THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
February 2026 Volume 16 Issue 2

Chronic Kidney Disease Pharmacotherapy: Guideline Updates & Practical Application

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In the United States, an estimated 1 in 7 adults, about 35 million people, have chronic kidney disease (CKD), This condition is more prevalent in adults aged 65 years and older.[1] CKD is defined as abnormalities of kidney structure or function for a minimum of 3 months and is classified based on estimated glomerular filtration rate (eGFR) (G1-G5) and albuminuria (A1-A3).[2] Patients with CKD have a profoundly increased risk of cardiovascular disease (CVD), as 50% of patients with stage 4 and 5 CKD have some type of CVD.[3]. Death from cardiovascular events accounts for 40-50% of mortality in CKD.[3]

In 2024, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines were updated for the management of CKD, with signficiant emphasis on medications that improve CKD outcomes .[2] The guidelines include graded recommendations based on a systematic review of the evidence and practice points based on expert consensus or limited evidence. This newsletter summarizes key guideline updates with a focus on pharmacotherapy.

Renin-angiotensin system inhibitors (RASi))

Consistent with previous versions of the KDIGO guidelines, renin-angiotensin system (RAS) inhibition with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) for people with CKD and moderate (urine albumin-to-creatine ratio [UACR] 30-300 mg/kg) to severe (UACR > 300 mg/kg) albuminuria is recommended (**Table 1**).

Table 1: KDIGO Guideline Recommendations for Renin-Angiotensin System Inhibitors.[2]

Recommendation	Evidence Grade
• We recommend starting RASi for people with CKD and severely increased albuminuria without diabetes	1B
• We suggest starting RASi for people with CKD and moderately increased albuminuria without diabetes	2C
• We recommend starting RASi for people with CKD and moderately-to-severely increased albuminuria with diabetes	1B

Certainty of Evidence: A: High; B: Moderate; C: Low; D: Very Low
Evidence Grade: Level I: We Recommend; Level 2: We Suggest
Abbreviations: CKD – chronic kidney disease; RASi – renin-angiotensin system inhibitors

There is strong and consistent evidence that RASi slow CKD progression and decrease the risk of kidney failure with a greater benefit when patients have albuminuria. Less evidence is available for those without diabetes, but data still supports benefit, particularly with more severe albuminuria.[2] KDIGO guidelines recommend avoiding any combination of ACEi and ARB due to a risk of acute kidney injury (AKI) and hyperkalemia without any therapeutic benefits.[2]

Due to risks of hyperkalemia and acute kidney injury (AKI), RASi are often discontinued in advanced CKD. A practice point in the guidelines recommends continuing ACEi or ARB in people with CKD even if the eGFR falls below 30 ml/min.[2] This is based upon data from the STOP-ACEi trial, a multicenter, open-label trial randomizing 411 patients with stage 4 or 5 CKD to continue or discontinue RASi.[4] After a follow up of 3 years, there was no benefit in eGFR in the discontinuation group compared to those who continued RASi therapy (mean eGFR 12.6 ml/min versus 13.3 ml/min; p=0.42).[4] There was also no significant difference in end stage renal disease (ESRD) events, cardiovascular events, or adverse safety events between groups. The lack of a clear kidney benefit or harm from RASi in advanced CKD highlights the need to evaluate specific indications for these medications (e.g. CKD, hypertension, heart failure) and the importance of shared decision making.

It is recommended to monitor serum creatinine and potassium levels within 2-4 weeks after starting or changing the dose of RASi and to increase to maximally tolerated doses if there is a <30% decrease in eGFR.[2] A greater decrease in eGFR should trigger an investigation into other causes (e.g. renal artery stenosis, use of NSAIDs, hypovolemia, heart failure exacerbation, or urinary obstruction).[2] Patients unable to tolerate a higher dose of RASi may still benefit from lower doses or retrials in the future, especially if confounding factors are reversed.

Sodium-Glucose Cotransporter-2 (SGLT2i) Inhibitors

Through direct and indirect effects, SGLT2i reduce the risk of kidney disease progression, CV death, and all-cause mortality in adults with CKD, with or without diabetes.[2] A recent Cochrane systematic review found high quality evidence of a reduced risk of all-cause death (relative risk [RR] 0.86; 95% confidence interval [CI] 0.81 – 0.92) and kidney outcomes (RR 0.68; 95% CI 0.59 – 0.78) with SGLT2i in patients with CKD and diabetes.[5] Moderate quality evidence showed a reduction in major adverse cardiovascular events (MACE), likely due to deaths due to heart failure and sudden cardiac death.[5] The

SGLT2i's probably have little to no effect on fatal or nonfatal myocardial infarction (MI) and fatal or nonfatal stroke.

