Diabetic nephropathy is a major cause of illness and premature death in diabetic patients, largely through accompanying cardiovascular disease and end-stage renal failure. Proteinuria heralds the clinical nephropathy, and the worsening of proteinuria parallels the progression of renal disease towards chronic renal failure.

A large body of evidence has accumulated that emphasizes the role of elevated blood pressure in the progression of renal disease, as well as the clear benefit of antihypertensive treatment. However, the choice of antihypertensive drug to protect renal function was less clear in the past. In earlier studies, a reduction in the rate of progressive renal failure in hypertensive subjects has been shown with diuretics, β-blockers, and vasodilators. However, there is now increasing evidence that angiotensin converting enzyme (ACE) inhibitors and some 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 nephroprotective effects.

Finally, 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 subjects at risk of metabolic disorders or people with diabetes. Am J Hypertens 1997;10:159S–166S © 1997 American Journal of Hypertension, Ltd.

**Key Words:** Diabetic nephropathy, insulin-dependent diabetes mellitus, noninsulin-dependent diabetes mellitus, hypertension, antihypertensive therapy.
nal diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM). Recent data from a German clinical study based on more than 700 diabetic patients showed a 48% and a 57% cumulative risk of overt nephropathy (proteinuria) after 25 years of diabetes in IDDM and NIDDM patients, respectively. Once initiated, the course of diabetic nephropathy is one of progressive and relentless declining renal function, ending in chronic renal failure. It therefore comes as no surprise to any diabetologist and nephrologist to be told that diabetic nephropathy is now the commonest single cause of end-stage renal disease. The most recent EDTA-Registry data for Europe show that now the number of diabetic patients alive on renal replacement therapy is likely to be approached at 100,000, and the overall rate for new patients accepted for renal replacement therapy was recorded as 17% for diabetics in 1992. 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 IDDM or NIDDM patients. A recent survey of 28 hemodialysis units all over Germany reported that 24.2% (16.6% to 41.6%) of individuals on dialysis were diabetic patients, of whom 34% had IDDM and 66% NIDDM, and only 57% of IDDM patients and 50% of NIDDM patients survived during the 45-month investigation period. The estimated annual incidence of terminal renal failure with diabetes in a period of January 1993 to June 1994 was recently described as 52 per million per year in the lower Neckar region (Heidelberg, Germany).

The natural course and stage of diabetic nephropathy (glomerulosclerosis) have been well described for patients with IDDM and NIDDM. Microalbuminuria (urinary albumin excretion rate of 30 to 300 mg/24 h) is an established marker of early renal damage (incipient nephropathy) and a reliable predictor of proteinuria (overt nephropathy) in patients with IDDM and NIDDM. However, a substantial number of patients with diabetic nephropathy die before reaching end-stage renal failure, as diabetic nephropathy confers an increased risk of macrovascular disease. A stratified random sample of almost 5,000 diabetic patients aged 35 to 55 years participating in the World Health Organization (WHO) Multinational Study of Vascular Disease in Diabetes has been followed up from 1975 to 1987. The recent report of the study clearly indicated that patients with both hypertension and proteinuria experienced a strikingly high mortality risk: 11-fold for men with IDDM and 18-fold for women with IDDM; fivefold for men with NIDDM and eightfold for women with NIDDM. A cohort study on the predictive effect of slightly elevated urinary albumin excretion in the development of atherosclerotic vascular disease clearly demonstrated that already patients with microalbuminuria had a 2.5 times higher risk of atherosclerotic vascular disease than those with lower excretion rates. They also found that for every 5 mg increase in 24 h urinary albumin excretion, the risk of atherosclerotic vascular disease increased by 6%. The predictive effect of albuminuria was independent of conventional atherogenic risk factors and of development of diabetic nephropathy, and duration and control of diabetes.

