

## Is There Added Value to Adding ARB to ACE Inhibitors in the Management of CKD?

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### ABSTRACT

Antagonism of the rennin-angiotensin-aldosterone-system (RAAS) decreases BP and reduces proteinuria in chronic kidney disease. BP is decreased approximately 5 mmHg when angiotensin II blockers are added to angiotensin-converting enzyme (ACE) inhibitors and is less than typically seen when other agents are added to existing ACE inhibitor regimens. Dual RAAS blockade results in additional reduction in proteinuria. Clinically insignificant increases in hyperkalemia and modest decreases in GFR occur. Data regarding long-term preservation of renal function are lacking. We suggest dual RAAS blockade be used in patients with chronic kidney disease with residual proteinuria on maximal ACE inhibitor or angiotensin II blocker therapy, anticipating additional data with ongoing trials.

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The role of the renin-angiotensin-aldosterone-system (RAAS) in processes that lead to heart disease, stroke, and kidney failure took a great leap forward when it became possible to antagonize this system. This work began with the peptides saralasin and teprotide, which, although available only intravenously (thus only short term), nonetheless provided proof of concept that the RAAS exerted a significant role in the regulation of BP and the mediation of target-organ damage. Thereafter, the first orally active angiotensin-converting enzyme (ACE) inhibitor, captopril, appeared in the summer of 1981. This drug made long-term clinical trials feasible in humans. In the intervening years, it has become clear that, in addition to BP regulation, the RAAS participates in inflammatory, thrombotic, and other vasculotoxic processes, which ultimately mediate target-organ damage attributable to atherosclerosis. As a result, the RAAS is a pivotal target for manipulation in primary and secondary prevention efforts to reduce the devastating ef-

fects of heart attack, heart failure, stroke, and further reduction in kidney function, particularly when increased amounts of urinary protein are present.

The complexity of the RAAS continues to unfold despite more than 100 yr of recognition of importance of the system by Tigerstedt and Bergman.<sup>1</sup> Currently, it is possible to block the system in three places. These places are at the level of ACE itself, by competitive blockade of the angiotensin II receptor site and through direct inhibition of renin activity. Another point of blockade includes interruption of aldosterone (whose production and secretion are stimulated by angiotensin II) effect through selective mineralocorticoid blockade. We do not address further the addition of aldosterone or renin inhibitors to dual therapy with ACE inhibitor and angiotensin II receptor blocker (ARB) treatment.

A substantial portfolio of human clinical trials, first in heart failure<sup>2</sup>; followed by type 1 diabetic nephropathy<sup>3</sup>; and then extending to coronary artery dis-

ease, patients with high cardiovascular risk, general hypertension, and secondary stroke prevention attest to the benefit of ACE inhibitor and ARB drugs when applied to patients with these diseases. It was soon noted that there is “ACE escape” in some patients<sup>4</sup> in which both angiotensin II and aldosterone levels return to pretreatment values despite the presence of suppressed ACE activity. When the ARB class was introduced in spring of 1995 with the approval of losartan, an oft-repeated question arose pondering whether additional benefit would evidence when an ARB was added to an existing ACE inhibitor treatment regimen. Arguing from the ACE escape phenomenon, the rationale for blocking rogue angiotensin II produced by chymases and other non-ACE inhibitor-suppressible systems provided clinical plausibility for benefit from dual RAAS blockade. In the rest of this clinical commentary, we focus our thoughts on aspects of this important clinical query with respect to patients with chronic kidney disease (CKD).

CKD affects millions of adults in the United States. Progressive loss of kidney

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function results in over 100,000 cases per year of ESRD in the United States alone. Hypertension and proteinuria are among the most important factors involved in the progressive loss of kidney function. Blockade of the RAAS in patients with CKD not only decreases BP but also reduces urine protein losses in a manner that seems to exceed that expected from BP reduction alone. Recognizing the principal agent classes used to accomplish RAAS blockade, ACE inhibitors and ARB, work on fundamentally different aspects of the RAAS interest in their combined benefit was first piqued with a report of additive antiproteinuric effect when losartan was added to an ACE inhibitor in eight normotensive patients with IgA nephropathy and 1 to 3 g/d proteinuria.<sup>5</sup> Dual suppression of the RAAS by combining ACE inhibitors and ARB has become increasingly common since this study was published. In the next sections, we look at the BP, antiproteinuria, safety, and outcome efficacies of this approach in CKD.

