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Review Article

RENOPROTECTIVE BENEFITS OF RENIN-ANGIOTENSIN SYSTEM INHIBITION: What is the evidence?

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Renin-angiotensin-System (RAS) plays a central role in the pathogenesis and progression of end-organ damage. The end organs include brain, blood vessels, heart and kidneys. Several adverse effects are mediated through AT_1 receptors by angiotensin II (Ang II), the end product of renin-angiotensin chemical cascade. Ang II contributes to the development of renal insufficiency. As the cardiac function deteriorates through LV hypertrophy, myocardial remodeling and fibrosis, concurrently the glomerular filtration rate decreases. A further increase in production of Ang II leads to proteinuria, increased aldosterone release and progressive glomerulosclerosis. Ang II induces cell growth and accumulation in glomerular cells. It has also been shown to influence the action of plasminogen activator inhibitor-1 and thus thrombotic and sclerotic effects. Ang II seems important in fibrotic and sclerotic injuries that lead to progressive renal disease. Therapies with specific angiotensin receptor antagonism have been developed to afford prevention or reversal of renal damage[1,2].

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Mechanism of Progressive Renal Dysfunction

Recognition that loss of renal function is progressive has lead to extensive investigations into risk factors and mechanism of injury due to Ang II. A large number of mediators of injury have been identified, as well as metabolic factors which act through these mediators and mechanisms.

Ang II promotes glomerular hypertension, there is increase in accumulation of macromolecules and enhancement of inflammatory process. Through these developments and also directly under the influence of Ang II there is stimulation of growth factors and enzymes like TGF-B_1. This leads to hypertrophy and extracellular matrix formation, resulting in glomerulo-sclerosis contributing to renal dysfunction. Glomerular hypertension also leads to permselectivity and leakage of serum proteins, with resultant proteinuria. Leakage of serum proteins increases the protein load in proximal tubules which promotes gene expression for inflammation and transformation of tubular cells to myofibroblasts. The result is tubulo-interstitial injury – a major factor for renal dysfunction. Many of these effects are intertwined and directly or indirectly attributable to Ang II[3].

Why is proteinuria so important ?

Renal end-organ damage manifests itself

through decrease in glomerular filtration rate (GFR), proteinuria and increased aldosterone release. All these effects are important as they contribute to ESRD (end-stage renal disease); however, proteinuria is the single-most important renal element which is known to be an independent risk factor for stroke and coronary heart disease as well as death especially in diabetes. Miettinen et al.[4], have shown that in three groups of proteinuria with urinary protein concentration of 150 mg/L, 150-300 mg/L and > 300 mg/L the risk of stroke increased to 8%, 12% and 24% respectively. Likewise the risk of coronary events worsened from 16%, 25% to 35% respectively. The risk of CV death also increased to 14%, 20% and 60% accordingly. As early as 1985, Samuelsson et al.[5], have eluded to the similar point of increased cardiovascular disease in the presence of proteinuria. This issue has also been highlighted in another study by Luft FC et al.[6], who reported a highly significant difference between patients with and without microalbuminuria for CAD, LV hypertrophy, peripheral vascular disease and stroke.

Benefits of RAS Inhibition in renal dysfunction

Ang II inhibition with ACE-inhibitors and more recently with Angiotensin Receptor Blockers (ARBs), has been shown to retard or even reverse the progression of renal dysfunction. It can also reduce cardiovascular morbidity and mortality. Early detection and treatment of renal function is crucial, regardless of the presence or absence of symptoms.

Selected data of evidence of reno-protection is presented here:

Hypertensive Renal Disease

Renoprotective effect of RAS blockade with ACEIs was demonstrated almost a decade earlier. In hypertensives with significant renal dysfunction creatinine ≥1.5 mg/dL) Captopril was compared with placebo.[7] After a 4 year follow-up, patients on Captopril showed 40% less doubling of baseline creatinine (p=0.001). Gansvoort et al.[8], compared an angiotensin receptor blocker, Losartan alternating with placebo and ACEI, in hypertensives with proteinuria. With placebo the blood pressure returned to the baseline while with ARB and ACEI there was a dose-related reduction of albuminuria which ranged between 40-50% ($p < 0.05$).

Valsartan has been shown to reduce proteinuria and microalbuminuria in patients with hypertension and moderate renal failure. The difference between active treatment and placebo was 60-80% for proteinuria and microalbuminuria respectively over a period of 6 months, when compared with run-in phase ($p < 0.05$)[9].