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. Published data provide a basis for preventive strategies both on the secondary and tertiary levels. In particular, aggressive blood pressure control, especially monotherapy or combined therapy with angiotensin converting enzyme (ACE) inhibitors and some calcium antagonists, promises to reduce the risk of diabetic end-stage renal disease by 50% or more, and it has been proposed that blood pressure control should commence as early as possible and, at the latest, when microalbuminuria becomes apparent.

PROTECTING THE RESIDUAL RENAL FUNCTION BY ANTHYPTERTENSIVE THERAPY

In subjects with IDDM elevated blood pressure may accompany rather than precede an increase in microalbuminuria, whereas in NIDDM patients elevated blood pressure may be detected prior to elevated albumin excretion rates. These findings suggest that high blood pressure may be a consequence as well as a cause of diabetic nephropathy, even in its earliest stages. Initial intervention studies with antihypertensive treatment were published in the early 1980s. Both studies clearly demonstrated that antihypertensive treatment could ameliorate the decline in glomerular filtration rate in patients with IDDM. According to the latest guidelines regarding blood pressure control by the National High Blood Pressure Education Program Working Group on Hypertension in Diabetes, intervention by change in lifestyle and, if required, by pharmacologic therapy, has been recommended for blood pressure ≥ 140/90 mm Hg, with target blood pressure ≤ 130/85 mm Hg. However, which are the antihypertensive drugs of choice remains to be determined.

Anthypertensive Drugs and Metabolic Risk The choice of antihypertensive drug therapy represents special problems in the diabetic patient. Most recently, it has become clear that essential hypertension, which is widespread in diabetic patients, is an insulin resistant state. Moreover, it has been shown that treatment with diuretics and β-blockers aggravates insulin
resistance and leads to a worsening of glucose tolerance despite an increase in circulating plasma insulin levels.24 Unfortunately, hyperinsulinemia has been implicated in the development of hypertension, dyslipidemia, and atherosclerotic cardiovascular disease.25 Long-term treatment with β-blockers and thiazide diuretics, is associated with a substantially increased risk for diabetes mellitus in both men and women.26 Furthermore, both diuretics and β-blockers promote a more atherogenic plasma lipid profile.27 This may be the reason why, in some large clinical studies of mild essential hypertension, therapy with a β-blocking agents failed to significantly reduce the risk of coronary events.28-30

These observations have led to a reevaluation of the treatment of hypertension in both IDDM and NIDDM patients, with emphasis on the use of angiotensin converting enzyme inhibitors and calcium antagonists, drugs that either enhance insulin sensitivity or are metabolically neutral with regard to both glucose and lipid metabolism.31 Therefore, the following considerations of antihypertensive treatment on the primary, secondary, and tertiary prevention levels are strictly devoted to studies using either ACE inhibitors or calcium antagonists.

Nephroprotective Effects of ACE Inhibitors and Calcium Antagonists Albuminuria was ascribed a surrogate endpoint for the course of diabetic nephropathy. However, there is now a bulk of evidence that urinary albumin excretion rate will also predict long-term renal function, and may not simply represent a marker of renal disease but may even pathogenetically contribute to its evolution. Reduction in albuminuria predicted diminished progression in diabetic nephropathy32; short-term antiproteinuric response to antihypertensive treatment predicted long-term GFR decline in patients with nondiabetic renal disease.33 Proteinuria may be a direct cause of renal morbidity and, in particular, glycated albumin affects mesangial cells and may play an important role in the pathogenesis of diabetic nephropathy.34 Multiple studies suggested that ACE inhibitors and certain types of calcium antagonists have distinctive advantages over conventional antihypertensive agents with regard to protecting the residual renal function. Several potential mechanisms may mediate the renal protective actions of both these classes of drugs35-37, some of them are listed in Table 1.

