REVIEW ARTICLE

Role of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in hypertension of chronic kidney disease and renoprotection. Study results

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Abstract

Chronic kidney disease (CKD) is a global health problem associated with considerable morbidity and mortality and despite advances in the treatment of end stage renal disease (ESRD) mechanisms to prevent and delay its progression are still being sought. The renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in many of the pathophysiologic changes that lead to progression of renal disease. Traditionally RAAS was considered as an endocrine system and its principal role was to maintain blood pressure (BP). In recent years local RAAS has been described to operate independently from systemic and local angiotensin II (AngII) in the kidney to contribute in hypertension and kidney damage. The benefits of strict BP control in slowing kidney disease progression have been demonstrated in several clinical trials and the question whether specific agents like angiotensin converting enzyme antagonists (ACEIs) and angiotensin receptor blockers (ARBs) provide renoprotective benefits beyond BP lowering is to be answered. Several studies support these agents reduce proteinuria and protect renal function, whereas the opposite is stated by others. According to guidelines, their use is recommended as first line agents in diabetic renal disease and non diabetic renal disease with albuminuria, whereas there is no data to support the same in non diabetic nonalbuminuric renal disease. Dual blockage of RAAS with the combination of ACEIs and ARBs could offer an alternative in strict RAAS blockade, but studies up to now can not prove its safety and the combination is not recommended until ongoing trials will provide new and unarguable results. Hippokratia 2011; 15 (Suppl 1): 27-32

Key words: Hypertension, renal disease, RAAS, ACEIs, ARBs

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CKD is a global health problem associated with considerable morbidity and mortality and one of the major challenges today, since its prevalence is increasing by approximately 8% per year[1], partially attributable to the increasing prevalence of diabetes mellitus (DM), hypertension, obesity, and an overall aging population[2]. However, despite advances in the treatment of ESRD over the past 20 years, minimal improvement in mortality has been made since the early 1990s, and mechanisms to prevent and delay progression to ESRD are still being sought[3]. The primary cause of ESRD is DM in a percentage reaching 50%, followed by arterial hypertension (H) 27%, glomerulonephritis 13% and other causes 10%[1].

Regardless of the primary entity, progression of renal disease is characterized by pathomorphologic changes that comprise early renal inflammation, followed by subsequent tubulointerstitial fibrosis, tubular atrophy, and glomerulosclerosis[4]. The RAAS plays a pivotal role in many of the pathophysiologic changes that lead to progression of renal disease.

Renin-Angiotensin-Aldosterone System (RAAS)/Angiotensin II

Traditionally, RAAS was considered as an endocrine system in which renin generates angiotensin I (AngI) through angiotensinogen. AngI turns into angiotensin II (AngII) through angiotensin-converting enzyme (ACE) and AngII binds to specific receptors in adrenal cortex, resulting in release of aldosterone.By this way the principal role of RAAS is to maintain BP by AngII-induced vasoconstriction and aldosterone-mediated sodium retention in the collecting duct[5]. However, the RAAS has become complex in recent years, with alternative ways of Ang II formation besides ACE, (Chymase, chymostatin-sensitive AngII-generating enzyme [CAGE], a second form of ACE- ACE2) and novel peptides such as AngIII, AngIV, Ang 1-9, and Ang 1-7. The multiple effects of AngII are mediated by different receptors, the two major being AT_1 and AT_2[6]. AngII binds to AT_2 and AngIV to a certain type of receptors, AT_4 that are not antagonized by ARBs possibly inducing proinflammatory and profibrotic effects[7]. Local RAAS has been described to operate independently from systemic. Systemic inhibition of AngII formation by an ACEI is not accompanied by a significantly reduced intrarenal AngII production[8].

