Combinations of Renin-Angiotensin-Aldosterone System Antagonists: True Advantages?

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Combinations of Renin-Angiotensin-Aldosterone System Antagonists: True Advantages?

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Running title: Dual RAAS blockade

Abstract
The renin angiotensin aldosterone system (RAAS) inhibitors induce an incomplete blockade of the system at different steps. Recently, the dual RAAS therapy is emerging in clinical practice, although there is a lack of evidence on safety and efficacy for this combination in several cardiovascular diseases. In this review, we evaluated the advantages and disadvantages of dual RAAS blockade in hypertension, proteinuric renal disease, heart failure and ischaemic heart disease. The role of DRIs in combination with ACEI or ARBs is promising, but still needs further studies. On the basis of the clinical outcomes and safety data the recommendations guidelines have not confirmed indications to dual RAAS blockade in essential hypertension treatment, heart failure and ischemic heart disease. Only proteinuric nephropaties and resistant hypertension may represent possible indications to dual RAAS blockade. Actually, rational combinations of either an ACEI or ARB or DRI with other classes of antihypertensives offer best solutions.

Keywords: renin-angiotensin-aldosterone system, hypertension, heart failure, proteinuria.

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Introduction.

Many drugs target the renin angiotensin aldosterone system (RAAS) at different points, either reducing renin release and activity (beta-blockers, central alpha-agonists and direct renin inhibitors, DRI) or preventing angiotensin II formation through angiotensin-converting enzyme inhibition (ACE inhibitor, ACEI) or angiotensin II action through the AT-1 receptor (angiotensin-receptor blocker, ARB) and blocking aldosterone receptors (aldosterone receptor antagonist, ARA), (Table 1). The dual inhibition of the RAAS induces biochemical and hormonal changes (Table 2) on many steps of the system, however the blockade of the RAAS remains always incomplete.
Recently the ACEI/ARB combination therapy has been included in international guidelines, although there is a lack of evidence on safety and efficacy for this combination in several cardiovascular diseases [1-7].
In this review, we highlight the pro and cons of the dual blockade of renin angiotensin system in hypertension, proteinuric renal disease, heart failure and ischaemic heart disease.

Table 1. RAAS inhibitors

ACEIs	**Captopril, enalapril, benazepril, lisinopril, quinapril, moexipril, delapril, fosinopril, perindopril, cilazapril, ramipril, trandolapril**
ARBs	**Valsartan, losartan, irbesartan, eprosartan, telmisartan, candesartan, olmesartan, azilsartan**
DRIs	**Aliskiren, remikiren, enalkiren, zankiren**
ARAs	**Spironolactone, canrenone, eplerenone**

Abbreviations:
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DRI, direct renin inhibitor; ARA, aldosterone receptor antagonist.

Table 2. Biochemical and hormonal changes with the combination of Renin-Angiotensin-Aldosterone System Antagonists (ACEI-ARB-DRI) [ref. 8-21].

Selectivity of blocking AT1 receptors
Inhibition of the ATII activity produced by ACE escape
Increase of the stimulation of AT2 receptors
Decrease of angiotensin I (PRA)
Increase of Angiotensin- (1-7)
Reduction of aldosterone
Increase of nitric oxide

Dual RAAS blockade in hypertension.

Several studies investigated use of ACEI plus ARB in the treatment of hypertension giving often conflicting results. Many of them enrolled small population. In the light of all data obtained and in particular of the most recent evidence, dual RAAS blockade with ARB and ACEI may be discouraged in clinical management of hypertension. Below are listed the most important clinical trials.

In 2000 Azizi et al. found that combination therapy with enalapril 10 mg and losartan 50 mg was more effective to reduce diastolic pressure than treatment with individual drugs; however 24-hour ambulatory mean diastolic blood pressure did not significantly differ between treatment groups [22].

In another trial conducted by Stergiou et al.[23] valsartan added to benazepril produced a significant antihypertensive effect with a benefit over placebo.

A large-scale, open-label, clinical trial evaluated the efficacy of the angiotensin II receptor blocker candesartan either alone or as add-on therapy in a large cohort of hypertensive patients. As add-on therapy to various background therapies, candesartan consistently reduced mean systolic/diastolic blood pressure further, irrespective of the background therapy, in particular when candesartan was added to ACEI was observed a decrease of systolic/diastolic pressure of 15.3/10.0 mmHg [24].

