Keywords: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, AT_1-receptors, hypertension, heart failure, diabetic renal disease, renin, chymase, kinins, end-organ protection

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Effectively targetting the renin-angiotensin-aldosterone system in cardiovascular and renal disease: rationale for using angiotensin II receptor blockers in combination with angiotensin-converting enzyme inhibitors

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Introduction

The renin-angiotensin-aldosterone system (RAAS) is activated in hypertension, cardiac and renal disease and is attributed as a major factor in the morbidity and mortality associated with these disease syndromes.[1-2] The beneficial effects of blocking the RAAS, using angiotensin-converting enzyme inhibitors (ACE-I), is well supported by the number of approved indications in hypertension, chronic heart failure (CHF) and diabetic renal disease. Despite the proven effectiveness of ACE-inhibition in cardiovascular disease there are inherent deficiencies in its ability to effectively block the RAAS. Numerous studies have demonstrated that long-term ACE-inhibition results in incomplete RAAS blockade as plasma angiotensin II (Ang II) and aldosterone concentrations return back to control levels, a phenomenon called 'ACE-escape'.[3-5] Incomplete RAAS blockade may explain the further progression in renal disease and heart failure (albeit at slower rates than with placebo) despite chronic ACE-inhibition.

It is now apparent that the activation of the RAAS not only affects circulatory regulation but also affects local tissue function (Table 1).[6-7] The circulatory response to RAAS activation is an acute elevation in blood pressure (BP), mediated through peripheral vasoconstriction and maintained by Na^+ and H_2O reabsorption. However, chronic stimulation of the RAAS leads to growth- and fibrotic-promoting processes at the tissue level which lead to further deleterious effects on end-organ function. The tissue-based RAAS is not acutely involved in blood pressure (BP) regulation but rather on the mitogenic effects of Ang II.[8] Thus, successful strategies employed to inhibit the RAAS must be directed to blocking the short- (circulating) and long-term (tissue-based) effects of RAAS stimulation.

The predominant actions of ACE-I are to block the activity of the RAAS by inhibiting both the circulating as well as the tissue effects of Ang II. Simply increasing the dose of the ACE-I to higher levels has resulted in further inhibition of the RAAS; however, the optimal ACE-I dose to maximally block the RAAS is not known and has not been studied. The tissue-based RAAS is known to be more difficult to block, due to difficulties in tissue penetration and to the existence of tissue-based enzymes, other than ACE, that are involved in the generation of Ang II and may account for the inability to maintain adequate RAAS blockade over time while using ACE-I therapy.[9] Thus, strategies employed to improve RAAS blockade while on chronic ACE-inhibition should be targetted to more effective blockade of the tissue RAAS. The most recent class of RAAS blockers that has joined the therapeutic armamentarium is Ang II receptor blockers (ARBs). These provide the potential for more complete blockade of the RAAS by being able to prevent the binding of Ang II to its primary biological receptor (Ang II type-1 receptor [AT_1]). The apparent low rate of side-effects when using ARBs (i.e. side-effects similar to placebo rates) has given this new drug class a special and unique benefit over all other RAAS blockers.[10-11]

The primary rationale to justify using ACE-I and ARBs in combination is to ensure a more specific and complete RAAS blockade by inducing blockade at different sites of the Ang II generation pathway. Furthermore, the counter-regulatory responses to RAAS blockade, using ACE-I or ARBs, will be antagonized by combined therapy.[12-13] In this way, the elevation in plasma Ang I levels on an ACE-I would not be able to overcome RAAS blockade, as an ARB would block all actions of Ang II generated via ACE or non-ACE pathways. The ACE-I induced fall in plasma Ang II would also help to counteract the rise in Ang II which could stimulate tissue angiotensin (AT_1 and Ang II type-2 [AT_2]) receptors not fully blocked.[14] Therefore, inhibition of the RAAS, using the combination, is more effective than with either agent alone, as recent studies have demonstrated greater increases in plasma renin activity (PRA) on the combination compared with ACE-inhibition.[15-17] Theoretically, the greater the RAAS blockade, the greater the attenuation of deleterious RAAS-induced local tissue trophic effects. As a consequence, long-term target organ protection occurs as a specific goal of combined RAAS therapy.

The purpose of this review is to present the rationale for the use of ACE-I and ARBs in combination. In the first part, the theoretical advantages of adding an ARB to existing ACE-I therapy and of maintaining patients on ACE-I treatment when using an ARB in cardiovascular therapy are presented (Table 2). In the second part, all basic and

Table 1 Systemic (acute) and tissue-based (chronic) effects of renin-angiotensin-aldosterone system (RAAS) activation[6-7]

Circulating RAAS	Tissue-based RAAS
Peripheral vasoconstriction	Cytokine activation
Stimulate release of aldosterone	Hypertrophy
Stimulate release of arginine vasopression	Hyperplasia
Stimulate thirst and Na^+ appetite	Remodelling
Renal Na^+ and H_2O reabsorption	Fibrosis (e.g. collagen deposition)

Table 2 Rationale for using ARBs and ACE-I in combination to inhibit the RAAS in cardiovascular disease

Combination therapy: ACE-I and ARBs	Proposed benefits
Advantages to adding an ARB:	Compensate for incomplete ACE inhibition
	More complete blockade of the RAAS, by blocking both the ACE and non-ACE pathways for the generation of Ang II
	Tissue RAAS blockade
	Angiotensin type-2 (AT_2) receptor stimulation
Advantages to maintaining ACE-I therapy:	Compensate for incomplete AT_1 receptor blockade
	Reduce plasma Ang II levels
	Prevent the degradation of kinins
	Inhibit tissue ACE activity
	Increase Ang-(1-7) levels

clinical trials will be reviewed that have evaluated the combined use of ACE-I and ARBs in order to assess the potential advantage of the combination in hypertension, chronic heart failure (CHF) and renal disease.

Rationale for adding an ARB to existing ACE-I therapy

The proposed limitations of ACE-I therapy in cardiovascular disease are related to its inability to effectively block the RAAS. The 'ACE-escape' effect, associated with the use of ACE-I, occurs by either incomplete ACE-inhibition or the generation of Ang II by ACE-independent enzymatic pathways. Additionally, ACE-I may not fully inhibit the actions of the local or tissue-based RAAS. The use of ARBs, which block the direct effect of Ang II at the AT_1-receptor, when added to ACE-I, can ensure more complete suppression of the RAAS.

Incomplete enzyme inhibition

Clinical studies have shown that, within the therapeutic dose range for ACE-I, plasma Ang II and aldosterone levels gradually return to control levels.[3,18-21] One possible mechanism for the 'ACE-escape' phenomenon with chronic ACE-I therapy may be attributed to the reactive rise in PRA and Ang I levels.[22-23] The body's counter-regulatory response to an ACE-I (i.e. hyperreninaemia) may, in some patients, reach high enough levels to overcome the enzyme inhibition, thus causing increases in Ang II.[4,24]

The acute reduction in plasma Ang II levels following ACE-inhibition attenuates the persistent negative feedback response on the renin-producing juxtaglomerular cells. Thus, the inhibitory signal for renin release is removed following ACE-inhibition resulting in elevated PRA and Ang I levels. Elevations in PRA and Ang I levels as great as 2–3 times above normal may be sufficient to overcome enzyme inhibition.[18,21] Non-sustained ACE-inhibition, for the complete 24 hours (e.g. plasma half-life differences between enalapril and lisinopril), may also be responsible for increases in plasma Ang II levels.

