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Title: Advances in the Management of Chronic Kidney Disease

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Advances in the Management of 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 (1). While we have benefitted from our training and positions in the health care system, all patients can benefit from early diagnosis.

RMF: I was diagnosed with ADPKD 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. After the transplant, I felt better immediately, and in the 13 years since then, I have continued to take medications daily, but have had few complications. I'm 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: As a kidney doctor, I knew that Roberta would develop kidney failure and hoped that there would be a living kidney donor 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 we 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.

1. Falke RM and Levey AS. Hereditary kidney disease: All family members are affected. J Am Soc Nephrol 2018;29(10): 2451-2452. doi: https://doi.org/10.1681/ASN.2018080854

Abstract

Chronic kidney disease (CKD) represents a global public health crisis, but awareness by patients and providers is low. Defined as persistent abnormalities in kidney structure or function for more than three months, manifest either as low glomerular filtration rate or 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. In this review, we discuss the evidence behind general principles of CKD management, such as blood pressure and glucose control, renin-angiotensin-aldosterone system blockade, statin therapy, and dietary management. We additionally report individualized approaches to treatment based on risk of kidney failure and cause of CKD. Finally, we review novel classes of kidney-protective agents including sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, nonsteroidal selective mineralocorticoid receptor antagonists, and endothelin receptor antagonists. Appropriate, widespread implementation of these highly effective therapies should improve the lives of individuals suffering from 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

hospitalizations are all heightened in individuals 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 underrecognized by both patients and providers.[1] A diverse entity, CKD is most commonly attributed to diabetes or high blood pressure (BP), but myriad other etiologies exist, from genetic causes to adverse drug effects 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 long-standing and novel treatment strategies. There have been notable advances in both general and cause-specific therapies, including sodium-glucose cotransporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RA), nonsteroidal 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 performed a search in PubMed of peer-reviewed articles in the English language from January 1, 2010 to July 14, 2023 using the keywords listed in the supplemental 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. Older articles were included if they were deemed to be of high importance. Finally, we reviewed guidelines from websites of professional societies and advisory committees (e.g., National Institute for Health and Care Excellence (NICE), Kidney Disease: Improving Global Outcomes (KDIGO), Centers for Disease Control and Prevention, U.S. 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 individuals have CKD, with greater burdens in low- and middle-income countries.[1,4] Determining the global, regional, and national burden of disease is challenging due 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 those over 70 years.[2] In the United States (US), compared with White individuals, Black individuals have substantially higher rates of kidney failure, followed by Native Americans, persons of Hispanic ethnicity, and persons of Asian descent.[5]

The most common 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 which are present in far greater proportions among individuals of African ancestry.[8-11] In Central America, Sri Lanka, Egypt, and Central India, there are defined geographic areas where many cases of CKD of unknown cause (CKDu) have been identified.[12] Some 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 afflicted patients, allowing the comparison of incidence across ages and countries.[13] For example, in 2020, the countries with the highest incidence of treated kidney failure were Taiwan, the United States, and Singapore whereas the countries with the highest prevalence were Taiwan, the Republic of Korea, and Japan.[5]

Definition and classification of CKD: The importance of Cause, GFR, and Albuminuria (CGA) staging

CKD is defined as persistent abnormalities in kidney structure or function for more than three months, manifest either as low GFR or a marker of kidney damage.[2] Specifically, diagnosis requires one or more of the following: 1) 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 per day; 2) GFR <60 ml/min/1.73 m^2; 3) abnormalities on urine sediment, histology, or imaging; 4) electrolyte or other abnormalities attributed to tubular disorders; or 5) history of kidney transplantation. The KDIGO heat map helps understand overall risk (low, moderately increased, high, and very high) of individuals based on level of albuminuria (A category), level of GFR (G category), and Cause of disease (**Figure 1**), such that people with normal eGFR but higher albuminuria have a similar risk compared to people with moderately reduced eGFR and no albuminuria.

Clinical manifestations of CKD

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

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, in clinical practice, this is relatively cumbersome and rarely done. Instead, GFR is most commonly estimated 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 vs. non-Black) to estimate GFR.[19-21] The newer European Kidney Function Consortium (EKFC) equation, which allows for seamless GFR evaluation from infancy to old age, uses a population-specific divisor to adjust creatinine values (e.g., 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 relationship with GFR compared with creatinine (**Figure 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 there are large differences between eGFRcr and that estimated solely using cystatin C (eGFRcys).[25,27,28] However, the newest GFR estimating equations have not been tested extensively in Asian populations.[29,30]

The third axis for classification is cause of CKD and 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 (e.g., obesity, diabetes, hypertension, systemic autoimmune disease) and the specific location of the kidney pathology (e.g., glomeruli, tubulointerstitium, vasculature, or cystic/congenital abnormality). Unfortunately, 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 kidney and urinary tract.[31] One study suggested that for appropriately selected patients, 34% had disease either reclassified or assigned based on genetic testing, thus changing clinical management.[32] The European Renal Association (ERA) and the European Rare Kidney Disease Reference Network (ERKNet) 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]

Individualized prognosis and treatment in CKD

Identifying cause of CKD is critical since 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 typically associated with faster progression than other disease entities.[32,34] Individualized prognosis is often determined using disease-specific risk classification or calculators (e.g., 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 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 two-fold higher risk of kidney failure in the general population, and are common in persons of African ancestry.[8,43-45] A recently published phase 2A study of targeted therapy for *APOL1*-related disease demonstrated promising reductions in albuminuria; the phase 3 study is ongoing.[46] Other disease-specific therapies are increasingly available, such as belimumab in lupus nephritis[47] and lumasiran for primary hyperoxaluria type 1.[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 individuals with GFR <60 ml/min/1.73 m^2.[49] Tested in more than 30 countries and 700,000 people, the tool provide probabilities of kidney failure at 2- and 5-years based on age, sex, eGFR 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 (i.e., distinguishing high-risk from low-risk individuals) 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 oldest, highest risk segments of the population.[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, the KFRE provides a wide estimate of risk prediction, which can be helpful in the counseling and referral of patients (**Figure 3**). For instance, some centers will refer patients with 2-year risk of kidney failure greater than 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 eGFR 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 take into account 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 individuals with eGFR <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 the many more patients with CKD suffer cardiovascular disease events compared with requiring KFRT.[58] Other equations incorporate eGFR and albuminuria into existing tools, like SCORE2 and the pooled cohort equation for the prediction of cardiovascular disease.[59,60]

Other patient-specific prognostic clues may stem from discrepant eGFR values between eGFRcr and eGFRcys.[61-63] When eGFRcys is substantially lower than eGFRcr, there is higher risk for kidney-related laboratory abnormalities (e.g., anemia, hyperuricemia, and hyperphosphatemia) and subsequent adverse outcomes (e.g., kidney failure, heart failure, and mortality).[61,64,65] In 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 older age, female sex, higher BMI, recent weight loss, and smoking.