Local AngII in the kidney has multiple roles contributing in hypertension and kidney damage. It enhances capillary filtration pressure, directly by efferent arterial

vasoconstriction and indirectly through TGF-β1 (transforming growth factor beta1) mediated impaired afferent arteriole autoregulation[9]. AngII decreases the synthesis of negatively charged proteoglycans and suppresses nephrin transcription[6,10], which results in podocyte apoptosis. Through VEGF (vascular endothelial growth factor) and TGF-β1, induces synthesis of the α3 chain of collagen type IV, the principal ingredient of the glomerular basement membrane[11], stimulates upregulation of adhesion molecules such as vascular cellular adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), and integrins, allowing circulating immune cells to adhere on capillaries. Ang II induces nuclear factor Kβ (NF-κB) –mediated transcription of chemokines, including monocyte chemoattractant protein-1 (MCP-1), RANTES, and others, resulting in renal tissue infiltration with leukocytes and also induces plasminogen activator inhibitor-1 (PAI-1) and tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) which inhibit metalloproteinases resulting in accumulation of extracellular matrix. Through all these mechanisms, AngII induces proteinuria, inflammation, growth effects, apoptosis and fibrosis[5].

Hypertension in Chronic Kidney Disease-Role of ACEIs and ARBs

Hypertension can be a cause, a complication and a result of CKD and has been identified as a key modifiable risk factor in patients with decreased renal function. The benefits of strict BP control in slowing kidney disease progression have been demonstrated in several clinical trials[12]. Questions regarding the choice of antihypertensive agent in patients with renal dysfunction and whether specific agents like ACEIs and ARBs provide renoprotective benefits beyond BP lowering will be discussed in this review.

Antihypertensive power

In a meta-analysis of 354 randomized double blind placebo controlled trials of thiazides, β blockers, ACEIs, ARBs, and calcium channel blockers (CCBs) in fixed dose, all five categories of drug produced similar reductions in BP. The average reduction was 9.1 mm Hg systolic and 5.5 mm Hg diastolic at standard dose[13]. Matchar et all found that ACEIs and ARBs had similar long-term effects on BP[14]. In meta-analysis of existing combination studies, there was general agreement that the amount of additional antihypertensive effect was approximately 5 mmHg and often less when maximal dosages of the ACE inhibitor were used before the addition of the ARB[15]. In a meta-analysis by Doulton, the combination of ACEI and ARB reduced 24-hour ambulatory BP by 4.7/3.0 mm Hg when compared with ACEI monotherapy, and by 3.8/2.9 mm Hg when compared with ARB monotherapy, in the second group the specific reduction being 6.8/4.7 mm Hg in diabetics, and 0.7/0.4 mm Hg (no reduction) in participants with CRF[16].

Renoprotective benefits beyond BP lowering

Apart from the obvious advantages in RAAS inhibition at 2 different points with ACEIs and ARBs, there are disadvantages. It has been suggested that "AngII escape" prevents complete RAAS inhibition during therapy with an ACEI, due to alternative non-ACE pathways. AngII synthesis via non-ACE pathways has been shown to be more significant, particularly when organ damage has occurred. Another limitation of ACEIs might be the minimal effect on local AngII production. Since ARBs have a direct impact on AT1, AngII escape observed during therapy with an ACEI will not occur with an ARB. Complete and selective blockade of the AT1 receptor may also inhibit all harmful effects of Ang II, systemic or local. However, blocking the receptor leads to a neurohumoral feedback–mediated increase in the level of Ang II molecules, which in turn bind to other AT receptors (eg, AT2, AT3, and AT4) that are not blocked by ARBs. AT3 and AT4 have unknown effects and although AT2 has been reported to have an opposite action to that of AT1, potentially unfavorable effects such as apoptosis, proinflammatory signal transduction, or chemokine induction have been reported. The use of combination therapy may overcome the limitations and enhance the benefits by carrying added benefits of ACE inhibition, positive outcomes of AT2 receptor stimulation, so as to obtain strong clinical protection, and if possible, to lessen negative effects[2,17].

Study results

It has been shown in experimental animals that ACEIs and ARBs improve and restore endothelial function[18]. Becker et al showed that in rabbits receiving highly atherogenic diet, ramipril preserved the vasodilative response to acetylocholine, compared to control group[19]. Clobanian et al showed that captopril decreased atherosclerotic lesions in normotensive rabbits with highly lipidemic diet compared to b-blockers and CCB[20]. In Cynomolgus monkeys olmesartan decreased atherosclerotic lesions[21].

In human trials, Val-MARC showed that valsartan reduced hsCRP independently of degree of BP reduction compared to valsartan plus HCTZ[22].

