

Are Two Better Than One? Angiotensin-Converting Enzyme Inhibitors Plus Angiotensin Receptor Blockers for Reducing Blood Pressure and Proteinuria in Kidney Disease

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Learning Objectives:

1. To examine the epidemiology and pathophysiology of stroke and cardiovascular disease in the chronic kidney disease population
2. To evaluate the efficacy of current therapies for the treatment of cardiovascular risk in patients with renal disease
3. To apply new clinical insights for the identification and treatment of cardiovascular risk to improve outcomes for patients with chronic kidney disease

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Target audience: Physicians in internal medicine, nephrology, endocrinology, and other health care providers who are interested in the treatment of hypertension and kidney disease.

Categories: Proteinuria, blood pressure, renin-angiotensin system

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers each reduce proteinuria and blood pressure. Several studies have compared the antiproteinuric and antihypertensive effects of combination therapy with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with those of therapy with either drug class alone. This article reviews those trials as well as evidence suggesting a mechanism for the benefits observed with combination therapy.

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) interfere with the renin-angiotensin system (RAS) at different points. Combination therapy with both drug classes may block the RAS more effectively than treatment with either ACEI or ARB alone. This article reviews studies of dual RAS-blocking therapy with an ACEI and an ARB and the effects of such treatment on hypertension and proteinuria. The terms "dual class" and "combination therapy" in this article refer to use of two RAS-blocking agents (ACEI plus ARB treatment); the terms "single class" and "monotherapy" refer to use of one RAS-blocking agent. Patients in many studies received additional, non-RAS-blocking agents (*e.g.*, other antihypertensive medications, such as diuretics).

Effect of Dual-Class Therapy on Proteinuria

Several studies have compared the effect of single- and dual-class therapy on albuminuria or proteinuria (Table 1) (1–7). Most are parallel-group or crossover studies, and many are small (<25 patients) and short term (≤ 12 wk). Most studies summarized in Table 1 reported that the antiproteinuric effect of dual-class therapy was superior to that of ARB treatment alone (1,2,5). Some compared dual therapy with ACEI treatment only and not with ARB therapy; patients were first stabilized on an ACEI treatment then randomly assigned to additional treatment with an ARB or placebo (3,4). One study found

Table 1. Antiproteinuria effect of dual- versus single-class RAS blockade^a

Subjects	Design	Dual-Class > ARB?	Dual-Class > ACEI?
Mogensen <i>et al.</i> (1); <i>n</i> = 199; HTN, type 2 diabetes, microalbuminuria	Candesartan 16 mg/d versus lisinopril 20 mg/d versus the combination; 12-wk monotherapy, then 12-wk monotherapy or combination therapy; prospective, randomized, parallel-group, double-blind study	Yes ^b ; adjusted mean difference 34% (95% CI 3 to 55%; <i>P</i> = 0.04)	No ^b ; adjusted mean difference 18% (95% CI –20 to 44%; <i>P</i> > 0.20)
Jacobsen <i>et al.</i> (2); <i>n</i> = 20; type 1 diabetes, diabetic nephropathy	Benazepril 20 mg/d versus valsartan 80 mg/d versus the combination; 8-wk randomized, double-blind, placebo-controlled, crossover trial	Yes; 43% (95% CI 29 to 54%; <i>P</i> < 0.001)	Yes; 43% (95% CI 29 to 54%; <i>P</i> < 0.001)
Jacobsen <i>et al.</i> (3); <i>n</i> = 24; type 1 diabetes, diabetic nephropathy, >3 mo enalapril 40 mg qd	Enalapril 40 mg/d plus either placebo or irbesartan 300 mg/d; 8-wk randomized, double-blind, controlled, crossover trial	NA	Yes; 25% (95% CI 15 to 34%; <i>P</i> < 0.001)
Agarwal (4); <i>n</i> = 16; HTN, proteinuria, moderate CRF	Lisinopril 40 mg/d with and without losartan 50 mg/d or placebo; 1-mo randomized, controlled, crossover trial	NA	No (<i>P</i> = 0.89)
Campbell <i>et al.</i> (5); <i>n</i> = 24; HTN, CKD	Full-dosage monotherapy (benazepril 20 mg/d, valsartan 160 mg/d) versus half-dosage combination therapy (benazepril 10 mg/d, valsartan 80 mg/d); 8-wk randomized, prospective, open-label, crossover trial	Yes; –14.5% (<i>P</i> = 0.002)	Yes; –10.1% (<i>P</i> = 0.024)
Esnault <i>et al.</i> (6); <i>n</i> = 18; proteinuric (>1 g/d), 6 mo ramipril 5 mg/d	Full-dosage monotherapy (ramipril 10 mg/d, valsartan 160 mg/d) versus half-dosage combination therapy (ramipril 5 mg/d, valsartan 80 mg/d); 4-wk randomized, prospective, open-label, crossover trial	No ^c ; 5.1% (<i>P</i> = 0.70)	No ^c ; –0.80% (<i>P</i> = 0.17)
Doulton <i>et al.</i> (7); meta-analysis	Eight trials reporting effect of dual versus single RAS blockade on proteinuria ^d	Yes; 39% (95% CI 31 to 48%)	Yes; 30% (95% CI 23 to 37%)