General principles of CKD management

The mainstays of therapy for individuals with CKD include treating the underlying cause if known, and addressing risk factors (e.g., albuminuria) for CKD progression and other CKD-related complications (**Figure 4**).[2]

BP targets

The three major studies for evaluating the optimal BP 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 BP control did not slow GFR decline overall.[67,68] However, in MDRD, participants with baseline proteinuria of ≥3 g/day appeared to benefit from intensive BP control, with slower mean rates of GFR decline compared with their counterparts in the usual BP control group.[67] Among SPRINT participants with baseline CKD (n=2,646), aiming for a systolic BP goal of <120 vs. <140 mm Hg did not significantly reduce the risk for a composite kidney outcome that included a ≥50% reduction in eGFR, long-term dialysis, or kidney transplant.[69,70] However, there were benefits of intensive BP control with respect to prevention of the composite cardiovascular outcome (defined as myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes) and all-cause mortality, regardless of CKD status. BP 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 eGFR <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%, 30%, and 65% lower risks of developing new onset ACR 30-300 mg/g, ACR >300 mg/g, and ESKD, respectively.

<u>*Specific classes of therapy*</u>

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers

When choosing anti-hypertension agents, those that act by inhibiting the renin-angiotensin-aldosterone system (RAASi) have particular relevance in CKD. A 2001 meta-analysis of 11 studies suggested that, for non-diabetic CKD, the use of angiotensin converting enzyme inhibitors (ACEi) resulted in a 30% reduction in risk of KFRT or doubling of serum creatinine.[75] Clinical trials in populations with CKD and diabetes (e.g., IDNT, RENAAL) have also shown benefit in angiotensin receptor blockers (ARB) in preventing CKD progression (**Table 1)**.[76,77] RAASi also plays a role in cardiovascular disease prevention. The Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that ACEi reduced the risks of myocardial infarction, stroke, and cardiovascular death in populations at high risk for cardiovascular disease, including those with diabetes and albuminuria.[78] The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) showed that ACEi and ARB are generally equivalent in the prevention of cardiovascular events.[79] Because of the increased risk of hyperkalemia and acute kidney injury, dual therapy with both an ACEi and an ARB is typically avoided.[80]

When GFR declines, providers often grapple with whether RAASi should be continued. The Benzapril in Advanced CKD study demonstrated that benazepril reduced the risk of the primary composite kidney endpoint by 43% compared with placebo, thus suggesting that RAASi are beneficial even in advanced CKD (baseline serum creatinine 3.1 to 5.0 mg/dL).[81] Three recent reports further explored this issue, also examining the benefits in prevention of death and cardiovascular events associated with RAASi continuation.[82-84] A retrospective, propensity-score matched study of patients with eGFR <30 ml/min/1.73 m^2 demonstrated higher risk of all-cause mortality and major adverse cardiovascular events in those who stopped RAASi compared to those who continued,[82] as did a Swedish trial emulation study.[83] The risk of kidney replacement therapy associated with RAASi cessation was not statistically significant in the former study and lower in the latter study.[82,83] In an open-label randomized trial, cessation of RAASi did not demonstrate significant between-group differences in long-term decline in eGFR nor initiation of kidney replacement therapy, providing reassurance that RAASi can be safely continued as eGFR declines.[84]

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 demonstrated an approximate 30% reduction in risk for diverse kidney outcomes among individuals with baseline eGFR values as low as 20 ml/min/1.73 m^2 (**Table 2**).[85-88] 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 due to meeting pre-specified efficacy criteria, with median follow-up times ranging from 2.0 to 2.6 years.[86-88] The overwhelming majority of trial participants were on an ACEi or ARB prior to randomization, demonstrating that the benefits of SGLT-2 inhibitors on slowing CKD progression are additive to RAASi. One simulation study estimated that a 50-year old adult with non-diabetic albuminuric CKD would have 7 extra years free from doubling of serum creatinine, kidney failure, or all-cause mortality, if treated with an SGLT2-inhibitor and RAASi.[89]

Subgroup analyses of the DAPA-CKD and EMPA-KIDNEY trials have provided additional insights on the wide swath of patients who are likely to benefit from SGLT-2 inhibitors.[87,88] In DAPA-CKD, dapagliflozin was favored over placebo in all prespecified subgroups by baseline age, sex, race, diabetes status, systolic BP, eGFR (<45 vs. ≥45 ml/min/1.73 m^2), and ACR (≤1000 vs. >1000 mg/g or ≤113 vs. >113 mg/mmol).[87] Similarly, in EMPA-KIDNEY, empagliflozin was associated with lower risk of the primary composite outcome compared with placebo regardless of baseline diabetes status or eGFR (<30 vs. ≥30 to <45 vs. ≥45 ml/min/1.73 m^2).[88] 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 eGFR decline compared with placebo among participants with ACR between 30 and 300 mg/g (approximately 3-30 mg/mmol) and slower chronic slope (from 2 months to the final follow-up visit) among all ACR subgroups.

The DAPA-CKD trial also demonstrated that the kidney protective effects of SGLT-2 inhibitors extend to individuals with IgA nephropathy and perhaps also focal segmental glomerulosclerosis (FSGS).[90,91] Among 270 participants with IgA nephropathy (mean eGFR 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.[90] Among the 104 participants with FSGS (mean eGFR 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). In exploratory analyses, dapagliflozin was associated with slower chronic eGFR decline in the FSGS population.[91] Investigations on the use of SGLT-2 inhibitors in other patient populations, such as 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,[92] 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 of CREDENCE, DAPA-CKD, and EMPA-KIDNEY, thus assuaging these concerns (**Table 3**).[85-88] 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 only a higher rate of mild genital infections with the SGLT-2 inhibitor.[93] A real-world study of patients receiving SGLT-2 inhibitors compared with dipeptidyl peptidase-4 (DPP-4) inhibitors found no increased risk with outpatient urinary tract infections nor severe, hospitalized urinary tract infection events.[94]

GLP-1 receptor agonists

GLP-1 RA have also been shown to improve kidney outcomes among individuals with type 2 diabetes, albeit in trials that were designed for primary cardiac outcomes (**Table 4**).[95-106] The 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 GLP-1 RA use 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 eGFR, kidney replacement therapy, or death due to kidney causes compared with placebo.[97] This risk reduction appeared to be driven by the reduction in incident albuminuria >300 mg/g; associations between GLP-1 RA 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 hemoglobin A1c. [107] 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 eGFR declines compared with the insulin glargine group, and 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 RA slow eGFR decline 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.[108-110] Adverse effects observed with this class of medications have included diarrhea, nausea, and vomiting.[100,101,104,106,107]

