,12] and risk is reduced even in patients with low eGFR, as shown by the EMPA-KIDNEY trial, which included 254 participants with a baseline eGFR of 15–20 mL/min per 1·73 m².[13] Rates of eGFR decline are slowed even with A1–A2 albuminuria.[13] SGLT2 inhibition also reduces risk of acute kidney injury by approximately a quarter.[11,141] Meta-analysis and long-term follow-up of trial participants show reductions in risk of cardiovascular death,[11,142] which appear largely due to fewer deaths attributed to heart failure and sudden cardiac death.[143] The use of SGLT2 inhibitors according to chronic kidney disease eligibility criteria has been shown to be cost-effective in some health-care settings.[144,145] More widespread, long-term use of affordable SGLT2 inhibitors, even in patients with early chronic kidney disease, would probably maximise lifelong kidney and cardiovascular benefits,[142] and future low pricing could have a major effect on the global burden of chronic kidney disease.

Glucose-lowering effects of SGLT2 inhibitors are generally weaker than those of other anti-diabetic agents and markedly attenuated in patients with decreased eGFR. SGLT2 inhibitors should not be expected to help reach glycaemic targets in patients with moderate or severe chronic kidney disease.[146] Patients with type 1 diabetes have been under-represented in chronic kidney disease trials.[147] SGLT2 inhibition appears to slow chronic kidney disease progression in patients with type 1 diabetes,[13] but such use would currently be off-label, and might require additional supervision to minimise risk of ketoacidosis (eg, with ketone monitors).[29] Future trials of SGLT2 inhibitors in patients with type 1 diabetes (NCT06217302) and new trials in patients with ADPKD are currently ongoing (NCT06217302).[81,148]

Additional treatments in diabetes with chronic kidney disease

In patients with chronic kidney disease, albuminuria, and type 2 diabetes, the non-steroidal mineralocorticoid receptor antagonist (nsMRA) finerenone has been shown to reduce the risk of kidney failure by approximately a quarter,[6] but had no effect on chronic eGFR slope in patients with heart failure, despite reducing albuminuria by approximately 30%.[149] Cardiac benefits of finerenone include an approximately one-fifth reduction in the risk of

heart failure hospitalisation compared with placebo.[150] nsMRAs increase blood potassium, and the definitive trials of finerenone required patients at screening to have potassium values of 4·8 mmol/L or less and intensive potassium monitoring. This restriction limits the generalisability of safety findings, but reassuringly, hyperkalaemia rarely led to hospitalisation using this approach (finerenone 0·9% *vs* placebo 0·2%).[6,8,151] Results from large-scale, placebo-controlled trials testing the use of nsMRAs or aldosterone synthase inhibitors in patients with chronic kidney disease without diabetes are awaited.[26,27]

Since the publication of the KDIGO 2024 guideline update,[1] the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide has shown efficacy in slowing kidney disease progression and reducing cardiovascular risk in patients with type 2 diabetes and chronic kidney disease.[14,152] In the FLOW trial,[14] in patients with an eGFR of 25–75 mL/min per 1·73 m² and albuminuria (with a mean BMI of 32·0 kg/m² [SD 6·3]), subcutaneous semaglutide 1·0 mg per week (ie, the anti-diabetic dose) reduced the risk of the primary major kidney disease event composite outcome by approximately a quarter compared with placebo.[14] Consistent effects were found across subgroups stratified by baseline BMI, glycaemic control, eGFR, and uACR.[14] The rate of eGFR decline was reduced by approximately a third, and although the FLOW trial was not powered to assess kidney failure alone, when results were combined with other large trials, GLP-1 receptor agonists reduced the risk of kidney failure in patients with diabetes by approximately a sixth.[15] Importantly, risk of the secondary composite cardiovascular outcome of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death was statistically significantly reduced by semaglutide.[153] The use of semaglutide appears generally safe in patients with chronic kidney disease, with its 8-week dose titration phase used to reduce the risk of gastrointestinal side-effects during initiation. Subcutaneous semaglutide at its weight loss dose (2·4 mg per week) also appeared to importantly slow loss of eGFR in individuals with obesity and cardiovascular disease in the SELECT trial.[154]

Glycated haemoglobin (HbA_{1c}) targets aim to minimise microvascular complications of diabetes (ie, nephropathy, retinopathy, and neuropathy) without risking serious hypoglycaemia. Intensive strategies reduce markers of microvascular disease but have not been shown to reduce kidney failure,[155] nor do they affect risk of stroke, heart failure, peripheral arterial disease, or mortality. Intensive strategies can modestly reduce the risk of myocardial infarction.[156,157] When considering blood glucose-lowering therapy in patients with chronic kidney disease and diabetes, safe interventions proven to reduce kidney failure or cardiovascular risk (eg, semaglutide) should be prioritised. Metformin has not been conclusively shown to reduce cardiovascular risk,[158] but is low in cost and generally well tolerated. Substantial dose reduction (eg, to 500 mg once or twice daily) is required in patients with an eGFR of less than 45 mL/min per 1·73 m², and metformin should be switched to an alternative therapy when eGFR declines to less than 30 mL/min per 1·73 m², due to risk of its accumulation and development of lactic acidosis.[159,160]

