

Treatment for Diabetic Nephropathy: Angiotensin Receptor Blockers do not have an Advantage over Angiotensin-Converting Enzyme Inhibitors

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Importance of inhibition of the RAS system

Inhibition of the renin-angiotensin system is essential in treating hypertension and delaying nephropathy. Since the 1980s, numerous studies have shown that the use of angiotensin-converting enzyme inhibitors has beneficial effects when treating hypertension and diabetic renal disease [1–3]. However, results of recently published trials – such as RENAAL (Reduction of End Points in NIDDM with Angiotensin II Antagonist Losartan), IDNT (Irbesartan Diabetic Nephropathy Trial), IRMA II (Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study II) – question whether angiotensin receptor type 1 blockers can replace ACE inhibitors as the agent of choice in treating diabetic nephropathy [4–6].

New clinical guidelines

According to the JNC-7 Report (May 2003), both ACE inhibitors and ARBs favorably affect the progression of diabetic nephropathy and reduce albuminuria in diabetic hypertension, but only ARBs have been shown to reduce progression to macroalbuminuria [7].

The American Diabetes Association guidelines, issued in January 2003, recommended that diabetic patients with albuminuria/nephropathy be treated with ACE inhibitors in the case of diabetes type 1, while in type 2 diabetes with albuminuria and renal failure (serum creatinine >1.5 mg/dl) the initial treatment of choice is ARBs [8].

ACE inhibitors as a first-choice renoprotective treatment

Lewis et al. [1] showed a relative risk reduction of 48% in doubling of serum creatinine by ACE inhibitors in patients with type 1 diabetes and nephropathy compared to placebo. The sub-study of this clinical trial [9], referring to a subgroup of 108 nephrotic patients (with daily proteinuria greater than 3.5 g), revealed a disproportionate randomization of nephrotic patients to the placebo group (66 vs. 42 patients, $P = 0.006$). Thus, the smaller number of patients who reached the endpoint in the captopril group may be related, at least partially, to the smaller number of high risk nephrotic patients in this group and not exclusively to the renoprotective action of captopril.

Powerful long-term trials on the course of nephropathy in type 2 diabetes prior to 2001 were disturbingly lacking. This therapeutic gap has now been filled by ARBs.

ARBs for renoprotective treatment

Diabetes mellitus type 2 is the single most common cause of end-stage renal disease in the western world [10,11]. Recent trial evidence has shown that in this group of patients ARBs slow the rate of progression of nephropathy and proteinuria [4,5] and also blunt an increase in microalbuminuria in patients with early diabetic nephropathy [6].

The RENAAL study [4] included 1,513 patients with type 2 diabetes, early renal failure and microalbuminuria. Compared with placebo, losartan significantly reduced proteinuria, ESRD, and new-onset congestive heart failure. Reduction of ESRD was 28% ($P = 0.002$). The RENAAL study is the only clinical trial to date to demonstrate that any drug is able to reduce statistically the incidence of ESRD as a single endpoint in diabetes, while trials using ACE inhibitors have not shown a statistically significant effect of ACE inhibitors on ESRD in diabetic nephropathy.

In the IDNT [5], irbesartan was better, not only than the placebo but also better compared to amlodipine in reducing the composite endpoint of doubling of serum creatinine, ESRD or death in 1,715 patients with type 2 diabetes, clinical proteinuria, and early renal insufficiency.

The IRMA II study [6] randomly assigned 590 hypertensive patients with type 2 diabetes and microalbuminuria to ARB irbesartan or placebo for 2 years. The risk of overt nephropathy in the patients treated with 300 mg irbesartan was reduced by 68%. This can be compared to the MicroHOPE study, where ramipril 10 mg/day was effective in only a 24% reduction of cases of overt nephropathy in a similar population [3]. It is important to note that overt nephropathy in the MicroHOPE study was defined as an albumin/creatinine ratio higher than 36 mg/mmol. Interestingly, when a more strict definition based on a 24 hour urine collection was applied (> 300 mg of albumin or >500 mg of protein/24 hours), reduction of overt nephropathy by ramipril did not reach statistical significance (22%, $P = 0.07$) [3].

Thus, where progression from microalbuminuria to overt nephropathy or from nephropathy to ESRD is considered, evidence-based medicine heavily favors ARBs. Moreover, growing

ACE = angiotensin-converting enzyme
ARBs = angiotensin receptor type 1 blockers

evidence supporting the beneficial role of ARBs not only in renal but also in cardiovascular protection has recently begun to appear in the literature. In the diabetic subpopulation of the LIFE trial, losartan was more effective than atenolol; it reduced total mortality by 39% and combined endpoint of cardiovascular death, myocardial infarction and stroke by 24% [12].

ARBs and ACE inhibitors vs. other drugs

In diabetic trials ACE inhibitors were found to be superior only to placebo [1–3] but not to any antihypertensive drug, such as beta-blocker in the UKPDS (UK Prospective Diabetes Study Group) [13] or calcium antagonist [14,15] in reducing renal endpoints.

Two trials of ARBs show that losartan was superior to the beta-blocker atenolol in reducing the incidence of new overt proteinuria in the LIFE study [12], and irbesartan was better than the calcium antagonist amlodipine in retarding development of renal failure in the IDNT [5].

ARBs vs ACE inhibitors: better tolerance

Direct comparisons between ARBs and ACE inhibitors in patients with renal diseases have been limited to the investigation of surrogate parameters as endpoints, such as proteinuria or adverse effects. Two recent trials that studied patients with type 2 diabetes and microalbuminuria emphasized the similarity of the effects of ARBs and ACE inhibitors on protein excretion [16,17]. ARBs are clearly better tolerated than ACE inhibitors, induce fewer adverse events and less frequently need to be withdrawn because of cough or angioneurotic edema [16,18,19]. The ARB valsartan increases serum potassium less than the ACE inhibitor lisinopril in diabetic patients with mild renal insufficiency [20].

Conclusions

ARBs proved to be effective in preventing progression of nephropathy in type 2 diabetic patients. According to several large clinical trials, the guidelines for treating diabetic nephropathy have now been changed. In type 1 diabetes, ACE inhibitors still remain the first-choice drugs, but in the case of intolerance they may be replaced by ARBs because of their effectiveness and excellent side effect profile. In type 2 diabetes, ARBs should now be considered first-choice drugs because of their unique ability to prevent ESRD. The clinical benefits in renal and cardiovascular protection indicate that these well-tolerated drugs are the most suitable for achieving newer strict therapeutic targets in the treatment of hypertension and for reducing renal damage in diabetic patients.

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