Blockade of Renin-Angiotensin-Aldosterone System in Kidney and Heart Disease: How Much Do We Need?

Salim Lim

ABSTRACT

The renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in both cardiac and renal injury. Inhibition of RAAS with either an angiotensin converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) provides both cardiac and renal protection, which is independent and additive to the benefit obtained from lowering blood pressure (BP). The combination of an ACE-I and an ARB should be used only for proteinuric renal disease and not for BP reduction. Patients with proteinuria > 1 g/day despite optimal BP control with maximal dose of ACE-I or ARB monotherapy may benefit from a combination therapy. Inhibition of aldosterone with spironolactone or eplerenone provides survival advantage in patients with low LV ejection fraction and may also have antiproteinuric effects. Until further information is available, the routine combined use of all three inhibitors of the RAAS cannot be recommended.

Key words: heart failure, angiotensin II, aldosterone, ACE inhibitor, angiotensin receptor blocker, proteinuria.

INTRODUCTION

The kidney and the heart are closely related in a number of hemodynamic and regulatory functions. It is no wonder that disease of one system profoundly influences the other. Patients with chronic kidney disease (CKD) has increased the risk of cardiovascular (CV) events. Even minor renal dysfunction is associated with high CV risk. Observations from a number of clinical studies suggest that both risk for kidney disease progression as well as CV events may be inversely related to the level of kidney function. It is well known that CVD is the most important cause of mortality and morbidity among patients with CKD. Therefore, treatment of CKD should also include interventions that will reduce the risk of CV mortality (e.g., smoking cessation, BP control and treatment of hyperlipidemia). The RAAS has received the greatest consideration in recent years as the mediator of both cardiac and renal injury. Therefore, many agents have been devised to antagonize the RAAS and hence ameliorate its damaging actions.

THE PATHOPHYSIOLOGICAL ROLE OF RAAS IN HEART AND KIDNEY DISEASE

Heart failure (HF) is the major cause of CV morbidity and mortality. The first response in the face of a failing heart is to activate the neurohormonal system including the sympathetic nervous system and the RAAS. The activation of the sympathetic nervous system results in both positive inotropic and chronotropic effects. The activation of the RAAS leads to the release of renin and the production of angiotensin I. The biologically inert decapeptide angiotensin I is converted into the active product angiotensin II by the action of ACE-I. Angiotensin II promotes vasoconstriction and stimulates the release of aldosterone. In addition to causing vasoconstriction and fluid retention, angiotensin II and aldosterone also exert other deleterious effects on the CV system, including endothelial damage, sympathetic activation, collagen formation, myocardial fibrosis, and decreased nitric oxide production. Thus, activation of these neurohormonal pathways is essential for survival in the acute setting of hemodynamic instability. However, in the longer term, these mechanisms are maladaptive and detrimental, which can lead to a progressive decline in cardiac function, resulting in a state in which the heart is unable to generate sufficient cardiac output to maintain adequate tissue perfusion, referred to as ‘decompensated’ HF.

In the classical view, the cardinal function of the RAAS is maintaining of BP by Angiotensin II-induced vasoconstriction and aldosterone-mediated sodium retention in the collecting duct. However, RAAS has become more complex in recent years. The RAAS plays a pivotal role in many of the pathophysiologic changes.
that lead to progression of renal disease. Besides hypertension, proteinuria is one of the most important risk factors for the progression of renal diseases. It is well known that angiotensin II is a mediator of proteinuria. It preferentially raises efferent glomerular arteriole resistance. Aside from its hemodynamic effect, angiotensin II has emerged in the past decade as a multifunctional cytokine that exhibits many nonhemodynamic properties, such as acting as a growth factor and profibrogenic cytokine, and even having proinflammatory properties. Aldosterone promotes hypertension through sodium retention in the collecting duct. These aldosterone effects have been explained as genomnic effects that are caused by increased transcription of different target genes after binding of aldosterone to cytoplasmic receptors. Newer data provide evidence that nongenomic effects of aldosterone, such as the activation of certain signal transduction pathways, occur in several organs, including the kidney. In various animal models of renal diseases, aldosterone is involved in endothelial dysfunction, inflammation, proteinuria, and fibrosis.

**ANTIHYPERTENSIVE THERAPY IN HEART AND KIDNEY DISEASE**

Epidemiologic studies indicate that hypertension is closely associated with CVD and progression of kidney disease. A large number of studies have repeatedly confirmed that treatment of increased BP decreases CV mortality and delay the progression of renal disease in patients with or without diabetes. Thus, the current evidence confirms that the risk of CV events follows a linear relationship with BP and achieving further BP reductions within the so-called ‘normal’ range indeed reduces the risk of CV events. JNC 7 guideline recommends the optimal target for BP control for most hypertensive patients as <140/90 mmHg, or <130/80 mmHg for patients with diabetes and CKD.

