Optimal blockade of the renin angiotensin system in cardiorenal dysfunction
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Addition of an Angiotensin Receptor Blocker to full-dose ACE-inhibition: Controversial or common sense?

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Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers interfere with the activity of the renin angiotensin system in a different way. Theoretically, one might expect beneficial effects when they are used in combination, as a more complete suppression of the renin angiotensin system can be achieved. But can this additional effect still be seen in patients on full-dose ACE inhibition? Several controlled trials demonstrated that combination therapy can have additional benefits in hypertensive patients, chronic heart failure patients and in both diabetic and non-diabetic nephropathy. However, the clinical benefit was not always as pronounced as expected and not every patient will benefit from dual blockade of the renin angiotensin system. There is some evidence of a less pronounced effect of combination therapy when a full dose of the ACE-inhibitor is given. However, it is well known that ACE inhibitors cannot completely suppress the formation of angiotensin II, in particular when the renin-angiotensin system is activated. Indeed, clinical trials indicated that add-on therapy with an angiotensin receptor blocker was especially of use when the renin-angiotensin system remained activated despite full-dose ACE inhibitor treatment. In summary, combination of a full-dose ACE inhibitor and an angiotensin receptor blocker can be a rational choice in selected patients.
Introduction

One of the evolutionary goals of the development of the renin angiotensin system (RAS) is to protect the body by preserving salinity. However, over the last few decades it has become clear that an activated RAS can provoke detrimental effects as well. Pharmacological blockade of the RAS has significantly improved prognosis of patients with cardiovascular disease. ACE inhibitors and angiotensin receptor blockers (ARBs) are capable of interfering with the activity of the RAS. At first sight, the modes of action of both ACE inhibitors and ARBs seem very similar, but after closer examination several differences are revealed. Theoretically, both groups could even have additional effects. Several studies confirmed this theoretical consideration. Others questioned whether the same effect is present when full-dose ACE inhibitors are used. Recent data from the ValHeFT trial indicated a trend towards a more pronounced effect of valsartan in patients with lower doses of the ACE inhibitor. However, this was a non-significant finding in a post-hoc analysis. Also, patients on lower doses of the ACE inhibitor might have reflected more diseased patients, with a higher activation of the RAS.

In the present paper, theoretical and practical considerations of add-on therapy with an ARB on top of an ACE inhibitor in hypertension, (non)-diabetic nephropathy, myocardial infarction, and heart failure will be discussed.

ACE inhibitors

The ACE, also known as kininase II exists in the entire human body in both free and membrane-bound form. ACE is one of the components of a complex system of regulating and counter-regulating mechanisms (Figure 1). It was originally thought that the majority of the effects of ACE inhibitors could be explained by the reduction of angiotensin II formation. However, in the early eighties, it was demonstrated that ACE inhibitors cannot fully suppress angiotensin II formation in hypertensive patients over a longer period of time. In normotensive male volunteers, ACE inhibition could not suppress angiotensin II increase during exercise. Interestingly, the chymase inhibitor nafamostat was able to significantly reduce angiotensin II formation in the same patients. In addition, increasing levels of both angiotensin II and aldosterone were eventually observed in a large proportion of patients. Jorde et al. demonstrated that even maximally recommended doses of ACE inhibitors could not completely prevent ACE-mediated angiotensin II formation. However, it is unknown whether
supra-maximal doses of ACE inhibitors might further suppress angiotensin II formation. There is experimental evidence against this hypothesis. In human arteries, even supra-physiological concentrations of ACE inhibitors were not able to suppress angiotensin I evoked vasoconstrictive response, whereas ARBs completely blocked this response. Furthermore, in almost half of our chronic heart failure patients we, and others, found elevated angiotensin II levels despite treatment with a (high dose) ACE inhibitor. These increased angiotensin II levels were independent of the dose and duration of use of the ACE inhibitor. Evidently, this could be the result of an inadequate ACE inhibitor dose, but it could also be the result of the existence of non-ACE angiotensin II-forming enzymes (e.g. human chymase). Elevated angiotensin II levels despite ACE inhibition are associated with a poorer prognosis. As a result of feedback mechanisms within the RAS high angiotensin II levels are also found in patients on spironolactone, but in these patients prognosis is not impaired.

Another important effect of ACE inhibitors is their influence on the breakdown of bradykinin into inactive peptides (Figure 1). By administering specific bradykinin antagonists the effect of ACE inhibitors can be (partly) inhibited.

