Combined Blockade of the Renin-Angiotensin System With
Angiotensin-Converting Enzyme Inhibitors and Angiotensin
II Type 1 Receptor Antagonists

Michel Azizi, MD, PhD; Joël Ménard, MD

Blockade of the renin-angiotensin system (RAS) with ACE inhibitors or angiotensin II type 1 receptor (AT1R) antagonists has become one of the most successful therapeutic approaches in medicine. Within 25 years, substantial evidence has accumulated to indicate that this therapy reduces blood pressure (BP),1 left ventricular (LV) mass,2 and proteinuria.3 RAS blockade results in a decrease in cardiovascular morbidity and mortality in patients with chronic heart failure (CHF)4–6 or LV systolic dysfunction7 and after myocardial infarction (MI).8,9 RAS blockers retard the progression of renal insufficiency in type 1 (ACE inhibitors10) and type 2 (AT1R antagonists11,12) diabetes mellitus and nondiabetic chronic renal disease.13–15 Finally, a high dose of an ACE inhibitor administered in the evening reduces the rate of death, cardiac events, and stroke in patients with a high cardiovascular risk at baseline.16 Several mechanisms contribute to the beneficial effects of RAS blockers in cardiovascular and renal therapy, schematically the hemodynamic consequences of angiotensin II (Ang II) neutralization and the suppression of the Ang II–dependent generation of growth-promoting cytokines, free oxygen radicals, and fibrosis mediators in tissues.17

Concept of Combined RAS Blockade by ACE Inhibitors and AT1R Antagonists

An ACE inhibitor administered at usual daily doses only suppresses plasma Ang II levels within a few hours after dose intake, and similarly, usual daily doses of an AT1R antagonist do not block AT1Rs over 24-hour periods.18,19 This has led to the concept of combined RAS blockade. The “escape” observed with single-site RAS blockers is due to the conjunction of the progressive clearance from the body of the drug at the end of the dosing interval and the counterregulatory reactive rise in plasma active renin that increases Ang I, the ACE substrate, or Ang II, the AT1R agonist, proportionally to the suppression of the Ang II negative feedback on renin release.18 These 2 phenomena can explain why, in the presence of persistent plasma ACE inhibition, an attenuation of the BP response to ACE inhibitors occurs 24 to 48 hours after last drug intake, with an even faster return of plasma Ang II level toward its initial level.18 This counterregulation contributes to the flat dose-response curve of BP measured at trough that has been reported for most RAS blockers tested in patients with essential hypertension.20 In many patients with CHF, incomplete RAS blockade21 may also contribute to deterioration of LV function and to a poor cardiac prognosis associated with persistence of neurohormonal activation despite maximally recommended doses of ACE inhibitors.

The combination of 2 pharmacological agents that inhibit 2 consecutive RAS steps, ACE and AT1R, can minimize or even overcome the escape observed with single-site RAS blockade. At the time when the ACE inhibitor dissociates from ACE active sites and Ang II reappears in the presence of an increased level of plasma and interstitial Ang I, the concurrent administration of an AT1R antagonist will protect the AT1R from the newly produced agonist. Reciprocally, when less AT1R antagonist is bound to the AT1Rs, an ACE inhibitor will reduce the production of Ang II available to compete with the antagonist. The alternative proposed to this physiological explanation is that an AT1R antagonist in combination with an ACE inhibitor blocks the effects of Ang II generated by pathways other than renin and ACE, such as CAGE (chymotrypsin-like angiotensin generating enzyme)22 or chymase.23

Demonstration of the Concept of Combined RAS Blockade

The additive or synergistic effect of an ACE inhibitor and an AT1R antagonist combination on the decrease in BP and on the increase in plasma active renin was first demonstrated in single oral dose studies with a human model of mild sodium depletion in normotensive subjects.24,25 Even in conditions of high sodium intake and low basal renin status, 2 conditions known to reduce or neutralize the hypotensive effects of drugs that interrupt the RAS at the level of ACE or AT1
receptors, the dual RAS blockade was shown to be more effective than doubling the usual dose of an AT1R antagonist through more efficient blockade of the RAS.26 This may offer an alternative strategy for treating patients with various renin levels and may potentially increase the cardioprotective and nephroprotective benefits by more complete RAS blockade.