During chronic ACE-inhibition, an effective means to maintain efficient RAAS blockade is to escalate the ACE-I dose.[13] The maximum, sustained antihypertensive response to ACE-inhibition is only achieved by using higher doses than typically recommended for BP control.[25-26] More effective and maximum long-term BP control can be achieved by using higher doses for benazepril (up to 80 mg/day),[26] enalapril (up to 40 mg/day),[27] captopril (up to 150 mg/day),[28] lisinopril (up to 80 mg/day),[29] ramipril (up to 20 mg/day),[30] and quinapril (up to 80 mg/day).[31] Further, the antihypertensive dosage used for ACE-inhibition is typically lower than the optimal recommended doses for patients with heart failure or renal disease.[26] Increases in the dose of the ACE-I have also demonstrated beneficial effects in patients with CHF and renal disease suggesting more effective long-term blockade of the RAAS.[32-35]

Increases in the ACE-I dose, above which no further antihypertensive response is observed, results in continual increases in PRA and, therefore, a more complete RAAS blockade.[36-37] Blockade of the tissue-based RAAS, which requires higher doses of ACE-I or ARBs, is important for optimal target organ protection. Using the low or recommended antihypertensive dose for the ACE-I may be effective in blocking the circulating RAAS but may have little effect on the tissue-based RAAS, and thus only a limited long-term effect in target organ disease protection.[38]

Incomplete ACE-inhibition would suggest that the antihypertensive and haemodynamic effects of ACE-I therapy would be short lived.[21] However, there have been no clinical reports of reduced BP lowering or haemodynamic efficacy with chronic ACE-I therapy.[22] Rather, incomplete ACE-inhibition may be more related to reduced inhibition of the tissue-based RAAS.[39] A study by Palla *et al.*[35] demonstrated that increasing the dose of lisinopril resulted in additional renal protective effects, independent of any BP reductions (Figure 1).[35] To com-

Figure 1 The effect of progressive increases in the ACE-I (lisinopril) dose on mean arterial pressure (MAP) and proteinuria in 16 normotensive, proteinuric patients (>1.5 g/day) with IgA nephropathy. The ACE-I was administered for four weeks at each dose with a three week placebo period between doses. Adapted from Palla *et al.*[35]

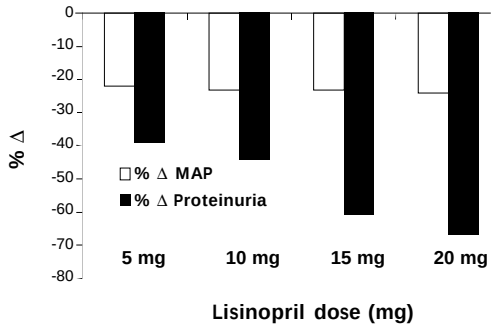
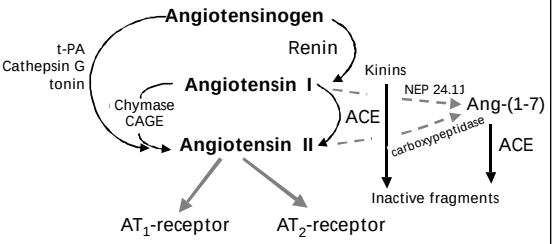


Figure 2 The renin-angiotensin-aldosterone system enzyme cascade depicting ACE and non-ACE pathways involved in the generation of Ang II. CAGE, chymostatin-sensitive Ang II-generating enzyme; t-PA, tissue plasminogen activator; NEP 24.11, neutral endopeptidase



pensate for incomplete ACE-inhibition, more effective and complete RAAS blockade can only be achieved by increasing the dose of the ACE-I or by adding another RAAS blocker, such as an ARB.[13] The effect of one of these two strategies will not necessarily result in further lowering of BP but will result in greater inhibition of the tissue RAAS.[40]

Non-ACE pathways for the generation of Ang II

Ineffective RAAS blockade while on ACE-I therapy may be due to Ang II generation by activation of other enzyme systems. Recent studies have demonstrated the existence of other enzymatic pathways that can form Ang II, independent of ACE, that are not blocked by ACE-I (Figure 2).[41-45] Ang II can be formed through the action of serine proteases (e.g. chymase) which are localised to the interstitium of a variety of tissues particularly cardiac, vascular and renal tissues.[46] In human heart tissue, chymase has been identified as the major Ang II-forming enzyme. Urata *et al.*[47] reported that in the heart, up to 70% of locally generated Ang II may be through chymase, whereas in the kidney, it is approximately 20%.[48] Hollenberg[42] recently reported that non-ACE pathways account for 30–40% of Ang II formed in the kidney in diabetics. Thus, the formation of Ang II through non-ACE pathways contributes substantially to the tissue-based RAAS while not contributing directly to the circulating RAAS.

The lack of information pertaining to the stimulation and/or inhibition of these serine proteases, makes it nearly impossible to determine the functional significance of these alternative Ang II-forming pathways. However, it can be speculated that they play important roles in local cell function and cell growth and are not thought to contribute to important systemic (i.e. circulating) cardiovascular effects. Furthermore, some investigators have speculated that, rather than playing an important role in normal cellular function, non-ACE pathways are activated in syndromes of disease where there are high levels of oxidative stress, such as vascular pro-inflammatory and atherogenic processes.[43,49] Furthermore, when plasma renin activity is low, the tissue RAAS may still be active through local Ang II production, via the enzymatic action of chymase.[50]

Previously, some investigators have failed to identify these 'non-ACE' pathways as being clinically significant for the generation of Ang II. Most animal studies have failed to demonstrate important differences between the tissue-protective effects of ARBs compared with ACE-I. However, more recently it has been shown that species-related differences in non-ACE pathways generation of Ang II can explain inconsistent results between various experimental animal models.[44] In rats, Ang II is generated entirely through ACE and does not involve any of the non-ACE pathways whereas in humans, monkeys, dogs, and hamsters chymase does generate Ang II.[43-44] Thus, rat studies showing equivalence between ACE-I and ARBs for cardiac and renal protection may not be applicable to man and are therefore not a good model to study differences between ACE-I and ARBs.[45-46]

If the 'ACE-escape' response is entirely due to the counter-regulatory response to ACE-inhibition ultimately overcoming enzyme inhibition through mass action, then there is no need to suggest other mechanisms, such as Ang II formation through alternative pathways.[24] However, if elevations in both PRA and Ang I, in response to ACE-inhibition, stimulate the activity of these non-ACE pathways it may account for the reduced long-term cardiac and renal protective effects of ACE-I.[51-52] Blocking both ACE and non-ACE pathways responsible for the generation of Ang II may be an important therapeutic goal for optimal cardiovascular protection.

Tissue RAAS

There is direct evidence supporting the existence and functional importance of a tissue-based RAAS at a variety of sites (e.g. blood vessels, heart, kidney).[53] Activation of the tissue RAAS accounts for the long-term effects (e.g. vascular remodelling, glomerular hypertrophy, left ventricular hypertrophy, angiogenesis) of Ang II (Table 1).[8,9] The endocrine or circulating RAAS is more focused on haemodynamic compensatory responses to main-

tain plasma flow and BP homeostasis.[8] The tissue-based RAAS functions as a regulator of local Ang II activity, such that it is possible to have increased tissue RAAS activity without any detectable changes in plasma RAAS activity.[42,54-55]

Blockade of the RAAS occurs through inhibition of Ang II in both plasma and tissues. Effective blockade of the circulating RAAS occurs at much lower doses than those necessary to effectively block the tissue RAAS.[24] Thus, the tissue-based RAAS functions independently from the peripheral circulation but is more difficult to completely block.[9,56] Incomplete tissue RAAS blockade while on an ACE-I may be due to the difficulties in penetrating various tissues with organ specific differences and/or to the existence of non-ACE pathways generating Ang II.[57] An advantage of ARB therapy, with respect to tissue RAAS blockade, is its ability to block the effects of Ang II at the AT_1-receptor regardless of whether Ang II is generated via ACE or non-ACE pathways.

