**Treatment for Diabetic Nephropathy: Angiotensin Receptor Blockers Preferred to Angiotensin-Converting Enzyme Inhibitors**

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**Key words:** diabetic nephropathy, angiotensin receptor blockers, angiotensin-converting inhibitors

The renin-angiotensin system has been shown to play a role in the pathogenesis of diabetic renal disease. Knowledge of the effects of local tissue as well as systemic RAS formed the basis for clinical trials that examined the question whether inhibition of RAS protects against the advent and progression of kidney disease in diabetes. On the whole, the trials provided a positive answer to this issue.

The renin-angiotensin system is activated by the release of renin from the juxtaglomerular apparatus in the kidney. Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is then converted by the action of angiotensin-converting enzyme to angiotensin II. Angiotensin II is also produced independently of ACE through the action of local tissue-specific enzymes such as chymase [1]. Angiotensin II, acting via the angiotensin-II receptor, is a potent vasoconstrictor and mediates hypertension and subsequent tissue remodeling. It further contributes to renal disease by stimulating transforming growth factor-beta expression, which leads to renal matrix expansion and fibrosis [2]. Angiotensin II-mediated aldosterone release further contributes to renal fibrosis, independent of blood pressure effects [3]. ACE inhibitors do not completely block the formation of angiotensin II, nonetheless they have renal and cardioprotective effects that are mediated, at least in part, by the action of kinins and nitric oxide whose production they enhance [4].

Renal protection

Given the role of RAS in hypertension and renal disease, ACE inhibitors and AT-I blockers are options for hypertension control and renal protection. The controversy, mainly in type 2 diabetes, relates to which of the two is superior for the prevention of kidney loss – ACE inhibitors or AT-I antagonists.

The effects of ACE inhibition on renal disease in type 1 diabetes

Clinical studies have shown that ACE inhibitors have a renoprotective effect in patients with type 1 diabetes [5–8]. In people with microalbuminuria, the degree of proteinuria is reduced and progression to overt nephropathy is slowed, even in those who are normotensive [5–8]. In patients with a serum creatinine >1.5

mg/dl, progression of renal insufficiency is retarded. [8]. Captopril reduces the risk for a combined endpoint of death, dialysis or transplantation by more than 50%. ACE inhibitors lead to remission of proteinuria and stabilize renal function with a relative risk reduction of 56% compared to placebo [9].

The effects of ACE inhibition on renal disease in type 2 diabetes

Prevention of diabetic nephropathy

There is evidence that lowering of blood pressure [10] and ACE inhibition regardless of blood pressure [11] prevent the onset of diabetic nephropathy. Indeed, the results of the MICRO-HOPE study, which examined the effects of ramipril versus placebo [11], suggest that even normoalbuminuric type 2 diabetic patients should be treated with ACE inhibitors primarily to prevent cardiovascular events – the renoprotective effect being an added benefit.

Prevention of progression of renal disease

In normotensive and hypertensive patients with type 2 diabetes, with and without microalbuminuria, ACE inhibitors delay progression to overt proteinuria and preserve renal function [12–14].

In the CALM study, microalbuminuric type 2 patients received lisinopril, candesartan, or a combination of the two. Both drugs lowered blood pressure and albumin excretion to a similar degree, lisinopril being slightly more effective. The combination was significantly more effective than either drug alone: 24% decrease in albumin excretion with candesartan alone, 39% with lisinopril alone, and 50% with the combination. The difference between lisinopril alone and the combination was not statistically significant [15].

In patients with overt nephropathy, ACE inhibitors have been shown to decrease proteinuria and preserve the glomerular filtration rate [16]. This is supported by histologic evidence [17]. However, large prospective long-term clinical trials to substantiate this beneficial effect are lacking.

In this specific patient population, evidence for the beneficial effects of AT-I blockade as manifested in the RENAAL [18] and IDNT [19] trials is impressive and may indeed suggest an advantage over ACE inhibitors. However, it must be remembered that no long-term large randomized trial using ACE inhibitors has been conducted in this population and no head-to-head comparison between ACE inhibitors and angiotensin receptor blockers exists. At present the
AT-1 blocker trials are the only basis for evidence-based recommendations in overt nephropathy and are likely to remain so.