The AMAZE (A Multicenter Trial Using Atacand and Zestril vs. Zestril to Evaluate the Effects on Lowering Blood Pressure) program was performed to determine if addition of the angiotensin receptor blocker candesartan was more effective in lowering blood pressure than up-titration of lisinopril. Authors concluded that for hypertensive patients not controlled by lisinopril , addition of candesartan or doubling the dose of lisinopril provides safe and additional reduction of blood pressure [25].

In 2005 an important meta-analysis of randomized trials using combination therapy was conducted. The results obtained with the combination therapy were superior compared to individual therapy, but most studies used submaximal doses or once-daily dosing of shorter-acting ACEI and, when a larger dose of shorter-acting ACEI was given or a longer-acting ACEI was used, there was generally no additive effect of the ARB on blood pressure. Proteinuria however was reduced by the combination compared with ACEI and ARB monotherapy, an effect that was independent of blood pressure in several studies [2].

One of the most important and large clinical trial conducted to establish usefulness of combination therapy versus single therapy with inhibitors of RAAS was the ONTARGET. Authors concluded that telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefits in terms of outcomes but reduces the pressure slightly more than single therapy [26]. For what concerns new therapies options, recently aliskiren has been shown to be efficacious in hypertensive patients. Several trials were conducted to assess aliskiren's efficacy in the therapy of hypertension when it was associated to other RAAS blockers.

Unlike the common association between RAAS's blocking drugs, when aliskiren was added to hydrochlorothiazide, ramipril, or irbesartan improve in RAAS system suppression and 24-hour blood pressure control was observed [27-28].

Similar findings were obtained in large clinical trials of aliskiren and valsartan association [29-30] and in the light of these results the aliskiren/valsartan association is considered an alternative option for management of blood pressure in patients with stage 2 hypertension.

Regarding safety of combination therapies including aliskiren, was recently demonstrated that profile of aliskiren in combination with an ARB, valsartan or losartan, or diuretic, is similar to aliskiren, ARB, or diuretics alone [31].

Based on the established efficacy and safety of aliskiren/valsartan combination, a single pill is been produced and can be used in the treatment of hypertension for those patients at high risk for cardiovascular disease and are not likely to achieve blood pressure goals with monotherapy.

The effects of aliskiren combined with another RAAS blockers and the mechanism of action of aliskiren suggest that aliskiren-based combinations may confer incremental vasculoprotective effects respect monotherapy, expecially in high risk patients. However the direct renin inhibition approach to RAAS suppression is still very recent and the ultimate role of aliskiren in combination therapies with ACEIs, ARBs, and other antihypertensives will be better defined through future studies (i.e the ASPIRE HIGHER program [32]).

Finally, an optional strategy for the treatment of true resistant hypertension is the combination of ACEI and ARB. Resistant hypertension, defined as a failure of three or more concomitant antihypertensive medications, including diuretics, to lower blood pressure below 140/90 mmHg, is an increasingly common clinical problem, affecting up to 30% of hypertensives [33-35].

It is well known that aldosterone receptor antagonists provide significant additive blood pressure reductions both in patients with and without primary aldosteronism, suggesting a role for aldosterone excess in resistant hypertension [36-37] .

Some clinical studies have showed the efficacy of double blockade of the RAAS in the resistant hypertension [38-41] . A recent controlled but small trial has demonstrated that spironolactone added to a regime of single RAAS blockade, has a greater blood pressure lowering effect than dual RAAS blockade in resistant hypertension [42]. According to JNC VII [33] and NICE [43] guidelines, the dual RAAS blockade (respectively ACEI/ARB combo and ACEI or ARB with ARA), represents an alternative strategy in the work-up treatment of resistant hypertension. Whereas, the European recommendations guidelines do not confirm the indication to dual RAAS blockade in essential hypertension treatment [34-35].

Dual RAAS blockade in renal disease.

Many studies indicate that greater kidney protection may be achieved by combination of ACEI with an ARB or DRI compared with either RAAS inhibitor alone in patients with diabetic and nondiabetic nephropathies [44-57].

In particular, the meta-analysis by Kunz [7] suggested that monotherapy with ARBs and ACEI induced similar decrease in patients with proteinuria and the dual blockade of the RAAS was more effective. The limit of this meta-analysis was only the short follow up (6 months). Further, the addition of spironolactone or eplerenone to an ACEI or ARB in patients with proteinuric chronic kidney disease showed both a decrease in proteinuria and in blood pressure [58-65] . However, there is still limited evidence to combine spironolactone or eplerenone to an ACEI or ARB in patients with nephropathies with or without proteinuria . Further, the dual (ACEI/Aldosterone receptor antagonist) combination is life-threatening, since hyperkalemia can occur [66-67].

