

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

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

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/96541> since

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

***[Current Pharmaceutical Design, volume e fascicolo: 18 [7], anno: 2012, DOI:
10.2174/138161212799436566]***

The definitive version is available at::

[<http://www.eurekaselect.com/76400/article>]

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

Franco Veglio*, Elisabetta Puglisi, Alberto Milan, Paolo Mulatero.

Department of Medicine and Experimental Oncology, Division of Internal Medicine and Hypertension Unit, University of Turin, Italy.

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.

*Corresponding author:

Franco Veglio, MD

Division of Internal Medicine and Hypertension,

AOU San Giovanni Battista, Via Genova 3, 10126, Torino, Italy

e-mail: franco.veglia@unito.it

fax:-39-011-6602707

ph:-39-011-6336959

Conflicts of interest: The authors have no conflicts of interest to declare.

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
DRI	Aliskiren, remikiren, enalkiren, zankiren
ARAs	Spirolactone, 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, especially 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 or 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].

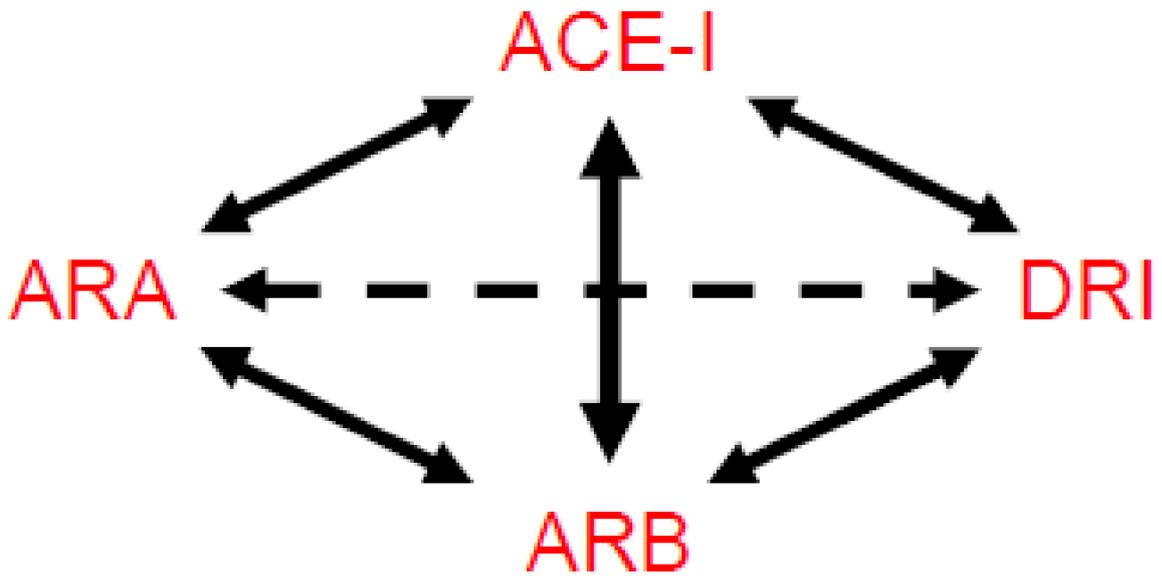
Conclusions

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.

References

1. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, Wang X, Maggioni A, Budaj A, Chaithiraphan S, Dickstein K, Keltai M, Metsarinne K, Oto A, Parkhomenko A, Piegas LS, Svendsen TL, Teo KK, Yusuf S: Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. *Lancet* 2008, 9638:547-553.,
2. Doultou T, He F, MacGregor G: Systematic review of combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade in hypertension. *Hypertension* 2005, 5:880-886.
3. Weir M, Smith D, Neutel J, Bedigian M: Valsartan alone or with a diuretic or ACE inhibitor as treatment for African American hypertensives: Relation to salt intake. *Am J Hypertens* 2001, 7(Pt1):665-671.
4. Cohn J, Tognoni G: A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001 23:1667-1675.
5. Yusuf S, Teo K, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C: Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008, 15:1547-1559.
6. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T: Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): A randomised controlled trial. *Lancet* 2003, 9352:117-124.
7. Kunz R, Friedrich C, Wolbers M, Mann JF: Meta-analysis: Effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008, 1:30-48.)
8. Fisher N, Hollenberg N. Renin inhibition: what are the therapeutic opportunities? *J Am Soc Nephrol* 2005; 16:592–599.
9. Burnier M, Brunner H. Angiotensin II receptor antagonists. *Lancet* 2000; 355: 637–645.
10. Schjoedt K, Rossing K, Juhl T, Boomsma F, Tarnow L, Rossing P, Parving H. Beneficial impact of spironolactone on nephrotic range albuminuria in diabetic nephropathy. *Kidney Int* 2006; 70:536–542.

