Advances in the management of chronic kidney disease

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Abstract

Chronic kidney disease (CKD) represents a global public health crisis, but awareness by patients and providers is poor. Defined as persistent abnormalities in kidney structure or function for more than three months, manifested as either low glomerular filtration rate or presence of a marker of kidney damage such as albuminuria, CKD can be identified through readily available blood and urine tests. Early recognition of CKD is crucial for harnessing major advances in staging, prognosis, and treatment. This review discusses the evidence behind the general principles of CKD management, such as blood pressure and glucose control, renin-angiotensin-aldosterone system blockade, statin therapy, and dietary management. It additionally describes individualized approaches to treatment based on risk of kidney failure and cause of CKD. Finally, it reviews novel classes of kidney protective agents including sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, non-steroidal selective mineralocorticoid receptor antagonists, and endothelin receptor antagonists. Appropriate, widespread implementation of these highly effective therapies should improve the lives of people with CKD and decrease the worldwide incidence of kidney failure.

Introduction

Chronic kidney disease (CKD) affects approximately 10% of the world's population and is associated with substantial morbidity and mortality.[1] Risks of kidney failure, acute kidney injury, heart failure, cardiovascular disease, and hospital admissions are all heightened in people with CKD.[2] The Global Burden of Disease Consortium projects that CKD will be in the top five conditions contributing to years of life lost by 2040.[3] However, CKD remains under-recognized by both patients and providers.[1] A diverse entity, CKD is most commonly attributed to diabetes or high blood pressure, but many other causes exist, from genetic causes to adverse effects of drugs to autoimmune processes.[2] In this review, we summarize the evidence for current paradigms of disease identification and classification, discuss new equations developed for estimating glomerular filtration rate (GFR) and harmonizing different measures of albuminuria, report major progress in individualized risk estimation of kidney failure and other adverse outcomes both for CKD in general and within specific disease entities, and describe longstanding and novel treatment strategies. Notable advances have been made in both general and cause specific therapies, including sodium-glucose cotransporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, non-steroidal selective mineralocorticoid receptor antagonists (MRA), and endothelin receptor antagonists. Finally, we describe major guidelines in CKD and highlight common themes as well as differences in their recommendations.

Sources and selection criteria

We searched PubMed for peer reviewed articles in the English language from 1 January 2010 to 14 July 2023 using the keywords listed in the web appendix. We additionally reviewed reference lists of selected articles, prioritizing randomized controlled trials, systematic reviews, and meta-analyses when possible but also including observational studies and reviews that were of high quality. We included older articles if we deemed them to be of high importance. Finally, we reviewed guidelines from websites of professional societies and advisory committees (for example, the National Institute for Health and Care Excellence (NICE), Kidney Disease: Improving Global Outcomes (KDIGO), US Centers for Disease Control and Prevention, US Department of Health and Human Services, and International Society of Hypertension).

Epidemiology

CKD is a global public health crisis. Recent estimates suggest that more than 700 million people have CKD, with greater burdens in low income and middle income countries.[1 4] Determining the global, regional,

and national burden of disease is challenging owing to inconsistent use of estimating equations for GFR, laboratory assay standardization, and albuminuria testing. Despite this, some important observations can still be made. The prevalence of CKD increases with age and is greatest in people over 70 years.[2] In the US, compared with White people, Black people have substantially higher rates of kidney failure, followed by Native Americans, people of Hispanic ethnicity, and people of Asian descent.[5]

The most commonly reported risk factors for CKD are diabetes mellitus and hypertension.[6 7] Social determinants of health are also important and likely contribute to racial disparities in kidney disease. Specific genetic variants increase risk of CKD, including variants in the *APOL1* and *HBB* genes that are present in far greater proportions among people of African ancestry.[8-11] In Central America, Sri Lanka, Egypt, and Central India, defined geographic areas exist where many cases of CKD of unknown cause have been identified.[12] Some experts postulate that heat stress or pesticides may contribute.

Whereas the incidence of CKD is difficult to estimate, reliant as it is on testing for GFR and albuminuria, the incidence of kidney failure with the receipt of replacement therapy (KFRT) is more readily captured. Many countries have developed national registries of patients with kidney failure, allowing comparison of incidence across ages and countries.[13] For example, the countries with the highest incidence of treated kidney failure in 2020 were Taiwan, the US, and Singapore, whereas the countries with the highest prevalence were Taiwan, the Republic of Korea, and Japan.[5]

Definition and classification of CKD: cause, GFR, and albuminuria staging

CKD is defined as persistent abnormalities in kidney structure or function for more than three months, manifest as either low GFR or presence of a marker of kidney damage.[2] Specifically, diagnosis requires one or more of the following: albuminuria, defined as an albumin-to-creatinine ratio (ACR) ≥30 mg per gram of creatinine (approximately ≥3 mg/mmol) or albumin excretion of ≥30 mg/day; GFR <60 mL/min/1.73 m^2; abnormalities on urine sediment, histology, or imaging; electrolyte or other abnormalities attributed to tubular disorders; or history of kidney transplantation. The KDIGO heat map helps with understanding of overall risk (low, moderately increased, high, and very high) of patients according to level of albuminuria (A category), level of GFR (G category), and cause of disease (fig 1), such that people with normal estimated GFR but higher albuminuria have a similar risk to people with moderately reduced estimated GFR and no albuminuria.

Clinical manifestations of CKD

Albuminuria

Albuminuria is often the first sign of kidney damage, and its detection drives many treatment decisions.[2] The prevalence of albuminuria in people with diabetes or hypertension is estimated to be 32% and 22%,

Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category			Persistent albuminuria categories Description and range		
			A1	A2	A3
			Normal to mildly increased	Moderately increased	Severely increased
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range					
G1	Normal or high	≥90	1 if CKD	1	2
G2	Mildly decreased	60-89	1 if CKD	1	2
G3a	Mildly to moderately decreased	45-59	1	2	3
G3b	Moderately to severely decreased	30-44	2	3	3
G4	Severely decreased	15-29	3	3	4+
G5	Kidney failure	<15	4+	4+	4+

Fig 1 | Kidney Disease: Improving Global Outcomes heat map with guidance on monitoring.[2] Numbers in boxes indicate recommended frequency of monitoring (number of times per year). Colors denote risk as follows: green (low risk), yellow (moderately increased risk), orange (high risk), and red (very high risk). CKD=chronic kidney disease; GFR=glomerular filtration rate

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respectively.[14] However, only a minority of patients receive urine screening tests.[14 15] For example, the mean albuminuria screening rates across health systems in the US were 35% among adults with diabetes and 4% among adults with hypertension.[14]

The gold standard for assessing albuminuria is either a sample collected mid-stream from an early morning urine void or a 24 hour urine collection; however, in situations where this is not possible, a spot collection is reasonable.[2] Quantification of albumin is preferred over that of total protein.[2 16] This preference is because the sensitivity of the total protein assay to different protein components can vary by laboratory, as well as the fact that proteinuria assessments do not easily discriminate A1 and A2 categories. Both urine albumin and urine protein are typically indexed to urine creatinine to account for differences in dilution, as urine ACR or urine protein-to-creatinine ratio (PCR). Dipstick protein assessment is generally more economical than both methods; however, like PCR, dipstick assessment can be insensitive in A1 and A2 categories. Although conversion calculators exist to aid in the harmonization of ACR and PCR measures; they do not work well at lower ranges of albuminuria.[17 18]

GFR

The second axis for CKD classification focuses on GFR.[2] The gold standard for assessing GFR is direct measurement from clearance of an exogenous filtration marker such as iohexol or iothalamate; however, this is relatively cumbersome and rarely done in clinical practice. Instead, GFR is usually estimated by using plasma or serum concentrations of endogenous filtration markers, such as creatinine and cystatin C, and demographic variables. Early equations for adults, such as Modification of Diet in Renal Disease (MDRD) and CKD Epidemiology Collaboration (CKD-EPI) 2009 equations, used filtration markers along with age, sex, and race (Black versus non-Black) to estimate GFR.[19-21] The newer European Kidney Function Consortium equation, which allows for seamless GFR evaluation from infancy to old age, uses a population specific divisor to adjust creatinine values (for example, separate values for Black European and White European populations).[22] However, the use of race in GFR estimation has faced strong criticism and, in 2021, the US based American Society of Nephrology-National Kidney Foundation Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease recommended immediate adoption of the race-free CKD-EPI 2021 estimating equations, which exist for creatinine alone (eGFRcr) as well as for creatinine and cystatin C (eGFRcr-cys).[23-25] Cystatin C has distinct confounders (non-GFR determinants) of its relation with GFR compared with creatinine (fig 2).[2 26] Thus, eGFRcr-cys is a more accurate estimate of GFR than eGFRcr alone, irrespective of equation used, in most scenarios, including those in which large differences exist between eGFRcr and that estimated solely using cystatin C (eGFRcys).[25-28] However, the newest GFR estimating equations have not been tested extensively in Asian populations.[29 30]

