Effects of Antihypertensive Drugs on Renal Function in Patients With Diabetic Nephropathy

Reinhard G. Bretzel

Hypertension occurs about twice as frequently in diabetics as in the general population, with a prevalence of approximately 25% in young patients with insulin-dependent diabetes mellitus (IDDM) and 50% in patients with newly diagnosed non-insulin-dependent diabetes mellitus (NIDDM). Studies strongly suggest that hypertension is involved in the progression and perhaps the onset of diabetic nephropathy, which is a major cause of illness and premature death in diabetic patients, largely through accompanying cardiovascular disease and end-stage renal failure.

A large body of evidence has accumulated that emphasizes the beneficial effects of antihypertensive treatment in reducing proteinuria and preserving renal function in both IDDM and NIDDM. It appeared that angiotensin converting enzyme inhibitors and certain calcium antagonists, notably nondihydropyridine, calcium antagonists, and second-generation dihydropyridine calcium antagonists, produce a more beneficial effect on nephropathy in terms of reducing proteinuria and slowing progression to renal failure. These drugs are attributed nephroprotective capacity beyond their systemic blood pressure lowering effects, and initial clinical trials with combinations have revealed additive effects on reduction in albuminuria and have led to the lowest rate of decline in glomerular filtration rates with the lowest incidence of adverse effects. Am J Hypertens 1997;10:208S–217S © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: Diabetic nephropathy, insulin-dependent diabetes mellitus (IDDM), non–insulin-dependent diabetes mellitus (NIDDM), hypertension, antihypertensive therapy, renal function.

Diabetic nephropathy is now the commonest single cause of end-stage renal disease (Table 1). The most recent report of the United States Renal Data System (USRDS) shows that, in 1992, 33.8% of all new patients accepted for renal replacement therapy were either insulin-dependent diabetes mellitus (IDDM) or non–insulin-dependent diabetes mellitus (NIDDM) patients.1 The recently available European Dialysis and Transplantation Association Registry data for Europe show that the number of diabetic patients alive on renal replacement therapy now is likely to be approached in 100,000 cases.2 The overall European rate of new patients accepted for renal replacement therapy was recorded as 17% for diabetics2 in 1992. A survey of 28 hemodialysis units all over Germany report that in the years 1985 to 1987, 24.2% (16.6% to 41.6%) of individuals newly entering dialysis programs were diabetic patients, of whom 34% had IDDM and 66% NIDDM.3 The estimated incidence of terminal renal failure with diabetes in a period of January 1993 to June 1994 was recently described as 52 per million per
The pathogenesis of diabetic nephropathy is multifactorial, and hypertension is one of the most relevant factors involved in the progression of diabetic nephropathy and in the development of end-stage renal disease in both IDDM and NIDDM. The kidney of the diabetic patient is more susceptible to any threshold, and because these individuals carry an increased risk of atherosclerosis and cardiovascular disease, it has been proposed that blood pressure control should commence as early as possible and, at the latest, when microalbuminuria becomes apparent.

PATHOGENESIS AND RISK FACTORS OF DIABETIC NEPHROPATHY

The pathogenesis of diabetic nephropathy is still not fully understood but is likely multifactorial. Intrarenal hemodynamic alterations, accumulation of sorbitol, and glycosylation of glomerular proteins are all thought to be involved in the pathogenesis of diabetic nephropathy. In insulin-dependent diabetic patients with poor glucose control, which may initially increase albumin excretion rate, an early rise of arterial pressure and smoking were implicated in the development of persistent microalbuminuria.

There is evidence that genetic predisposition plays a major role in development of diabetic nephropathy, clustering within families, both in IDDM and NIDDM. The responsible gene is not known, but the genes of the renin-angiotensin systems have been considered candidate genes. However, recent data that in patients with IDDM the I/D polymorphism in the angiotensin converting enzyme (ACE) gene is related to the presence of nephropathy was not confirmed in another study. Furthermore, it has been suggested that the risk of developing clinical nephropathy in IDDM patients is associated with a genetically determined predisposition to essential hypertension mediated by an altered Na/Li countertransport activity assessed in red blood cells, whereas in two other studies these data could not be confirmed.