11. Phillips CO, Kashani A, Ko DK, Francis G, Krumholz HM. Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: a quantitative review of data from randomized clinical trials. *Arch Intern Med* 2007; 167:1930–1936.
12. Azizi M, Webb R, Nussberger J, Hollenberg NK. Renin inhibition with aliskiren: where are we now, and where are we going? *Journal of Hypertension* 24 (2), 243–256, 2006.
13. Luque M, Martin P, Martell N, et al. Effects of captopril related to increased levels of prostacyclin and angiotensin-(1–7) in essential hypertension. *J Hypertens* 1996; 14:799–805.
14. Ferrario CM, Martell N, Yunis C, et al. Characterization of angiotensin-(1–7) in the urine of normal and essential hypertensive subjects. *Am J Hypertens* 1998; 11:137–146.
15. Schindler C, Brosnihan KB, Ferrario CM, et al. Comparison of inhibitory effects of irbesartan and atorvastatin treatment on the renin angiotensin system (RAS) in veins: a randomized double-blind crossover trial in healthy subjects. *J Clin Pharmacol* 2007; 47:112–120.
16. Ferrario CM. ACE2: more of Ang-(1–7) or less Ang II? *Current Opinion in Nephrology and Hypertension* 2011, 20:1–6
17. Chrysant, S.G., Chrysant, G.S. The pleiotropic effects of angiotensin receptor blockers. *J Clin Hypertens* 2006, 8(4): 261-268.
18. Phillips, C.O., Kashani, A., Ko, D.K., Francis, G., Krumholz, H.M. Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: A quantitative review of data from randomized clinical trials. *Arch Intern Med* 2007, 167(18):1930-6.
19. Lakhdar, R., Al-Mallah, M.H., Lanfear, D.E. Safety and tolerability of angiotensin-converting enzyme inhibitor versus the combination of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker in patients with left ventricular dysfunction: A systematic review and meta-analysis of randomized controlled trials. *J Card Fail* 2008, 14(3): 181-8.
20. Messerli, F.H. The sudden demise of dual renin-angiotensin system blockade or the soft science of the surrogate end point. *J Am Coll Cardiol* 2009, 53(6): 468-70.

21. Chrysant, S.G. Current status of dual renin angiotensin aldosterone system blockade for the treatment of cardiovascular diseases. (*Am J Cardiol* 2010;105:849–852)
22. Azizi M, Linhart A, Alexander J et al. Pilot study of combined blockade of the renin-angiotensin system in essential hypertensive patients. *Hypertension* 2000; 18: 1139–1147).
23. Stergiou GS, Skeva II, Baibas NM et al. Additive hypotensive effect of angiotensin-converting enzyme inhibition and angiotensin-receptor antagonism in essential hypertension. *Cardiovasc Pharmacol* 2000; 35: 937–941.
24. Weir MR, Weber MA, Neutel JM, for the ACTION Study Investigators. Efficacy of candesartan cilexetil as add-on therapy in hypertensive patients uncontrolled on background therapy: a clinical experience trial. *Am J Hypertens* 2001; 14: 567–572.)
25. Izzo JL, Weinberg MS, Hainer JW et al. Antihypertensive efficacy of candesartan-lisinopril in combination vs up-titration of lisinopril: the AMAZE trials. *J Clin Hypertens* 2004; 6: 485–493.
26. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358: 1547–1559.
27. O’Brien E, Barton J, Nussberger J, et al. Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker. *Hypertension*. 2007;49(2):276–284.
28. Uresin Y, Taylor AA, Kilo C, et al. Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension. *J Renin Angiotensin Aldosterone Syst*. 2007;8(4):190–198.
29. Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet*. 2007;370(9583):221–229.
30. Yarows SA, Oparil S, Patel S, Fang H, Zhang J. Aliskiren and valsartan in stage 2 hypertension: subgroup analysis of a randomized, doubleblind study. *Adv Ther*. 2008;25(12):1288–1302.
31. White WB, Bresalier R, Kaplan AP, Palmer BF, Riddell RH, Lesogor A, Chang W, Keefe DL. Safety and Tolerability of the Direct Renin Inhibitor Aliskiren in Combination With Angiotensin Receptor Blockers and Thiazide Diuretics: A Pooled Analysis of Clinical Experience of 12,942 Patients *J Clin Hypertens* . 2011;13:506–516.

