Renoprotection with antihypertensive effect by inhibition of rennin - angiotensin system

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ABSTRACT

Hypertension is a common cause of chronic kidney disease (CKD) and even more common sequelae of CKD. It is essential to preserve renal function while controlling blood pressure. There is growing evidence that reduction and normalization of proteinuria is a key treatment goal for renal protection. Several clinical studies, mainly but not exclusively in diabetic patients were reviewed, subsequently suggested that anti-hypertensive agents inhibiting the renin–angiotensin system (RAS), such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs), achieved better renoprotection than other anti-hypertensive drugs. Inhibition of the renin-angiotensin system (RAS), either by ACE inhibitors or angiotensin-Receptors blocker (ARB) slows the progression of CKD by reducing the level of proteinuria in the diabetic and non-diabetic CKD resulting in less renal structural damage.

Keywords: Chronic kidney disease, Renin angiotensin system, Angiotensin receptors blocker. Angiotensin-converting enzyme inhibitor,
controlled clinical trials have demonstrated that inhibitors of the RAS, i.e. angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) ameliorate the progression of CKD [15,16]. Although some studies utilizing BP radiotelemetry showed renoprotection by ACEi or ARB was completely BP dependent in animal models, these observations do not exclude a role for the RAS blockade-mediated, BP independent mechanisms. There is ample evidence both in primary renal disease and in nephropathy of type 1 and type 2 diabetes that pharmacological blockade of the RAS by ACEi or ARB has BP-independent renoprotective effects [17, 18].

RAS Inhibition in Diabetic Nephropathy

Diabetes-related nephropathy occurs in 20–40% of patients with diabetes and is the leading cause of ESRD (End Stage Renal Disease) [19]. Persistent microalbuminuria has been shown to be a marker for the development of nephropathy in patients with type 2 disease. Additionally, microalbuminuria is well established as a marker for CVD risk. It is clear that inhibition of the renin-angiotensin system (RAS) is useful in slowing down the progression of nephropathy in patients with demonstrable microalbuminuria. Infact, the American Diabetes Association (ADA) is clear in recommending the use of RAS inhibition (with converting enzyme inhibitors or ARBs) in non-pregnant type 2 diabetic patients with microalbuminuria [19].

Remuzzi G [20] et.al conducted a study (BENEDICT study) reported that the use of the ACE inhibitor trandolapril in hypertensive, normoalbuminuric patients with type 2 diabetes was associated with a reduction in the development of diabetic nephropathy. Similarly Lewis EJ [21] et.al and Parving HH [2] et.al conducted a randomized clinical trial which shows that ARBs can reduce the rate of progression from microalbuminuria to macroalbuminuria and to ESRD in patients with type 2 diabetes.

Two high-quality, randomized studies compared reduction of ESRD in type 2 diabetic patients treated with ARB vs placebo. Brenner [22] and colleagues performed double blind randomized controlled studies enrolling 1513 type 2 diabetic patients with nephropathy in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study. The primary end point was the composite of the double of serum creatinine, ESRD, and death. Losartan showed a 16% reduction in the composite primary end point (95% CI, 2 to 28). While 25.5% of the placebo group reached a primary end point of ESRD, only 19.6% of the patients treated with losartan developed ESRD (relative risk reduction, 28% (95% CI, 11 to 42). These effects were independent of BP, which was similar in the two groups throughout the study.

There are several randomized controlled clinical studies (list shown in Table 1) which clearly demonstrates that inhibition of RAS either by ACEi or ARB is a key treatment goal for renal protection beyond B.P reduction.

KIDNEY PROTECTION BY INHIBITION OF RAS

All these experimental and clinical studies show BP independent renoprotective effects of ACEi and ARB. Recent researches have focused on mechanisms of protection of the kidney by inhibition of RAS. ACEi and ARB have each been shown to reduce glomerular capillary pressure and ameliorate glomerular hyperfiltration effectively [14]. Pharmaceutical reagents that block RAS reduce oxidative stress in the kidney. Inhibition of RAS has direct immunomodulatory effects [23-25]. Potential mechanisms of renoprotective effects of ACEi and ARB are listed below.

