Hypertension Research (2023) 46:2048–2050
https://doi.org/10.1038/s41440-023-01318-7

COMMENT

Need to continue or discontinue RAS inhibitors as CKD stage advances? Any alternative?

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Keywords RAS blockade · Advanced CKD · Hyperkalemia

Received: 13 April 2023 / Accepted: 21 April 2023 / Published online: 30 May 2023

Renin-angiotensin system (RAS) inhibitors, namely angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), are now positioned as key drugs for the treatment of hypertensive patients with proteinuric chronic kidney disease (CKD). A number of clinical trials so far have demonstrated their effectiveness in decreasing proteinuria and slowing the decline in kidney function [1–3]. Additionally, RAS inhibitors have been reported to be effective in cardiovascular disease [4, 5]. In preclinical studies, RAS inhibition reveals renoprotective effects through dilation of glomerular efferent arterioles, resulting in reducing intraglomerular pressure. In addition, RAS inhibition suppresses the excretion of aldosterone, thereby decreasing oxidative stress, tissue inflammation and fibrosis. Thus, RAS blockade potentially results in mitigating organ injury such as the kidney, heart, and blood vessels. RAS inhibitors are now recommended as the first-line pharmacologic strategy for the patients with proteinuric CKD in major clinical guidelines [6–8], and are the most widely used classes of antihypertensive drugs in patients with CKD having proteinuria regardless of their clinical stages.

As the CKD stage advances, however, renal potassium excretion gradually decreases, and the incidence of hyperkalemia increases. RAS inhibitors are considered as one of the main risk factors of aggravating hyperkalemia. Moreover, because the discontinuation of RAS inhibitors has a possibility to delay the initiation of renal replacement therapy (RRT) through the increase of glomerular filtration [9], they are often discontinued as CKD stage progresses in real-world clinical practice. Recently, several observational cohort studies and a randomized controlled trial (RCT) have been published concerning this issue; nevertheless, the benefits and disadvantages of RAS inhibitors discontinuation in patients with advanced CKD have yet to be clearly elucidated and still controversial [10, 11].

In a report of the current issue, Nakayama et al. performed a systematic review of the literature and meta-analysis to build scientific evidence for this problem [12]. The authors analyzed the impact of withdrawing RAS inhibitors on the risk of all-cause mortality, end-stage kidney disease (ESKD), major adverse cardiovascular events (MACE), and hyperkalemia. One of the studies included has been conducted by Bhandari et al. [13] (STOP-ACEi trial), which is a multicenter, randomized controlled trial. They randomly assigned patients with advanced CKD (eGFR <30 ml/min/1.73m^2) either to continue or to discontinue RAS inhibitors and during 3 years of follow-up, they evaluated change of eGFR values as a primary outcome. Other outcomes included the development of ESKD, hospitalization from any cause, cardiovascular events, and deaths. They concluded that there was no significant difference as for renal outcomes, cardiovascular events, and deaths. However, several limitations can be pointed out. The authors mentioned sample size insufficiency and the open-labeled study design. Furthermore, approximately 20% of the patients had autosomal dominant polycystic kidney disease while only 21% had diabetes, so that the overall average level of proteinuria was relatively low (continuation group: 1035 mg/gCr vs. discontinuation group: 960 mg/gCr). Consequently, beneficial effects of RAS inhibitors might have been less for those patients as the background of CKD.

As mentioned in the current paper in *Hypertension Research*, one of the main reasons for stopping RAS inhibitors could be concern for and occurrence of hyperkalemia. With regard to this issue, there is a suggestive report