Hyperglycemia and hypertension play a crucial part in the development and progression of diabetic nephropathy (see Figure 1). Growth factors and, among them, transforming growth factor–β as a key factor, may act as mediators between hyperglycemia/hypertension and the stimulation of mesangial cells towards overproduction of extracellular matrix (collagen types IV and V). It has been clearly demonstrated in animal experiments that glomerular expression of the key mediator transforming growth factor (TGF)-β is stimulated by hyperglycemia and/or hypoinsulinemia, hemodynamic factors, the renin-angiotensin system (angiotensin II, insulin-like growth factor (IGF-I), and activation of protein kinase C.

The pathogenetic factors involved in the development and progression of diabetic nephropathy and interventions on different levels have been investigated in extensive animal experiments. Interventions such as establishing normoglycemia by islet transplantation, dietary protein restriction, antihypertensive treatment, and application of TGF-β antibodies proved as efficient in preventing the development and progression of diabetic glomerulosclerosis (see Figure 1).

From clinical work it is accepted that poor glycemic control is an important risk factor for the development of diabetic nephropathy (Table 2). It is therefore reasonable to propose that meticulous glycemic control is important in preventing and delaying the progression of diabetic nephropathy. This has been demonstrated best by two prospective studies in IDDM. The benefits of strict glycemic control should apply in NIDDM as well. Indeed, a

<table>
<thead>
<tr>
<th>TABLE 1. EPIDEMIOLOGY AND PROGNOSIS OF IDDM AND NIDDM PATIENTS WITH SPECIAL REFERENCE TO DIABETIC NEPHROPATHY</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prevalence of diabetes mellitus</td>
</tr>
<tr>
<td>• USA, 7%</td>
</tr>
<tr>
<td>• Germany, 5%</td>
</tr>
<tr>
<td>• IDDM, 0.22%</td>
</tr>
<tr>
<td>• NIDDM, 4.82%</td>
</tr>
<tr>
<td>• Prevalence of nephropathy after 25 years of diabetes</td>
</tr>
<tr>
<td>• IDDM, 48%</td>
</tr>
<tr>
<td>• NIDDM, 57%</td>
</tr>
<tr>
<td>• Diabetes mellitus accounts for all new patients per year accepted for renal replacement therapy by</td>
</tr>
<tr>
<td>• 33.8% in the USA</td>
</tr>
<tr>
<td>• 17.0% in Europe</td>
</tr>
<tr>
<td>• 24.2% in Germany (34% IDDM; 66% NIDDM)</td>
</tr>
<tr>
<td>• Annual incidence 52 per million in the lower Neckar region, Germany</td>
</tr>
<tr>
<td>• 45 month survival rate of diabetic patients on hemodialysis</td>
</tr>
<tr>
<td>• IDDM, 57%</td>
</tr>
<tr>
<td>• NIDDM, 50% (62% death rate due to cardiovascular events)</td>
</tr>
</tbody>
</table>

Data source: References 1–6.
recent prospective study of NIDDM patients clearly demonstrated the beneficial effects of strict glycemic control on the progression of nephropathy in NIDDM, although these Japanese patients were quite different from NIDDM patients in Western countries as they were lean, normotensive, and normolipemic.

Hyperlipoproteinemia (hypercholesterolemia) was implicated as possible risk factor for diabetic nephropathy in IDDM and NIDDM (Table 2), and patients with diabetic nephropathy and low serum cholesterol tend to show a slower decline in renal function than do those with a high serum cholesterol level. It is therefore reasonable that, in patients with nephropathy and nephrotic syndrome, treatment with lipid-lowering substances was accompanied by a delay of the progression of nephropathy, at least in two studies.

Renal function and structure are significantly influenced by dietary protein load (Table 2). Dietary protein restriction has been shown to delay the progression of renal failure in patients with IDDM, and patients with NIDDM may also benefit from it.

