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COMMENT

# Reconsidering discontinuation of RAS inhibitors after hyperkalemia

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With the global increase in aging populations and the rising prevalence of cardiovascular disease (CVD) and chronic kidney disease (CKD), addressing these conditions has become a major global healthcare challenge. Renin-angiotensin system inhibitors (RASi) remain a cornerstone in the management of CVD and CKD. RASi have demonstrated kidney protective effects in CKD patients, regardless of disease severity. Moreover, recent evidence has clearly established the cardio- and kidney protective benefits of mineralocorticoid receptor antagonists (MRAs), further expanding the therapeutic armamentarium [1, 2].

A decline in estimated glomerular filtration rate (eGFR) is progressively associated with an increased risk of mortality and cardiovascular events [3]. In such high-risk populations, the absolute benefit derived from the use of RASi may be greater. However, in patients with advanced CKD, the use of RASi has been associated with an increased risk of hyperkalemia-related hospitalization [4], and hyperkalemia is often a reason for discontinuation of these agents. In this context, the decision to continue or discontinue RASi in CKD patients has become a key issue of interest, particularly from the perspectives of safety and therapeutic benefit.

The present study by Hashimoto et al. provides important insights into the prognostic implications of discontinuing RASi following the development of hyperkalemia, utilizing a rigorous target trial emulation framework and real-world data [5]. Observational studies allow the investigation of clinical questions that are challenging to address through randomized controlled trials and leverage the strengths of real-world data, including greater external validity. However, they are inherently susceptible to various sources of bias. In this study, the authors adopted a target trial emulation approach to address potential biases and found no significant difference in the risk of the composite kidney outcomes between patients who discontinued RASi and those who continued RASi (adjusted hazard ratio, 1.01; 95% confidence interval, 0.81–1.26). On the other hand, discontinuation of RASi was associated with an increased risk of all-cause mortality (adjusted hazard ratio, 1.16; 95% confidence interval, 1.02–1.33), while the risk of severe hyperkalemia was reduced (adjusted hazard ratio, 0.83; 95% confidence interval, 0.69–0.99) [5].

These findings suggest that complex clinical decision-making is required when managing pharmacotherapy in patients receiving RASi who develop hyperkalemia. While discontinuation of RASi may reduce the risk of severe hyperkalemia, it may come at the cost of increased all-cause mortality. This trade-off underscores the importance of individualized treatment strategies based on careful assessment of the risks and benefits in each patient.

The increased risk of mortality associated with discontinuation of RASi may be attributable to the loss of their inherent cardiovascular protective effects. Even in patients with advanced CKD—who are at higher risk of developing hyperkalemia—RASi have been shown to reduce the risks of CVD and end-stage kidney disease [6]. In CKD patients, discontinuation of RASi has been shown to have no favorable impact on kidney outcomes in randomized controlled trials [7]. Additionally, meta-analyses of observational studies have revealed unfavorable results regarding all-cause mortality and end-stage kidney disease [8]. Moreover, in CKD patients, even after discontinuation of RASi, restarting RASi therapy has been shown to reduce the risk of kidney function decline and all-cause mortality

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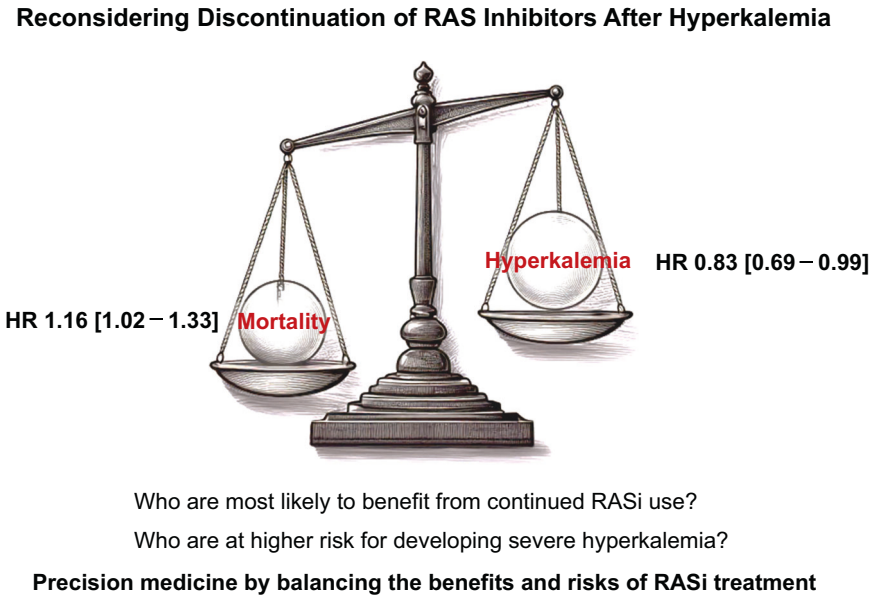


**Fig. 1** Schematic of key considerations for discontinuing RAS inhibitors in hyperkalemia

[9]. Furthermore, reducing renin-angiotensin-aldosterone inhibitors after a hyperkalemia episode results in increased hospitalization days and fewer days alive and out of hospital compared to maintaining the treatment [10]. Taken together, these findings emphasize the importance of carefully managing RASi therapy to balance the risks of hyperkalemia with the potential benefits of cardiovascular protection.

Importantly, recent advances in potassium binders such as patiromer and sodium zirconium cyclosilicate have made the management of hyperkalemia more manageable than before. As a result, the potential to manage hyperkalemia without discontinuing RASi has expanded. The use of potassium binders in the event of hyperkalemia has been shown to increase RASi continuation rates, potentially contributing to renal protection [11].

In clinical practice, one of the critical decision points regarding RASi discontinuation is often the occurrence of hyperkalemia. This study addresses the clinically relevant question of whether to discontinue or continue RASi therapy following a hyperkalemia episode. Given the heterogeneity observed among CKD patients, future research should focus on identifying which patients are most likely to benefit from continued RASi use, as well as which populations are at higher risk for developing severe hyperkalemia. Such efforts may ultimately contribute to achieving truly individualized therapy by balancing the benefits and risks of RASi treatment (Fig. 1).

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

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