^aLength of treatment in crossover studies refers to time on each therapy rather than total study length. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; CRF, chronic renal failure; HTN, hypertensive; RAS, renin-angiotensin system.

^bUrinary albumin-to-creatinine ratio.

^cUrinary protein-to-creatinine ratio.

^dProteinuria refers to albuminuria, proteinuria, or urinary albumin-to-creatinine ratio.

that a dual-class regimen resulted in a greater antiproteinuric benefit compared with ARB therapy but not compared with ACEI treatment (1).

Ineffectual drug dosage, severity of hypertension, and increased sodium intake are among the explanations for the negative findings. Several studies comparing single and dual RAS blockade used the same drug dosages typically used in monotherapy and combination regimens (1–4). Two small

crossover studies of patients with hypertension (5,6) compared full-dosage ACEI and ARB monotherapy with half-dosage combination RAS blockade and obtained different results, with only one study showing benefit from dual therapy. Authors of the study that showed no antiproteinuric benefit with dual-class RAS blockade noted that their study population had more severe hypertension (mean systolic BP >149 mmHg, despite treatment with ramipril 5 mg and a mean of 2.6 antihyperten-

sive agents) than did patients in the other investigation, whose BP was controlled with fewer than two antihypertensive agents and no RAS blockade (6). In addition, patients in the negative study excreted less sodium than those in the study that showed a positive finding (mean sodium excretion 129 to 168 versus 192 to 204 mEq/d) (5,6). Higher sodium intake can blunt the antiproteinuric effect of ACEI (8,9), which might account for the significant reduction in proteinuria when ARB treatment was added (6).

Severity of illness in the study population and ineffective medication dosages were cited as reasons for negative findings in another study (4). Patients were hypertensive (mean baseline seated BP 156/88 mmHg, with a mean of 3.13 antihypertensive medications) and had moderately advanced chronic renal failure (mean serum creatinine 2.0 mg/dl) (4). Patients had received a relatively high dosage of lisinopril (40 mg/d) for 3 mo before being randomly assigned to relatively low-dosage ARB therapy (losartan 50 mg/d) or placebo (4).

Dosage and Antiproteinuria Effect

Two small, short-term studies evaluated the effect of dosage on the antiproteinuric benefit of RAS blockade (10,11). One of these, a randomized, crossover study that examined normotensive, proteinuric (1 to 3 g/d) patients with IgA nephropathy ($n = 10$) for four 1-wk-long treatment periods, reported that antiproteinuric effects were dosage dependent only with dual-agent therapy (10). Doubling the dosages of enalapril and losartan during the single-agent phase of the study (from 10 to 20 mg/d for enalapril and from 50 to 100 mg/d for losartan) did not further reduce proteinuria when compared with treatment at lower dosages (10). However, combination therapy with each agent at the lower dosages produced significantly greater antiproteinuric effects than did single-agent treatment (0.72 ± 0.14 g/d; $P < 0.05$). Double-dosage combination therapy further increased antiproteinuric effects (0.57 ± 0.12 g/d versus lower-dosage dual therapy; $P < 0.05$) (10).

