



## Changing the course of diabetic nephropathy: angiotensin-converting enzyme inhibition in type I diabetic renal disease

**D**IABETES, with its attendant complications of kidney and heart disease, stroke, blindness, and amputation, continues to be a major public health concern today, affecting 100 to 150 million people worldwide according to the International Diabetes Foundation. In the United States, there are 14 million patients with diabetes, 10% of whom are insulin-dependent (type I) and 90% non-insulin-dependent (type II). It is estimated that 30% to 40% of type I and 20% to 30% of type II diabetic patients will develop nephropathy, with a significant number of these patients progressing to end-stage renal disease (ESRD).<sup>1,2</sup> In the United States, ESRD due to diabetes is increasing at almost twice the average rate for all causes of ESRD, and in 1990 constituted almost 35% of all new ESRD patients—over 15 000 new patients per year.<sup>3</sup>

Diabetic patients with ESRD face severe personal, social, and financial burdens. In general, patients with ESRD have from one fourth to one fifth the life expectancy of the general population, and the survival rate for diabetic patients with ESRD is one and a half to two and a half times lower than for nondiabetic patients with ESRD.<sup>3-6</sup>

In addition to increasing morbidity, decreasing life expectancy, and reducing quality of life, ESRD is expensive. In the United States, government payments for care of ESRD patients totaled \$7.2 billion in 1990, with a per-patient cost of \$44 800 per year.<sup>3</sup> Thus, the importance of *preventing* the renal complications of diabetes and *delaying* the development of ESRD due to diabetic nephropathy is of obvious importance.

A landmark study has been published that should

dramatically improve the fate of diabetic patients with kidney disease. The Collaborative Study Group on the Effect of Angiotensin-Converting Enzyme Inhibition on Diabetic Nephropathy<sup>7</sup> now has provided convincing evidence that angiotensin-converting enzyme (ACE) inhibition with captopril preserves renal function in patients with type I diabetes and, more importantly, reduces the risk of progressing to ESRD or death.

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### RATIONALE FOR ACE INHIBITION IN TREATING DIABETIC NEPHROPATHY

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Hypertension and diabetes mellitus are commonly associated diseases. As many as 70% of diabetic patients are hypertensive. It has long been known that there is a strong interrelationship between hypertension, diabetes, and nephropathy.<sup>8-10</sup> Elevated blood pressure not only may result from renal disease per se but also has been shown to be a major risk factor for the progression of renal disease in diabetic patients.<sup>11-13</sup> In fact, all levels of hypertension are associated with declining renal function.

Almost 35 years ago, Stalder and Schmid<sup>14</sup> noted that patients with early-stage diabetes had elevated glomerular filtration rates. This clinical observation of "glomerular hyperfiltration" was subsequently confirmed by Mogensen and Christiansen.<sup>15,16</sup> In the early 1980s, basic experimental research totally unrelated to diabetes demonstrated that increased filtration and pressure in the glomerulus promotes renal damage and is responsible for progressive renal failure.<sup>17,18</sup> These experimental studies in rats focused on the adaptation of the kidney to the acute reduction of renal mass induced by renal ablation.

Elevations of glomerular capillary plasma flow and glomerular capillary pressure were noted as part of the pathophysiologic response to reduced numbers of nephrons. These alterations in glomerular capillary hemodynamics were also observed with experimental renal ablation in diabetic animals<sup>19</sup> and were associated with the subsequent development of proteinuria, decreased glomerular filtration rate, and glomerulosclerosis.

Thus, it was suggested that glomerular damage in patients with diabetes mellitus might be the result of a state of chronic glomerular hyperfiltration in a manner similar to that which was described in the experimental model of renal ablation.<sup>20</sup> Subsequent experimental observations in rats with reduced renal mass indicated that lowering blood pressure with an ACE inhibitor could normalize glomerular capillary pressures and attenuate glomerular injury.<sup>21,22</sup> This provided strong rationale for the notion that ACE inhibitors might be useful in the treatment of patients with diabetic nephropathy.