## BLOOD PRESSURE

At the onset, we think there are three points to make about the value of dual RAAS blockade in CKD. First, most studies of this question use submaximal dosages of an ACE inhibitor or an ARB, thus leaving unaddressed the issue of how much additional blockade an ARB addition would have if maximal ACE inhibitor dosing were used. Second, many studies enroll small numbers of patients, are short term ( $\leq 3$  mo), and focus on surrogate outcomes such as BP and proteinuria instead of long-term issues such as velocity of kidney function loss and need for dialysis or transplantation. Third, CKD is a heterogeneous set of disorders, and there are likely to be variations in responsiveness to dual RAAS blockade when diabetic nephropathy is compared with, for example, IgA nephropathy or hypertensive nephrosclerosis.

The early work of Gansevoort *et al.*<sup>6</sup> showed a phenomenon that has generally been repeated with respect to the an-

ti-hypertensive benefit of dual RAAS blockade. In that study, enalapril was given alone at dosages of 10 then 20 mg/d and compared with losartan 50 and 100 mg/d in 11 patients without diabetes and with proteinuria and CKD. There was significant additional antiproteinuric effect but very little BP decrease at the higher compared with the lower drug dosages.

In meta-analyses that sought to combine existing studies of addition of ARB to existing ACE inhibitor therapy, there was general agreement that the amount of additional antihypertensive effect when the ARB was added to an ACE inhibitor was usually approximately  $\leq 5$  mmHg (systolic or diastolic) and often less when maximal dosages of the ACE inhibitor were used before the addition of the ARB.<sup>7,8</sup> This amount of BP reduction was usually less than the typical additive amounts noted when a different antihypertensive agent class such as a diuretic or a calcium channel blocking drug was added to an ACE inhibitor.

## PROTEINURIA

Proteinuria reduction and kidney function preservation—renoprotection—have convincingly been shown in both diabetic and nondiabetic CKD with proteinuria using ACE inhibitors or ARB alone.<sup>3,9–11</sup> These renoprotective effects are most apparent when there is  $>1$  g/d proteinuria present, particularly in nondiabetic CKD, and when the average dosage of the RAAS-blocking drug is close to the maximum proposed by the manufacturer.

The meta-analysis by MacKinnon *et al.*<sup>8</sup> showed an additional 440 mg/d proteinuria reduction when ARB were added to ACE inhibitors. The decrease in proteinuria with dual RAAS blockade was larger in nondiabetic CKD (mean reduction 582 mg/d; 95% confidence interval 371 to 793 mg/d) compared with diabetic CKD (mean proteinuria reduction 210 mg/d; 95% confidence interval 4 to 336 mg/d). The only trial with long-term outcomes of dual RAAS blockade showing the value of added antiproteinuric effect is the COOPERATE (Combi-

nation treatment of Angiotensin-II Receptor blocker and Angiotensin-converting enzyme inhibitor in non-diabetic renal disease) study, which treated 263 Japanese patients with non-diabetic CKD.<sup>12</sup> Patients were randomly assigned to losartan 100 mg/d, trandolapril 3 mg/d, or both after their BP was controlled to  $<130/80$  mmHg systolic by non-RAAS-blocking drugs. To their credit, these investigators determined before randomly assigning patients that the dosage of trandolapril producing maximal antiproteinuric effects in Japanese without diabetes and with proteinuric CKD was 3 mg/d. After 3 yr, the benefits of trandolapril and losartan alone were similar, with 23% of patients receiving these agents progressing to the renal end points of doubling of serum creatinine or ESRD. Trandolapril and losartan both reduced baseline proteinuria by 40%. The dual RAAS blockade group had significantly lower kidney end point occurrences (11%) and approximately a 75% reduction in baseline proteinuria. To their additional credit, this group performed an ambulatory BP monitoring substudy (92 of 263 patients) and demonstrated the kidney function benefit from dual RAAS blockade was not due to better BP levels in those receiving combination trandolapril and losartan<sup>13</sup>; however, the ambulatory BP monitoring findings of the COOPERATE trial have been challenged, although no formal retraction has been issued to date.<sup>14</sup>

## SAFETY

There is an increased incidence of hyperkalemia when using dual RAAS blockade, but this seems to have minimal clinical impact. Potassium values generally increase by 0.11 to 0.20 mEq/L in the meta-analyses of dual RAAS blockade.<sup>7,8</sup> The effect on GFR from dual RAAS blockade is also modest and in the range of 1 to 4 ml/min.