Earlier findings that cigarette smoking may contribute to the development and progression of diabetic renal disease have recently been confirmed.

**TABLE 2. RISK FACTORS OF DIABETIC NEPHROPATHY**

- Hyperglycemia (and hypoinsulinemia?)
- Hyperlipoproteinemia
- Hypertension
- Protein overload
- Smoking
- Duration of diabetes mellitus

**FIGURE 1.** Simplified scheme of the pathophysiologic changes associated with hyperglycemia and hypertension leading to glomerulosclerosis as evidenced in animal studies. –, different levels of antiproteinosis measures. According to references: (1) 26–29; (2) 30, 31; (3) 32; (4) 33; (5) 34; (6) 29, 35; (7) 36, 37; (8) 38.

**ANTIHYPERTENSIVE THERAPY IN IDDM AND NIDDM PATIENTS WITH OVERT DIABETIC NEPHROPATHY (MACROALBUMINURIA)**

Ten years ago, a beneficial effect of captopril on heavy proteinuria in diabetic patients was first described. Later on, additional studies have documented the beneficial effect of ACE inhibitors on macroalbuminuria and on renal function in patients with IDDM and NIDDM. However, most of these studies have been relatively small, open-label, and of short duration, and have not addressed critical endpoints such as mortality or progression to end-stage renal disease. In this respect, the article published by Lewis et al in 1993 was regarded as a landmark study. In this study the effects of captopril in IDDM patients who had macroalbuminuria and serum creatinine levels of $\geq 2.5$ mg/dL but who were normotensive (treated other than with ACE inhibitors or calcium antagonists) were randomized to receive either captopril 25 mg three times daily or placebo. The primary endpoint of the study was the rate of doubling of serum creatinine, secondary endpoints included death or the need for dialysis or transplantation. The average length of follow-up was 3 years, and ACE treatment resulted in a 50% risk reduction for primary and secondary endpoints.

As opposed to ACE inhibitors, the role of calcium antagonists in overt diabetic nephropathy is unclear because of the lack of large-scale trials. Diltiazem, verapamil, and nicardipine appeared to be equal in efficacy to ACE inhibitors, whereas isradipine was found to be less effective. Studies with the dihydropyridine-type calcium antagonist of the first generation, nifedipine, are contradictory. In most of the short-term studies on overt albuminuria, a worsening was observed.

At least three meta-analyses of the effect of different
antihypertensive drugs on diabetic nephropathy have been published.67–69 The recent extended metaanalysis of Weidmann et al revealed the ACE inhibitors tend to preserve GFR in such patients better than do conventional antihypertensive drugs or nifedipine70 (see Table 3). Considering the changes in mean blood pressure, proteinuria, and GFR under treatment with different antihypertensives in diabetic subjects with micro- or macroalbuminuria, and adding data from three different studies with nitrendipine,71–73 the following results emerged: Changes in GFR per year averaged 2.8% in patients on placebo; 2.9% in patients on diuretics or β-blockers; 2.1% in patients on ACE inhibitors; 2.12% in patients on calcium antagonists other than nifedipine/nitrendipine; and +30% in patients on nifedipine; and +30% in patients on nitrendipine. The differences observed within the group of calcium antagonists may be partially explained by different hemodynamic effects or by proposed different patterns of calcium channels and receptors on different target organs.

### Table 3. Changes (Percent/Year) of Mean Blood Pressure (MBP), Proteinuria (UProt), and Glomerular Filtration Rate (GFR) Under Treatment with Different Antihypertensives in IDDM and NIDDM Subjects with Micro- or Macroalbuminuria

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>n</th>
<th>ΔMBP (%)</th>
<th>ΔUProt (%)</th>
<th>ΔGFR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>244</td>
<td>−2</td>
<td>+39</td>
<td>−8</td>
</tr>
<tr>
<td>Conventional*</td>
<td>213</td>
<td>−10</td>
<td>−20</td>
<td>−9</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>489</td>
<td>−16</td>
<td>−52</td>
<td>−1</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• All except Nif/Nit</td>
<td>63</td>
<td>−16</td>
<td>−42</td>
<td>+2</td>
</tr>
<tr>
<td>• Nifedipine</td>
<td>63</td>
<td>−12</td>
<td>+2</td>
<td>−48</td>
</tr>
<tr>
<td>• Nitrendipine</td>
<td>39</td>
<td>−17</td>
<td>−48</td>
<td>+30</td>
</tr>
</tbody>
</table>

* Diuretics and β-blockers.

