NARRATIVE REVIEW

Dual Blockade of the Renin-Angiotensin System for Cardiorenal Protection: An Update

Mustafa Arıcı, MD, and Yunus Erdem, MD

The renin-angiotensin system (RAS) has an important role in hypertension and the continuum of cardiovascular and kidney disease. The inhibition of this system, either with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), has been shown to be beneficial for cardiorenal protection. Dual blockade with an ACE inhibitor and ARB may have additional benefits due to the more complete inhibition of the system. Most published trials, including recent large studies and meta-analyses, have reported either limited or no additional benefit. Dual-blockade therapy seems to have some benefit on proteinuria and blood pressure reduction, and on morbidity and mortality in patients with heart failure, compared with monotherapy. The major issue arising from these published trials and meta-analyses is the increased frequency of dual therapy discontinuation and adverse effects on kidney function. There is a lack of hard end-point data for renal outcomes and long-term safety data in most published trials. Until the results of ongoing trials become available and as further safety data emerge, a wise approach would be to withhold use of ACE inhibitor and ARB combination therapy in general practice. When used in selected conditions, patients need to be closely monitored.
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INDEX WORDS: Renin-angiotensin system; angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; dual blockade; hypertension; cardiovascular disease; chronic kidney disease; proteinuria; clinical trials.

Since 1898, when renin was isolated from the renal cortex, the inhibition of the renin-angiotensin system (RAS) has been a major focus in the field of hypertension and hypertension-induced cardiorenal damage research. Classically, the system is activated by renin secretion from the kidney, which stimulates enzymatic cleavage of angiotensinogen, also known as the renin substrate, to produce the 10–amino acid peptide angiotensin I (Ang I). Subsequently, angiotensin-converting enzyme (ACE) converts Ang I to angiotensin II (Ang II), the system's major effector molecule. The effects of Ang II, including elevation of blood pressure, are mediated through cell membrane receptors, in particular through the Ang II type 1 (AT_1) receptor. Therefore, it has been established that the RAS can be inhibited at a minimum of 3 different levels (Fig 1).[1]

The first clinical approach to blocking the RAS was ACE inhibition. Captopril was developed in 1975 and received US Food and Drug Administration (FDA) approval in 1981.[2] The initial studies demonstrated the efficacy of captopril against hypertension and hypertension-induced organ damage. Following captopril, more than 10 ACE inhibitors have been developed and introduced into clinical practice. Losartan, developed in 1986, provided a different means to inhibit the system, namely, preventing binding of Ang II to the AT_1 receptor.[3] After losartan received FDA approval in 1995, it was demonstrated that angiotensin receptor blockers (ARBs) were also effective in preventing hypertension-induced end-organ damage. Currently, 7 molecules of this group are being used in clinical practice.

ACE inhibitors and ARBs have been regarded as alternatives and/or competitors, as a result of the different mechanisms they use to inhibit the RAS.[4,5] The fact that both classes of drugs have antihypertensive effects and offer organ protection has led clinicians to debate whether to use ACE inhibitors or ARBs.[6] While a conclusive

From the Department of Nephrology, Hacettepe University Faculty of Medicine, Ankara, Turkey.

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Address correspondence to Mustafa Arıcı, MD, Hacettepe Hastanesi, Nefroloji Bolumu, 06100 Sihhiye, Ankara, Turkey. E-mail: marici@hacettepe.edu.tr

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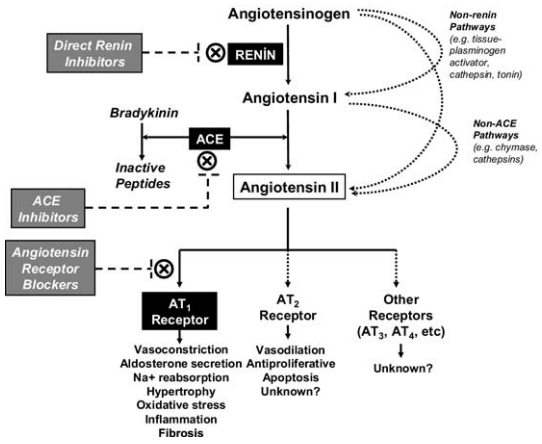

Figure 1. The renin-angiotensin system and clinical inhibition points. The system is activated by cleavage of angiotensinogen (renin substrate) to angiotensin I (Ang I) by renin. Ang I is converted to angiotensin II (Ang II) by angiotensin-converting enzyme (ACE). Ang II then acts via its angiotensin II type 1 (AT_1) receptor to produce its effects on vasculature, heart, and kidney. The dashed lines ending with ⊗ indicate clinical inhibition points for RAS. Aldosterone effect may also be inhibited by aldosterone antagonists (not shown). Each inhibition may alter feedback mechanisms of the system (not shown) and may provoke alternative pathways. The alternative pathways and other angiotensin II receptors that are mainly documented in experimental systems but of unproven physiological significance in vivo are depicted with dotted lines. Adapted with permission from Staessen and Richart.[48]

answer to that question is yet to be provided, a better understanding of the critical role of the RAS in cardiovascular and kidney damage has made clinicians consider the question from a different perspective, namely, whether the combination of these agents to inhibit the RAS in 2 different ways can lead to improved results.[7] This review focuses on dual RAS blockade by ACE inhibitors and ARBs in light of recently published data, and also provides some insight into the future of RAS blockade in clinical practice.

