

Is It Time to Rethink the Age-Old Practice of Permissive Hyperkalemia in Renin-Angiotensin-Aldosterone Inhibition?



Sophia L. Ambruso¹

¹Rocky Mountain Regional VA Medical Center, Renal Division, Aurora, Colorado, USA

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The immediate consequences of acute, severe hyperkalemia are well recognized in medicine. High extracellular potassium levels result in decreased cardiac membrane potential resulting in fatal arrhythmias, including ventricular fibrillation, asystole, and cardiac arrest. Chronic kidney disease, diabetes mellitus, heart failure, and their associated medications that interfere with the renin-angiotensin-aldosterone system predispose patients to hyperkalemia and associated acute adverse outcomes. Although the association between severe hyperkalemia and increased mortality is well established, the clinical significance of mild hyperkalemia remains poorly described.¹ Part of the challenge has been the confusion that results from the presence of comorbidities that confer worse outcomes as well as the adverse consequences associated with the initiation of

potassium-lowering treatments, such as sodium polystyrene sulfonate or the discontinuation of renin-angiotensin-aldosterone system inhibition (RAASi) medications.

The widespread use of nonsteroidal anti-inflammatory drugs and RAASi has led to increased rates of hyperkalemia. Among those with chronic kidney disease, diabetes mellitus, and heart failure on RAASi, permissive hyperkalemia is considered an acceptable consequence to be able to gain the inferred renal and cardioprotective benefits of RAASi. Interestingly, recent observational studies suggest that patients with low-grade hyperkalemia (serum K = 5.0–5.5 mmol/l) may also have higher mortality risk. Unfortunately, longitudinal analyses of the association of hyperkalemia and outcomes have been largely limited to the acute, inpatient population, thus limiting the generalizability of the results. Although Hughes-Austin *et al.*² described increased cardiovascular events and mortality risk with even small increases in serum potassium in community-living

individuals in 2017, the cohort was relatively small.

In this issue, Hougen *et al.*³ have described the association between hyperkalemia and mortality, cardiovascular events, hospitalizations, and intensive care unit admissions, leveraging provincial administrative health databases in Manitoba, Canada, with both inpatient and outpatient laboratory results to identify patients with hyperkalemia and a propensity-matched cohort. Of the 93,667 patients identified to have had a hyperkalemic episode, 88,541 were propensity matched to patients without hyperkalemia by age, sex, baseline comorbidities, and the use of medications that affect serum potassium levels in a 1:1 fashion. Among hyperkalemic events, the majority were mild (<5.5 mmol/l) with a mean baseline serum potassium of 5.29 mmol/l.

Not surprisingly, and in congruence with previous observational studies, hyperkalemia was associated with increased short-term and all-cause mortality, cardiovascular events, incidence of hospitalizations, and ICU admissions. Individuals who experienced hyperkalemia in the outpatient setting, 2 or more hyperkalemic episodes, or more severe hyperkalemia (≥ 5.5 mmol/l) also experienced increased risk of all-cause mortality and cardiovascular events.

As a very large, well-designed, propensity-matched cohort study, the authors uniquely demonstrate a persistent association of hyperkalemia with long-term outcomes beyond 30 days and describe the association between hyperkalemia and intensive care unit admissions. Although the use of a population-based sample contributes to the generalizability and strength of the

Correspondence: Sophia L. Ambruso, Rocky Mountain Regional VA Medical Center, Renal Division, 1700 N Wheeling Street, Aurora, Colorado, USA. E-mail: Sophia.ambruso@cuanschutz.edu

study, the authors were unable to account for several important confounders, most specifically the acute cause of the hyperkalemic event and the consequences related to the interventions used as a result of hyperkalemia (i.e., short-term management with sodium polystyrene sulfonate) or longer-term management through the discontinuation of renal and cardioprotective RAASi, all of which could confer worse outcomes.

Where do we go from here? We know that hyperkalemia is associated with adverse outcomes, both in the short- and long-term clinical setting and likely contributes substantially to the health care cost burden associated with increased hospitalizations and intensive care unit admissions. In doing so, the prevention and management of hyperkalemia become convoluted and more nuanced. For example, in higher-risk patients who would benefit from the use of RAASi, where is the greater risk? Is it in stopping RAASi or in permitting low-grade hyperkalemia to enable the resumption or continued use of RAASi? In fact, this risk-benefit ratio remains poorly described and represents an area in need of further investigation.

Perhaps the introduction of the newer serum potassium-lowering agents patiromer and sodium zirconium cyclosilicate will alleviate such conundrums as they are increasingly used to facilitate the resumption and continued use of

RAASi. Although the newer potassium-lowering agents have yet to demonstrate mortality benefit, they have demonstrated successful reduction of hyperkalemia in a variety of higher-risk populations.⁴⁻⁹ As clinicians are becoming more comfortable using these newer serum potassium-lowering agents in the acute and chronic setting, future investigation is warranted to examine whether they also lower consequences such as long-term mortality, cardiovascular events, hospitalizations, and health care costs.

Finally, the growing body of literature supporting low-grade hyperkalemia-associated adverse events calls into question the safety of permissive hyperkalemia with RAASi, identifying a need to better define both the thresholds at which serum potassium-lowering agents ought to be considered as well as the therapeutic goal.

DISCLOSURE

The author declared no competing interests.

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