Subsequently, studies in various rat models of hypertension with either normal 27,28 or high renin levels 29 confirmed that the BP-lowering effect of the combined RAS blockade enables the individual dosages of each drug in the combination to be 3 to 10 times lower than when used separately to achieve the same BP-lowering effect. However, this BP response to the combined RAS blockade appears to be finite. If the doses of each single-site blocker are increased toward a “maximal” inhibition of the RAS, the synergistic effect of combination therapy is not observed at peak effect,28 and the magnitude of the decrease in BP remains salt-dependent as it is with a single-site RAS blocker.

Biochemical Consequences of Combined Blockade of the RAS by an ACE Inhibitor and an AT1R Antagonist

Dual blockade of the RAS combines the biochemical consequences of ACE inhibition and AT1R antagonism on the RAS cascade (Table 1). Although combination of an AT1R antagonist and an ACE inhibitor allows essentially for a more complete and sustained blockade of both circulating and tissue RAS, alternative mechanisms involving bradykinin and Ang(1-7) accumulation and angiotensin II type 2 (AT2) receptor stimulation, and consequently NO release, may participate in its overall pharmacodynamic effect. Indeed, like ACE inhibitors, the combination induces accumulation of vasodilatory and natriuretic peptides such as bradykinin30 and Ang(1-7) 31 and of the hematologic peptide AcSDKP. 32 The reduced breakdown of bradykinin by ACE inhibitors activates the B2 receptor and consequently the release of NO, prostacyclin, and other potent endothelium-derived local vasodilator substances,30 which in turn may participate in their short-term hemodynamic effect. During chronic ACE inhibition and dual RAS blockade, elevation of Ang(1-7) levels may serve to potentiate the vasodilator actions of bradykinin by stimulating NO release.31 The combination should also stimulate potentially functioning AT2 receptors, although less strongly than does an AT1R antagonist given alone, because of the ACE inhibitor. Stimulation of AT2 receptors per se could trigger a vasodilator and natriuretic cascade involving bradykinin, NO, and cGMP.33 Finally, in

<table>
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<tr>
<th>Enzymes</th>
<th>ACE Inhibitors</th>
<th>AT1R Antagonists</th>
<th>ACE Inhibitors + AT1R Antagonists</th>
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<tbody>
<tr>
<td>Plasma ACE</td>
<td>Inhibited</td>
<td>Not inhibited</td>
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<tr>
<td>Tissue ACE</td>
<td>Inhibited</td>
<td>Not inhibited</td>
<td>Inhibited*</td>
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<tr>
<td>Plasma renin</td>
<td>Increased</td>
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<td>Additive effect</td>
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<td>Renal renin</td>
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<td>Prorenin</td>
<td>Increased</td>
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Substrates

| Ang I               | Increased     | Increased        | Additive effect                  |
| Bradykinin          | Increased     | No change         | Increased                        |
| AcSDKP              | Increased     | No change         | Increased                        |
| Angiotensinogen     | Decreased     | Decreased         | Additive effect                  |

Receptors

| AT1R                | Not stimulated | Blocked           | Not stimulated and blocked       |
| AT2R                | Not stimulated | Stimulated        | Minor stimulation*               |
| AT(n) Rs            | Not stimulated | Stimulated        | Minor stimulation*               |
| Bradykinin (B2)     | Stimulated    | Stimulated        | Additive effect                  |

End products

| Ang II              | Decreased     | Increased        | Decreased or normal              |
| Non–ACE-dependent Ang II | Present    | Blocked            | Blocked*                        |
| Ang III             | Decreased     | Increased        | Decreased or normal*            |
| Ang IV              | Decreased     | Increased        | Decreased or normal*            |
| Ang (1–7)           | Increased     | Increased        | Additive effect                  |
| Aldosterone         | Decreased     | Decreased         | No major additive effect         |

Miscellaneous

| Tissue RAS          | Inhibited     | Blocked           | Additive effect*                 |
| ACE induction       | Increased     | No change         | Increased*                       |

*Based on theoretical grounds.

AT(n)R indicates AT(n) receptor.
The cardioprotective effects of combined RAS blockade are demonstrated by the results of the ValHeft trial and even more by the results of CHARM-Added (Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity) trial, which both showed consistently that the addition of an AT1R antagonist to an ACE inhibitor–based treatment improves cardiovascular outcome in patients with CHF. In the CHARM-Added trial, administration of a high dose of candesartan titrated to 32 mg daily (mean daily dose 24 mg) to patients with class II to IV CHF and LV ejection fraction ≤40% who were being treated with a standard daily dose of an ACE inhibitor for at least 6 months resulted in a 15% relative risk reduction (hazard ratio 0.85, 95% CI 0.75 to 0.96; P = 0.011) in cardiovascular death and admission to the hospital for HF compared with a placebo (Tables 2 and 3). In other words, 23 CHF patients previously treated with an ACE inhibitor have to be treated for 3 years by a high, once-daily dose of candesartan to prevent 1 first event of cardiovascular death and admission to the hospital for HF. The beneficial effects of candesartan were consistent among all prespecified subgroups, including patients treated with β-blockers.