Based on these pathogenetic considerations, prospective long-term studies with a follow-up of at least 1 year have been meanwhile performed with either ACE inhibitors or calcium antagonists in hypertensive IDDM and NIDDM patients with microalbuminuria (Table 2; Table 3). These 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).38-45 As far as the effect on kidney function is concerned, the outcome was less clear. Using ACE inhibitors, glomerular filtration rates were either maintained or slightly reduced, whereas, using the calcium antagonist nitrendipine (dihydropyridine type calcium antagonist), a 20% to 40% increase of glomerular filtration rate was observed along

### Table 1. Potential Mechanism Mediating the Renal Protective Actions of ACE Inhibitors

<table>
<thead>
<tr>
<th>Substance</th>
<th>Pat. Type</th>
<th>Duration (Years)</th>
<th>Change in Albuminuria</th>
<th>Change in Kidney Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindopril</td>
<td>20* (I/II)</td>
<td>1</td>
<td>49 mg/24 h (-29%)</td>
<td>138 mL/min (-11%)</td>
<td>38</td>
</tr>
<tr>
<td>Perindopril</td>
<td>8 (I/II)</td>
<td>3</td>
<td>68-16 mg/24 h (-77%)</td>
<td>94-96 mL/min (+2%)</td>
<td>39</td>
</tr>
<tr>
<td>Enalapril</td>
<td>10 (I)</td>
<td>1</td>
<td>51-19 mg/24 h (-63%)</td>
<td>103-87 mL/min (-16%)</td>
<td>40</td>
</tr>
<tr>
<td>Enalapril</td>
<td>16 (II)</td>
<td>1</td>
<td>ND (-73%)</td>
<td>ND (-11%)</td>
<td>41</td>
</tr>
<tr>
<td>Enalapril</td>
<td>6 (II)</td>
<td>1.25</td>
<td>58-44 mg/24 h (-24%)</td>
<td>59-79 mL/min (+34%)</td>
<td>42</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>9 (II)</td>
<td>3</td>
<td>71-52 mg/24 h (-27%)</td>
<td>73-67 mL/min (-8%)</td>
<td>43</td>
</tr>
<tr>
<td>Total/mean</td>
<td>69</td>
<td>1-3</td>
<td>-45%</td>
<td>-2%</td>
<td></td>
</tr>
</tbody>
</table>

*About 70% of the patients with normal blood pressure at the start. ND, not determined.
TABLE 3. PROSPECTIVE LONG-TERM STUDIES (≥1 YEAR) IN HYPERTENSIVE DIABETICS WITH MICROALBUMINURIA TREATED WITH CALCIUM ANTAGONISTS

<table>
<thead>
<tr>
<th>Substance</th>
<th>Pat. Type</th>
<th>Duration (Years)</th>
<th>Change in Albuminuria</th>
<th>Change in Kidney Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>23*</td>
<td>1</td>
<td>59-48 mg/24 h</td>
<td>150-136 mL/min</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>(I/II)</td>
<td></td>
<td>(-20%)</td>
<td>(-9%)</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>15</td>
<td>1</td>
<td>ND</td>
<td>ND</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>(II)</td>
<td></td>
<td>(-15%)</td>
<td>(-12%)</td>
<td></td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>22</td>
<td>1</td>
<td>114-38 mg/24 h</td>
<td>108-133 mL/min</td>
<td>44, 45</td>
</tr>
<tr>
<td></td>
<td>(I/II)</td>
<td></td>
<td>(-49%)</td>
<td>(+21%)</td>
<td></td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>10</td>
<td>1</td>
<td>42-24 mg/24 h</td>
<td>107-148 mL/min</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>(I)</td>
<td></td>
<td>(-54%)</td>
<td>(+38%)</td>
<td></td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>7</td>
<td>1.25</td>
<td>47-29 mg/24 h</td>
<td>70-97 mL/min</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>(II)</td>
<td></td>
<td>(-40%)</td>
<td>(+39%)</td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>9</td>
<td>3</td>
<td>71-52 mg/24 h</td>
<td>73-67 mL/min</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>(II)</td>
<td></td>
<td>(-27%)</td>
<td>(-8%)</td>
<td></td>
</tr>
<tr>
<td>Total/mean</td>
<td>86</td>
<td>1-3</td>
<td>-34%</td>
<td>+12%</td>
<td></td>
</tr>
</tbody>
</table>

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

with significant reduction of albuminuria. It is still unclear whether the short-term diminution in glomerular filtration rate under the treatment with ACE inhibitors indicates a potentially adverse effect or simply the correction of hyperfiltration.

