REVIEW

Role of Renin-Angiotensin-Aldosterone System (RAAS) Inhibition in the Renal Continuum

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Published: 05 November 2012
Ibnosina J Med BS 2012,4(6):222-230
Received: 03 September 2012
Accepted: 15 Ocotber 2012
This article is available from: http://www.ijmbs.org

Abstract

Renal involvement in patients with type 2 diabetes carries a risk of increased cardiovascular mortality. This is particularly true in the presence of microalbuminuria being an early marker of endothelial dysfunction. The use of Renin Angiotensin Aldosterone System (RAAS) blockers has been found beneficial in improving endothelial dysfunction as well as preventing development of microalbuminuria and its progression to macroalbuminuria. This class of drugs has been proved effective in delaying the development of end stage renal disease. However; in patients with established end stage renal disease, it becomes controversial whether using these drugs may still be beneficial. Indeed, some studies have shown that they may even be harmful if used in late stages of chronic kidney disease. In this article, we will review firstly, the renovascular changes in health and disease and secondly appraise the different trial data pertaining to the assessment of the use of various RAAS inhibitors at different stages of the renal continuum. We hope the review will help put together a physiologically-based fundamental knowledge and a trial-derived evidence base for to help inform day to day decision-making in clinical practice.

Key Words: RAAS, Diabetes, Microalbuminuria, Hypertension, Endothelial dysfunction,

Introduction

Diabetes is one of the commonest causes of end-stage-renal disease (ESRD) worldwide. It is also a major risk factor for cardiovascular disease (1,2). Over twenty eight per cent of patients with type 2 diabetes mellitus (T2DM) have microalbuminuria, and about 8% have clinical proteinuria (3). Without treatment, around 20-40% of these would progress to overt nephropathy (2,3). In some studies. aggressive glycemic control was shown to delay progression of diabetic nephropathy (4,5). Use of renin angiotensin aldosterone system (RAAS) blockers in treatment of hypertension

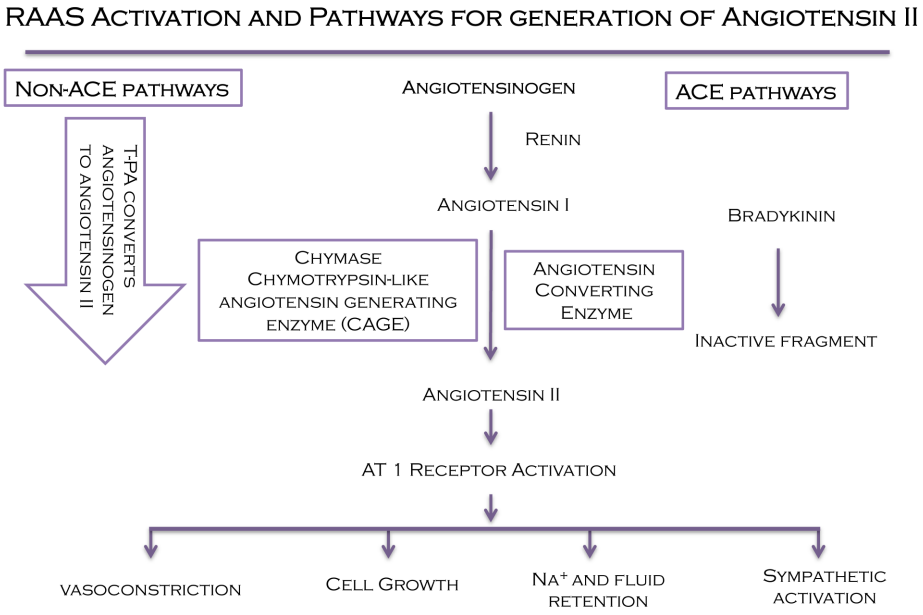
associated with proteinuria has delayed progression of nephropathy in many studies. It is also established that RAAS play an important role in cardiovascular disease (CVD) including heart failure.