ACE, angiotensin converting enzyme; Nif, nifedipine; Nit, nitrendipine. n, number of patients.

Data adapted from the metaanalysis of Weidmann et al70 and from three different studies using nitrendipine.71–73

### Table 4. Prospective Long-Term Studies (≥1 Year) in Hypertensive IDDM (I) or NIDDM (II) Patients with Microalbuminuria Treated with ACE Inhibitors

<table>
<thead>
<tr>
<th>Substance</th>
<th>No. of Patients (Type of DM)</th>
<th>Duration of Px (years)</th>
<th>Percent Change in Albuminuria</th>
<th>Percent Change in Kidney Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindopril</td>
<td>20* (I/II)</td>
<td>1</td>
<td>−29%</td>
<td>−11%</td>
<td>77</td>
</tr>
<tr>
<td>Perindopril</td>
<td>8 (I/II)</td>
<td>3</td>
<td>−77%</td>
<td>+2%</td>
<td>78</td>
</tr>
<tr>
<td>Enalapril</td>
<td>10 (I)</td>
<td>1</td>
<td>−63%</td>
<td>−16%</td>
<td>71</td>
</tr>
<tr>
<td>Enalapril</td>
<td>16 (II)</td>
<td>1</td>
<td>−73%</td>
<td>−11%</td>
<td>79</td>
</tr>
<tr>
<td>Enalapril</td>
<td>6 (II)</td>
<td>1.25</td>
<td>−24%</td>
<td>+34%</td>
<td>72</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>9 (II)</td>
<td>3</td>
<td>−27%</td>
<td>−8%</td>
<td>80</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>147 (II)</td>
<td>1</td>
<td>−40%</td>
<td>+3%</td>
<td>81</td>
</tr>
<tr>
<td>Total/mean</td>
<td>216</td>
<td>1–3</td>
<td>−48%</td>
<td>−1%</td>
<td></td>
</tr>
</tbody>
</table>

* About 70% of the patients with normal blood pressure at start.

DM, diabetes mellitus; Px, treatment.

### Antihypertensive Therapy in IDDM and NIDDM Patients with Incipient Diabetic Nephropathy (Microalbuminuria)

Since the first intervention study in microalbuminuric patients, several other studies have confirmed the beneficial effect of antihypertensive treatment on the progression of diabetic nephropathy.74–76 Based on these more or less short-term studies in hypertensive IDDM and NIDDM patients with microalbuminuria, prospective long-term studies performed with either ACE inhibitors or calcium antagonists, with a follow-up of at least 1 year, have meanwhile been reported (Tables 4 and 5). These long-term studies clearly show that strict blood pressure control in this early stage of diabetic nephropathy significantly reduces albuminuria, thus preventing progression to macroalbuminuria (overt nephropathy). As far as the effect on kidney function is concerned, the outcome was less clear. Using ACE inhibitors, glomerular filtration rates either were maintained or were slightly reduced, whereas using the calcium antagonist nitrendipine (dihydropyridine-type calcium antagonist) a 20% to 40% increase of glomerular filtration rate was observed, along with a significant reduction of albuminuria. It is still unclear whether the short-term diminution in glomerular filtration rate under treatment with ACE inhibitors indicates a potentially adverse effect or simply the correction of hyperfiltration.77–81

These observational studies support the hypothesis that angiotensin converting enzyme inhibitors and...
certain calcium antagonists have a unique ability, independent of their antihypertensive effect, to slow the progression of diabetic nephropathy. This hypothesis is further supported by the interesting findings that treatment with ACE inhibitors or calcium antagonists prevented progression to macroalbuminuria even in normotensive IDDM and NIDDM patients with microalbuminuria82–90 (see Table 6).

