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REVIEW
Hypertension

Cardiorenal protection during chronic renin–angiotensin–aldosterone system suppression: evidences and caveats

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Blocking the renin–angiotensin–aldosterone system (RAAS) has widely shown to be good for the protection of both cardiovascular and renal systems. A large number of trials have demonstrated clear benefits of using angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) to treat patients with established cardiovascular and renal disease during the last decades. Even more, simultaneous protection of cardiovascular and renal system with RAAS blockade has also been shown. However, some caveats of this therapy as the effectiveness lack in long-term, hyperkalaemia risk in patients with chronic kidney disease or aldosterone and albuminuria breakthrough limit their use, lead that new therapeutic strategies are needed for the RAAS blockade. At this time, new horizons are opened to manage the RAAS blockade in the cardiorenal disease through using the positive combination of an ACEi or an ARB plus and aldosterone antagonist, renin inhibitors, or other forms of blockade using new members as LCZ696.

Keywords Renin–angiotensin–aldosterone system • chronic kidney disease • cardiovascular disease

Introduction

The participation of angiotensin II and aldosterone in the evolution of cardiovascular and renal disease has been amply demonstrated.[1–3] The aim of this brief review is to update the benefits and caveats of blocking renin–angiotensin–aldosterone system (RAAS) in both cardiovascular and renal disease and to comment on future strategies in this type of therapy.

Effects of renin–angiotensin–aldosterone system blockade on cardiovascular system

The benefits of blocking the RAAS in heart failure (HF) and post-myocardial infarction (MI) were largely proved many years ago.[4–6] On the other hand, analysis of combined findings of three large trials the Heart Outcomes Prevention Evaluation (HOPE),[7] the European trial on Reduction Of cardiac events with Perindopril among patients with stable coronary Artery disease (EUROPA),[8] and the Prevention of Events with ACE inhibition (PEACE),[9] showed clear benefits of using angiotensin-converting enzyme inhibitors (ACEis) in patients with established cardiovascular disease (CVD) by reducing cardiovascular and total mortality and serious cardiovascular events.[10] This combined analysis established the recommendation of ACEi use for all those patients with vascular disease.[10] In the same line, several trials have demonstrated that RAAS blockade with ACEis or angiotensin receptor blockers (ARBs) is highly effective to reduce morbidity, mortality and cardiovascular events and then improving the survival in patients after acute MI[11,12] or with HF.[13,14] More recently, the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study has also showed the cardiovascular effectiveness of RAAS blockade with monotherapy to reduce cardiovascular events in patients with high global cardiovascular risk.[15] All these positive effects together with the good anti-hypertensive capacity alone or in combination of ACEi and ARB[16] has led to a very wide use of these drugs in arterial hypertension. In fact, in Europe ~40–50% of hypertensive patients receive one of these classes of drugs.[17]

Caveats of renin–angiotensin–aldosterone system blockade

Since the original description by Biollaz *et al.*,[18] it has been clearly demonstrated that during long-term therapy with ACEis and ARBs, there is an escape to the effect of blockade of the RAAS. Thus, chronic RAAS blockade is frequently followed by an increase activity of angiotensin II[18] and also aldosterone,[19] leading to a facilitation of

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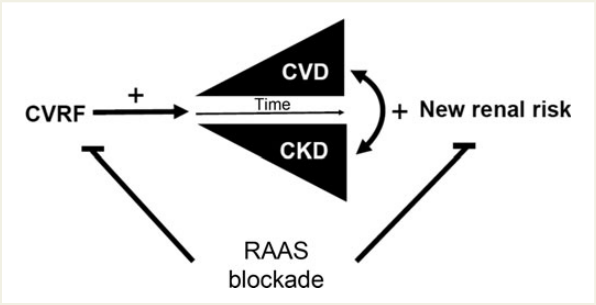

Figure 1 Renin–angiotensin–aldosterone system blockade cross-talk between cardiovascular and renal disease. Risk factors as aging process, diabetes, and hypertension are common for the development of cardiovascular disease and chronic kidney disease. The progression of the cardiorenal disease depends on the individual evolution of cardiovascular disease and chronic kidney disease and the other risk factors as endothelial dysfunction, oxidative stress, or chronic inflammation, among others. CVRF, cardiovascular risk factors; CVD, cardiovascular disease; CKD, chronic kidney disease; RAAS, renin–angiotensin–aldosterone system.