## OUTCOME

Kidney studies here are lacking outside of the COOPERATE study. The recently

reported ON-TARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) trial randomly assigned 80 mg of telmisartan or 10 mg of ramipril or both to more than 25,620 patients with high cardiovascular risk or diabetes.<sup>15</sup> The primary end points of cardiovascular death, heart attack, stroke, and heart failure hospitalization were no different in any of the three groups. No significant safety issues emerged from dual RAAS blockade.

### CONCLUSIONS

Our impression of the benefit of dual RAAS blockade in the form of a report card is shown in Figure 1. The most recent meta-analysis of dual RAAS blockade points out the problems interpreting existing studies noting that patients often

are middle aged and have few comorbidities and, sometimes, as in the case of the COOPERATE study, that preselection is based on tolerance to an ACE inhibitor before randomization.<sup>16</sup> We think the current niche for dual RAAS blockade is of patients with residual proteinuria on maximal ACE or ARB therapy, anticipating more long-term data on such benefit from studies such as Preventing ESRD in Overt Nephropathy of Type 2 Diabetes (VALID; NCT00494715 at <http://clinicaltrials.gov>).

### DISCLOSURES

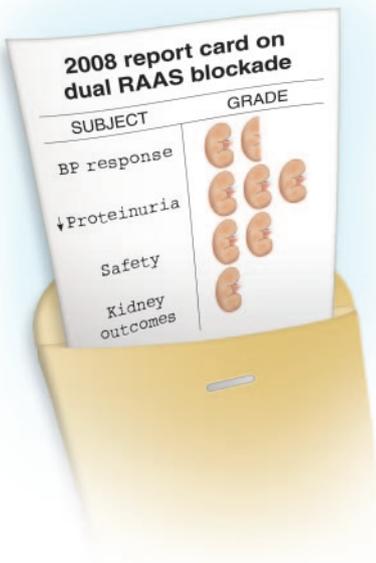
None.

### REFERENCES

1. Tigerstedt R, Bergman PG: Kidney and circulation. *Scand Arch Physiol* 8: 223–271, 1898
2. The CONSENSUS Trial Study Group: Effects of enalapril on mortality in severe congestive heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *Clin Nephrol* 316: 1429–1435, 1987
3. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *Clin Nephrol* 329: 1456–1462, 1993
4. Biollaz J, Brunner HR, Gavras I, Waeber B, Gavras H: Antihypertensive therapy with MK 421: Angiotensin II–renin relationships to evaluate efficacy of converting enzyme blockade. *J Cardiovasc Pharmacol* 4: 966–972, 1982
5. Russo D, Pisani A, Balletta MM, De Nicola L, Savino FA, Andreucci M, Minutolo R: Additive antiproteinuric effect of converting enzyme inhibitor and losartan in normotensive patients with IgA nephropathy. *Am J Kidney Dis* 33: 851–856, 1999
6. Gansevoort RT, De Zeeuw D, De Jong PE: Is the antiproteinuric effect of ACE inhibition mediated by interference in the renin-angiotensin system? *Kidney Int* 45: 861–867, 1994
7. Jennings DL, Kalus JS, Coleman CI, Manierski C, Yee J: Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy:

A meta-analysis. *Diabet Med* 24: 486–493, 2007

8. MacKinnon M, Shurraw S, Akbari A, Knoll GA, Jaffey J, Clark HD: Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: A systematic review of the efficacy and safety data. *Am J Kidney Dis* 48: 8–20, 2006
9. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, Ponticelli C, Ritz E, Zucchelli P: Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med* 334: 939–945, 1996
10. Brenner BM, Cooper ME, De Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001
11. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851–860, 2001
12. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T: Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): A randomised controlled trial. *Lancet* 361: 117–124, 2003
13. Nakao N, Seno H, Kasuga H, Toriyama T, Kawahara H, Fukagawa M: Effects of combination treatment with losartan and trandolapril on office and ambulatory blood pressures in non-diabetic renal disease: A COOPERATE-ABP substudy. *Am J Nephrol* 24: 543–548, 2004
14. Bidani A: Controversy about COOPERATE ABPM trial data. *Am J Nephrol* 26: 629–632, 2006
15. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C: Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 358: 1547–1559, 2008
16. Kunz R, Friedrich C, Wolbers M, Mann JF: Meta-analysis: Effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med* 148: 30–48, 2008



**Figure 1.** Estimates of demonstrated value of dual RAAS blockade. Scale is 1 kidney (modest) to 4 kidneys (outstanding) value; in the case of safety, 1 (none) to 4 (significant) represent concern over hyperkalemia or drug-related reduction in kidney function.