Progress in treatment of rare causes of chronic kidney disease

Trials of treatments that target distinct primary kidney disease pathology have also been conducted. Such trials tend to have small sample sizes and use reductions in albuminuria or proteinuria for proof-of-concept or dose-finding trials. To support that such reductions translate into safe slowing of eGFR decline in the long term—which is not always the case[140,149]—subsequent larger trials should assess the effects on eGFR slope over the course of 2 or more years and adequately assess safety.[161]

The most common cause of glomerulonephritis worldwide is IgA nephropathy.[162] Targeting the final common pathways is effective in IgA nephropathy. SGLT2 inhibition has been assessed in more than 1000 patients with IgA nephropathy in two placebo-controlled trials that found moderately large beneficial effects on kidney disease progression outcomes on the basis of sustained 50% decline or more in eGFR.[11,12,163] Endothelin receptor antagonists were originally studied in patients with diabetic kidney disease but found to increase the risk of fluid retention and heart failure.[164,165] More recently, endothelin-receptor antagonists have been shown to reduce proteinuria and rate of eGFR decline in patients with IgA nephropathy.[19–21] The proteinuria-lowering effects of endothelin receptor antagonists are also evident in patients with other glomerular diseases.[166]

IgA nephropathy also responds to immunosuppression. The TESTING trial randomly assigned 503 patients with highly proteinuric IgA nephropathy and showed that methylprednisolone reduced risk of kidney failure by approximately two-fifths compared with placebo over 4 years.[22] Trials recruiting patients with IgA nephropathy and proteinuria of at least 1·5 g per day (ie, >1500 mg/g) have led to other immunosuppression regimens, including gut mucosal-targeted release budesonide[23] and the complement factor B inhibitor iptacopan,[167] receiving approval for clinical use.[168,169] Modulating B-cell proliferation and differentiation by targeting a proliferation-inducing ligand and B-cell activating factor separately or with combined inhibitors has also been shown to reduce proteinuria in initial phase 2 trials.[162,170]

The standard of care for ADPKD is intensive blood pressure control, prescribing RAS inhibitors as first-line therapy, and encouraging liberal water intake (although the supporting evidence base is weak).[171] For patients with ADPKD and large total kidney volume, or previous rapid eGFR decline, the aquaretic vasopressin V2 receptor blocker tolvaptan is indicated.[81]

Drug stewardship and intravenous contrast

Chronic kidney disease confers increased susceptibility to the nephrotoxic effects of medications, including

over-the-counter drugs, such as non-steroidal anti-inflammatory drugs. Avoiding acute kidney injury is advisable as it can accelerate chronic kidney disease progression (and be a primary cause of chronic kidney disease). Many providers implement what are known as sick-day rules in the case of poor oral intake, diarrhoea, or vomiting, to reduce risk of acute kidney injury by temporarily discontinuing using RAS inhibitors, SGLT2 inhibitors, and mineralocorticoid receptor antagonists.[1] Use of SGLT2 inhibitors should be reviewed upon admission to hospital, especially if oral intake is reduced, but data on the safety of use of SGLT2 inhibitors in patients with acutely decompensated heart failure and COVID-19 infection requiring hospitalisation are reassuring.[172,173]

Many medications require dosing adjustment in patients with chronic kidney disease. Necessary adjustment can be calculated using standard eGFR formulas, with deindexing of body surface area, particularly when medications have a narrow therapeutic range or when patients have very high or very low BMI.[1]

The use of iodinated contrast agents when conducting imaging for patients with chronic kidney disease has been controversial due to observations of periprocedural creatinine increases; however, permanent harm from contrast-induced acute kidney injury (ie, death, dialysis, or sustained important reductions in eGFR after 6 months) is uncommon[174] and can usually be attributed to other causes. Therefore, delaying or withholding diagnostic tests and angiographic procedures should be avoided in patients with chronic kidney disease to avoid misdiagnosis or undertreatment.[175] Limiting contrast agent volume, and using non-ionic, low-osmolar, or iso-osmolar agents should be the priority in patients with chronic kidney disease.[176]

Management of other complications of chronic kidney disease

Several abnormalities commonly develop as chronic kidney disease progresses; fortunately, they are simple to screen for with blood tests.[1,177–179] Abnormalities such as renal anaemia and chronic kidney disease–mineral bone disorder are generally managed by nephrologists (figure 4).