Pertinent to the consideration of therapeutic intervention in diabetes was the observation that, in contrast to the effects of ACE inhibition in modulating glomerular hemodynamic and structural changes after renal ablation, other antihypertensive agents appeared to have little effect. Anderson et al<sup>23,24</sup> reported that controlling systemic blood pressure in the experimental ablation model using reserpine, hydralazine, and hydrochlorothiazide did *not* result in the same positive effects as had been reported with lowering the systemic blood pressure with ACE inhibitors (enalapril or captopril). The experimental animals whose blood pressure was lowered without the use of an ACE inhibitor did not manifest similar improvement in the course of proteinuria or glomerulosclerosis as did animals treated with ACE inhibitors. The authors attributed these benefits of ACE inhibition to relative efferent glomerular arteriolar dilatation, which would be expected to occur with ACE inhibition but not when other antihypertensive agents are used. These interpretations agree with the concept that ACE inhibitors have specific intrarenal effects, independent of their systemic antihypertensive properties.

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#### THE EFFECT OF ACE INHIBITION WITH CAPTOPRIL IN PATIENTS WITH TYPE I DIABETIC NEPHROPATHY

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The principles derived from the use of ACE inhibition in experimental diabetes mellitus was the ra-

tionale for the Collaborative Study Group's multicenter controlled clinical trial of the effect of captopril on diabetic nephropathy. The enthusiasm generated from the experimental observations discussed above had prompted many nephrologists to start using ACE inhibitors in diabetic patients as well as in patients with nondiabetic chronic renal disease, in the hope of delaying progression to ESRD. Clinical studies by Taguma et al,<sup>25</sup> Parving et al,<sup>26,27</sup> Bauer et al,<sup>28</sup> and Björck et al<sup>29,30</sup> indicated that use of captopril or enalapril reduced protein excretion and slowed the progression of renal disease in patients with diabetic nephropathy. In addition, a meta-analysis of 100 clinical trials showed that ACE inhibition reduced urinary protein excretion and preserved glomerular filtration rate more consistently than other antihypertensive drugs with similar blood pressure control in patients with diabetes. The beneficial effects of ACE inhibitors on renal function were present in patients with type I or type II diabetes, in patients with or without hypertension, and in patients with early or more advanced diabetic nephropathy.<sup>31</sup>

Given this favorable preliminary evidence for the benefits of ACE inhibitors in the treatment of diabetic nephropathy, the Collaborative Study Group conducted a multicenter trial to determine whether long-term administration of captopril to patients with type I diabetes with nephropathy prevents the progression of renal disease and improves their clinical outcome as reflected by a reduction in mortality and ESRD (dialysis or renal transplantation).<sup>7</sup> The hypothesis of the Collaborative Study Group's trial was that captopril would reduce the progression of renal disease in patients with diabetic nephropathy by a mechanism that is independent of its systemic antihypertensive effect.

The study design was a randomized, double-blind, placebo-controlled trial, which enrolled 409 patients with type I diabetes and *overt* nephropathy. Patients 18 to 49 years of age were eligible if they had had insulin-dependent diabetes mellitus for at least 7 years, with an onset before the age of 30 years, and had diabetic retinopathy, urinary protein excretion of 500 mg/24 hours or more, and a serum creatinine concentration of 2.5 mg/dL or less. If patients did not have diabetic retinopathy, they were required to undergo a renal biopsy to establish the diagnosis of diabetic nephropathy. Thus, these patients had clinical evidence of significant diabetic renal disease.

The study was conducted in 30 centers in the United States and Canada. Patient enrollment began in December 1987 and ended in September 1990. Patient follow-up was completed in September 1992. Every patient was followed up for a minimum of 1.8 years, with a maximum follow-up of 4.8 years and a median follow-up of 2.7 years.

Eligible patients were randomized to receive captopril 25 mg three times a day or matching placebo. Additional antihypertensive medications could be given to both groups to control blood pressure to predefined levels. The use of calcium channel blockers was not allowed (since some calcium channel blockers had been reported to have favorable effects on renal function), and ACE inhibitors were not allowed other than the "study medication" (captopril or placebo).

