

Dual Blockade of the Renin-angiotensin-aldosterone System in Type 2 Diabetic Kidney Disease

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Abstract

Objective: To examine the efficacy and safety of dual blockade of the renin-angiotensin-aldosterone system (RAAS) among patients with type 2 diabetic kidney disease.

Data Sources: We searched the major literature repositories, including the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE, for randomized clinical trials published between January 1990 and October 2015 that compared the efficacy and safety of the use of dual blockade of the RAAS versus the use of monotherapy, without applying any language restrictions. Keywords for the searches included “diabetic nephropathy,” “chronic kidney disease,” “chronic renal insufficiency,” “diabetes mellitus,” “dual therapy,” “combined therapy,” “dual blockade,” “renin-angiotensin system,” “angiotensin-converting enzyme inhibitor,” “angiotensin-receptor blocker,” “aldosterone blockade,” “selective aldosterone blockade,” “renin inhibitor,” “direct renin inhibitor,” “mineralocorticoid receptor blocker,” etc.

Study Selection: The selected articles were carefully reviewed. We excluded randomized clinical trials in which the kidney damage of patients was related to diseases other than diabetes mellitus.

Results: Combination treatment with an angiotensin-converting enzyme inhibitor supplemented by an angiotensin II receptor blocking agent is expected to provide a more complete blockade of the RAAS and a better control of hypertension. However, existing literature has presented mixed results, in particular, related to patient safety. In view of this, we conducted a comprehensive literature review in order to explain the rationale for dual blockade of the RAAS, and to discuss the pros and cons.

Conclusions: Despite the negative results of some recent large-scale studies, it may be immature to declare that the dual blockade is a failure because of the complex nature of the RAAS surrounding its diversified functions and utility. Further trials are warranted to study the combination therapy as an evidence-based practice.

Key words: Diabetes Mellitus, Type 2; Diabetic Nephropathies; Dual Blockade; Renin-angiotensin-aldosterone System

INTRODUCTION

Diabetes mellitus is a serious global public health problem. In 2010, the worldwide diabetic population had reached 284 million and is expected to reach 438 million by 2030.^[1] A study conducted in 2010 by the China Noncommunicable Disease Surveillance Group^[2] estimated a national prevalence of diabetes of 11.6% with prediabetes occurring among 50.1% of the Chinese adults.

Approximately, 30–40% of diabetic patients will develop kidney disease, which might lead to end-stage renal disease (ESRD).^[3] Proteinuria is a primary characteristic of type 2 diabetic kidney disease (DKD) and an independent risk factor for ESRD.^[4-6] As demonstrated in recent studies, blockade of the renin-angiotensin-aldosterone system (RAAS)

is effective in blood pressure (BP) control, as well as reducing proteinuria, slowing the progression of kidney disease^[7-9] and helping to prevent cardiovascular disease (CVD).^[10-12] Current guidelines have recommended RAAS blocker medications as a preferred agent for the treatment of kidney diseases,^[13,14] as a reduction of proteinuria may further reduce the risk of disease progression.^[15] Treatment with a combination of an

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angiotensin-converting-enzyme inhibitor (ACEI) and an angiotensin II (AII)-receptor blocker (ARB) has formed the basis for dual blockade of the RAAS.^[16]

That said, recent trials of dual blockers have not rendered clear support for the use of dual blockers, given a variety of methodological concerns, conflicting results, and the occurrence of adverse events. Without a systematic review of existing studies, it is unclear whether these conflicting findings have nullified the combination theory or warranted further studies. This review describes the rationale for dual blockade of the RAAS, gives possible explanations to the conflicting results, and discusses the pros and cons of this treatment approach based on clinical research evidence.

