Dual Blockade of the Renin-Angiotensin System: A Strategy that Should Be Reconsidered in Cardiorenal Diseases?

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Keywords

Dual blockade strategy · Renin-angiotensin system · Cardiorenal diseases

Abstract

Studies on pharmacological mechanisms demonstrated that a strategy of dual renin-angiotensin system (RAS) blockade may have a synergistic effect in the treatment of cardiorenal diseases and may reduce adverse reactions. However, some previous clinical studies reported that dual RAS blockade did not significantly benefit many patients with cardiorenal diseases and increased the risk of hyperkalemia, hypotension and renal function damage. Therefore, the current clinical guidelines suggest that the combined use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) should be used with caution in the clinic. However, these studies enrolled older patients with cardiovascular risk factors, and the results of these trials may not be generalized to the overall population. Some clinical evidence suggests that the combination of low-dose ACEIs and ARBs leads to more effective RAS blockade with few adverse effects. The advent of new RAS inhibitors with superior pharmacological effects provides a more suitable

drug choice for individualized therapy for dual RAS blockade. Therefore, the choice of appropriate ARBs/ACEIs for individualized therapy based on patient condition may be a better way to improve the efficiency and safety of the dual RAS blockade strategy.

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Introduction

The renin-angiotensin system (RAS) has been among the most important therapeutic targets in the field of cardiorenal vasculature since it was proposed in the 1990s. RAS inhibitors (RASIs), ranging from angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) to renin inhibitors, are continuously developed. RASIs are widely used in the clinic, and each drug has unique characteristics that play a very important role in the treatment of cardiorenal diseases. However, the combined use of RASIs in the clinic is con-

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troversial because the pharmacological mechanisms may achieve synergistic effects, but clinical observations are contradictory. The benefit of dual RAS blockade in the field of cardiorenal diseases was first documented in the CALM study, which found that combination therapy reduced albuminuria more effectively than candesartan or lisinopril monotherapy in patients with hypertension, type 2 diabetes, and microalbuminuria [1]. Therefore, some scholars proposed that the combined use of RASis would improve treatment efficacy in patients [2]. Because reduced proteinuria is correlated with reduced renal and cardiovascular events, the antiproteinuric effect of the dual RAS blockade strategy was expected to achieve long-term renoprotection and cardioprotection. Nephrologists are more supportive of this combination therapy than cardiovascular doctors [3]. However, due to the results of some clinical randomized controlled trials (RCTs) on the possible risks of combined blockade regimens, the European Drug Administration issued a clear warning for the combined use of ARBs and ACEIs in 2014 [4]. This report highlights the results of the following clinical randomized studies: ONTARGET, ALTITUDE, and VANEPHRON-D. The results of these studies suggest that dual RAS blockade regimens increase the incidence of adverse events, including hyperkalemia, hypotension, and renal failure, in patients with cardiovascular risk factors [5–7]. Therefore, ACEIs and ARBs are not recommended in current clinical guidelines. However, some clinical studies showed that dual RAS blockade may significantly benefit some specific populations [8]. The advent of new RASis with superior pharmacological effects provides a more suitable drug choice for individualized therapy for dual RAS blockade. Based on this background, the present article primarily reviews some important research results published in this field in recent years and analyzes and evaluates the safety and clinical value of the dual RAS blockade strategy.

Regulation and Balance of the Renin-Angiotensin System

The components of the RAS primarily include renin, angiotensin peptides, angiotensin-converting enzyme (ACE), and receptors (Fig. 1) [9]. AngII is especially important because it is the strongest pressor substance currently known [10]. However, ACE2 and angiotensin 1–7 (Ang1–7) also play important roles in maintaining the balance of the RAS [11–13]. ACE2 is a monopeptidase that cleaves an amino acid from the carboxyl end

of a substrate. The substrates of ACE2 include AngI and AngII. ACE2 directly changes AngII into Ang1–7, which has vasodilating effects, and it degrades AngI into Ang1–9, which further forms Ang1–7 via other enzymes *in vivo*. Similar to bradykinin, Ang1–7 is a vasodilator that maintains balance in the RAS. Therefore, the activity of ACE2 plays an important role in regulating the balance of the RAS. Scientists are developing new therapies that are in preclinical and early clinical stages, including recombinant ACE2 protein [14]. However, not all ACEIs have the ability to modulate ACE2. Early drugs, such as captopril and enalapril, have almost no regulatory effect on ACE2, but subsequent drugs, such as perindopril, upregulate ACE2, which strengthens its capacity to control blood pressure and protect the heart, kidney, and other target organs via the ACE2/Ang1–7/MAS axis. Notably, some ACEIs and ARBs (e.g., olmesartan, losartan, and azilsartan) regulate the activity of ACE2 and promote the production of Ang1–7 and bradykinin [15]. These new RASis with superior pharmacological effects should be given priority in the dual RAS blocking strategy.