Two hundred and two patients were randomized to the placebo group, and 207 patients were randomized to the captopril group. Fifty-three percent of the patients were men, 47% women, and 90% white (consistent with the demographics of type I diabetes in the general population). At entry, the mean age was 35 years, duration of diabetes mellitus 22 years, total urinary protein excretion between 2.5 and 3.0 g/24 hours (indicating substantial proteinuria), baseline serum creatinine concentration 1.3 mg/dL, and iothalamate clearance as a reflection of glomerular filtration rate 76 mL/min/1.73 m<sup>2</sup>. Seventy-five percent of patients had preexisting hypertension.

The goals of antihypertensive treatment included a seated office diastolic pressure of less than 90 mm Hg in all patients. The systolic blood pressure was reduced to less than 140 mm Hg in most patients; if the baseline systolic pressure was greater than 150 mm Hg, a decrease of at least 10 mm Hg was required. The maximum allowed systolic blood pressure was 160 mm Hg. Other than the "study medication," drugs used to treat hypertension included diuretics, beta blockers, central or peripheral alpha adrenergic agents, and peripheral vasodilators such as hydralazine or minoxidil. Excellent blood pressure control was achieved in both randomization cohorts, and there were no significant differences in blood pressure control in the patients who were hypertensive at entry between the captopril and placebo groups.

The primary outcome of the study was the time to doubling of the entry serum creatinine concentration (corresponding to halving the glomerular filtra-

tion rate); the secondary outcome was the time to reach ESRD or death.

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#### RESULTS OF THE TRIAL

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During the trial, 68 patients doubled their baseline serum creatinine concentrations, 25 in the captopril group and 43 in the placebo group. Captopril significantly reduced the risk of doubling the serum creatinine concentration by 48.5% ( $P = .007$ ) compared with placebo. Two years after randomization, 14.4% of patients receiving placebo had doubled their entry serum creatinine concentrations, in contrast to 6.4% of captopril-treated patients. At 3 years, 20.8% of patients receiving placebo doubled their entry serum creatinine concentrations, in contrast to 12.8% of captopril-treated patients. At the end of the trial, 65 patients had developed ESRD or died, 23 in the captopril group and 42 in the placebo group. Captopril significantly reduced the risk of ESRD or death by 50.5% ( $P = .006$ ) compared with placebo. Doubling of the serum creatinine concentration was a bad omen: the median time to reaching ESRD after doubling of the serum creatinine concentration was 9.3 months. Eighty percent of patients who went on to ESRD did so within one and a half years after doubling their serum creatinine concentrations.

The effect of captopril on reducing the risk of doubling the baseline serum creatinine concentration and of reaching ESRD or dying was assessed over a wide range of baseline serum creatinine concentrations. To the surprise of many of the investigators, patients with higher baseline serum creatinine concentrations ( $> 1.5$  mg/dL) who received captopril had a greater risk reduction for doubling their serum creatinine concentrations or for reaching ESRD or death in comparison to patients with lower baseline serum creatinine concentrations. As the baseline serum creatinine concentration increased from 1.0 to 2.25 mg/dL, the effect of captopril in reducing the risk of doubling the serum creatinine concentration increased from 17% to over 75%. As the baseline serum creatinine concentration increased from 1.0 to 2.25 mg/dL, the effect of captopril in reducing the risk of reaching ESRD or death increased from 6.7% to over 75%. Although patients with higher entry serum creatinine concentrations had greater benefits for the duration of the study, one cannot rule out similar benefits for patients with lower baseline serum creatinine concen-

trations had the study continued for a longer period of time. For patients with less advanced renal disease at baseline, progression of the renal disease is expected to take longer to develop than in patients with more advanced renal disease.

In addition to the broad conclusions described above, the effect of preexisting hypertension on doubling of baseline serum creatinine concentrations was also assessed. Captopril was associated with a 47.7% reduction in risk of doubling the serum creatinine concentration in hypertensive patients and a 58.2% reduction in risk in normotensive patients. Thus, the beneficial effect of captopril was independent of the existence of hypertension. The rate of increase in serum creatinine concentration and rate of decline in 24-hour creatinine clearance were worse for patients in the placebo group than in the captopril-treated patients. The mean percent reduction from baseline in urinary protein excretion was also significantly greater in the captopril-treated patients.