RAS blockade tends to produce better renoprotective effect compared to calcium antagonists. In the African American Study of Kidney Disease and Hypertension (AASK) Ramipril was compared with Amlodipine, in patients with hypertension and renal dysfunction. The baseline characteristics in two groups were similar. There was a significant risk reduction of 38% for cumulative incidence of renal events (decrease in GFR, ESRD) and death in favour of Ramipril (p=0.005)[10].

Renal dysfunction caused by lgA nephropathy also responds favourably to RAS blockade. Russo et al., reported a significant reduction ($p < 0.05$) of proteinuria with ACEIs and ARBs either alone or in combination, compared with baseline[11]. Combination of an ACEI with ARB, Losartan brings about significant reduction in urinary protein excretion compared to ACEI alone ($p < 0.05$).

Diabetic Nephropathy

In type 1 diabetes, ACEIs are more renoprotective than conventional therapy. With the baseline creatinine ≥ 1.5 mg/dL captopril, compared with placebo significantly reduced percentage with doubling

of baseline creatinine over a 4 – year follow-up by > 50% ($p < 0.001$)[7], with an equal decrease in mean arterial pressure.

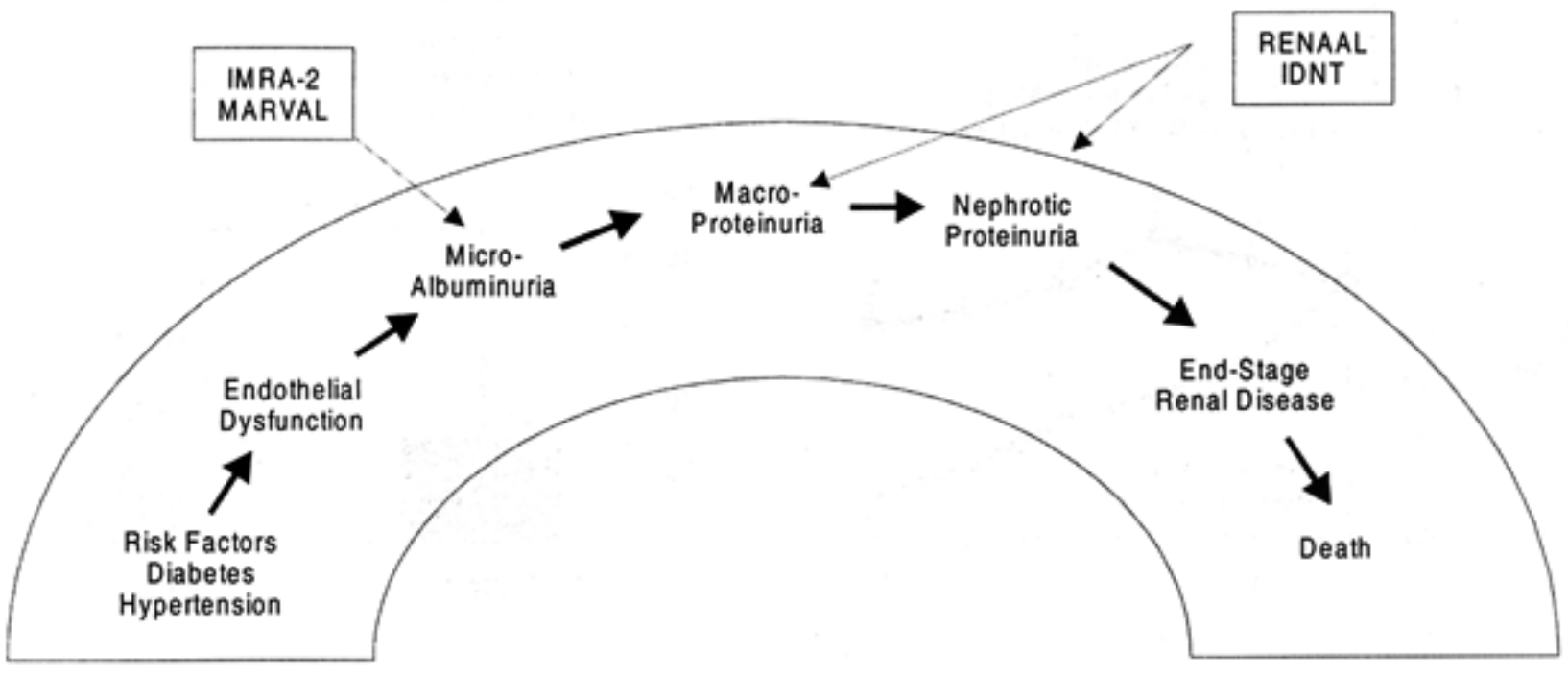
Renal dysfunction goes through progressive stages of microalbuminuria, macroalbuminuria, nephrotic proteinuria and end-stage renal disease which contributes to morbidity and eventually death. This can be termed as morbidity and mortality along the renal continuum. Several studies have been carried out in the recent years in type 2 diabetes – related nephropathy, along this continuum.[12] to observe the effects of RAS blockade (Fig 1).