RATIONALE FOR DUAL RAS BLOCKADE

RAS inhibition at 2 different points by using ACE inhibitors and ARBs has various clinical and pathophysiological advantages and disadvantages (Box 1).[5,8-10] It has been suggested that "Ang II escape" prevents complete RAS inhibition during therapy with an ACE inhibitor. Studies have detected evidence of the escape phenomenon occurring in long-term ACE inhibitor use due to alternative non-ACE pathways.[5,10,11] Ang II synthesis via non-ACE pathways has been shown to be more significant, particularly when organ damage has occurred.[12] Another limitation of ACE inhibitors might be the minimal effect on local Ang II production. Consequently, local Ang II production presumably continues despite blockade of the RAS systemically by ACE inhibition.[5]

Since ARBs have a direct impact on receptor binding with Ang II, Ang II escape observed during therapy with an ACE inhibitor will not

Box 1. Advantages and Disadvantages of Combination Therapy With ACE Inhibitors and ARBs

Advantages of ACE Inhibitors	Advantages of ARBs
Partial preservation of Ang II–related inhibition on renin release	Complete blockade of the AT_1 receptor
Less stimulation of the AT_2 receptor (if harmful)	Vasodilation as a result of the stimulation of the AT_2 receptor
Protective effect independent of RAS inhibition	No aldosterone escape
Disadvantages of ACE Inhibitors	**Disadvantages of ARBs**
Continued Ang II production through non-ACE pathways	Elevated Ang II levels
No inhibition of intrarenal ACE	Elevated renin levels
Inhibition of the formation of Ang 1-7, which partially antagonizes the effects of Ang II	Stimulation of the AT_2 receptor with Ang II (effects such as apoptosis, etc)
	Metabolization of Ang II through other peptidases and effects of the resulting peptides
	Drop in BP due to the vasodilating effect of AT_2 and failure to administer the drug at a sufficient dose

Abbreviations: ACE, angiotensin-converting enzyme; Ang II, angiotensin II; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; AT_2, angiotensin II type 2; BP, blood pressure; RAS, renin-angiotensin system.

Adapted and reproduced with permission from Wolf and Ritz.[5]

Table 1. Changes Occurring as a Result of ACE Inhibitor and ARB Effects at Different Steps of the Renin-Angiotensin System

	ACE Inhibitors	ARBs	Combination
Ang II	↓→	↑	↑→
Aldosterone	↓→	↓→	↓
Kinins	↑	↑→	↑
Nitric oxide	↑	↑	↑
AT_2 stimulation	↓	↑	↑→

Note: ↑, increase; ↓, decrease; ↑→, increase or no change; ↓→, decrease or no change. Summarized from Wolf and Ritz,[5] Unger and Stoppelhaar,[8] and Staessen and Richart.[48]

Abbreviations: ACE, angiotensin-converting enzyme; Ang II, angiotensin II; ARB, angiotensin receptor blocker; AT_2, angiotensin II type 2 (receptor).

occur with an ARB. Complete and selective blockade of the AT_1 receptor may also inhibit all harmful effects of Ang II regardless of its origin, whether systemic or local.[8] However, blocking the receptor leads to a neurohumoral feedback–mediated increase in the level of Ang II molecules, which in turn bind to other AT receptors (eg, AT_2, AT_3, and AT_4) that are not blocked by ARBs. Of those receptors, AT_3 and AT_4 have unknown effects. Although the AT_2 receptor has been reported to have an opposite action to that of AT_1, the effects of unopposed stimulation of AT_2 receptors are controversial. In certain experimental models, potentially unfavorable effects such as apoptosis, proinflammatory signal transduction, or chemokine induction have been reported.[1,5,13] Therefore, the advantages and disadvantages of Ang II binding to other receptors have still not been elucidated. The efficacy of ARBs may be further compromised with long-term use, because increased Ang II may compete with and displace ARBs from AT_1 receptors.[14] Moreover, ARBs lack the bradykinin-increasing effect, which may have a positive impact on clinical tolerance of these drugs; however, it is not known whether this condition has a detrimental effect on clinical benefits.[8-10]

Consequently, RAS inhibition at 2 separate points may lead to activation or inhibition of different feedback mechanisms (Table 1).[5,8] These alterations may cause both favorable effects and limitations to each treatment choice. The use of combination therapy may overcome the limitations and enhance the benefits by carrying added benefits of ACE inhibition, positive outcomes of AT_2 receptor stimulation, diverse effects on bradykinin, and more local RAS suppression.[8] In clinical practice, the main desired effects are to achieve better RAS inhibition through the drugs' complementary effects, to obtain strong clinical protection, and if possible, to lessen negative effects.

DUAL INHIBITION OF THE RAS IN CLINICAL PRACTICE

ACE Inhibitor–ARB Combination and Hypertension

There are numerous studies that have investigated use of an ACE inhibitor in combination with an ARB (Table 2), but most of them do not have the primary aim of blood pressure and lack sufficient statistical significance and an adequate sample size.[15] Another complication is that most studies are disparate in their methodology. An important issue is drug dosing used for both hypertension and other clinical indications (see discussion that follows). Most studies used submaximal doses of ACE inhibitors or ARBs as monotherapy and/or in combination. Earlier studies had also used short-acting ACE inhibitors as once-daily medications, a strategy which interferes with the ultimate lowering of blood pressure at trough.[15] When an ACE inhibitor was used at the full dose, no additive effect of ARB was found on blood pressure.[16] In spite of these shortcomings, a meta-analysis involving only 434 patients reported that ACE inhibitor–ARB combination therapy yielded a further drop in blood pressure (4 mm Hg systolic and 3 mm Hg diastolic) compared with monotherapies.[15] Although it was not envisioned primarily as a hypertension study, ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) has provided the most substantial data pertinent to this issue.[17] The blood pressure values of over 8,000 patients receiving combination therapy with ramipril (10 mg, once daily) and telmisartan (80 mg, once daily) were decreased 2.4/1.4 mm Hg and 1.5/0.8 mm Hg more when compared with patients receiving the corresponding monotherapies.[17] Despite all these data, there is not sufficient evidence to warrant use of an ACE inhibitor and an ARB in combina-

Table 2. Main Trials of ACE Inhibitor–ARB Combination in Hypertension, Cardiovascular Disease, and Kidney Disease