Adverse effects in this study were minimal and essentially the same in both randomization cohorts: specifically, there were only three episodes of hyperkalemia (defined as an increase in the serum potassium concentration to  $> 6.0$  mEq/L), all in the captopril group. Despite the use of conventional antihypertensive drugs (diuretics, beta blockers, clonidine) and the absence of calcium channel blockers in the antihypertensive regimens, only four patients reached a "failure to control blood pressure" stop-point.

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#### LESSONS LEARNED

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What then are the lessons learned from *The Study of The Effect of Angiotensin-Converting Enzyme Inhibition on Diabetic Nephropathy*? The obvious lessons are that long-term oral administration of captopril to diabetic patients with nephropathy delays the progression of renal disease, improves clinical outcome, protects the kidney, and demonstrates an acceptable safety profile. My conclusion is that all patients with documented diabetic glomerulopathy should be treated with an ACE inhibitor unless they cannot tolerate it.

Do these results in type I diabetes apply to type II diabetes as well? Type I diabetes was chosen because the natural history of nephropathy in type I diabetes has been well defined and certainly better defined than for type II diabetes. Although further investi-

gations will be required to confirm similar benefits in type II diabetes, most experts agree that the pathology of diabetic kidney disease appears to be similar in both type I and type II diabetes.<sup>32</sup> In addition, preliminary evidence suggests that diabetic nephropathy in type II diabetes follows a similar time course, except that it occurs later in life.<sup>33,34</sup> Accordingly, and until prospective trials are done regarding the use of ACE inhibitors in type II diabetes, my bias would be to treat such patients with captopril when the clinical evidence for diabetic renal disease seems secure. Whether or not the results of this study apply to other nondiabetic glomerular diseases is conjectural, but the experimental underpinnings supporting the use of ACE inhibitors in nondiabetic glomerular diseases are certainly present.

But there are other lessons. This study demonstrates that carefully designed collaborative trials with strong leadership and rigorous monitoring can make major contributions to the care of our patients. Good collaborative studies are feasible. Physician collaborators in such study groups relinquish their biases and clinical habits and, instead, follow a preset protocol agreed to by compromise. Our patients, the real heroes of such collaborative studies, willingly and without selfishness agreed to take the chance of being randomized to the group that might not derive immediate benefits. Finally, basic research must continue to be funded so that clinical questions might derive from such research, even if the basic research does not have an obvious clinical application. These lessons from the study of captopril in type I diabetic nephropathy take us from bench to bedside in our endeavor to find cures for disease and improve the quality of life for our patients.

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#### REFERENCES

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1. Epstein M, Sowers Jr. Diabetes mellitus and hypertension. *Hypertension* 1992; 19:403-418.
2. Nelson RG, Newman JM, Knowler WC, et al. Incidence of end-stage renal disease in type II (non insulin dependent) diabetes mellitus in Pima Indians. *Diabetologia* 1988; 31:730-736.
3. United States Renal Data System 1993 Annual Report. Bethesda, Md; The National Institute of Diabetes and Digestive and Kidney Diseases; March, 1993.

