

Balancing Hyperkalemia Risks with Clinical Benefits of Renin-Angiotensin-Aldosterone Inhibitors/Mineralocorticoid Receptor Antagonists Blockade: It's Apples and Oranges

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Introduction

CKD affects nearly 800 million adults worldwide and represents a major public health problem. The prevalence of CKD in US adults is approximately 13% (1). Impaired kidney function commonly leads to hyperkalemia as the kidneys lose the ability to excrete the dietary potassium load. Hyperkalemia is a common electrolyte disorder and an independent risk factor for arrhythmia, mortality, and cardiovascular (CV) events (2).

Several large retrospective cohort studies have shown that patients with hyperkalemia are at increased risk of hospitalization and higher health care costs compared with patients with normal potassium levels (2). CKD, heart failure (HF), diabetes mellitus (DM), and their therapies are associated with an increased risk of hyperkalemia. In the general population, the prevalence of hyperkalemia is only 4%, whereas in those with CKD, the prevalence of hyperkalemia can reach 14%–20% (2). The increasing prevalence of chronic diseases, along with increased use of disease modifying therapy, is thought to be contributing to an increasing prevalence of hyperkalemia.

Although the acute treatment of hyperkalemia is described in several clinical guidelines, there is currently no standard of care for the management of chronic hyperkalemia in patients with CKD. Observational studies have shown that discontinuation of kidney-protective therapies or dose reduction is the single most common management strategy in chronic hyperkalemia (3). Although hyperkalemia can be acutely concerning and lead to additional blood test and visits in the short term, it is important to recognize that the benefits of renin-angiotensin-aldosterone (RAAS) inhibitors or mineralocorticoid receptor antagonists (MRA) for patients with CKD or HF are clinically meaningful and only realize with chronic long-term treatment.

Benefits of RAAS Inhibitors and MRA Therapy

Irrespective of the cause of CKD, its treatment focuses on BP control and reduction of intraglomerular

pressure, leading to lower urinary protein excretion. The role of the RAAS in the pathophysiology of hypertension and CV and kidney diseases is well known (4). Randomized controlled trials (RCTs) have shown that blockage of the renin-angiotensin system (RAS) can reduce the risk of death and slow the progression of kidney disease (4). As a result, clinical guidelines recommend RAS inhibitors—angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs)—as first-line agents for patients with CKD (5). Moreover, the recommendation is for their use at the maximum tolerated dose because RCT results have shown the best benefits with moderate to high doses (5). Currently, seven ARBs and ten ACEIs are available plus several combined preparations of RAS inhibitors and calcium channel blockers or diuretics.

DM is the leading cause of kidney failure. Several large studies have shown that inhibition of the RAS slows the progression of kidney disease (relative risk=0.84; $P=0.02$; number needed to treat=28) and reduces the risk of mortality and CV events in patients with diabetic kidney disease (DKD) (5). Studies comparing the effects of ACEIs versus ARBs in patients with DKD have shown similar results in short- and long-term renoprotection in DKD. A network meta-analysis the effects of ACEIs and ARBs on CV and renal outcomes in patients with DM concluded that ARBs were not superior to ACEIs in terms of all-cause and CV mortality, kidney failure, or doubling of serum creatinine level (6). Although evidence of RAS blockade in the treatment of non-DKD is more limited, a pooled analysis of 11 randomized trials showed that ACEIs were superior in slowing progression of non-DKD compared with other antihypertensive therapies (7).

Despite favorable renal effects of RAS blockade, CKD progression to ESKD still occurs in many patients. Growing evidence suggest that overactivation of the mineralocorticoid receptor contributes to CKD progression, indicating that antagonism of this receptor could provide therapeutic benefit.

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MRAs prevent binding of aldosterone to mineralocorticoid receptors.

Available steroidal MRAs—spironolactone and eplerenone—are both effective in reducing mortality and hospitalization in the treatment of heart failure (8). Meta-analyses have demonstrated that steroidal MRAs in conjunction with RAS blockers further reduce proteinuria in patients with CKD (8). The effects of steroidal MRAs on major CV outcomes in patients with CKD are unknown (8).

Finerenone is a novel selective nonsteroidal MRA approved for the management of DKD (9). Phase 2 and 3 trials have shown significant cardiorenal protective benefits on top of standard of care (optimized RAS inhibition) (9). Compared with placebo, finerenone reduced the primary composite outcome of kidney failure by 18% and sustained >40% decline in eGFR or death from renal causes (hazard ratio [HR]=0.82; 95% confidence interval [CI], 0.73 to 0.93) (9). FIDELITY, a meta-analysis of individual patient data from FIDELIO-DKD and FIGARO-DKD, showed that finerenone significantly reduced the risk of composite CV outcomes by 14% and also reduced significantly the risk of composite renal outcomes by 23% (HR=0.77; 95% CI, 0.67 to 0.88) (9). FIDELITY demonstrated that finerenone is effective for cardiorenal protection across a wide range of CKD in patients with type 2 DM.