Renoprotective Mechanisms of ACEi and ARB

- Decrease of systemic BP
- Amelioration of glomerular hypertension and hyperfiltration
- Reduction of oxidative stress
- Direct immunomodulatory effects
- Reduction of proteinuria
- Improvement of oxygenation of the tubulointerstitium

CLINICAL IMPLICATION

Hypertension is a common coexisting condition among patients with CKD as either the primary etiology or as a secondary event. Epidemiological data have convincingly shown that blood pressure (BP) is linked to CKD [26, 27] and kidney disease-related mortality. Results of large-scale, randomized studies (shown above) support that Inhibition of the renin-angiotensin system (RAS), either by ACE inhibitors or angiotensin- Receptors blocker (ARB) slows the progression of CKD by reducing the level of proteinuria in the diabetic and non-diabetic CKD resulting in less renal structural damage.

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Table 1: Clinical Trial/Study showing Renoprotective effect of ARB and ACEi

<table>
<thead>
<tr>
<th>Trial/Study</th>
<th>Design</th>
<th>Subjects</th>
<th>No.</th>
<th>Drug</th>
<th>Dose</th>
<th>Primary End Point</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAAL</td>
<td>multicenter double-blind randomized placebo controlled</td>
<td>Type 2 diabetic patients with nephropathy</td>
<td>1,513</td>
<td>Losartan</td>
<td>50–100 mg</td>
<td>Doubling of serum creatinine level, ESRD, or death</td>
<td>ARB superior to placebo</td>
</tr>
<tr>
<td>ORIENT</td>
<td>multicenter double-blind randomized placebo controlled</td>
<td>Type 2 diabetic patients</td>
<td>577</td>
<td>olmesartan</td>
<td>10–40 mg</td>
<td>Doubling of serum creatinine level, ESRD, or death</td>
<td>ARB superior to placebo</td>
</tr>
<tr>
<td>MARVAL</td>
<td>multicenter double-blind randomized Active controlled</td>
<td>Type 2 diabetes and microalbuminuria, with or without hypertension,</td>
<td>332</td>
<td>Valsartan v/s Amlodipine</td>
<td>80mg v/s 5mg</td>
<td>percent change in Elevated urine albumin excretion (UAER)</td>
<td>Valsartan superior to Amlodipine</td>
</tr>
<tr>
<td>IDNT</td>
<td>Prospective randomized double-blind placebo controlled</td>
<td>Type 2 diabetic patients with nephropathy</td>
<td>1715</td>
<td>Irbesartan Amlodipine</td>
<td>75-150 mg v/s 2.5-5 mg</td>
<td>Doubling of serum creatinine level, ESRD, or death</td>
<td>ARB superior to placebo</td>
</tr>
<tr>
<td>ROADMAP</td>
<td>randomized double-blind placebo-controlled parallel-group multicenter</td>
<td>Type 2 diabetic patients</td>
<td>4449</td>
<td>olmesartan</td>
<td>40 mg</td>
<td>First onset of microalbuminuria</td>
<td>Olmesartan was associated with a delayed onset of microalbuminuria superior to placebo</td>
</tr>
<tr>
<td>Yayoi Nishida et al</td>
<td>Retrospective Database study</td>
<td>mild to moderate hypertension</td>
<td>6,724 v/s 11,069</td>
<td>Olmesartan v/s Candesartan</td>
<td>5-40 mg v/s 1-12 mg</td>
<td>Potassium, creatinine and urea nitrogen.</td>
<td>Both shows improvement in renal function (small)</td>
</tr>
<tr>
<td>Jan Galle et al</td>
<td>Prospective randomized double-blind multicentre parallel-group</td>
<td>Type 2 diabetes and overt nephropathy</td>
<td>885</td>
<td>telmisartan v/s valsartan</td>
<td>40-80 mg v/s 80-160 mg</td>
<td>24-h urinary protein excretion rate (UPER)</td>
<td>Similar renoprotection by both</td>
</tr>
<tr>
<td>AIPRI</td>
<td>multicenter double-blind randomized placebo controlled</td>
<td>Non-diabetic CKD</td>
<td>300 v/s 283</td>
<td>Benazepril</td>
<td>10 mg/day</td>
<td>Doubling of serum creatinine level or ESRD</td>
<td>ACEi superior to placebo</td>
</tr>
<tr>
<td>REIN</td>
<td>multicenter double-blind randomized placebo controlled</td>
<td>Non-diabetic CKD</td>
<td>352</td>
<td>Ramipril</td>
<td>2.5-5 mg/day</td>
<td>Decline in GFR</td>
<td>ACEi superior to placebo</td>
</tr>
</tbody>
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REFERENCES