IRMA 2 studied the effect of Irbesartan in microalbuminuria in Type 2 diabetes with normal renal function[13]. Compared to placebo, Irbesartan reduced progression to nephropathy by 70% ($p=0.0004$) and increased the percentage of patients in whome microalbuminuria was abolished (34% vs 24%, $p=0.006$). In MARVAL study[14] the effect of Valsartan was compared with Amlodipine in Type 2 diabetes with microalbuminuria. The patients were either normotensives or hypertensives. For the same level of BP control, Valsartan showed > 40% better decrease in urinary albumin excretion rate than Amlodipine. Almost 30% patients returned to normoalbuminuric status compared to 14.5% with Amlodipine ($p < 0.001$). (Fig 2)

Muirhead N et al. observed changes in urinary albumin excretion in diabetics were observed with Valsartan and Captopril and compared with placebo. There was a comparable reduction from baseline with the active drugs and significantly more than placebo ($p=0.005$)[15].

In IDNT study[16], the composite endpoint was doubling of serum creatinine, end-stage renal disease and/or death. 1715 patients were hypertensives with nephropathy due to type 2 diabetes. Irbesartan was compared with amlodipine and placebo. Primary end-point was reached by 32.6%, 41.1% and 39% patients respectively. There was 20% better risk reduction with Irbersartan vs placebo ($p=0.02$) and 23% better risk reduction vs Amlodipine ($p=0.006$). There was no difference between Amlodipine and placebo. Same end-points as IDNT study were used in RENAAL study[17] comparing Losartan and placebo in patients with diabetes and nephropathy. In Losartan group 16% less patients had deterioration in renal functions with 32% risk reduction vs placebo ($p=0.005$).

Fig 1: Morbidity and mortality along the renal continuum



Burgess E, 2001

Salt, Renal Blood Flow (RBF) and RAS Inhibition

ACEIs and ARBs invariably increase the renal blood flow as much as a median of 100-140 mL/min/1.73m^2 [18]. However, the increase is very much dependant on salt intake status. With low salt diet (50mEqNa$^+$) the RBF increase is almost similar with ACEI and ARB[19]. But with high salt intake (250mEqNa$^+$), there is a significant higher increase of RBF in favour of ARBs compared to ACEIs. (100mL/min vs 30mL/min).

The poor response with ACEIs in high salt diet has a bearing in their antihypertensive response, especially in communities like Africans and black Americans. ARBs, on the other hand, have a significantly better antihypertensive response with high salt diet in these communities, even though this response is somewhat muted compared to low salt diet[20]. An even better BP reduction can be observed when a diuretic is combined with ARB compared to monotherapy, in high salt diet. Combination with a diuretic (hydrochlorothiazide) gives a better antihypertensive response than a combination of ARB and ACEI.

Apprehensions about RAS inhibition

A perception of adverse effects persists with the use of RAS inhibition in the presence of renal dysfunction. The apprehensions include the possible risk of worsening of renal function and rise of serum potassium especially with ACEIs. The common observation is that by and large the increase in creatinine, if does occur, is transient or the level of creatinine soon gets stabilized.