Renovascular physiology

Fundamentally, RAAS is a cascade of reactions in which angiotensinogen is cleaved by renin to form angiotensin I as the initial step (Figure 1). Angiotensin converting enzyme (ACE) then converts angiotensin I to angiotensin II. The resulting Angiotensin II in turn stimulates aldosterone synthesis from zona glomerulosa of the adrenal cortex, stimulates thirst, and leads to antidiuretic hormone release. These changes consequently result in sodium and water retention. Angiotensin II is also known to be a potent vasoconstrictor and a stimulant of inflammatory cytokines, adhesion and chemotaxis of inflammatory cells (6-8). RAAS inhibition has been found to be effective in reducing cardio-renal mortality and morbidity commonly known as the cardio-renal continuum (CRC) (Figure 2).

The mechanism through which the capillary pressure remains controlled within 5mmHg, despite varying perfusion pressures is described as *renal autoregulation* (9-10). It is mainly controlled by the vascular tone of the afferent and efferent glomerular arteriolar system. In cases of high systemic blood pressure, the afferent arterioles initiate reflex contraction that reduces renal blood flow to a level that is appropriate for filtration (usually a mean arterial pressure 70-80 mm Hg) (9, 10). Increased delivery of sodium chloride to the distal nephron is another mechanism that causes afferent arteriolar constriction through a tubular glomerular feedback mechanism (11). Conversely when there is hypovolemia, the efferent glomerular arteriole constricts to maintain filtration pressure (12). With early development of atherosclerotic vascular disease in diabetics, the autoregulation at the afferent arteriole become impaired, and hence systemic pressures can easily be transmitted to glomerular vessels.

Another characteristic feature of endothelial dysfunction is an impaired nitric oxide (NO) activity which constitutes an early step in the pathogenesis of atherosclerotic disease. Nitric oxide is derived from L-arginine through the action of NO synthases and has a key role in maintaining vascular wall integrity through a variety of mechanisms, including inhibition of inflammation, cellular proliferation, and thrombosis. Moreover, due to its vasodilating properties, NO is an important regulator of afferent and efferent arteriolar tone of renal glomeruli and thus has a crucial role



Adapted from: Hollenberg et al. Hypertension 1998;32:387-92.

Figure 1. The RAAS Activation and Pathways for generation of Angiotensin II (Adapted from reference 6).