4. Marks HH. Longevity and mortality of diabetics. *Am J Public Health* 1965; 55:416-423.
5. Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of 31. *Diabetologia* 1978; 14:363-370.
6. Andersen AR, Andersen JK, Christiansen JS, Deckert T. Prognosis for juvenile diabetics with nephropathy and failing renal function. *Acta Med Scand* 1978; 201:131-134.
7. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD, for the Collaborative Study Group. The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; 329:1456-1462.
8. Working Group on Hypertension in Diabetes. Statement on hypertension in diabetes mellitus. *Arch Intern Med* 1987; 147:830-842.
9. National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group Report on Hypertension and Chronic Renal Failure. *Arch Intern Med* 1991; 151:1280-1287.
10. Sowers JR, Levy J, Zemel MB. Hypertension and diabetes. *Med Clin North Am* 1988; 72:1299-1414.
11. Parving H-H, Hommel E. Prognosis in diabetic nephropathy. *Br Med J* 1989; 299:230-233.
12. Mogensen CE. Renal function changes in diabetes. *Diabetes* 1976; 25(Suppl 2):872-879.
13. Ravid M, Savin H, Lang R, Jutrin I, Shoshana L, Lishner M. Proteinuria, renal impairment, metabolic control, and blood pressure in type 2 diabetes mellitus. *Arch Intern Med* 1992; 152:1225-1229.
14. Stalder G, Schmid R. Severe functional disorders of glomerular capillaries and renal hemodynamics in treated diabetes mellitus during childhood. *Ann Pediatr* 1959; 193:129-138.
15. Mogensen CE. Glomerular filtration rate and renal plasma flow in short-term and long-term juvenile diabetes mellitus. *Scand J Clin Lab Invest* 1971; 28:91-100.
16. Christiansen JS, Gammelgaard J, Frandsen M, Parving H-H. Increased kidney size, glomerular filtration rate and renal plasma flow in short-term insulin-dependent diabetics. *Diabetologia* 1981; 20:451-456.
17. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 1981; 241:F85-F93.
18. Dworkin LD, Feiner HD. Glomerular injury in the uninephrectomized spontaneously hypertensive rat. A consequence of glomerular capillary hypertension. *J Clin Invest* 1986; 77:797-809.
19. Zatz R, Meyer TW, Rennke HG, Brenner BM. Predominance of hemodynamic rather than metabolic factors in the pathogenesis of diabetic glomerulopathy. *Proc Natl Acad Sci USA* 1985; 82:5963-5967.
20. Hostetter TH, Rennke HG, Brenner BM. The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. *Am J Med* 1982; 72:375-380.
21. Anderson S, Meyer TW, Rennke HG, Brenner BM. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest* 1985; 76:612-619.
22. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 1986; 77:1925-1930.
23. Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibition: Arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest* 1986; 77:1993-2000.
24. Anderson S, Rennke HG, Garcia DL, Brenner BM. Short and long term effects of antihypertensive therapy in the diabetic rat. *Kidney Int* 1989; 36:526-536.
25. Taguma Y, Kitamoto Y, Futaki G, et al. Effect of captopril on heavy proteinuria in azotemic diabetics. *N Engl J Med* 1985; 313:1617-1620.
26. Parving H-H, Hommel E, Smidt UM. Protection of kidney function and decrease in albuminuria by captopril in insulin dependent diabetics with nephropathy. *Br Med J* 1988; 297:1086-1091.
27. Parving H-H, Hommel E, Nielsen MD, et al. Effect of captopril on blood pressure and kidney function in normotensive insulin dependent diabetics with nephropathy. *Br Med J* 1989; 299:533-536.
28. Bauer JH, Reams GP, Hewett J, et al. A randomized, double-blind, placebo-controlled trial to evaluate the effect of enalapril in patients with clinical diabetic nephropathy. *Am J Kidney Dis* 1992; 20:443-457.
29. Björck S, Nyberg G, Mulec H, Granerus G, Herlitz H, Aurell M. Beneficial effects of angiotensin converting enzyme inhibition on renal function in patients with diabetic nephropathy. *Br Med J* 1986; 293:471-474.
30. Björck S, Mulec H, Johnsen SA, Nordén G, Aurell M. Renal protective effect of enalapril in diabetic nephropathy. *Br Med J* 1992; 304:339-343.
31. Kasiske BL, Kalil RSN, Ma JZ, Liao M, Keane WF. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann Intern Med* 1993; 118:129-138.
32. Gambara V, Mecca G, Remuzzi G, Bertani T. Heterogeneous nature of renal lesions in type II diabetes. *J Am Soc Nephrol* 1993; 3:1458-1466.
33. Hasslacher C, Ritz E, Wahl P, Michael C. Similar risks of nephropathy in patients with type I or type II diabetes mellitus. *Nephrol Dial Transplant* 1989; 4:859-863.
34. Kunzelman CL, Knowler WC, Pettit JD, et al. Incidence of proteinuria in type 2 diabetes mellitus in the Pima Indians. *Kidney Int* 1989; 35:681-687.