ACEIs and ARBs have similar side effects, namely hypotension, hyperkalemia, renal function deterioration, and fetal malformations [16]. Because these 3 drugs act on different parts of the RAS, they should theoretically have synergistic effects. For example, ACEIs inhibit ACE activity, reduce the production of AngII, aldosterone, and vasopressin, and increase renin secretion, but their blockade efficiency does not reach 100%. Some early marketed drugs did not modulate AngII or aldosterone. In contrast, ARBs block the binding of AngII to the angiotensin 1 receptor (AT1R), which directly blocks the post-receptor effect of AT1 and partially activates the AT2 receptor. Because AngII cannot bind AT1R or be rapidly decomposed, the concentration of AngII in the body increases. As previously mentioned, newly listed ACEIs, such as perindopril, upregulate ACE2 and convert AngII into Ang1–7 [11]. Therefore, the combination of ACEIs and ARBs make good pharmacological sense because ARBs directly block AT1R, and ACEIs convert elevated AngII into the vasodilator Ang1–7. The combination of ACEIs with ARBs had a greater effect than monotherapy on blood pressure and left ventricular hypertrophy in spontaneously hypertensive rats [17]. Thangaraju et al. [18] demonstrated that the combination of ACEI (ramipril) and ARB (telmisartan) showed improvement in the histopathological and biochemical changes in the kidneys of diabetic rat model. These animal experiments support the hypothesis that ACEIs with ARBs are possibly synergistic,

Fig. 1. ANG peptides and receptors in the RAS signaling pathway. Renin cleaves angiotensinogen into Ang I. Ang I can also be cleaved by ACE to Ang II, which stimulates AT1R and AT2R. Ang I can be cleaved into Ang(1–9) by ACE2, and Ang(1–9) can further diverge into Ang(1–7) via ACE/PEP/NEP. Ang II may further di-

verge via ACE2 into Ang(1–7), which binds to the AT2R and MAS receptor. RAS, renin-angiotensin system; ACE, angiotensin-converting enzyme; ACEIs, angiotensin-converting enzyme inhibitors; ANG, angiotensin; Ang I, angiotensin I; Ang II, angiotensin II; AT1R, angiotensin 1 receptor; AT2R, angiotensin 2 receptor.

which is the basis for a concept of “dual blockade strategy.” Cherney et al. [19] found that a combination of renin inhibitors and ACEIs had a good synergistic effect on endothelial function, arteriosclerosis, and renal function in type 1 diabetes [19]. Although the dual blockade is theoretically feasible, the clinical observations are controversial.

The Efficacy and Safety of Dual Renin-Angiotensin System Blockade Strategy

As mentioned above, RASIs with different targets in the RAS are the basis of combination therapy. Because of the promise of the dual blockade effect on RAS, scholars initially investigated the effects of combining ACEIs and ARBs. Some studies, such as CALM and COOPERATE, showed positive effects of the combination for reducing proteinuria [1, 20]. The Valsartan Heart Failure Trial (Val-HeFT) and CHARM-added studies showed that combination therapy was beneficial for patients with chronic heart failure, and it reduced the readmission rate of patients with heart failure [21, 22]. However, there are

too few similar studies, the sample size collected in this study was small, its persuasive power is limited, and the COOPERATE study was withdrawn because of an issue with informed consent. Several subsequent clinical trials, including the ONTARGET, ALTITUDE, and VA NEPHRON-D studies [5–7], found that combination therapy did not significantly increase the clinical benefits for the cardiac and renal endpoint events but increased the risk of hyperkalemia, hypotension, and acute renal injury. Therefore, the current cardiovascular guidelines, including the 2017 American Heart Association (AHA) guidelines and the 2018 European Society of Cardiology (ESC) guidelines [23, 24], do not recommend the combination of ACEIs and ARBs. Other studies clearly showed that dual blockade of RAS was not recommended, and the optimal dose of a single inhibitor remained the preferred strategy [25, 26]. A review of the details of the classic ONTARGET study, which compared the efficacy of ramipril and telmisartan in high-risk cardiovascular patients (nearly 10,000 high-risk diabetic patients with terminal organ damage), showed that the combination therapy increased the risk of renal endpoint events, hypotension, and renal injury. The ALTITUDE study used the renin