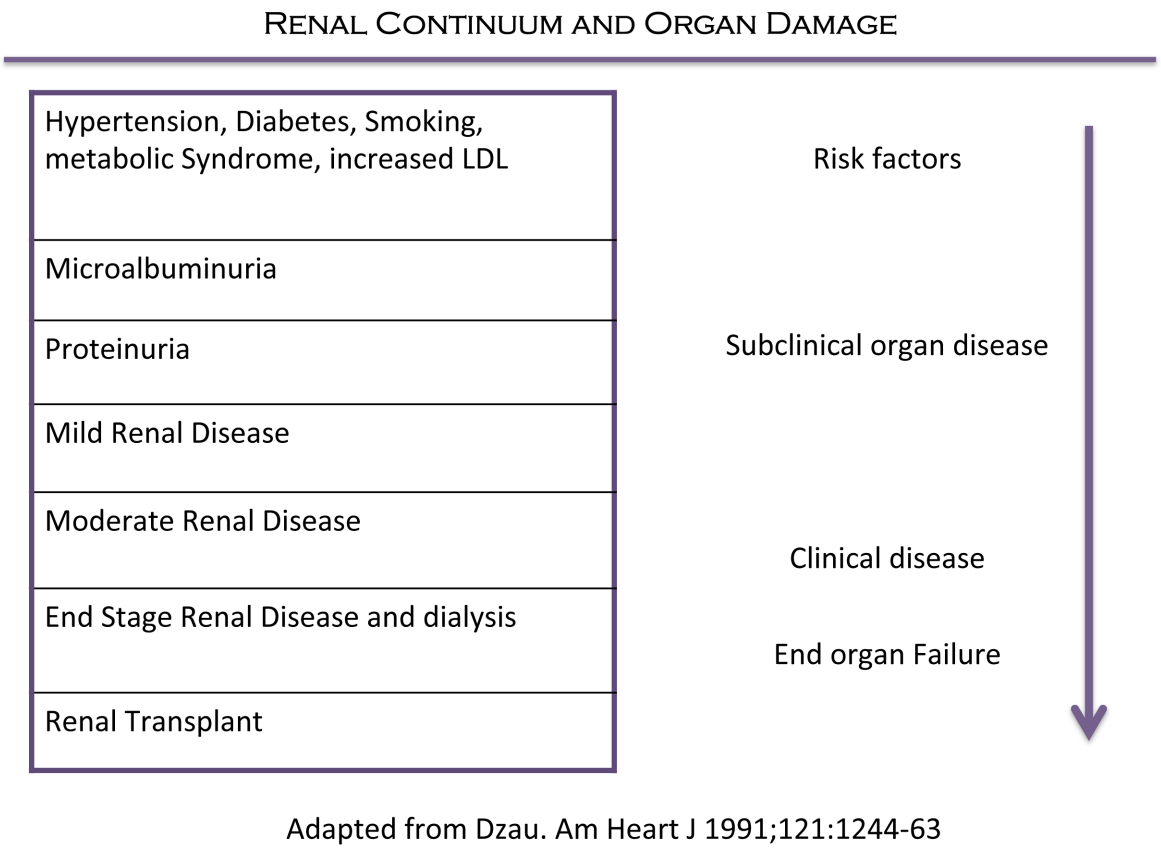


Figure 2. Renal continuum and organ damage (Adapted from reference 7).

in determining renal hemodynamics. Increased reactive oxygen species formation and altered basal NO activity contribute to endothelial dysfunction in patients with T2DM and arterial hypertension. This and has been linked to the initiation and progression of atherosclerosis and overt cardiovascular and renal disease (13).

Role of RAAS blockade in the renal continuum

Endothelial dysfunction

Endothelial dysfunction is the earliest stage of vascular involvement, followed by a cascade of cardiovascular and renal events that include microalbuminuria as depicted in figure 2. RAAS blockade has been proved effective in renal protection at different stages of the renal continuum. Perhaps the best known "proof of concept" trial was the TRENDY trial (13). The investigators evaluated the effect of Telmisartan and Ramipril on renal hemodynamics and renal endothelial function. They included 66 patients with hypertension and T2DM, with or without microalbuminuria. Endothelial dysfunction was evaluated by measuring renal plasma flow after infusion of N-monomethyl-L-arginine (L-NMMA), indicating increased basal NO activity of the renal vasculature. The authors demonstrated that both drugs led to a significant NO activity in response to L-NMMA infusion after 9 weeks of treatment (13).

Prevention of microalbuminuria

Microalbuminuria is a progressive step in the development of diabetic nephropathy. Several studies have investigated the effect of RAAS inhibition in prevention of microalbuminuria. The primary end point for BENEDICT trial was the development of persistent microalbuminuria. The trial included 1204 subjects who were randomized to receive Trandolapril plus Verapamil, Trandolapril alone, Verapamil alone or placebo for three years. The onset of microalbuminuria was delayed in the arms of

Trandolapril plus verapamil and trandolapril alone. The authors concluded that use of trandolapril in patients with type 2 diabetes and hypertension reduces the incidence of microalbuminuria (14). More recently, the ROADMAP trial evaluated the effect of Olmesartan in prevention of microalbuminuria. The study was conducted in 19 centres across Europe and included 4447 patients with type2 DM. The primary end point was the first occurrence of microalbuminuria. Olmesartan resulted in significant risk reduction of 23% with hazard ratio of 0.77; P=0.0104. However, cardiovascular mortality was greater in the Olmesartan group and this was attributed to its effect in reducing blood pressure in patients with existing coronary heart disease (CHD) (15). The DIRECT trial was larger and it included 5,231 patients. DIRECT consisted of three large placebo controlled multicenter trials. It evaluated the effects of ARB (Candesartan) on diabetic retinopathy and nephropathy. The study was not adequately powered for assessment of renal outcomes. Microalbuminuria developed in 401 over a period of 4.7 years of follow up. Candesartan did not result in significant reduction in risk for microalbuminuria. However, the rate of change of urinary albumin excretion was significantly reduced in patients assigned to Candesartan (P=0.02) (16).

