Rationale for Combining Blockers of the Renin-Angiotensin System

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Summary: Blockade of the renin-angiotensin system (RAS) with angiotensin I–converting enzyme (ACE) inhibitors and AT1-receptor (AT1R) blockers has become one of the most successful therapeutic approaches in medicine. The question is no longer whether RAS inhibition helps, but rather how we can optimize inhibition to achieve optimal cardiovascular and renal protection. Indeed, numerous data have shown that the RAS is not blocked fully over 24 hours with current doses of RAS blockers because they trigger a counter-regulatory renin release that can offset pharmacologic inhibition of the RAS. This absence of full blockade may have clinical implications. Combination therapy with ACE inhibitors and AT1R antagonists thus has been proposed to inhibit the biological effects of the reactive renin release triggered by single-site RAS inhibition. By using this approach, numerous experimental and clinical studies have suggested that this combination therapy has additive or synergistic effects on blood pressure and on the prevention of cardiovascular and renal lesions. Although similar intensity of RAS blockade can be achieved by either combination therapy or by using high doses of an AT1-receptor antagonist given alone, the ACE inhibitor present in the combination interferes with the bradykinin–nitric oxide pathway and the N-acetyl-Ser-Asp-Lys-Pro metabolism, which both may have additional biological effects.
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Blockade of the renin-angiotensin system (RAS) with angiotensin I–converting enzyme (ACE) inhibitors, AT1 receptor (AT1R) blockers, or a combination of these drugs[1] has become one of the most successful therapeutic approaches in medicine. There is considerable evidence to show that this treatment reduces blood pressure (BP),[2] left ventricular mass,[3] and proteinuria.[4] RAS blockade decreases cardiovascular morbidity and mortality in patients with chronic heart failure,[5-7] or left ventricular systolic dysfunction,[8] and in patients after myocardial infarction.[9,10] RAS blockers retard the progression of renal insufficiency in type 1 (ACE inhibitors[11]) and type 2 (AT1R antagonists[12,13]) diabetes mellitus and nondiabetic chronic renal disease.[14-17] Finally, 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.[18] A beneficial effect of ACE inhibition in the prevention of cardiovascular diseases, even in the absence of high BP, also was reported in the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) trial,[19] and in a meta-analysis,[20] including the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial.[21]

OVERVIEW OF THE RAS

The RAS is a coordinated hormonal cascade that regulates fluid and electrolyte balance and arterial pressure, and it plays a major role in cardiovascular, renal, and adrenal function (for review see Carey and Siragy[22] and Paul et al[23]). In the classic view of the RAS, angiotensin (Ang) II, the biologically active octapeptide,

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is generated by a 2-step enzymatic process in which its precursor, the inactive decapeptide Ang I, is cleaved from angiotensinogen by renin, a glycosylated aspartyl protease secreted by the renal juxtaglomerular granular epithelioid cells. The second step of Ang II synthesis is the removal of the C-terminal dipeptide of Ang I by ACE, a zinc dipeptidyl carboxypeptidase with 2 catalytic sites.[24] ACE has multiple substrates both in vitro and in vivo.[24] For instance, in vivo it cleaves and thus inactivates bradykinin (BK), a vasodilator and natriuretic peptide,[24] substance P,[24] and also N-acetyl-Ser-Asp-Lys-Pro (AcSDKP), a hemoregulatory peptide.[25] Therefore, ACE generates a potent vasoconstrictor and antinatriuretic peptide, Ang II, while simultaneously degrading a potent vasodilator and natriuretic peptide, BK. Ang II binds to its receptors to activate intracellular signals, and it also very rapidly is cleaved by other enzymes, such as angiotensinases. into other shorter angiotensin-related peptides (Ang III, Ang [1-7], and Ang [3-8]).[22] The biological functions of Ang III are well known. Although Ang (1-7) and Ang (3-8) are biologically active, their functions in vivo have not been elucidated fully. The majority of the effects of Ang II—vascular smooth muscle cell contraction and pressor response, aldosterone secretion, inhibition of renin release (negative feedback loop), renal sodium reabsorption, vasopressin secretion, dipsogenic responses, generation of growth-promoting cytokines, free oxygen radicals, and fibrosis mediators in tissues—are mediated by the AT1 receptor.[22] Ang II also binds the Ang II type 2 receptor, whose functions remain controversial.[26]