Mineralocorticoid receptor antagonists

Several MRAs are available and can be useful adjuncts to RAASi, 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 ACEi and/or ARB was associated with a significant reduction in proteinuria albeit higher risk of hyperkalemia.[111] Finerenone, a nonsteroidal selective MRA, was also recently approved.[112] Compared with the steroidal non-selective MRAs, finerenone has a stronger selectivity for the mineralocorticoid receptor, a shorter half-life, less of a BP lowering effect, and a more favorable side effect profile as well as potentially greater anti-inflammatory and anti-fibrotic effects.[112-114] 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**).[113,115] Both trials included patients on maximally tolerated ACEi 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.[116] Hyperkalemia was more frequent among patients randomized to finerenone (14%) compared with placebo (7%). In prespecified analyses, baseline SGLT-2 inhibitor use (n=877) or GLP-1 RA use (n=944) did not modify the beneficial effect finerenone on the kidney composite outcome, thus suggesting a potential role for dual therapy (e.g., finerenone plus SGLT-2 inhibitor or GLP-1RA) among individuals 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, eGFR 25-75 ml/min/1.73 m^2, and urine ACR 300-5,000 mg/g on a stable dose of ACEi or ARB.[117] After a 6-week enrichment period during which everyone received atrasentan 0.75 mg daily (n=5,517), 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/gL and 20% from baseline; n=2,648) underwent randomization 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, though fluid retention and anemia were more frequent in the former. Of note, the frequency of hyperkalemia was low (1%) in each treatment group. Sparsentan, a dual endothelin and angiotensin II receptor antagonist, is also being investigated as a treatment for FSGS and IgA nephropathy.[118,119] In a phase 2, randomized, double-blind, active-control trial, 109 adults with biopsy-proven FSGS (eGFR >30 ml/min/1.73 m^2 and urine PCR ≥1 g/g) received varying doses of sparsentan (i.e., 200, 400, or 800 mg daily) or irbesartan 300 mg daily.[118] At 8 weeks, participants receiving sparsentan

had greater reductions in urine PCR compared with 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 3-fold higher odds of achieving complete remission of proteinuria at any point compared with their counterparts who were randomized to irbesartan 300 mg daily.[119] Based in part on the results of this study, the US Food and Drug Administration granted accelerated approval for the use of this medication among adults with primary IgA nephropathy considered to be at risk of rapid disease progression.[120]

Endothelin 1 has been implicated in the pathogenesis of kidney disease via various mechanisms including vasoconstriction, vascular hypertrophy, endothelial and podocyte injury, inflammation, cell proliferation, extracellular matrix accumulation, and fibrosis.[121] Systemic and local kidney production of endothelin 1 is augmented in CKD.

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 (e.g., eGFR <25 ml/min/1.73 m^2, on maintenance dialysis with residual daily urine output of >500 mL, and kidney transplant recipients with eGFR ≤45 ml/min/1.73 m^2; NCT05374291); finerenone in non-diabetic CKD (NCT05047263); and monteluklast (NCT05362474) and pentoxyifylline (NCT03625648) in diabetic CKD. There are also several therapies 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 anti-glomerular 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 which are recognized as autoantigens, triggering glomerular deposition of immune complexes.[122] Monoclonal antibodies to signaling molecules that enhance IgA production are in phase 3 trials as are immunosuppressive and non-immunosuppressive agents (e.g., those acting upon the endothelin-1 and angiotensin II pathways): budesonide (NCT03643965), sparsentan (NCT03762850), atrasentan (NCT04573478), LNP023 (NCT04578834), RO7434656 (NCT05797610), atacicept (NCT04716231), and sibeprenlimab (NCT05248646; NCT05248659).

Other nephroprotective and cardiovascular risk reduction strategies

There is a bidirectional association between CKD and cardiovascular disease: cardiovascular disease is both a risk factor for CKD and a common outcome in individuals with CKD.[123,124] Thus, individuals with CKD are likely to benefit from efforts at CVD risk reduction including administration of a statin as well as the gamut of lifestyle changes.[2,125]

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 eGFR of 27 ml/min/1.73 m^2).[126] Treatment with these LDL-cholesterol (LDL-C) lowering agents led to a 17% risk reduction for developing a first major atherosclerotic event compared with placebo, although this benefit was only seen in the patients not requiring maintenance dialysis. Those at very high risk (e.g., prior major atherosclerotic cardiovascular disease events) may benefit from additional therapies to lower LDL-C, including evolocumab.[127] Evolocumab is a monoclonal antibody for proprotein convertase subtilisin/kexin type 9 (PCSK9) which increases LDL-C receptors and hence clearance of LDL; this novel therapy also appears to be safe and efficacious in patients with CKD.[127,128]

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.[129-133] Whether these interventions also slow CKD progression remains to be determined, as many of these studies were underpowered for this outcome.

Diet

For individuals 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, in observational studies, from bariatric surgery.[134-136] Micro- and macronutrient composition of diets may also matter.[137]

Traditional recommendations regarding 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.[138-140] Observational data from large cohort studies suggests 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.[141,142] For example, an observational study in Singapore found a strong correlation between red meat intake and risk of ESKD.[143] However, there is little clinical trial evidence for protein restriction. The Modification of Diet in Renal Disease (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 dialysis start.[144] 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 individuals with CKD and chronic metabolic acidosis.[145] Other double-blinded studies using veverimer suggested that treating acidosis in CKD improves quality of life and overall physical function.[146] However, a recent trial evaluating veverimer in slowing progression of CKD was negative.[147]

Although patients with CKD are prone to hyperkalemia, potassium intake has a beneficial effect on BP, cardiovascular disease, and death independent and opposite to that of sodium intake.[148-151] 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.[152] Similarly, small studies suggest that diets rich in potassium may be beneficial in CKD. A feeding trial in persons with CKD G3 observed that 100 mmol compared with 40 mmol of dietary potassium per day increased serum potassium by 0.21 mmol/L,[153] similar to the increase seen with finerenone.[154] 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 fibre. Observational data from prospective cohorts suggest that plant-based diets are associated with less CKD progression.[141,155,156] There is also emerging evidence that increasing fibre intake benefits the gut microbiome, decreases inflammation, and possibly slows CKD progression.[157]

Appropriate drug dosing and nephrotoxin avoidance

An important component of care for the patient 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 medication or its metabolites resulting in adverse effects.[158] Careful estimation of GFR is generally a first step in determining drug dosage for renally excreted medications.[159] The US Food and Drug Administration guidance to industry suggests that eGFR based on serum creatinine may be used in pharmacokinetic studies.[160] If drugs are dosed based on eGFR (rather than estimated creatinine clearance from the Cockcroft-Gault equation, an equation that is known to be flawed), eGFR must be "de-indexed," or multiplying the standardized eGFR by the individual's calculated BSA and dividing by 1.73 m^2.[161-163] This is because drug clearance is thought to be proportional to an individual's GFR, and not the GFR standardized to body surface area (BSA). Antibiotics and antiviral agents, direct oral anticoagulants, medications for diabetes mellitus, and chemotherapeutic agents are the most common medications which require attention to dosing in CKD.[2,158,162]

Some medications should be avoided or minimized in CKD because of their potential to worsen kidney function. For example, NSAIDs can exacerbate hypertension, cause fluid retention, and contribute to the risk of AKI.[164] Particularly when used with RAASi and diuretics, NSAIDs are ideally avoided.[165] 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.[166] Proton pump inhibitors (PPIs) can lead to acute or chronic interstitial nephritis and have been associated with incident CKD, progression of CKD and ESKD.[167,168] Although the mechanism by which PPI contribute to CKD remains unclear, most experts agree that these agents should be used judiciously.