By contrast, in 14,703 high-risk patients with evidence of acute HF, LV systolic dysfunction, or both after acute MI (anterior type: 58.7% to 60.3%, Q-wave type 65.8% to 67.5%), combination therapy with valsartan (80 mg BID) and captopril (50 mg TID), begun a median of 4.8 days after the qualifying event, did not reduce total or cardiovascular mortality or the rate of secondary end points compared with captopril (50 mg TID) or valsartan (160 mg BID) in the VALIANT (Valsartan in Acute Myocardial Infarction) trial (Tables 2 and 3). However, post hoc analysis showed that combination therapy resulted in a significant reduction in the cumulative rate of admission for recurrent MI or HF. Combination therapy had a small additional significant BP-lowering effect (−2.2 mm Hg) compared with captopril 50 mg TID but increased the rate of drug-related adverse events, especially hypotension and renal-related causes, and the rate of permanent discontinuation of study treatment. The effect of dual RAS blockade on the incidence of recurrent hospitalizations and on systemic and renal hemodynamics indicates that biological blockade of the RAS achieved by combination therapy was indeed greater than that achieved by captopril alone. The use of a high dose of captopril (50 mg TID) reduced the probability of detecting a difference between the combination therapy and captopril groups, because the selected ACE inhibitor dose was at the maximum of its dose-response curve.

As also shown by Pfeffer et al and summarized in Tables 2 and 3, differences between patients in terms of baseline prognosis factors, absolute cardiovascular risk, basal activation of the RAS, selected study treatment doses and dosing intervals, and adherence to the therapeutic regimen may explain the apparent discrepancy in terms of cardiovascular mortality between the CHARM-Added and VALIANT trials. Patients recruited in VALIANT had less severe HF at baseline than those recruited in CHARM-Added, as assessed by LV ejection fraction (35.3% versus 28.8%, respectively) and past history of HF (15% versus 77.6%, respectively) and differed in terms of cardiovascular drug prescription before
randomization (β-blockers and ACE inhibitors; Table 2). The main reason for discrepancy between the 2 trials is probably due to the difference in the therapeutic dosing scheme. In CHARM-Added, candesartan was titrated to 32 mg administered once daily and added to preexisting, investigator-chosen optimal ACE inhibitor therapy given once (enalapril, lisinopril, ramipril) or twice (captopril) daily and not uptitrated concurrently with candesartan.46 In contrast, in the VALIANT trial, the dose of captopril, alone or in combination, was titrated to 50 mg 3 times daily, and valsartan alone was titrated to 160 mg twice daily. When the dosing interval prescribed for a single-site RAS blocker is short (BID or TID prescriptions), the intermittent neurohormonal reactivation between each dose intake is more efficiently neutralized than when the dosing interval is 24 hours (once-daily prescriptions) or even longer (noncompliance).18,19

The results of both trials can thus be reconciled. They both emphasize the critical choice of the right dose and dosing interval of a RAS blocker in high-risk post-MI patients and especially in patients with CHF for achieving more complete and sustained neutralization of Ang II effects, especially at trough, to avoid intermittent neurohormonal reactivation between each drug intake. The neurohormonal escape phenomenon to RAS blockade can be reduced by the once-daily administration of the combination of an AT1R antagonist with an ACE inhibitor at lower doses or by the administration of either an AT1R antagonist or an ACE inhibitor alone at high doses provided that a 24-hour-blockade of the RAS can be achieved by the choice of the appropriate dosing interval. In addition to or as an alternative to RAS blockade, a specific blockade to target aldosterone might remain necessary to neutralize its Ang II–independent secretion, especially in patients with CHF.48

Combined RAS Blockade and Nephroprotection
The renal effects of combined RAS blockade require special attention. The 2 main strategies for protection against loss of renal function in patients with chronic nephropathies have been to lower BP and to restrict dietary protein,49 although the latter approach remains controversial. Although lowering BP results in reduced urine protein excretion, a specific blockade of the RAS has additional effects and retards the progressive course of chronic renal disease more than other nonspecific antihypertensive treatments.11,12,50 Most of the nephroprotective effect of RAS inhibitors is observed in proteinuric nephropathies and is related to their major efficacy in reducing proteinuria. 13 Because the antiproteinuric response to treatment is the strongest predictor of long-term nephroprotective efficacy, and the presence of a residual proteinuria during treatment is an independent risk factor for progression of renal disease,13 the focus of nephroprotection has shifted toward maximal reduction of proteinuria, in addition to optimal control of BP.