RATIONALE FOR DUAL BLOCKADE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

RAAS is a key in regulating BP [Figure 1]. The mechanism can be described as follows. First, the renin enzyme initiates a cascade reaction, followed by the production of protease in the juxtaglomerular apparatus of the kidney. Protease then converts the angiotensinogen to an inactive substance, angiotensin I (AI), which is further converted to the vasorelaxant substance, AII, by angiotensin-converting enzymes (ACE) produced mostly in the lungs. The AII

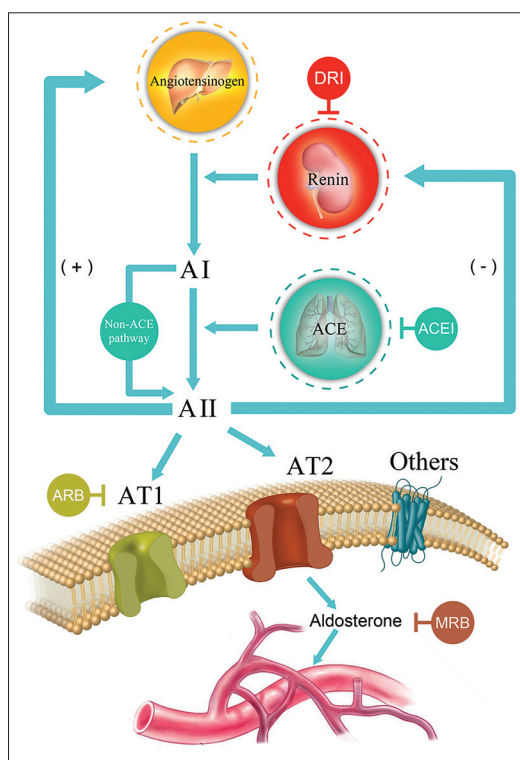


Figure 1: Renin-angiotensin-aldosterone system and the targets for therapeutic interventions in the renin-angiotensin-aldosterone system cascade. AI: Angiotensin I; AII: Angiotensin II; AT1: Type 1 angiotensin II receptor; AT2: Type 2 angiotensin II receptor; ACE: Angiotensin-converting enzyme; DRI: Direct renin inhibitor; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; MRB: Mineralocorticoid receptor blocker.

promotes the release of aldosterone by binding to the receptor, which directly induces renal vasoconstriction, and increases myocardial contractility and water-sodium retention. All these reactions increase the circulating blood volume and maintain the stability of BP. Finally, inducing negative feedback among the juxtaglomerular cells, the sodium reabsorption completes the canonical pathways.

On the other hand, ACEI competitively blocks the action of ACE and thus the conversion of AI to AII, thereby reducing circulating and the local levels of AII. It further decreases aldosterone and vasopressin secretion and sympathetic nerve activity. However, the ARB produces a selective, dose-dependent blockade of the AT1 receptor, independently of the different pathways of AII generation that do not reduce AII concentrations. These interventions can reduce glomerulosclerosis, tubulointerstitial fibrosis, albuminuria, and loss of glomerular filtration rate (GFR), as demonstrated in animal experimental models and/or human randomized clinical trials (RCTs).

However, the RAAS is complicated in that alongside the pathways mentioned above; the AII can be activated by autocrine and paracrine pathways in local organs. Because aldosterone is related to tissue and vascular remodeling, the RAAS induces kidney damage by proinflammatory and oxidative reactions. These non-ACE pathways may partly explain the aldosterone “escape” phenomenon, i.e., both the angiotensin and aldosterone levels that are initially lowered by ACE inhibition eventually return to the baseline level in the long run.

The benefits of monotherapy using an RAAS blocker have been demonstrated in the cardiovascular and renal systems, and in overall prognosis. However, there is value in the study of whether a combination treatment, or dual blockade of the RAAS, has the potential to yield additional benefits. The combination theory arises primarily for two reasons. Monotherapy can result in an incomplete blockade of AI or renin, and the “escape” phenomenon of AII or aldosterone.^[17-20] Moreover, many DKD patients have a high residual level of proteinuria after using RAAS blockers; the use of an additional RAAS blocker may further reduce proteinuria to improve the long-term outcome.^[21-24]

Ménard *et al.*^[25] first proposed the potential additive or synergistic effects of ACEI and ARB through a mouse model. With the goal of maximizing the antagonistic effect on the escape phenomenon, supplementing ACEI with an ARB has been expected to provide a more complete blockade of the RAAS and enhance the BP control.