Guidelines

Major guidelines in CKD are issued by the international Kidney Disease: Improving Global Outcomes (KDIGO) group (https://kdigo.org/), and locally in the United Kingdom by the National Institute of Health and Care Excellence (NICE) (https://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 (e.g., diabetes, BP, lipids, anemia, mineral and bone disease, hepatitis C, autosomal dominant polycystic kidney disease, glomerular diseases, etc). With the expansion of therapeutic options, both organizations are updating recommendations frequently. Other guideline 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.[169-172]

Annual screening for CKD (including testing for albuminuria) is widely recommended in diabetes.[171-175] Guidelines in hypertension are less clear.[176] 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 glomerular filtration rate (eGFR) in people with hypertension.[170] KDIGO and NICE also recommend testing anyone who is at risk for CKD, which includes those with hypertension, cardiovascular disease, diabetes, and prior acute kidney injury, along with multiple other, less common conditions.[177] For CKD, the KDIGO guidelines recommend at least annual albuminuria testing with greater frequency in higher risk categories (**Figure 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 it is not appropriate to use "race as a distinct variable in the computation of GFR."[177] NICE recommends using the CKD-EPI 2009 equation, which did include race, but using the computed value for non-Black individuals for everyone, a position that is also endorsed by other European groups.[16,178,179] 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.[2,177] 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 patents with CKD. The NICE guidelines suggest that primary care providers counsel patients using the KFRE 5-year risk estimate, with referral to a specialist if risk is greater than 5%.[16] KDIGO 2023 additionally suggests that the 2-year risk estimate can drive referral for multidisciplinary care (>10%) and preparation for kidney replacement therapy, including vascular access planning and referral to transplantation (>40%).[177] The KDIGO 2023 guidelines also emphasize the importance of cardiovascular risk assessment using equations developed in people with CKD or that encompasses eGFR and albuminuria, and the use of disease-specific tools in IgA nephropathy and ADPKD[177].

Multiple guidelines comment on target blood pressures in the setting of CKD. The NICE guidelines recommend a BP target of <140/90 mmHg, or <130/80 mmHg 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 BP target of <130 mmHg as a best practice target, with the European Society of Cardiology and European Society of Hypertension specifically advising against lower targets.[169] The KDIGO guidelines on hypertension in CKD advocate for a systolic BP goal of <120 mmHg, as assessed using standardized office

measurements.[180] This recommendation is based largely on data from the Systolic Blood Pressure Intervention Trial (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 BP techniques, which can result in measured BP that is substantially lower than measurement in an uncontrolled setting.[181] Joint statements from several international groups including KDIGO stress the importance of proper technique when assessing BP.[182] Both NICE and KDIGO recommend RAASi (either ACEi or ARB) as first-line antihypertensive treatment for people without diabetes but with albuminuria (NICE: urine ACR >70 mg/mmol and KDIGO: A3) as well as those with diabetes and CKD G1-G4, A2-A3.[16,180] KDIGO 2023 suggests continuation of RAASi even when eGFR <30 ml/min/1.73 m^2.[177]

For patients with diabetes and CKD not treated with dialysis, KDIGO recommends an HbA1c 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 <7% for people with diabetes on medications associated with hypoglycemia and <6.5% for people with diabetes managed by lifestyle or a single drug not associated with hypoglycemia.[183]

KDIGO and ADA guidelines recommend SGLT-2 inhibitors as first-line drug therapy for all people with type 2 diabetes, CKD, and an eGFR ≥20 ml/min/1.73 m^2 (**Figure 5**).[72,171,172,177] The NICE guidelines recommend that a SGLT-2 inhibitor 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 on an ACEi or ARB and meet eGFR thresholds.[183] The NICE guidelines further specify that dapagliflozin also be considered among people with eGFR 25-75 ml/min/1.73 m^2 and ACR ≥22.6 mg/mmol (approximately 200 mg/g) regardless of diabetes status;[184] KDIGO is broader and recommends SGLT-2 inhibitors in general in persons with ACR ≥200 mg/g and eGFR ≥20 ml/min/1.73 m^2 as well as in those with CKD and heart failure.[177] KDIGO further specifies that once started, a SGLT-2 inhibitor can be continued even if the eGFR drops below 20 ml/min/1.73 m^2, as long as it is tolerated and kidney replacement therapy has not yet been initiated.[72,177] The KDIGO and ADA guidelines recommend the use of GLP-1 RA in patients with type 2 diabetes and CKD who are unable to tolerate metformin or a SGLT-2 inhibitor or fail to meet their individualized glycemic target with these medications.[72,171,172,177]

In patients with diabetes and CKD, the KDIGO and ADA guidelines recommend that finerenone be used as add-on therapy to maximally tolerated ACEi or ARB if ACR is ≥30 mg/g [approximately ≥3 mg/mmol] and potassium is within normal limits (i.e., ≤4.8 mmol/L based on trial and ≤5.0 mmol/L per FDA) .[72,171,172,177] More specifically, the starting dose should be 10 mg daily when eGFR is 25-59 ml/min/1.73 m^2 and 20 mg daily when eGFR is ≥60 ml/min/1.73 m^2. The guidelines also recommend that a potassium level be checked at 4 weeks after initiation, with each dose change, and routinely during treatment. If potassium is >5.5 mmol/l, the medication 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 eGFR falls below 25 ml/min/1.73 m^2 as long as the patient is normokalemic.[171,172]

With respect to cardiovascular risk reduction, the KDIGO guidelines suggest that all patients over the age of 50 years with CKD G3-G5 but not treated with chronic dialysis or kidney transplantation be treated with a statin, irrespective of cholesterol levels, or a statin/ezetimide combinations.[177,185] The NICE recommendation is broader, recommending initiating atorvastatin 20 mg for all people with CKD.[186] KDIGO recommends regular physical activity for individuals with CKD, for at least 150 minutes per week of moderate-intensity exercise.[177] NICE simply suggests providing lifestyle advice, including encouragement of exercise, maintenance of healthy weight, and smoking cessation, and specifically recommend against offering low protein diets (defined as dietary protein intake <0.8 g/kg/day).[16] KDIGO recommends maintaining sodium intake <2g per day and a protein intake of 0.8 g/kg/day but no higher than 1.3 g/kg/day.[177]

Summary

In summary, individuals with CKD face high risks of many adverse outcomes, including requirement for kidney replacement therapy, cardiovascular events, and death. Fortunately, there have been major advances 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; BP and glucose control; and statin therapy and RAAS blockade – to provide effective preventative strategies for CKD progression and cardiovascular events.

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Table 1. Landmark randomized clinical trials on ACEi or ARB in CKD.