Study	Study Type & Duration	Clinical Setting	Sample Size*	Intervention	Main Efficacy Results for Combination	Main Safety Results for Combination	Main Limitations
Hypertension							
Azizi et al,[55] 2000	Randomized, double-blind, parallel group, multicenter trial, 6 wk	Primary HTN with DBP 95-115 mm Hg	60/177	▪ Enalapril (10 mg, 1×/d) + losartan (50 mg, 1×/d) ▪ Enapril (10 mg, 1×/d) ▪ Losartan (50 mg, 1×/d)	More reduction in clinic DBP (3.2 mm Hg [cf losartan] and 4.0 mm Hg [cf enalapril], $P < 0.05$)	No difference in adverse events, no change in SCr and serum potassium	Submaximal doses in combination, short duration
Stergiou et al,[56] 2000	Randomized, placebo-controlled, crossover trial, 5 wk	Primary HTN with DBP 90-115 mm Hg	20	▪ Benazepril (20 mg, 1×/d) + valsartan (80 mg, 1×/d) ▪ Benazepril (20 mg, 1×/d) + placebo	More reduction in BP (6.8 ± 9.7/4.9 ± 6.8 mm Hg, $P < 0.05$)	No change in SCr and serum potassium	Submaximal doses in combination, small group, short duration
Weir et al,[57] 2001	Open-label, single arm, add-on therapy, multicenter trial, 8 wk	Untreated or uncontrolled primary HTN and isolated systolic HTN	600/6,465	▪ Candesartan (16-32 mg, 1×/d) + diuretics or CCBs or β-blockers or ACE inhibitors	More reduction in BP ($P < 0.05$)	4× more orthostatic hypotension with add-on therapy than monotherapy (0.8% *v* 0.2%, $P < 0.05$)	Various ACE inhibitors with varying doses, nonrandomized, not properly controlled, no detailed safety data, short duration
Weir et al,[58] 2001	Randomized, open-label, parallel group, 2-center trial, 6 wk	African American, untreated primary HTN with DBP 95-114 mm Hg	23/81	▪ Benazepril (20 mg 1×/d) + valsartan (160 mg, 1×/d) ▪ Valsartan (320 mg, 1×/d) ▪ Valsartan (160 mg, 1×/d) + HCTZ (12.5 mg, 1×/d)	No significant BP reduction	No data	Small group, no safety data in combination group, short duration
Morgan et al,[16] 2004	Randomized, double-blind, placebo-controlled, crossover trial, 6 wk	Primary HTN, uncontrolled with 1 drug or required 2 or more drugs for control	23	▪ Lisinopril (20 mg, 1×/d) + candesartan (16 mg, 1×/d) ▪ Corresponding and double dose of monotherapies	More reduction in 24-h SBP when compared only to usual dose of monotherapies, but not double doses	More rise in SCr and serum potassium in combination arm	Small group, short duration
Anan et al,[59] 2005	Randomized, open-label, parallel group trial, 40 wk	Untreated primary HTN with LVH (ambulatory SBP > 135 or DBP > 85 mm Hg)	10/31	▪ Perindopril (4 mg, 1×/d) + valsartan (80 mg, 1×/d) ▪ Perindopril (8 mg, 1×/d) ▪ Valsartan (160 mg, 1×/d)	No change in ambulatory BP, greater reduction in LVMI	No data	Half doses in combination
Petrovic et al,[60] 2005	Randomized, open-label, parallel group trial, 6 mo	Untreated primary HTN (SBP 160-190, DBP 90-110 mm Hg)	25/75	▪ Ramipril (2.5 mg, 1×/d) + telmisartan (40 mg, 1×/d) ▪ Ramipril (5 mg, 1×/d) ▪ Telmisartan (80 mg, 1×/d)	No change in BP, more reduction in LVMI and CIMT	No data	Half doses in combination
Doulton et al,[15] 2005	Meta-analysis of 14 randomized trials	Primary HTN, type 1 and 2 DM and non-DM CKD with albuminuria	434	▪ ACE inhibitor + ARB combinations compared with monotherapies	More reduction in ambulatory BP (4.7/3.0 mm Hg [cf ACE inhibitors] and 3.8/2.9 mm Hg [cf ARBs])	No significant concern, more hyperkalemia in combination arms	Relatively small trials with short-term follow-up, HTN not primary outcome in most trials
Cardiovascular Disease							
RESOLVD,[61] 1999	Randomized, double-blind, placebo-controlled, parallel group, multicenter trial, 43 wk	Class 2-4 CHF with LVEF < 40%	659/768	▪ Enalapril (10 mg, 2×/d) + candesartan (4-8 mg, 1×/d) ▪ Enalapril (10 mg, 2×/d) ▪ Candesartan (4-8-16 mg, 1×/d)	More reduction in BP (6 ± 1/4 ± 1 mm Hg, $P <$ 0.05), more benefit in preventing LV remodeling	More increase in serum potassium	Submaximal doses in combination
Baruch et al,[62] 1999	Randomized, double-blind, placebo-controlled, parallel group, multicenter trial, 4 wk	Class 2-4 CHF with LVEF ≤ 40%	55/83	▪ Background ACE inhibitor therapy + placebo or valsartan (80 mg, 2×/d) or valsartan (160 mg, 2×/d)	Significant reductions in SBP (6.8 mm Hg, $P =$ 0.013), and hemodynamic and hormonal parameters	More hypotension, slight increase in serum potassium	Small group, short duration, various ACE inhibitors with varying doses
Hamroff et al,[63] 1999	Randomized, double-blind, placebo-controlled, multicenter trial, 6 mo	Class 3-4 CHF with LVEF ≤ 35%	16/33	▪ Background ACE inhibitor therapy + placebo or losartan (50 mg, 1×/d)	More improvement in functional class of CHF	No change in serum electrolytes or SCr	Small group, short duration, various ACE inhibitors with varying doses

(Continued)

Table 2 (Cont'd). Main Trials of ACE Inhibitor–ARB Combination in Hypertension, Cardiovascular Disease, and Kidney Disease