Chronic elevations in plasma and tissue Ang II concentrations stimulate cardiac, vascular and renal mitogenic processes, partly mediated through elevations in cytokines. Increases in Ang II will stimulate the release of cytokines such as transforming growth factor-beta-1 (TGF-β_1), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) which promote extracellular matrix accumulation (e.g. fibronectin, type I, III and IV collagen deposition and osteopontin) leading to fibrotic changes.[55,58] Evidence suggests that inhibition of cytokine expression is a primary mechanism by which RAAS blockade prevents progressive glomerular, vascular and cardiac disease.[59-60] Both ARBs and ACE-I, through similar mechanisms, prevent the negative growth promoting effects of Ang II through indirect (haemodynamically mediated) and direct inhibition of cytokine expression.[61-62] However, since cytokine stimulation affects tissue mitogenic processes, higher doses of RAAS blockers are required to effectively suppress cytokine expression.[10] The degree of reduction of cytokine expression has been used as an index of the extent of tissue RAAS inhibition.[58] Due to the limitations in tissue RAAS blockade by ACE-I, blockade may be more effectively accomplished by adding an ARB to existing ACE-I therapy without trying to titrate the ACE-I dose to some undefined optimal level.

Ang II type-2 receptor

There are multiple receptors for Ang II, but only two receptors whose biological effects are known, the AT_1- and AT_2-receptors (Figure 2). Stimulation of the AT_1-receptor results in the characteristic effects of Ang II, vasoconstriction, renal Na^+ reabsorption and cell proliferation. The AT_2-receptor, which is of secondary importance to the AT_1-receptor, was originally thought to be important only for foetal growth and development. However, more recent data has suggested that the AT_2-receptor may have the important role of modulating the effects of chronic AT_1-receptor stimulation. Stimulation of the AT_2-receptor by Ang II in the adult results in vasodilation and cell growth inhibition.[63] Thus, the AT_2-receptor-mediated effects are inhibitory to AT_1-receptor-mediated mitogen-induced growth effects, indicating a balancing mechanism for Ang II-controlled mechanisms.[64]

In clinical syndromes of cardiovascular disease, such as ventricular remodelling and myocardial ischaemia, the AT_2-receptor has been reported to be re-expressed or up-regulated.[65-66] Stimulation of the AT_2-receptor may control excessive growth mediated, in part, by AT_1-receptors.[64] The cardiovascular effects of AT_2-receptor stimulation are primarily of local benefit, mediated through increases in nitric oxide and other local vasodilator, antimitogenic substances, contributing to the tissue-protective effects of ARBs.[67,68] This 'turning-on' of AT_2-receptors could serve to counterbalance or modulate excessive effects of AT_1-receptor stimulation in cardiovascular disease. However, despite the supposed benefits of chronic AT_2-receptor stimulation by ARBs, the combination of an ACE-I and ARB would act to reduce plasma Ang II levels, removing this theoretical advantage.[13,69]

Rationale for maintaining ACE-I therapy when adding an ARB

The benefits of ACE-I therapy in hypertension, cardiac and renal disease are well-documented. The notion of adding new pharmacological treatments to existing ACE-I therapy is much more acceptable than that of replacing existing ACE-I therapy, particularly considering the documented benefits of ACE inhibition. It could be argued that the theoretical benefits and advantages of ARBs outweigh the advantages of ACE-I therapy. However, the potential advantages of ARBs over ACE-I have not yet been proven in randomised clinical trials. Until those studies are completed, ARBs will not replace ACE-I therapy but will be used in patients who are ACE-intolerant or as 'add-on' therapy to ACE-I, primarily in cardiac and renal disease.

One of the reasons for maintaining patients on ACE-I therapy when combining ARBs is related to the ability to prevent the counterregulatory responses to AT_1-receptor blockade. ACE-inhibition will prevent the increase in plasma Ang II levels, thereby reducing the competition between endogenous Ang II and the ARB for the receptor site. Additionally, and perhaps more importantly, the ability of ACE-I to block tissue-ACE activity and to potentiate local vasodilator and antiproliferative substances (i.e. bradykinin and angiotensin peptide fragment, Ang-[1-7]) may increase the tissue protective effects of therapy.

Reduction of plasma Ang II levels

Adding an ACE-I to ARB therapy reduces the formation of Ang II and thus reduces the competition at the AT_1-receptor between vasoactive hormone and drug. Following the administration of an ACE-I, there is an acute reduction in plasma Ang II concentrations. However, recent studies have demonstrated that chronic ACE-inhibition results in plasma Ang II levels returning back to control levels over a period of weeks to months.[20,70-71] It is not known if chronic ACE-I therapy, when combined

with an ARB, will still result in elevation of plasma Ang II levels over time due to the 'ACE-escape' effect. It is well appreciated that the therapeutic efficacy of most ARBs is not affected by elevated plasma Ang II levels. Thus, the benefit of reducing plasma Ang II levels, while on an ARB, may be only for ARBs such as losartan, where competition at the AT_1-receptor reduces their therapeutic effect.[72-73]

Elevations in plasma Ang II levels while on an ARB, will result in the production of Ang IV, a by-product of aminopeptidase-induced Ang II metabolism.[74] Ang IV (Ang-3-8) is believed to have its own receptor and to stimulate the expression of plasminogen-activator inhibitor 1 (PAI-1) in the vascular endothelium.[75] Stimulation of PAI-1, through increases in plasma Ang IV levels, is prothrombotic, as it inhibits tissue plasminogen activator (t-PA).[76] The addition of an ACE-I to ARB therapy might be beneficial by reducing plasma Ang II levels, thereby reducing the formation of Ang IV. However, recent studies are conflicting as to whether or not elevations in Ang II levels, while on ARB therapy, pose a risk since a direct link between plasma Ang IV and PAI-1 levels has not been confirmed.[58,74,77-79]

Incomplete Ang II – AT_1-receptor blockade

Clinical doses of ARBs produce incomplete blockade of AT_1-receptors and the increased Ang II levels in plasma and extrarenal tissues counteract (to an unknown degree) their effects at the AT_1-receptor.[24] Thus, the rise in plasma Ang II levels may compete with the ARB at the AT_1-receptor site, thereby reducing its effectiveness. One possible benefit of using an ACE-I/ARB combination is to block the reactive increase in plasma Ang II in response to ARBs. Combination of an ACE-I with an ARB prevents the rise in plasma Ang II levels that occurs with ARB therapy alone.[14,15]

However, different ARBs display varying degrees of affinity for the AT_1-receptor. Using ARBs with a high affinity for the AT_1-receptor (e.g. the 'insurmountable' antagonists, candesartan and irbesartan) compared with those with lower affinity (e.g. the surmountable antagonists, eprosartan and losartan) will determine whether elevated Ang II levels while on ARB therapy can overcome AT_1 blockade.[80] As a result, ARBs with high affinity for the AT_1-receptor would not be displaced from the receptor, regardless of the plasma or tissue concentrations of Ang II. Thus, the addition of an ACE-I, to decrease plasma Ang II levels, in order to reduce compensatory responses to AT_1-receptor blockade, could be important in surmountable ARBs but not necessary in insurmountable ARBs.

