Hyperkalemia Associated With Inhibitors of the Renin-Angiotensin-Aldosterone System
Balancing Risk and Benefit
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Maintenance of normal potassium homeostasis is increasingly an important limiting factor in the therapy of cardiovascular disease. Many pharmacological agents that reduce morbidity and mortality in patients with complicated myocardial infarction and chronic heart failure, including β-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers (ARBs), and aldosterone receptor antagonists, are also known to raise serum potassium and augment the risk of life-threatening hyperkalemia. Conversely, loop diuretics, a mainstay of heart failure treatment, tend to enhance the risk of hypokalemia and ventricular arrhythmias, which may in part account for their consistent dose-related association with increased mortality in observational studies. Because combination drug therapy may simultaneously improve clinical outcomes and enhance the risk of potassium-related adverse events, an appropriate balance of benefit and risk depends heavily on careful patient selection and adequate surveillance of serum potassium and renal function.

The ability of the kidney to maintain potassium homeostasis even as the glomerular filtration rate declines depends critically on adequate sodium delivery to the distal nephron, normal production of aldosterone, and adequate sodium/potassium exchange in the cortical collecting duct. Reduction in the filtered sodium load (as a consequence of decreased renal perfusion or reduced cardiac output), diminished aldosterone production, or impaired potassium secretion by the cortical collecting duct (related, for example, to tubulointerstitial disease or use of potassium-sparing diuretics) may attenuate tubular compensatory mechanisms and precipitate hyperkalemia in the vulnerable patient. Aldosterone production is decreased in the elderly, in diabetic patients, and in those receiving drugs that block the production or action of renin (eg, β-blockers, nonsteroidal antiinflammatory drugs, and plasma renin inhibitors) and angiotensin II (angiotensin-converting enzyme inhibitors and ARBs); as a result, these groups, as well as those with already impaired potassium excretion due to progressive age or disease-related decline in glomerular filtration rate, are particularly vulnerable to the development of hyperkalemia. Because other patient-related factors including dietary potassium intake, consumption of potassium-containing supplements, and use of selected noncardiovascular medications (eg, trimethoprim, pentamidine, and heparin) may further complicate potassium homeostasis, the net balance of safety and efficacy associated with combination drug therapy for any given patient with cardiovascular disease may be difficult to predict.

Although inhibitors of the renin-angiotensin-aldosterone system (RAAS) reduce renal potassium excretion, elevations of serum potassium associated with use of these agents in heart failure patients are typically modest (<1 mEq/L), and severe or life-threatening hyperkalemia is thought to be uncommon. However, several patient factors associated with development of serious hyperkalemia in chronic heart failure are now well established. In a recent analysis of patients enrolled in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program, in which a broad spectrum of heart failure patients were randomized to treatment with candesartan or placebo in addition to optimal medical therapy, we identified age, diabetes mellitus, renal dysfunction (creatinine ≥2.0 mg/dL), starting serum potassium ≥5.0 mEq/L, background therapy with angiotensin-converting enzyme inhibitors or spironolactone, and randomization to the ARB as multivariable predictors of clinically important hyperkalemia. Those patients with multiple risk factors, and in particular those with renal dysfunction treated simultaneously with multiple inhibitors of the RAAS, were at highest risk for hyperkalemia. Importantly, the incremental benefit of addition of candesartan to optimal heart failure therapy with regard to reducing cardiovascular death and heart failure hospitalizations was maintained even in subgroups at highest risk for hyperkalemia, perhaps because of the careful protocol-mandated surveillance of serum potassium conducted during the course of the clinical trial.

In the current issue of Circulation, Pitt et al present data on serum potassium and outcomes from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) that amplify and extend these observations from CHARM. In EPHESUS, randomization to treatment with the selective aldosterone antagonist eplerenone or placebo within 3 to 14 days of acute myocardial infarction complicated by heart failure and left ventricular ejection fraction ≤40% was associated with an increase...
in the incidence of hyperkalemia, defined either as serum K⁺>5.5 mEq/L (15.6% versus 11.2%, eplerenone versus placebo, P<0.001) or as serum K⁺≥6.0 mEq/L (5.4% versus 3.8%, P=0.002), as well as a decrease in the frequency of hypokalemia (serum K⁺<3.5 mEq/L, 8.4% versus 13.1%, P<0.001). Hyperkalemia events were most common during the first 30 days after randomization, coinciding with the period of study drug titration, but occurred sporadically throughout the period of trial follow-up. In multivariable analyses, predictors of serum K⁺≥6.0 mEq/L were an estimated glomerular filtration rate (eGFR) <60 cc · min⁻¹ · 1.73 m⁻², baseline potassium above the median (4.3 mEq/L), the presence of diabetes mellitus, and prior use of antiarrhythmic drugs, but not eplerenone treatment. The authors conclude that use of eplerenone in patients after acute myocardial infarction with heart failure and left ventricular ejection fraction ≤40% is associated with improved all-cause mortality without excess risk of hyperkalemia in the context of appropriate patient selection and adequate laboratory surveillance.