inhibitor alizarin in combination with ACEIs/ARBs in the treatment of high-risk cardio-cerebrovascular patients with type 2 diabetes complicated with hypertension and renal injury. The results showed that the combination treatment did not improve the cardiorenal endpoint events in the diabetic kidney disease patients, but it increased the incidence of adverse events. However, the patients included in these studies were generally older and had multiple risk factors. For example, the ALTITUDE trial included patients >35 years old, and the enrolled subjects were 65 years old on average. Therefore, these patients naturally belong to a high-risk group of cardiorenal endpoint events. However, this finding does not exclude the feasibility of combined therapy strategies in specific populations and specific disease stages. For example, young patients or patients without multiple cardiovascular risk factors may gain more benefits and have fewer adverse reactions using a dual RAS blockade strategy in the early stage of diabetic nephropathy.

A key problem associated with the dual RAS blockade strategy is adverse reactions. Currently, the most important safety problem related to the dual RAS blockade strategy is hypotension, which may lead to syncope and impaired renal function (indirectly leading to acute renal injury and hyperkalemia). The second-most important safety issue is hyperkalemia. Previous studies showed that the incidence of hyperkalemia (serum potassium >5.5 mmol/L) in hypertensive patients without risk factors for hyperkalemia treated with 1 RASi was 2%, and the corresponding value in patients treated with a dual RAS blockade strategy was as high as 5%. The incidence of hyperkalemia was also higher in patients with CKD or heart failure [27, 28]. Makani et al. [29] performed a meta-analysis of 33 RCTs with 68,405 patients and noted that dual RAS blockade did not have significant benefits for patients compared with 1 RASi and did not reduce cardiovascular mortality. However, the double RAS blockade therapy reduced the admission rate of patients with heart failure by approximately 18%, increased the risk of hyperkalemia by approximately 55%, increased the risk of low blood pressure by approximately 66%, and increased the risk of renal failure by approximately 41%. Although the conclusion of the above study argues against the use of dual RAS blockade, a subgroup analysis based on age and risk factors was not performed. Therefore, the feasibility of a dual RAS blockade strategy in specific populations cannot be simply denied. Nussberger and Bohlender [30] define “optimal” RAS blockade as the maximal blockade achieved without causing hypotension, hyperkalemia, or renal dysfunction. Therefore, individualized dual RAS

blockade may be considered an “optimal” RAS blockade strategy. The possible safety problems caused by the dual RAS blockade strategy may be improved using various measures, such as education for patients, families, and doctors (e.g., familiarity with the sources of dietary or supplemental potassium and measures to reduce potassium intake), the use of potassium binders, such as sodium zirconium cyclic silicate powder, to reduce the risk of complications, and more accurate screening for suitable patients, which involves 2 parameters. The first parameter involves screening patients who are more likely to benefit from the treatment, and the second parameter involves screening patients who are not prone to adverse reactions [27, 31, 32]. Therefore, young people who are in the early stage of cardiorenal diseases, such as hypertension and diabetes, with fewer risk factors, good compliance, and a high potential benefit-to-risk ratio, may be the “ideal” group to use the dual RAS blockade strategy. Therefore, we can consider selecting drugs with superior pharmacological characteristics and designing large sample prospective RCTs to evaluate the long-term effects of dual RAS blockade strategy in this population. Due to the theoretically lower incidence of adverse reactions in these patient populations, longer follow-up time may be required to assess the impact on the prognosis of cardiorenal endpoint events. Therefore, patients with better compliance must be included in this study design, and an efficient chronic disease management team should be established for the follow-up management of patients. Proteinuria remission rate and blood pressure control rate may also be used as evaluation indexes of this study to evaluate the efficacy of dual RAS blocking strategy more comprehensively. If the benefits from cardiorenal endpoint events are demonstrated in this “ideal” group, then we have more reasons to examine and optimize the use of dual RAS blockade strategy in high-risk groups.