Prevention of progression to macroalbuminuria

RAAS inhibitors were also studied in patients with microalbuminuria. IRMA2 study is a double blind, randomized, placebo-controlled trial that evaluated the renoprotective effects of Irbesartan in 590 patients with T2DM. , hypertension, and persistent microalbuminuria over a period of 2 years. The primary outcome was the onset of overt diabetic nephropathy as evidenced by the first occurrence of an albumin excretion rate of >200 ug/min, or an increase of at least 30% from base line on two successive evaluations. The unadjusted hazard ratio for diabetic nephropathy was 0.62 (P=0.08) in the 150mg Irbesartan group, and 0.30 (P<0.001) in the 300mg Irbesartan group. After adjustment for baseline level of microalbuminuria and blood pressure the adjusted hazard ratio for diabetic nephropathy in the 150mg group was 0.56 (P=0.05) (17). The effects of Enalapril on reducing progression to macroalbuminuria in 95 normotensive T2DM patients with microalbuminuria in a placebo-controlled trial conducted over 5 years (18). The difference in change in albuminuria was quite significant in favour of Enalapril (p< 0.005). It was also concluded that there was a close correlation between serum cholesterol levels and the decline in kidney function (18). The DETAIL trial was the first to compare an ACE and an ARB in prevention of progression to ESRD from a baseline of microalbuminuria (19). It included 250 patients with T2DM and hypertension. It concluded that there was no difference between ACE inhibitors and ARBs in prevention of progression to ESRD (19).

Macroalbuminuria

Most of the studies conducted for the prevention of progression of nephropathy were in patients with macroalbuminuria. Irbesartan in diabetic nephropathy trial has included 1715 patients with T2DM , hypertension, and nephropathy (urine protein excretion of >900mg/day and serum creatinine between 1-3mg/dl in women and 1.2-3mg/dl in men). The primary end point was a composite of doubling serum creatinine, ESRD (indicated by starting dialysis, serum creatinine >6mg/dl or renal transplantation), or death. Patients were assigned to either Irbesartan, Amlodipine, or a placebo (20). The study concluded that Irbesartan was more effective than Amlodipine in reducing primary end points (risk reduction 23%, P=0.006). It was also more effective than placebo with risk reduction of 20%; P=0.02 (20). RENAAL is another landmark trial that studied Losartan in renal protection. The study included 1531 T2DM patients with nephropathy [defined as 24 hours urine protein excretion of at least 300mg/day and serum creatinine between 1.3-3mg/dl]. Patients were followed up for a period of 4.5 yrs. The primary outcome was the first event of composite end point of doubling serum creatinine. Losartan has reduced the incidence of doubling serum creatinine time by 25% (P=0.006) and end stage renal failure by 28% (P=0.002). The composite of morbidity and mortality from CVD was equal in both groups. The rate of first hospitalization for heart failure was significantly lower with Losartan (32% risk reduction, P=0.005) (21). AMADEO trial compared two ARBs with respect to reducing urinary albumin creatinine clearance (22). A total of 860 patients with T2DM, hypertension, and an early morning spot urine albumin creatinine ratio of >700 were included. Patients were randomized to either Losartan (an ARB with a low lipophilicity and short half life) or Telmisartan (a highly lipophilic ARB with long half-life). They were followed up for 52 weeks. Both Telmisartan and Losartan resulted in significant reduction in Albumin:Creatinine ratio (29.8% for Telmisartan, and 21.4% for Losartan, P=0.0001 for both drugs). However, Telmisartan was superior to Losartan in reducing albumin excretion (P < 0.03) (22). Chronic activation of renin system was demonstrated to cause end organ damage and that plasma renin activity is an independent risk factor

for cardiovascular events and death. This has lead to the exploration of a third blockade point in RAAS namely the blocking of renin directly. In the AVOID trial, Aliskerin was used in addition to Losartan treatment and the dual blockade was compared to placebo in patients with T2DM, hypertension and albuminuria (>300mg/gm). Aliskerin resulted in 20% reduction in microalbuminuria and this was significantly greater than placebo (p=0.0009). It has also resulted in reduction of progression to ESRD especially in those with uncontrolled blood pressure (23).