The other study investigated the optimal antiproteinuric dosages of lisinopril and losartan in each patient, then used those dosages in a combination therapy regimen. Participants did not have diabetes and had proteinuria (mean 4.5 g/d) and renal disease ($n = 9$), and all treatment periods lasted 6 wks (11). Antiproteinuric effects of both medications were dosage dependent. Maximum efficacy for losartan occurred at a median dosage of 100 mg/d; increasing the dosage to 150 mg/d yielded no additional benefit. Titration identified no such ceiling for lisinopril; the most effective antiproteinuric dosage varied with the individual, suggesting the importance of per-patient titration (11). A dosage of 40 mg/d was the highest dosage evaluated (11).

Combination treatment with the most effective dosages of each medication resulted in a significantly greater antiproteinuric response than did dosage-optimized monotherapy ($P < 0.05$ versus optimal monotherapy dosage of each medication) (11). Mean arterial pressure (MAP) was also reduced significantly more than with the optimal losartan dosage but did not differ significantly from that seen with the optimal lisinopril dosage (11). Optimal-dosage lisinopril lowered proteinuria and MAP significantly more than did optimal-dosage losartan ($P < 0.05$) (11).

Dosage and RAS Blockade

Part of the premise for evaluating ACEI and ARB in combination is the finding that ACEI therapy does not fully prevent angiotensin II formation and thus seems unable to achieve complete RAS blockade. A study in 20 healthy normotensive individuals questioned whether ARB dosages higher than those normally recommended for hypertension would achieve a degree of RAS blockade similar to that of ACEI plus ARB therapy (12). Authors compared once- and twice-daily dosing regimens of a short- and long-acting ARB (telmisartan and telmisartan, respectively) given alone and with an ACEI (lisinopril 20 mg/d). Patients received each regimen for 7 d (12).

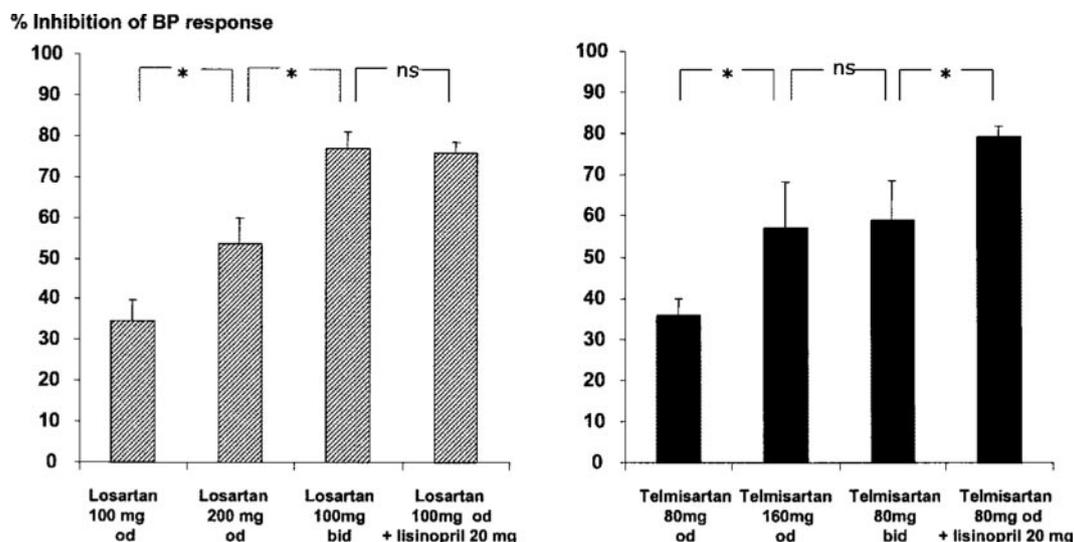


Figure 1. Summary of blockade of BP response to exogenous angiotensin I at trough in study groups ($n = 5$ to 10 according to study protocols). Data are means \pm SD; * $P < 0.01$. Reprinted from reference (12), with permission.