Nephrologists want to try dual RAS blockade to reduce proteinuria in proteinuria nephropathy and improve the renal prognosis of CKD patients [33]. Early CKD patients tolerate RASi better when there is no multitarget organ damage. Therefore, nephrologists are more likely to use a dual RAS blockade strategy than cardiologists, especially in patients with proteinuria nephropathies who are not suitable for immediate use of immunosuppressants, such as IgA nephropathy [34]. Personalized medication and observation of adverse reactions are very important in these patients. Ruggenenti et al. [35] used individualized double RAS blockade for the treatment of nondiabetic nephropathy and found that it more effectively reduced proteinuria and slowed the progression of nephropathy

Table 1. Pharmacological characteristics of ACEIs

	Captopril	Benazepril	Enalapril	Ramipril	Perindopril	Fosinopril
eGFR >30 mL/min/1.73 m ²	No need to adjust dose	No need to adjust dose	Initial dose: 5–10 mg/d	Initial dose: 1.25 mg/d; Maintenance dose: usually 2.5 mg/d; Maximum dose should not exceed 5 mg/d	When eGFR >60 mL/min/1.73 m ² , 4 mg/d is recommended; eGFR is 30–60 mL/min/1.73 m ² , 2 mg/d is recommended	No need to adjust dose
eGFR <30 mL/min/1.73 m ²	Initial dose or frequency should be reduced	Initial dose is 5 mg/d and can be added to 10 mg/d if necessary	Initial dose: 2.5–5 mg/d		When eGFR is 15–30 mL/min/1.73 m ² , 2 mg/d is recommended; for ESRD, 2 mg is recommended on the day of dialysis	No need to adjust dose
Hepatic insufficiency	No need to adjust dose	No need to adjust dose	No need to adjust dose	No need to adjust dose	No need to adjust dose	No need to adjust dose
Elimination half-life time, h	4–6	20–22	11	13–17	25–30	12
ACE2 activity	No	No	No	No	Yes	Yes
Tissue affinity	Low	High	Moderate	Moderate	High	Low
ACEIs, angiotensin-converting enzyme inhibitors.						

Table 2. Pharmacological characteristics of ARBs

	Valsartan	Losartan	Candesartan	Irbesartan	Telmisartan	Olmesartan
eGFR >30 mL/min/1.73 m ²	No need to adjust dose	No need to adjust dose	No need to adjust dose	No need to adjust dose	No need to adjust dose	No need to adjust dose
eGFR <30 mL/min/1.73 m ²	Lack of data	No need to adjust dose	Starting from 2 mg with caution	For ESRD, 75 mg/d should be considered as the initial dose	The recommended initial dose is 20 mg/d	No need to adjust dose
Hepatic insufficiency	No need to adjust dose	50% initial dose	Start with small doses	No need to adjust dose	It is forbidden for biliary obstructive disease and severe liver function impairment	No need to adjust dose
Elimination half-life time, h	5–9	6–9	9–13	11–15	>20	12–18
ACE2 activity	No	Yes	No	No	Yes	Yes
Selectivity of AT1/AT2 receptor	High	Low	Moderate	Moderate	Low	High
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.						

than single RAS blockade. Many subsequent meta-analyses confirmed the hypothesis that dual RAS blockade was more effective in regulating albuminuria than single RAS blockade. For patients to obtain additional benefits, it is necessary to choose individualized treatments [34, 36]. However, for possible safety reasons, such as high potassium and adverse reactions of renal function injury, the VA NEPHRON-D study was stopped prematurely, which led many nephrologists to abandon the dual RAS blockade strategy.