**TRIALS WITH ANTIHYPERTENSIVE COMBINATION THERAPY**

Many diabetic patients with hypertension and renal disease require the combination of various antihypertensive drugs to effectively control their hypertension. The concept of combination therapy is attractive also from a pathophysiologic aspect, because two drugs from different classes with different modes of action may provide even greater additive effects than would be expected from each drug given separately. This has recently been documented for a combination of ACE inhibitors and calcium antagonists in reducing proteinuria and arresting progression towards renal failure91–93 (Table 7).

The rationale of antihypertensive combination therapy may be underlined by confirmative animal studies. In an isolated perfused kidney pretreated with an ACE inhibitor, it was found that the efferent arteriolar dilatation was potentiated by adding a calcium antagonist.94 Long-term studies in a canine model of chemically induced diabetes mellitus demonstrated that combinations of an ACE inhibitor and a calcium antagonist had additive antiproteinuric effects.95,96 Beneficial effects of such combinations on proteinuria, intraglomerular pressure, and histomorphological glomerulosclerosis index were described in subtotal nephrectomy models of the rat.97,98 Interestingly, a very recent study with nonhypotensive doses of the fixed-dose combination drug VeraTran, of the nondihydropyridine calcium antagonist verapamil (V), and the ACE inhibitor trandolapril (T), slowed the development of glomerular sclerosis better than any of these agents alone in stroke-prone spontaneously hypertensive rats (SHRSP).99 Despite persisting hypertension, the rise in proteinuria was attenuated, creatinine clearance was better preserved, and there was a significant lower degree of glomerulosclerosis in rats treated with the same combination (Figure 2). This study further supports the concept that such combinations may have effects on the glomerulus that are independent of blood pressure reduction. Moreover, along with improved kidney function, a significantly increased survival rate for the animals was observed.100 Finally, the same combination given as fixed-dose combination drug VeraTran to hyperten-
sive NIDDM patients proved as metabolically neutral in contrast to a β-blocker/low-dose chlortalidine combination drug.101

In summary, it is obvious that a number of arguments can be advanced for combining ACE inhibitors and calcium antagonists. However, whether a combination therapy will offer any benefits in prolonging either overall survival or renal survival in patients with diabetes is not yet known.

**COST–BENEFIT CONSIDERATIONS OF ANTIHYPERTENSIVE THERAPY OF DIABETIC PATIENTS**

Due to the increasing numbers of diabetics, the excessive morbidity and mortality (particularly of those with nephropathy), and the high costs associated with dialysis and renal transplantation, the currently enormous socioeconomic burden of diabetes may still exponentially increase. Therefore, prevention of diabetic nephropathy and end-stage renal failure by means of antihypertensive therapy would be beneficial in economic terms, quite apart from the benefits to the health of individuals and to society overall. In particular, either monotherapy or combined therapy with ACE inhibitors and certain calcium antagonists (notably of the nondihydropyridine type or of the second-generation, dihydropyridine-type calcium antagonists) promises to reduce the risk of diabetic end-stage renal disease by 50% or more. It is thus of particular interest that a recent computer-simulated cost–benefit

---

**TABLE 7. EFFECTS OF COMBINATION THERAPY WITH ACE INHIBITORS AND CALCIUM ANTAGONISTS ON URINARY ALBUMIN EXCRETION (UAE) AND GLOMERULAR FILTRATION RATE (GFR) IN HYPERTENSIVE IDDM OR NIDDM PATIENTS WITH PERSISTENT MICRO- OR MACROALBUMINURIA**