Study	Study Type & Duration	Clinical Setting	Sample Size*	Intervention Hypertension	Main Efficacy Results for Combination	Main Safety Results for Combination	Main Limitations
ADEPT,[64] 2001	Randomized, double-blind, placebo-controlled, parallel group, single-center trial, 8 wk	Class 2-4 with LVEF ≤ 35%	18/36	▪ Background ACE inhibitor therapy + placebo or eprosartan (800 mg, 2×/d)	No change in LVEF, significant reduction in DBP	No increase in adverse events	Small group, short duration, various ACE inhibitors with varying doses
ValHeFT,[19] 2001	Randomized, double-blind, placebo-controlled, parallel group, multicenter trial, 23 mo	Class 2-4 with LVEF < 40%	2,511/5,010	▪ Background ACE inhibitor (93%) + placebo or valsartan (160 mg, 2×/d)	Combined end point of mortality and morbidity was reduced	More adverse events (hypotension, dizziness, and renal impairment), more increase in SCr and serum potassium	Not designed as a combination trial, various ACE inhibitors with varying doses
CHARM-Added,[20] 2003	Randomized, double-blind, placebo-controlled, parallel group, multicenter trial, 41 mo	Class 2-4 with LVEF ≤ 40%	1,276/2,548	▪ Background ACE inhibitor therapy + placebo or candesartan (32 mg, 1×/d)	Risk of CV death and hospital admission for CHF was reduced	Similar increase in SCr, more patients have hyperkalemia, BP decreased more (4.6/3.0 mm Hg, $P < 0.05$)	Not designed as a combination trial, various ACE inhibitors with varying doses
VALIANT,[21] 2003	Randomized, double-blind, parallel group, multicenter trial, 24.7 mo	Recent MI (0.5-10 d previously) complicated by heart failure with LVEF ≤ 35%	4,885/14,703	▪ Captopril (50 mg, 3×/d) + valsartan (80 mg, 2×/d) ▪ Valsartan (160 mg, 2×/d) ▪ Captopril (50 mg, 3×/d)	Similar primary (mortality from any cause) and secondary (combined CV end point) outcomes	More discontinuations, more BP decrease, more drug-related adverse events seen, more hypotension and decreased kidney function	Half doses in combination
ONTARGET,[17] 2008	Randomized, double-blind, parallel group, multicenter trial, 56 mo	Coronary, peripheral, or cerebrovascular disease or DM with end-organ damage	8,502/25,620	▪ Ramipril (10 mg, 1×/d) + telmisartan (80 mg, 1×/d) ▪ Ramipril (10 mg, 1×/d) ▪ Telmisartan (80 mg, 1×/d)	Similar primary outcome (death from CV causes, MI, stroke, or hospitalizations from heart failure); more renal impairment (secondary outcome)	More discontinuations, more hypotension and syncope, more hyperkalemia	—
Lakhdar et al,[23] 2008	Safety and tolerability meta-analysis of 9 randomized trials	CHF with LVEF ≤ 4% or LV dysfunction acutely post-MI	9,199/18,160	▪ ACE inhibitor + ARB combinations compared with ACE inhibitor alone	—	More risk of developing any adverse events, more hypotension, worsening of kidney function and hyperkalemia	Small number of events per study
Chronic Kidney Disease							
CALM,[28] 2000	Randomized, double-blind, parallel group, multicenter trial, 24 wk	Type 2 DM with HTN and microalbuminuria	67/197	▪ Lisinopril (20 mg, 1×/d) + candesartan (16 mg, 1×/d) ▪ Lisinopril (20 mg, 1×/d) ▪ Candesartan (16 mg, 1×/d)	More reduction in DBP, more reduction in urinary ACR	No significant adverse events, slight increases in SCr and serum potassium, slight decrease in creatinine clearance	Small group, short duration
COOPERATE,[30] 2003	Randomized, double-blind, parallel group, single center trial, 36 mo	Non-DM CKD with proteinuria	88/263	▪ Trandolapril (3 mg, 1×/d) + losartan (100 mg, 1×/d) ▪ Trandolapril (3 mg, 1×/d) ▪ Losartan (100 mg, 1×/d)	Risk of primary outcome (doubling of SCr or ESRD) was reduced, greater reduction of proteinuria	Slightly higher occurrence of hyperkalemia	Small group, implausibilities in the design and data
CALM II,[29] 2005	Randomized, double-blind, parallel group, single center trial, 12 mo	Type 1 and 2 DM with HTN	38/75	▪ Lisinopril (20 mg, 1×/d) + candesartan (16 mg, 1×/d) ▪ Lisinopril (40 mg, 1×/d)	No change in BP and albuminuria	>No significant difference	Small group

(Continued)

Table 2 (Cont'd). Main Trials of ACE Inhibitor–ARB Combination in Hypertension, Cardiovascular Disease, and Kidney Disease