Olmesartan reduced in one study markers of vascular microinflammation like hsCRP, TNFa,IL6 and MCP-1[23], while in another study showed decreased (intra)renal vascular resistance and increased renal perfusion despite significant BP reduction and decreased concentration of plasma 8-isoprostane 15(S)-8-iso-prostaglandin F(2a), biochemical marker of oxidative stress[24]. Renke et al showed that a combined therapy with telmisartan and high-dose cilazapril (doubling the dose recommended for antihypertensive treatment) has no additional effect on proteinuria, however reduced urinary excretion of 15-F_{2t}-isoprostane, marker of oxidative stress[25].

Protein Excretion

Several studies concerning protein exertion show benefit with ACEIs and ARBS. Meta analysis by Regina Kunz, in 49 randomized trials (6181 patients) of ARBs versus placebo, ACEIs, CCBs, or the combination of

ARBs and ACEIs in patients with or without diabetes and with microalbuminuria or proteinuria showed that ARBs reduce proteinuria, independently of the degree of proteinuria and of underlying disease. The magnitude of effect is similar regardless of whether the comparator is placebo or CCB. Reduction in proteinuria from ARBs and ACEIs is similar, but their combination is more effective than either drug alone. Most of these studies were small, varied in quality, and did not provide reliable data on adverse drug reactions and renal endpoints[26].

In the MicroAlbuminuria Reduction with VALsartan (MARVAL) study, for the same degree of BP reduction, valsartan lowered urine albumin exertion rate (UAER) more effectively than amlodipine in patients with non insulin dependent DM (NIDDM) and microalbuminuria, including the subgroup with baseline normotension[27]. The decrease in albuminuria was significantly greater with losartan vs atenolol in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) substudy[28]. In the large international study MIcroalbuminuria, Cardiovascular, and Renal Outcomes in the Heart Outcomes Prevention Evaluation study (MICRO- HOPE) there was significant reduction in mean Alb/Cr ratio with ramipril vs placebo[29]. In BErgamo NEphrologic DIabetic Complications Trial (BENEDICT) trandolapril significantly reduced the risk for microalbuminuria vs conventional therapy, while non dihydropyridine (NDH)CCB Verapamil did not independently affect microalbuminuria[30]. In IRbesartan in patients with Type 2 Diabetes and Microalbuminuria (IRMA 2) study, treatment with irbesartan significantly reduced the rate of progression to clinical albuminuria, in patients with NIDDM. Furthermore, the restoration of normoalbuminuria was significantly more common in the group receiving irbesartan at a dose of 300 mg, benefits independent of BP[31].

Preservation of Renal function

Several studies show that changes in proteinouria in six months to a year following treatment, predict long term renal outcomes. In Reduction in End Points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, in NIDDM nephropathy, reduction in albuminuria was associated with a proportional effect on renal protection, (the greater the reduction the greater the renal protection). The residual albuminuria on therapy (month 6) was strong as a marker of renal outcome as was baseline albuminuria[32]. In African American Study of Kidney disease (AASK), initial change in proteinuria from baseline to 6 months predicted subsequent progression of GFR decline, with this relationship extending to participants with baseline urinary protein levels less than 300 mg/d[33] and in the Irbesartan Diabetic Nephropathy Trial (IDNT) for each halving of proteinuria level between baseline and 12 months, risk for kidney failure was reduced by more than half. For the same proportional change in proteinuria, the reduction in risk for kidney failure was significantly greater for irbesartan compared to amlodipine[34].