RAAS blockade in Acute Kidney Injury

Acute kidney injury (AKI) is defined as an acute insult that results in a functional or structural changes in the kidney resulting in an increase in serum creatinine. Recent epidemiological studies have detected a wide variation in the causation and risk factors associated with AKI. This condition increases hospital mortality rates, particularly if dialysis is required (24). Furthermore, there is an emerging body of evidence that even minor, short-term changes in serum creatinine are associated with increased mortality (25). Other important consequences of AKI are progression of pre-existing chronic kidney disease and even development of ESRD. Introducing RAAS blockade in the presence of acute kidney injury caused by hypotension, volume depletion or dehydration and over-diuresis, further worsens renal function (26). Normalization of kidney function to the baseline has been observed following ACEI/ ARB withdrawal. The proposed mechanism is that the normal pathways that protect kidney perfusion in the case of hypovolemia are blocked by the use of RAAS-inhibitors (27). The role of ACEI/ARB in contrast nephropathy has been evaluated by many studies. Rim et al prescribed ACEI/ARB to 64% of patients undergoing coronary angiography. In a multivariable analysis, the use of these agents remained an independent and significant predictor of contrast-induced AKI in an unmatched cohort (OR, 1.39; P=0.06). In the matched cohort, use of ACE inhibitors/ ARBs was also associated with a higher adjusted OR of contrast-induced AKI (OR: 1.43; P=0.02) (28). There are still controversial views over the preoperative use of ACE inhibitors in patients undergoing surgical procedures including coronary artery bypass graft (CABG). While some authors suggest that the preoperative administration of ACE inhibitors in cases of CABG results in hypotension and renal dysfunction (29-30), others suggest that their use does not cause hypotension and can be safely used in patients undergoing cardiac surgery (31,32). A retrospective cohort study included data from 3,139 consecutive patients undergoing isolated CABG in a Brazilian tertiary care hospital over 14 years (33). They were followed up until discharge or death. Clinical outcomes after surgery were analyzed between users and nonusers of ACE inhibitors preoperatively. Patients on ACE inhibitors had a higher risk of developing post-operative acute kidney injury (AKI) (OR 1.23; P=0.042), as well as elderly patients, patients with chronic obstructive pulmonary disease (COPD), heart failure, and patients with early stages of CKD as compared to patients were not on ACE inhibitors preoperatively (33).

RAAS blockade in Chronic Kidney Disease

It is well established that inhibiting RAAS slows progression of CKD in earlier stages (34), Suissa et al. studied 6102 diabetic patients with hypertension who were treated with either beta-blockers, calcium channel blockers or ACEIs (34). The influence of long term use of ACE inhibition on the incidence of end stage renal failure (ESRF) was assessed. Patients treated with ACEI's reached ESRF, faster than others who were treated with either beta-blockers or calcium antagonist (2.5% compared to 0.8% and 0.7% respectively. The authors proposed that the use of ACEI's does not appear to decrease the long-term risk of ESRF in diabetic patients. Instead, ACEI's might be associated with an increased risk. Apparently, the actual stage of CKD seems to play an important role in taking the decision of whether to commence ACE inhibitors (35). Onuigbo et al evaluated 26 patients 12 of them were diabetics and found that older patients with CKD and serum creatinine > 2 mg/dl or GFR < 35ml/min progresses faster after initiating RAAS blockade. The mean eGFR increased from (P=0.001) 26 months after withdrawal of RAAS blockade. In the group of patients who did not undergo renal PTA or stent placement, 10 patients out of 17 had shown significant improvement in their eGFR (P=0.005), 23 months following discontinuation of RAAS blockade. This indicates ischemic nephropathy is under-diagnosed in this group of patients (36). Recently, it was reported that stopping RAAS inhibitors in patients with advanced CKD (mainly stage 5) delayed the onset of renal replacement therapy, 46% of the population in the study were diabetics, eGFR increased by 25-50% and proteinuria was not affected as proteinuria will be minimal in such group due to glomerulosclerosis (37). These authors suggested that a macrovascular disease affecting the renal vasculature in diabetics causing ischemic nephropathy could be the attributing factor for this deterioration, and this will be more prominent in the elderly populations with diffuse atherosclerosis. Moreover using a dual blockade did not add to the renal protection as seen in ONTARGET study;