ACE inhibitors versus the “others”: the added value in nephropathy
More than 60% of people with diabetes also have hypertension, which plays a major role in the onset as well as progression of diabetic nephropathy, the leading cause of end-stage renal disease [20]. The beneficial effects of blood pressure lowering on cardiovascular outcome in addition to the preservation of kidney function were demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS) in which hypertensive type 2 diabetics were randomized to “tight” (144/82 mmHg) versus ‘less tight’ control (154/87 mmHg). There was a significant reduction in the risk for any diabetes endpoint, diabetes-related death, congestive heart failure and stroke, as well as a significant 37% reduction in microvascular disease in the tight-control group. Twenty-nine percent of the patients required three or more drugs to achieve tight control [21]. Blood pressure targets as well as macromolecular or microvascular outcomes were similarly achieved with enalapril or metoprolol, however patients treated with beta-blockers gained more weight and more often required additional glucose-lowering medication than patients on enalapril [21].

A sub-study of the Appropriaten Blood Pressure Control in Diabetes (ABCD) trial randomized 470 diabetic patients to nisoldipine or enalapril. The achieved blood pressure was the same, however there was a higher rate of myocardial infarction in the nisoldipine group [22].

The Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) was an open-label study of 380 hypertensive type 2 patients randomly assigned to fosinopril or amlodipine [23]. Despite the fact that systolic blood pressure control was better in the amlodipine group, the fosinopril group had fewer combined cardiovascular events, although total mortality, renal function and albumin excretion did not differ.

A subgroup analysis of 572 diabetics in the Captopril Prevention Project (CAPP) [24], which randomly assigned people with hypertension to captopril or beta-blockers and diuretics, found similar blood pressure in all groups, however in the ACE inhibitor group the risk for all-cause mortality, cardiovascular events and myocardial infarction was lower.

All of the above constitute convincing evidence for the use of ACE inhibitors as first-line drugs in the management of hypertension in diabetics with and without renal disease.

ACE inhibition and AT-1 antagonists in combination
ACE inhibitors and AT-1 antagonists interrupt RAS by different mechanisms, and their combination is therefore expected to produce better results than the use of either alone. Recent evidence from clinical trials supports this hypothesis [15,25].

Conclusion
The relative benefits of the various antihypertensive drugs in the prevention and treatment of diabetic renal disease are mainly academic, since at least three such agents are required to achieve the necessary blood pressure targets that have been shown to afford renal protection. Nonetheless, from the evidence presented it is clear that ACE inhibitors are the first-line treatment of choice for both type 1 and type 2 diabetic hypertensive patients with and without microalbuminuria. They also constitute the best choice for normotensive diabetic patients in terms of both renal and cardiovascular protection. In addition, their low cost makes them more attractive option than the more expensive AT-I blockers. AT-I antagonists are an option for treating ACE-intolerant patients and for type 2 diabetic patients with overt nephropathy or left ventricular hypertrophy. These conclusions are mirrored in the current recommendations of the American Diabetes Association [26] and the Israel Hypertension Society [27]. The added benefit of combining ACE inhibitors and AT-I antagonists needs to be strengthened by additional long-term randomized studies.

References

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When I'm good, I'm very, very good, but when I'm bad, I'm better

Mae West (1892-1980), American actress and mistress of the double entendre who claimed to have written all her own lines. After appearances in vaudeville, she wrote and produced a play, Sex (1926), for which she spent a week in prison for 'corrupting the morals of youth'. She transformed her vampish persona to the screen in a series of successful films.

**Capsule**

**A genetic element to leprosy?**

An international team led by Canadian scientists has identified a DNA region that renders people susceptible to leprosy. This region contains part of two genes that have been linked to certain forms of Parkinson's disease, suggesting that both disorders may share some biochemical pathways. Leprosy affects around 1 million people worldwide. The WHO has identified 91 countries in which leprosy infection is prevalent, while concerns have been raised that the disease may make a comeback in places such as Canada. It has long been suspected that the disorder has a strong genetic component; a leprosy susceptibility locus to chromosome 6 region q25-q26 was recently discovered. The same authors who mapped this locus decided to investigate the region further. They took blood samples from 197 Vietnamese families composed of two parents and one leprosy-affected child. Then they analyzed single nucleotide polymorphisms (SNPs) within the chromosome 6 region. They found a significant association between leprosy and 17 markers located in a DNA block 80 kb long. This DNA stretch included the Parkinson's disease gene PARK2 and the co-regulated gene PACRG. Possession of as few as two of the 17 risk alleles was highly predictive of leprosy. These findings were fully reproduced in an independent sample of 587 unrelated Brazilian individuals affected by leprosy. Moreover, none of 388 unaffected controls were found to have this particular DNA stretch. In a further experiment, the researchers found that the PARK2 gene was expressed by human Schwann cells and macrophages, which are the primary host cells of Mycobacterium leprae.

**Nature** 2004;427:636

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