the progression of CVD. The good effects already demonstrated and the possibility to escape RAAS blockade during chronic therapy led to test an increment in the degree of blockade of the system initially with uptitration of the initial doses and later with the possibility of a dual blockade using ACEi and ARB together. This last possibility was excluded for cardiovascular protection after the date of ONTARGET[15] and ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints).[20] However, the combination of either an ACEi or an ARB with a mineralocorticoid receptor blocker (MRB) as spironolactone or eplerenone has proved to be of great value for patients with HF and low ejection fraction, reducing the number of hospitalizations and cardiovascular mortality.[21–23] However, the effect of the combination ACEi/ARB plus MRB on the outcome of patients with high global cardiovascular risk is unfortunately still lacking.

Effects of renin–angiotensin–aldosterone system blockade on renal system

With respect to the renal system, ACEis or ARBs have proved to be of great value protecting renal function while diminishing albuminuria particularly in diabetic nephropathy[24,25] but also in non-diabetic nephropahy[26] when used alone or in combination with other drugs. Both groups of drugs are frequently used as first-line therapy in hypertensive patients especially when high global cardiovascular risk, target organ damage, metabolic syndrome or chronic kidney disease (CKD) are present. Of particular interest is the fact that ACEi or ARB is compelling indication in hypertension with albuminuria due to the simultaneous capacity of these drugs to regress target organ damage, to retard the development of diabetes, and to slow nephropathy progression more effectively than other anti-hypertensive agents.[27,28] Interestingly, a recent study has shown important results of ACEi/ARB treatment on mortality of patients with CKD.[29] This study has examined a large cohort of patients with nondialysis-dependent CKD exposed *de novo* to these drugs. Angiotensin-converting enzyme inhibitor or ARB treatment was associated with lower mortality independently of estimated glomerular filtrate rate (eGFR) level in this cohort; hence, this benefit on mortality includes all stages of CKD development. Moreover, because of the frequent discontinuation rates of ACEi/ARB and other forms of treatment in these patients, it is possible that the decrease in mortality is underestimated in this study.

Caveats of renin–angiotensin–aldosterone system blockade

The chronic RAAS blockade with ACEis or ARBs is effective to control-dependent actions of RAAS during a period of time, but not forever. Similar that for CVD, after long-term treatment with angiotensin II blockers the aldosterone systemic levels can be increased again, appearing the aldosterone breakthrough phenomenon, especially among diabetic patients.[30] In addition, we have recently described another example of the ineffective actions of RAAS blockers used in a long term in the clinical practice with the appearance of *de novo* albuminuria or albuminuria breakthrough, even in conditions of adequate control of blood pressure values in hypertensive population.[31] This albuminuria breakthrough is a new-onset albuminuria observed in patients treated chronically at maximal doses of ACEi or ARB alone and accompanied by a diuretic or calcium-channel blocker if it was necessary to maintain BP values $<$140/90 mmHg. Moreover, this phenomenon was more frequent for those patients with previous established CVD and also predicted future cardiovascular events. One of the reasons that may explain, at least in part, this albuminuria breakthrough is the increased oxidative damage observed at systemic level in these well-controlled hypertensive patients treated with RAS blockers and in an early stage of CKD.[32] An uncontrolled and increased oxidative stress in the vascular wall of glomeruli may favour a filtration barrier damage by the loss of negative charge of the glycocalyx covering glomerular endothelium allowing albumin breakthrough to urine. Hence, chronic RAAS protection must be also focused to avoid development of *de novo* albuminuria and also its oxidative damage associated. On the other hand, as for cardiovascular protection, dual blockade of angiotensin II with ACEis plus ARBs has demonstrated no evidence of additional benefit in CKD.[15,20,33] However, similarly as observed on CVD, when a regimen using maximal doses of an ACEi or an ARBs is complemented with the addition of an MRB as spironolactone, greater renoprotection, consisting of a significant further fall in proteinuria is observed independently of the effect on BP.[34] The evolution of renal disease seems to be more dependent on well BP control than specific therapy used.[35]