32. Lee HY, Oh BH. Cardio-renal protection with aliskiren, a direct renin inhibitor, in the ASPIRE HIGHER program. *Expert Rev Cardiovasc Ther.* 2009;7(3):251–257.
33. Chobonian AV, Bakris GL, Black HR, et al. Seventh report of the Joint national Committee on prevention, detection, evaluation and treatment of high blood pressure. *Hypertension* 2003;42:1206–52.
34. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2007;25:1105-1187.
35. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens.* 2009; 27:2121 – 58.
36. Mulatero P, Verhovez A, Morello F, Veglio F. Diagnosis and treatment of low-renin hypertension. *Clinical Endocrinology*, 2007;67:324-334.
37. Mulatero P, Milan A, Williams TA, Veglio F. Mineralocorticoid receptor blockade in the protection of target organ. *Cardiovascular & Hematological Agents in Medicinal Chemistry*, 2006;4:75-91.
38. Moser M, Setaro JF. Resistant or difficult to control hypertension. *N Engl J Med* 2006; 355:385–394.
39. Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens.*2003;16:925-30.
40. Chapman N, Dobson J, Wilson S, et al. Effect of spironolactone on BP in subjects with resistant hypertension. *Hypertension.* 2007;49:839–45.
41. de Souza F, Muxfeldt E, Fiszman R, et al. Efficacy of spironolactone therapy in patients with true resistant hypertension. *Hypertension.* 2010;55:147–52.
42. Alvarez-Alvarez B, Abad-Cardiel M, Fernandez-Cruz A, Martell-Claros N. Management of resistant arterial hypertension: role of spironolactone versus double blockade of the renin–angiotensin–aldosterone system. *J Hypertens.* 2010 Nov; 28(11):2329-35.

43. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B, on behalf of the Guideline Development Group Management of hypertension: summary of NICE guidance. *BMJ*, 2011;343:d4891.
44. Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, Cooper IME. Randomised controlled trial of dual blockade of renin– angiotensin system in patients with hypertension, microalbuminuria, and noninsulin dependent diabetes: the Candesartan and Lisinopril Microalbuminuria (CALM) Study. *BMJ* 2000; 321:1440–1444.
45. Jacobsen P, Andersen S, Jensen BR, Parving HH: Additive effect of ACE inhibition and angiotensin II receptor blockade in type II diabetic patients with diabetic nephropathy. *J Am Soc Nephrol* 2003; 14: 992–999.
46. Song JH, Cha SH, Lee HJ, Lee SW, Park GH, Lee SW, Kim MJ: Effect of low-dose dual blockade of renin-angiotensin system on urinary TGF- 2 diabetic patients with advanced kidney disease. *Nephrol Dial Transplant* 2006; 21: 683–689.
47. Ferrari P, Marti HP, Pfister M, Frey FJ: Additive antiproteinuric effect of combined ACE inhibition and angiotensin II receptor blockade. *J Hypertens* 2002; 20: 125–130.
48. Russo D, Pisani A, Balletta MM, De Nicola L, Savino FA, Andreucci M, Minutolo R: Additive antiproteinuric effect of converting enzyme inhibitory and losartan in normotensive patients with IgA nephropathy. *Am J Kidney Dis* 1999; 33: 851–856.
49. Russo D, Minutolo R, Pisani A, Esposito R, Signoriello G, Andreucci M, Balletta MM: Coadministration of losartan and enalapril exerts additive antiproteinuric effect in IgA nephropathy. *Am J Kidney Dis* 2001; 38:18-25.
50. Berger ED, Bader ED, Ebert C, Risler T, Erley CM: Reduction of proteinuria; combined effects of receptor blockade and low dose angiotensin-converting enzyme inhibition. *J Hypertens* 2002; 20: 739–743.
51. Tylicki L, Rutkowski P, Renke M, Rutkowski B: Renoprotective effect of small doses of losartan and enalapril in patients with primary glomerulonephritis. *Am J Nephrol* 2002; 22: 356–362.
52. Rutkowski P, Tylicki L, Renke M, Korejwo G, Zdrojewski Z, Rutkowski B: Low-dose dual blockade of the renin-angiotensin system in patients with primary glomerulonephritis. *Am J Kidney Dis* 2004; 43: 260–268.