Inhibition of tissue ACE activity

Tissue ACE activity is one component of the tissue RAAS and thus the effectiveness of ACE-I therapy is not only dependent on inhibition of circulating ACE activity but also on its ability to antagonise tissue ACE activity. Perhaps tissue ACE-inhibition is more important for blocking the long-term actions of the RAAS and for conferring maximal cardio- and renoprotective effects (Table 1).[81-82] In order to effectively block the actions of the RAAS and to fully inhibit tissue ACE activity, it is necessary to use ACE-I at doses higher than normally prescribed.[9] Some ACE-I, due to their lipophilic properties (e.g. ramipril and quinapril), are better able to block tissue ACE activity than others (e.g. enalapril).[25] Clinical studies such as MERCATOR, MARCATOR and QUIET, which have examined the potential benefit of ACE-inhibitors with high tissue ACE-binding properties have, however, been disappointing.[83-85] Whether or not one ACE-I is better able to inhibit tissue ACE activity than another, is still inconclusive. The importance of blocking the local RAAS, however, is vital in order to confer maximal target organ protection. It is unknown whether combining ACE-I and ARB can block the tissue-RAAS more effectively than monotherapy, but it may be done more easily at lower doses of each drug.

Kinins

Because ACE is identical to kininase II (which inactivates the nonapeptide bradykinin), several studies have documented that potentiation of kinins might be responsible for the additional effects of ACE-I (Figure 2).[86] Activation of the bradykinin B_2 receptor results in the release of NO and prostacyclin, potent endothelial-derived local vasodilator substances.[87] Interestingly, ARB therapy may also result in higher bradykinin levels, not due to interference in bradykinin metabolism, but secondary to AT_2-receptor stimulation.[67] Recent studies have reported that bradykinin and nitric oxide levels are increased in response to ARB therapy due to AT_2-receptor stimulation, which can lead to similar physiological effects from kinins as those found following the use of ACE-I.[67, 88]

The prime physiological action of kinins is to promote local vasodilation (e.g. improving coronary blood flow) and natriuresis. Kinins have been recently reported to have important short-term effects on BP, but results from previous studies have been conflicting.[89] However, it has yet to be demonstrated whether kinins exert any important long-term effects on BP control.[90]

Kinins respond to acute and chronic changes in salt and water intake, as do renin and aldosterone. Thus, the antihypertensive effect of kinins follows the activity of the RAAS and kinins are ineffective in lowering BP in low-renin hypertension.[86,91] Conversely, in sodium depleted states, kinins are stimulated, thereby serving to dampen or offset the effects of enhanced Ang II levels and increased activation of the RAAS. In syndromes of disease where vasoactive peptide systems are stimulated and serve to regulate tissue blood flow, kinins may play an important role to antagonise or counterbalance the effects of powerful vasoconstrictor systems, such as the RAAS.

It is well known that ACE-I prevents the degradation of bradykinin, but less widely known is the finding that combining an ARB to ACE-I therapy does not affect kinin degradation or may actually result in reduced degradation.[92] Thus, one of the proposed benefits of ACE-inhibition, kinin stimula-

tion, is preserved and unaffected by the addition of an ARB and stresses the value of the ACE-I and ARB combination over high-dose ARB monotherapy.

Angiotensin peptide, Ang-(1-7)

The use of ACE-I or ARBs results in compensatory stimulation of the RAAS, via inhibition of the negative feedback signal, resulting in greatly elevated Ang I and Ang II levels. Levels of angiotensin peptides, such as Ang-(1-7), a by-product of Ang I or Ang II metabolism, are elevated in patients on ACE-I but not ARB monotherapy (Figure 2).[93] Ang-(1-7) is a vasodilator peptide that has opposite actions to those of Ang II. Under normal conditions, Ang-(1-7) does not play an important role, since it is rapidly degraded by ACE and this may explain why levels are not elevated in patients on ARBs (Figure 2).[93] However, following chronic ACE-I therapy, elevation in Ang-(1-7) levels may serve to potentiate the vasodilator actions of bradykinin by helping to stimulate the release of NO, prostaglandins and prostacyclin.[13] Adding an ACE-I to ARB therapy would reduce degradation of Ang-(1-7) and thus potentiate its local vasodilator effect, potentially contributing to the tissue protective effects of RAAS blockade. It was recently demonstrated that levels of Ang-(1-7) were elevated on combined ARB and ACE-I therapy, providing additional vasodilation in rats.[94]

Clinical and basic studies

Hypertension

To evaluate the effectiveness of combining ACE-I and ARBs, a comparison of the antihypertensive responses would help to determine the important mechanisms involved in the lowering of BP for each drug. The antihypertensive mechanism for ACE-I has been attributed to reduced formation of Ang II and for ARBs to a reduced Ang II binding at the AT_1-receptor.Thus, both of these two classes of drugs block the actions of the RAAS system, but at different sites. If there are any differences in the antihypertensive action of ACE-I or ARBs, they must be related to bradykinin-related effects of ACE-I or to a more complete blockade of the RAAS with ARBs at the AT_1-receptor. Examining the BP-lowering effects of ACE-I in combination with other RAAS blockers such as β-blockers and renin inhibitors will also provide insight into the value of combining ACE-I with ARBs for additive antihypertensive effects.

ACE-I vs.ARB

Even though ACE-I and ARBs block the RAAS at different sites, they both prevent plasma Ang II levels from causing peripheral vasoconstriction and renal Na^+ retention, the two primary mechanisms involved in the hypertensive response associated with RAAS activation. If the antihypertensive responses of these agents is dependent solely on effective blockade of the circulating RAAS, then the antihypertensive effect of ACE-I and ARBs should be similar. Comparative short-term trials between ACE-I (e.g. enalapril and lisinopril) and ARBs, such as losartan, valsartan, irbesartan, candesartan, and telmisartan, have all shown equivalent BP reductions.[95-106] This overwhelming evidence suggests that the bradykinin-related effects of ACE-inhibition do not affect long-term BP control. Furthermore, these results suggest that more complete blockade of the RAAS using ARBs, through tissue blockade of both ACE and non-ACE pathways, is not important for BP control. If the bradykinin-related effects of ACE-I and more effective tissue blockade of the RAAS with ARBs are important physiologically, they will be related to ensuring more effective protection of end-organ function in clinical syndromes of disease (e.g. diabetic renal disease).

However, a few studies have found smaller BP reductions with losartan compared with ACE-I.[107-109] More recent evidence suggests that losartan may not effectively block the AT_1-receptors throughout the 24-hour dosing period.[70,110] The less potent antihypertensive effects of losartan compared with enalapril appear to be specific for losartan. Comparative studies of other ARBs against losartan have also consistently shown greater BP lowering effects.[110-116] Losartan, being a competitive antagonist, displays weak binding properties to the AT_1-receptor and probably accounts for its reduced efficacy when compared with enalapril, rather than any kinin-related effects of ACE-inhibition.[73,117]

In summary, BP responses to ARBs and ACE-I are generally similar, suggesting similar antihypertensive mechanisms of action. Based on these results, combination therapy with ACE-I and ARBs should not result in any additive antihypertensive effects, independent of dose-related effects, and thus, the benefit, if any, of combined therapy would be related to the extent of their long-term beneficial effects on target organ function.