Study	Study Type & Duration	Clinical Setting	Sample Size*	Intervention Hypertension	Main Efficacy Results for Combination	Main Safety Results for Combination	Main Limitations
MacKinnon et al,[33] 2006	Meta-analysis of 21 randomized trials	Chronic proteinuric kidney diseases	423/654	▪ ACE inhibitor + ARB combinations compared with ACE inhibitor alone	More reduction in proteinuria	Small, but significant increase in serum potassium, nonsignificant decrease in GFR	Relatively small trials with short-term follow-up, significant statistical heterogeneity
IMPROVE,[37] 2007	Randomized, double-blind, placebo-controlled, parallel group, multicenter trial, 20 wk	HTN with microalbuminuria and elevated CV risk, age ≥ 55 y	204/405	▪ Ramipril (10 mg, 1×/d) + irbesartan (150-300 mg, 1×/d) ▪ Ramipril (10 mg, 1×/d) + placebo	Similar reduction in AER, greater reduction in AER in patients with overt nephropathy or DM, significantly greater reduction in SBP and DBP	Similar incidence of adverse events	Underpowered study, short duration
VALERIA,[38] 2008	Randomized, double-blind, parallel group, multicenter trial, 30 wk	Primary HTN with microalbuminuria	43/133	▪ Lisinopril (20 mg, 1×/d) + valsartan (320 mg, 1×/d) ▪ Lisinopril (40 mg, 1×/d) ▪ Valsartan (320 mg, 1×/d)	Significantly greater reduction in AER, similar BP reduction	Slightly higher incidence of adverse events, more hypotension, more notable hyperkalemia	Small group with short duration, half dose of ACE inhibitor in combination
Kunz et al,[34] 2008	Meta-analysis of 49 randomized trials (23 trials compared combination with ACE inhibitor or ARB monotherapy)	Patients with or without DM and with microalbuminuria or proteinuria	581/6,181	▪ ACE inhibitor + ARB combinations compared with ACE inhibitor or ARB alone	Greater reduction in proteinuria	Not enough safety data	Most studies were small, varied in quality, no reliable data on adverse events
ONTARGET-Renal,[25] 2008	Randomized, double-blind, parallel group, multicenter trial, 56 mo	Coronary, peripheral, or cerebrovascular disease or DM with end-organ damage	8,502/25,620	▪ Ramipril (10 mg, 1×/d) + telmisartan (80 mg, 1×/d) ▪ Ramipril (10 mg, 1×/d) ▪ Telmisartan (80 mg, 1×/d)	Increased events for composite primary outcome (dialysis, doubling of SCr or death) and secondary renal outcome (dialysis, doubling of SCr), less increase in urinary ACR	More reduction in GFR, more discontinuations, more hypotension	Characteristics of the study cohort, low number of events
Catapano et al,[35] 2008	Meta-analysis of 13 randomized trials	Primary glomerulonephritis	271/425	▪ ACE inhibitor + ARB combinations compared with ACE inhibitor or ARB alone	Greater decrease in proteinuria, similar reduction in BP	Moderate, but significant increase in potassium, no effect on GFR	Most studies were small, varied in quality

Abbreviations: ACE, angiotensin-converting enzyme; ACR, albumin-creatinine ratio; ADEPT, Addition of the AT_1 Receptor Antagonist Eprosartan to ACE Inhibitor Therapy in Chronic Heart Failure; AER, albumin excretion rate; ARB, angiotensin receptor blocker; BP, blood pressure; CALM, Candesartan and Lisinopril Microalbuminuria; CCB, calcium channel blocker; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality; CHF, congestive heart failure; CIMT, carotid intima-media thickness; CKD, chronic kidney disease; COOPERATE, Combination Treatment of Angiotensin II Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor in Nondiabetic Renal Disease; CV, cardiovascular; DBP, diastolic blood pressure; DM, diabetes mellitus; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HTN, hypertension; HCTZ, hydrochlorothiazide; IMPROVE, Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; MI, myocardial infarction; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study; SCr, serum creatinine; SBP, systolic blood pressure; VALERIA, Valsartan in Combination With Lisinopril Versus the Respective High Dose Monotherapies in Hypertensive Patients With Microalbuminuria; ValHeFT, Valsartan Heart Failure Trial; VALIANT, Valsartan in Acute Myocardial Infarction Trial.

*First number represents the number of participants receiving ACE inhibitor–ARB combination.

tion for blood pressure management. In fact, the latest Arterial Blood Pressure Guidelines by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) have not included it among the recommended combinations for first-line antihypertensive therapy.[18]

ACE Inhibitor–ARB Combination and Cardiovascular Disease

Almost all of the studies except ONTARGET have included patients with various degrees of congestive heart failure (CHF; Table 2).[7,9,10] Most studies have shown either no further benefit in hard outcomes or just limited efficacy. Most of the positive findings emerged from small studies or add-on trials and showed benefit in surrogate parameters (improvement in symptoms, left ventricular remodeling, neurohumoral changes, or hospitalizations).

The Valsartan Heart Failure Trial (Val-HeFT) was not originally designed as a combination therapy trial.[19] It compared valsartan with a placebo as an add-on to existing therapy among patients with CHF. An ACE inhibitor was administered to over 90% of the patients. There was no difference between the groups in terms of mortality. However, the composite end point (both mortality and morbidity) revealed a significant difference in the valsartan-treated arm. The difference was attributed to the decreased risk of hospitalization due to heart failure. Subgroup analysis of the study demonstrated valsartan to be of benefit in patients not receiving an ACE inhibitor, while its use together with an ACE inhibitor and a β-blocker yielded negative results. Among those who were receiving both drugs at baseline, valsartan had a significant adverse effect on mortality and was associated with a trend toward an increase in the combined end point of mortality and morbidity. Renal parameters were slightly impaired in the valsartan arm.[19]

The CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity)-Added trial randomized patients receiving an ACE inhibitor at an optimal dosage into 2 groups who were then given either placebo or candesartan (32 mg, once daily).[20] The study revealed 15% less risk in the candesartan group compared with the placebo group in terms of the primary composite end point (cardiovascular mortality and hospitalization due to heart failure). Unlike Val-HeFT, this trial demonstrated that the combination therapy had a favorable impact on both components of the composite end point. Although statistical significance was not established, the patients in CHARM-Added had further impairment in kidney function.[20] The Valsartan in Acute Myocardial Infarction Trial (VALIANT) had a different design from the 2 trials described above.[21] As the study was planned to carry out dual inhibition in patients with recent myocardial infarction and heart failure, only 1 ACE inhibitor (captopril) was used and administered as of the beginning of the trial. The study had 3 arms (captopril, valsartan, or captopril and valsartan) in addition to the conventional therapy provided. The drug dosages were titrated and approximately half of the patients reached the target doses. No differences were observed between the groups in terms of primary end point (death from any cause) or secondary end point (death from cardiovascular causes, recurrent myocardial infarction, and hospitalization for heart failure). In the combination therapy group, there were more side effects and therapy discontinuations. Kidney function–related side effects were observed more frequently in the combination arm.[21]