These 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, which is further substantiated by the interesting findings that treatment with ACE inhibitors or calcium antagonists prevented progression to macroalbuminuria even in normotensive IDDM and NIDDM patients with microalbuminuria.46-53 (see Table 4). Ten years ago, the beneficial effect of captopril on heavy proteinuria in diabetic patients with overt nephropathy was first described.54 Additional studies have documented the beneficial effect of ACE inhibitors on macroalbuminuria and renal function in patients with IDDM and NIDDM.55-57 However, most of these studies have been relatively small, open-label, and of short duration, and have not addressed clinical endpoints such as mortality or progression to end stage renal disease. In this respect, the paper published by Lewis et al in 1993 was regarded as a landmark study.58 In this study, the effects of captopril in IDDM patients with macroalbuminuria and serum creatinine levels of 2.25 mg/dL but normotensive (otherwise treated but not ACE inhibitors or calcium antagonists) were randomized to receive either captopril 25 mg or placebo three times daily. 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.

TABLE 4. STUDIES WITH ACE INHIBITOR OR CALCIUM ANTAGONIST LONG-TERM THERAPY IN NORMOTENSIVE IDDM OR NIDDM PATIENTS WITH MICROALBUMINURIA

<table>
<thead>
<tr>
<th>Substance</th>
<th>Study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>Mathiesen et al 1991</td>
<td>46</td>
</tr>
<tr>
<td>Captopril</td>
<td>Lafiel et al 1993</td>
<td>47</td>
</tr>
<tr>
<td>Captopril</td>
<td>Viberti et al 1994; MCG 1996</td>
<td>48, 49</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Marre et al 1988</td>
<td>50</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Ravid et al 1993</td>
<td>51</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Hallab et al 1993</td>
<td>52</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Melbourne Study 1991</td>
<td>38</td>
</tr>
<tr>
<td>Calcium Antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Melbourne Study 1991</td>
<td>36</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Schnack et al 1994</td>
<td>53</td>
</tr>
</tbody>
</table>

Prevention of progression to macroalbuminuria in each study. Only studies with a follow-up of ≥1 year in >six patients were included.
tagonists and ACE inhibitor treatment resulted in a 50% risk reduction for primary and secondary end-points. As opposed to ACE inhibitors, the role of calcium-antagonists in overt diabetic nephropathy is more unclear because of the lack of large-scale trials. Diltiazem, verapamil, and nicardipine appeared to be of efficacy equal to ACE inhibitors, whereas isradipine was found to be less effective.\(^5\)\(^7\),\(^5\)\(^9\)\(^-\)\(^6\)\(^2\)\(^\) Studies with the dihydropyridine-type calcium antagonist of the first generation, the short-acting nifedipine, are contradictory. In most of the short-term studies on overt albuminuria, a worsening was observed.\(^6\)\(^3\)

The recent extended metaanalysis of Weidmann's group revealed the ACE-inhibitors tend to preserve GFR in such patients better than conventional antihypertensive drugs or nifedipine.\(^6\)\(^4\) (Table 5). Based on a 2% lowering of the mean blood pressure by placebo treatment and adding data from three different studies with nifendipine,\(^4\)\(^0\),\(^4\)\(^2\),\(^4\)\(^5\) changes in proteinuria and GFR under treatment with different antihypertensives in diabetic subjects with micro- or macroalbuminuria, the results noted in Table 5 emerged. The differences observed among 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.