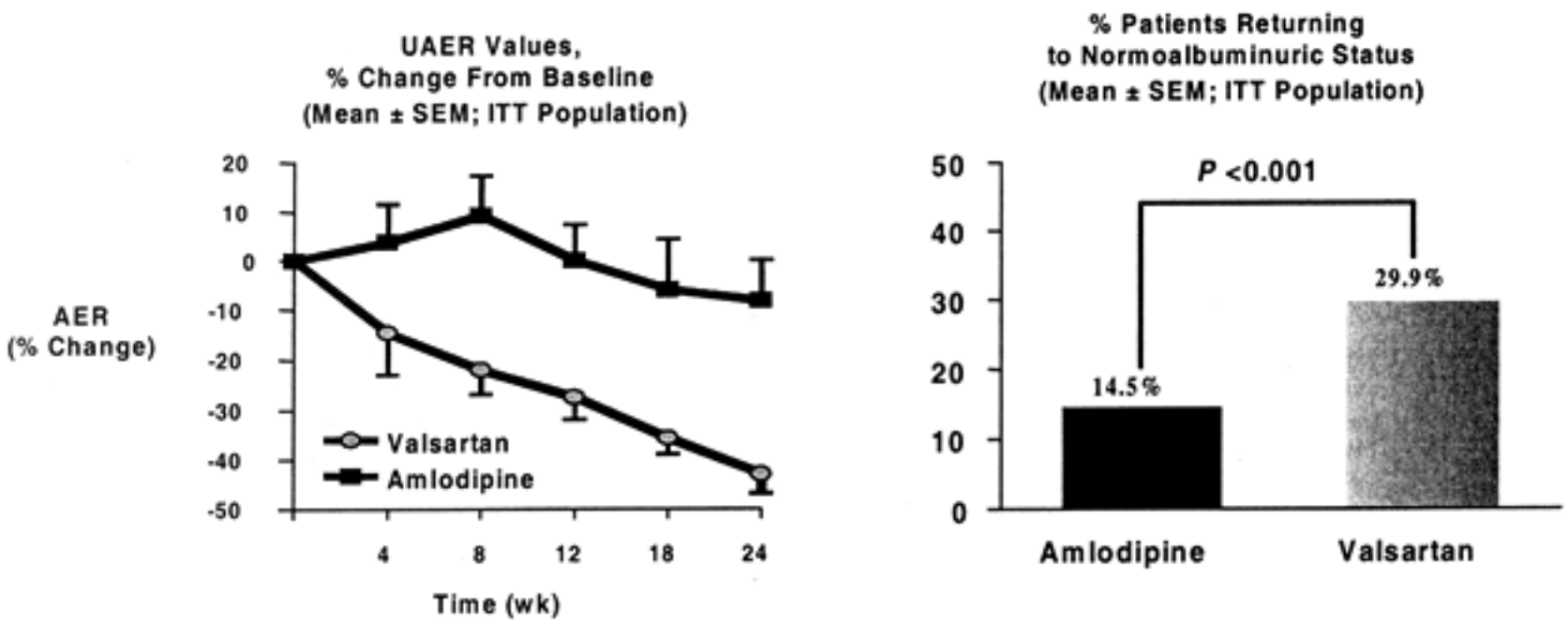
However, there are certain conditions in which there may be a continued rise of serum creatinine with continued RAS inhibition. These conditions include diuretic overuse along with severe sodium restriction in diet, bilateral renal artery stenosis or a solitary kidney, renal vein stenosis or thrombosis, ureteric stenosis or vesico-ureteric reflux, continued use of non-steroidal anti-inflammatory drugs or cyclosporin.

The tolerability and safety of ARBs is already proving to be better over a long term use and with increasing dose compared to ACEIs. This fact has a strong bearing on the longer term compliance of RAS inhibitors. ARBs clearly standout on this account[21] not only in comparison to ACEIs but also calcium antagonists[22].

CONCLUSIONS

Renin-Angiotensin-System (RAS) plays a pivotal role in end-organ damage, including kidneys. Through a complex and multifaceted

Fig 2: MARVAL results (for same level of BP reduction)



UAER = urinary albumin excretion rate.

effect of Ang II, there is deterioration in renal function, manifested by proteinuria and changes in glomerular filtration rate. The degree of proteinuria is an independent cardiovascular risk factor contributing to cardiovascular events, stroke and death.

There is an overwhelming evidence that inhibition of RAS with ACEIs and ARBs results in slowing the progression of renal dysfunction and also a reversal of proteinuria in a significant number of patients with diabetes. The expectation is that it will positively contribute towards reduction of morbidity and mortality from renal disease. ARBs, which are relatively recent mode of RAS inhibitions, hold a better promise as these are better tolerated than ACEs and may afford better compliance over longer term.

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