Studies support dapagliflozin and empagliflozin use in patients with CKD without diabetes. In a meta-analysis including the EMPA-KIDNEY and the DAPA-CKD trials, SGLT2i's showed a 37% reduction in risk of kidney disease progression (RR 0.63; 95% CI 0.58 – 0.69) with similar relative risks in patients with and without diabetes, a 23% reduction in the risk of AKI, and a 23% reduced risk of CV death or hospitalization for heart failure, regardless of diabetes status.[6]

These benefits are seen across the spectrum of kidney function and albuminuria levels and extend to patients with an eGFR as low as 20 ml/min. A systematic review and meta-analysis of 10 trials found a reduced incidence of a composite kidney outcome across all UACR groups, including < 30mg/kg (hazard ratio (HR) 0.62; 95% CI 0.50- 0.78).[7] Due to this evidence, KDIGO guidelines recommend SGLT2i in patients with CKD, with or without diabetes (**Table 2**).[2]

Table 2: Recommendations for Sodium-glucose Co-Transporter 2 Inhibitors[2]

Recommendation	Evidence Grade
• We recommend treating patients with T2D, CKD, and an eGFR ≥ 20 ml/in with an SGLT2i	1A
• We recommend treating adults with CKD with an SGLT2i with urine ACR ≥ 200 mg/g, or heart failure	1A
• We suggest treating adults with eGFR 20 to 45 ml/min with urine ACR < 200 mg/g with an SGLT2i	2B

Certainty of Evidence: A: High; B: Moderate; C: Low; D: Very Low
Evidence Grade: Level I: We Recommend; Level 2: We Suggest
Abbreviations: ACR – albumin to creatine ratio; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate; SGLT2i – sodium-glucose cotransporter-2 inhibitor; T2D – type 2 diabetes.

The guidelines include a practice point that once an SGLTi is initiated, it is reasonable to continue if the eGFR falls below 20ml/min, unless it is not tolerated. [2] There is an increased risk of mycotic genital infections with SGLTi but these are generally mild and responsive to treatment. Other risks, including ketoacidosis and acute kidney injury (AKI) are low and the benefits of therapy outweigh these risks. [2] Similar to RASi, there is an expected hemodynamically mediated bump in serum creatinine (i.e. permissive AKI) after initiation with SGLT2i. If it remains stable, there is not volume depletion, and the rise in serum creatinine is less than 30%, it is not harmful. There is a low overall risk of hypoglycemia with SGLT2i but the risk is increased when used in combination with insulin and sulfonylureas. In advanced CKD, SGLTi loses its glucose lowering benefits and the A1c reduction is diminished.

Mineralocorticoid Receptor Antagonists (MRAs)

Mineralocorticoid Receptor Antagonists (MRAs) reduce BP and albuminuria in CKD. Finerenone is a nonsteroidal MRA approved for CKD associated with T2DM and heart failure with preserved ejection fraction.[2] Compared to spironolactone, which is a steroidal MRA, finerenone is more cardioselective with a lower risk of sexual and hormonal side effects, including gynecomastia and decreased libido. In a large, phase 3 randomized controlled trial (RCT) (n=5,734) in patients with T2DM and CKD on maximally tolerated RASi, patients were randomized to finerenone or placebo.[8] Over a follow up of 2.6 years, there was a reduction in the primary renal composite outcome (renal death, decrease in eGFR of 40% or more, or dialysis) with finerenone compared to placebo (17.8% vs 21.1%; hazard ratio [HR] 0.82; 95% CI 0.73 – 0.93).[8] In a similarly designed trial, finerenone reduced the risk of the composite of CV death, non-fatal MI,stroke, and heart failure hospitalizations compared to placebo (12.4% vs. 14.2%; HR 0.87; 95% CI 0.76 to 0.98).[9] This was driven by heart failure hospitalizations with little effect on myocardial infarction (MI) or stroke. These studies only included patients with diabetes and participants had an eGFR ≥ 25 ml/min. In clinical trials, 2.3% and 11% of participants in the finerenone group discontinued or held treatment due to hyperkalemia compared to 0.9% and 5.2% in the placebo group. [9] To reduce the risk of hyperkalemia, patients should have a normal serum potassium at baseline (≤ 4.8 mmol/l) and serum potassium should be monitored within 1 month of initiating an MRA and then every 4 months. [2] Finerenone has no glucose lowering effects or substantial impact on blood pressure, and other medications with these benefits may be preferred.

Table 3: Recommendations for Mineralocorticoid Receptor Antagonists[2]

Recommendation	Evidence Grade
• We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for adults with T2D, an eGFR >25 ml/min per 1.73 m2, **normal** serum potassium concentration, and albuminuria (>30 mg/g [>3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor	2A

Certainty of Evidence: A: High; B: Moderate; C: Low; D: Very Low
Evidence Grade: Level I: We Recommend; Level 2: We Suggest
Abbreviations: eGFR – estimated glomerular filtration rate; RAS – renin angiotensin system; T2D – type 2 diabetes.

