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COMMENT

Another evidence that supports the continued use of RAS inhibitors in end-stage kidney diseases

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Chronic kidney disease (CKD) contributes not only to mortality but also is a crucial risk factor for cardiovascular (CV) disease [1]. Advanced CKD requires renal replacement therapy, including hemodialysis and peritoneal dialysis. Moreover, end-stage kidney disease (ESKD) patients suffer from a higher risk of CV events, resulting in increased mortality [2].

It is widely accepted that renin-angiotensin system inhibitors (RASIs) delay progression to advanced chronic kidney disease [3]. On the other hand, RASIs medication in CKD patients increases the risk of hyperkalemia and acute decline in kidney function. Therefore, several guidelines recommend to use RASIs in advanced CKD patients with intensive monitoring for hyperkalemia and kidney function [4, 5]. STOP ACEi trial evaluated whether RASIs discontinuation affected the decline of estimated glomerular filtration ratio (eGFR). In 3 years of observational period, there were no significant differences in eGFR levels between RASIs continuation and discontinuation groups (95% confidence interval (CI), $-2.5 \sim 1.0$; $p = 0.42$) [6]. However, this study excluded the patients who received renal-replacement therapy.

In the issue of Hypertension Research, the study by Nakamura et al. demonstrates that the discontinuation of RASIs is associated with higher CV events [7]. This retrospective cohort study evaluated the data of 717 incident dialysis patients. The patients' mean ± SD age of HD initiation are 67 ± 13 years, and 68% are male. They divided continuing RASIs ($n = 650$, 91%) and discontinuing RASIs ($n = 67$, 9.3%). Nakamura et al. recruited patients who had used angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) 3 months prior to hemodialysis initiation. The median follow-up is 3.5 years in mortality, and 3.2 years in CV events. In patient characteristics, discontinuing RASIs group showed shorter duration of nephrology care (1.5 years versus 2.3 years), requiring urgent dialysis (33% versus 22%), faster eGFR decline (4.0 ± 3.3 years versus 2.6 ± 2.6 years), and higher CRP (0.55 mg/dL versus 0.20 mg/dL). During the follow-up, Nakamura et al. found that discontinuing RASIs group had a shorter life in Kaplan-Meier curve ($p = 0.014$) and increased CV event risk (hazard ratio (HR) 1.59; 95% CI, 1.06–2.38) than continuing RASIs group, respectively. Moreover, CV event risk of stopping RASIs is higher in <75 years.

Improvement in mortality and CV events with RASIs in non-dialysis-dependent CKD patients has been previously demonstrated. Quio et al. reported that RASI discontinuation is associated with CV event in low eGFR rate [8]. During a median follow-up of 2.9 years, RASIs discontinuation group was associated with a higher risk of mortality (hazard ratio (HR) 1.39; 95% CI, 1.20–1.60) and major adverse cardiovascular event (MACE) (HR, 1.37; 95% CI, 1.20–1.56) [8]. Fu et al. also tried to evaluate the adverse effects of RASI discontinuation in advanced CKD patients [9]. They showed that stopping RASIs were associated with 5-years high mortality (40.9% v.s. 54.5%) and MACE (47.6% v.s. 59.5%) [9]. However, it was unclear from these studies whether the continued use of RASI is associated with the altered CV risk in ESKD patients receiving renal replacement therapy. Tai et al. found that RASI medication was not associated with a statistically significant reduction in the risk of CV events in a meta-analysis [10]. However, studies by Takahashi et al. and by Suzuki et al., included in the above-mentioned meta-analysis, showed reduced CV events by RASI [11, 12]. Currently, more data are needed to determine the protective effects of RASI in maintenance hemodialysis patients.