it was rather associated with hypotension and worsening of renal function (38).

RAAS blockade in ESRD

Once the patient reaches ESRD stage , the beneficial effect of RAAS blockade on renal protection is abolished. However, cardiac advantages of RAAS blockade persist. The effect on the vasculature helps preservation of vascular access as the effect of RAAS blockade in reversing endothelial dysfunction and prevention of atherosclerosis. The risk of cardiac events in dialysis patients is greater than in the general population. This renders them the group that requires the RAAS blockade the most. In addition to that blockade RAAS is required for BP control. Hyperkalemia in hemodialysis (HD) patients is one of the limiting factors for their use in this group of patients. This is in contrast to patients receiving peritoneal dialysis who are more prone to hypokalemia. It is therefore recommended to individualize the treatment, as hyperkalemia in HD patients as it is highly dependent on the diet and residual renal function. Patients on peritoneal dialysis therapy are prone to develop peritoneal membrane failure due to fibrosis and neoangiogenesis resulting in loss of ultrafiltration. This is related to up-regulation of growth factors (TGFß and VEGF) and other factors such as aldosterone, which can promote fibrosis in the peritoneal membrane in response to exposure to glucose (39-41). In addition, peritoneal membrane expresses angiotensinogen, ACE, angiotensin 1 and 2 (42). It seems that, the peritoneal membrane has its own internal RAAS system. Studies in rats revealed RAAS blockade inhibits synthesis of TGFß and VEGF. In humans, Kolesnyk et al (43) reported that the group of patients who were treated with ACEI or ARBs did not show increased solute transport with time on therapy which is seen in the control group. On the other hand, Fang et al (44) were able to prove in a retrospective study the powerful survival benefit in those PD patients who received an ACE inhibitors or ARBs. Peritoneal dialysis patient's benefits from RAAS blockade as it acts as an anti-fibrotic agent and prevent peritoneal membrane sclerosis, which is responsible for ultrafiltration failure. In patient going for renal transplant, it is recommended to discontinue RAAS blockade prior to the operation as Stevens et al (45) reported renal transplant recipients who were taking a renin-angiotensin-aldosterone system blocker at the time of transplantation were more likely to develop impaired graft function postoperatively in the absence of other explanations (45).

Conclusion

It is currently well established that RAAS blockade plays an important role in renal protection, especially in diabetic patients, where they were proven to be effective in prevention of microalbuminuria, delay of progression to macroalbuminuria, and to ESRD. Use of RAAS blockade has clearly regressed proteinuria dramatically in early stages of disease. However, treatment should be individualized, particularly in the elderly and in patients with GFR less than 35 ml/min (CKD Stages 4-5) as they may progress to ESRD faster on initiating RAAS blockers. Recent work suggested that using RAAS blockers in late stages of CKD is unwise and mostly harmful with resulting deterioration in kidney function attributable to the associated atherosclerotic vascular disease. Some controversies remain unsettled pertaining to the use of RAAS blockers in patients undergoing major surgery, and in patients undergoing dialysis. Some studies showed beneficial effect in peritoneal dialysis patients, and their cardio-protective effect could be useful in patients on dialysis. Further work is required to establish the role of RAAS blockers in patients with ESRD and patients on renal replacement therapy.

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