Hypertension Research (2022) 45:1072–1075
https://doi.org/10.1038/s41440-022-00902-7

COMMENT

Role of renin-angiotensin system blockade in advanced CKD: to use or not to use?

Masashi Mukoyama[1] · Takashige Kuwabara[1]

Received: 13 February 2022 / Revised: 27 February 2022 / Accepted: 1 March 2022 / Published online: 31 March 2022

Renin-angiotensin system (RAS) inhibitors, namely, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), are key agents for the treatment of hypertension in patients with proteinuric chronic kidney disease (CKD). Based on many clinical trials demonstrating their effectiveness in decreasing proteinuria and delaying CKD progression, the use of RAS inhibitors is recommended as the first-line pharmacologic strategy for patients with CKD and proteinuria in major clinical practice guidelines [1–3]. In a recent meta-analysis including 119 randomized trials in patients with CKD with or without diabetes [4], both ACE inhibitors and ARBs reduced the risk of kidney failure (a composite of the doubling of serum creatinine, a 50% decline in the estimated glomerular filtration rate [eGFR], or end-stage kidney disease [ESKD]) and major cardiovascular events (a composite of myocardial infarction, stroke, heart failure, or cardiovascular death); in addition, ACE inhibitors reduced the odds ratio of all-cause death compared to that of the active control. Thus, RAS inhibitors are now the most widely used classes of antihypertensive drugs in patients with CKD with proteinuria, regardless of their clinical stages. However, most guidelines recommend avoiding any combination of ACE inhibitors, ARBs, and direct renin inhibitor therapy in patients with CKD with or without diabetes because their combination does not lead to long-term cardiovascular or kidney benefit, whereas it can lead to an increased risk of hyperkalemia and acute kidney injury (AKI) [1–3].

The antiproteinuric effect of RAS inhibitors is thought to contribute to slowing the progression of CKD. However, the benefits of using RAS inhibitors in advanced stages of CKD, i.e., CKD stage 4 or stage 5, are less certain and still under debate. In fact, a meta-analysis investigating the combined associations of eGFR and albuminuria with mortality in a general population showed that the advantage of less urinary albumin excretion for lower cardiovascular mortality risk disappeared in patients with eGFR less than 30 mL/min per 1.73 m^2 [5]. Furthermore, the continued use of RAS inhibitors in the setting of severely reduced kidney function may cause undesirable outcomes, including a potential risk of hyperkalemia, hemodynamic effects leading to kidney function decline, and the vulnerable response to AKI events [6]. Accordingly, in patients with CKD stage 5 (eGFR <15 mL/min per 1.73 m^2), the guidelines recommend reducing the dose or discontinuing ACE inhibitors or ARBs in the setting of either symptomatic hypotension or uncontrolled hyperkalemia [1–3]. Nevertheless, the disadvantages and benefits of RAS inhibitor initiation or withdrawal in patients with advanced CKD have yet to be clearly answered in randomized controlled trials.

Although the evidence level is not high enough, there have been limited observational and randomized studies that have investigated the risks and benefits of RAS inhibition in patients with advanced CKD (Table 1). One of the studies investigating the initiation of ACE inhibitor treatment and renal outcome in patients with moderate to advanced CKD was conducted by Hou et al. [7]. In this trial, more patients with advanced CKD (serum creatinine, 3.1–5.0 mg/dL) reached the primary end point (the composite renal outcome: doubling of serum creatinine, ESKD or death) than those with moderate CKD (serum creatinine, 1.5–3.0 mg/dL), and the ACE inhibitor benazepril was found to be superior to placebo in delaying the renal outcome among those with advanced CKD. Another trial that tested the effect of RAS inhibitor initiation compared to calcium channel blocker (CCB) treatment in patients with advanced CKD was reported by Fu et al. [8]. They found that fewer patients with RAS inhibitor treatment reached the primary renal end point than those with CCB treatment (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.69–0.89). There

✉ Masashi Mukoyama
mmuko@kumamoto-u.ac.jp

[1] Department of Nephrology, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan

Table 1 Studies on RAS blockade and the benefit or risk of cardiovascular and renal outcomes in patients with advanced CKD