Simultaneous cardiorenal protection

Albuminuria is one of the most important risk factors underlying the cross-talk of both axes cardiovascular and renal.[36] Albuminuria together with a decreased eGFR is additive and independent cardiovascular risk factors,[37] in the sense that as eGFR decreases and albuminuria increases is the risk of cardiovascular events and death rises very significantly.[38] On the other hand, low eGFR together with moderate (albumin–creatinine ratio of 30–300 mg/g) or severe albuminuria (albumin–creatinine ratio of $>$300 mg/g) predicts the development of end-stage renal disease and also death.[39] In turn, several studies have shown that the drop in the amount of albumin excreted in urine is followed by a decreased renal risk especially in

patients with type 2 diabetes and severe albuminuria.[25,40] Similarly, other studies have also shown that the decrease in albuminuria is followed by a diminution in cardiovascular events and death.[24,41]

In a recent publication, we have reviewed several aspects related to simultaneous cardiorenal protection.[42] In this sense, cardiovascular and renal disease are often promoted by similar risk factors among which aging process, diabetes, and hypertension are the most frequent.[42] As shown in the *Figure 1*, it is frequently observed that the development of CVD is accompanied by the development of CKD and vice versa in clinical practice. This gave rise to the development of the term cardiorenal disease.[35] The term cardiorenal disease is actually amply accepted[35,36] and the progression of cardiorenal disease depends on the degree of activity of different mechanisms promoting simultaneous damage at the level of the heart, brain, kidney, and vessels among which endothelial dysfunction, oxidative stress, chronic inflammation or overactivity of the RAAS and sympathetic nervous system are the most important. Cardiorenal protection through RAAS blockade is a multiorgan protection where the three main classes of RAAS inhibitors ACEis, ARBs, and MRBs interfere at different levels. ACEis reduce angiotensin II release for blocking ACE and inhibiting the breakdown of bradykinin favouring its vasodilatory action, ARBs bind competitively to angiotensin type 1 receptors (AT_1) avoiding their vasoconstriction effect and reducing sodium retention and water reabsorption, and MRBs bind competitively to minlocorticoid receptors avoiding the number of available epithelial sodium channels in the distal renal tubule.[43] An adequate RAAS blockade with these different strategies might prevent the evolution of the cardiorenal disease (*Figures 1* and *2*). However, the approach for the study of cardiorenal protection is still lacking in cardiovascular trials. That is because patients with 3–4 stages of CKD are excluded in this type of trials, and those with severe albuminuria are frequently included in renal trials characterized by small number of patients followed up during a short period of time. Both situations are not suitable for obtaining conclusions of cardiovascular outcomes.

Interestingly, the concept of a simultaneous cardiovascular and renal protection with RAAS blockers is particularly unrecognized by KDIGO guidelines for patients with CKD without albuminuria. However, this has to be contemplated due to the high cardiovascular risk accompanying CKD with eGFR < 60 mL/min/1.73 m^2. In addition, CKD has to be considered as one of the five major risk factors for acute coronary syndrome.[44] As it is shown over RAAS blockade including aldosterone blockade is particularly useful in patients with HF and low ejection fraction. The situation is especially worrying for patients with eGFR < 45 mL/min/1.73 m^2. As it is shown in *Figure 3*, KDIGO guidelines establish that these patients have high and very high cardiorenal risk even with normal to mildly increased albuminuria. The situation with these patients is limited by the risk of hyperkalaemia counteracts this therapy when CKD is present. For this reason, these patients are really under low doses or non-dose of RAAS blockers.

Another class of RAAS blockade drugs with cardiovascular and renal actions is renin inhibitors of which aliskiren has been the most widely used. The first trials in CKD and HF showed promising data.[45,46] Unfortunately, the results shown in and ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes) study comparing the effects of a combination of aliskiren and ACEi or ARB has discouraged its use in CKD and HF.[20,47] However, the effects of the drug as anti-hypertensive remain as valid with the demonstration of its good effect in resistant hypertension[48] as well as those obtained in the APOLLO study (Aliskiren Prevention of Later Life Outcomes) performed in elderly patients.[49] The results of the ATMOSPHERE (Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE) trial[50] where a head-to-head comparison with enalapril is being investigated are still pending.