ACE-I and renin inhibitors

Renin inhibitors were developed after ACE-I and they offer a more attractive approach to blocking the RAAS. Although both agents reduce plasma Ang II levels, renin inhibitors can provide a more effective chronic blockade of Ang II, unlike ACE-I, by preventing the formation of Ang II through both ACE and non-ACE pathways.[42,117] Acute human studies have demonstrated a greater renal vasodilator response with renin inhibitors compared with ACE-I supporting a more effective tissue RAAS blockade.[42] However, despite more complete tissue and circulating RAAS blockade with renin-inhibitors, no BP lowering differences were found, in acute and chronic studies, between renin-inhibitors and ACE-I.[36,118-121]

Based on the different sites of action on the RAAS, adding renin inhibitors to existing ACE-I might be expected to provide an additive antihypertensive response. Although some studies demonstrated greater increases in PRA with the combination, there was no additional antihypertensive response.[122-123] In one study, when renin inhibitors were added to hypertensive guinea pigs already on ACE-I, there was a further reduction in BP. However, the reductions in BP were no greater than when one of the drugs was used at its maximum antihypertensive dose.[124] Thus, combination

therapy with ACE-I and renin-inhibitors will result in more complete RAAS blockade, but not in any additive antihypertensive response.[125-126] However, the theoretical benefit of more complete RAAS blockade, achieved by combination therapy, is apparent in disease states where the tissue-based RAAS is chronically activated.[127]

ACE-I and β-blockers

Although the precise antihypertensive mechanism of β-blockers is not known, their ability to inhibit sympathetically stimulated renin-release is believed to be of chief importance.[128] A recent study showed that β-blockers are effective in reducing the compensatory rise in renin and Ang I levels in response to ACE-I therapy.[129] The effect of β-blockers on the RAAS is very similar to the actions of renin inhibitors. Like renin-inhibitors, β-blockers reduce BP in a comparable fashion to ACE-I.[130-131]

When combining β-blockers and ACE-I in therapy, study results have been mixed, as some studies have demonstrated an additive antihypertensive effect while others showed no additive effect.[131-144] The mechanism for the added hypotensive effect may be unrelated to dual effects on the RAAS, since non-RAAS related antihypertensive effects of β-blockade may be involved.[145]

However, the additive antihypertensive effect of combining ACE-I and β-blockers is small and is clinically insignificant.[132,138,141] The primary benefit of combining β-blockers and ACE-I is in a more complete inhibition of the RAAS, independent of further BP reduction, in syndromes of disease where the tissue RAAS is chronically stimulated. More complete RAAS blockade, achieved by adding a β-blocker to existing ACE-I therapy, may explain some of the positive results recently reported in CHF trials.[146-147]

ACE-I and ARBs

Previous studies combining another RAAS blocker (e.g. renin inhibitor or β-blocker) with an ACE-I have demonstrated little or no additional hypotensive response. However, this was never the primary rationale for using the drugs in combination and neither should it be for ACE-I and ARBs. The BP response for the ACE-I and ARB combination, based on a review of multiple studies, shows a small additional antihypertensive response.[13-17,147-162] A sample of clinical studies in hypertension, renal disease and heart failure demonstrates an additive effect on BP when combining the two classes of drugs; however, in most cases, the magnitude of the effect is modest (range 0-6 mm Hg ΔDBP) (Table 3).[16,17,147,153-157,161-162]

Unfortunately, many of the hypertension studies examining the efficacy of combined ACE-I and ARB therapy are difficult to interpret and have the following criticisms:

1. Doses of ACE-I used in combination studies are usually not at optimal or FDA-recommended therapeutic levels. Thus, increasing the dose of an ACE-I or ARB by itself will result in an additional antihypertensive response obviating the need of combination therapy. Furthermore, the additive effect of the combination is frequently compared to a relatively lower monotherapy dose, thereby making any conclusions of the benefits of combination therapy difficult to make.

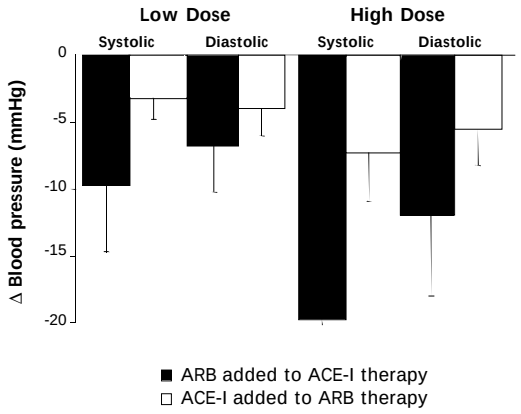
   Some of the combination studies have reported that the addition of an ARB to ACE-I results in a greater antihypertensive response than that obtained by doubling of the ACE-I.[149-150] Since the maximum or optimal antihypertensive effect of monotherapy (ACE-I or ARBs) is not known in these studies, it is difficult to attribute a greater antihypertensive response to the combination.[26]
2. Using moderate doses, the order of treatment appears to determine the magnitude of the antihypertensive response to the combination. In one four week study of 30 hypertensives, the antihypertensive response was enhanced when the ARB (losartan, 25-50 mg/d) was added to existing ACE-I therapy (ramipril, 2.5-5 mg/d) (Figure 3).[151] Conversely, when the ACE-I was added to the existing ARB therapy, the additive antihypertensive response was small and not significant. It is not known if the same results would be observed in the long term, but it warrants further consideration since all studies to date examine the additive effects of an ARB to existing ACE-I therapy.
3. In some studies, the addition of ARBs to ACE-I therapy does not allow enough time for the antihypertensive agents to exert their maximal effects and reach a steady state. For example, the maximum antihypertensive response reported in clinical trials for ACE-I is approximately two weeks, whilst for ARBs it is four weeks. Interestingly, a recent study demonstrated continuous reductions in BP up to eight months following the initiation of ARB therapy, suggesting a secondary time-dependent antihypertensive response that develops after months of therapy (Figure 4).[163] Thus, in acute and short-term studies, it is difficult to separate out the BP-related effects of the combination

Table 3 Effect of combination (ARB + ACE-I) therapy on blood pressure response in animal and clinical studies.[16,17,147,153-157,161-162]

Combination therapy: ACE-I and ARBs	Blood pressure reduction ΔSBP / ΔDBP (mm Hg)	Reference
Clinical studies		
Hypertensive patients*	5-7/4-5	153-155
Diabetics & renal patients	2-4/0-6	17, 156-157
CHF patients	2-7/1-3	16, 147, 161-162

Changes in systolic (ΔSBP) and diastolic (ΔDBP) blood pressure (mmHg) from ACE-I or ARB monotherapy;
*Comparison of ACE-I and ARB combination dose to lower ACE-I dose

Figure 3 Comparison of the blood pressure response between adding the Ang II receptor blocker (ARB) to existing ACE-inhibitor (ACE-I) therapy or vice versa. Thirty hypertensive patients were randomised to receive either low dose losartan (25 mg) or ramipril (2.5) for four weeks. Thereafter, patients on the ACE-I or the ARB either doubled the dosage of monotherapy or had low dose losartan or low dose ramipril, respectively, added to therapy. For the last four weeks of the study all patients, who were randomised to high dose monotherapy, had either high dose ramipril (5 mg) or high losartan (50 mg) added to therapy. Adapted from Bentivoglio *et al.*[151]



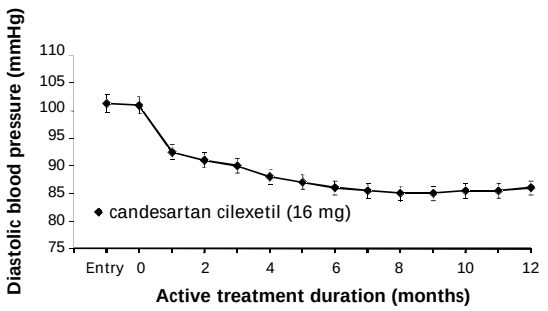
from the time-dependent BP effects associated with monotherapy.

4. Reductions in dietary sodium consumption and/or diuretic usage will also increase the magnitude of the antihypertensive response to the combination, resulting in larger BP changes than normally observed in the clinical practice setting.