Typically, MRAs are reserved for persistent albuminuria despite optimized therapy with RASi and SGLT2 inhibitors. A recent RCT randomly assigned participants with CKD, albuminuria, and T2DM on a RASi to receive finerenone, empagliflozin, or a combination of finerenone and empagliflozin.[10] Overall, the combination of finerenone and empagliflozin in addition to background RASi, was more effective at reducing the UACR compared to both agents

alone.[10] Although further studies are needed to evaluate if this benefit translates to a reduction in kidney and CV outcomes, this initial data supports combination therapy.

While spironolactone, a steroidal MRA, may decrease albuminuria when added to an ACEi or ARB in CKD, there is a lack of large, high-quality trials demonstrating improvements in renal or CV outcomes in CKD populations. Given its proven efficacy for resistant hypertension, spironolactone may be preferred when additional blood pressure reduction is a primary therapeutic goal.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

The 2024 KDIGO guidelines recommend a long-acting GLP-1 RA to reach glycemic targets in patients with CKD and T2DM (**Table 4**).[2]

Table 4: Recommendations for Glucagon-Like Peptide-1 Receptor Agonists[2]

Recommendation	Evidence Grade
• We recommend a long-acting GLP-1 RA in adults with T2DM and CKD who have not achieved glycemic targets despite use of metformin and SGLT2 inhibitor	1B

Certainty of Evidence: A: High; B: Moderate; C: Low; D: Very Low
Evidence Grade: Level I: We Recommend; Level 2: We Suggest

However, since the guidelines were released, semaglutide was FDA approved to reduce risk of sustained eGFR decline, ESRD, and CV death in patients with T2DM and CKD. This approval was based on a phase 3, placebo-controlled, RCT (n=3534) that randomized patients with T2DM and high-risk CKD on maximal RASi to semaglutide or placebo.[11] The baseline mean eGFR was 47 ml/min and the median UACR was 568. While most patients were on an ACEi or ARB (95%), only 15% were on a SGLT2 inhibitor. Overall, there was a reduction in kidney disease events with semaglutide compared to placebo (18.7% vs. 23.2%; HR 0.76; 95% CI 0.66 – 0.88) and a reduction in MACE (12% vs. 14.4%; HR 0.82; 95% CI 0.68 to 0.98).[11]

While both SGLT2i and GLP-1 RA are recommended in CKD and DM, cost may limit use of both agents. SGLT2i are generally favored when albuminuria or CKD progression is present, while GLP-1 RA may be favored when additional glycemic control or weight loss is needed.

Conclusion

With new evidence supporting multiple pharmacologic treatments for reducing renal and CV outcomes in patients with CKD, treatment of CKD is shifting from a stepwise approach to a pillar approach using a combination of medications, analagous to heart failure management . The four pillars of CKD treatment include RASi, SGLT2i, nonsteroidal MRA, and long-acting GLP-1 RA. Additional evidence is needed to better define the clinical implications of combination therapy, the optimal order of initiation, the level of benefit in patients without albuminuria, and if this data can be applied to patients with CKD without T2DM.

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References

1. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2023. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2023.
2. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.* 2024;105(4s):S117-s314.
3. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. *Circulation.* 2021;143(11):1157-1172.
4. Bhandari S, Mehta S, Khwaja A, et al. Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease. *The New England journal of medicine.* 2022;387(22):2021-2032.
5. Natale P, Tunnicliffe DJ, Toyama T, et al. Sodium-glucose co-transporter protein 2 (SGLT2) inhibitors for people with chronic kidney disease and diabetes. *Cochrane Database Syst Rev.* 2024;5(5):Cd015588.
6. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet (London, England).* 2022;400(10365):1788-1801.
7. Chun KJ, Jung HH. SGLT2 Inhibitors and Kidney and Cardiac Outcomes According to Estimated GFR and Albuminuria Levels: A Meta-analysis of Randomized Controlled Trials. *Kidney Med.* 2021;3(5):732-744.e731.
8. Bakris GL, Agarwal R, Anker SD, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *The New England journal of medicine.* 2020;383(23):2219-2229.
9. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. *The New England journal of medicine.* 2021;385(24):2252-2263.
10. Agarwal R, Green JB, Heerspink HJL, et al. Finerenone with Empagliflozin in Chronic Kidney Disease and Type 2 Diabetes. *The New England journal of medicine.* 2025;393(6):533-543.
11. Perkovic V, Tuttle KR, Rossing P, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. *The New England journal of medicine.* 2024;391(2):109-121.