![Figure 1. Complex effects of ACE-inhibitor on renin angiotensin system](image-url)

ACE, angiotensin converting enzyme; Ac-SDKP, N-acetyl-Ser-Asp-Lys-Pro; ANP, atrial natriuretic peptide; AT 1-7 R, angiotensin 1-7 receptor; AT1R, angiotensin II type 1 receptor; BK, bradykinin; B2R, bradykinin type 2 receptor; CAGE, chymostatin-sensitive angiotensin II-generating enzyme; MEP, metalloendopeptidase; NEP, neutral endopeptidase; NO, nitric oxide; PEP, prolyl endopeptidase; PGE2, prostaglandin E2; VSMC, vascular smooth muscle cell.
Bradykinin induces vasodilation by stimulating the formation of nitrogen oxide and metabolites of arachidonic acid in vascular endothelium.\textsuperscript{26} Additionally, bradykinin induces natriuresis by direct tubular effects.\textsuperscript{27} Thus, ACE regulates the balance between the vasodilative and natriuretic properties of bradykinin and the vasoconstrictive and salt-retaining properties of angiotensin II.

Beside destroying bradykinin, ACE also is the exclusive enzyme that catabolizes N-acetyl-Ser-Asp-Lys-Pro (AcSDKP). Results from a recent experimental study suggest that high levels of this peptide lower cardiac collagen content.\textsuperscript{28} These findings explain the antifibrotic effects of ACE inhibitors.

Furthermore, ACE inhibitors lead to elevated angiotensin 1-7 levels.\textsuperscript{29} This metabolite of both angiotensin I and II can stimulate the synthesis and excretion of vasodilatory prostaglandins, fortify the metabolic effects of bradykinin, and increase nitric oxide production. The clinical value of these final two additional effects needs to be clarified in future research.

**Angiotensin II receptor blockers**

Angiotensin II mediates its wide variety of effects through four angiotensin II receptors (AT1R, AT2R, AT3R en AT4R).\textsuperscript{30} The functions of AT3R and AT4R remain unclear, but these receptors seem to be of secondary importance.\textsuperscript{31,32} In humans, the AT2R disappears after fetal stage, but expression increases in certain situations (e.g. coronary ischemia or heart failure).\textsuperscript{33} In general, stimulation of AT2R and AT1R induces opposite effects. The AT1R is usually associated with the detrimental effects of angiotensin II. By selectively blocking AT1R, excess angiotensin II will stimulate AT2R. The currently available ARBs specifically block the AT1R. ARBs probably also block the stimulation of aldosterone release, since this pathway is mediated by the AT1R. Still, other stimulants, for example potassium, can also induce aldosterone release.\textsuperscript{34} According to current views aldosterone is an important moderator of the unfavorable effects of angiotensin II.\textsuperscript{35}

**Differences between ACE inhibitor and ARB**

Previous findings demonstrate that ACE inhibitors and ARBs have a marked different pharmacology. Obviously, the most apparent difference is the primary point of action, which leads to a differentiated neurohormonal activation. Accordingly, in patients using an ACE inhibitor slightly reduced angiotensin II
The relatively high angiotensin II level in patients on ARB therapy offers the advantage of supplementary stimulation of AT2R. Since plasma angiotensin II levels are supposed to decrease in patients using an ACE inhibitor and consequently less AT2R stimulation will occur, this is the second distinction between both groups. A third difference is the increase in angiotensin 1-7 that will take place when an ACE inhibitor is used. However, in an animal model administration of losartan also induced a slight increase in angiotensin 1-7, but the clinical implications of this observation are not yet fully understood.

A fourth distinction between ACE inhibitor and ARB is their influence on bradykinin catabolism and the accompanying increase in nitric oxide. ACE inhibitors impede the breakdown of nitric oxide by a direct inhibiting effect. In fact, some studies indicated that a substantial part of the effects of ACE inhibitors is contributed to the accumulation of bradykinin. ARBs might also induce higher bradykinin levels, possibly through an AT2R-mediated mechanism, although the magnitude of this effect in clinical practice remains doubtful.

Dual RAS blockade and hypertension

Several studies demonstrated that the antihypertensive action of ACE inhibitors and ARBs is comparable to that of other blood pressure lowering compounds. Furthermore, it was demonstrated that blood pressure lowering using a dual RAS blockade strategy is more effective than using monotherapy. Another study showed that addition of an ARB to an ACE inhibitor is more effective than doubling ACE inhibitor dose. This suggests that both medication groups exercise a different mode of action to achieve their goal. However, the most important question is whether the combination of ACE inhibitor and ARB is equally effective as combining an ACE inhibitor and another antihypertensive agent, for example a diuretic. Unfortunately, up till now no studies have addressed this question.