CLINICAL EVIDENCE FOR DUAL BLOCKADE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Effect of dual blockade of renin-angiotensin-aldosterone system on blood pressure

Current studies show that combination therapy for DKD patients with hypertension has a dose-response relationship

in lowering BP. That is, larger doses of dual blockers may lead to larger effects in the BP control.

In a 2005 meta-analysis, Doulton *et al.* concluded that use of dual blockers in hypertensive patients reduced BP by 4.7/3.0 mm Hg (1 mm Hg = 0.133 kPa), contrasting with a 3.8/2.9 mm Hg reduction achieved with ACEI/ARB monotherapy treatment. Further subgroup analysis showed an even more effective reduction – by 6.8/4.7 mm Hg – in the patients with diabetes.^[26]

As shown in a more recent meta-analysis, combination therapy outperforms monotherapy in reducing the systolic BP (SBP), diastolic BP, and mean arterial pressure, or in controlling the rate of BP in chronic kidney disease (CKD).^[27] Some studies have reached similar conclusions.^[28,29]

Some other trials, however, have differed. Fernandez Juarez *et al.*^[30] randomly assigned patients with type 2 diabetic nephropathy to treatment with lisinopril, irbesartan, or a combination of the two (1/2 dose of each). After a median follow-up of 32 months, they failed to find benefits of the combination vis-a-vis monotherapy in the BP control. This conclusion was concurred in a study of Asian type 2 patients with nephropathy.^[31]

In a recent trial on 1448 patients with type 2 diabetes, all participants initially received losartan and were then randomly assigned to two groups, to additionally receive lisinopril or placebo.^[32] The combination therapy group received losartan and lisinopril at a dose of 100 mg/d and 10–40 mg/d, respectively, while the monotherapy group received only losartan at the same dose and placebo. After a median follow-up of 2.2 years, the combination therapy group had a slightly lower BP than the monotherapy group (within 2 mm Hg).

It is noted that most of these studies drew their conclusions based on short-term observations; long-term evidence remains elusive. Furthermore, researchers have not yet determined the optimal dose of dual blockers – the antihypertensive effect is similar when both agents are prescribed at half of their routine mono use dosage.^[30,31] It seems necessary to study titration to the highest or the next-highest dose to maximize the dual effect.

Effect of reduction in proteinuria using dual blockade of the renin-angiotensin-aldosterone system

The effect of reducing proteinuria by using ACEI or ARB alone has been established among the type 2 DKD patients;^[7-9] at the highest tolerable dosage, the effect is even more pronounced among the patients whose level of proteinuria is at least 300 mg/d, independent of BP control.^[6] ACEI or ARB agents are thus the first-line choices for DKD patients with hypertension.

Some early studies^[28,31,33-41] suggested that ACEI combined with ARB could further reduce proteinuria and result in about 20% reduction in albuminuria.^[16,42-44] However, many of these studies were inadequately powered with small sample sizes or with insufficient length of follow-up.

A meta-analysis showed that as compared with ACEI or ARB alone, combination therapy results in 20–30% additional reduction in proteinuria.^[16,45,46]

The “Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint” trial (ONTARGET) involved the largest cohort of patients to date ($n = 25,620$).^[47] Patients were assigned to receive telmisartan alone, ramipril alone, or a combination of both. After 56-month follow-up, it was reported that the risks of development and progression of microalbuminuria and macroalbuminuria were lower for those receiving combination therapy (hazard ratio [HR] = 0.88, $P = 0.003$ and $HR = 0.76$, $P = 0.019$, respectively), compared to the ramipril alone treatment.