This view of the RAS has been expanded by additional findings. First, besides the circulating RAS, numerous studies have proven the importance of a local tissue RAS in the kidney, brain, heart, blood vessels, and adrenal glands in mediating diverse physiologic functions.[23] Second, alternative non–ACE-dependent pathways of Ang II generation, such as chymase[27] and chymotrypsin-like angiotensin-generating enzyme,[28] and new enzymes such as the zinc metallo-carboxypeptidase ACE2, have been described.[29,30] ACE2 hydrolyzes Ang I to Ang (1-9), Ang II to Ang (1-7), and BK to des-Arg[9]-BK and other substrates in vitro, but its functions in vivo remain to be elucidated.[29,30] ACE2 counterbalances the functions of ACE and the balance between these 2 proteases may determine local and systemic levels of RAS peptides such as Ang II and Ang (1-7).[30] Third, besides the AT1 and AT2 receptors, other receptors (AT4) and other signaling pathways have been characterized.[31] Finally, the discovery of the prorenin/renin receptor has given renin and prorenin a direct biological role in stimulating intracellular pathways independently of Ang II.[32,33]

MECHANISM OF ACTION OF SINGLE-SITE RAS BLOCKERS

ACE Inhibitors and AT1R Antagonists

Several mechanisms contribute to the beneficial effects of RAS blockers in cardiovascular and renal therapy: the hemodynamic consequences of Ang II neutralization[34] and the suppression of the Ang II–dependent generation of growth-promoting cytokines, free oxygen radicals, and fibrosis mediators in tissues[35] However, the various methods used to inhibit the RAS differ in terms of their biochemical effects (Table 1).[36] Although single-site RAS inhibitors allow mainly for inhibition of both the circulating and tissue RAS, depending on their primary target and the distribution of the drug, alternative mechanisms may be involved in their overall pharmacodynamic effect. AT1R antagonists block the effects of Ang II generated by pathways other than ACE, such as chymotrypsin-like angiotensin-generating enzyme[28] or chymase.[27] In some organs, such as the kidneys,[37] heart,[27] and blood vessels,[38,39] Ang II continues to be produced in patients treated with ACE inhibitors. Non-ACE pathways may be activated in some pathologic situations. ACE inhibitors induce the accumulation of vasodilator and natriuretic peptides, such as BK and Ang (1-7),[40] and of the hematologic peptide AcSDKP.[25] ACE inhibitors decrease BK degradation, thereby activating the B2 receptor, leading to the release of nitric oxide (NO), prostacyclin, and other potent endothelial-derived local vasodilator substances,[41] which may in turn increase their short-term hemodynamic effects. During chronic ACE inhibition, increases in Ang (1-7) levels may enhance the vasodilator activity of BK by stimulating NO release.[40] AT1R antagonists stimulate potentially functional AT_2

Table 1. Biochemical Effects of RAS Blockers Given Alone or in Combination

	Single-Site RAS Blockade			Dual RAS Blockade		
	ACE Inhibitors	AT_1R Antagonists	Renin Inhibitors	ACE Inhibitors + AT1R Antagonists	Renin Inhibitors + AT1R Antagonists	Renin Inhibitors + ACE Inhibitors
Enzymes						
Plasma renin activity	Increased	Increased	Inhibited	Additive effect	Inhibited	Inhibited
Plasma renin concentration	Increased	Increased	Increased	Additive effect	Additive effect	Additive effect
Plasma ACE	Inhibited	Not inhibited	Not inhibited	Inhibited	Not inhibited	Inhibited
Tissue ACE	Inhibited	Not inhibited	Not inhibited	Inhibited	Not inhibited	Inhibited
Substrate concentrations						
Angiotensinogen	Decreased	Decreased	No change	Additive effect	No change	No change
Ang I	Increased	Increased	Decreased	Additive effect	Decreased or normal	Decreased or normal
BK	Increased	No change	No change	Increased	No change	Increased
AcSDKP	Increased	No change	No change	Increased	No change	Increased
Receptors						
AT1 receptors	Not stimulated	Blocked	Not stimulated	Not stimulated and blocked	Not stimulated and blocked	Not stimulated
AT2 receptors	Not stimulated	Stimulated	Not stimulated	Minor stimulation	Not stimulated	Additive effect
BK (B2) receptors	Stimulated	Stimulated	Not stimulated	Additive effect	Not stimulated	Stimulated
End-products						
Ang II	Decreased	Increased	Decreased	Decreased or normal	Decreased or normal	Additive effect
Non–ACE-dependent Ang II	Present	Blocked	Not stimulated	Blocked	Blocked	Inhibited
Angiotensin-related peptides	Decreased	Increased	Decreased	Decreased or normal	Decreased or normal	Additive effect
Aldosterone	Decreased	Decreased	Decreased	No major additive effect	Additive effect	Additive effect