Anaemia of kidney disease develops due to low iron bioavailability and diminished erythropoietin synthesis. Management of anaemia of kidney disease typically involves the use of oral or intravenous supplementation to augment iron stores to higher than normal physiological amounts, and then subcutaneous injections of erythropoiesis-stimulating agents. Erythropoiesis-stimulating agents are used cautiously and with tight haemoglobin targets, as aiming for complete anaemia correction with these agents increases cardiovascular risk.[179–182] Nephrologists generally initiate treatment when haemoglobin falls to 9·0–10·0 g/dL, and maintain it between 10·0–11·5 g/dL. New hypoxia-inducible factor prolyl hydroxylase inhibitors are an oral alternative to erythropoiesis-stimulating agents, but have not been shown to be superior in cardiovascular safety trials.[84,183,184]

Decreased GFR results in reduced urinary phosphate excretion and abnormalities in calcium and parathyroid hormone regulation.[177] These abnormalities are collectively referred to as chronic kidney disease–mineral bone disorder.[82] Dietary phosphate restriction and the use of phosphate binders can reduce the risk of premature vascular calcification and is often implemented when chronic kidney disease is severe. Additionally, vitamin D analogues or calcimimetics (eg, cinacalcet) can be used to control hyperparathyroidism with the aim of maintaining bone health.[83] Metabolic acidosis can also develop in patients with severe chronic kidney disease. Oral alkali therapy with sodium bicarbonate can be considered, although neither definitive evidence for a bicarbonate threshold for initiation, nor an optimal safe treatment target, have been established.[1]

Controversies and uncertainties

Different clinical practice guidelines are generally aligned on recommendations for standards of pharmacological care in patients with chronic kidney disease.[1,57,139,185–187] Well designed clinical outcome trials are needed to establish an uncontroversial evidence base for dietary interventions. Guidelines disagree on protein intake advice for patients with chronic kidney disease.[188–191]

Data on the clinical efficacy of combining SGLT2 inhibitors, nsMRAs, and GLP-1 receptor agonists in patients with chronic kidney disease are limited to subgroup analyses of relevant trials stratified by patients treated with these medications at baseline.[192–195] The mechanisms of action of these three drug classes target distinct pathophysiology, which suggests hypothetical benefits of combination therapy. Non-clinical outcome trials of SGLT2 inhibitors and aldosterone pathway-targeting treatments show that combined treatment lowers albuminuria more than either treatment alone.[16–18] Assuming combination therapy is beneficial, the optimal order and timing of initiation of each treatment is uncertain. A rapid-sequence approach to starting treatment has been suggested to ensure maximum absolute benefits in a short period of time, but has time resource implications for health-care systems. This approach could be prioritised for patients with the highest predicted risk of kidney failure or cardiovascular disease.[196]

On initiation of SGLT2 inhibitors and GLP-1 receptor agonists, additional monitoring is not routinely necessary. Monitoring of potassium concentration and eGFR within 1–4 weeks after initiation of a RAS inhibitor or nsMRA is prudent if the patient's pretreatment potassium concentration is not in the low or low-normal range.[1] SGLT2 inhibitors modestly reduce the risk of hyperkalaemia and therefore concomitant use can facilitate tolerance of RAS inhibitors or mineralocorticoid receptor antagonists.[146,197]

RAS inhibitors, SGLT2 inhibitors, and nsMRAs cause an acute dip in eGFR upon initiation. The dip reverses upon discontinuation,[198] and its predicted size does not modify

the acute kidney injury and chronic kidney disease progression benefits of SGLT2 inhibition.[141] With RAS inhibitors and nsMRAs, clinicians typically accept an acute dip in eGFR of up to 30% without recommending treatment discontinuation.[1] A better understanding of the optimal approach to acute eGFR dips of more than 30% is needed, particularly when multiple treatments are initiated.[16]

Conclusion

Chronic kidney disease is a condition that is generally simple to identify and stage using GFR and uACR, and is present in hundreds of millions of individuals globally. Chronic kidney disease substantially increases the risk of a wide range of cardiovascular diseases and kidney failure. Since the 2021 *Lancet* Seminar on chronic kidney disease, the effectiveness of several classes of medications that favourably modify kidney failure risk and cardiovascular risk in a broad range of people with chronic kidney disease has become evident. Guidelines highlight core evidence-based approaches, including use of SGLT2 inhibitors, RAS inhibitors, statin-based regimens, and intensive blood pressure targets. GLP-1 receptor agonists and the nsMRA finerenone should be considered in patients with chronic kidney disease and type 2 diabetes alongside lifestyle advice and personalised or suitably intensive HbA_{1c} targets. These interventions make up a new standard of care for patients with chronic kidney disease and can be implemented in many different clinical settings. If health-care services can ensure early use of cost-effective pharmacological and non-pharmacological treatments across all resource settings, the global burden of chronic kidney disease complications could be substantially alleviated.

Contributors

WGH and CW developed the focus of the Seminar. WGH and PKJ specified the scope of the literature review. WGH wrote the first draft. All authors contributed to the interpretation of the literature and provided critical review and revision.

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