Table 2. BP-lowering effect of dual- versus single-class RAS blockade^a

Subjects	Design	Dual-Class > ARB?	Dual-Class > ACEI?
Mogensen <i>et al.</i> (1); <i>n</i> = 199; HTN, type 2 diabetes, microalbuminuria	Candesartan 16 mg/d versus lisinopril 20 mg/d versus the combination; 12-wk monotherapy, then 12-wk monotherapy or combination therapy; prospective, randomized, parallel group, double-blind study	Yes; 11.2/5.9 mmHg; <i>P</i> = 0.002, 0.003 ^b	Yes; 8.6/5.6 mmHg; <i>P</i> = 0.02, 0.005 ^b
Jacobsen <i>et al.</i> (2); <i>n</i> = 20; type 1 diabetes, diabetic nephropathy	Benazepril 20 mg/d versus valsartan 80 mg/d versus the combination; 8-wk randomized, double-blind, placebo-controlled, crossover trial	Yes; 7/7 mmHg; <i>P</i> = 0.04, <0.001 ^b	No (SBP); <i>P</i> = 0.06 Yes (DBP); <i>P</i> < 0.001 6/7 mmHg
Jacobsen <i>et al.</i> (3); <i>n</i> = 24; type 1 diabetes, diabetic nephropathy, >3 mo enalapril 40 mg/d	Enalapril 40 mg/d plus placebo or irbesartan 300 mg/d 8 wk randomized, double-blind, placebo-controlled, crossover trial	N/A	Yes; 8/4 mmHg; <i>P</i> = 0.002, 0.003 ^b
Stergiou <i>et al.</i> (13); <i>n</i> = 20; HTN, 6 wk benazepril 20 mg/d	Benazepril 20 mg/d plus placebo or valsartan 80 mg/d; 5-wk randomized, double-blind, crossover trial; change in 24-h ambulatory BP	N/A	Yes; 6.8/4.9 mmHg; <i>P</i> < 0.01
Agarwal (4) <i>n</i> = 16; HTN, proteinuria, moderate CRF	Lisinopril 40 mg/d with and without losartan 50 mg/d or placebo; 1-mo randomized, controlled crossover trial	N/A	No; 4.6/1.5 mmHg; <i>P</i> = 0.95, 0.59 ^b
Campbell <i>et al.</i> (5); <i>n</i> = 24; HTN, CKD	Full-dosage monotherapy (benazepril 20 mg/d, valsartan 160 mg/d) versus half-dosage combination therapy (benazepril 10 mg/d, valsartan 80 mg/d); 8-wk randomized, prospective, open-label, crossover trial ^c	No; −5 mmHg	No; −2 mmHg
Esnault <i>et al.</i> (6); <i>n</i> = 18; proteinuric (>1 g/d), 6 mo ramipril 5 mg/d	Full-dosage monotherapy (ramipril 10 mg/d, valsartan 160 mg/d) versus half-dosage combination therapy (ramipril 5 mg/d, valsartan 80 mg/d); 4-wk randomized, prospective, open-label, crossover trial	No; 144.12 ± 26.5/77.65 ± 13.5 mmHg (ACEI/ARB) versus 148.88 ± 26.5/81.25 ± 13.4 mmHg (ARB)	No; 144.12 ± 26.5/77.65 ± 13.5 (ACEI/ARB) versus 142.44 ± 30.0/78.94 ± 14.4 mmHg (ACEI)
Doulton <i>et al.</i> (7); meta-analysis	14 trials reporting effect of dual versus single RAS blockade on BP	Yes; 3.8/2.9 mmHg (95% CI 2.4 to 5.3/0.4 to 5.4 mmHg)	Yes; 4.7/3.0 mmHg (95% CI 2.9 to 6.5/1.6 to 4.3 mmHg)

^aLength of treatment in crossover studies refers to time on each therapy rather than total study length. DBP, diastolic BP; SBP, systolic BP.

^bThe two *P* values refer to SBP and DBP, respectively.

^cGoal was comparable BP control in single- and dual-class RAS blockade.

Complete 24-h blockade of exogenous angiotensin I effects on BP did not occur with the standard recommended dosages of either ARB (losartan 100 mg/d; telmisartan 80 mg/d) (12). However, adding an ACEI to these regimens increased the blockade effect and produced nearly complete (75 to 80%) inhibition of BP response to exogenous angiotensin I at trough levels. Comparable results occurred with single-agent losartan 100 mg twice daily but not when the same total dosage (200 mg) was given once daily. Doubling the recommended dosage of telmisartan to 160 mg/d (given as 80 mg twice daily) did not boost RAS blockade to the level seen with combination ACEI plus maximum-recommended-dosage ARB therapy (Figure 1) (12). Findings may differ in hypertensive individuals with a less active RAS (12). These results suggest that the additive effect seen with combination ACEI and ARB therapy may result from pharmacologic (e.g., duration of action) rather than physiologic interactions.