receptors, which then may trigger a vasodilator and natriuretic cascade involving BK, NO, and cyclic guanosine monophosphate,[26] and other Ang II receptors, the functions of which remain unclear. Little is known about the physiologic consequences of activating these receptors but if their activation should prove to be deleterious, an issue that remains seriously debated,[42,43] then renin inhibitors would have clinical advantages over alternative RAS inhibitors. During chronic ACE inhibition, increases in AcSDKP levels may have beneficial cardiac and renal effects. AcSDKP has been shown to have an antiproliferative effect on renal fibroblasts and human mesangial cells in vitro,[44,45] and on cardiac fibroblasts in vitro and in vivo.[46] It also has an antifibrotic effect on the heart and the kidney in different experimental models[47,48] via inhibition of Smad2, the transforming growth factor β signal transduction pathway, and thus inhibition of expression of extracellular matrix proteins.[49-51] Finally, AcSDKP has been shown to have a direct nephroprotective effect in diabetic db/db mice[52] and in rats with anti-glomerular basement membrane nephritis.[53]

Blocking the RAS at its Initial Step: Renin Inhibition

Renin long has been recognized as the preferred, logical target for RAS blockade because it corresponds to the first, highly regulated and rate-limiting step of the system. Renin also has a remarkably high specificity for only one known substrate, angiotensinogen contrary to ACE. The clinical development of the first transition-state synthetic analogs capable of inhibiting renin has faced a number of technical problems. The oral administration of these renin inhibitors in human beings—CGP32860A,[54] remikiren,[55,56] and zankiren[57]—did not meet all the necessary criteria (specificity, potency, pharmacokinetic profile, and development costs) for these drugs to be considered clinically useful. Molecular modeling

and determination of the structure of the active site of renin have led to the identification of new renin inhibitors.[58] The first representative of this class of nonpeptide drugs is aliskiren, a potent hydrophilic transition-state mimetic alkane carboxamide renin inhibitor with a very high binding affinity for renin, resulting in selectivity for this enzyme over other aspartyl proteases.[59,60] It is a potent competitive renin inhibitor (IC_{50}: 0.6 nmol/L) that binds strongly to renin and is highly specific for human and primate renin, and is less active against renin from dog, rat, rabbit, pig, and cat.[60] This compound is available in an orally active form and, according to preclinical and clinical investigations, may be valuable for patients with cardiovascular and renal disorders.

As with ACE inhibitors and AT1R antagonists, the administration of a renin inhibitor increases circulating and intrarenal enzyme (renin) levels by interrupting the Ang II–renin negative feedback loop. However, with a renin inhibitor, the catalytic activity of the renin molecules newly released from the kidney is inhibited completely throughout the day, resulting in very low circulating levels of Ang I, Ang II, and other Ang I–derived peptides, thereby rendering the RAS quiescent. In contrast, the renin molecules newly released from the kidney remain enzymatically active after administration of an AT1R antagonist or an ACE inhibitor, resulting in high circulating levels of Ang I, with variable levels of Ang II depending on the drug used. This counterregulatory renin release could offset the pharmacologic inhibition of the RAS at the end of each dosing interval, when the amount of competitive inhibitor or antagonist on the enzyme (ACE) or receptor (AT1R) is decreasing.[1]