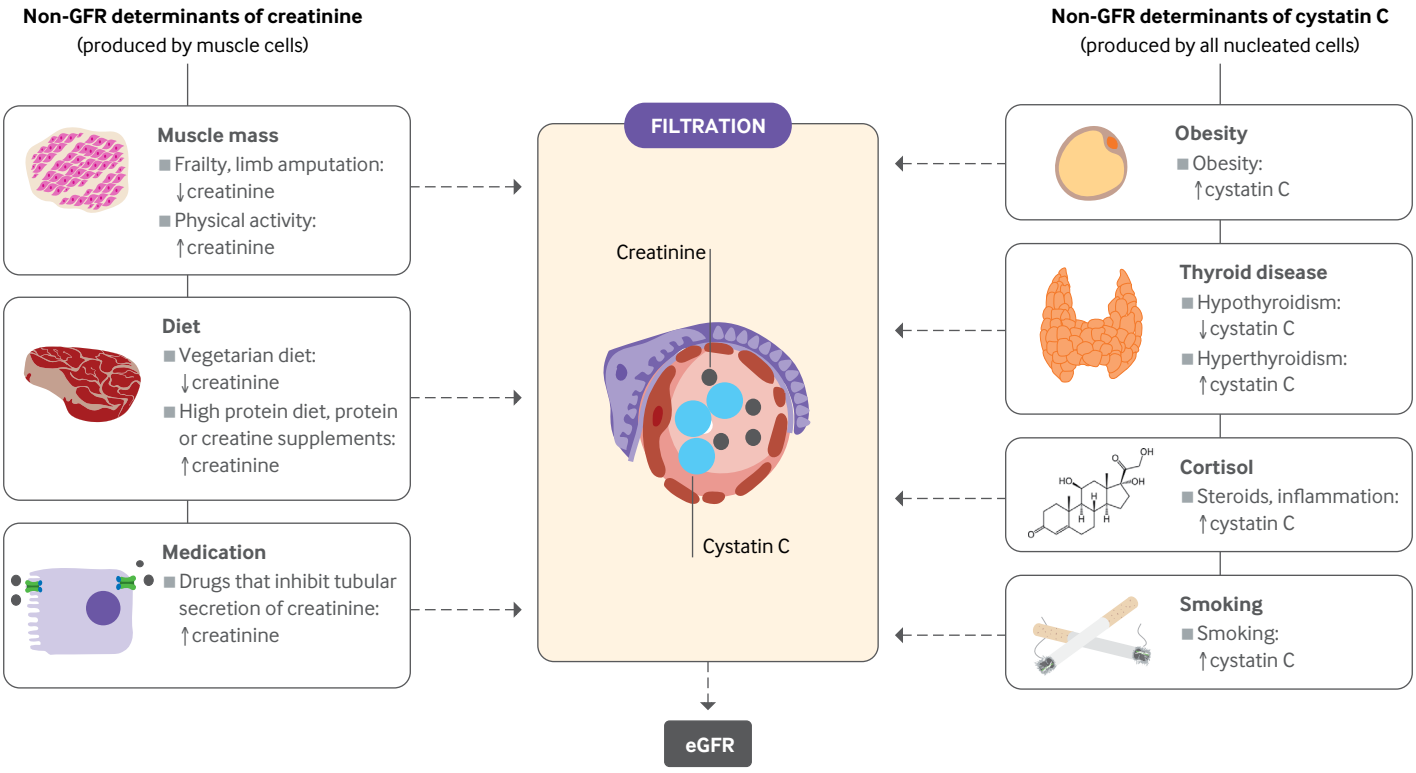

Fig 2 | Common non-glomerular filtration rate (GFR) determinants of blood concentrations of creatinine and cystatin C.[2 26] eGFR=estimated glomerular filtration rate

Box 1: European Renal Association and European Rare Kidney Disease Reference Network recommendations for settings in which genetic testing might be considered[33]

- Most tubulopathies
- Glomerulopathies:
  - Congenital nephrotic syndrome
  - Nephrotic syndrome refractory to standard steroid therapy
  - Multi-organ phenotypes suggestive of syndromic steroid resistant nephrotic syndrome
- Complement disorders:
  - Immune complex mediated membranoproliferative glomerulonephritis
  - C3 glomerulopathy
  - Atypical hemolytic uremic syndrome
- Renal ciliopathies
- Congenital anomalies of the kidney and urinary tract
- Patients aged ‹50 years with severe CKD of unknown cause
- Patients aged ›50 years with adult onset CKD and family history of CKD

CKD=chronic kidney disease

Cause

The third axis for classification is cause of CKD, which is generally ascertained through imaging, assessment of extrarenal manifestations and biomarkers, or kidney biopsy.[2] Classification of cause typically hinges on the presence or absence of systemic disease (for example, obesity, diabetes, hypertension, systemic autoimmune disease) and the specific location of the kidney pathology (for example, glomeruli, tubulointerstitium, vasculature, or cystic/congenital abnormality). Unfortunately, the cause of CKD is often unknown, limiting its utility. Molecular phenotyping and genetic testing are increasingly being used to assign cause of disease. Targeted gene panels offered commercially may have high diagnostic yields in select populations, such as patients with glomerular disease, nephrotic syndrome, or congenital anomalies of the kidney and urinary tract.[31] One study suggested that for appropriately selected patients, 34% had disease either reclassified or assigned on the basis of genetic testing, thus changing clinical management.[32] The European Renal Association and the European Rare Kidney Disease Reference Network have issued a joint statement providing recommendations for how to provide genetic testing, including specific settings in which it may be considered (box 1).[33]

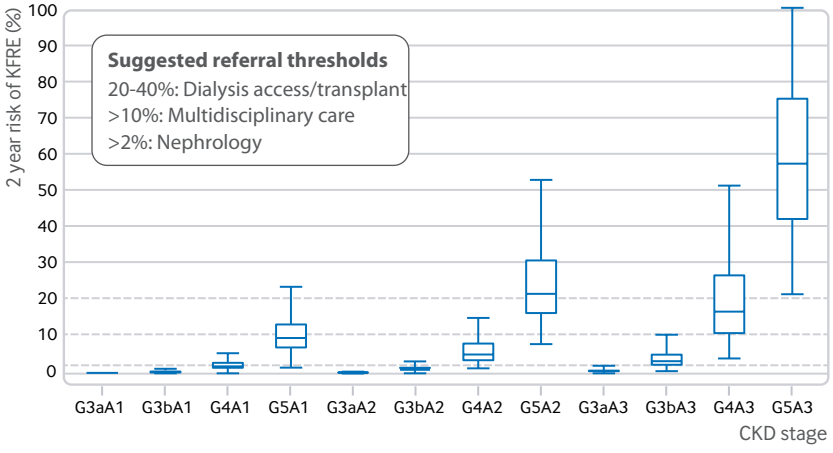

Fig 3 | Range of predicted risk of kidney failure using the kidney failure risk equation (KFRE) within G and A categories of chronic kidney disease (CKD). The KFRE (ckdpcrisk.org/kidneyfailurerisk) was used to estimate two year risk of kidney failure in 350 232 patients with estimated glomerular filtration rate (eGFR) ‹60 mL/min/1.73 m^2 from the Optum Laboratories Data Warehouse (OLDW). OLDW is a longitudinal, real world data asset with deidentified administrative claims and electronic health record data. Patients with eGFR and albuminuria (urine albumin-to-creatinine ratio (ACR), protein-to-creatinine ratio, or dipstick protein) within a two year window were included in this analysis. Different measures of albuminuria were harmonized to ACR levels for A categories (ckdpcrisk.org/pcr2acr)

Individualized prognosis and treatment

Identifying the cause of CKD is critical as different causes of CKD carry different prognoses and can have distinct treatments.[2] For example, autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of CKD and is typically associated with faster progression than other disease entities.[32 34] Individualized prognosis is often determined by using disease specific risk classification or calculators (for example, the Mayo classification or the ADPKD Prognostic Tool), and screening and treatment recommendations such as increased fluid intake and tolvaptan are unique to this entity.[35-38] IgA nephropathy, the most common type of glomerulonephritis worldwide, particularly in East Asian and Pacific Asian countries,[39] has its own prognostic aids, such as the International IgA Nephropathy Prediction Tool,[40 41] and treatments specific to IgA nephropathy are in various stages of development.[42] The *APOL1* high risk genotypes confer about twofold higher risk of kidney failure in the general population and are common in people of African ancestry.[8 43-45] A recently published phase 2A study of targeted therapy for *APOL1* related disease showed promising reductions in albuminuria; the phase 3 study is ongoing.[46] Other disease specific therapies are increasingly available, such as belimumab in lupus nephritis and lumasiran for primary hyperoxaluria type 1.[47 48]

Individualized risk prediction is also available for more general populations of patients with CKD. The most widely known and validated is the kidney failure risk equation (KFRE), which is used in patients with GFR <60 mL/min/1.73 m^2.[49] Tested in more than 30 countries and 700 000 people, the tool provides probabilities of kidney failure at two years and five years based on age, sex, and estimated GFR and albuminuria levels.[50] Like all risk equations, the KFRE may perform better with recalibration to absolute risk levels of local populations, but the discriminatory ability (that is, distinguishing people at high risk from those at low risk) has been extremely consistent across all studies. The KFRE has also been validated in recipients of kidney transplants.[51 52] Although the KFRE does not explicitly take into account the competing risk of death, estimates are quite accurate except among the members of the