Relationship between Antiproteinuria and Decreased BP

Most studies that evaluated dual-class antiproteinuric effects also assessed impact on BP (Table 2) (1–7,13). Some reported a significant benefit for combination therapy (1,7,13), but other reports were mixed (2–6). A meta-analysis by Doultou et al. (7) reported that combination RAS blockade resulted in a statistically significant BP-lowering effect, but the authors questioned the clinical significance of this finding, suggesting instead that the observed difference could stem from the design of studies included in the analysis rather than from an additive or synergistic effect of combination RAS blockade on BP (7).

Some of the small, short-term studies cited previously reported a correlation between antihypertensive and antiproteinuric effects on linear regression or multivariate analysis but could not establish causation (2,3,10). Other evidence suggests

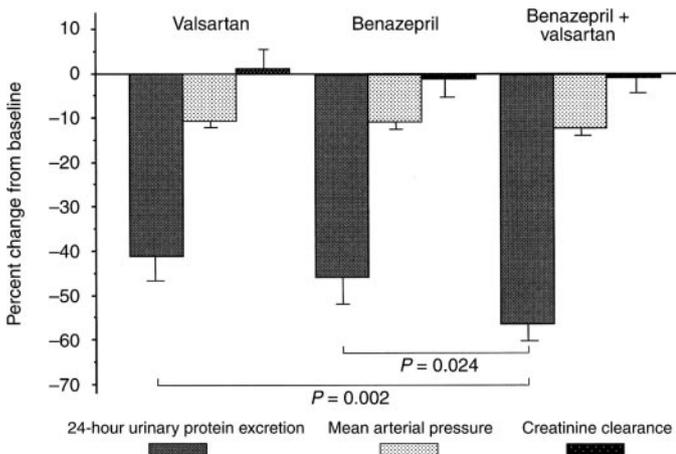


Figure 2. Percentage change from baseline for 24-h urinary protein excretion rate, mean arterial pressure, and creatinine clearance. $P < 0.025$ with Bonferroni adjustment. Data are means \pm SEM; $n = 24$. Dosage: valsartan 160 mg/d; benazepril 20 mg/d; benazepril + valsartan 10 mg/d + 80 mg/d, respectively. Design: 8-wk crossover study. Reprinted from reference (5), with permission.

that ACEI and ARB reduce proteinuria through mechanisms other than decreased BP. In their meta-analysis, Doultou et al. (7) concluded that ACE-I and ARB combination therapy reduced proteinuria significantly more than did either agent alone; they proposed a possible synergistic effect of dual RAS blockade on the intrarenal RAS.

The Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-Diabetic Renal Disease (COOPERATE) trial ($n = 263$; median follow-up 2.9 yrs), a randomized, controlled clinical trial, reported improved renal survival with dual-class compared with single-class therapy and attributed this benefit to the additional proteinuria reduction seen with combination therapy ($P = 0.01$ versus monotherapy). This antiproteinuric effect did not seem to stem from antihypertensive effects, because BP decreases were similar among all treatment groups (14).

Campbell et al. (5) speculated that the superior antiproteinuric benefit of combination therapy could result from hemodynamic effects. Combination therapy in this study did not significantly reduce BP when compared with single-agent RAS blockade but did significantly decrease proteinuria (Figure 2). Effective renal plasma flow increased with all treatments when compared with baseline; the increase was largest with combined treatment and benazepril monotherapy. These changes strongly correlated with reduction in renal vascular resistance (5). In the study group as a whole, the reduction in renal vascular resistance was predictive of the decrease in proteinuria. In contrast, however, the effect on glomerular membrane size selectivity seemed to be similar with both monotherapy and combination treatment. The authors controlled for the effect of BP lowering on proteinuria by using half-dosage combination therapy and full-dosage monotherapy (5).