However, the combining of RASis for multitarget therapy may improve the efficiency of RAS blockade and the antiproteinuric effect and reduce the incidence of adverse reactions while retaining their unique renal protection mechanisms in theory. A review published in *Nature Reviews Nephrology* titled “Welcome Back” clearly proposed reconsideration of the dual blockade strategy for RAS [37]. The CALM study reviewed previous clinical studies and reported the benefits of dual blockade of RAS in humans for the first time. Although early clinical studies showed a higher incidence of adverse reactions, these studies included older groups, and most patients had cardiovascular complications, which placed these patients in high-risk groups for the use of RASis. For patients who are younger with no cardiovascular complications, a systematic evaluation is lacking [38]. Esteras et al. [39] systematically evaluated the risks of hyperkalemia, hypotension, and impaired renal function with the combination of 2 types of RASis and summarized that the door was left open to dual blockade therapy individualization although renal function, electrolytes, and blood pressure should be closely monitored [39]. Another study investigating a combination of RASi drugs from German sanatoriums derived the same conclusion: the risks and benefits of dual RAS blockade must be evaluated on an individual level, and strict safety inspection and subsequent regulatory actions are key to ensure the safe use of drugs [40]. These studies show that the adverse reactions may be effectively avoided via better patient education and prescribing skills, and should not be used as a reason to simply deny dual blockade strategy.

In the latest systematic review and meta-analysis of dual RAS blockade for the treatment of heart failure and renal insufficiency, 34,131 patients were selected from 12 of 2,258 articles. The hospitalization and adverse events, including all-cause death, heart failure, and cardiovascular death, in patients receiving dual RAS blockade, were investigated. Compared to monotherapy, dual RAS blockade reduced the death risk ratio of all individuals, significantly reduced the hospitalization

rate of heart failure and cardiovascular death, reduced the hospitalization rate of heart failure and cardiovascular death in patients with renal disease, and reduced the cardiovascular hospitalization rate, hyperkalemia, and hypotension. These results suggest that dual RAS blockade reduced the risk of cardiovascular death and hospitalization for heart failure but did not increase the risk of renal damage. However, specific adverse events must be monitored during treatment [41]. In a RCT, Saglimbene et al. [42] reported that patients may tolerate ARBs better than ACEIs. However, the data reported in this article showed no differences in mortality or renal outcomes with ACEIs or ARBs as dual or monotherapy in patients with albuminuria and other cardiovascular risk factors.

Individualized Drug Selection According to Pharmacological Characteristics

Instead of debating whether ACEIs or ARBs are the better drug, clinicians should focus on understanding the pharmacological characteristics of each drug and provide individualized medication. The physicochemical properties and pharmacological characteristics of RASis, including the drug half-life time, antihypertensive ability, tissue affinity, metabolic pathway, and interactions with other drugs, are quite different. Only by understanding their basic characteristics can we make individualized and accurate drug choices for patients. For example, given their pharmacological characteristics, the early developed drugs captopril and fosinopril should not be used for dual RAS blockade because of their low-tissue affinity, RAS escape, and inability to increase ACE2 activity. Subsequently developed drugs, such as perindopril, overcome the aforementioned shortcomings and are good drug candidates for dual RAS blockade because of the reduced probability of adverse reactions. For ARBs, we can focus on the selectivity of AT1/AT2 receptors, half-life time, metabolic pathways, and compatibility with ACEIs. Only via a reasonable combination of ACEIs and ARBs can we maximize their strengths, avoid weaknesses, and achieve the purpose of dual RAS blockade. We provide a summary of the characteristics of clinical ACEIs and ARBs in Tables 1 and 2. After weighing their pharmacological characteristics, we think that perindopril/olmesartan may be a better option for future RCT study of dual RAS blockade strategy.

Conclusion

The optimal RAS blockade should be defined by the maximum blocking effect that does not cause adverse reactions, such as hyperkalemia, hypotension, or renal failure. Therefore, it is time to reconsider the strategy of combination therapy because this strategy may be an effective tool to safely reduce or prevent the progression of cardiorenal diseases and provide individualized dosing and tolerance. The abandonment of this plan because of adverse reactions that may be avoided via technical means is logically similar to stop eating for fear of choking. The other good news is that the newly developed RASi have superior pharmacological characteristics, such as better tissue permeability, a better capacity to regulate ACE2, and a better trough-to-peak ratio and half-life time, which are likely to compensate for the shortcomings of earlier drugs to a large extent. Therefore, the use of newly developed RASi drugs in new head-to-head RCTs to reevaluate the dual RAS blockade strategy is very important. If we can achieve individualized treatment via careful dose adjustment and the reasonable selection of patients, combined treatment with RASi could become an effective tool for cardiorenal protection.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mei Mei, Zulian Zhou, Qian Zhang, Yi Chen, Hongwen Zhao, and Bingbing Shen reviewed the literature and wrote the manuscript.

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