Several recent analyses examining these 3 trials and a number of other heart failure studies reported that combination therapy resulted in more adverse effects, particularly hypotension, hyperkalemia, and worsening of kidney failure.[22,23] Although overall rate of these adverse events was low, they were nearly doubled in combination arms compared to control groups.[24]

For some time, it was hoped that when the results of ONTARGET were revealed, they would provide definitive clinical evidence for the effect of combination therapy. This particular trial[17] enrolled patients with high cardiovascular risk, while excluding those with evident heart failure, unlike the studies[19-21] mentioned previously. This trial also differed from the earlier trials by being the largest study with the longest follow-up period. It had a planned combination arm with maximal recommended doses, and the targeted dosages were reached by the majority of the patients. At the end of the study, all 3 of the therapy arms were similar in terms of primary

composite end point (death from cardiovascular causes, myocardial infarction, or stroke, or hospitalization for heart failure). The observed relative risks for primary end points were consistent across a range of subgroups in all treatment arms. There were also no differences in the rates of various secondary outcomes, except for a significant increase in the relative risk of decreased kidney function in patients assigned to combination therapy. In the combination group, there was a significantly higher number of therapy discontinuations and more hypotension, syncope, decreased kidney function, and hyperkalemia.[17] The renal data of the ONTARGET study were recently published as a prespecified secondary outcome. The frequency of the composite primary renal outcome of dialysis, doubling of serum creatinine, and death was found to be similar with ramipril and telmisartan, but increased significantly with combination therapy.[25] The secondary renal end point of dialysis or doubling of serum creatinine was also more frequent with combination therapy. There was no difference in the incidence of long-term dialysis between the groups, but acute dialysis was more frequent for the combination therapy. Subgroup analysis has shown no clear benefit for combination therapy even in the highest renal risk groups, such as among patients with overt diabetic nephropathy. Although end-stage renal disease events were similar, combination therapy had beneficial effects on proteinuria. It decreased progression of microalbuminuria to macroalbuminuria, and also reduced the risk of developing new micro- or macroalbuminuria.[25] The increased risk of renal events, especially the need for acute dialysis in the ONTARGET study may be attributed to the patient characteristics (eg, elderly, high cardiovascular risk with low renal risk, and an increased probability of renovascular disease) and to the increased frequency of hypotension and hyperkalemia in combination therapy.[26]

ACE Inhibitor–ARB Combination and Chronic Kidney Disease

Combination therapy with 2 drugs has been most frequently used to prevent kidney disease.[27] Most of those studies have limited numbers of patients, short follow-up periods, and tested intermediate end points (proteinuria) regarding kidney disease. Few of them have critical end points such as kidney disease progression, death, or requirement for dialysis (Table 2).

The first noteworthy trial is the CALM (Candesartan and Lisinopril in Microalbuminuria) study.[28] After a 24-week follow up, a greater decrease (of about 8 mm Hg) in systolic blood pressure was observed in the combination therapy group. Similarly, albuminuria decreased a further 50% as a result of combination therapy. While all drugs were well tolerated in the trial, serum creatinine and potassium levels were slightly more elevated in the combination group.[28] The CALM II study, published 5 years after the first trial, used a high dose of ACE inhibitor (40 mg lisinopril, once daily) and showed no difference in systolic blood pressure and albumin excretion rates in comparison to combination therapy. The differences between the groups with respect to side effects were also not significant.[29]

The COOPERATE (Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor in Nondiabetic Renal Disease) study, which examined combination therapy in nondiabetic kidney disease, was the only trial powered for renal outcomes (time to doubling of serum creatinine concentration or end-stage renal disease).[30] While 11% of the patients reached the primary end point in the combination group, 23% of the patients did so in the monotherapy arms. This result indicated a decrease of about 60% in terms of risk and it was reported that the value was independent of the change in blood pressure. The decrease in proteinuria that was observed in the combination group of the trial was about 30% more than that seen in the other groups. The researchers reported slightly higher serum potassium values in the combination therapy arm.[30] This particular trial, which is regarded to present the most substantial evidence in terms of combination therapy in the nephrology literature, has been criticized regarding its methodology and the results have been viewed as unreliable.[31,32]

Kidney data for combination therapy were recently analyzed in several meta-analyses. Doulton et al demonstrated that combination therapy provided a further 30% to 39% drop in proteinuria when compared to monotherapy with an ACE inhibitor or an ARB. Although no complications were reported regarding safety, it was

stressed that the characteristics of the trials had to be borne in mind.[15] In the meta-analysis from MacKinnon et al, combination therapy resulted in a significant decline in proteinuria both in diabetic and nondiabetic patients.[33] It was stated that dual therapy led to a slight but significant increase in serum potassium concentrations, while resulting in an insignificant drop in glomerular filtration rate. The analysis also stressed the need for a trial with a longer follow-up period.[33] An analysis published in early 2008 reported a further drop of 27% to 34% in proteinuria, while adding that discontinuation was more common with combination therapy.[34] A meta-analysis of the trials carried out on patients with primary glomerulonephritis revealed that combination therapy led to a marked decrease in proteinuria, resulted in a further drop in blood pressure, increased serum potassium concentrations, and did not have an impact on glomerular filtration rate.[35] It can be concluded from these analyses that there are not enough data concerning the safety and efficacy of combination therapy.[36]

Some important trials, including ONTARGET, have been published after these meta-analyses were performed. The IMPROVE (Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events) study has shown no further benefit on albuminuria reduction in patients treated with combination therapy despite the fact that blood pressure reduction was slightly better in the combination group. Subgroup analyses showed the largest reduction in albuminuria occurred in patients with overt nephropathy but it did not reach statistical significance.[37] A similar finding was observed in the ONTARGET study. In patients with the highest risk (overt diabetic nephropathy), the point estimate for the primary outcome was in favor of combination therapy, but it was not significant. Similarly, in high-kidney-risk groups (eg, with micro- or macroalbuminuria), combination therapy showed no benefit, but tended to show worse results in low-kidney-risk groups.[25] In contrast to these studies, the VALERIA (Valsartan in Combination With Lisinopril Versus the Respective High Dose Monotherapies in Hypertensive Patients With Microalbuminuria) trial demonstrated that combination therapy was more effective in reducing microalbuminuria despite the fact that patients received the maximal recommended doses of lisinopril or valsartan as monotherapy. There was no difference in blood pressure between the groups. Adverse events were slightly higher in the combination therapy arm, most notably hypotension.[38] The different results of the IMPROVE, VALERIA, and ONTARGET studies may be attributed to the methodological differences between the studies.