A positive secondary finding in one negative study suggested

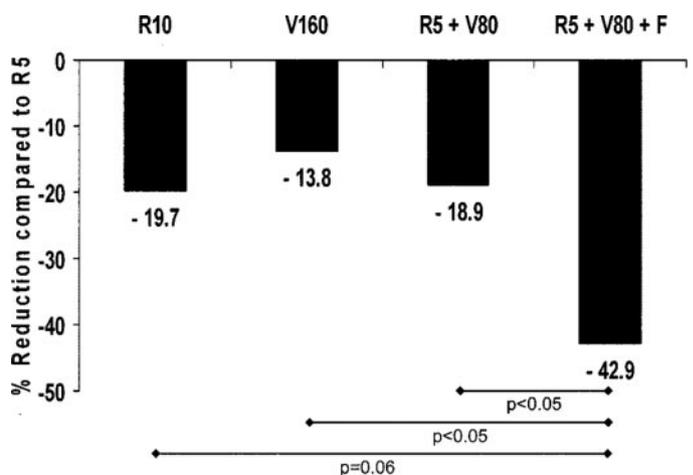


Figure 3. Urinary protein-to-creatinine ratio: Changes (in percentage) compared with ramipril 5 mg/d (R5) after ramipril 10 mg/d (R10); valsartan 160 mg/d (V160); combined ramipril 5 mg/d + valsartan 80 mg/d (R5 + V80); combined ramipril 5 mg/d + valsartan 80 mg/d + increased furosemide dosage (R5 + V80 + F); $n = 18$. Design: Crossover study, 4 wk per treatment period. Reprinted from reference (6), with permission.

that cautiously increasing diuretic dosage may affect the antiproteinuric impact of dual-agent RAS blockade, perhaps by counteracting the effect of sodium intake (6). As noted previously, higher sodium intake can blunt the antiproteinuric effect of ACEI (8,9); adding a diuretic to ACEI therapy in patients who were consuming a high-sodium diet restored this benefit (9).

Esnualt *et al.* (6) found that combination half-dosage therapy (ramipril 5 mg/d and valsartan 80 mg/d) did not further reduce proteinuria compared with full-dosage ACEI or ARB therapy (ramipril 10 mg/d or valsartan 160 mg/d). Adding furosemide to dual RAS blockade or increasing furosemide dosage in patients who were already receiving it led to a significant reduction in urinary protein-to-creatinine ratio when compared with combination therapy and with ARB therapy alone ($P < 0.05$ for both comparisons; Figure 3) (6). The authors speculated that restoration of sodium balance by the diuretic could have improved the combined antiproteinuric effect, thereby explaining some of the additional benefit seen with adding furosemide or increasing furosemide dosage (6).

Is It RAS Blockade Only? ACE-I + ARB = ACE-I + Calcium Channel Blocker

Krimholtz *et al.* (15) took another approach to isolate the cause of additional antiproteinuric benefit seen with dual RAS inhibition by comparing ACEI plus ARB therapy with ACEI plus a non-RAS-blocking antihypertensive agent. Patients with type 1 diabetes and diabetic renal disease ($n = 28$) were randomly assigned to receive either candesartan (titrated to 16 mg/d) or amlodipine (titrated to 10 mg/d) in addition to ≥ 4 wk of lisinopril (20 mg/d) (15). The regimens had similar effects on albuminuria and MAP. At week 24, albumin-to-creatinine ratio had fallen by 56% with candesartan plus ACEI ($P < 0.01$) and by 53% with amlodipine plus ACEI ($P < 0.01$) when compared with baseline measurements with ACEI therapy alone (15). MAP fell by 3 to 6 mmHg in both groups (15).

Changes in BP did not correlate with changes in albumin-to-creatinine ratios (15), which suggests an antiproteinuric mechanism independent of BP. However, both the ARB and the calcium channel blocker (CCB) resulted in similar antiproteinuric effects when added to ACEI treatment, even though CCB do not affect RAS (15). This suggests an alternative mechanism for affecting albuminuria.