Conclusions and perspectives

The treatment with RAAS blockers introduces a cardiovascular and renal protection that is of great value for the patients (see *Table 1* of summarizing trials). However, more data are needed for a better knowledge of the benefits of long-term maintenance of this therapy. In addition, new drugs are appearing in this field being one of them is LCZ696 (ARNI: angiotensin receptor and neprilysin inhibitor) which simultaneously blocks the AT1 receptor while increasing natriuretic peptides. LCZ696 has recently demonstrated

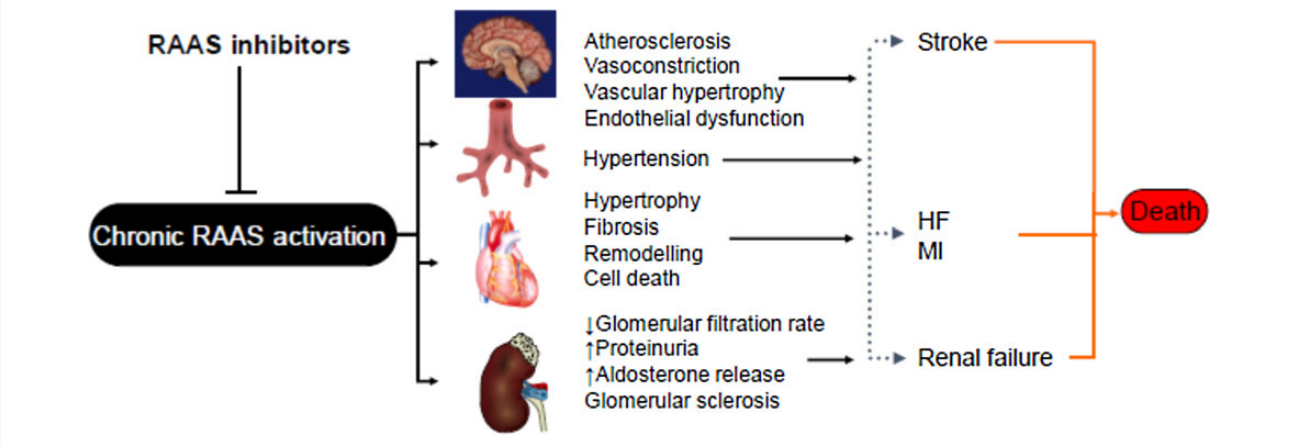

Figure 2 Deleterious effects of chronic renin–angiotensin–aldosterone system activation on cardiovascular and renal system.