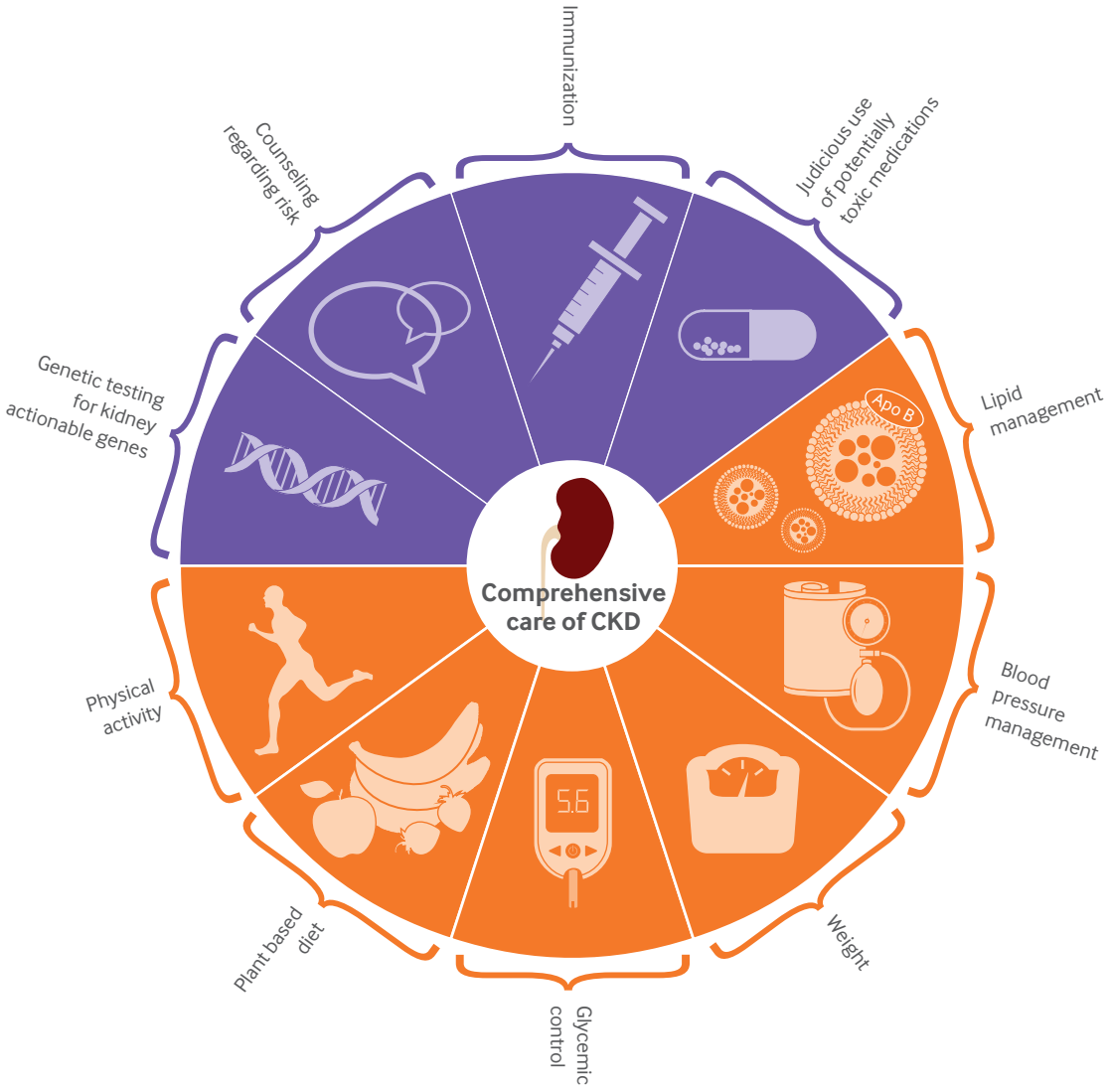

Fig 4 | Comprehensive care of patients with chronic kidney disease (CKD), irrespective of cause

oldest segments of the population at the highest risk.[53] One study suggested that the KFRE provides more accurate prediction of kidney failure than both patients and providers.[54] Even within categories of GFR and urine ACR, the KFRE provides a wide estimate of risk prediction, which can be helpful in the counseling and referral of patients (fig 3). Some centers will refer patients with a two year risk of kidney failure greater than 20-40% for vascular access and kidney transplantation evaluation, on the basis that tools that incorporate albuminuria provide more accurate and unbiased time to kidney failure than does estimated GFR alone.[55] Studies suggest that the KFRE is robust to different GFR equations (specifically, CKD-EPI 2009 and CKD-EPI 2021) and that many patients value being counseled using this information.[53 56]

Other risk equations exist to predict the risk of cardiovascular disease and death in CKD; some of these do consider the competing risk of death (www.ckdpcrisk.org). For example, the advanced CKD risk tool provides simultaneous estimates of kidney failure, cardiovascular disease, and death for patients with estimated GFR <30 mL/min/1.73 m^2, which can inform decisions on access placement and reinforce the importance of cardiovascular risk reduction.[57] Estimating risks of cardiovascular disease is particularly relevant given that many more patients with CKD have cardiovascular disease events than need KFRT.[58] Other efforts incorporate estimated GFR and albuminuria into existing tools, such as SCORE2 and the pooled cohort equation for the prediction of cardiovascular disease.[59 60]

Patient specific prognostic clues may stem from discrepant estimated GFR values between eGFRcr and eGFRcys.[61-63] When eGFRcys is substantially lower than eGFRcr, the risk for kidney related laboratory abnormalities (for example, anemia, hyperuricemia, and hyperphosphatemia) and subsequent adverse outcomes (for example, kidney failure, heart failure, and mortality) is higher.[61 64 65] By contrast, having a lower eGFRcr than eGFRcys is associated with lower risk of adverse outcomes.[66] Risk factors for having a discrepancy between eGFRcr and eGFRcys include

Table 1 | Landmark randomized clinical trials on angiotensin converting enzyme inhibitors or angiotensin receptor blockers in chronic kidney disease

Parameter	REIN Stratum 2[76](n=166)	RENAAL[77] (n=1513)	IDNT[78] (n=1715)	AASK[68] (n=1094)	Benazepril for Advanced CKD, Group 2[79] (n=224)
Kidney related inclusion criteria	CrCl 20-70 mL/min/1.73 m^2 and protein excretion ≥3 g/day	SCr 1.3-3.0 mg/dL and ACR ≥300 mg/g or protein excretion ≥0.5 g/day	SCr 1.0-3.0 mg/dL in women and 1.2-3.0 mg/dL in men and protein excretion ≥900 mg/day	GFR 20-65 mL/min/1.73 m^2 and PCR ≤2.5 g/g	SCr 3.1-5.0 mg/dL and protein excretion >0.3 g/day
Drug	Ramipril 1.25-5 mg daily	Losartan 50-100 mg daily	Irbesartan 300 mg daily	Ramipril 2.5-10 mg daily	Benazepril 20 mg daily
Comparator(s)	Placebo	Placebo	Placebo; amlodipine 10 mg daily	Metoprolol 50-200 mg daily; amlodipine 5-10 mg daily	Placebo
Follow-up	Mean ~1.3 years	Mean 3.4 years	Mean 2.6 years	Median ~3-4 years	Mean 3.4 years
% with diabetes	0% with insulin dependent diabetes	100%	100%	0%	0%
Baseline GFR, eGFR, or SCr	Mean GFR ~39 mL/min/1.73 m^2	Mean SCr ~1.9 mg/dL	Mean SCr ~1.7 mg/dL	Mean GFR 46 mL/min/1.73 m^2	Mean eGFR ~26 mL/min/1.73 m^2
Baseline PCR, ACR, protein or albumin excretion*	Mean protein excretion ~5.3 g/day	Median ACR 1261 mg/g for placebo group and 1237 mg/g for losartan group	Median protein excretion ~2.9 g/day and albumin excretion ~1.9 g/day	Median PCR 0.08 g/g	Mean protein excretion ~1.7 g/day
Primary outcome	Mean GFR decline† 0.53 (SE 0.08) mL/min per month for ramipril *v* 0.88 (0.13) for placebo (P=0.03)	Hazard ratio for composite of doubling SCr, ESKD, or death 0.84 (95% CI 0.72 to 0.98)	Relative risk for composite of doubling SCr, ESKD, or death 0.80 (95% CI 0.66 to 0.97) for irbesartan *v* placebo; 0.77 (0.63 to 0.93) for irbesartan *v* amlodipine	Mean difference for total GFR slope (mL/min/1.73 m^2 per year) 0.61 (SE 0.22) for ramipril *v* metoprolol (P=0.007); −0.34 (0.38) for ramipril *v* amlodipine (P=0.38)	Risk reduction for composite of doubling SCr, ESKD, or death 43% (P=0.005)

ACR=urine albumin-to-creatinine ratio; CI=confidence interval; CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate; ESKD=end stage kidney disease; GFR=glomerular filtration rate; IDNT=Irbesartan Diabetic Nephropathy Trial; AASK=African American Study of Kidney Disease and Hypertension; PCR=urine protein-to-creatinine ratio; SCr=serum creatinine; SE=standard error; REIN=Ramipril Efficacy In Nephropathy; RENAAL=Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan.
*To convert ACR from mg/g to mg/mmol, multiply by 0.113.
†n=117 with ≥3 GFR evaluations.

older age, female sex, higher body mass index, recent weight loss, and smoking.

General principles of management

The mainstays of therapy for patients with CKD include treating the underlying cause if known, and correcting risk factors (for example, albuminuria) for CKD progression and other CKD related complications (fig 4).[2]

Blood pressure targets

The three major studies for evaluating the optimal blood pressure target in CKD were the Modification of Diet in Renal Disease Study (MDRD), African American Study of Kidney Disease and Hypertension (AASK), and Systolic Blood Pressure Intervention Trial (SPRINT).[67-69] In both MDRD and AASK, intensive blood pressure control did not slow GFR decline overall.[67 68] However, in MDRD, participants with baseline proteinuria of ≥3 g/day seemed to benefit from intensive blood pressure control, with slower mean rates of GFR decline compared with their counterparts in the usual blood pressure control group.[67] Among SPRINT participants with baseline CKD (n=2646), aiming for a systolic blood pressure goal of <120 mm Hg versus <140 mm Hg did not significantly reduce the risk for a composite kidney outcome that included a ≥50% reduction in estimated GFR, long term dialysis, or kidney transplant.[69 70] However, benefits of intensive blood pressure control were seen with respect to prevention of the composite cardiovascular outcome (defined as myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes—hazard ratio 0.75, 95% confidence interval 0.64 to 0.89) and all cause mortality (hazard ratio 0.73, 0.60 to 0.90), regardless of CKD status.[69] Blood pressure control can also reduce albuminuria, as shown in the Chlorthalidone in Chronic Kidney Disease (CLICK) trial of chlorthalidone in advanced CKD.[71]

Glycemic targets

Among patients with diabetes and CKD, glycemic control is an important component of comprehensive care.[72] The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) was the largest trial of intensive glucose control to enroll patients with CKD.[73] Among the 11 140 trial participants, 19% had an estimated GFR <60 mL/min/1.73 m^2 and 31% had albuminuria at baseline.[74] Compared with standard glucose control, intensive glucose control was associated with 9% (hazard ratio 0.91, 0.85 to 0.98), 30% (0.70, 0.57 to 0.85), and 65% (0.35, 0.15 to 0.83) lower risks of developing new onset ACR 30-300 mg/g, ACR >300 mg/g, and end stage kidney disease (ESKD), respectively.