This analysis includes several reassuring features. First, despite background therapy with angiotensin-converting enzyme-inhibitors or ARBs in 86% of patients and β-blockers in 75% of patients, <1% of subjects randomized to eplerenone had to discontinue the study drug because of hyperkalemia, and only 1 hyperkalemia-associated death was observed (in the placebo group). Second, the magnitude of increase in serum potassium early during eplerenone-dose titration was not systematically associated with increases in all-cause mortality at the end of trial follow-up. And finally, with the ARB in CHARM, no reduction was observed in the benefits of eplerenone with regard to all-cause mortality in the subgroups at highest risk for hyperkalemia.

Nonetheless, this experience of hyperkalemia in the context of a controlled clinical trial may not define the expected rates in routine clinical practice. By design, clinical trial populations are carefully selected, with deliberate exclusion of those thought to be at high risk for adverse effects. In EPHESUS, for example, patients with baseline K⁺>5.0 mEq/L or serum creatinine >2.5 mg/dL, subgroups expected a priori to be at high risk for development of hyperkalemia, were deemed ineligible, leading to identification of a younger study population (mean age 64 years) with better renal function (mean serum creatinine 1.1±0.3 mg/dL) than that likely to be seen in a random community sample. Although the authors highlight that no interaction was found between eGFR and eplerenone efficacy with regard to all-cause mortality, the observed rates of hyperkalemia in subjects with eGFR <60 cc · min⁻¹ · 1.73 m⁻² in EPHESUS were more than twice the rates in those with eGFR >60 cc · min⁻¹ · 1.73 m⁻², independent of treatment assignment, highlighting potential for a substantially elevated risk for adverse events outside the carefully monitored context of a clinical trial. Use of aldosterone antagonists in the subset of patients with more advanced kidney disease (eg, eGFR <30 cc · min⁻¹ · 1.73 m⁻²) remains of particular concern, because this is a population of patients for whom intrinsic renal adaptive mechanisms may be inadequate to maintain potassium hemostasis and for whom net benefit is difficult to quantify because of poor representation in EPHESUS and other cardiovascular trials.

Further, the scheme for frequent patient follow-up and laboratory monitoring prescribed as part of a clinical trial may be difficult to match in “real world” practice. The observed rates of hyperkalemia in EPHESUS occurred within the context of a standardized regimen of laboratory surveillance of serum potassium, including measurement of serum K⁺ within 1 week of starting eplerenone, again at 4 weeks, and every 3 to 6 months thereafter, with adjustment of study drug dosing according to a prespecified protocol. However, if recent data on the adequacy of laboratory surveillance in heart failure patients managed with spironolactone are any guide, many patients experience suboptimal monitoring of serum potassium after drug initiation, generating substantially higher rates of hyperkalemia than that predicted from the experience in clinical trials. In addition, because the very factors that enhance the likelihood of hyperkalemia with RAAS antagonists (eg, diabetes mellitus and renal failure) also identify the subgroup of patients with the highest cardiovascular risk and therefore the greatest opportunity to derive benefit from drug treatment, pressure is increasing to expand the use of these agents to populations outside the strict boundaries of the inclusion criteria for the clinical trials. Expanded use of RAAS antagonists to treat populations at greater baseline risk for hyperkalemia with suboptimal surveillance of potassium and renal function has proven to be an especially dangerous combination. As an example, enhanced prescription of spironolactone, spurred by the results of the landmark Randomized Aldactone Treatment Evaluation Study (RALES), was associated with a dramatic increase in the rates of hospitalization for hyperkalemia in a large community-based sample.

Overall, therefore, these data presented by Pitt et al from EPHESUS underscore that the potential opportunity for incremental mortality reductions with addition of aldosterone antagonists to the therapeutic regimen of patients presenting with myocardial infarction should be tempered by respect for the risk of hyperkalemia, especially in patients with diabetes mellitus, chronic kidney disease, and elevated serum potassium at baseline. Because nearly 40% of the population in EPHESUS had a baseline eGFR <60 cc · min⁻¹ · 1.73 m⁻² despite a priori exclusion of patients with serum creatinine >2.5 mg/dL, these data further highlight that creatinine alone is likely an insufficient marker of renal function and attendant risk for adverse drug effects. Whereas even patients at high baseline risk for hyperkalemia may experience important mortality reductions with aldosterone antagonists, such benefits are likely to be realized only in the context of careful surveillance of potassium and renal function with periodic adjustment of drug dosing. Further, because all patients with heart failure appear to be at elevated risk for hyperkalemia, general strategies to limit the toxicity of RAAS antagonists, including restriction of potassium supplements, reduction in dietary potassium intake, and elimination of concomitant medications that may impair renal potassium excretion (such as nonsteroidal antiinflammatory drugs) should be routinely considered. The opportunity to improve outcomes with use of RAAS inhibitors in heart failure patients without compromis-
ing safety is tightly coupled to appropriate patient selection, individualized drug dosing, and attentive monitoring in accordance with established guidelines.¹⁰

**Disclosures**

None.

**References**


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