	REIN Stratum 2[187] (n=166)	**RENAAL[76] (n=1,513)**	**IDNT[77] (n=1,715)**	**AASK[68] (n=1,094)**	**Benazepril for Advanced CKD, Group 2[81] (n=224)**
Kidney-related inclusion criteria	CrCl 20-70 ml/min/1.73 m^2 & Protein excretion ≥3 g/day	SCr 1.3-3.0 mg/dL & 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 & Protein excretion ≥900 mg/day	GFR 20-65 ml/min/1.73 m^2 & PCR ≤2.5 g/g	SCr 3.1-5.0 mg/dL & 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	Metoprolol 50-200 mg daily	Placebo
			Amlodipine 10 mg daily	Amlodipine 5-10 mg daily	
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[a]	Mean protein excretion ~5.3 g/day	Median ACR 1,261 mg/g for placebo group and 1,237 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
	Mean Decline [SE][b]	**Hazard Ratio (95% CI)**	**Relative Risk (95% CI)[c]**	**Mean difference [SE]**	**Risk Reduction**
Primary outcome	GFR decline (ml/min per month)	Composite of doubling SCr, ESKD, or death	Composite of doubling SCr, ESKD, or death	Total GFR slope (ml/min/1.73 m^2 per year)	Composite of doubling SCr, ESKD, or death
	0.53 [0.08] for ramipril vs. 0.88 [0.13] for placebo (p=0.03)	0.84 (0.72, 0.98)	0.80 (0.66, 0.97) for irbesartan vs. placebo	+0.61 [0.22] for ramipril vs. metoprolol (p=0.007)	43% (p=0.005)
			0.77 (0.63, 0.93) for irbesartan vs. amlodipine	-0.34 [0.38] for ramipril vs. amlodipine (p=0.38)	

[a] To convert ACR from mg/g to mg/mmol, multiply by 0.113.

[b] In REIN, n=117 with ≥3 GFR evaluations.

Abbreviations: ACEi=angiotensin converting enzyme inhibitor ; ARB=angiotensin receptor blocker; CKD=chronic kidney disease; CrCl =creatinine clearance; GFR=glomerular filtration rate; eGFR=estimated glomerular filtration rate; SCr=serum creatinine; SE=standard error; ESKD=end-stage kidney disease; ACR=urine albumin-to-creatinine ratio; PCR=urine protein-to-creatinine ratio; REIN=Ramipril Efficacy In Nephropathy; RENAAL=Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan); IDNT=Irbesartan Diabetic Nephropathy Trial; AASK=African American Study of Kidney Disease and Hypertension.

Table 2. Landmark randomized clinical trials on SGLT-2 inhibitors in CKD.

	CANVAS Program[85,188] (n=10,142)	**CREDENCE[86] (n=4,401)**	**DAPA-CKD[87,189] (n=4,304)**	**EMPA-KIDNEY[88] (n=6,609)**
Kidney-related inclusion criteria	eGFR >30 ml/min/1.73 m^2	eGFR 30 to <90 ml/min/1.73 m^2 & ACR >300 to 5,000 mg/g	eGFR 25 to 75 ml/min/1.73 m^2 & ACR 200 to 5,000 mg/g	eGFR ≥20 to <45 ml/min/1.73 m^2 OR eGFR ≥45 to <90 ml/min/1.73 m^2 & 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	n/a	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/1.7 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 vs. Placebo				
Primary Outcome	Composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes	Composite of doubling of serum creatinine, ESKD, or death from kidney or cardiovascular causes	Composite of sustained decline in eGFR of ≥50%, ESKD, or death from kidney or cardiovascular causes	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
	0.86 (0.75, 0.97)	0.70 (0.59, 0.82)	0.61 (0.51, 0.72)	0.72 (0.64, 0.82)
CKD progression[a]	0.60 (0.47, 0.77)	0.66 (0.53, 0.81)	0.56 (0.45, 0.68)	0.71 (0.62, 0.81)
ESKD[b]	0.77 (0.30, 1.97)	0.68 (0.54, 0.86)	0.64 (0.50, 0.82)	0.73 (0.59, 0.89)

Difference (95% CI) in ml/min/1.73 m^2 per year comparing SGLT-2 inhibitor vs. Placebo				
eGFR slope[c]	Total: 2.0 (1.5, 2.6) Long-term: 1.2 (1.0, 1.4)	Total: 1.52 (1.11, 1.93) Long-term: 2.74 (2.37, 3.11)	Total: 0.93 (0.61, 1.25) Long-term: 1.92 (1.61, 2.24)	Total: 0.75 (0.54, 0.96) Long-term: 1.37 (1.16, 1.59)

[a]CKD progression defined as a 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.

[b]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.

[c]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.

Abbreviations: SGLT-2=sodium-glucose co-transporter 2; CKD=chronic kidney disease; ESKD=end-stage kidney disease; eGFR=estimated glomerular filtration rate; CVD=cardiovascular disease; ACR=urine albumin-to-creatinine ratio; n/a=not available; FSGS=focal segmental glomerulosclerosis; 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.

To convert ACR from mg/g to mg/mmol, multiply by 0.113.

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

	CANVAS[85]	CREDENCE[86]	DAPA-CKD[87]	EMPA-KIDNEY[88]
Urinary tract infection	↔	↔	NR	↔
Serious genital infection	↑[a]	↑ in men	Too few events	Too few events
Hyperkalemia	↔	↔	NR	↔
Acute kidney injury	↔	↔	↔	↔
Liver injury	↔	↔	NR	↔
Ketoacidosis	↔	↑	↔	Too few events
Limb amputation	↑	↔	↔	↔
Bone fracture	↑	↔	↔	↔
Severe hypoglycemia	↔	↔	↓	↔
Volume depletion	↑	↔	↑	↔
Pancreatitis	↔	Too few events	NR	NR

[a]defined as infection of male genitalia and mycotic genital infection in women.

Abbreviations: SGLT-2=sodium-glucose co-transporter 2; NR=not reported; 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.

Table 4. Landmark randomized clinical trials on associations of GLP-1 RA with secondary kidney outcomes among individuals with type 2 diabetes mellitus.