The combination of ACE inhibitor and ARB has shown to be more effective than the individual compounds in the treatment of microalbuminuric diabetics, diabetic nephropathy and non-diabetic nephropathy. In hypertensive patients, monotherapy was not as effective as the combination candesartan and lisinopril in reducing urinary albumin excretion. These circumstantial findings link microalbuminuria to activation of the renin angiotensin system, but to our knowledge, no controlled studies have confirmed this linkage.
These studies suggest that both ACE inhibitor and ARBs are effective blood pressure lowering drugs when they are used as single-agent therapy. In the uncomplicated patient the combination of a diuretic agent and an ACE inhibitor or an ARB is advocated by the guidelines of the European Society of Hypertension. However, the complicated (diabetic) hypertension patient with (micro)albuminuria might benefit from dual RAS blockade as the combination is reportedly more effective as the use of either type of drug alone.

**Dual RAS blockade after acute myocardial infarction**

In VALIANT valsartan, captopril, and their combination were compared, when added to standard treatment within 10 days after acute myocardial infarction, complicated by heart failure. Mortality and combined cardiovascular endpoints did not differ significantly in any of the groups, although significantly less patients were hospitalized in the combination group when compared to the patients on captopril. Therefore, in these patients, a substantial effect of combination therapy could not be demonstrated. Several explanations for these findings have been proposed. The most likely explanation however, is the consistent finding that angiotensin II levels eventually rise when ACE inhibitors are administered chronically. For that reason, after myocardial infarction, during the early phase when cardiac remodeling occurs, ACE inhibitors might be able to suppress RAS activity adequately. Also, the untoward hypotensive effects of combination therapy might have counteracted possible beneficial effects. So acute myocardial infarction complicated by left ventricular dysfunction is not an indication for starting the combination ACE inhibitor and ARB. This might change when the condition progresses to chronic heart failure.

**Dual RAS blockade and systolic heart failure**

In systolic heart failure the RAS is activated. Elevated levels of renin, angiotensin II, and aldosterone are accompanied by activation of the sympathetic nerve system, and by elevated blood levels of brain natriuretic peptide (BNP) and vasopressin. Despite current standard therapy (diuretic, beta-blocker, and ACE inhibitor) morbidity and mortality in heart failure remains high. Roig et al. demonstrated that elevated angiotensin II concentrations despite ACE-inhibition in heart failure patients bears prognostic value. In the accompanying editorial we already suggested that combination of ARB and ACE inhibitor theoretically provides a more complete suppression of the RAS, while preserving the positive effects of bradykinin potentiation. This is probably
not true for every patient, but we hypothesize that especially patients with an activated RAS despite full-dose ACE-inhibition will benefit most from more complete suppression of the system, and thus from combination therapy.

Val-HeFT and CHARM demonstrated that by combining an ACE inhibitor and an ARB (valsartan and candesartan, respectively) a synergistic effect can be achieved, thus reducing the combined endpoint mortality and morbidity. A recent post-hoc analysis of Val-HeFT demonstrated a trend towards a more pronounced effect of combination therapy in patients with a left ventricular ejection fraction of <30%. This suggests that combination therapy is more effective in severe chronic heart failure, with an highly activated RAS. Both Val-HeFT and the ATLAS trial suggested that the difference in efficacy between intermediate and high dosed ACE inhibition is likely to be very small. We recently demonstrated that increased angiotensin II levels in chronic heart failure patients were independent of dose, type or duration of ACE-inhibitor use.

**Dual RAS blockade in combination with beta blockade**

Beta blockers are strong renin inhibitors. ELITE II already suggested that the combination of a beta blocker with an ACE inhibitor was better than the combination of a beta blocker and an ARB in patients with heart failure. This might be due to residue angiotensin II formation despite ACE inhibition, which will not occur when the AT1R is blocked directly, and to positive feedback mechanisms that increase plasma renin activity. So, from a pharmacological point of view, the combination of an ACE-inhibitor with a beta blocker seems to be more appropriate than the combination of an angiotensin receptor blocker and a beta blocker. However, this hypothesis has not been tested in a randomized clinical trial. There have also been some concerns in using both an ACE-inhibitor, a beta blocker and an ARB (‘triple therapy’) in patients with chronic heart failure. Subgroup analyses of Val-HeFT suggested an increased mortality in the group of patients treated with ‘triple therapy’ compared to patients treated with an ACE-inhibitor and a beta blocker. However, both CHARM-added and VALIANT clearly demonstrated that ‘triple-therapy’ does not confer any additional risk.
**Conceptual frame for combined use of ACE inhibitor and ARB**

In the previous paragraphs, we concluded that combination of an ACE inhibitor and an ARB is not first choice treatment in all patients with hypertension, heart failure, or myocardial infarction. However, under certain circumstances the RAS will become progressively activated. In hypertensive patients, a small percentage (e.g. diabetic subgroup, renal dysfunction) may be at risk for developing high RAS activity. Several authors have demonstrated that in post-myocardial infarction patients, RAS activity remains higher when left ventricular dysfunction develops.\(^{72,73}\) In the majority of chronic heart failure patients RAS markers will rise as the disease advances. Particularly in these subgroups, dual RAS-blockade might be beneficial, whereas in the remaining subgroups more conventional therapies are preferred. This concept is illustrated in Figure 2.