**Evidence for Additive Nephroprotective Effects of Combinations of ACE Inhibitors and Calcium Antagonists** The request for antihypertensive combination therapy is of clinical relevance because 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 pathophysiological aspect, because it is likely that in arresting progression of renal failure the salutary effects of ACE inhibitors and calcium antagonists are complementary and probably synergistic.\(^6\)\(^5\)

A few studies of combination therapy in animal models have been performed. 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.\(^6\)\(^6\) 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.\(^6\)\(^7\) Beneficial effects of such combinations on proteinuria, intraglomerular pressure, and histomorphological glomerulosclerosis index were described in subtotal nephrectomy models of the rat.\(^6\)\(^8\) Interestingly, a very recent study with nonhypotensive doses of the fixed-dose combination drug Veratran, of a nondehidropyridine calcium antagonist, verapamil (V), and an ACE inhibitor, trandolapril (T), slowed the development of glomerular sclerosis better than either agent alone in stroke-prone spontaneously hypertensive rats (SHRSP).\(^6\)\(^9\) 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 of the study animals was observed.\(^7\)\(^0\)

Only a few human studies utilizing combination therapy have been reported. Three initial reports of such either short-term or long-term combination therapy in IDDM or NIDDM patients with nephropathy were very promising.\(^6\)\(^0\),\(^6\)\(^1\),\(^7\)\(^1\) Moreover, controlled studies showed that combinations of ACE inhibitors and calcium antagonists mutually reduce somewhat the frequency of their side effects,\(^4\)\(^2\) and once again confirmed the metabolic neutrality of such combinations in contrast to combinations of \(\beta\)-blockers and low-dose diuretics in treating hypertensive NIDDM patients.\(^7\)\(^2\)

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 overall or renal survival is not yet known.

**CONCLUSION**

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 antihypertensive agents to first-line drugs when treating subjects at risk for metabolic disorders, or persons with diabetes. Moreover, a number of studies exist that show that ACE inhibitors and certain types of calcium antagonists have distinctive advantages over conventional antihypertensive agents.

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>(\Delta)Proteinuria (%)</th>
<th>(\Delta)GFR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>+39</td>
<td>-8.0</td>
</tr>
<tr>
<td>Conventional*</td>
<td>-4.0</td>
<td>-1.8</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>-6.5</td>
<td>±0</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>all except Nif/Nit</td>
<td>5.3</td>
<td>±0</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>±0</td>
<td>-8.0</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>-5.6</td>
<td>+3.5</td>
</tr>
</tbody>
</table>

* Diuretics and \(\beta\)-blockers. Nif, nifedipine; Nit, nitrendipine.

\(n = \text{number of patients included}.\)

Data adapted from the meta-analysis of Weidmann et al.\(^6\)\(^4\) and three different studies using nitrendipine.\(^4\)\(^0\),\(^4\)\(^2\),\(^4\)\(^5\)
with regard to protecting the residual renal function. Experimental and initial clinical trials with combinations of these substances have been revealed additive nephroprotective effects. In addition, prevention would be beneficial in economic terms quite apart from the benefits to the health of individuals and to society. Recently published data provide a basis for preventive strategies both on the secondary and tertiary levels. In particular, aggressive blood pressure control, especially monotherapy or combined therapy with ACE inhibitors and the calcium antagonists of the verapamil, diltiazem, or nitrendipine class, 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 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 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. Moreover, data based on the Lewis et al trial suggested that if all diabetic patients (both IDDM and NIDDM) with nephropathy were started on an ACE inhibitor, captopril, in 1994, it would prolong life and save the health care system over US $2 billion by the year 2004.

To conclude, screening programs for detection of the earliest stage of diabetic nephropathy (microalbuminuria) should be performed on a regular basis and intervention programs including strict blood pressure control, preferably by treatment with ACE inhibitors or certain calcium antagonists, should commence as early as possible and, at the latest, when microalbuminuria becomes apparent. This screening and intervention strategy is likely to improve quality of life, save lives, and lead to considerable economic savings.

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PROTECTING THE RESIDUAL RENAL FUNCTION