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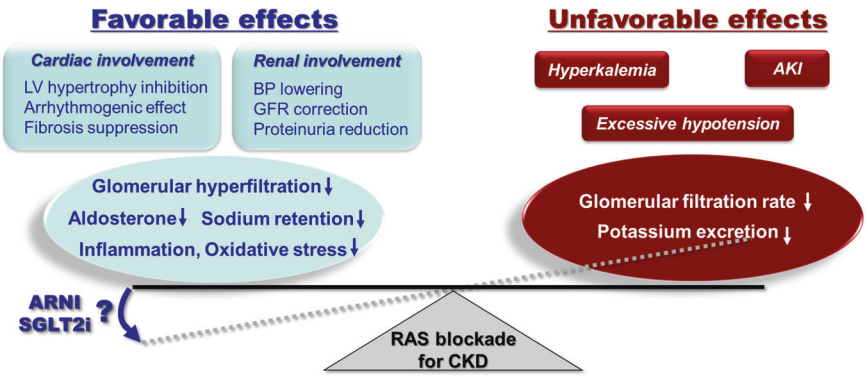

Fig. 1 Favorable and unfavorable effects of RAS blockade on advanced CKD patients, and potential benefit of ARNI and SGLT2i

comparing RAS inhibitors with an angiotensin receptor-neprilysin inhibitor (ARNI). Xu et al. performed a systematic review and meta-analysis to evaluate the renal outcome of ARNI and RAS inhibitors [14]. In this study, they compared adverse events including severe hyperkalemia (potassium å 6.0 mmol/L), and the ARNI group showed a significantly lower incidence of severe hyperkalemia (six studies, 16,653 patients, RR 0.80; 95% CI: 0.68–0.93, $p = 0.003$, $I^2 = 25\%$). In the secondary analysis of PARADIGM-HF trial [15], incidence of severe hyperkalemia (potassium å 6.0 mmol/L) was lower in the ARNI group compared to the enalapril group (3.1 vs 2.2 per 100 patient-years; HR, 1.37 [95% CI: 1.06–1.76]; $p = 0.02$) among patients taking mineralocorticoid receptor antagonists (MRA) for HFrEF (heart failure with reduced ejection fraction) [16]. Although more pieces of evidence are urgently needed, ARNI could be potentially beneficial by sparing severe hyperkalemia compared to conventional RAS inhibitors.

Recently, there have been several studies reported which investigated the effects of RAS blockade monotherapy and the combination with sodium glucose co-transporter 2 (SGLT2) inhibitors. In the subgroup analysis of DAPA-HF trial [17], among patients taking MRA, moderate/severe hyperkalemia (potassium >6.0 mmol/L) occurred in 21 of 1683 (1.3%) patients treated with dapagliflozin and in 40 of 1666 (2.4%) patients treated with placebo, giving a HR of 0.50 (0.29 to 0.85) [18]. Similar results were shown in other studies, subgroup analyses of EMPEROR-Reduced trial [19] and FIDELIO-DKD trial [20]. The average eGFR levels at baseline of these trials were relatively high (approximately 45 to 60 mL/min/1.73m^2), thus, those results cannot be directly applied to advanced CKD patients. Nonetheless, it is suggested that combination with SGLT2 inhibitors may reduce the risk of severe hyperkalemia for the patients who are taking RAS inhibitors with or without MRA. Possible mechanisms by which SGLT2 inhibitors prevent hyperkalemia are proposed as follows. SGLT2 inhibitors increase sodium delivery to the distal nephron, thus enhancing sodium reabsorption coupled with potassium excretion in the cortical collecting duct. Preserved kidney function and other mechanism outside of the kidney might also contribute to it [21].

As discussed thus far, there are both favorable and unfavorable effects of RAS blockade on CKD patients (Fig. 1). Considering potential cardiac and renal benefits obtained from RAS inhibitors, it seems reasonable to reconsider their continuation before giving them up. In summary, it is not recommended uniformly to discontinue RAS inhibitors in advanced CKD patients. For the concern of rapid decline of eGFR or AKI, it is no doubt required to carefully evaluate and avoid potential risk factors such as excessive hypotension or dehydration. For the concern of severe hyperkalemia, combination with SGLT2 inhibitors or alternative use of ARNI could be considered without decreasing cardiac and renal benefits of RAS inhibitors. Advances in potassium binders have made potassium management much easier than before. These actions will altogether enable us to maximize favorable effects while minimize unfavorable effects of RAS blockade in patients with advanced CKD.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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