Specific classes of therapy

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers

When choosing antihypertensive agents, those that act by inhibiting the renin-angiotensin-aldosterone system (RAAS) have particular relevance in CKD. A 2001 meta-analysis of 11 studies suggested that, for non-diabetic CKD, the use of angiotensin converting enzyme (ACE) inhibitors resulted in a 30% reduction in risk of KFRT or doubling of serum creatinine.[75] Clinical trials in populations with CKD and diabetes

Table 2 | Landmark randomized clinical trials on sodium-glucose co-transporter 2 inhibitors in chronic kidney disease (CKD)

Parameter	CANVAS Program[86 87] (n=10 142)	CREDENCE[88] (n=4401)	DAPA-CKD[89 90] (n=4304)	EMPA-KIDNEY[91] (n=6609)
Kidney related inclusion criteria	eGFR >30 mL/min/1.73 m^2	eGFR 30 to <90 mL/min/1.73 m^2 and ACR >300 to 5000 mg/g	eGFR 25 to 75 mL/min/1.73 m^2 and ACR 200 to 5000 mg/g	eGFR ≥20 to <45 mL/min/1.73 m^2 or eGFR ≥45 to <90 mL/min/1.73 m^2 and ACR ≥200 mg/g
Drug	Canagliflozin 100 mg daily; canagliflozin 300 mg daily	Canagliflozin 100 mg daily	Dapagliflozin 10 mg daily	Empagliflozin 10 mg daily
Median follow-up	2.4 years	2.6 years	2.4 years	2.0 years
% with diabetes	100%	100%	68%	46%
Cause of CKD	NA	100% diabetes	58% diabetes; 16% hypertension/ischemic; 6% IgA nephropathy; 3% FSGS; 2% chronic pyelonephritis; 1% chronic interstitial nephritis; 9% other; 5% unknown	31% diabetes; 22% hypertension/renovascular; 25% glomerular; 12% other; 10% unknown
Baseline eGFR	Mean 77 mL/min/1.73 m^2	Mean 56 mL/min/1.73 m^2	Mean 43 mL/min/1.73 m^2; 14% with eGFR <30 mL/min/1.73 m^2	Mean 37 mL/min/1.73 m^2; 35% with eGFR <30 mL/min/1.73 m^2
Baseline ACR*	Median 12.3 mg/g; 23% with ACR 30-300 mg/g; 8% with ACR >300 mg/g	Median 927 mg/g	Median 949 mg/g; 90% with ACR >300 mg/g; 48% with ACR >1000 mg/g	Median 329 mg/g; 52% with ACR >300 mg/g
Hazard ratio (95% CI) comparing SGLT-2 inhibitor v placebo				
Primary outcome	Composite of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes: 0.86 (0.75 to 0.97)	Composite of doubling of serum creatinine, ESKD, or death from kidney or cardiovascular causes: 0.70 (0.59 to 0.82)	Composite of sustained decline in eGFR of ≥50%, ESKD, or death from kidney or cardiovascular causes: 0.61 (0.51 to 0.72)	Composite of sustained decrease in eGFR to <10 mL/min/1.73 m^2 or by ≥40% from baseline, ESKD, or death from kidney or cardiovascular causes: 0.72 (0.64 to 0.82)
CKD progression†	0.60 (0.47 to 0.77)	0.66 (0.53 to 0.81)	0.56 (0.45 to 0.68)	0.71 (0.62 to 0.81)
ESKD‡	0.77 (0.30 to 1.97)	0.68 (0.54 to 0.86)	0.64 (0.50 to 0.82)	0.73 (0.59 to 0.89)
Difference (95% CI) in mL/min/1.73 m^2 per year comparing SGLT-2 inhibitor v placebo				
eGFR slope§	Total: 2.0 (1.5 to 2.6); long term: 1.2 (1.0 to 1.4)	Total: 1.52 (1.11 to 1.93); long term: 2.74 (2.37 to 3.11)	Total: 0.93 (0.61 to 1.25); long term: 1.92 (1.61 to 2.24)	Total: 0.75 (0.54 to 0.96); long term: 1.37 (1.16 to 1.59)

ACR=urine albumin-to-creatinine ratio; CANVAS=Canagliflozin Cardiovascular Assessment Study; CREDENCE=Canagliflozin and Renal Events in Diabetes and Established Nephropathy Clinical Evaluation; CVD=cardiovascular disease; DAPA-CKD=Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; EMPA-KIDNEY=Study of Heart and Kidney Protection with Empagliflozin; ESKD=end stage kidney disease; eGFR=estimated glomerular filtration rate; FSGS=focal segmental glomerulosclerosis; NA=not available.
*To convert ACR from mg/g to mg/mmol, multiply by 0.113.
†CKD progression defined as 40% reduction in eGFR, need for dialysis or kidney transplantation, or death from kidney causes in CANVAS; doubling of serum creatinine, ESKD, or kidney death in CREDENCE; decline in eGFR of ≥50%, ESKD, or death from kidney causes in DAPA-CKD; sustained decrease in eGFR to <10 mL/min/1.73 m^2 or by ≥40% from baseline, ESKD, or death from kidney causes in EMPA-KIDNEY.
‡ESKD defined as dialysis for ≥30 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2 in CANVAS; dialysis for ≥30 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2 in CREDENCE; maintenance dialysis for ≥28 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2 in DAPA-CKD; initiation of maintenance dialysis or kidney transplantation and includes death from cardiovascular causes in EMPA-KIDNEY.
§Long term eGFR slope defined as 13 weeks onwards in CANVAS, 3 weeks onwards in CREDENCE, 2 weeks onwards in DAPA-CKD, and 2 months onwards in EMPA-KIDNEY.

(for example, IDNT, RENAAL) have also shown benefit of angiotensin receptor blockers (ARB) in preventing CKD progression (table 1).[77 78] RAAS inhibition also plays a role in prevention of cardiovascular disease. The Heart Outcomes Prevention Evaluation (HOPE) study showed that ACE inhibitors reduced the risks of myocardial infarction, stroke, and cardiovascular death in populations at high risk for cardiovascular disease, including those with diabetes and albuminuria.[80] The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) showed that ACE inhibitors and ARB were generally equivalent in the prevention of cardiovascular events.[81] Because of the increased risk of hyperkalemia and acute kidney injury, dual therapy with both an ACE inhibitor and an ARB is typically avoided.[82]

When GFR declines, providers often grapple with whether RAAS inhibitors should be continued. The Benazepril in Advanced CKD study showed that benazepril reduced the risk of the primary composite kidney endpoint by 43% compared with placebo, thus suggesting that RAAS inhibitors are beneficial even in advanced CKD (baseline serum creatinine 3.1-5.0 mg/dL).[79] Three recent reports further explored this question, also examining the benefits in prevention of death and cardiovascular events associated with continuation of RAAS inhibitors.[83-85] A retrospective, propensity score matched study of patients with estimated GFR <30 mL/min/1.73 m^2 showed higher risk of all cause mortality and major adverse cardiovascular events in those who stopped RAAS inhibitors compared with those who continued them,[83] as did a Swedish trial emulation study.[84] The risk of kidney replacement therapy associated with cessation of RAAS inhibitors was not statistically significant in the first study and lower in the second study.[83 84] In an open label randomized trial, cessation of RAAS inhibitors did not show significant between group differences in long term decline in estimated GFR or initiation of kidney replacement therapy, providing reassurance that RAAS inhibitors can be safely continued as GFR declines.[85]

SGLT-2 inhibitors

One of the biggest advancements in CKD management over the past decade was the discovery that SGLT-2 inhibitors have robust protective effects on the heart and kidneys in patients with and without diabetes. Recent trials showed an approximate 30% reduction in risk for diverse kidney outcomes among patients with baseline estimated GFR values as low as 20

Table 3 | Adverse effects of SGLT-2 inhibitors* in CANVAS, CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials

Adverse event	CANVAS[86]	CREDENCE[88]	DAPA-CKD[89]	EMPA-KIDNEY[91]
Urinary tract infection	Similar	Similar	NR	Similar
Serious genital infection	Higher†	Higher in men	Too few events	Too few events
Hyperkalemia	Similar	Similar	NR	Similar
Acute kidney injury	Similar	Similar	Similar	Similar
Liver injury	Similar	Similar	NR	Similar
Ketoacidosis	Similar	Higher	Similar	Too few events
Limb amputation	Higher	Similar	Similar	Similar
Bone fracture	Higher	Similar	Similar	Similar
Severe hypoglycemia	Similar	Similar	Lower	Similar
Volume depletion	Higher	Similar	Higher	Similar
Pancreatitis	Similar	Too few events	NR	NR

CANVAS=Canagliflozin Cardiovascular Assessment Study; CREDENCE=Canagliflozin and Renal Events in Diabetes and Established Nephropathy Clinical Evaluation; DAPA-CKD=Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; EMPA-KIDNEY=Study of Heart and Kidney Protection with Empagliflozin NR=not reported; SGLT-2=sodium-glucose co-transporter 2.
*Reported as similar, higher, or lower risk, event rate, or frequency for SGLT-2 inhibitor versus placebo.
†Defined as infection of male genitalia and mycotic genital infection in women.

mL/min/1.73 m^2 (table 2).[86 88 89 91] Importantly, the three trials designed with primary kidney outcomes (Canagliflozin and Renal Events in Diabetes and Established Nephropathy Clinical Evaluation (CREDENCE), Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD), and Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY)) were terminated early because pre-specified efficacy criteria were met, with median follow-up times ranging from 2.0 to 2.6 years.[88 89 91] The overwhelming majority of trial participants were taking an ACE inhibitor or ARB before randomization, showing that the benefits of SGLT-2 inhibitors on slowing CKD progression are additive to those of RAAS inhibitors. One simulation study estimated that a 50 year old adult with non-diabetic albuminuric CKD would have seven extra years free from doubling of serum creatinine, kidney failure, or all cause mortality if treated with an SGLT-2 inhibitor and RAAS inhibitor.[92]

Subgroup analyses of the DAPA-CKD and EMPA-KIDNEY trials have provided additional insights on the wide range of patients who are likely to benefit from SGLT-2 inhibitors.[89 91] In DAPA-CKD, dapagliflozin was favored over placebo in all pre-specified subgroups by baseline age, sex, race, diabetes status, systolic blood pressure, estimated GFR (<45 *v* ≥45 mL/min/1.73 m^2), and ACR (≤1000 *v* >1000 mg/g or ≤113 *v* >113 mg/mmol).[89] Similarly, in EMPA-KIDNEY, empagliflozin was associated with lower risk of the primary composite outcome compared with placebo regardless of baseline diabetes status or estimated GFR (<30 *v* ≥30 mL/min/1.73 m^2 to <45 *v* ≥45 mL/min/1.73 m^2).[91] The risk of the primary outcome was not lower among patients with ACR ≤300 mg/g (approximately ≤30 mg/mmol). In exploratory analyses, however, empagliflozin was associated with slower annual rates of decline in estimated GFR compared with placebo among participants with ACR between 30 and 300 mg/g (approximately 3-30 mg/mmol) and slower chronic slope (from two months to the final follow-up visit) among all ACR subgroups.