Finally, since there are limited studies of combinations of ACEI or ARBs with DRIs in patients with chronic kidney disease, larger-scale studies of dual combination are needed. In conclusion, nowadays, the National Kidney Foundation recommends that ACEI and ARBs may be used in combination only to reduce proteinuria in nondiabetic and diabetic patients with kidney disease [68].

Dual RAAS blockade in heart failure.

The American College of Cardiology/American Heart Association heart failure guidelines recommend to combine ARB to ACEI in congestive heart failure (CHF) with ejection fraction (EF) <40%, if there are still CHF symptoms despite optimal standard therapy with ACE inhibitors and beta blockers [69] .

The RESOLVD [70] was one of the first trials conducted to investigate the effects of ARB (candesartan) and ACEI (enalapril) combination in congestive heart failure (CHF). Seven hundred sixty-eight patients in New York Heart Association functional class (NYHA-FC) II to IV with EF <0.40 received either candesartan alone, candesartan plus enalapril, or enalapril. There were no differences among groups with regard to symptoms, but EF increased more with candesartan-plus-enalapril therapy. End-diastolic and end-systolic volumes increased less with combination therapy.

The Valsartan Heart Failure Trial (Val-HeFT) determined whether valsartan could further reduce morbidity and mortality in patients with heart failure, who already receiving optimal therapy (ACEIs and β-blockers). The primary end point of mortality was similar for the valsartan and placebo groups, whereas the combined primary end point of morbidity and mortality was significantly reduced in patients receiving valsartan. This benefit was primarily due to a reduction in hospitalizations for heart failure in valsartan-treated patients. A subgroup analysis of patients on different background therapies revealed that valsartan had a favorable effect on the combined primary end point in those receiving an ACEI, a β-blocker, or no background therapy. In contrast, in patients receiving both an ACEI and a β-blocker, valsartan had an adverse effect on mortality, suggesting that ARB could be harmful in this context [71].

In spite of these results, in CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) study the addition of candesartan to ACEI and other treatment leads to a clinically important reduction in relevant cardiovascular events in patients with CHF and reduced left-ventricular ejection fraction. Instead, hypotension and renal dysfunction were more common in the combination group compared to those treated with ACEI monotherapy [72].

Regarding association of ACEI o ARB with a DRI, usefulness was demonstrated when aliskiren was added to conventional heart failure therapy (ACEI plus beta-blockers); in this clinical trial was observed a BNP and urinary (but not plasma) aldosterone reduction in patients taking aliskiren. Clinically important differences in blood pressure and biochemistry were not seen between aliskiren

and placebo [73]. When in ASPIRE trial aliskiren was compared to losartan in promoting left ventricular mass (LVM) regression, it was equally effective. Reduction in LVM with the combination of aliskiren plus losartan was not significantly different from that with losartan monotherapy, independent of blood pressure lowering; then the ASPIRE study does not support the addition of aliskiren to an ACEI or an ARB in post-myocardial infarction patients with impaired left ventricular function [74]. Also treatment with ACEI or ARB with aldosterone antagonists was investigated. ACEI or ARB plus spironolactone [75] or eplerenone [76] were evaluated in severe chronic heart failure and symptomatic postmyocardial infarction left ventricular dysfunction; in both these trials the drug association was useful and reduced the mortality.

Although it is clear that monotherapy with ACEIs or ARBs is effective in reducing cardiovascular mortality and morbidity in patients with heart failure, different results in trials examining ACEI/ARB combinations may relate to different patient populations, previous or concurrent successful treatment with other drugs, or study design (small trials and of short duration, submaximal doses of ACEIs and ARBs). In addition, many studies may promote ACE escape using once-daily dosing of short-acting ACEIs; many others used diuretics that increase PRA. Increases in both PRA and ACE escape have been associated with adverse clinical outcomes in patients on ACEI or ARB therapy, for this reason Aliskiren could be a valid choice.
In conclusion, the dual RAAS blockade is not recommended as first line therapy in patients with chronic heart failure patients and never in the postmyocardial infarction period.

Dual blockade in ischemic heart disease.
In VALIANT study the patients were randomly assigned after acute myocardial infarction, to additional therapy with valsartan, valsartan plus captopril, or captopril. The primary end point was death from any cause. Valsartan was effective as captopril. This combination increased significantly more adverse events without improving mortality [77]. More recently, ONTARGET study showed that the combination of ramipril and telmisartan did not reduce the risk of death from cardiovascular causes, myocardial infarction or stroke when compared with ramipril alone [5]. On this basis, current Canadian guidelines recommendations do not support dual blockade therapy in patients with coronary artery disease [78].