Risk of Hyperkalemia with RAAS Inhibitors and MRAs

Hyperkalemia is a common occurrence among patients prescribed RAAS inhibitors. In clinical trials involving RAS inhibitors, the rates of hyperkalemia events ranged from 5% to 20% (10). The guideline on CKD management recommends assessing serum potassium within 1 week after initiating or increasing the dose of an ACE-I or ARB, regardless of baseline potassium level (5).

MRAs are also associated with hyperkalemia. Due to the risk of hyperkalemia, steroidal MRAs have a limited role in CKD (8). Hyperkalemia occurred more frequently with finerenone (14%) compared with placebo (7%); however, the increase in hyperkalemia was manageable, and routine potassium monitoring decreased its clinical effect (only 2% led to permanent treatment discontinuation) (9).

Current Management of Hyperkalemia

Treatment and prevention of recurrent hyperkalemia involve a low potassium diet, correction of metabolic acidosis, and the use of cation-exchange resins or binders (11). Observational studies have shown that discontinuation of kidney-protective therapies or dose reduction is the single most common management strategy in chronic hyperkalemia (3).

Dietary restriction of potassium has variable adherence and may deprive patients with CKD of other nutrients obtained in potassium rich diets (12). Sodium polystyrene sulfonate is a commonly used cation-exchange resin, but its use is limited by its association with severe gastrointestinal complications (12). The approval in the recent years of two new potassium binders—patiromer and sodium zirconium

cyclosilicate—have shown efficacy in short-term trials for the management of hyperkalemia while allowing for the continuation of RAS inhibitor therapy (11).

Recent studies have shown that discontinuing RAS inhibitors in patients with a clear RAS inhibitor indication is associated with adverse outcomes. A Canadian observational study showed that ACEi/ARB discontinuation is associated with higher risk of death (HR=1.32; 95% CI, 1.22 to 1.41) and CV events (HR=1.17; 95% CI, 1.11 to 1.24) compared with continuation among patients with hyperkalemia and CKD (13). These associations were consistent in several sensitivity analyses and highlight the potential benefit of continuing RAAS inhibitor therapy in patients with CKD and hyperkalemia (13).

In support of these studies, clinical practice guidelines from Kidney Disease Improving Global Outcomes (14) and the American Heart Association (15) also recommend that hyperkalemia associated with the use of RAAS inhibitors be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RAAS inhibitors. Strategies include a low potassium diet, a nonpotassium-sparing diuretic, or, if already receiving a diuretic, increasing the dose and using potassium binders. If short-term discontinuation of RAAS inhibitors or MRAs is deemed necessary, guidelines recommend them to be reintroduced as soon as possible while monitoring potassium levels. Finally, careful monitoring of serum potassium at initiation and follow-up is recommended.

Conclusion

Current clinical evidence supports the use of triple therapy (RAAS inhibitors, sodium/glucose cotransporter 2 inhibitors [SGLT-2is], and nonsteroidal MRAs) in patients with DKD and RAAS inhibitors and SGLT-2i as baseline therapy in nearly all patients with CKD (14). SGLT-2i trials have further shown that they reduce hyperkalemia risk in people with type 2 DM and CKD who are using RAAS inhibitors (16).

It is likely that combination therapy with both SGLT-2is and finerenone may further reduce cardiorenal risk because they have potentially complementary mechanisms of action. Clinical data analyzing the potential value of a combination therapy are currently limited, but these studies are underway. These agents have shown cardiorenal protection and reduced CV risk on CKD. Previous studies have reported hyperkalemia as one of the main barriers to prescribing or maintaining RAAS inhibition therapies, and physicians should monitor potassium levels in these patients. Observational studies have shown that discontinuation of RAAS inhibitors is associated with higher risk of death and CV events (13).

Hyperkalemia is common and often recurs. Once a patient has a recurrence, treatment of hyperkalemia should be prioritized over RAAS inhibitor or MRA discontinuation. It is important to recognize that these agents provide long-term benefit that may outweigh the short-term risk and inconvenience of the acute hyperkalemia episode. RCTs are needed to evaluate the clinical benefit of using binders to enable disease modifying therapy in this population.

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Author Contributions

N. Tangri was responsible for supervision, and both authors were responsible for conceptualization and validation, wrote the original draft of the manuscript, and reviewed and edited the manuscript.

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