However, many patients with chronic diabetic or nondiabetic nephropathy do not reach BP targets and have persistently elevated proteinuria, despite treatment with several
antihypertensive agents, including recommended doses of ACE inhibitors. Apart from age, individual susceptibility, genetic factors, implication of multiple biological pathogenic factors, and the lag time between proteinuria appearance and treatment initiation, this insufficient response may be explained by incomplete blockade of the RAS, especially if intrarenal RAS is regulated independently of circulating RAS. The huge amount of renin synthesized and released locally, the limited amount of renal endothelial ACE, the compartmentalization of Ang II in interstitial and tubular fluids, the intrarenal consumption of angiotensinogen, and the uptake of Ang II by the renal AT1Rs influences the intrarenal levels of Ang I and Ang II, which differ from their plasma levels. By increasing and prolonging intrarenal Ang II neutralization, specific renal benefits are expected from the combined blockade in renal tissue under pathological circumstances, but adverse renal effects may also be expected as a consequence of renal hypoperfusion and vasodilatation under certain circumstances.

**Experimental Results**

Experimentally, combined RAS blockade has been shown to be more effective than or equivalent to single-site blockade in terms of BP and proteinuria reduction. Results are dependent on the experimental model, the rat strain, the severity of the pretreatment histological damage, the doses of the drugs used alone or in combination, and the time of treatment initiation and its duration. In the short term, the majority of the experimental studies did not demonstrate any additional benefit of combined blockade over single-site RAS blockade for prevention of glomerulosclerosis and tubulointerstitial injury, or consequently for short-term prevention of a decline in glomerular filtration rate in animal models. A multitargeted approach is probably necessary to achieve full nephroprotection.

**Diabetic and Nondiabetic Chronic Nephropathy: Clinical Results**

The additive effects of the combination of an ACE inhibitor with an AT1R antagonist were first demonstrated on clinical surrogate end points. Combined RAS blockade with usual daily or even maximally recommended doses of an ACE inhibitor and an AT1R antagonist reduced BP, microalbuminuria, and albuminuria further than did single-site RAS blockade in patients with type 1 or type 2 diabetes. Similarly, in patients with nondiabetic proteinuric nephropathies, the hypotensive and antiproteinuric effects of combined RAS blockade were larger than those of single-site RAS blockade even when administered at high dose, or the addition of an AT1R antagonist to a background of ACE inhibition had an additional hypotensive and antiproteinuric effect. Although some studies have found a positive correlation between BP fall and albuminuria reduction in patients with chronic nephropathy, which suggests that the nephroprotective effect of combined RAS blockade is in part due to changes in systemic, local, and glomerular capillary pressures as observed in experimental models, others have not.

The most relevant demonstration of the nephroprotective effects of combined RAS blockade came from the COOPERATE trial, which showed the superiority of combined RAS blockade over single-site RAS blockade after 3 years of...
treatment.63 After determination of the maximally antiproteinuric dose of trandolapril (3 mg/d), 263 patients with nondiabetic chronic nephropathy (65% glomerulopathies) and persistent proteinuria >0.3 g/24 hours were randomly assigned to 3 mg of trandolapril daily, or 100 mg of losartan daily, or a combination of both drugs.63 The trial was stopped after the first interim analysis at 3 years because of a difference in end-point incidence in favor of the combination. Ten patients (11%) taking combination treatment reached the combined primary end point, ie, time to doubling of serum creatinine concentration or end-stage renal disease, compared with 20 (23%) given trandolapril alone (hazard ratio 0.38, 95% CI 0.18 to 0.63; P=0.018) and 20 (23%) given losartan alone (hazard ratio 0.40, 95% CI 0.17 to 0.69; P=0.016).63 The benefit of the combination treatment was independent of baseline proteinuria and was preferentially observed in patients with glomerulonephritis. The 3 treatment groups showed the same reductions in BP, but the combination had a greater proteinuria-reducing effect over the whole trial duration (maximum median change −75.6%) than either losartan (−42%) or trandolapril (−44.3%). Finally, whether similar beneficial BP and renal effects would be achieved by increasing the dose of the individual single-site RAS blockers toward the top of their dose-response curves with twice-daily administrations remains controversial.61