**Figure 2.** This conceptual figure illustrates that activity of the RAS in cardiovascular disease changes over time, and depends on severity of the disease and comorbidity. In uncomplicated hypertension RAS activity is fairly constant (panel A), but when hypertension occurs in combination with renal dysfunction, diabetes or microalbuminuria RAS activity might increase. Shortly after myocardial infarction the activity of the RAS will peak and then return back to baseline level. However, when progressive left ventricular dysfunction develops after myocardial infarction, RAS chronic heart failure patients elevated RAS parameters will be found (panel C). The higher the activity of the RAS, the more effect one might expect from dual RAS blockade.

*Abbreviations: RAS, renin angiotensin system; ma, microalbuminuria; DM, diabetes mellitus*
**Table 1. Indications and evidence for combining ACE-inhibitor and Angiotensin Receptor Blocker**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Indication for dual RAS inhibition?</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Hypertension Systolic heart failure</td>
<td>Not standard, possibly in LVH, microalbuminuria, DM hypertension. Yes, when symptoms persist despite diuretic, betablocker and ACE-inhibitor (when RAS remains activated despite ACE inhibition?)</td>
<td>42-44; 62;63</td>
</tr>
<tr>
<td>Post-myocardial infarction</td>
<td>No</td>
<td>54;74</td>
</tr>
<tr>
<td>Nephroprotection (diabetics)</td>
<td>Yes</td>
<td>44;47</td>
</tr>
<tr>
<td>Nephroprotection (non-diabetics)</td>
<td>Yes</td>
<td>43;50-52</td>
</tr>
</tbody>
</table>

Abbreviations: RAS; Renin angiotensin system, CHF; chronic heart failure, LVH; left ventricular hypertrophy, DM; diabetes mellitus

**Safety and risks**

A few large trials indicated that when both ACE inhibitor and ARB were used, significantly more patients discontinued study medication.\(^{54,63}\) In these trials almost one in four patients discontinued study medication because of primarily hypotension, hyperkalemia, and renal dysfunction.\(^{75}\) When a patient is treated with an ACE inhibitor and an ARB, the treating physician needs to be aware of these adverse effects and strict monitoring is warranted.

As dual RAS blockade is a relatively new concept, several questions remain unanswered. The duration of action of different ACE inhibitors and ARBs might influence the effect of different combinations. Furthermore, the effect of a combination might depend on the order and timing of intake of both agents.\(^{76}\) Finally, more complete RAS-suppression and thus a higher dose or a shorter dosing interval might be needed to obtain organ protection, where lower doses are sufficient to treat hypertension.\(^{77}\)

Besides maintaining salt and fluid balance in the body, the RAS has undoubtedly more physiological implications of which we are not even aware of at the present time. Completely blocking the RAS might lead to side effects that will become evident only after a much longer time span than the duration of a scientific trial. These unknown potential side effects warrant a word of caution, in particular when triple blockade of the RAS is used.
Conclusion

First, ACE inhibitors and ARBs have a fundamentally different mode of action. ACE inhibitors initially reduce angiotensin II formation, but levels increase again over time, probably through non-ACE angiotensin II forming pathways (i.e. chymase). The persistent effects of ACE inhibitors, despite a rise in angiotensin II levels can be explained by several other modes of action of ACE inhibitors, such as the decreased breakdown of bradykinin. ARBs more effectively suppress angiotensin II mediated effects, but seem to have less pronounced bradykinin effects. Beneficial effects of combination therapy were demonstrated in hypertension, (non)-diabetic nephropathy, and chronic heart failure. Some studies indicated that the effects of ACE inhibitors were less pronounced when a full-dose ACE-inhibitor was given. In contrast, a large body of evidence suggests that ACE is not the rate-limiting step in the RAS cascade, and that elevated angiotensin II levels are not related to the dose of the ACE-inhibitor, but more to the activation of the RAS. Consequently, this leads to the concept that combination therapy will be more effective in conditions where the RAS is intensively activated. Clinically, combination therapy in uncomplicated hypertension is not a wrong choice, but other combinations may be better. In patients with an acute myocardial infarction, complicated by heart failure, combination therapy is not preferred. However, combination therapy seems to be a rational choice in patients with a chronic activation of the RAS, such as patients with renal disease and (severe) chronic heart failure.
References