Renin inhibitors also may provide additional protection over other RAS inhibitors by interfering with the enhanced catalytic activity of renin and prorenin after the binding of these molecules to the (pro)renin receptor or by interfering with the binding of these molecules to their receptor. If renin inhibitors not only block the enzymatic activity of renin in vivo but also change the conformation of prorenin,[61,62] then they also may modify renin metabolism[63] and binding to various receptors, including the mannose 6–phosphate/insulin-like growth factor 2 receptor[64,65] or the renin receptor.[33] These putative effects of renin inhibitors potentially may be useful in patients with diabetes mellitus in whom prorenin levels are increased and are a powerful predictor of microvascular complications,[66] or if prorenin has a direct toxic effect.[67]

Some of the properties of renin inhibitors may have important clinical implications. Renin inhibitors induce a stronger renal vasodilator response than ACE inhibitors in sodium-restricted healthy subjects.[68] In circumstances in which Ang II generation within the kidney is activated by pathways dependent on or independent of ACE, as in patients with diabetic nephropathy,[69] or in African American hypertensive patients on a high-salt diet,[70] we would expect to see specific renal benefits of renin inhibition in renal tissue[71] after the administration of an orally active renin inhibitor.

Taking into account the very different angiotensin profiles achieved with the various single-site RAS blockers, the similarity of acute and long-term BP reductions achieved with certain doses of aliskiren and AT1R antagonists in different clinical settings should improve our understanding of the potential role of increased Ang (1-7) and BK-cyclic guanosine monophosphate-NO–mediated Ang II type 2 receptor stimulation on the hemodynamic effects of AT1R antagonists and ACE inhibitors.

THE NECESSITY OF OPTIMIZING THE RAS BLOCKADE

We have entered a new era in which the question is no longer whether RAS inhibition helps, but rather how we can optimize inhibition to achieve optimal cardiovascular and renal protection. The usual once-daily doses of ACE inhibitors and AT1R antagonists initially were selected on the basis of hypertension trial results, but the dose-response curve for decreasing proteinuria and retarding progression of renal failure,[12,72] for retarding vascular lesions,[18] and for preventing cardiovascular death in patients with chronic heart failure[73] may not be the same as for BP reduction. For instance, in type 2 diabetic patients

with microalbuminuria or macroalbuminuria, a 1.25-mg daily dose of ramipril was not effective to decrease cardiovascular risk in the Noninsulin-dependent Diabetes, Hypertension, Microalbuminuria, Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR) study,[74] whereas a 10-mg dose reduced cardiovascular mortality and morbidity in the Microalbuminuria, Cardiovascular, and Renal Outcomes HOPE (MICROHOPE) substudy.[75] In the Peridopril Protection Against Recurrent Stroke (PROGRESS) study,[76] a 4-mg daily dose of perindopril alone was not effective to prevent cardiovascular events in patients with a previous stroke, whereas an 8-mg daily dose of the same ACE inhibitor was effective in patients with coronary heart disease.[19] In hypertensive patients with type 2 diabetes and microalbuminuria, the highest dose of irbesartan (300 mg/d) was effective to reduce urine albumin excretion and the incidence of overt nephropathy, whereas the low dose of 150 mg of irbesartan was not.[77]

Numerous data have shown that the RAS is not blocked fully over 24 hours with current doses of RAS blockers, and that this absence of full blockade may have clinical implications. An ACE inhibitor administered at the usual daily dose only suppresses plasma Ang II levels for a few hours after dose intake; similarly, the usual daily dose of an AT1R antagonist does not block AT1Rs over a 24-hour period.[78,79] The escape observed with single-site RAS blockers is caused by the progressive clearance from the body of the drug at the end of the dosing interval in conjunction with the counter-regulatory reactive increase in plasma active renin, which 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.[78] Low drug concentrations at the end of the dosing interval and the counter-regulatory increase in renin release triggered by these drugs both could offset pharmacologic inhibition of the RAS. Similarly, the administration of a renin inhibitor increases circulating and intrarenal enzyme (renin) levels. However, given its high affinity for renin, its potency to inhibit renin (IC_{50}= 0.6 nmol/L), its very slow apparent dissociation rate, and its long pharmacokinetic half-life, the renin inhibitor, aliskiren, should inhibit each new renin molecule released into the bloodstream or kidney, making it less sensitive than ACE inhibitors and AT1R antagonists to this counter-regulatory phenomenon.

