JAMA Clinical Guidelines Synopsis

# Delaying Progression of Chronic Kidney Disease

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**GUIDELINE TITLE:** Delaying Progression and Management of Chronic Kidney Disease

**RELEASE DATE:** April 2024

**PRIOR VERSION:** 2012

**DEVELOPER AND FUNDING SOURCE:** Kidney Disease: Improving Global Outcomes (KDIGO)

**TARGET POPULATION:** Adult patients with chronic kidney disease (CKD)

**SELECTED RECOMMENDATIONS:**

- For patients with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 $m^2$, limiting daily protein intake to 0.8 mg/kg of body weight is suggested (2C).
- A target systolic blood pressure of less than 120 mm Hg using standardized office blood pressure measurement, when tolerated, is suggested (2B).
- Renin-angiotensin (RAS) inhibitors such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be initiated for patients with diabetes and moderately to severely increased albuminuria (urine albumin/creatinine [UACr] >30 mg/g) and for patients without diabetes who have moderate (2C) or severe (1B) albuminuria (UACr >300 mg/g).
- Sodium-glucose cotransporter 2 (SGLT2) inhibitors are recommended for patients with type 2 diabetes who have an eGFR of at least 20 mL/min/1.73 $m^2$ and for patients without diabetes who have CKD and either albuminuria (UACr >200 mg/g) or heart failure (1A), and they are suggested for those without diabetes or albuminuria who have an eGFR of 20 to 45 mL/min/1.73 $m^2$ (2B).
- Addition of a nonsteroidal mineralocorticoid receptor antagonist (nsMRA) (finerenone) is suggested for patients with type 2 diabetes who have normal serum potassium, an eGFR greater than 25 mL/min/1.73 $m^2$, and persistent albuminuria greater than 30 mg/g despite maximally tolerated RAS inhibitors (2A).

## Summary of the Clinical Problem

The global prevalence of CKD is approximately 9%,[1,2] and patients with CKD are at increased risk of morbidity and mortality.[2] Risk factors such as higher levels of albuminuria are a major contributor to CKD progression. Herein, we focus specifically on recommendations for management of CKD and to delay progression of CKD in adults.[2]

## Characteristics of the Guideline Source

The work group comprised pediatric, adult, and geriatric nephrologists; internists; and specialists in methodology, laboratory medicine, and public health. Systematic reviews from the 2012 KDIGO CKD guidelines were updated, and new systematic reviews were conducted when appropriate. An independent evidence review team used a grading system to review the data and quantify certainty of evidence (eTable in the Supplement). Strength of recommendations was rated as 1 ("we recommend") or 2 ("we suggest") based on the balance of net benefits and harms. Certainty of evidence was rated from A (high) to D (very low) based on confidence that the effect estimate is the true effect.

Supplemental content

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## Evidence Base

In total, 145 randomized clinical trials (RCTs) and 232 observational studies were included in the evidence review. Fourteen recommendations on delaying CKD progression were issued; 7 were level 1 recommendations, of which 6 were informed by A or B certainty-of-evidence ratings.

Limiting daily protein intake to 0.8 g/kg of body weight in patients with an eGFR of less than 60 mL/min/1.73 $m^2$ is suggested based on physiological studies reporting that accumulation of urea and other uremic toxins leads to increased intraglomerular pressure, glomerular hyperfiltration, and kidney disease progression.[2] In a 13-year prospective cohort study conducted in South Korea (9226 participants aged 40-69 years), those in the highest quartile of daily protein intake (mean, 1.7 g/kg of body weight) had increased risk of rapid eGFR decline, defined as at least a 3-mL/min/1.73 $m^2$ annual decrease in eGFR, vs those in the lowest quartile (mean, 0.6 g/kg of body weight) (odds ratio, 1.31; 95% CI, 1.02-1.69) after adjustment for age, sex, baseline eGFR, and daily intake of total energy, but without adjustment for level of albuminuria.[3] A meta-analysis of 10 RCTs (1010 participants with eGFR <30 mL/min/1.73 $m^2$ and without diabetes) reported a lower risk of kidney failure among those with a very low-protein diet (estimated 293/1000 kidney failure events) vs low- or normal-protein diets (458/1000 events; risk ratio, 0.64; 95% CI, 0.49-0.85).[4] However, large RCTs comparing outcomes with various levels of protein intake are lacking, and low-protein diets are not recommended for patients at risk of malnutrition.[2]