The DAPA-CKD trial also showed that the kidney protective effects of SGLT-2 inhibitors extend to patients with IgA nephropathy and perhaps also those with focal segmental glomerulosclerosis (FSGS).[93 94] Among 270 participants with IgA nephropathy (mean estimated GFR 44 mL/min/1.73 m^2; median ACR 900 mg/g (102 mg/mmol)), dapagliflozin was associated with a 71% lower risk of developing the primary outcome and a 70% lower risk of ESKD compared with placebo.[93] Among the 104 participants with FSGS (mean estimated GFR 42 mL/min/1.73 m^2; median ACR 1248 mg/g (141 mg/mmol)), dapagliflozin was not associated with a lower risk of the primary composite outcome, although this analysis was limited in power (only 11 events).[94] In exploratory analyses, dapagliflozin was associated with slower chronic decline in estimated GFR in the FSGS population. Investigations on the use of SGLT-2 inhibitors in other patient populations, such as those with polycystic kidney disease and kidney transplant recipients, are ongoing (clinicaltrials.gov).

SGLT-2 inhibitors, which act at the level of the proximal tubule to block the reabsorption of glucose and sodium,[95] are generally safe to use in patients with CKD. Early signals of heightened risks of volume depletion, serious genital infections, bone fractures, and need for limb amputation in the Canagliflozin Cardiovascular Assessment Study (CANVAS) were not observed in subsequent studies—CREDENCE, DAPA-CKD, and EMPA-KIDNEY—thus assuaging these concerns (table 3).[86 88 89 91] A pooled analysis of 15 081 participants with type 2 diabetes and CKD G3-4 showed similar rates of serious adverse events for empagliflozin versus placebo, with a higher rate only of mild genital infections with the SGLT-2 inhibitor.[96] A real world study of patients receiving SGLT-2 inhibitors compared with dipeptidyl peptidase-4 (DPP-4) inhibitors found no increased risk of outpatient urinary tract infections or severe urinary tract infection events requiring hospital admission.[97]

GLP-1 receptor agonists

GLP-1 receptor agonists have also been shown to improve kidney outcomes among patients with type 2 diabetes, albeit in trials that were designed for primary cardiac outcomes (table 4).[98-109] The

Table 4 | Landmark randomized clinical trials on associations of glucagon-like peptide-1 (GLP-1) receptor agonists with secondary kidney outcomes among patients with type 2 diabetes mellitus

Parameter	ELIXA[98-101] (n=6068)	LEADER[102 103] (n=9340)	SUSTAIN-6[100 104] (n=3297)	EXSCEL[105 106] (n=14 752)	REWIND[107 108] (n=9901)	AMPLITUDE-O[109] (n=4076)
Kidney related inclusion criteria	eGFR ≥30 mL/min/1.73 m^2	Age ≥50 years with ≥1 cardiovascular coexisting condition (eg, CKD G3+) or age ≥60 years with ≥1 cardiovascular risk factor (eg, albuminuria or proteinuria)	Age ≥50 years with CVD or CKD G3+ or age ≥60 years with ≥1 CVD risk factor (eg, albuminuria or proteinuria)	eGFR ≥30 mL/min/1.73 m^2	eGFR ≥15 mL/min/1.73 m^2	Age ≥18 years with history of CVD or age ≥50 (men) or ≥55 (women) years with eGFR 25 to <60 mL/min/1.73 m^2 and ≥1 cardiovascular risk factor
Drug	Lixisenatide 10-20 µg daily	Liraglutide 1.8 mg daily (or maximum tolerated dose)	Semaglutide 0.5 or 1.0 mg weekly	Exenatide 2 mg weekly	Dulaglutide 1.5 mg weekly	Efpeglenatide 4 mg or 6 mg weekly
Median follow-up	2.1 years	3.8 years	2.1 years	3.2 years	5.4 years	1.8 years
Baseline eGFR	Mean 76 mL/min/1.73 m^2	Mean ~80 mL/min/1.73 m^2	Mean 80 mL/min/1.73 m^2	Median 76 mL/min/1.73 m^2 for placebo group and 77 mL/min/1.73 m^2 for exenatide group	Mean 78 mL/min/1.73 m^2	Mean 72 mL/min/1.73 m^2
Baseline ACR*	Median 10.5 mg/g for placebo group and 10.2 mg/g for lixisenatide group; 6.5% with ACR ≥300 mg/g	10% with ACR >300 mg/g	NA	NA	Median 1.94 mg/mmol; 35% with ACR ≥3.39 mg/mmol	Median 28 mg/g
Kidney outcomes	ACR >300 mg/g	ACR >300 mg/g, doubling of serum creatinine with eGFR ≤45 mL/min/1.73 m^2, need for maintenance kidney replacement therapy, or death from kidney disease†	ACR >300 mg/g, doubling of serum creatinine with eGFR <45 mL/min/1.73 m^2, or need for maintenance kidney replacement therapy	ACR >300 mg/g, ≥40% decline in eGFR, kidney replacement therapy, or death from kidney causes	ACR >300 mg/g, ≥30% decline in eGFR, or maintenance kidney replacement therapy	ACR >300 mg/g and increase in ACR ≥30% from baseline, ≥40% decline in eGFR or eGFR <15 mL/min/1.73 m^2, maintenance kidney replacement therapy
Hazard ratio (95% CI) comparing GLP-1 receptor agonists *v* placebo	0.85 (0.69 to 1.05)	0.78 (0.67 to 0.92)	0.64 (0.46 to 0.88)	0.85 (0.74 to 0.98)	0.85 (0.77 to 0.93)	0.68 (0.57 to 0.79)

ACR=urine albumin-to-creatinine ratio; AMPLITUDE-O=Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes; CI=confidence interval; CVD=cardiovascular disease; ESKD=end-stage kidney disease; eGFR=estimated glomerular filtration rate; ELIXA=Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL=Exenatide Study of Cardiovascular Event Lowering; LEADER=Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; NA=not available; REWIND=Researching cardiovascular Events with a Weekly Incretin in Diabetes SUSTAIN-6=Trial to Evaluate Cardiovascular and Other Long term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.
*To convert ACR from mg/g to mg/mmol, multiply by 0.113.
†Most of the risk reduction was due to prevention of the albuminuria endpoint.

reduction in risk of kidney outcomes, which included albuminuria, ranged from 15% to 36%. A large meta-analysis of approximately 44 000 participants from the six trials in table 4 reported that use of GLP-1 receptor agonists was associated with a 21% lower risk of developing the composite kidney outcome, defined as new onset albuminuria >300 mg/g, doubling of serum creatinine, ≥40% decline in estimated GFR, kidney replacement therapy, or death due to kidney causes, compared with placebo.[100] This risk reduction seemed to be driven by the reduction in incident albuminuria >300 mg/g; associations between GLP-1 receptor agonists and CKD progression and kidney failure were not statistically significant. However, results were more promising in A Study Comparing Dulaglutide with Insulin Glargine on Glycemic Control in Participants with Type 2 Diabetes and Moderate or Severe Chronic Kidney Disease (AWARD-7), a clinical trial designed to evaluate change in glycated hemoglobin.[110] Among 577 adults with type 2 diabetes and CKD G3-4 randomized to open label dulaglutide 1.5 mg once weekly, dulaglutide 0.75 mg once weekly, or insulin glargine daily, both dulaglutide groups had slower estimated GFR declines compared with the insulin glargine group; among participants with baseline albuminuria >300 mg/g, dulaglutide was associated with greater ACR reductions in a dose dependent manner over the one year follow-up.

Exact mechanisms by which the GLP-1 receptor agonists slow decline in estimated GFR and/or reduce albuminuria are not entirely clear, but proposed mechanisms include improved glycemic control, weight loss, increased natriuresis, and reduced inflammation and oxidative stress.[111-113] Adverse effects observed with this class of drugs have included diarrhea, nausea, and vomiting.[103 104 107 109 110]

Mineralocorticoid receptor antagonists

Several MRAs are available and can be useful adjuncts to RAAS inhibitors, particularly among populations with albuminuria and/or diabetes. Two common steroidal non-selective MRAs, spironolactone and eplerenone, both lower albuminuria.[72] In a meta-analysis of 372 participants from seven trials, combination therapy with a non-selective MRA and an ACE inhibitor and/or ARB was associated with a significant reduction in proteinuria, albeit with a higher risk of hyperkalemia.[114] Finerenone, a non-steroidal selective MRA, was also recently approved.[115] Compared with the steroidal non-selective MRAs, finerenone has a stronger selectivity for the mineralocorticoid receptor, a shorter half life,

Table 5 | Landmark randomized clinical trials on finerenone in chronic kidney disease