In order to determine the clinical significance of combined ACE-I and ARB therapy, further well-controlled studies are needed in patients with hypertension. Even if combined therapy of an ACE-I and ARB only results in a modest additional antihypertensive response, its use may be more efficient since the same blood pressure reduction can be achieved by combining the ACE-I or ARB dose rather than titrating the individual ACE-I dose to maximum.[155]

However, if the combination is no different than using maximal antihypertensive doses of one agent alone, what is the advantage of combining therapies? The primary advantage, if any, has to be an enhanced ability of the combination to antagonise the circulating and tissue-based system RAAS. Combination studies have shown a greater effect on PRA despite no additional antihypertensive response when ARBs are combined with ACE-I.[13,149] The benefit of more effective RAAS blockade should lead to enhanced tissue protective effects which can, indirectly, influence long-term BP control. Thus, combining ACE-I and ARBs may not lead to additive antihypertensive effects, in response to initial therapy, but is targetted to more effective RAAS blockade, resulting in long-term beneficial tissue protective effects (e.g. reduced vascular smooth muscle hypertrophy).

Figure 4 Time course of sitting diastolic blood pressure in 244 patients undergoing long-term open label treatment with 16 mg of candesartan cilexetil. Adapted from Sever *et al.*[163]



Chronic heart failure (CHF)

During the past several years, the administration of ACE-I therapy has become the current standard of care in CHF. Studies with ACE-I have shown both haemodynamic and non-haemodynamic benefits in patients with CHF. Improvements in left ventricular (LV) mass, LV ejection fraction, and neurohumoral activity, coupled with benefits in mortality and morbidity outcomes, are well accepted in CHF studies following ACE-I therapy. However, despite the well-known benefits of ACE-I in CHF, the mortality in CHF remains unacceptably high.[51,164]

Long-term therapy with ACE-I may result in incomplete suppression of the RAAS and may contribute to the progressive worsening in cardiac function in patients with CHF.[28,165] The following factors may account for the incomplete suppression of the RAAS in CHF:

1. Following an initial reduction in plasma Ang II levels in patients on ACE-I therapy, there is a gradual increase in the plasma concentrations of Ang II back towards baseline levels ('ACE-escape').[166]
2. The optimal dose of ACE-I in subjects with CHF is not known, despite data from a recent clinical trial (i.e. ATLAS study) which suggested that the optimal dose needs to be higher than that commonly used by practising physicians.[32,34] Even using standard doses of ACE-I in clinical practice results in incomplete blockade of the RAAS.[28] One of the current problems in the management of CHF patients is not so much utilisation of ACE-I as the under-dosing of ACE-I therapy.[167] It is recommended, in CHF, that the ACE-I be titrated to the highest dose tolerable for optimal cardiovascular protection.[28]
3. Recent trials in CHF demonstrate additional benefits derived following the addition of an aldosterone-antagonist (e.g. RALES study) or β-blocker (e.g. MERIT-HF study) to existing ACE-I therapy. These studies suggest that more complete blockade of the RAAS in CHF may contribute to the mortality benefit and is the primary factor justifying the use of ARBs with ACE-I in CHF.[146]

Animal and clinical studies examining the combination of ACE-I and ARBs have demonstrated

haemodynamic improvements, neurohumoral reductions, and beneficial tissue effects on cardiac volumes and left ventricular hypertrophy (Table 4).[16,147,159-161,165-166,168-178] Two recently completed studies, involving patients on combined ACE-I and ARB therapy, found that the combination group had greater effects on left ventricular volumes and mass, independent of BP changes, compared with ACE-I or ARB monotherapy.[147,160] In both studies, the beneficial effect on cardiac tissue remodelling was associated with a more complete blockade of the RAAS.

These initial beneficial results with the combination group in CHF were all associated with reduced RAAS activation, which may be the most important reason justifying the combined use of ACE-I and ARBs in CHF. However, the therapeutic benefit of combined therapy has yet to be proved and is currently being evaluated in large prospective randomised clinical trials in CHF and post-myocardial infarction patients (e.g. CHARM, Val-HeFt; VALIANT) (Table 5).[69,92, 179-181] Results from these trials will directly answer whether combining ACE-I and ARBs for use in CHF provides additional cardiac and vascular protective benefits, independent of BP reduction.

Chronic renal disease

The beneficial action of ACE-I, in reducing the progression of chronic renal disease, has been primarily through its direct antagonism of the RAAS by reducing the formation of Ang II.[33] Following the use of ACE-I in renal disease, the beneficial effects of RAAS inhibition have been attributed to a combination of both haemodynamic and non-haemodynamic mechanisms.[182-183] The non-haemodynamic effects of RAAS blockade have previously demonstrated that ACE-I have greater renoprotective effects than all other classes of antihypertensive medications, with the possible exception of the ARB class which is under current investigation.[182] During ACE-I therapy, blockade of the renal RAAS helps to ameliorate urinary protein excretion, elevated glomerular capillary pressure, and mesangial cell hypertrophy.[184]

However, ACE-I must be used with caution in some syndromes of chronic renal disease. Although ACE-I are indicated for use in hypertension, CHF, and diabetic renal disease, the optimal renoprotective dose of ACE-I in long-term therapy is not known. The renoprotective effects of RAAS blockers (i.e. using ACE-I or ARB) are dose-dependent, with maximum benefit occurring at higher doses at which no additional BP changes have been demonstrated (Figure 5).[185] It has been recently suggested that improving RAAS blockade by using maximal ACE-I doses should yield the greatest reduction in proteinuria.[184] Unfortunately, clinical trials with ACE-I have not been designed to evaluate the dose-response curve for renoprotection. Additional renoprotective effects have been demonstrated when the standard dose of ACE-I has been increased, which suggests that the doses of ACE-I commonly used in clinical practice may be suboptimal in renal disease.[184]

A review of the literature reveals that ARBs possess no advantage over ACE-I in the reduction of proteinuria and prevention of the progression of renal disease, as evaluated in a variety of animal models such as the spontaneously hypertensive rat, streptozotocin-induced diabetic rat, reduced renal mass and two-kidney, one-clip hypertension model.[186-187] Similarly, animal studies examining the combined use of ARBs and ACE-I have not demonstrated any additional renoprotective effects over ACE-I monotherapy.[188-189] Using combination therapy, Ots *et al.* showed no additional renoprotective benefit in reducing urinary protein excretion, or differences in BP response to ACE-I and ARB monotherapy.[189] The renoprotective effects of antihypertensive animal models correlate very highly with the magnitude of the reduction in BP.[187] Thus, the difficulty in interpreting results from the animal studies to examine the potential benefit of combination therapy may be due to important species differences. In humans, non-ACE pathways

Table 4 Potential advantages of combination therapy (ACE + ARB) in chronic heart failure[16,147,159-161,165-166,168-178]

	Outcome
Basic / clinical studies	Enhanced blockade of the RAAS (e.g. increase in PRA; reduced plasma Ang II levels)[16,159-160,168-169]
	Reduced neurohormonal activation (e.g. reduced plasma norepinephrine and aldosterone levels)[16,169-170]
	Improvements in CHF functional class[165]
	Improvements in exercise tolerance and increase in peak VO_2[161, 165-166,169]
	Reductions in total peripheral resistance and improved regional blood flow distribution[171-173]
	Improved LV function (e.g. increased cardiac output and LVEF)[147,160,166,170,173-176]
	Reduce ventricular volumes (e.g. ESV, EDV)[147,160-161]
	Additive reductions in LV mass[177-178]