<table>
<thead>
<tr>
<th>ACE Inhibitor</th>
<th>Calcium Antagonist</th>
<th>No. of Patients</th>
<th>Type of Diabetes Mellitus</th>
<th>Duration of Px (weeks)</th>
<th>Change in UAE (g/day)</th>
<th>Change in GFR (mL/min)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>Nicardipine</td>
<td>12</td>
<td>NIDDM</td>
<td>4</td>
<td>1.2–0.3 (−75%)</td>
<td>113–115 (±2%)</td>
<td>91</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Verapamil SR</td>
<td>8</td>
<td>NIDDM</td>
<td>52</td>
<td>6.8–1.7 (−75%)</td>
<td>67–64 (−4%)</td>
<td>92</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>Verapamil SR</td>
<td>16</td>
<td>IDDM</td>
<td>12</td>
<td>0.26–0.06 (−77%)</td>
<td>90–92 (+2%)</td>
<td>93</td>
</tr>
<tr>
<td>Total/mean</td>
<td></td>
<td>36</td>
<td></td>
<td>23</td>
<td>−76%</td>
<td>±0</td>
<td></td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; Px, treatment; NIDDM, non–insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; SR, slow release formulation.

---

**FIGURE 2.** Individual and combined effects of the nondihydropyridine calcium antagonist, verapamil, or the angiotensin converting enzyme inhibitor trandolapril on hypertension-induced glomerulosclerosis in the stroke-prone rat model. **Left:** Progression of daily protein excretion. Adult SHRSP were treated with placebo (filled squares), verapamil (filled triangles), trandolapril (filled diamonds), or the combination of both (open circles). The values represent mean ± SE. N = 6, n = 5 in the combination group. *P < .05 v control; #P < .05 v trandolapril; and &P < .05 v verapamil (tested by ANOVA). **Right:** Summary of the histopathological findings in the kidney of older SHRSP. The severity grading was as follows: Grade 1, minimal; Grade 2, slight; Grade 3, moderate; Grade 4, moderate to marked; Grade 5, marked to severe. The mean severity score values of each group represent the sum of the grades divided by the number of rats. *P < .05 v control; #P < .05 v trandolapril; and &P < .005 v verapamil (ANOVA). (From Münter et al99 with permission.)
study on the impact of screening and intervention for microalbuminuria—the indicator and predictor of renal and cardiovascular lesions in general—in IDDM described that, assuming treatment effects of 33% and 67%, respectively, the average life expectancy increased by 4 to 14 years, respectively, and the need for dialysis or renal transplantation decreased by 21% and 63%. Costs and savings would balance if the annual rate of increase of albuminuria was decreased from 20% to 18% per year. In our own study, we found that appropriate antihypertensive treatment in IDDM and NIDDM patients would be followed by savings of US $6,700 and US $14,000 during the lifespan of an IDDM and NIDDM patient, respectively, or approximately US $500 per patient and year (Bretzel et al, in preparation). Moreover, data based on the collaborative study suggested that if all diabetic patients (both IDDM and NIDDM) with nephropathy were started on the ACE inhibitor captopril in 1994, it would prolong life and save the health care system over US $2 billion by the year 2004.

CONCLUSION

Screening programs for the detection of the earliest stage of diabetic nephropathy—that is, microalbuminuria—should be performed in diabetic subjects on a regular basis, and intervention programs including strict blood pressure control should commence as early as possible and, at the latest, when microalbuminuria becomes apparent. There is now increasing evidence that ACE inhibitors and certain calcium antagonists do have nephroprotective capacity beyond their systemic blood pressure lowering effects, and initial clinical trials with combinations have revealed additive nephroprotective effects as well. Moreover, ACE inhibitors and calcium antagonists have no adverse effects on glycemic control or lipid levels, and may even improve insulin sensitivity. This further promotes these antihypertensives to first-line drugs when treating persons at risk for metabolic disorders or for treating patients with diabetes. Finally, the strategy of screening for albuminuria and antihypertensive intervention for strong blood pressure control is likely to improve quality of life, to have life-saving effects, and to result in considerable economic savings.

REFERENCES


AJH–SEPTEMBER 1997–VOL. 10, NO. 9, PART 2


67. Kasiske BL, Kalil RS, Ma JZ, et al: Effect of antihyper-