	ELIXA[95-98] (n=6,068)	**LEADER[99,100] (n=9,340)**	**SUSTAIN-6[97,101] (n=3,297)**	**EXSCEL[102,103] (n=14,752)**	**REWIND[104,105] (n=9,901)**	**AMPLITUDE-O[106] (n=4,076)**
Kidney-related inclusion criteria	eGFR ≥30 mL/min/1.73 m^2	Age ≥50 years with ≥1 cardiovascular coexisting condition (e.g., CKD G3+) OR Age ≥60 years with ≥1 cardiovascular risk factor (e.g., albuminuria or proteinuria)	Age ≥50 years with CVD or CKD G3+ OR Age ≥60 years with ≥1 CVD risk factor (e.g., 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 mcg 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	n/a	n/a	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	ACR >300 mg/g, doubling of serum creatinine with eGFR <45 ml/min/1.73 m^2,	ACR >300 mg/g, ≥40% decline in eGFR, kidney replacement	ACR >300 mg/g, ≥30% decline in eGFR, or maintenance kidney	ACR >300 mg/g and increase in ACR ≥30% from baseline, ≥40% decline in eGFR or

		ml/min/1.73 m^2, need for maintenance kidney replacement therapy, or death from kidney disease*	or need for maintenance kidney replacement therapy	therapy, or death from kidney causes	replacement therapy	eGFR <15 ml/min/1.73 m^2, maintenance kidney replacement therapy
Hazard Ratio (95% CI) comparing GLP-1 RA to Placebo	0.85 (0.69, 1.05)	0.78 (0.67, 0.92)	0.64 (0.46, 0.88)	0.85 (0.74, 0.98)	0.85 (0.77, 0.93)	0.68 (0.57, 0.79)

*Most of the risk reduction was due to prevention of the albuminuria endpoint.

Abbreviations: GLP-1 RA=glucagon-like peptide-1 receptor agonist; ESKD=end-stage kidney disease; eGFR=estimated glomerular filtration rate; CVD=cardiovascular disease; ACR=urine albumin-to-creatinine ratio; ELIXA=Evaluation of Lixisenatide in Acute Coronary Syndrome; LEADER=Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6=Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; EXSCEL=Exenatide Study of Cardiovascular Event Lowering; REWIND=Researching cardiovascular Events with a Weekly Incretin in Diabetes; AMPLITUDE-O=Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes.

To convert ACR from mg/g to mg/mmol, multiply by 0.113

Table 5. Landmark randomized clinical trials on Finerenone in CKD.

	FIDELIO-DKD[113] (n=5,674)	**FIGARO-DKD[115] (n=7,352)**
Kidney-related inclusion criteria	ACR 30 to <300 mg/g & eGFR 25 to <60 ml/min/1.73 m^2 & diabetic retinopathy OR ACR 300 to 5,000 mg/g & eGFR 25 to <75 ml/min/1.73 m^2	ACR 30 to <300 mg/g & eGFR 25 to 90 ml/min/1.73 m^2 OR ACR 300 to 5,000 mg/g & 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 vs. 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, 0.93)	0.87 (0.76, 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, 0.90)	0.77 (0.60, 0.99)
ESKD: initiation of maintenance dialysis for ≥90 days or kidney transplantation.	0.86 (0.67, 1.10)	0.64 (0.41, 0.995)
Ratio of Least Squares (95% CI) comparing Finerenone vs. Placebo		
Mean ACR change from baseline to month 4	0.69 (0.66, 0.71)	0.68 (0.65, 0.70)

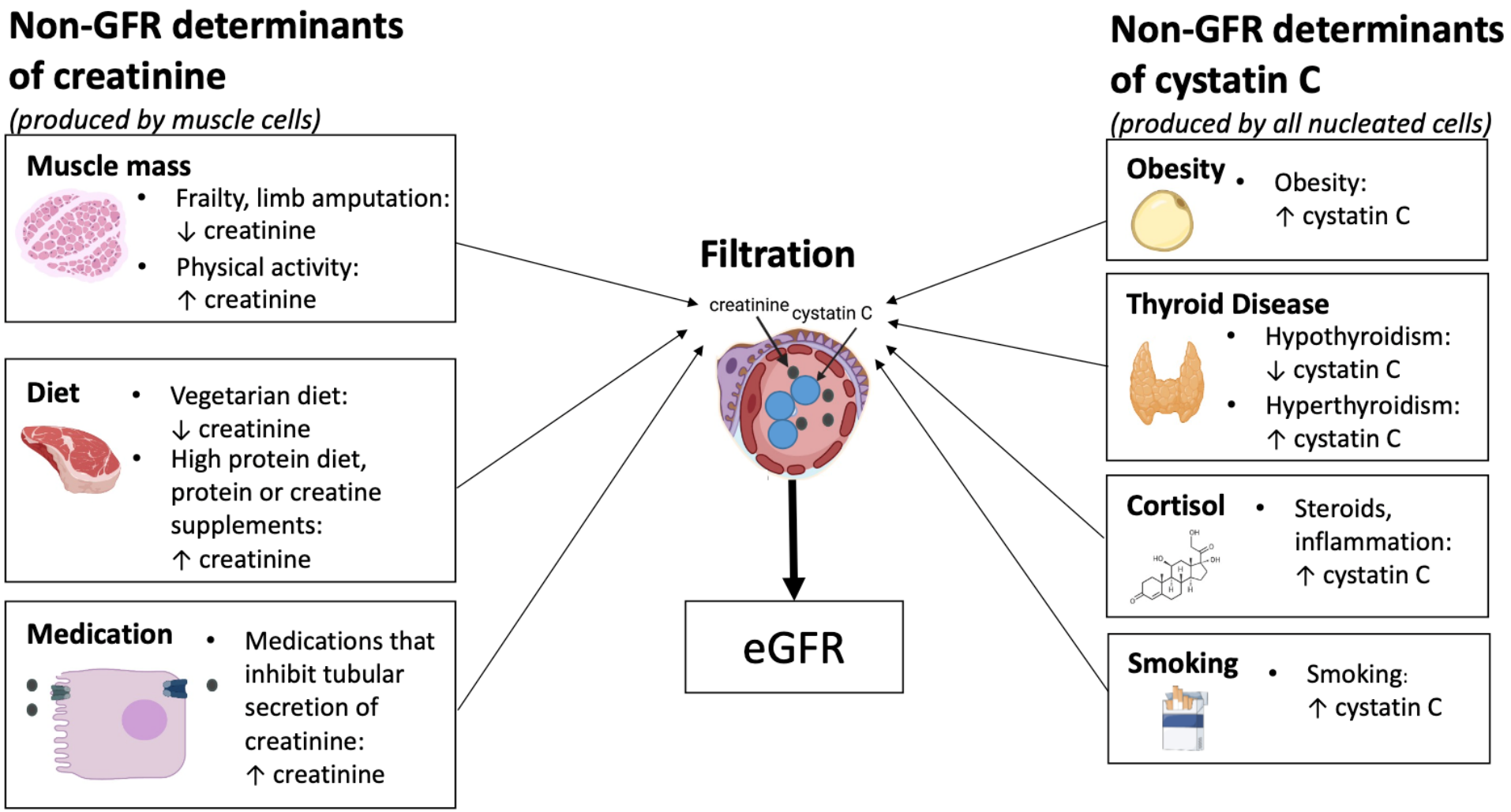
Abbreviations: CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; ACR=urine albumin-to-creatinine ratio; FIDELIO-DKD=Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; FIGARO-DKD=Finerenone in Reducing Cardiovascular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

Figure 1. KDIGO heat map with guidance on monitoring.[2]

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 >30mg/mmol
GFR categories (ml/min/1.73 m^2) 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+