Conclusions

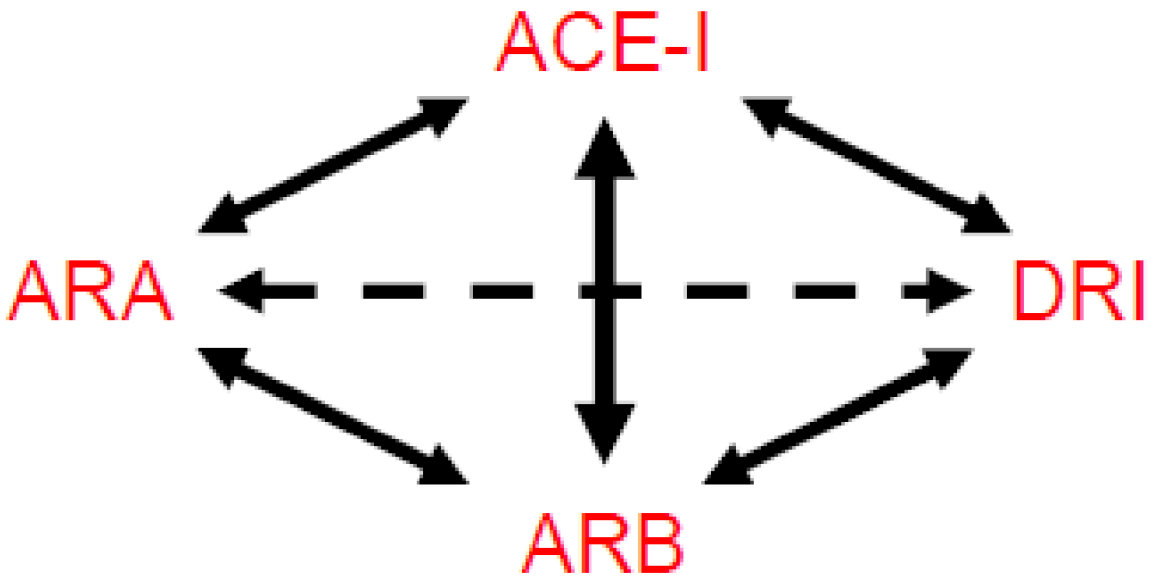
Based on all these evidences, the advantages of dual RAAS blockade (beyond blood pressure decrease) are limited, since the risk of morbidity and mortality in patients with hypertension, heart failure and ischemic cardiac disease is not reduced. Preferably, ACEI/ARB or DRI combo may be used only in patients with proteinuric kidney disease and, as other possible indication, in patients with resistant hypertension (Fig.1). Actually, rational combinations of either an ACE inhibitor or ARB or DRI with other classes of antihypertensives offer best solutions. Finally, in Table 3 are summarized key points discussed in this review.

Table 3. Summary of recommendations and warnings for use of RAAS blockers combination

Hypertension [34,35]	RAAS blockers combination therapy shows a significant blood pressure reduction. However, all recent international hypertension guidelines (ESH-ESC, and NICE) do not support large scale use of the dual blockade therapy in hypertension. This combination may result in more adverse events (such as hyperkalemia and an elevation in serum creatinine), without any additional clinical benefit.
Kidney disease [66-68]	In proteinuric nephropathy patients with or without hypertension or diabetes, ACEI and ARB combination is recommended.
Heart failure [69]	Combination therapy with RAAS inhibitors is not routinely recommended by American College of Cardiology/American Heart Association Heart Failure.
Ischemic heart disease [76,77]	There are no clinical evidences that suggests dual RAAS blockade in coronary artery disease patients with or without preserved ejection fraction.
Resistant hypertension [33,43]	Dual RAAS blockade represents an alternative strategy in the treatment of resistant hypertension (JNC 7 and NICE Guidelines)
Safety profile of RAAS inhibitors combination [5,66,67]	Randomized controlled trials (RCTs) have reported that the combination of RAAS blockers is associated with an increased risk of adverse renal effects, hyperkalemia and symptomatic hypotension in patients with and without chronic renal disease. It is important to check renal function and kalemia before and after ACEI/ARB/DRI/ARA combination therapy.

Fig. 1

PROPOSAL OF COMBINATIONS BETWEEN RAAS INHIBITORS WITH POSSIBLE INDICATIONS (PROTEINURIA AND TRUE RESISTANT HYPERTENSION)



Abbreviations:
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DRI, direct renin inhibitor; ARA, aldosterone receptor antagonist.

The preferred combinations are represented as thick lines. The frame indicates a combination has not been proven.

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