The mechanisms by which combinations of ACE inhibitors and AT1R antagonists provide an additional antiproteinuric response are probably multifactorial and involve either systemic and glomerular capillary hemodynamic changes,61 a more complete neutralization of Ang II cellular effects, or both. In addition to the systemic BP-lowering effect, the intrarenal hemodynamic changes induced by dual RAS blockade are certainly one of the mechanisms for its increased efficacy.61 Many other explanations can be offered: more complete neutralization of the Ang II autocrine effects on intrarenal hemodynamics,64 glomerular size permeability,65 or structure,66 decreased transforming growth factor-β1 production,58,67 and glomerular nephrin expression.68,69 The downregulation in both gene and protein expression of the transmembrane protein nephrin, a major component of the slit diaphragm of the glomerular podocyte that plays a key role in the function of the glomerular filtration barrier, which accompanies the development of albuminuria in experimental models of hypertension and diabetes, has been shown to be reversed by an AT1R antagonist or an ACE inhibitor.68,69

Safety of Combined Blockade of the RAS

Theoretically, the price to be paid for combining an ACE inhibitor with an AT1R antagonist will be the addition of side effects, especially those dependent on ACE inhibition (cough, angioneurotic edema),36,38 and the potential hazards of a complete RAS blockade, especially in situations in which BP and renal function are renin dependent.27,70 If treatments that combine an ACE inhibitor and an AT1R antagonist are to become commonly used, it is important to be aware of any increased risk of functional renal insufficiency associated with this combination. There is undoubtedly an increased risk for some patients exposed to an intensified blockade of the RAS by high doses of a single-site blocker or combined usual doses of 2 RAS blockers: elderly or salt-depleted patients, patients receiving cyclooxygenase inhibitors, patients with renal artery stenosis, and during anesthetic induction. In the CHARM-Added trial, 4.5% of the candesartan-treated patients with CHF compared with 3.1% of the placebo-treated patients (P=0.079) experienced significant hypotension that led to treatment interruption.46 In addition, the incidence of significant creatinine increase was almost doubled in the candesartan group (7.8% versus 4.1% in the placebo group), as was the incidence of hyperkalemia, especially when spironolactone was part of the combination therapy in patients with CHF (Table 3).46 The risk of hyperkalemia is also increased when baseline glomerular filtration rate is <35 mL/min.37 In the VALIANT trial,47 combination therapy increased the rate of intolerance to treatment and permanent discontinuation of study treatment (Table 3). In addition to surveillance of serum potassium levels, especially in patients with renal failure, the hematocrit should be monitored.59,61

A more complete and rigorous assessment of these risks is needed. It will require pharmacoepidemiological studies of a large number of diverse patients with hypertension, renal insufficiency, and CHF in the general population.

Conclusions

The usual once-daily doses of ACE inhibitors and AT1R antagonists were selected initially on the basis of hypertension trial results, but the dose response for lowering proteinuria and retarding progression of renal failure,11,63 for retarding vascular lesions,16 and for preventing cardiovascular death in patients with CHF71 may not be the same as for BP reduction. All the results from randomized controlled clinical trials have convincingly demonstrated that the higher the doses of the ACE inhibitor16,71 and the AT1R antagonist,5,50 the greater the effect on target-organ damage. There is a large body of data now available from (1) the physiological analysis of the effects of dual RAS blockade in normotensive volunteers, (2) numerous investigations in a variety of experimental models over a wide dose range, (3) the results of large clinical trials in patients with CHF and chronic nephropathies, (4) the analysis of the biological effects of the multiple peptides involved in this biochemical intervention, and (5) the development of a biologically plausible model of its beneficial and adverse effects, to pay due attention to the tolerability in general populations and to the cost-effectiveness of this new therapeutic alternative, eg, dual blockade of the RAS. The combination of 2 RAS blockers maximizes the cardio- protection46 and nephroprotection49 afforded by even high doses of single-site RAS blockers. It maintains over 24 hours a permanent and complete blockade of the RAS,19 which is more easily achieved by combining 2 different RAS blockers than by increasing the once-daily dose of a single drug. By making possible a once-daily administration to achieve permanent blockade of the RAS over 24 hours, combined RAS blockade may also improve treatment compliance.

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