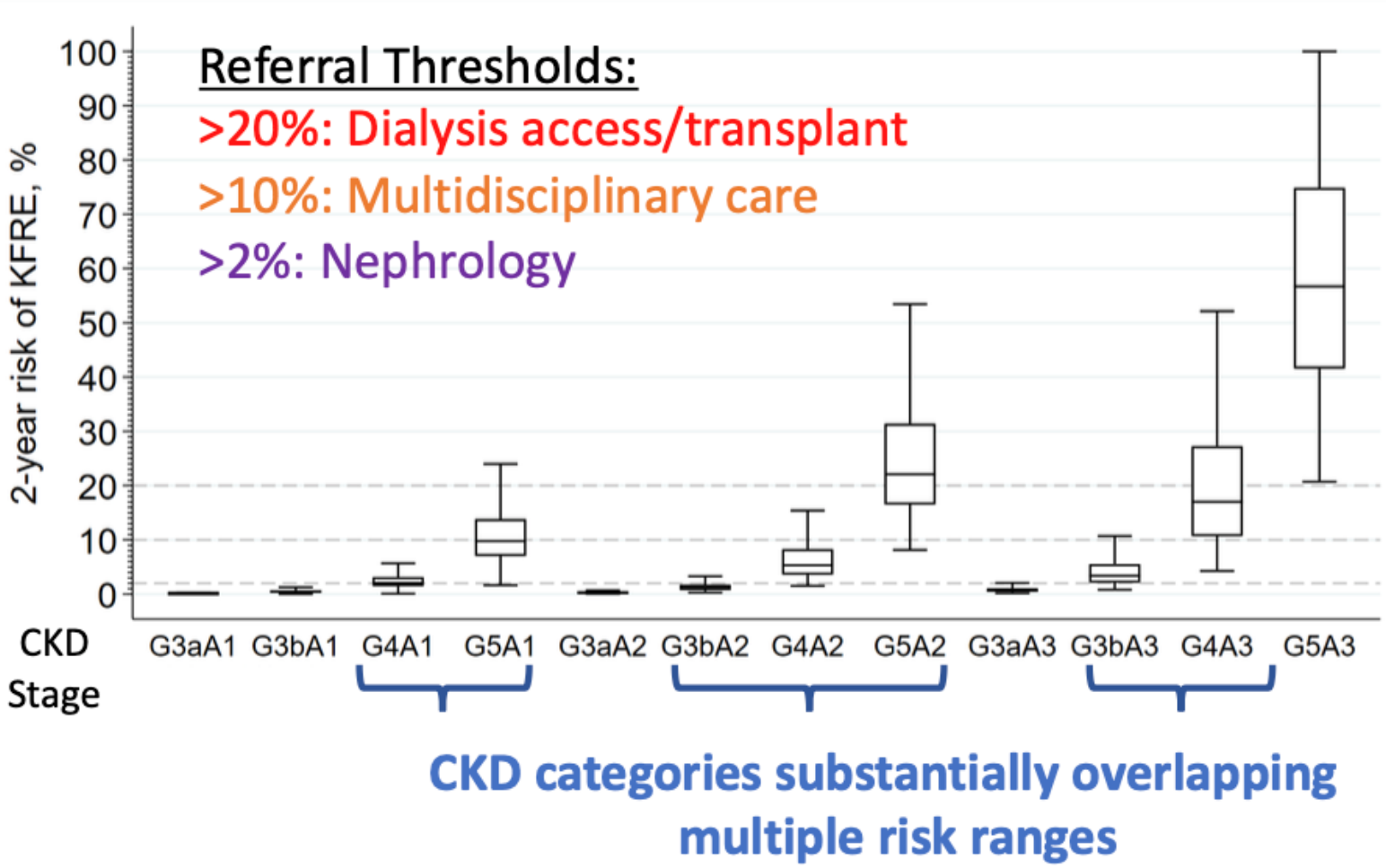
Numbers in boxes indicated recommended frequency of monitoring (number of times per year).
Colors denote risk as follows: green (low risk), yellow (moderately increased risk), orange (high risk), and red (very high risk)
Abbreviations: KDIGO=Kidney Disease: Improving Global Outcomes; GFR=glomerular filtration rate; CKD=chronic kidney disease.

Figure 2. Common non-GFR determinants of blood levels of creatinine and cystatin C.[2,26]



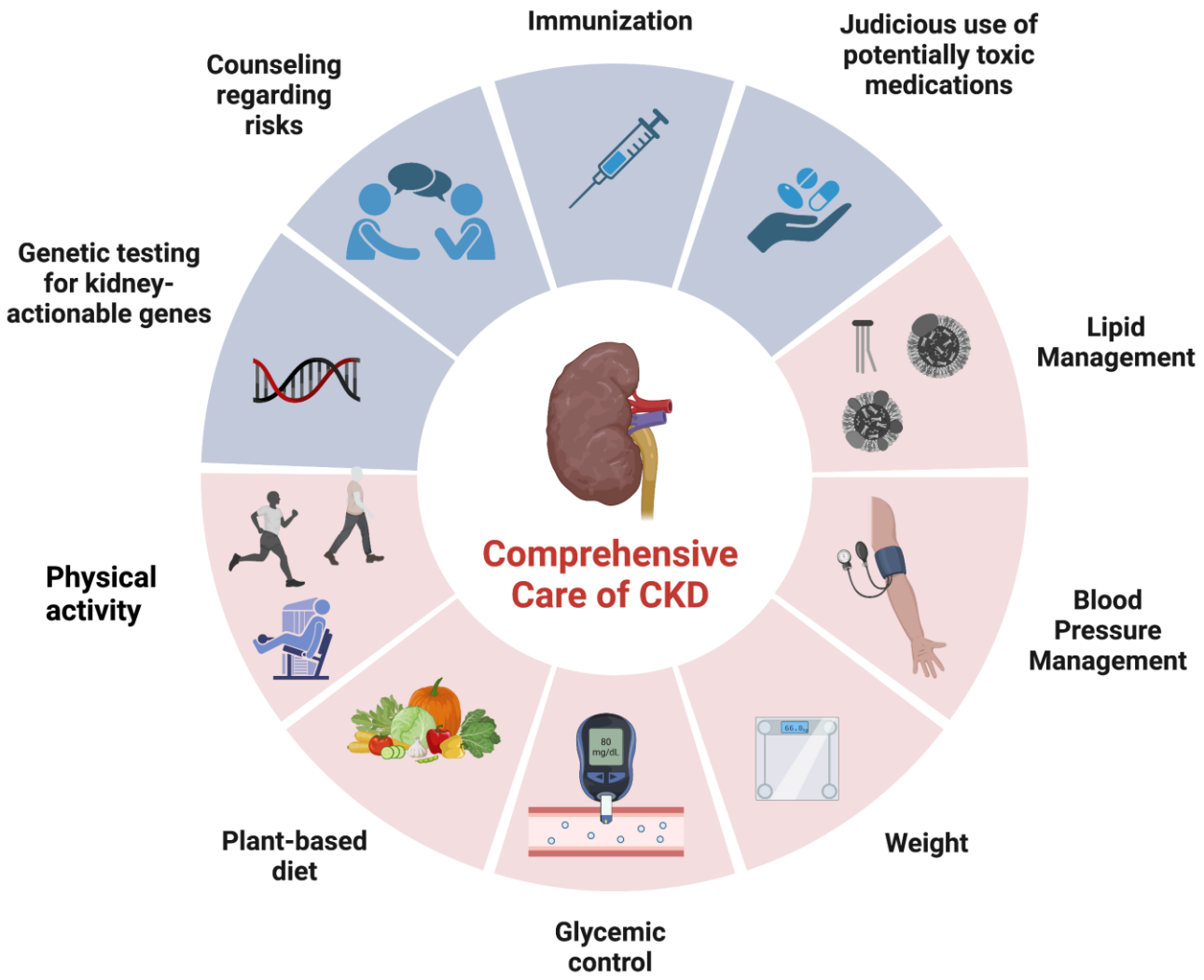
Abbreviations: GFR=glomerular filtration rate; eGFR=estimated glomerular filtration rate.