Safety and prognosis of dual blockade of the renin-angiotensin-aldosterone system

Due attention must be paid to the evaluation of the risks and prognosis of using dual blockade of the RAAS under contested conditions. Current hypertension treatment guidelines^[48] do not recommend a therapy that combines ACEI and ARB, in consideration of increased risks of adverse events such as hyperkalemia and hypotension.

Among the DKD patients, however, proteinuria is usually comorbid with hypertension. The effects of reduction of proteinuria theoretically correlate with renal function and CVD. Thus, control of proteinuria can result in parallel benefits to all conditions. These potential benefits cannot be sought without consideration of the associated treatment risks, however.

A meta-analysis of dual blockade among the DKD patients found an only slightly increased incidence of hyperkalemia; the increase in the level of potassium was limited to 0.2 mmol/L, and the decrease in renal function to 3 ml/min.^[29] Unfortunately, most similar studies used either proteinuria or albuminuria alone as the end point, with follow-up <4 months, and were not powered to assess potential long-term effects.

The ONTARGET study did not find additional benefits of the combination therapy in reducing the mortality rate and risk of cardiovascular events^[47] but rather a significantly higher incidence of hyperkalemia, hypotensive symptoms, and over declined estimated GFR (eGFR) than treatment with ramipril or telmisartan alone. Moreover, the decline of eGFR and dialysis (especially acute dialysis) was higher than that of monotherapy group.^[47]

The Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) clinical trial assessed the safety and efficacy of the combination of losartan with lisinopril in diabetes patients with progression of kidney disease.^[32] This study was suspended for safety concerns: Among 148 patients with a median follow-up of 2.2 years, combination therapy increased the risk of hyperkalemia and acute kidney injury.

In terms of kidney disease prognosis, the existing studies have provided mixed results on reduction of proteinuria. The Olmesartan Reducing Incidence of ESRD in Diabetic

Nephropathy Trial enrolled type 2 diabetic patients who were receiving ACEI and ARB. The evaluation indicators consisted of reduced BP, proteinuria, and the rate of decline of the serum creatinine reciprocal ($1/sCr$). *Post-hoc* analysis found no significant difference between the combination therapy group and monotherapy group in cardiovascular and renal outcomes.^[49]

However, the newest network meta-analysis^[50] evaluated the prognosis of dual blockade of the RAAS, the researchers did a network analysis of randomized trials from around the world comparing BP lowering agents in adults with DKD and found that ESRD was significantly less likely after dual treatment with ACEI plus ARB (odds ratio = 0.62, 95% confidence interval = 0.43–0.90). These results fully confirm the possibility of improving prognosis when using combination therapy.

Makani *et al.*^[51] analyzed all RCTs between January 1990 and August 2012 to compare treatment with dual blockers of RAAS to monotherapy. The authors examined data of studies measuring long-term efficacy for at least 1 year, and with a sample size of at least 50 participants. Although dual therapy was associated with an 18% reduction in hospitalization for heart failure as compared with monotherapy, it was also associated with a 55%, 66%, and 41% increase in the risks of hyperkalemia, hypotension, and renal failure, respectively. These outcomes introduce the caveat that dual RAAS blockade treatment should be used with abundant caution in clinical practice.

Use of dual blockade for selected populations

Most of the existing large-scale studies limited enrollment to those patients with BP <160/100 mm Hg, while in clinical practice the BP of DKD patients is frequently higher than this cut-off value. However, because of the related health risks such as CVD and increased mortality, the strategy of combination antihypertensive treatment is already widely adopted for this population.

Wong *et al.*^[52] designed a case-control study that assessed the prognosis of the dual blockade in patients with BP below and above 160/100 mm Hg. After a median follow-up of more than 3.7 years, among patients with BP lower than 160/100 mm Hg, the incidence of a decline of more than 20 ml/min in eGFR was higher than that in the monotherapy group; among patients with BP higher than 160/100 mm Hg, however, the opposite was observed. While this finding does not necessarily nullify the risks associated with ACEI/ARB combination reported in recent studies such as ONTARGET, it merits further exploration.