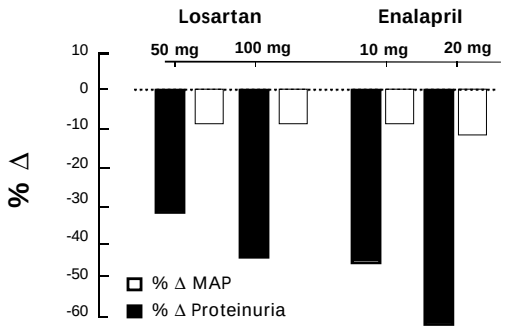
RAAS = renin-angiotensin-aldosterone system; PRA = plasma renin activity; Ang II = angiotensin II; CHF = chronic heart failure; VO_2 = oxygen uptake; LV = left ventricle; LVEF = left ventricular ejection fraction; ESV = end systolic volume; EDV = end diastolic volume

Table 5 Ongoing clinical trials examining the combined use of ACE-I and ARBs[69,92,157,179-181]

Study name	Doses	Patient type	Efficacy variables	Expected completion
CALM – effect of candesartan cilexetil and lisinopril on microalbuminuria study[157]	Candesartan cilexetil (16 mg q.d.) and lisinopril (20 mg q.d.)	180 type II diabetic hypertensive patients with microalbuminuria	Renal protection study: microalbuminuria, tolerability and BP	2000
VALIANT – valsartan in acute myocardial infarction trial[179]	Valsartan (80 mg b.i.d.) and captopril (50 mg t.i.d.)	14,500 post-MI patients for 3–5 years. (endpoint = 2700 deaths)	Post-MI study: morbidity and mortality	2003
Val-HeFT – valsartan heart failure trial[69]	Valsartan (160 mg b.i.d.) added to existing ACE-I therapy	5200 CHF patients (class II-IV) for 2–4 years. (endpoint = 906 deaths)	CHF study: morbidity and mortality, disease progression, cardiac structure and function and quality of life	2000
CHARM – Candesartan heart failure assessment of reduction in mortality and morbidity[180]	Candesartan (16 mg q.d.) and enalapril (10 mg b.i.d.)	6500 class II-IV CHF patients for 3–5 years	CHF study: morbidity and mortality, disease progression, cardiac structure and function and quality of life	2002
RAAS – Randomized angiotensin receptor antagonist – angiotensin -converting enzyme inhibitor study[92,181]	Losartan (50 mg q.d.) and enalapril (10 mg b.i.d.)	120 CHF patients with moderate to severe LV dysfunction randomized to 1 or the 3 groups and followed for 6 weeks	CHF study: safety, quality of life, neurohormonal activation, exercise performance	2000

BP = blood pressure; CHF = chronic heart failure; MI = myocardial infarction; LV = left ventricle; q.d. = dosing once-a-day; b.i.d. = dosing twice-a-day; t.i.d. = dosing three times a day

Figure 5 The effect of increasing the dose of losartan (50 to 100 mg) or enalapril (10 to 20 mg) in 16 type-1 diabetic patients on mean arterial pressure (MAP) and proteinuria. Patients were randomised to treatment periods that lasted two months for each dose. Adapted from Andersen *et al.*[185]



(e.g. chymase) have a functional role in the local generation of Ang II, thereby affecting tissue/organ function. In animal studies, it appears, that BP control and renoprotection are directly correlated, regardless of which antihypertensive agent is used.[190] It is in man, when BP is aggressively controlled, where this relationship does not hold, as numerous studies have demonstrated important non-haemodynamic effects of RAAS blockade beyond systemic BP lowering on renoprotection.[184,191]

Since Ang II can be partly generated in human cardiac, vascular and renal tissue by non-ACE pathways, animal studies cannot be used to draw conclusions in human disease models.[43] Studies by Hollenberg *et al.*[42] have shown that the acute renal vasodilator response to ACE-I and ARB therapy in humans correlates with PRA and serves as an acute marker of intrarenal (i.e. tissue) RAAS activity. In these studies, the renal vasodilator response, following administration of ARBs, is enhanced over ACE-inhibition, supporting the functional significance of non-ACE pathways in humans and the importance of studying species differences.[44] Clearly, human studies will need to be designed to examine the contribution of the non-haemodynamic aspects of RAAS blockade, that is the role of non-ACE pathways and the tissue RAAS in chronic, progressive renal disease.

However, so far, in the limited number of clinical studies comparing ARBs with ACE-I, no differences have been shown between these two groups in terms of renoprotection.[192] In two studies comparing the antiproteinuric effects of losartan with enalapril, both drugs resulted in similar effects on renal haemodynamics and reductions in BP and proteinuria. The additional reductions in urinary protein excretion after doubling the dose in both studies were primarily independent of BP-lowering or haemodynamic effects (Figure 5).[33,185]

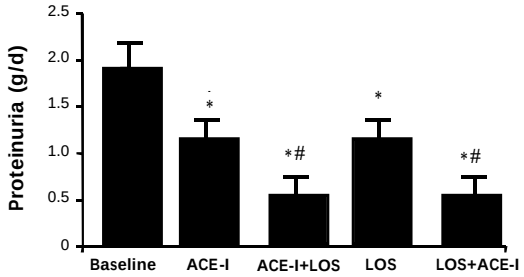
Clinical studies that have combined ACE-I and ARBs, have shown more complete inhibition of the RAAS, resulting in enhanced renal vasodilation and additional reductions in proteinuria (Table 6).[10,17,58,156,193-196] In one study, when losartan (50 mg/day) was added to a moderate dose of an ACE-I in normotensive patients with IgA nephropathy, proteinuria was more profoundly reduced than with either agent alone (Figure 6).[194] Urinary protein excretion was reduced by 69% on combined ACE-I and ARB therapy compared with either drug as monotherapy (-39% on ACE-I; -27% on ARB). The additional effect on urinary protein excretion was

Table 6 Potential benefits of combination therapy (ACE-I + ARB) in renal disease patients[10,17,58,156,193-196]

	Outcome
Clinical studies	Enhanced blockade of the RAAS (e.g. increase in PRA)[20,191]
	No change or slight reduction in plasma aldosterone levels[20]
	Increased RPF[191]
	Preserved or no Δ GFR[20,191]
	Reductions in proteinuria[157,195]
	Greater ability to suppress cytokine expression (e.g TGF-B_1)[13,59,193]

RAAS = renin angiotensin-aldosterone system; PRA = plasma renin activity; RPF = renal plasma flow; GFR = glomerular filtration rate; TGF-B_1 = transforming growth factor beta-1

Figure 6 The antiproteinuric effect of combining losartan (LOS; 50 mg) with an ACE-inhibitor (ACE-I) in eight normotensive, non-nephrotic proteinuria (1-3 g/day) patients with IgA nephropathy was compared to monotherapy. Urinary protein excretion was measured at the end of each four week period for ACE-I monotherapy, ACE-I + LOS combination therapy, LOS monotherapy and LOS + ACE-I combination therapy periods. Adapted from Russo *et al.*[194]



* p<0.05 *vs.* baseline;
# p<0.05 *vs.* ACE-I or losartan monotherapy

not dependent on changes in systemic BP or glomerular filtration rate (GFR), but was secondary to the improvements of haemodynamics and/or membrane permeability at the glomerular level.[194]

Recently, a multi-centre trial, combining lisinopril and candesartan, the CALM study, was completed though the results are not yet published (see Table 5).[157] There are no other on-going, large, multicentre trials in diabetic or renal patients involving the combined use of an ACE-I and ARB. Further studies are required to examine the role of combined ACE-I and ARB therapy in renal disease. The difficulty with most of the studies has been related to the use of sub-optimal drug doses, short study duration, slow rate of renal disease progression and inadequate measures to better examine the relative importance of non-ACE pathways. These results suggest that, in order for combination therapy to provide optimal renoprotection over monotherapy, the doses currently used must be increased to effectively suppress markers of renal disease progression, such as cytokine expression.[10] Thus, the benefit of combining ACE-I and ARB in renal disease must be directed to ensuring more complete blockade of the RAAS.