53. MacKinnon M, Shurraw S, Akbari A, Knoll GA, Jaffey J, Clark HD: Combination therapy with an angiotensin receptor blockers and an ACE inhibitor in proteinuria renal disease: a systematic review of the efficacy and safety data. *Am J Kidney Dis* 2006; 48: 8–20.
54. Toto R, Palmer BF. Rationale for Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor Treatment and End-Organ Protection in Patients with Chronic Kidney Disease . *Am J Nephrol* 2008;28:372–380.
55. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK; AVOID Study Investigators. Aliskiren combined with losartan in type 2 diabetes and nephropaty. *N Engl J Med*. 2008;358(23):2433–2446.
56. Parving HH, Brenner BM, McMurray JJ, et al. Aliskiren trial in type 2 diabetes using cardio-renal endpoints (ALTITUDE): rationale and study design. *Nephrol Dial Transplant*. 2009;24(5):1663–1671.
57. Uresin Y, Taylor AA, Kilo C, et al. Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension. *J Renin-Angiotensin-Aldosterone System*. 2007;8(4):190–200.
58. Bomback AS, Kshirsagar AV, Amamoo AH, Klemmer PJ. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. *Am J Kidney Dis*. 2008;51:199-211.
59. Chrysostomou A, Becker GJ. Spironalactone in addition to ACE inhibition to reduce proteinuria in patients with chronic renal disease. *N Eng J Med* 2001; 345: 925–926.
60. Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. *Kidney Int* 2006; 70: 2116–2123.
61. Chrysostomou A, Pedagogos E, MacGregor L et al. Double-blind, placebo-controlled study on the effect of the aldosterone receptor antagonist spironolactone in patients who have persistent proteinuria and are on long-termangiotensin-converting enzyme inhibitor therapy, with or without an angiotensin II receptor blocker. *Clin J Am Soc Nephrol* 2006; 1: 256–262.
62. Tylicki L, Rutkowski P, RenkeMet al. Triple pharmacological blockade of the renin–angiotensin–aldosterone system in nondiabetic CKD: an open-label crossover randomized controlled trial. *AmJ Kidney Dis* 2008; 52: 486–493.
63. Furumatsu Y, Nagasawa Y, Tomida K et al. Effect of renin– angiotensin–aldosterone system triple blockade on non-diabetic renal disease: addition of an aldosterone blocker, spironolactone, to

combination treatment with an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker. *Hypertens Res* 2008; 31: 59–67.

64. Rachmani R, Slavachevsky I, Amit M et al. The effect of spironolactone, cilazapril and their combination on albuminuria in patients with hypertension and diabetic nephropathy is independent of blood pressure reduction: a randomized controlled study. *Diabet Med* 2004; 21: 471–475.

65. Saklayen MG, Gyebi LK, Tasosa J et al. Effects of additive therapy with spironolactone on proteinuria in diabetic patients already on ACE inhibitor or ARB therapy: results of a randomized, placebo-controlled, double-blind, crossover trial. *J Investig Med* 2008; 56: 714–719.

66. Schepkens H, Vanholder R, Billiouw JM et al. Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. *Am J Med* 2001; 110: 438–44.

67. Weinberg JM, Appe LJ, Bakris G, Gassman JJ; Greene T, Kendrick CA; Wang X; Lash J; Lewis JA, Pogue V, Thornley-Brown D, Phillips RA, for the African American Study of Hypertension and Kidney Disease Collaborative Research Group Risk of Hyperkalemia in Nondiabetic Patients With Chronic Kidney Disease Receiving Antihypertensive Therapy. *Arch Intern Med*. 2009;169(17):1587-1594.

68. Kidney Disease Outcomes Quality Initiative (K/QODI): K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004; 43:S1–S290.

69. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:1977-2016.

70. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. *Circulation*. 1999;100:1056-1064.

71. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345:1667-1675.

72. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003;362:767-771.

73. McMurray JJ, Pitt B, Latini R, et al. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail*. 2008;1:17-24.

74. Solomon SC, Appelbaum, Manning WJ, et al. Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation*. 2009;119:530-537.
75. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709-717.
76. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309-1321.
77. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893-1906.
78. Campbell NR, Khan NA, Hill MD, Tremblay G, Lebel M, Kaczorowski J et al. 2009 Canadian Hypertension Education Program recommendations: the scientific summary – an annual update. *Can J Cardiol*. 2009; 25: 271–277.