OTHER ADVANCES IN DUAL BLOCKADE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

New RAAS blockers are being developed and introduced into clinical practice. Apart from the traditional ACEI/ARB combination therapy, combination treatment of mineralocorticoid receptor blockers (MRB) or direct renin

inhibitors (DRI) with ACEI or ARB therapy has emerged recently. For example, among the 200,000 patients who were treated with dual blockade of the RAAS, more than 8% of them used ACEI or ARB in combination with a DRI.^[53] However, the long-term efficacy and safety of such treatment has not been well supported so far.

Mineralocorticoid receptor blockers and angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker combination

Mineralocorticoid receptor blocking agents reduce the sodium and water reabsorption along epithelial sites, as well as cardiovascular and renal fibrotic injury at nonepithelial sites by inhibiting binding of aldosterone to mineralocorticoid receptors.^[54]

Krum *et al.* found that adding eplerenone (50–100 mg daily) to ACEI or ARB in patients with poor BP control may contribute to a better SBP control with no significant difference in adverse events as compared to eplerenone alone.^[55] Meanwhile, Epstein *et al.* concluded that eplerenone in combination with enalapril reduced albuminuria more than enalapril alone in patients with diabetes and did not result in any significant increase in serum potassium levels.^[37]

Although an early review of MRB combined with ACEI or ARB showed that these pairings can significantly reduce proteinuria without increasing the incidence of hyperkalemia or impairing renal function, the authors acknowledged that the results reported were insufficient to conduct a meta-analysis because of the impaired reliability. This study did not constitute a reasonable basis for endorsing the combination of MRB with ACEI or ARB as a conventional treatment strategy.^[56]

Recently, Bakris *et al.* evaluated the safety and efficacy of the novel nonsteroidal MRB finerenone for 90 days among patients with diabetes and high or very high albuminuria who received an ACEI or an ARB.^[57] It was found that the addition of finerenone compared with placebo resulted in some improvement in albumin-to-creatinine rate (ACR). However, the short duration of the study did not allow assessment of any long-term effects of finerenone.

The most recent Cochrane analysis on this topic concluded that MRB may reduce proteinuria and BP among patients with mild to moderate CKD, who were treated with ACEI or ARB, but may also increase the risks of hyperkalemia and gynecomastia. It is unclear, however, how this may further influence the risks of CVD and ESRD.^[58]

Direct renin inhibitors and angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker combination

DRI agents can antagonize the ACEI-, ARB-, or even MRB-induced renin increase by blocking renin activities.^[59,60] The result of using DRI and other RAAS blockers in combination has been reported in a few small-scale studies,^[61] which suggested that efficacy does not significantly differ between DRI and ACEI or ARB alone though a combination treatment may have additional benefits of reducing proteinuria.

The Aliskiren in the Evaluation of Proteinuria in Diabetes trial was one of the largest studies that evaluated the value of the DRI and aliskiren among DKD patients.^[42] In this study, 599 type 2 DKD patients who received losartan (100 mg/d) were assigned to either the 6-month aliskiren treatment group (150 mg/d for the first 3 months, then 300 mg/d) or the placebo group. At 3 months posttreatment, the aliskiren group experienced an 11% decrease of ACR as compared with placebo group, and an additional 20% decrease when the dose of aliskiren was increased to 300 mg/d. No difference in the rates of adverse events were found, nor was a delay in progression of renal failure.