Figure 3. Range of predicted risk of kidney failure using the kidney failure risk equation (KFRE) within G and A categories of CKD.



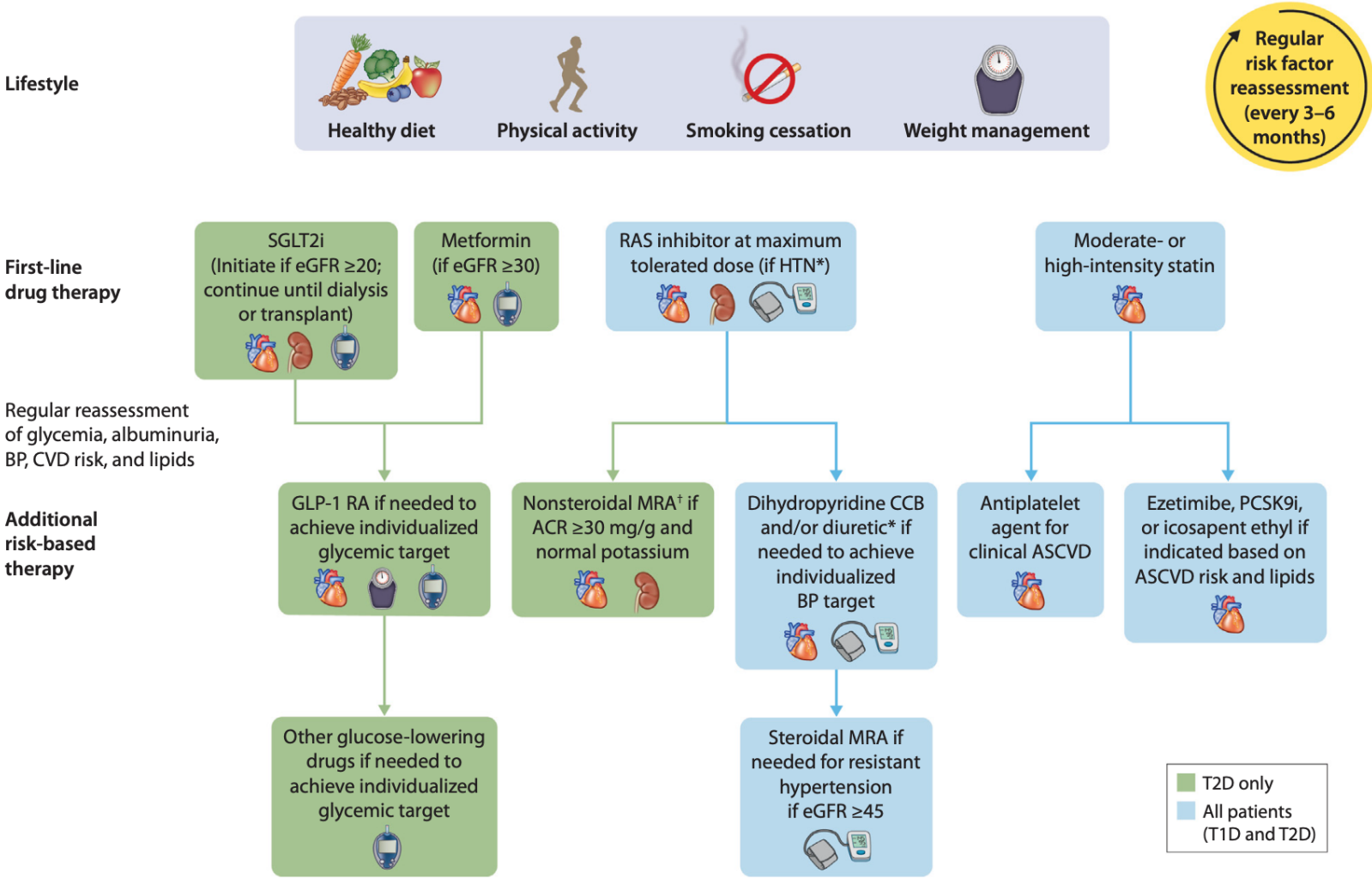
Abbreviations: CKD=chronic kidney disease; KFRE=kidney failure risk equation.
We used the KFRE (ckdpcrisk.org/kidneyfailurerisk) to estimate the 2-year risk of kidney failure in 350,232 patients with eGFR <60 ml/min/1.73 m^2 from the Optum Labs Data Warehouse (OLDW). OLDW is a longitudinal, real-world data asset with de-identified administrative claims and electronic health record (EHR) data. Individuals with eGFR and albuminuria (urine ACR, PCR, 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).

Figure 4. Comprehensive care of patients with CKD, irrespective of cause.



Abbreviations: CKD=chronic kidney disease.

Figure 5: KDIGO/ADA recommendations on the management of diabetes in populations with CKD.[72,171]



Abbreviations: BP=blood pressure; CVD=cardiovascular disease; SGLT2i=sodium-glucose cotransporter-2 inhibitor; GLP-1 RA=glucagon-like peptide-1 receptor agonist; MRA=mineralocorticoid receptor antagonist; HTN=hypertension; eGFR=estimated glomerular filtration rate; T2D=type 2 diabetes; ASCVD=atherosclerotic cardiovascular disease; PCSK9i=proprotein convertase subtilisin/kexin type 9 inhibitor; RAS=renin-angiotensin system; KDIGO=Kidney Disease: Improving Global Outcomes; ADA=American Diabetes Association.

Box 1: The European Renal Association (ERA) and European Rare Kidney Disease Reference Network (ERKNet) 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 abnormalities of the kidney and urinary tract
- Patients <50 years of age with severe CKD of unknown etiology
- Patients >50 years of age with adult-onset CKD and family history of CKD

Box 2: 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 CKD be incorporated into risk prediction tools?
- How can medical therapy be best tailored for the individual patient with CKD?