Authors	Design	Patient's number included	Follow-up	Comparison	CKD stage	Outcome			
						Cardiovascular outcome		Renal outcome	
Hou et al. [7]	Prospective observation	Group 1: 141	3.4 years	Before vs. after initiating RASi	sCr 1.5–3.0	NA		Composite of 2xsCr, RRT, or death	22% primary end point (better than Group 2 RASi)
	RCT	Group 2: 281	3.4 years	Initiating RASi vs. placebo	sCr 3.1–5.0	NA		Composite of 2xsCr, RRT, or death	Favors initiating RASi (41% RASi and 60% placebo)
Fu et al. [8]	Retrospective cohort	4803	4.1 years	Initiating RASi vs. CCB	G4-5	MACE	NS	RRT	Favors initiating RASi
Ahmed et al. [9]	Prospective observation	52	>12 months	Before vs. after stopping RASi	G4-5	NA		eGFR slope (mL/min/year)	−0.39 vs. +4.38
Qiao et al. [10]	Retrospective cohort	3909	2.9 years	Continuing vs. stopping RASi	G4-5	5-year all-cause death MACE	Favors continuing RASi Favors continuing RASi	RRT	NS
Walther et al. [11]	Retrospective cohort	141,252	4.87 years	Continuing vs. stopping RASi	G3-4	All-cause death	Favors continuing RASi	RRT	Favors continuing RASi
Fu et al. [12]	Retrospective cohort	10,254	>5 years	Continuing vs. stopping RASi	G4-5	5-year all-cause death MACE	Favors continuing RASi Favors continuing RASi	RRT	Favors stopping RASi
Nakayama et al. [13]	Retrospective cohort	334	>6 months	With RASi vs. without RASi	G5D	NA		Unplanned RRT	Favors using RASi
Bhandari et al. [14] (STOP-ACEi trial)	RCT	410	3 years	Continuing vs. stopping RASi	G4-5	Hospitalization from any cause Cardiovascular events or death	Ongoing	eGFR RRT or eGFR decline >50% Time to RRT	Ongoing

RCT randomized controlled trial, *RASi* renin-angiotensin system inhibitor, *CCB* calcium channel blocker, *sCr* serum creatinine level, *NA* not applicable, *MACE* major adverse cardiovascular event, *NS* not significant, *2xsCr* doubling of the serum creatinine level, *RRT* renal replacement therapy, *eGFR* estimated glomerular filtration rate

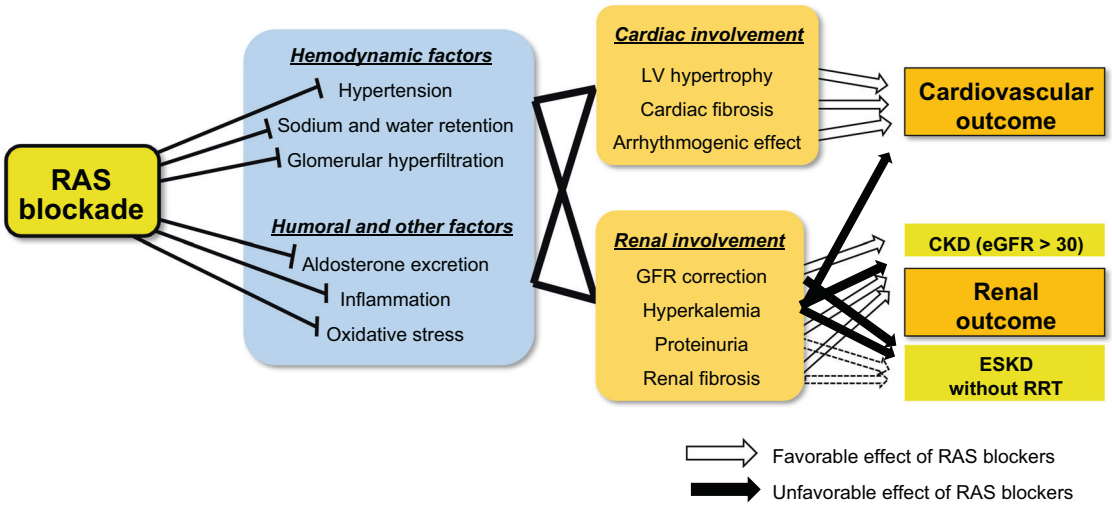

Fig. 1 Effects of renin-angiotensin system (RAS) blockade on cardiovascular and renal outcomes in patients with advanced chronic kidney disease (CKD)

was no significant difference between the therapies in mortality (HR, 0.97; 95% CI, 0.88–1.07) or major adverse cardiovascular events (MACEs; HR, 1.00; 95% CI, 0.88–1.15). They concluded that the study provides evidence that the initiation of RAS inhibitor therapy compared with CCBs may confer kidney benefits among patients with advanced CKD, with similar cardiovascular protection.