Safety of Combination Therapy

Potential safety considerations with dual RAS blockade include hyperkalemia and reduced renal function (increased serum creatinine or decreased GFR). One trial that was designed to evaluate the safety of dual RAS blockade in patients with progressive chronic renal failure found that higher dosage valsartan monotherapy, lower dosage valsartan plus benazepril, and higher dosage valsartan plus benazepril all resulted in a small, statistically significant, but clinically irrelevant rise in serum creatinine after 5 wks (16). Serum potassium increased significantly from baseline in the two combination therapy groups, but only two patients were withdrawn from therapy because of this complication (16). This study was not designed

to compare differences in antihypertensive or antiproteinuric effects (16).

A meta-analysis of 21 randomized, controlled trials ($n = 654$) examined the safety of combination RAS blockade. Dual-class therapy resulted in a small but significant increase in serum potassium levels (weighted mean difference 0.11 mEq/L; 95% confidence interval 0.05 to 0.17). Investigators characterized this as clinically insignificant (17). Dual RAS blockade therapy also produced a nonsignificant decrease in GFR (weighted mean difference 1.4 ml/min [0.02 ml/s]; 95% confidence interval -2.6 to 0.2). The authors concluded that the available data demonstrate the safety of combination therapy in the short term (17).

Other trials reported changes in potassium levels or incidence of hyperkalemia with single- or dual-agent RAS blockade. Benazepril 20 mg/d plus valsartan 80 mg/d resulted in significantly higher plasma potassium levels when compared with monotherapy with either agent (0.3 to 0.4 mEq/L *versus* monotherapies; $P < 0.01$) during 8 wks of treatment (2). Only one in 20 patients developed a plasma potassium level ≥ 5 mEq/L (2). Another study recorded a small but significant increase in serum potassium with half-dosage dual therapy compared with full-dosage monotherapy during 8 wk (mean increase 0.18 to 0.30 mEq/L *versus* benazepril or valsartan; $P < 0.05$) (5). No patient required therapy change or cessation because of hyperkalemia (5).

Plasma potassium did not differ significantly when irbesartan 300 mg/d or placebo was added to >3 mo of enalapril 40 mg/d ($P = 0.18$) (3). Two of 24 patients developed plasma potassium levels >5.2 mEq/L after placebo or irbesartan was added to enalapril (3). Both received a 50% increase in furosemide dosage and had GFR <40 ml/min per yr (3).

Authors of the nearly 3-yr-long COOPERATE trial deemed ACEI plus ARB therapy (trandolapril 3 mg three times daily and losartan 100 mg three times daily) safe (14). None of the 263 randomized patients was withdrawn from the trial, no severe adverse events were reported, and few cases of hypotension (2) or hyperkalemia (18) occurred. The authors attributed these findings to gradual increases in drug dosages (14).

Unresolved Issues

Mechanism of Benefit

Dual RAS blockade seems to enhance the antiproteinuric effect of single-agent ACEI or ARB therapy. Additional studies are needed to ascertain the mechanism(s) of this effect. Decreased BP, synergistic action on RAS blockade, and other explanations have been proposed. The finding that treatment with an ACEI plus a CCB produces antiproteinuric effects similar to those produced by treatment with an ACEI plus an ARB, even though antiproteinuric effects were independent of BP reduction, suggests that effects other than RAS blockade and decreased BP can decrease protein excretion (15).

Effect of Dosing Regimen, Patient Characteristics, and Duration of Action

Whether combination therapy is superior to monotherapy in its antiproteinuric effects depends on the dosage and the fre-

quency at which each agent is administered as well as each agent's duration of action (6,12). The optimal dosage of combination ACEI and ARB therapy for antiproteinuric effect also varies by individual (11). Current data point to a synergistic antiproteinuric effect with dual ACEI and ARB therapy at plasma concentrations below those that affect BP (7). Data are insufficient to determine whether higher dosages of either drug class alone may reduce proteinuria as much as the two classes combined (7).

Effect of Race and Ethnicity

Studies have not addressed whether the effect of combination ARB and ACEI therapy varies among different race or ethnic groups. Enalapril is associated with a reduction in risk for hospitalization for heart failure in white but not black patients with left ventricular dysfunction (19). Carvedilol, a β blocker with α_1 adrenergic blocking properties, has demonstrated a similar reduction in heart failure risk in black and other patients (18).