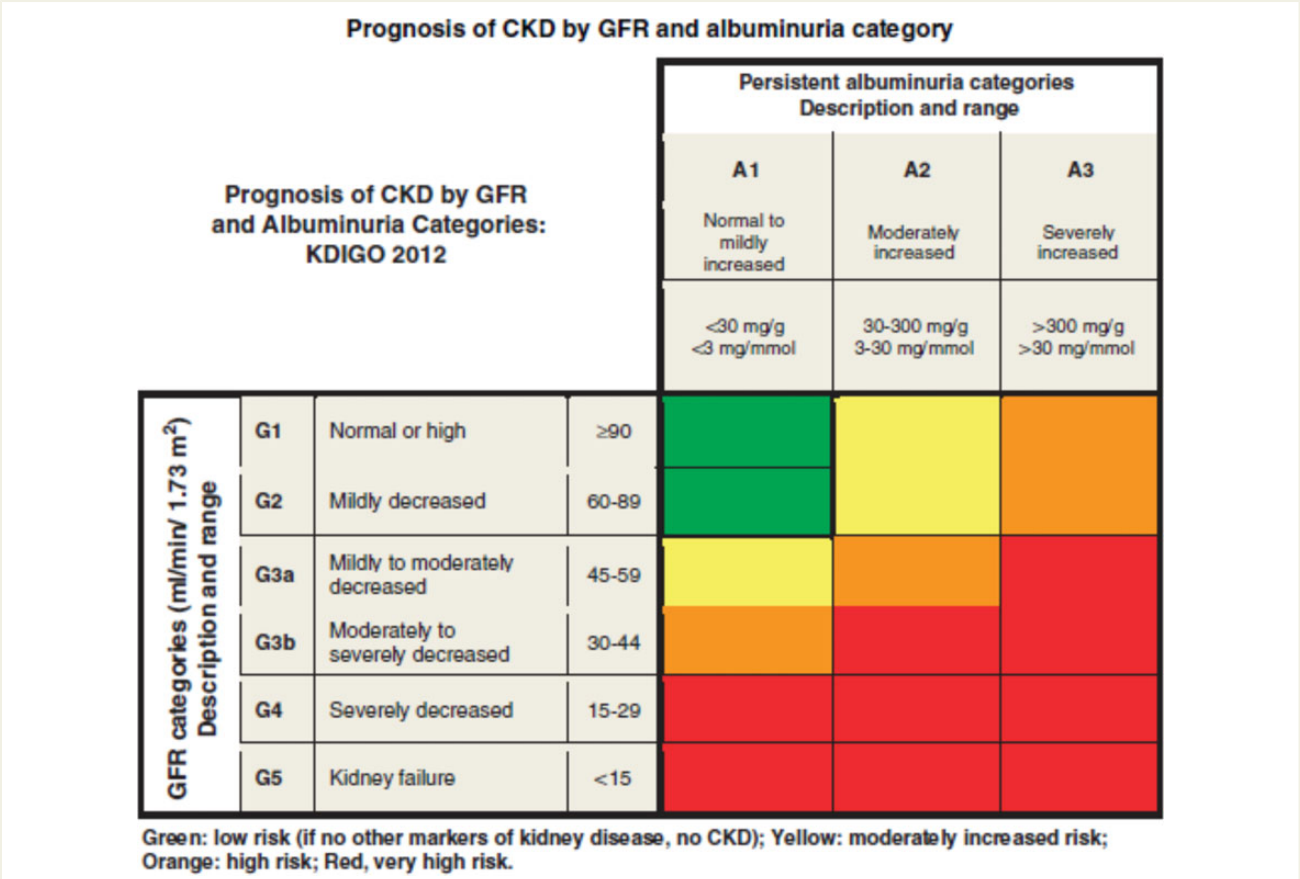

Figure 3 Risk of developing chronic kidney diseaseby estimated glomerular filtrate rate and albuminuria categories.[38]

Table 1 Clinical trials with renin–angiotensin–aldosterone system blockade

Trial	Treatment	Patients	Conclusions
HOPE[7]	Ramipril (10 mg)	High-risk patients with vascular disease or diabetes	Reduction in deaths from CV causes and CV events (MI, stroke, HF)
EUROPA[8]	Perindopril (8 mg)	With previous MI, CAD, or coronary revascularization	Reduction in CV risk (CV deaths, MI, cardiac arrest, acute coronary syndrome, HF)
PEACE[9]	Trandolapril (4 mg)	With stable CAD or reduced LV function	Lower CV events (deaths from CV causes, MI, coronary revascularization)
TRACE[11]	Trandolapril (1–4 mg)	Survivors of acute MI	Reduction in deaths from CV causes, progression to severe HF
ELITE[14]	Losartan (12.5, 25, 50 mg) Captopril (12.5, 25, 50 mg)	With NYHA class (II–IV) HF and LVEF $\leq$ 40%	No significant differences in all-cause mortality, sudden death, or resuscitated arrest
ONTARGET[15]	Ramipril (10 mg) Telmisartan (80 mg) Both	With vascular disease or high-risk diabetes	Dual blockade excluded for CV protection
ALTITUDE[20]	Aliskiren (150–300 mg) added to standard therapy	With type 2 DM and CKD, CVD, or both	Discouraged strategy
ASTRONAUT[47]	Aliskiren (150 mg) added to standard therapy	With chronic HF, LVEF $\leq$ 40% and eGFR $\geq$ 40 mL/min/1.73 m^2	Discouraged strategy
ATMOSPHERE[50]	Aliskiren (150 mg) added to tolerated dose of enalapril	With NYHA (II–IV) HF with LVEF $\leq$ 35% and elevated plasma BNP level	Pending

CV, cardiovascular; MI, myocardial infarction; HF, heart failure; CAD, coronary artery disease; LV, left ventricle; NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; DM, diabetes mellitus; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtrate rate; BNP, B-type natriuretic peptide.

to be superior in reducing BP than valsartan in mild-to-moderate hypertensive patients[51] or in reducing risk of death and hospitalizations in HF better than enalapril exhibiting simultaneous cardiorenal protection.[52]

Key points

(1) Renin–angiotensin–aldosterone system blockade with either monotherapy (ACEi, ARB) protects simultaneously the cardiovascular and renal systems.
(2) The combination of an ACEi/ARB and MRB has been shown to protect in HF and to diminish albuminuria.
(3) Data of the protection during long-term therapy are required.
(4) The value of combining ACEi/ARB plus MRB for simultaneous cardiorenal protection is also required.

Data sources

PubMed and the Cochrane library were searched for more recent clinical studies published in relationship with cardiovascular and renal system and RAAS suppression.

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