Parameter	FIDELIO-DKD[116] (n=5674)	FIGARO-DKD[118] (n=7352)
Kidney related inclusion criteria	ACR 30 to <300 mg/g and eGFR 25 to <60 mL/min/1.73 m^2 and diabetic retinopathy or ACR 300 to 5000 mg/g and eGFR 25 to <75 mL/min/1.73 m^2	ACR 30 to <300 mg/g and eGFR 25 to 90 mL/min/1.73 m^2 or ACR 300 to 5000 mg/g and eGFR ≥60 mL/min/1.73 m^2
Median follow-up	2.6 years	3.4 years
Baseline eGFR	Mean 44 mL/min/1.73 m^2; 55% with eGFR <45 mL/min/1.73 m^2	Mean 68 mL/min/1.73 m^2; 17% with eGFR <45 mL/min/1.73 m^2
Baseline ACR*	Median 852 mg/g; 87% with ACR ≥300 mg/g	Median 308 mg/g; 51% with ACR ≥300 mg/g
Hazard ratio (95% CI) comparing finerenone v placebo		
≥40% kidney composite outcome: sustained decrease in eGFR by ≥40% or to <15 mL/min/1.73 m^2, ESKD, or death due to kidney causes	0.82 (0.73 to 0.93)	0.87 (0.76 to 1.01)
≥57% kidney composite outcome: sustained decrease in eGFR by ≥57% or to <15 mL/min/1.73 m^2, ESKD, or death due to kidney causes	0.76 (0.65 to 0.90)	0.77 (0.60 to 0.99)
ESKD: initiation of maintenance dialysis for ≥90 days or kidney transplantation.	0.86 (0.67 to 1.10)	0.64 (0.41 to 0.995)
Ratio of least squares (95% CI) comparing finerenone v placebo		
Mean ACR change from baseline to month 4	0.69 (0.66 to 0.71)	0.68 (0.65 to 0.70)

*To convert ACR from mg/g to mg/mmol, multiply by 0.113.
ACR=urine albumin-to-creatinine ratio; CI=confidence interval; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; FIDELIO-DKD=Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; FIGARO-DKD=Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease.

less of a blood pressure lowering effect, and a more favorable side effect profile, as well as potentially greater anti-inflammatory and antifibrotic effects.[115-117] The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial and the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial were two complementary phase 3 clinical trials designed to investigate the kidney and cardiovascular benefits of finerenone, respectively, in people with albuminuria levels ≥30 mg/g and type 2 diabetes (table 5).[116 118] Both trials included patients taking maximally tolerated ACE inhibitor or ARB, with participants in FIDELIO-DKD generally having more severe baseline CKD. In a pooled analysis of the two trials, finerenone was associated with a 15-23% lower risk of developing the kidney composite outcomes and a 32% lower mean change in ACR from baseline to four months.[119] Hyperkalemia was more frequent among patients randomized to finerenone (14%) compared with placebo (7%). In pre-specified analyses, baseline SGLT-2 inhibitor use (n=877) or GLP-1 receptor agonist use (n=944) did not modify the beneficial effect of finerenone on the kidney composite outcome, thus suggesting a potential role for dual therapy (for example, finerenone plus SGLT-2 inhibitor or GLP-1 receptor agonist) among patients with type 2 diabetes and CKD.

Endothelin receptor antagonists

Endothelin receptor antagonists have emerged as novel treatments for a variety of kidney diseases. The Study of Diabetic Nephropathy with Atrasentan (SONAR) evaluated the effect of atrasentan on a composite kidney outcome (defined as a doubling of serum creatinine or ESKD) among adults with type 2 diabetes, estimated GFR 25-75 mL/min/1.73 m^2, and urine ACR 300-5000 mg/g taking a stable dose of ACE inhibitor or ARB.[120] After a six week enrichment period during which all participants received atrasentan 0.75 mg daily (n=5517), those who responded (defined as a ≥30% reduction in urine ACR without the development of substantial fluid retention or increase in serum creatinine by >0.5 mg/dL and 20% from baseline; n=2648) were randomized to receive atrasentan or placebo. Over a median follow-up of 2.2 years, the atrasentan group had a 35% lower risk of developing the composite kidney outcome compared with the placebo group, although fluid retention and anemia were more frequent in the former. Of note, the frequency of hyperkalemia was low (1%) in both treatment groups. Sparsentan, a dual endothelin and angiotensin II receptor antagonist, is also being investigated as a treatment for FSGS and IgA nephropathy.[121 122] In a phase 2, randomized, double blind, active control trial, 109 adults with biopsy proven FSGS (estimated GFR >30 mL/min/1.73 m^2 and urine PCR ≥1 g/g) received varying doses of sparsentan (200, 400, or 800 mg daily) or irbesartan 300 mg daily.[121] At eight weeks, participants receiving sparsentan had greater reductions in urine PCR compared with those receiving irbesartan. In an interim analysis of the PROTECT phase 3 trial, adults with biopsy proven IgA nephropathy (urine PCR ≥1 g/day) randomized to sparsentan 400 mg daily had a 41% greater reduction in urine PCR over 36 weeks and threefold higher odds of achieving complete remission of proteinuria at any point compared with their counterparts who were randomized to irbesartan 300 mg daily.[122] Based in part on the results of this study, the US Food and Drug Administration (FDA) granted accelerated approval for the use of this drug in adults with primary IgA nephropathy considered to be at risk of rapid disease progression.[123]

Endothelin 1 has been implicated in the pathogenesis of kidney disease via various mechanisms including vasoconstriction, vascular hypertrophy, endothelial and podocyte injury,

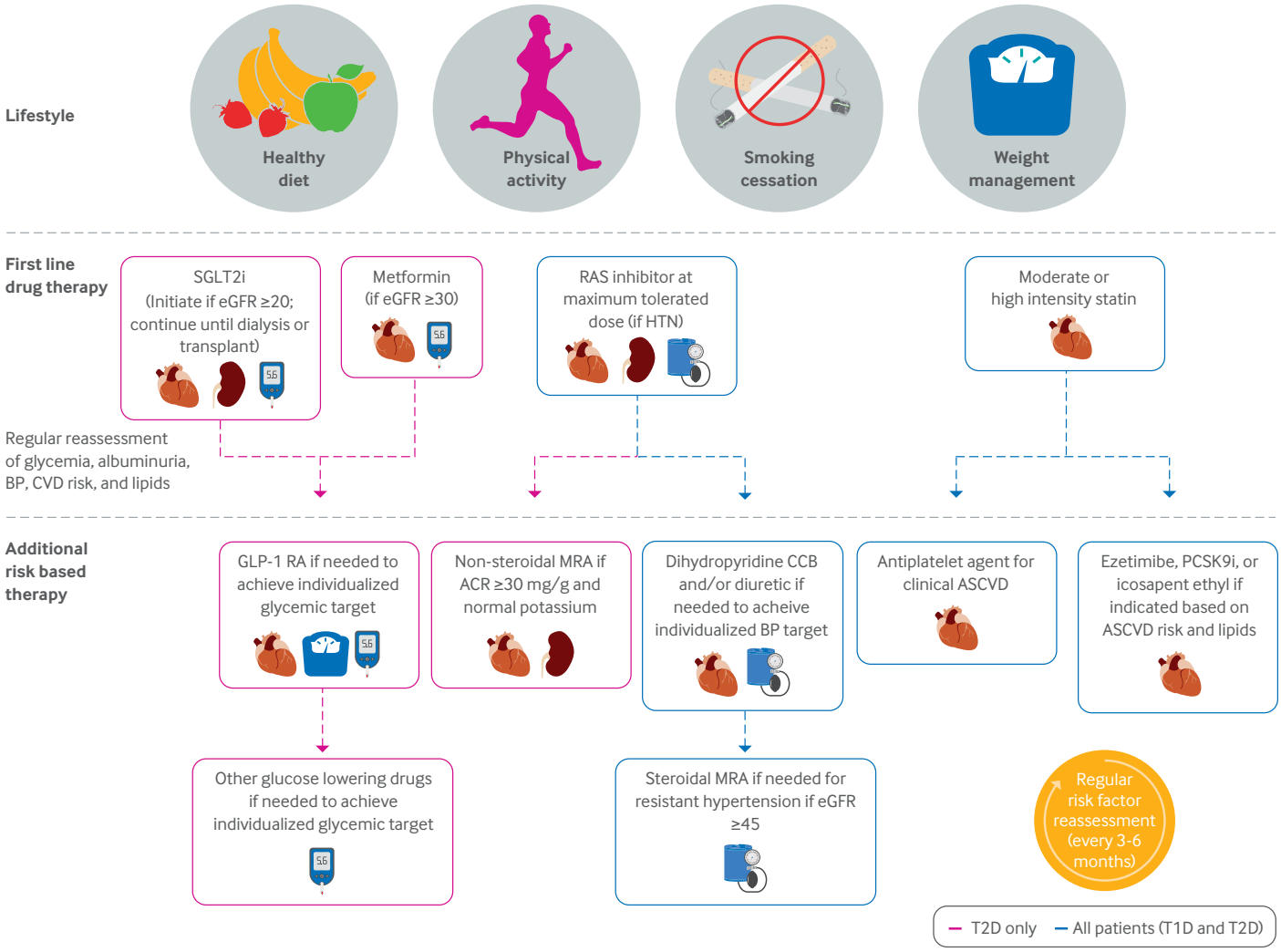

Fig 5 | Kidney Disease: Improving Global Outcomes/American Diabetes Association recommendations on the management of diabetes in populations with chronic kidney disease.[72 174] ACR=albumin-to-creatinine ratio; ASCVD=atherosclerotic cardiovascular disease; BP=blood pressure; CCB=calcium channel blocker; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; GLP-1 RA=glucagon-like peptide-1 receptor agonist; HTN=hypertension; MRA=mineralocorticoid receptor antagonist; PCSK9i=proprotein convertase subtilisin/kexin type 9 inhibitor; RAS=renin-angiotensin system; SGLT2i=sodium-glucose cotransporter-2 inhibitor

inflammation, cell proliferation, extracellular matrix accumulation, and fibrosis.[124] Systemic and local kidney production of endothelin 1 is augmented in CKD.