These phenomena can explain why, in the presence of persistent plasma ACE inhibition, an escape of the BP response to ACE inhibitors occurs 24 to 48 hours after last drug intake,[80] with an even faster return of the plasma Ang II level toward its initial level.[78] This counter-regulation contributes to the flat dose-response curve of BP measured at trough that has been reported for most RAS blockers tested in hypertensive patients.[81,82] In addition to the escape of aldosterone,[83] the incomplete RAS blockade[84] in many patients with congestive heart failure contributes to the deterioration of left ventricular function and to a poor cardiac prognosis, associated with a persistence of neurohormonal activation despite maximally recommended doses of ACE inhibitors.[85]

Finally, this phenomenon also may explain why many patients with chronic diabetic or nondiabetic nephropathy do not reach BP targets and have persistently increased proteinuria, despite treatment with several antihypertensive agents, including recommended doses of ACE inhibitors or AT1R antagonists. Apart from age, individual susceptibility, genetic factors, implication of multiple biological pathogenic factors, and the lag time between proteinuria appearance and treatment initiation, the insufficient response may be explained by incomplete RAS blockade,[86] especially if intrarenal RAS is regulated independently of circulating RAS.[87–90] The huge amount of renin synthesized and released locally, the limited amount of renal endothelial ACE,[91] the compartmentalization of Ang II in interstitial and tubular fluids,[92] the intrarenal consumption of angiotensinogen,[87] and the uptake of Ang II by the renal AT1Rs[93] influences the intrarenal levels of Ang I and Ang II, which differ from their plasma levels.

AVAILABLE THERAPEUTIC STRATEGIES TO OPTIMIZE RAS BLOCKADE: DUAL RAS BLOCKADE WITH ACE INHIBITORS AND AT1R ANTAGONISTS VERSUS ULTRAHIGH DOSES OF SINGLE-SITE RAS BLOCKERS

All the results from experimental models of renal insufficiency,[94] myocardial infarction,[95] and atherosclerosis,[96–98] and those from randomized controlled clinical trials, have shown convincingly that the higher the doses of ACE inhibitor[18,73,99] and AT1R antagonist,[77,100] the greater the effect on target organ damage.

Numerous experimental and clinical studies have suggested that a combination of currently available ACE inhibitors and AT1R antagonists has additive or synergistic effects on BP and on the prevention of cardiovascular and renal lesions,[1,72,101] with the combination of 2 RAS blockers maximizing the cardioprotection[101] and nephroprotection[72] afforded by even high doses of single-site RAS blockers. This may be because AT1R antagonists inhibit the effects of non–ACE-dependent Ang II production or because ACE inhibition has an impact on BK–NO or AcSDKP-related effects. However, the synergistic/additive effects of low doses of 2 different RAS inhibitors probably are explained better by inhibition of the biological effects of the reactive renin release triggered by single-site RAS inhibition. One problem with these studies involves the issue of dose. The question of dose selection and dosing interval is critical for all RAS inhibitors and substantially may influence their effects on BP and target organ protection. The additive or synergistic effects of such combinations are most evident at low doses (which are the usual doses) than at high doses.[102]

An alternative strategy to overcome the effects of the counter-regulatory renin release is to use single-site RAS inhibitors at doses much higher than usual and/or by fractionating the daily doses over 24 hours.[103,104] The dose range for ACE inhibitors is limited because of their adverse effects, but this does not apply to AT1R antagonists. They are well tolerated and can be used in doses far greater than those used for BP control. The short-term administration of ultrahigh doses of an AT1R antagonist to patients with type 2 diabetes and persistent microalbuminuria[105] or to patients with chronic nephropathy and persistent proteinuria[106] was accompanied by a further reduction in urine albumin excretion/proteinuria with no additional BP reduction. Although these studies emphasized the use of high doses of single-site RAS blockers, we still need more long-term and safety data, even though there was no safety issues in these 2 short-term studies performed in selected patients.