Adverse effects

Possible adverse effects associated with the use of ARBs in combination with ACE-I are presented in Table 7.[12,16-17,147,153,155-156,159-162,165,193] Studies have demonstrated the tolerability of the combination to be similar to monotherapy with ACE-inhibition. The incidence of cough, the most troublesome and common reaction to ACE-I therapy, is also expected to be similar in the combination group.[153]

It has been suggested that renal-impaired patients, who are sensitive to RAAS blockade, particularly with high doses of ACE-I, may fare better by using lower doses of ACE-I and an ARB to preserve GFR, rather than using a high dose of either drug.[12,197] In addition, this should lead to less hyperkalaemia.[198] A slight increase in serum creatinine (15 µmol/l) was recently reported in a study of renal-impaired patients on combined ARB and ACE-I therapy, but the response was not thought serious, since this is a typical effect of ACE-inhibition in patients with a reduced GFR. Thus, the use of combination ACE-I and ARB therapy in renal and diabetic patients should follow the same protocol as when one initiates ACE-I therapy. If an ARB is to be added to existing ACE-I therapy, a low dose should be initiated and titrated upwards thereafter based on need.

In a recently completed large CHF study (n= 768 patients), discontinuation rates did not differ between the combination and the ACE-I therapy group.[147] Therefore, side-effects should not be different with combination therapy when compared with low-dose ACE-I monotherapy. To date, there are no data to suggest that side-effects using the combination are any greater than that expected with the agents alone as monotherapy. Perhaps, if the dose of the ACE-I needs to be increased and there is a concern, lower doses of both drugs can be used for greater RAAS blockade than ACE-I alone.

Conclusions

Incomplete tissue RAAS blockade using ACE-I therapy in subjects with abnormal clinical syndromes of disease, such as CHF and renal disease, may account for the continued deterioration of function in these patients. Determining an optimal dose of ACE-inhibition that is based on BP control alone does not provide adequate inhibition of the tissue-based RAAS. A recent clinical trial, the HOPE study, demonstrated the importance of tissue RAAS blockade, as the reduced cardiovascular morbidity and mortality benefits were primarily attributed to non-haemodynamic effects.[199] The RAAS plays an important short-term role in the circulation through haemodynamic and renal effects while the long-term tissue effects are integral in multiple other functions and systems that regulate inflammation and cellular growth, such as fibrosis,

Table 7 Possible adverse effects associated with the use of ARBs in combination with ACE-I [12,16-17,147,153,155-156,159-162,165,193]

Proposed adverse effect	Incidence / outcome
Hypotension, dizziness	Hypertensive patients – mild or not observed[153,155]
	Diabetics – transient episode in 2/7 patients[17]
	CHF and post-MI patients – not observed[159-160]
Tachycardia	Not observed[155, 161]
Reduced GFR (acute renal failure)	Hypertensive patients – not observed[193]
	Renal-impaired patients – slight increase in serum creatinine levels (0.15 µmol/l), no acute renal failure or progressive renal failure observed[156,162]
Cough	Incidence of coughing similar to ACE-I monotherapy[153]
Angioneurotic oedema	Observed in one combined therapy study, thus potential still exists; follow same precaution as ACE-I[162]
Hyperkalaemia	Plasma aldosterone levels not affected in hypertensive and diabetic patients[13,17]
	Plasma aldosterone levels slightly reduced in CHF patients[16,147,160]
	No significant changes in plasma potassium or reports of hyperkalemia in hypertensive or diabetic patients[13]
	Slight increase (+0.11) in plasma potassium concentration in CHF patients[149, 162]
	Plasma potassium levels slightly increased in renal-impaired patients but incidence of hyperkalaemia was low[156]
Decompensation in heart failure patients	Aggravated CHF symptoms and fluid overload incidence low, similar to placebo[161-162,165]
Anaphylactoid/sensitivity reactions	Not observed
Foetal / neonatal morbidity and mortality	Same contraindications as ACE-I and ARBs

CHF = chronic heart failure; MI = myocardial infarction

hypertrophy, and remodelling of organ beds. Therefore, long-term activation of the tissue RAAS has been implicated as a major factor influencing progressive dysfunction of target organs. To effectively antagonise the actions of the tissue-based RAAS requires either higher doses of one RAAS blocker or a combination of two different RAAS blockers to ensure maximal tissue protection.

To date, most investigators have employed the dominant strategy to improve the level of RAAS blockade by increasing the dose of the ACE-I or ARB. Unfortunately, this approach has limited data since few studies have employed supraphysiological doses of drug to maximally inhibit the tissue-based RAAS. In order to provide more complete and sustained blockade of the RAAS, the object of several recent investigations has been the combined use of ACE-I and ARBs. An advantage of combining these agents, to provide more effective tissue-based RAAS blockade, is achieved by targetting both the ACE and non-ACE pathways involved in the generation of Ang II. Combining ACE-I and ARBs will also prevent the counterregulatory responses that occur on monotherapy, the 'ACE-escape' effect, whilst the potentially beneficial effects of prolonged kinin tissue levels are maintained.

Clinical studies comparing the antihypertensive response of ACE-I and ARBs have conclusively demonstrated similar BP lowering effects. Furthermore, studies combining ACE-I and ARBs have shown little additional hypotensive benefits when compared with increasing the dose of one of the agents alone. Greater antihypertensive effects, if that is the therapeutic goal, can be more easily achieved by adding a diuretic to one of the RAAS blockers. Thus, the potential benefit of combining the two RAAS blockers is specifically targetted to preserving end-organ function, preventing the progression of vascular, cardiac or renal dysfunction, and not for added BP control. Several investigators in both basic and clinical sciences have demonstrated that tissue-protective effects, independent of any BP reduction, of the combination were achieved by the beneficial effects on such factors as neurohumoral activity, LV ejection fraction, cardiac remodelling, proteinuria, and cytokine expression (see Tables 4 and 6).

Although the proposed benefits of therapeutically combining ACE-I and ARBs are attractive, it is still not clear whether or not the same effects can be achieved by simply increasing the dose of one of the agents alone. Unfortunately, the lack of data on optimal doses of ACE-I or ARBs in CHF, diabetes and renal disease has left many of these questions unanswered. Formal investigation is awaiting completion to address these very important issues. Only a few studies have examined the dose-response relationship to provide insights into the cardiac-

and renal-protective effects of using ACE-I or ARBs. We are encouraged that final results from current, ongoing studies, in diabetes, post-myocardial infarction and CHF, which examine the combined therapeutic use of ACE-I and ARBs *vs.* high-dose monotherapy, will help to optimise target organ protection strategies (see Table 5). Until those studies begin to provide some rational starting points for therapy, using ACE-I and ARBs in combination will play a secondary role to using supra-physiological doses of ACE-I or ARBs to block the RAAS. Interestingly, in many cardiovascular syndromes of disease, current evidence strongly recommends the use of ACE-I or ARBs at higher doses than normally used for optimal BP control. Thus, combining therapy, using moderate doses of ACE-I and ARBs, may provide a more complete tissue RAAS blockade, through the synergistic antagonism at different sites of the renin-angiotensin cascade, rather than attempting to titrate monotherapy upwards to some unspecified level. In this manner, combination therapy should allow optimal tissue protective effects when combined with routine risk reduction strategies such as aggressive BP control, cholesterol and diet management, smoking cessation, exercise and diabetic control.

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