Kim Pham, DO; Carli Beyer, DO
Methodist Charlton Family Medicine Residency, Dallas, TX

DEPUTY EDITOR
Rick Guthmann, MD, MPH
Advocate Health Care Illinois Masonic Medical Center Program, Chicago

doi: 10.12788/jfp.0577

Q/ Should RAAS blockade therapy be continued in patients with advanced renal disease?

EVIDENCE-BASED ANSWER

A/ **PROBABLY.** Renin-angiotensin-aldosterone system (RAAS) blockade therapy should be continued in most patients with advanced renal disease and comorbid conditions; however, individualized treatment is warranted as data on the benefits and harms in all-cause mortality, cardiovascular mortality, and risk for renal replacement therapy are inconclusive (strength of recommendation [SOR]: **B**, based on observational studies, systematic reviews, and meta-analyses of randomized controlled trials [RCTs]). Certain patient populations, such as patients with diabetes or those with cardiovascular risk or history, may benefit most from continued RAAS blockade therapy (SOR: **A**, based on systematic reviews and meta-analyses of RCTs).

Evidence summary

Mixed results, Yes, but no evidence of harm in continuing RAAS therapy

A 2014 cohort study assessed the effect of treatment with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) on all-cause mortality in US veterans (N = 141,413) with non-dialysis chronic kidney disease (CKD)—defined as either a stable estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or a stable eGFR ≥ 60 mL/min/1.73 m^2 and an elevated urine microalbumin measurement.[1] In an intention-to-treat analysis, ACEI/ARB treatment was associated with a significantly decreased risk for all-cause mortality (hazard ratio [HR] = 0.81; 95% CI, 0.78-0.84).

A 2018 meta-analysis analyzed data from 9 RCTs comparing RAAS blockade therapy to placebo or alternative antihypertensive agents in patients with non-dialysis CKD stages 3 to 5.[2] Although the meta-analysis authors focused on patients with comorbid diabetes and non-dialysis CKD (N = 9797), some included studies had a mixed population (ie, only a subset of patients had diabetes). This, among other variances in characteristics, participants, interventions, and endpoints, resulted in different numbers of participants included in the data extraction and analysis of outcomes. Overall, there was no difference between the RAAS group and the control group in terms of all-cause mortality (N = 5309; risk ratio [RR] = 0.97; 95% CI, 0.85-1.10), cardiovascular mortality (N = 3748; RR = 1.03; 95% CI, 0.75-1.41), or adverse events (N = 1822; RR = 1.05; 95% CI, 0.89-1.25). Compared to the control group, the RAAS group was less likely to experience a nonfatal cardiovascular event (N = 6138; RR = 0.90; 95% CI, 0.81-1.00). For the composite endpoint of need for renal replacement therapy/doubling of serum creatinine, RAAS therapy was associated with reduced risk in both the overall population (N = 5202; RR = 0.81; 95% CI, 0.70-0.92) and in patients with comorbid diabetes (N = 3314; RR = 0.78; 95% CI, 0.67-0.90).

A 2022 open-label trial (STOP ACEi) randomly assigned 411 patients with stage 4 or 5 CKD to either continue (N = 205) or discontinue (N = 206) RAAS inhibitor therapy.[3] The primary outcome measure was eGFR at 3 years. The difference in the rate of decline in eGFR between groups was –0.7% (95% CI,

–2.5 to 1.0; P = .42), favoring the group that continued therapy.

Recommendations from others

After reviewing data from multiple clinical trials, the authors of the 2018 report from the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF–KDOQI) concluded that the decision to continue or stop RAAS therapy in patients with advanced CKD should be individualized.[4] Criteria that should be considered in the decision-making process include the presence or absence of large acute declines in eGFR (> 20% in the absence of a significant decrease in proteinuria), hypotension, or acute kidney injury with significant risk for worsening.

In 2021, the Renal Association and the Association of British Clinical Diabetologists published updated clinical practice guidelines for the management of hypertension and RAAS blockade in adults with diabetic kidney disease.[5] Collective data indicated that, although outcomes varied based on type of diabetes (1 vs 2) and degree of proteinuria, blockade therapy overall led to improved outcomes; this was hypothesized to be due to the effects of reduced blood pressure. However, discontinuation of RAAS blockade therapy may be warranted when the patient (1) has a potassium level > 5 mmol/L pretreatment or ≥ 6 mmol/L with treatment, (2) demonstrates a decrease in eGFR > 25% or an increase in serum creatinine > 30% upon initiation of blockade, without another cause of renal deterioration, (3) is pregnant, or (4) has an acute illness with fluid depletion (in which case, RAAS therapy can be restarted 24 to 48 hours after recovery).

Editor's takeaway

Evidence supports continuation of RAAS blockade, particularly in patients with significant comorbidities (diabetes and cardiovascular disease). Study data indicate continuation is either beneficial or neutral to further morbidity. The only caveat is that these patients should have their renal function and potassium level continuously monitored. The evidence should provide reassurance to patients and physicians that continuation is the correct course of action. JFP

References

1. Molnar MZ, Kalantar-Zadeh K, Lott EH, et al. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker use, and mortality in patients with chronic kidney disease. *J Am Coll Cardiol*. 2014;63:650-658. doi: 10.1016/j.jacc.2013.10.050
2. Nistor I, De Sutter J, Drechsler C, et al. Effect of renin-angiotensin-aldosterone system blockade in adults with diabetes mellitus and advanced chronic kidney disease not on dialysis: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2018;33:12-22. doi: 10.1093/ndt/gfx072
3. Bhandari S, Mehta S, Khwaja A, et al. Renin-angiotensin system inhibition in advanced chronic kidney disease. *N Engl J Med*. 2022;387:2021-2032. doi: 10.1056/NEJMoa2210639
4. Weir MR, Lakkis JI, Jaar B, et al. Use of renin-angiotensin system blockade in advanced CKD: an NKF–KDOQI controversies report. *Am J Kidney Dis*. 2018;72:873-884. doi: 10.1053/j.ajkd.2018.06.010
5. Banerjee D, Winocour P, Chowdhury TA, et al. Management of hypertension and renin-angiotensin-aldosterone system blockade in adults with diabetic kidney disease: Association of British Clinical Diabetologists and the Renal Association UK guideline update 2021. *BMC Nephrol*. 2022;23:9. doi: 10.1186/s12882-021-02587-5

PHOTO ROUNDS

CONTINUED FROM PAGE 143

26. Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. *Am J Ophthalmol*. 2013;155:429-437. doi: 10.1016/j.ajo.2012.09.026
27. Ip MS, Scott IU, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. *Arch Ophthalmol*. 2009;127:1101-1114. doi: 10.1001/archophthalmol.2009.234
28. The Central Vein Occlusion Study Group. A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. The Central Vein Occlusion Study Group N report. *Ophthalmology*. 1995;102:1434-1444.