Effect of Sodium Intake

Few studies have controlled for the effect of sodium balance on the interaction among ACEI, ARB, or combination therapy and resultant effects on proteinuria, BP, or renal disease progression. Sodium intake blunts ACEI antiproteinuric effect; adding a diuretic can restore this benefit (9). Some evidence suggests that diuretic therapy may have the same effect on ACEI/ARB therapy (6).

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References

- Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, Cooper ME: Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: The Candesartan and Lisinopril Microalbuminuria (CALM) Study. *BMJ* 321: 1440–1444, 2000
- Jacobsen P, Andersen S, Jensen BR, Parving HH: Additive effect of ACE inhibition and angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. *J Am Soc Nephrol* 14: 992–999, 2003
- Jacobsen P, Andersen S, Rossing K, Jensen BR, Parving HH: Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy. *Kidney Int* 63: 1874–1880, 2003
- Agarwal R: Add-on angiotensin receptor blockade with maximized ACE inhibition. *Kidney Int* 59: 2282–2289, 2001
- Campbell R, Sangalli F, Perticucci E, Aros C, Viscarra C, Perna A, Remuzzi A, Bertocchi F, Fagiani L, Remuzzi G, Ruggenti P: Effects of combined ACE inhibitor and angiotensin II antagonist treatment in human chronic nephropathies. *Kidney Int* 63: 1094–1103, 2003
- Esnault VLM, Ekhlasi A, Delcroix C, Moutel MG, Nguyen JM: Diuretic and enhanced sodium restriction results in improved antiproteinuric response to RAS blocking agents. *J Am Soc Nephrol* 16: 474–481, 2005
- Doulton TW, He FJ, MacGregor GA: Systematic review of combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade in hypertension. *Hypertension* 45: 880–886, 2005
- Heeg JE, Dejong PE, Van Der Hem GK, De Zeeuw D: Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. *Kidney Int* 36: 272–279, 1989
- Buter H, Hemmeler MH, Navis G, de Jong PE, de Zeeuw D: The blunting of the antiproteinuric efficacy of ACE inhibition by high sodium intake can be restored by hydrochlorothiazide. *Nephrol Dial Transplant* 13: 1682–1685, 1998
- Russo D, Minutolo R, Pisani A, Esposito R, Signoriello G, Andreucci M, Balletta MM: Coadministration of losartan and enalapril exerts additive antiproteinuric effect in IgA nephropathy. *Am J Kidney Dis* 38: 18–25, 2001
- Laverman GD, Navis G, Henning RH, De Jong PE, De Zeeuw D: Dual renin-angiotensin system blockade at optimal doses for proteinuria. *Kidney Int* 62: 1020–1025, 2002
- Forclaz A, Maillard M, Nussberger J, Brunner HR, Burnier M: Angiotensin II receptor blockade: Is there truly a benefit of adding an ACE inhibitor? *Hypertension* 41: 31–36, 2003
- Stergiou GS, Skeva II, Baibas NM, Roussias LG, Kalkana CB, Achimastos AD, Mountokalakis TD: Additive hypotensive effect of angiotensin-converting enzyme inhibition and angiotensin-receptor antagonism in essential hypertension. *J Cardiovasc Pharmacol* 35: 937–941, 2000
- Nakao N, Yoshimura A, Morita H, Takeda M, Kayano T, Ideura T: Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): A randomized controlled trial. *Lancet* 361: 117–124, 2003
- Krimholtz MJ, Karalliedde J, Thomas S, Bilous R, Viberti G: Targeting albumin excretion rate in the treatment of the hypertensive diabetic patient with renal disease. *J Am Soc Nephrol* 16: S42–S47, 2005
- Ruilope LM, Aldigier JC, Ponticelli C, Oddou-Stock P, Botteri F, Mann JF: Safety of the combination of valsartan and benazepril in patients with chronic renal disease. *J Hypertension* 18: 89–95, 2000
- 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. *Am J Kidney Dis* 48: 8–20, 2006
- Yancy CW, Fowler MB, Colucci WS, Gilbert EM, Bristow MR, Cohn JN, Lukas MA, Young ST, Packer M, US Carvedilol Heart Failure Study Group: Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. *N Engl J Med* 344: 1358–1365, 2001
- Exner DV, Dries DL, Domanski MJ, Cohn JN: Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Engl J Med* 344: 1351–1357, 2001