Other nephroprotective and cardiovascular risk reduction strategies

A bidirectional association exists between CKD and cardiovascular disease: cardiovascular disease is both a risk factor for CKD and a common outcome in patients with CKD.[125 126] Thus, patients with CKD are likely to benefit from efforts at cardiovascular risk reduction including administration of a statin as well as the gamut of lifestyle changes.[2 127]

Lipid management

The Study of Heart and Renal Protection (SHARP) trial evaluated the efficacy of ezetimibe and simvastatin combination therapy in patients with moderate to severe CKD (33% on dialysis; 67% not on dialysis with mean estimated GFR of 27 mL/min/1.73 m^2).[128] Treatment with these low density lipoprotein (LDL) cholesterol lowering agents led to a 17% risk reduction for development of a first major atherosclerotic event compared with placebo, although this benefit was seen only in the patients not requiring maintenance dialysis. Those at very high risk (for example, with previous major atherosclerotic cardiovascular disease events) may benefit from additional therapies to lower LDL cholesterol, including evolocumab.[129] Evolocumab is a monoclonal antibody for proprotein convertase subtilisin/kexin type 9, which increases LDL cholesterol receptors and hence clearance of LDL; this novel therapy also seems to be safe and efficacious in patients with CKD.[129 130]

Physical activity

Exercise has been shown to benefit patients with CKD. Several small, randomized trials have reported that exercise training programs in patients with moderate

to severe CKD are safe, feasible, and effective in improving physical activity levels, cardiorespiratory fitness, and quality of life.[131-135] Whether these interventions also slow CKD progression remains to be determined, as many of these studies were underpowered for this outcome.

Diet

For patients with obesity, weight loss may reduce the risk of CKD progression, whether it comes from intensive lifestyle intervention such as in the Look AHEAD (Action for Health in Diabetes) trial or, as in observational studies, from bariatric surgery.[136-138] Micronutrient and macronutrient composition of diets may also matter.[139]

Traditional recommendations about diet in the setting of CKD have focused on limiting protein and dietary acid intake. Experimental evidence suggests that protein intake can increase intraglomerular pressure and cause glomerular hyperfiltration.[140-142] Observational data from large cohort studies suggest that the type of protein may be important; a diet high in animal protein may increase risk, whereas protein from plant sources may be better tolerated.[143 144] For example, an observational study in Singapore found a strong correlation between red meat intake and risk of ESKD.[145] Little clinical trial evidence for protein restriction exists. The MDRD study randomized patients to different levels of protein restriction but found no statistically significant difference in the rate of GFR decline.[67]

A second line of investigation has been into the benefits of increasing nutritional alkali intake, with a body of open label trials suggesting benefits on kidney function and prevention of starting dialysis.[146] A phase 3 double blinded, placebo controlled trial reported that veverimer (a potent acid binder that acts in the intestine) was effective in raising or normalizing serum bicarbonate among patients with CKD and chronic metabolic acidosis.[147] Other double blinded studies using veverimer suggested that treating acidosis in CKD improves quality of life and overall physical function.[148] However, a recent trial evaluating veverimer in slowing progression of CKD was negative.[149]

Although patients with CKD are prone to hyperkalemia, potassium intake has a beneficial effect on blood pressure, cardiovascular disease, and death independent of and opposite to that of sodium intake.[150-153] One large randomized controlled trial suggested that substituting 25% of sodium chloride intake with potassium chloride reduced the risk of major adverse cardiovascular events by 13% in the general population.[154] Similarly, small studies suggest that diets rich in potassium may be beneficial in CKD. A feeding trial in people with CKD G3 observed that 100 mmol compared with 40 mmol of dietary potassium per day increased serum potassium by 0.21 mmol/L,[155] similar to the increase seen with finerenone.[156] Many dietary studies have evaluated patterns of diet rather than potassium alone: for example, plant based diets tend to be rich in not only potassium but also alkali and fiber. Observational data from prospective cohorts suggest that plant based diets are associated with less CKD progression.[143 157 158] Evidence is also emerging to suggest that increasing fiber intake benefits the gut microbiome, decreases inflammation, and possibly slows CKD progression.[159]

Appropriate drug dosing and nephrotoxin avoidance

An important component of care for patients with CKD is avoidance of additional insults. Many drugs are cleared by glomerular filtration or tubular secretion by the kidney, and reduced GFR can lead to accumulation of the drug or its metabolites resulting in adverse effects.[160] Careful estimation of GFR is generally a first step in determining dosage for renally excreted drugs.[161] The US FDA guidance to industry suggests that estimated GFR based on serum creatinine may be used in pharmacokinetic studies.[162] If drugs are dosed on the basis of estimated GFR (rather than estimated creatinine clearance from the Cockcroft-Gault equation, an equation that is known to be flawed), estimated GFR must be "de-indexed" by multiplying the standardized estimated GFR by the individual's calculated body surface area and dividing by 1.73 m^2.[163-165] This is because drug clearance is thought to be proportional to a person's GFR and not the GFR standardized to body surface area. Antibiotics and antiviral agents, direct oral anticoagulants, drugs for diabetes mellitus, and chemotherapeutic agents are the most common drugs that require attention to dosing in CKD.[2 160 164]

Some drugs should be avoided or minimized in CKD because of their potential to worsen kidney function. For example, non-steroidal anti-inflammatory drugs (NSAIDs) can exacerbate hypertension, cause fluid retention, and contribute to the risk of acute kidney injury.[166] Particularly when used with RAAS inhibitors and diuretics, NSAIDs are ideally avoided.[167] In select patients with CKD, however, some clinicians will prescribe an abbreviated course of NSAIDs given that the most common alternative, opioids, also have significant adverse effects.[168] Proton pump inhibitors can lead to acute or chronic interstitial nephritis and have been associated with incident CKD, progression of CKD, and ESKD.[169 170] Although the mechanism by which proton pump inhibitors contribute to CKD remains unclear, most experts agree that these agents should be used judiciously.

Emerging treatments

Many phase 3-4 clinical trials are ongoing to evaluate emerging treatments for kidney disease (clinicaltrials.gov). These include, but are not limited to, investigations on the use of dapagliflozin in advanced CKD (for example, estimated GFR <25 mL/min/1.73 m^2, on maintenance dialysis with residual daily urine output of >500 mL, and kidney transplant recipients with estimated GFR ≤45 mL/min/1.73 m^2; NCT05374291); finerenone in non-diabetic CKD (NCT05047263); and monteluklast (NCT05362474)

and pentoxyifylline (NCT03625648) in diabetic CKD. Several therapies are also being tested for rarer causes of kidney disease: obinutuzumab (NCT04629248), zanubrutinib (NCT05707377), and SNP-ACTH (1-39) gel (NCT05696613) in membranous nephropathy; voclosporin (NCT05288855), atacicept (NCT05609812), anifrolumab (NCT05138133), inanalumab (NCT05126277), secukinumab (NCT04181762), obinutuzumab (NCT04221477), and ACTHar gel (NCT02226341) in lupus nephritis; VX-147 in *APOL1* related kidney disease (NCT05312879); imlifidase in antiglomerular basement membrane disease (NCT05679401); sparsentan in focal segmental glomerulosclerosis (NCT03493685); and pegcetacoplan (NCT05067127) in immune complex glomerulonephritis. IgA nephropathy, in particular, is an area of high interest, as recent work suggests that disease activity may be driven by the overproduction of galactose deficient IgA antibodies that are recognized as autoantigens, triggering glomerular deposition of immune complexes.[171] Monoclonal antibodies to signaling molecules that enhance IgA production are in phase 3 trials, as are immunosuppressive and non-immunosuppressive agents (for example, those acting on the endothelin-1 and angiotensin II pathways): budesonide (NCT03643965), sparsentan (NCT03762850), atrasentan (NCT04573478), LNP023 (NCT04578834), RO7434656 (NCT05797610), atacicept (NCT04716231), and sibeprenlimab (NCT05248646; NCT05248659).

Guidelines

Major guidelines in CKD are issued by the international KDIGO group (https://kdigo.org/), and locally in the UK by NICE (www.nice.org.uk/guidance/ng28/chapter/Recommendations#chronic-kidney-disease), with the most recent issuances primarily from 2023 (currently in public review) and 2021, respectively. KDIGO publishes guidelines on the evaluation and management of patients with CKD in general, as well as myriad other aspects (for example, diabetes, blood pressure, lipids, anemia, mineral and bone disease, hepatitis C, ADPKD, glomerular diseases). With the expansion of therapeutic options, both organizations are updating recommendations frequently. Other guideline producing organizations such as the American College of Cardiology, the American Heart Association, the European Society of Cardiology, the European Society of Hypertension, the International Society of Hypertension, and the American Diabetes Association (ADA) provide more limited statements of recommendation for the specific aspects of the management of patients with CKD.[172-175]

Annual screening for CKD (including testing for albuminuria) is widely recommended in people with diabetes.[72 174-177] Guidelines in hypertension are less clear.[178] The 2020 Global Hypertension Practice Guideline from the International Society of Hypertension is a notable exception and now recommends routine assessment of albuminuria in addition to estimated GFR in people with hypertension.[173] KDIGO and NICE also recommend testing anyone who is at risk for CKD, which includes those with hypertension, cardiovascular disease, diabetes, and previous acute kidney injury, along with multiple other, less common conditions.[179] For CKD, the KDIGO guidelines recommend at least annual albuminuria testing with greater frequency in higher risk categories (fig 1).[2] The NICE guidelines, on the other hand, recommend annual ACR testing with individualization based on clinical characteristics, risk of progression, and whether a change in ACR would lead to a change in management.[16]

KDIGO guidelines and those from NICE differ slightly on staging CKD. KDIGO recommends using a validated equation for GFR estimation and suggests that using "race as a distinct variable in the computation of GFR" is not appropriate.[179] NICE recommends using the CKD-EPI 2009 equation, which did include race, but using the computed value for non-Black people for everyone, a position that is also endorsed by other European groups.[16 180 181] The KDIGO guidelines recommend staging CKD by eGFRcr-cys when cystatin C is available, as well as when precise estimates of GFR are needed for clinical decision making.[2 179] The NICE guidelines recommend direct measurement of GFR rather than the use of cystatin C in clinical situations requiring additional precision.[16]