The Aliskiren Trial in Type 2 Diabetes Using Cardio-renal Endpoints study investigated whether the use of aliskiren would reduce cardiovascular and renal events among patients with type 2 diabetes and CKD.^[62] A total of 8561 patients were randomly assigned to the aliskiren (300 mg/d) or placebo group, in addition to receiving an ACEI or ARB. Unfortunately, the trial was stopped after a median follow-up of about 32.9 months following the results of the second efficacy analysis. They suggested that although there was a greater ACR decrease in the combination therapy, the incidence of hypotension and hyperkalemia events was higher than that in the placebo group. Therefore, the author recommended against the use of this combination therapy among type 2 patients with CKD or CVD.

ANALYTICAL ISSUES WITH STUDIES OF DUAL BLOCKADE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Even most small-scale clinical studies that used proteinuria as the end point demonstrated the additional effect of the dual blockade on reducing proteinuria and decreasing BP in DKD patients, findings from more recent large-scale studies, however, have not confirmed such results.

The most authoritative source of evidence, the ONTARGET study, does not exhibit ideal reliability. Participants in the ONTARGET study had near normal levels of albuminuria or microalbuminuria, and insignificant increases in BP. The benefits of dual blockade therapy, however, have occurred only in patients with overt proteinuria,^[7-9,63] thus the populations are not comparable. In the *post-hoc* analysis of ONTARGET, the deleterious effects were only experienced by patients with nondiabetes and normal BP, who had no indications for ACEI or ARB treatment.^[64] Additionally, the selection of endpoints in the study was very debatable. Specifically, the researchers found that the incidence rate of dialysis (including acute dialysis) could not fully reflect long-term treatment effects. After excluding the rate of acute dialysis events, the actual incidence of dialysis was low, exhibiting no significant differences. In addition, the declines in eGFR ($\text{ml}\cdot\text{min}^{-1}\cdot\text{year}^{-1}$) were 0.27 (ramipril), 0.44 (telmisartan), and 0.53 (combination) where age bias could not be eliminated (the age-related decline was 0.6–1.1).^[65] Had the trial continued, the possibility of

additional risk of adverse events could have been avoided, as the incidence of hyperkalemia was low with combination therapy.

The results of the VA NEPHRON-D study have further discredited the combination therapy. However, there were several issues with this study. First, the average age of the study population was over 64 years, and the average SBP was <140 mm Hg (no subgroup analyses were conducted). These patients failed to meet the condition of intensive treatment of BP due to much increased risks of adverse events, irrespective of the type of the antihypertension drugs. Subsequent addition of ACEI to ARB may result in a higher incidence of adverse events.^[66] Although combination therapy may increase the risk of hyperkalemia, the level of potassium can be reduced via nondialysis methods before resorting to acute dialysis, and the potential benefit of reducing the risk of the progression of ESRD ($HR = 0.66$, $P = 0.07$) was the more exciting finding in this study.

Finally, the proper dosage of the dual blockade is still debatable. Almost, all the early studies suggested that in monotherapy a supramaximal dose might idealize the reduction of albuminuria.^[67-71] As shown in the existing clinical studies, however, the choice between the maximal dose and half-maximal dose in combination therapy represents a trade-off between the effect of reducing proteinuria and the risk of adverse events. Thus, the best balance between benefits and safety is the key issue for future studies.

In summary, based on our reviews of some large trials such as ONTARGET, ALTITUDE, or VA NEPHRON-D we have found that these trials have some obvious flaws in study designs that should be factored in when forming clinical medication guidelines. We tend to believe that age, the grade of hypertension, the clinical stage, and the quantity of proteinuria are the important considerations in selecting drugs which previous studies precisely lack. The use of dual blockade of the RAAS may not be a contraindication in DKD patients and may be suitable for the early DKD patients with younger and higher stress levels.

CONCLUSION

Despite the negative results of some recent large-scale studies, it is unclear that the concepts of the dual blockade are a failure. The complexity of the RAAS determines the diversity of its blockers, influencing the utility of dual blockade. Further trials are needed to study the combination therapy as an evidence-based practice.

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Conflicts of interest

There are no conflicts of interest.

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