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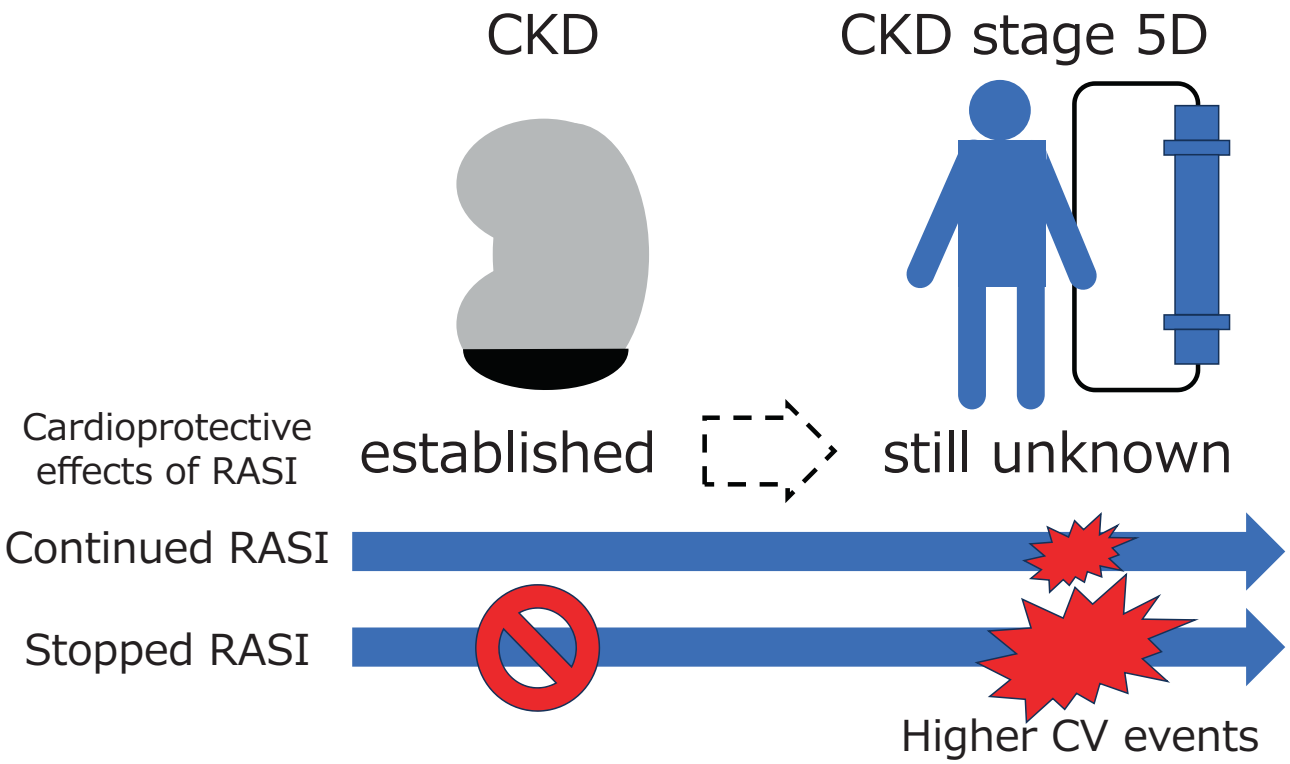
Graphical Opinion



The study by Nakamura et al. found that CV risk after stopping RASI is significantly higher in <75 years in subgroup analysis. Interestingly, Gan et al. reported that age is a strong predictor of CV risk ($p < 0.0001$) in hemodialysis patients in systematic review [13]. Kovesdy et al. analyzed the data of 300,424 cohorts with incident CKD patients in US veterans [14]. They reported that a linear association of systolic blood pressure with the occurrence of coronary heart disease, stroke, and ESKD is attenuated with age, particularly in those with 80 years or older. They discussed that the competing, BP-unrelated risks of death, such as malignancies and infections, might explain their observation in the elderly. The study by Nakamura et al. seems to be consistent with the data and may indicate that the cardiovascular protective effects of RASI are clinically relevant especially in ESKD patients with younger age. Future investigation is needed to obtain more detailed insights on this matter.

Several new cardioprotective drugs have emerged in recent years. The usefulness of mineralocorticoid receptor antagonists (MRAs) in chronic heart failure with reduced ejection fraction is well-established in non-dialysis patients [15, 16]. Nevertheless, the protective effects of MRAs in cardiovascular system in maintenance hemodialysis patients are not established, although a recent Cochrane review concluded that MR antagonists probably reduce the risk of all-cause and cardiovascular death in ESKD patients [17]. Given that MRAs can increase plasma potassium levels even in ESKD patients, its use needs to be decided by considering the balance between the cardioprotective effects and the risk of hyperkalemia [18]. Sodium-glucose cotransporter-2 inhibitors (SGLT2Is) are also established to reduce the CV risk in patients with chronic heart failure [19]. The protective effects seem to involve multiple mechanisms, including natriuresis, hemodynamic alterations, weight loss, natriuresis, ketone body metabolism, and improving anemia [20–22]. However, it is generally recommended that SGLT2I should be initiated in those with an eGFR of at least 20 mL/min/1.73 m^2 [23]. Almost all of SGLT2I trials do not include patients with ESKD or those on renal replacement therapy at baseline. Future investigation is required to analyze the long-term effect of SGLT2Is in these populations.

In summary, the study by Nakamura et al. provides another clinical evidence that stopping RASIs before hemodialysis is associated with CV events after hemodialysis.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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