How can we choose between these 2 available strategies? Pharmacologically, a combination of an ACE inhibitor with an AT1R antagonist provides a more effective RAS blockade than each drug alone, and to achieve the same inhibition, much higher doses of AT1R antagonists than those presently prescribed, or a twice-daily prescription, would be necessary.[103,104] Combined RAS inhibition therefore makes it possible to use lower doses of each component to achieve a more effective and long-lasting RAS inhibition, and preserves the effects of ACE inhibitors on the BK–NO pathway (Table 1). Combined RAS inhibition also may recruit more responders to this therapeutic strategy owing to pharmacokinetic or pharmacodynamic reasons.[107,108] On the other hand, combinations including an ACE inhibitor will be subject to the specific side effects of ACE inhibition (cough, angioneurotic edema), which will not be the case when using ultrahigh doses of an AT1R antagonist.

In terms of safety, both strategies (dual blockade or ultrahigh doses) share the same potential hazards of complete RAS inhibition, especially in situations in which BP and renal function are renin-dependent: elderly or salt-depleted patients, patients receiving cyclo-oxygenase inhibitors, patients with renal artery stenosis, and patients placed under anesthesia. The risks of hyperkalemia and anemia also may be increased, especially in patients with renal insufficiency. A more complete and rigorous assessment of these risks is needed. This will require studies of large numbers of diverse patients with hypertension, renal insufficiency, or congestive heart failure.

Finally, another potential pharmacologic approach to reinforce RAS blockade is to combine a renin inhibitor with an AT1R antagonist (Table 1).[109] Indeed, in sodium-depleted normoten-

sive subjects, the increase in the plasma concentration of immunoreactive active renin caused by the interruption of the Ang II–renin feedback by a single oral dose of an AT1R antagonist, valsartan, was enhanced synergistically by the concomitant inhibition of renin activity by the co-administration of aliskiren, which also neutralized the valsartan-induced increase in plasma Ang II concentration.[60,109] This proof-of-concept study subsequently has been confirmed by investigations of a BP decreasing effect of combined RAS blockade in experimental and clinical hypertension studies. In telemetered spontaneously hypertensive rats, the decrease in BP after treatment with a submaximal dose of benazeprilate (3 mg/kg/d) or valsartan (3 mg/kg/d) was more pronounced when aliskiren (30 mg/kg/d) was co-administered by osmotic minipumps.[110] In a factorial design study including 1,123 patients with mild to moderate hypertension, an 8-week treatment with a combination of 75 mg aliskiren and 80 mg valsartan induced a decrease in BP similar to that achieved with doses 4 times higher than each monotherapy (aliskiren 300 mg or valsartan 320 mg), even though the BP effects of 75 mg aliskiren or 80 mg valsartan alone were not significantly greater than placebo.[111] In another double-blind study including 1,797 patients with hypertension, the combination of maximum recommended doses of aliskiren (300 mg/d) and valsartan (320 mg/d) provided significantly greater reductions in BP than each component monotherapy.[112] In terms of safety, the proportion of patients with a transient increase of serum potassium above 5.5 mmol/L was higher in the combination group (4%) than in the aliskiren (2%) and valsartan monotherapy groups (2%) or in the placebo group (3%). These approaches need additional evaluation.

CONCLUSIONS

Over the past 2 or 3 decades, studies of RAS blockade have addressed the question of whether such blockades reduce morbidity and/or mortality in various patient populations. We now need to determine how to optimize RAS blockade. The use of ACE inhibitor/AT1R antagonist combinations,[1] or of ultrahigh doses of AT1R antagonists,[105,106] has been proposed as a means of maximizing the cardiovascular and renal benefits of RAS blockade. These approaches still are under investigation. The largest study to date with a combined RAS blockade, The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), is ongoing.[113] It explores the risk/benefit ratio of a more intense RAS blockade obtained by combining 10 mg ramipril with 80 mg telmisartan, compared with 10 mg ramipril once daily, a treatment that prevented cardiovascular events in the high cardiovascular risk patients of the Heart Outcomes Prevention Evaluation (HOPE) study.[18] If the combination of 80 mg telmisartan and 10 mg ramipril has a superior protective cardiovascular effect than 10 mg ramipril alone in these patients, this will confirm that as complete as possible RAS blockade is the preferred option for maximal protection, irrespective of the mechanism (tissular or hemodynamic). Therefore, this combination may become the gold standard to provide optimal cardiovascular prevention in high-risk normotensive and hypertensive individuals. Such a result will greatly impact the future use of RAS blockers, ACE inhibitors, AT1R antagonists, and the new class of renin inhibitors.[36]

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