The suggested target systolic blood pressure for patients with CKD and hypertension is less than 120 mm Hg using standardized office blood pressure measurement. In the SPRINT trial (9361 participants; 28% with eGFR <60 mL/min/1.73 $m^2$ at baseline), those assigned a blood pressure target of less than 120 mm Hg vs less than 140 mm Hg had decreased annual risk of a primary composite end point of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, or death from cardiovascular causes (1.65% vs 2.19%; $P$ = .003); effect sizes were similar among patients with CKD at baseline.[5]

RAS inhibitors are first-line pharmacological therapy for CKD with diabetes and CKD without diabetes with albuminuria. For patients with CKD, type 2 diabetes, and an eGFR of 20 mL/min/1.73 $m^2$ or greater and for those with CKD without diabetes who have albuminuria (UACr >200 mg/g) or heart failure, addition of an SGLT2 inhibitor is recommended. Multiple placebo-controlled RCTs have reported reductions in risk of CKD progression, acute kidney injury, heart failure hospitalizations, and cardiovascular death with use of SGLT2 inhibitors. A meta-analysis of 13 RCTs (90 409 patients with CKD) reported that SGLT2 inhibitors were associated with reduced risk of kidney disease progression vs placebo (1.97% vs 3.16%; relative risk, 0.63; 95% CI, 0.58-0.69) and reduced death from cardiovascular causes or heart failure hospitalizations (7.9% vs 9.96%; relative risk, 0.77; 95% CI, 0.74-0.81), with similar results for patients with or without diabetes.[6]

Nonsteroidal MRAs such as finerenone have been reported to reduce cardiovascular risk and heart failure hospitalizations in patients with CKD with an eGFR of 25 mL/min/1.73 $m^2$ or greater, type 2 diabetes, and albuminuria (UACr ≥30 mg/g). A pooled analysis of 2 RCTs including 13 026 patients showed that compared with placebo, finerenone decreased the risk of kidney failure (defined as end-stage kidney disease or sustained decrease in eGFR to <15 mL/min/1.73 $m^2$) and resulted in a sustained 57% decrease in eGFR.[7] Patients treated with finerenone had decreased mortality from kidney causes vs placebo (5.5% vs 7.1%; $P < .001$)[7] as well as reduced risk of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (12.7% vs 14.4%; $P = .002$).[7]

## Potential Harms

The potential harms from treatment are based on adverse events related to medications alone or in combination. For example, 14% of patients receiving finerenone develop hyperkalemia vs 6.9% receiving placebo, so regular monitoring of potassium is required after initiation (at 1 month, then every 4 months).[2,7] For patients with CKD and heart failure, maintaining guideline-directed medical therapies for heart failure may require adjustment of CKD pharmacotherapy, given the risk of worsening hypotension when treating patients with heart failure.

## Discussion

High protein intake has been associated with progression of kidney disease; however, data supporting moderation of dietary protein are based primarily on observational studies. Similarly, a low-sodium diet (<2 g/d) is suggested for patients with CKD based primarily on observational evidence that lowering dietary sodium lowers blood pressure and albuminuria levels.[1] Therefore, pharmacotherapy remains first-line treatment for CKD, including RAS inhibitors for most patients, as tolerated with adverse effects such as hypotension, cough, or hyperkalemia. Studies have suggested reduced 5-year mortality and decreased major adverse cardiovascular events with RAS inhibitors in patients with CKD who have an eGFR of less than 30 mL/min/1.73 $m^2$ vs those who stop taking RAS inhibitors.[8] Multiple new therapies, including SGLT2 inhibitors, are associated with improved kidney and cardiovascular outcomes for patients with diabetes and CKD.[9]

## Areas in Need of Future Study or Ongoing Research

High-quality studies are needed to inform dietary and salt intake recommendations for patients with CKD. Several studies of new medication classes, including glucagon-like peptide 1 (GLP-1) receptor agonists, have been published since the release of the 2024 guidelines. For example, an RCT of 3533 patients with type 2 diabetes and CKD reported that semaglutide reduced major kidney disease outcomes (kidney failure: dialysis, transplant, or eGFR <15 mL/min/1.73 $m^2$), resulted in at least a 50% reduction in eGFR from baseline, or reduced mortality from kidney causes by 21% and from cardiovascular causes by 29%.[10] Additionally, few studies have investigated combination therapies of SGLT2 inhibitors, GLP-1 receptor agonists, and nsMRAs or the efficacy of these medication classes in patients at lower risk of CKD progression, such as those with lower levels of albuminuria.


### ARTICLE INFORMATION

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