**DOES BLOCKADE OF RAAS WITH ACE-I OR ARB PROTECT BOTH HEART AND KIDNEY DISEASE?**

Numerous studies consistently show that ACE-I reduces the risk for death and CV events after myocardial infarction. In addition, ACE-I has also been shown to increase survival in patients with decreased LV function. Recently, cardioprotective effects of ARB has also been demonstrated in several randomized controlled trials. The renoprotective effect of RAAS inhibition with ACE-I or ARB has also been documented in patients with or without diabetes. The greater the magnitude of reduction in proteinuria, the greater the slowing of glomerular filtration rate decline that is independent of BP level. In summary, inhibition of RAAS with either an ACE-I or an ARB provides both cardiac and renal protection, which is independent and additive to the benefit obtained from lowering BP.

**DOES COMBINATION THERAPY WITH ACE-I AND ARB PROVIDE MORE CARDIO AND RENAL PROTECTION?**

Although effective, the response to treatment with an ACE-I or an ARB is incomplete, leading to the speculation that more RAAS blockade by synergistically combining the two drugs, is better than single therapy with each drug. It has been shown that constant treatment with an ACE-I or an ARB eventually leads to the return of angiotensin II and aldosterone to their pretreatment level. A number of investigations have reported that dual blockade of the RAAS with ACE-I and ARB in combination is superior to single blockade with either ACE-I or ARB in both diabetic and nondiabetic nephropathy. Three major studies have explored the utility of combining ACE-I with ARB in patients with HF; the CHARM-Added study, the Val-HeFT study and the VALIANT study. The CHARM-added trial showed a significant (15%) reduction in the combined end point of CV death or HF hospitalization with the addition of candesartan therapy to patients with HF, who were also receiving ACE-I. The addition of valsartan to patients with HF with background treatment of ACE-I in the ValHeFT Trial was shown to significantly reduce morbidity (combined end point of total mortality or HF hospitalization) without reducing total mortality alone. A post hoc analysis of mortality and morbidity showed an adverse effect of valsartan in the subgroup of patients who were also receiving an ACE-I. The VALIANT trial compared the effects of captopril with valsartan and the combination of captopril and valsartan in patients with clinical signs of HF and/or left ventricular dysfunction following acute myocardial infarction. The result showed that combining valsartan with captopril increased the rate of adverse events without improving outcomes. In summary, there is little information available about the cardioprotective effect of the combination therapy with both ACE-I and ARB. The combination of an ACE-I and an ARB should be used only for proteinuric renal disease and not for BP reduction. Patients with proteinuria >1 g/day despite optimal BP control with maximal dose of ACE-I or ARB monotherapy may benefit from a combination therapy.
USE OF ALDOSTERONE ANTAGONISTS IN HEART AND KIDNEY DISEASE

Although short-term therapy with both ACE-I and ARB can lower circulating levels of aldosterone, such suppression may not be sustained during long-term treatment.\(^{26}\) The lack of long-term suppression may be important, because experimental data suggest that aldosterone exerts adverse effects on the heart and the kidney, independently of and in addition to the deleterious effects produced by angiotensin II.\(^ {6,33}\) The use of aldosterone inhibitors such as spironolactone or eplerenone has been found to significantly decrease mortality in patients with advanced HF.\(^ {34,35}\) The Randomized Aldactone Evaluation Study (RALES) demonstrated that spironolactone, in conjunction with other standard therapy, conferred a 30% reduction in mortality rates, compared with placebo, among patients with severe HF.\(^ {34}\) The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) showed that eplerenone treatment among patients with left ventricular dysfunction after myocardial infarction resulted in a significant 15% relative risk reduction in all-cause mortality compared with placebo.\(^ {35}\) In patients with proteinuric renal disease, addition of aldosterone antagonists to either ACE-I or ARB was shown to have more antiproteinuric effect compared to monotherapy with ACE-I or ARB alone.\(^ {36-39}\) The major risk of aldosterone antagonists is hyperkalemia. The wider use of spironolactone in HF regimens has led to increased incidence of hyperkalemia.\(^ {40}\) Whether the risk for hyperkalemia can be managed by careful patient selection, dietary potassium restriction, and kaliuretic agents in a manner that might permit the wider use as dual cardiorenoprotective therapies remains to be determined. In summary, inhibition of aldosterone provides survival advantage in patients with low LV ejection fraction and may also have antiproteinuric effects.

COMBINATION OF ALDOSTERONE ANTAGONISTS WITH ACE-I AND ARB

There is little information available about the addition of aldosterone antagonists to therapy with both ACE-I and ARB in heart disease. In proteinuric renal disease, triple therapy was not significantly more effective than an ACE-I and spironolactone.\(^ {37}\) Until further information is available, the routine combined use of all three inhibitors of the RAAS cannot be recommended.

CONCLUSION

It is well established that RAAS mediates both cardiac and renal injury. Inhibition of RAAS with either an ACE-I or an ARB provides both cardiac and renal protection, which is independent and additive to the benefit obtained from lowering BP. The combination of an ACE-I and an ARB should be used only for proteinuric renal disease and not for BP reduction. Patients with proteinuria >1 g/day despite optimal BP control with maximal dose of ACE-I or ARB monotherapy may benefit from a combination therapy. Inhibition of aldosterone with spironolactone or eplerenone provides survival advantage in patients with low LV ejection fraction and may also have antiproteinuric effects. Until further information is available, the routine combined use of all three inhibitors of the RAAS cannot be recommended.

REFERENCES