There have also been limited observational studies that investigated the role of RAS inhibitor treatment continuation versus withdrawal in patients with advanced CKD already receiving RAS inhibition. One small observational study by Ahmed et al. [9] showed that the negative eGFR slope before stopping RAS inhibitors was reversed 12 months after their withdrawal among patients with advanced CKD, and this effect persisted for up to 24 months. The authors concluded that the discontinuation of RAS inhibition could delay the onset of renal replacement therapy (RRT) in the majority of those patients. Thereafter, relatively large-scale retrospective cohort studies have been planned and performed, focusing on not only renal but also cardiovascular outcomes. Among them, Qiao et al. [10] reported that ACE inhibitor or ARB therapy discontinuation in patients with advanced CKD was associated with a higher risk of mortality (HR, 1.39; 95% CI, 1.20–1.60) and MACEs (HR 1.37; 95% CI, 1.20–1.56), with no statistically significant difference in ESKD risk (HR, 1.19; 95% CI, 0.86–1.65). Walther et al. [11] showed that the discontinuation of RAS inhibitors in patients with CKD stages 3 and 4 was associated with a higher risk of death (HR, 1.74; 95% CI, 1.70–1.78) and ESKD (HR, 1.59; 95% CI, 1.48–1.71). The authors concluded that physicians should assess eligible patients who are not on ACE inhibitor or ARB therapy and identify the reasons why these agents are not being used. In contrast, Fu et al. [12] demonstrated that stopping RAS inhibitor therapy in patients with CKD stages 4 and 5 was associated with a higher absolute 5-year risk of death (40.9% vs. 54.5%) and MACEs (47.6% vs. 59.5%) but with a lower risk of RRT (36.1% vs. 27.9%). The authors further showed that the results were consistent whether patients stopped RAS inhibition at higher or lower eGFR, across prespecified subgroups, and after adjustment and stratification for albuminuria and potassium. In summary, although the observed risks of stopping RAS inhibition obtained from those studies could not eliminate the possible influence of reverse causality, it is conceivable that continuing RAS inhibitor therapy in patients with advanced CKD may exert cardiovascular protection, with an equivocal or somewhat detrimental effect on renal protection (Fig. 1).

In the most recent issue of *Hypertension Research*, Nakayama et al. [13] reported a retrospective study investigating the comparison between continued use of RAS inhibitors and stopping or nonuse of them in patients with advanced CKD on the incidence of unplanned dialysis. They showed that continuing RAS inhibitor therapy was significantly and independently associated with a lower incidence of unplanned dialysis initiation (continuing, 32.4%, stopping, 58.8%, nonuse, 50.7%; HR, 0.36; 95% CI, 0.20–0.66). Currently, the advancement of potassium binding therapy has brought about better tolerability of RAS inhibition in the setting of advanced CKD. The authors propose that until the negative effects of RAS inhibitors on renal outcome are confirmed by randomized trials, it is reasonable to use these agents in patients with advanced CKD. An ongoing randomized controlled trial (STOP-ACEi trial) [14] investigated the renal and cardiovascular outcomes of stopping versus continuing RAS blockade in patients with advanced CKD. We should wait to decide on

the treatment strategy consensus until this trial has provided additional data on the risks and benefits of RAS inhibition in this patient population.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019). Hypertens Res. 2019;42:1235–481.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99(Suppl):S1–87.
3. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104 https://doi.org/10.1038/s41440-022-00877-5.
4. Xie X, Liu Y, Perkovic V, Li X, Ninomiya T, Hou W, et al. Renn-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: a bayesian network meta-analysis of randomized clinical trials. Am J Kidney Dis. 2016;67:728–41.
5. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–81.
6. Weir MR, Lakkis JI, Jaar B, Rocco MV, Choi MJ, Kramer HJ, et al. Use of renin-angiotensin system blockade in advanced CKD: an NKF-KDOQI controversies report. Am J Kidney Dis. 2018;72:873–84.
7. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med. 2006;354:131–40.
8. Fu EL, Clase CM, Evans M, Lindholm B, Rotmans JI, Dekker FW, et al. Comparative effectiveness of renin-angiotensin system inhibitors and calcium channel blockers in individuals with advanced CKD: a nationwide observational cohort study. Am J Kidney Dis. 2021;77:719–29.
9. Ahmed AK, Kamath NS, El Kossi M, El, Nahas AM. The impact of stopping inhibitors of the renin-angiotensin system in patients with advanced chronic kidney disease. Nephrol Dial Transplant. 2010;25:3977–82.
10. Qiao Y, Shin JI, Chen TK, Inker LA, Coresh J, Alexander GC, et al. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. JAMA Intern Med. 2020;180:718–26.
11. Walther CP, Winkelmayer WC, Richardson PA, Virani SS, Navaneethan SD. Renin-angiotensin system blocker discontinuation and adverse outcomes in chronic kidney disease. Nephrol Dial Transplant. 2021;36:1893–9.
12. Fu EL, Evans M, Clase CM, Tomlinson LA, van Diepen M, Dekker FW, et al. Stopping renin-angiotensin system inhibitors in patients with advanced CKD and risk of adverse outcomes: a nationwide study. J Am Soc Nephrol. 2021;32:424–35.
13. Nakayama T, Morimoto K, Uchiyama K, Kusahana E, Washida N, Azegami T, et al. Effects of renin-angiotensin system inhibitor on the incidence of unplanned dialysis. Hypertens Res. 2022;45. https://doi.org/10.1038/s41440-022-00877-5.
14. Bhandari S, Ives N, Brettell EA, Valente M, Cockwell P, Topham PS, et al. Multicentre randomized controlled trial of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker withdrawal in advanced renal disease: the STOP-ACE trial. Nephrol Dial Transplant. 2016;31:255–61.