Current Evidence Regarding Efficacy and Safety of Dual Inhibition of the RAS

The studies performed in the last 30 years have revealed that inhibition of the RAS yields favorable results in each step of the cardiovascular and kidney disease continuum.[24] Although the number of comparative studies is not satisfactory, when data from ONTARGET and other trials are considered, it can be suggested that ACE inhibitors and ARBs are of identical efficacy. ARBs may provide a further advantage as they are better tolerated in most trials.[6,17] Using those 2 agents in combination has a strong pathophysiological basis, but most clinical trials have failed to sustain full support of this rationale.

A major problem of the published trials that have examined combination therapy is the "methodological turbulence," especially in the dose selection criteria. The ideal dose for an ACE inhibitor or ARB as monotherapy or in combination for a complete inhibition of the RAS is unknown.[39,40] It is therefore impossible to make a "pure" comparison between positive and negative trials. Combination therapy usually leads to a slightly greater decrease in blood pressure.[15] It is not known whether this decrease does in fact lead to the benefits reported by several studies. Moreover, the data regarding organ-protective effects of combination therapy are also controversial. A small benefit was observed in studies conducted on patients with heart failure.[19,20] This extra benefit is more pronounced only in patients with incomplete neurohumoral inhibition (eg, due to lower-dose or no ACE inhibitor administration or no use of β-blockers).[19] However, it should be borne in mind that neither of the 2 studies was designed to test combination therapy. Both the VALIANT and ONTARGET studies, which were planned for testing combination therapy from the beginning, not only failed to show any further benefit but also revealed the existence of more adverse events.[17,21] The most striking data for combination therapy were reported in ONTARGET. Although the blood pres-

sure drop was superior in the combination arm, no added benefit was noted with respect to the primary end point, while hypotension, decreased kidney function, and hyperkalemia were more common.[21] The kidney outcome data of the ONTARGET study also showed no further benefit with combination therapy even in the high-kidney-risk group.[21] Although the ONTARGET study was not specifically powered for primary kidney outcomes, and the patient cohort has distinctive characteristics,[26] these results may offer insights on the safety of combination therapy, if interpreted with caution.

Kidney data for combination therapy should be separately analyzed. Most of the trials were conducted over a short period of time and with a limited number of patients. Moreover, most studies did not have definitive end points and failed to provide long-term follow-up data. Although some studies presented conflicting data,[37,38] meta-analyses have reported a greater antiproteinuric effect for combination therapy. Given the significance of proteinuria control in terms of kidney disease progression, this specific outcome is of critical importance. However the discrepancy between greater reduction in proteinuria and worsening of major kidney outcomes in combination therapy in the ONTARGET study needs further scrutiny, even if the study cohort is unusual.[25]

In light of the available data, combination therapy probably plays a role only in patients with CHF who have incomplete neurohumoral blockade or in a minority of proteinuric patients with suboptimal therapeutic response to monotherapies. The major issue, however, is the absence of hard end-point data for kidney outcomes and the lack of long-term safety data in general. There are some ongoing trials which may clarify these issues (Table 3), but they may also suffer from issues either in dosage, patient numbers, or duration of the study. Among these studies, the VA NEPHRON-D (Veterans Affairs Nephropathy in Diabetes) study, which is sponsored by the US Department of Veterans Affairs, is planning to enroll enough patients with sufficient duration for testing major kidney outcomes.[41]

Until the results of ongoing trials and further safety data emerge, it is wise to withhold use of ACE inhibitor and ARB combination in general practice, especially for low-kidney-risk patients, the elderly, and high-vascular-risk patients similar to the ONTARGET cohort, and maybe for those with advanced kidney disease. If we do decide to use combination therapy, patients have to be monitored with extreme caution, as we do not have sufficient evidence of safety.

THE FUTURE OF RAS INHIBITION

The rationale to use an ACE inhibitor in combination with an ARB is to obtain complete RAS inhibition. To understand whether this is the ideal approach, there is an urgent need for a large-scale, long-term, head-to-head randomized controlled trial. The trial should start with optimal doses of an ACE inhibitor, ARB, and their combination, and the doses should be escalated accordingly. This study should include a moderate- to high-kidney-risk patient group, should seek a primary outcome of major kidney events (doubling of serum creatinine, dialysis, or death) and cardiovascular events (cardiovascular and all-cause mortality), and should scrutinize safety issues judiciously.

There are some other ways to inhibit the RAS and these alternatives may complement existing strategies during the search for an ideal approach. Use of ACE inhibitors or ARBs in very high doses beyond their approved doses may have further cardiorenal protective effects.[40,42] Most, but not all studies suggest that high doses of either drug may cause a further decrease in proteinuria.[40] However, the effect of very high doses on major kidney outcomes and safety issues is yet to be determined.