Both KDIGO and NICE emphasize the importance of risk assessment in patients with CKD. The NICE guidelines suggest that primary care providers should counsel patients using the KFRE five year risk estimate, with referral to a specialist if risk is greater than 5%.[16] KDIGO 2023 additionally suggests that the two year risk estimate can drive referral for multidisciplinary care (>10%) and preparation for kidney replacement therapy, including vascular access planning and referral for transplantation (>40%).[179] The KDIGO 2023 guidelines also emphasize the importance of cardiovascular risk assessment using equations developed in people with CKD or that encompasses estimated GFR and albuminuria and the use of disease specific tools in IgA nephropathy and ADPKD.[179]

Multiple guidelines comment on target blood pressures in the setting of CKD. The NICE guidelines recommend a target of <140/90 mm Hg, or <130/80 mm Hg if ACR is ≥70 mg/mmol (approximately 700 mg/g).[16] Guidelines from the American College of Cardiology, American Heart Association, European Society of Cardiology, and European Society of Hypertension recommend a systolic blood pressure target of <130 mm Hg as a best practice target, with the European Society of Cardiology and European Society of Hypertension specifically advising against lower targets.[172] The KDIGO guidelines on hypertension in CKD advocate for a systolic blood pressure goal of <120 mm Hg, as assessed using standardized office measurements.[182] This recommendation is based largely on data from SPRINT and the observed benefits in cardiovascular

endpoints and survival rather than benefits in kidney endpoints.[70]

Of note, disparate guideline recommendations may reflect different emphasis on standardized blood pressure measurement techniques, which can result in measured blood pressure that is substantially lower than measurement in an uncontrolled setting.[183] Joint statements from several international groups including KDIGO stress the importance of proper technique when assessing blood pressure.[184] Both NICE and KDIGO recommend RAAS inhibitors (either ACE inhibitor or ARB) as first line antihypertensive treatment for people without diabetes but with albuminuria (NICE: urine ACR >70 mg/mmol; KDIGO: A3) as well as those with diabetes and CKD G1-G4, A2-A3.[16 182] KDIGO 2023 suggests continuation of RAAS inhibitors even when estimated GFR is <30 mL/min/1.73 m^2.[179]

For patients with diabetes and CKD not treated with dialysis, KDIGO recommends a hemoglobin A_{1c} target ranging from <6.5% to <8%.[72] NICE does not provide specific recommendations for people with CKD, instead emphasizing shared decision making but a general goal of hemoglobin A_{1c} <7% for people with diabetes treated with drugs associated with hypoglycemia and <6.5% for people with diabetes managed by lifestyle or a single drug not associated with hypoglycemia.[185]

KDIGO and ADA guidelines recommend SGLT-2 inhibitors as first line drug therapy for all people with type 2 diabetes, CKD, and an estimated GFR ≥20 mL/min/1.73 m^2 (fig 5).[72 174 175 179] The NICE guidelines recommend that an SGLT-2 inhibitor should be offered when ACR is >30 mg/mmol (approximately >300 mg/g) and considered when ACR is between 3 and 30 mg/mmol (approximately 30 to 300 mg/g) in patients with type 2 diabetes and CKD who are already taking an ACE inhibitor or ARB and meet estimated GFR thresholds.[185] The NICE guidelines further specify that dapagliflozin should also be considered in people with estimated GFR 25-75 mL/min/1.73 m^2 and ACR ≥22.6 mg/mmol (approximately 200 mg/g) regardless of diabetes status[186]; KDIGO is broader and recommends SGLT-2 inhibitors in general in people with ACR ≥200 mg/g and estimated GFR ≥20 mL/min/1.73 m^2, as well as in those with CKD and heart failure.[179] KDIGO further specifies that once started, a SGLT-2 inhibitor can be continued even if the estimated GFR drops below 20 mL/min/1.73 m^2, as long as it is tolerated and kidney replacement therapy has not yet been started.[72 179] The KDIGO and ADA guidelines recommend the use of GLP-1 receptor agonists in patients with type 2 diabetes and CKD who are unable to tolerate metformin or an SGLT-2 inhibitor or do not meet their individualized glycemic target with these drugs.[72 174 175 179]

In patients with diabetes and CKD, the KDIGO and ADA guidelines recommend that finerenone should be used as add-on therapy to maximally tolerated ACE inhibitor or ARB if ACR is ≥30 mg/g (approximately ≥3 mg/mmol) and potassium is within normal limits (that is, ≤4.8 mmol/L based on trial and ≤5.0 mmol/L as per FDA).[72 174 175 179] More specifically, the starting dose should be 10 mg daily when estimated GFR is 25-59 mL/min/1.73 m^2 and 20 mg daily when it is ≥60 mL/min/1.73 m^2. The guidelines also recommend that potassium concentration should be checked at four weeks after starting treatment, with each dose change, and routinely during treatment. If potassium is >5.5 mmol/L, the drug should be stopped and restarted at the lower dose of 10 mg daily when potassium is ≤5.0 mmol/L. Additionally, finerenone need not be stopped when estimated GFR falls below 25 mL/min/1.73 m^2 as long as the patient is normokalemic.[174 175]

With respect to cardiovascular risk reduction, the KDIGO guidelines suggest that all patients aged over 50 with CKD G3-G5 but not treated with chronic dialysis or kidney transplantation should be treated with a statin, irrespective of cholesterol concentrations or a statin/ezetimide combination.[179 187] The NICE recommendation is broader, recommending starting atorvastatin 20 mg for all people with CKD.[188] KDIGO recommends regular physical activity for people with CKD, for at least 150 minutes a week of moderate intensity exercise.[179] NICE simply suggests providing lifestyle advice, including encouragement of exercise, maintenance of healthy weight, and

GLOSSARY OF ABBREVIATIONS

- ACE—angiotensin converting enzyme
- ACR—albumin-to-creatinine ratio
- ADA—American Diabetes Association
- ADPKD—autosomal dominant polycystic kidney disease
- ARB—angiotensin receptor blockers
- CKD—chronic kidney disease
- CKD-EPI—CKD Epidemiology Collaboration
- DPP-4—dipeptidyl peptidase-4
- eGFRcr—estimated glomerular filtration rate using creatinine
- eGFRcr-cys—estimated glomerular filtration rate using creatinine and cystatin C
- eGFRcys—estimated glomerular filtration rate using cystatin C
- ESKD—end stage kidney disease
- FDA—Food and Drug Administration
- FSGS—focal segmental glomerulosclerosis
- GFR—glomerular filtration rate
- GLP-1—glucagon-like peptide-1
- KDIGO—Kidney Disease: Improving Global Outcomes
- KFRE—kidney failure risk equation
- KFRT—kidney failure with replacement therapy
- LDL—low density lipoprotein
- MDRD—Modification of Diet in Renal Disease
- MRA—mineralocorticoid receptor antagonists
- NICE—National Institute for Health and Care Excellence
- NSAID—non-steroidal anti-inflammatory drug
- PCR—protein-to-creatinine ratio
- RAAS—renin-angiotensin-aldosterone system
- SGLT-2—sodium-glucose cotransporter-2

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QUESTIONS FOR FUTURE RESEARCH

- How do the race-free estimating equations perform in global populations?
- Where can genetic testing add value in patient care?
- Can cause of chronic kidney disease be incorporated into risk prediction tools?
- How can medical therapy be best tailored for the individual patient with chronic kidney disease?

PATIENT PERSPECTIVE

Increasing awareness of chronic kidney disease is key to empowering patients to make lifestyle changes and seek treatments to improve their health outcomes. We are pleased to offer our perspective as husband and wife, and as physicians, who have been affected by kidney disease. Roberta M Falke is a patient with autosomal dominant polycystic kidney disease (ADPKD), a kidney transplant recipient, and a retired hematologist-oncologist. Andrew S Levey is a kidney donor and a nephrologist. Our knowledge of Roberta's family history enabled early diagnosis and treatment.[189] Although we have benefited from our training and positions in the healthcare system, all patients can benefit from early diagnosis.

RMF—My ADPKD was diagnosed when I developed pyelonephritis at age 22 years. Thereafter, I had prophylaxis and prompt treatment of recurrent urinary tract infections and, as the disease progressed, complications of kidney and liver cysts, hypertension, hyperparathyroidism, vitamin D deficiency, acidosis, hyperkalemia, and ultimately kidney failure, with fatigue, dietary restrictions, and a long list of medications to take every day. I had always known that living donor kidney transplantation would be the best treatment for my kidney failure. Over time, family members without ADPKD donated to others, and when I was ready at age 60 years no family members were available. Fortunately, Andy stepped up. I felt better immediately after the transplant, and in the 13 years since then I have continued to take medications daily but have had few complications. I am grateful to all those who have cared for me for many years and enabled me to make the best choices I could to help myself, and I'm especially grateful to Andy who gave me the gift of life.

ASL—I knew that Roberta would develop kidney failure and hoped that a living kidney donor would be available for her. I wanted to donate, but our blood group incompatibility was an obstacle, so it was exciting when paired donor exchange was conceived and implemented in our region. I believe that kidney donors benefit from donation, not only by fulfilling their spirit of altruism but by improving their own lives. In my case, donating has been life changing. Roberta and I have been able to have an active, fulfilling life for more than a decade after the transplant, without the demands and complications of kidney failure or dialysis. I hope that we will have many more years together. I am also grateful to all those who enabled me to achieve my goal and to Roberta, who always takes full responsibility for caring for her kidney disease.

smoking cessation, and specifically recommends against offering low protein diets (defined as dietary protein intake <0.8 g/kg/day).[16] KDIGO recommends maintaining sodium intake <2 g/day and a protein intake of 0.8 g/kg/day but no higher than 1.3 g/kg/day.[179]

Conclusion

People with CKD face high risks of many adverse outcomes, including requirement for kidney replacement therapy, cardiovascular events, and death. Fortunately, major advances have been made in the field of CKD over the past decade. Estimating equations for GFR and ACR have evolved for more precise classification of disease. Individualized risk prediction tools exist to assist in the counseling, referral, and treatment of patients. Novel therapies build on the fundamentals—a healthy lifestyle, blood pressure and glucose control, and statin therapy and RAAS blockade—to provide effective preventive strategies for CKD progression and cardiovascular events.

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Web appendix: Search terms