Several studies have been held concerning renal end points such as ESRD, doubling of serum creatinin (DSC), decline of glomerular filtration rate (GFR) and adverse events such as high potassium. Several studies show that ACEIs and ARBs favour renal function compared to other antihypertensives. In non diabetic nephropathy, Hannedouche et.al showed that in hypertensive patients with CKD (and albuminuria) enalapril slowed progression towards ESRF compared with b- blockers, effect not mediated through controlling BP[35]. In AIPRI (Angiotensin converting enzyme inhibition in renal insufficiency) trial , benazepril decreased DSC, ESRD in patients with various renal diseases (and diabetics) and mild to moderate renal failure, with the best survival of renal function in proteinuria >1.0 g/24 h[36]. In REIN (Ramipril Efficacy In Nephropathy) trial in patients with chronic nephropathies and proteinuria of >3 g/24 h, ramipril reduced the rate of GFR decline and halved the combined risk of DSC or ESRF, as compared with placebo plus conventional antihypertensive drugs for the same level of BP[37]. In REIN-2, no additional benefit from further BP reduction by felodipine could be shown[38]. Hou et.al showed that compared with placebo, benazepril reduced the risk of the primary end point (DSC, ESRD, death), the level of proteinuria and rate of decline in renal function, benefit not attributable to BP control[39]. In AASK trial in hypertensive nephrosclerosis, ramipril appeared to be more effective than metoprolol and amlodipin in slowing GFR decline. Better preservation with ramipril was seen in patients with UAER>200 mg/24h[40]. The special characteristic of all these studies was the presence of albuminuria, finding which agrees with Jafar et al that the antiproteinuric effects of ACEIs are greater in patients with a higher baseline UAER[41].

Diabetic nephropathy studies suggest this beneficial effect in all stages and UAER. In Captopril Trial, Captopril protected against deterioration in renal function in insulin-dependent diabetic (IDDM) nephropathy, effect beyond BP control alone[42]. Bakris et al showed that in persons with renal insufficiency secondary to NIDDM, similar levels of BP control with either lisinopril or NDHCCBs slowed progression of renal disease to a greater extent than atenolol, correlated with sustained and significant reductions in proteinuria[43]. In IDNT study, irbesartan was renoprotective independently of its BP lowering effect in patients with NIDDM and microalbuminuria[29]. In RENAAL losartan vs placebo conferred significant renal benefits in patients with NIDDM and nephropathy, benefit not attributable to changes in BP[44]. In IRMA 2, the proportion of patients progressing to overt nephropathy was significantly lower for recipients of irbesartan 300mg than placebo, renoprotective effect partly independent of the BP-lowering effect[30]. Meta-analysis of Sarafidis et all mentioned that ACEIs and ARBs in diabetic nephropathy reduced the risks of ESRD and DSC, but did not affect all-cause mortality[45].

On the other hand there are trials and meta- analysis which suggest no benefit in renal outcomes with ACEIs or ARBs. Antihypertensive and Lipid-Lowering Treatment

to Prevent Heart Attack Trial (ALLHAT) concerning patients with H and at least one other coronary heart disease factor, showed that in patients who had renal disease but unknown urine exertion, there was no benefit[46], as no benefit was seen in TRANSCENT with patients of known cardiovascular disease or diabetes but low background renal risk[47]. In a meta-analysis Casas and colleagues state that in patients with diabetes additional renoprotective actions beyond lowering BP remain unproven and there is uncertainty about the greater renoprotection seen in non diabetic renal disease[48]. It seems that among patients at low risk of renal progression, ESRD occurs rarely and only after many years or even decades. This probably explains the lack of renal benefit reported in large general population trials and meta-analyses of such trials[17]. A review article by Onuigbo supports that despite this progressively increasing utilization of the various ACEIs and ARBs in clinical medicine in the US, they have continued to witness an ever increasing epidemic of CKD and ESRD, that had outpaced the rate of diabetes increase[49,50]. Suissa et al, in a population-based,cohort analysis of 6102 diabetic patients in Canada, demonstrated an increased rate of ESRD with ACEIs[51]. The conclusions of the MICRO-HOPE trial have been called into question by a recent subset analysis of HOPE which demonstrated that the ramipril group actually achieved substantially greater reductions in arterial BP (10/4mm Hg) when compared to the placebo arm[52]. The often cited RENAAL, IRMA II and IDNT trials depict benefits of renoprotection beyond BP lowering, but failed to show improved patient outcomes in terms of cardiovascular mortality and/ or all-cause mortality, a disparagingly unexpected result, given the well documented high annual mortality rates usually associated with ESRD patients[50].