Aldosterone is the final effector of the RAS (Fig 1), and increased aldosterone levels have been shown to contribute to cardiorenal damage.[43] Aldosterone antagonism as monotherapy or as a complement to other inhibitors of the RAS has been shown to have further cardiac[44,45] and kidney protective effects.[46] Following the publication of the landmark trial RALES (Randomized Aldactone Evaluation Study), there was a change in clinical practice causing an increase in the incidence of hyperkalemia-associated morbidity and mortality.[47] For renal protection, available data are scarce and mainly from short-term, small-scale trials concentrated primarily on the effect on proteinuria.[46] There is no clinical evidence on the effect of an aldosterone antagonist on long-term progression of chronic kidney dis-

Table 3. Main Ongoing Trials of ACE Inhibitor–ARB Combination in CKD

Study Name & ClinicalTrials.gov Identifier	Study Type & Duration	Clinical Setting	N	Intervention	Primary Outcome	Secondary Outcome	Study Start & Completion Date
Preventing ESRD in Overt Nephropathy of Type 2 Diabetes (VALID),[65] NCT00494715	Randomized, open-label, active control, parallel assignment, safety/ efficacy study, 3 y	High-risk patients with type 2 DM and overt nephropathy, defined as 1.8 < SCr < 3.2 mg/dL and urine spot ACR > 2,000 mg/g	120	▪ Benazepril (10 mg, 1×/d) + valsartan (80 mg, 1×/d) ▪ Benazepril (20 mg, 1×/d) + valsartan (160 mg, 1×/d)	Progression to ESRD (need for RRT by dx or tx)	Doubling of SCr, rate of GFR decline, incidence of fatal and nonfatal CV events (stroke, AMI, sudden death), ACR and 24-h urinary protein excretion	May '07-Dec '12
VA NEPHRON-D Study,[41] NCT00555217	Randomized, double-blind, active control, parallel assignment, efficacy study, 2-5 y	Type 2 DM and overt nephropathy	1,850	▪ Lisinopril (10-20-40 mg, 1×/d) + losartan (50-100 mg, 1×/d) ▪ Losartan (50-100 mg, 1×/d)	Composite end point of reduction in eGFR of 30 (individuals with an eGFR ≥ 60); reduction in eGFR of > 50% (individuals with an eGFR < 60); progression to ESRD (need for dx, tx, or an eGFR < 15) or death	Renal composite end point, defined as reduction in eGFR of > 50% (for individuals with a baseline eGFR < 60); reduction in eGFR of > 30 (for individuals with a baseline eGFR ≥ 60) or progression to ESRD (defined as need for dx, tx, or eGFR < 15)	Jul '08-Jul '13
Safety of Dual Blockage of Renin-Angiotensin System in Patients With Advanced Renal Insufficiency (SDBRAS),[66] NCT00630708	Randomized, open-label, active control, parallel assignment, safety study	Non-DM patients with advanced decreased kidney function	309	▪ Benazepril (10 mg, 1×/d) + losartan (50 mg, 1×/d) ▪ Benazepril (20 mg, 1×/d) ▪ Losartan (100 mg, 1×/d)	Proportion of patients with increase in serum potassium ≥ 6.0 mmol/L	The proportions of patients with SCr increase of > 30%, with drug-related cough, with hypotension (SBP < 110 mm Hg), with nonfatal CV events	Feb '08-May '10
HALT Progression of Polycystic Kidney Disease (HALT PKD),[67] NCT00283686	Randomized, double-blind, placebo-controlled, factorial assignment, efficacy study	ADPKD patients with GFR > 60 (age 15-49 y, Study A) & GFR 25-60 (age 18-64 y, Study B)	1,018	Study A: ● Arm 1: Lisinopril (5-10-20-40, 1×/d) + telmisartan (40-80 mg, 1×/d) and standard BP control of 120-130/70-80 mm Hg ● Arm 2: Lisinopril (5-10-20-40, 1×/d) + telmisartan (40-80 mg, 1×/d) and low BP control of 95-110/60-75 mm Hg ● Arm 3: Lisinopril (5-10-20-40, 1×/d) + placebo and standard BP control of 120-130/70-80 mm Hg ● Arm 4: Lisinopril (5-10-20-40, 1×/d) + placebo and low BP control of 95-110/ 60-75 mm Hg Study B: ● Arm 1: Lisinopril (5-10-20-40, 1×/d) + telmisartan (40-80 mg, 1×/d) and standard BP control of 110-130/80 mm Hg ● Arm 2: Lisinopril (5-10-20-40, 1×/d) + placebo and standard BP control of 110-130/80 mm Hg	Study A: Change in total kidney volume, as assessed by abdominal MR Study B: Time to the 50% reduction of baseline eGFR, ESRD (initiation of dx or preemptive tx), or death	Not available	Jan '06-Apr '13

Note: GFR levels are given in mL/min/1.73 m^2.

Abbreviations: ACR, albumin-creatinine ratio; ADPKD, autosomal dominant polycystic kidney disease; AMI, acute myocardial infarction; BP, blood pressure; CV, cardiovascular; DM, diabetes mellitus; dx, dialysis; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RRT, renal replacement therapy; SBP, systolic blood pressure; SCr, serum creatinine; tx, transplantation.

ease. The issue may also be resolved with a proper study.

Inhibition of the renin enzymatic activity in the very first and rate-limiting step of the RAS provides a novel therapeutic tool. The biochemical consequences of renin inhibition differ from those of ACE inhibitors or ARBs.[48] Combination of aliskiren with ramipril[49] or valsartan[50] at the maximum recommended doses provided significantly greater reductions in blood pressure than monotherapy and there was no increase in adverse events. The AVOID (Evaluation of Proteinuria in Diabetes) trial showed that addition of aliskiren (300 mg daily) to maximal recommended dose of losartan (100 mg, once daily) in patients with type 2 diabetes, hypertension, and proteinuria reduced the albumin-creatinine ratio by 20%. There was no increase in the number of adverse events in the combination group.[51] However, all these studies should be considered as preliminary and concerns about safety issues should be kept in mind with widespread use of such combinations.[52,53] There are studies in progress from which more hard end-point and safety data may appear.[54]

The future of RAS inhibition with these agents on the agenda will undoubtedly provide us with more information for answering some old questions, but will likely generate many new questions as well. Whether dual or even triple blockade of the RAS can provide safe and effective cardiorenal protection is yet to be established.

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