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

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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-1 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

RAS = renin-angiotensin system
ACE = angiotensin-converting enzyme
AT-I = angiotensin-I

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-I 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 macrovascular 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 Appropriate 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 (CAPPP) [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-I antagonists in combination

ACE inhibitors and AT-I 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 a 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

1. Weir MR, Dzau VJ. The renin-angiotensin-aldosterone system: a specific target for hypertension management. *Am J Hypertens* 1999;12(Suppl): 205–13S.
2. Border WA, Noble NA. Interaction of transforming growth factor-beta and angiotensin II in renal fibrosis. *Hypertension* 1998;31:181–8.
3. Hostetter T, Rosenberg H, Ibrahim H, Juknevicius I. Aldosterone in progressive renal disease. *Semin Nephrol* 2001;21:573–9.
4. Hutchison FN, Cui X, Webster SK. The anti-proteinuric action of angiotensin-converting enzyme is dependent on kinin. *J Am Soc Neprol* 1995;6:1216–22.
5. Parving HH, Hommel E, Smidt UM. Protection of kidney function and decrease in albuminuria by captopril in insulin-dependent diabetics with nephropathy. *Br Med J* 1988;297:1086–91.
6. Viberti G, Mogensen CE, Groop LC, Pauls JF. European Microalbuminuria Captopril Study Group. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes and microalbuminuria. *JAMA* 1994;271:275–9.
7. The Microalbuminuria Captopril Study Group. Captopril reduces the risk of nephropathy in IDDM patients with microalbuminuria. *Diabetologia* 1996;39:587–93.
8. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329: 1456–62.
9. Lewis JB, Berlt T, Bain RP. Collaborative Study Group. Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. *Am J Kidney Dis* 1999;34:308–14.
10. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and stroke. *Kidney Int* 2002;61:1086–97.
11. Heart Outcomes Prevention Evaluation Study Investigators. Effects of Ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253–9.
12. Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. *Ann Intern Med* 1998;128:982–8.
13. Sano T, Kawamura T, Matsumae H, et al. Effects of long-term enalapril treatment on persistent micro-albuminuria in well-controlled hypertensive and normotensive NIDDM patients. *Diabetes Care* 1994;17:420–4.
14. Ahamad J, Siddiqui MA, Ahmad H. Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. *Diabetes Care* 1997;20:1576–81.

15. Mogensen CE, Neldam S, Tikkanen I, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: The Candesartan and Lisinopril Microalbuminuria (CALM) study. *Br Med J* 2000;321:1440–4.

16. Yokoyama H, Tomonaga O, Hirayama M, et al. Predictors of the progression of diabetic nephropathy and the beneficial effects of angiotensin-converting enzyme inhibitors in NIDDM patients. *Diabetologia* 1997;40:405–11.

17. Cordonnier DJ, Pinels N, Barro C, et al. Expansion of cortical interstitium is limited by converting enzyme inhibition in type 2 diabetic patients with glomerulosclerosis. *J Am Soc Nephrol* 1999;10:1253–63.

18. Brenner B, Cooper M, de Zeeuw D, et al., for the RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861–9.

19. Lewis E, Hunsicker L, Clarke W, et al., for the Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851–60.

20. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. *N Engl J Med* 1999;341:1127–33.

21. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J* 1998;317:703–13.

22. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin dependent diabetes and hypertension. *N Engl J Med* 1998;338:645–52.

23. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998;21:597–603.

24. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomized trial. *Lancet* 1997;353:611–16.

25. Jacobsen P, Andersen S, Jensen BR, Parving HH. Additive effect of ACE inhibition and angiotensin II receptor blockade in type I diabetic patients with diabetic nephropathy. *J Am Soc Nephrol* 2003;14:992–9.

26. American Diabetes Association: Diabetic nephropathy. *Diabetes Care* 2003;26:S94–8.

27. Stern N, Grossman E. Indications for the use of AT-1 blockers in hypertension. *Harefuah* 2003;142: 09–11 (Hebrew).

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