Dual blockage of RAAS with ACEIs and ARBs-What's new

Dual blockade of RAAS at different steps with ACEI and ARB would be an attractive alternative. However, there is continuing uncertainty about the balance of benefits and harms, in terms of kidney disease progression. The first noteworthy trial is CALM (Candesartan and Lisinopril in Microalbuminuria) study. Greater decrease in systolic-SBP was observed in the combination therapy group and albuminuria decreased a further 50%, with SC and potassium slightly more elevated in the combination group[53]. The CALM II study, published 5 years later, used a high dose of ACEI (40 mg lisinopril) and showed no difference SBP and UAER in comparison to combination therapy[54]. In meta-analysis, Doulton et al demonstrated that combination therapy provided a further 30% - 39% drop in proteinuria compared to monotherapy[55] and in MacKinnon et al resulted in a significant decline in proteinuria both in diabetic and nondiabetic patients with a slight but significant increase in potassium, and an insignificant drop in GFR[56]. An analysis published in early 2008 reported a further drop of 27% - 34% in proteinuria, while adding that discontinuation was more common with combination therapy[26]. A meta-analysis of the trials on patients with primary glomerulonephritis revealed that combination therapy led to a marked decrease in proteinuria, to a further drop in BP, increased potassium and not impact on GFR[57]. The IMPROVE (Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events) study has shown no further benefit on albuminuria reduction in patients treated with combination therapy despite the fact that BP reduction was slightly better in the combination group. Subgroup analyses showed the largest reduction in albuminuria occurred in patients with overt nephropathy but it did not reach statistical significance[58]. In contrast to these studies, the VALERIA (Valsartan in Combination With Lisinopril Versus the Respective High Dose Monotherapies in Hypertensive Patients With Microalbuminuria) trial demonstrated that combination therapy was more effective in reducing microalbuminuria despite the fact that patients received the maximal recommended doses of lisinopril or valsartan as monotherapy. There was no difference in BP. Adverse events were slightly higher in the combination group, mainly hypotension[59]. The most striking data for combination therapy were reported in ONTARGET. Although the BP drop and albuminuria reduction was superior in the combination arm, no added benefit was noted with respect to the primary end point, while hypotension, decreased kidney function, and high potassium were more common. The kidney outcome data of the ONTARGET study also showed no further benefit with combination therapy even in the high-kidney-risk group. Although the ONTARGET study was not specifically powered for primary kidney outcomes, and the patient cohort had distinctive characteristics (high cardiovascular, low renal risk), these results may offer insights on the safety of combination therapy, if interpreted with caution. In patients with the highest risk (overt diabetic nephropathy), the point estimate for the primary outcome was in favor of combination therapy, but it was not significant. Similarly, in high-kidney-risk groups (eg, with micro- or macroalbuminuria), combination therapy showed no benefit, but tended to show worse results in low-kidney-risk groups[60].

Ongoing trials with selected patients with CKD may enlighten the dual blockage of RAAS. Preventing ESRD in Overt Nephropathy of Type 2 Diabetes (VALID) trial, with high-risk patients with NIDDM and overt nephropathy, VA NEPHRON-D, in NIDDM and overt nephropathy, Safety of Dual Blockage of Renin-Angiotensin System in Patients With Advanced Renal Insufficiency (SDBRAS), in non-DM patients with advanced decreased kidney function and HALT Progression of Polycystic Kidney Disease (HALT PKD),in patients with polycystic disease and GFR > 60 (Study A) / GFR 25-60 (Study B)[55].

Conclusions

Guidelines for the management of hypertension in CKD are that for diabetic and non diabetic proteinuric patients with CKD, anti-hypertensive therapy should

include ACEI or ARB. For patients with non diabetic nonproteinuric CKD, anti-hypertensive therapy should include either ACEI, ARB, diuretic, b-blocker, or long-acting CCB[61,62]. These drugs should be used with caution, with strict monitoring of the renal function and plausibly temporarily withdrawn during situations of low renal flow (e.g. major surgeries, hypovolemic situations).

As for the combination treatment, until the results of ongoing trials and further safety data emerge, it is wise to withhold its use in general practice, especially for low-kidney-risk patients and maybe for those with advanced kidney disease. If used, patients should be monitored with extreme caution, as there is no sufficient evidence of safety.

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