The effects of long-term treatment with captopril and conventional therapy on albuminuria and metabolic parameters were compared in 74 hypertensive type II diabetics with normal serum creatinine. Patients were treated double-blind with either captopril monotherapy or combined with hydrochlorothiazide or therapy with metoprolol, hydrochlorothiazide, or both for 36 months. The treatment was titrated to achieve goal diastolic blood pressure of ≤85 mm Hg. The reductions in blood pressures during treatment were similar in patients with (n=21) and without (n=53) microalbuminuria treated with either captopril or conventional therapy. No significant changes in albuminuria occurred in normoalbuminuric patients with either therapy. Although albuminuria fell in nearly all patients with microalbuminuria treated with captopril, it rose in eight of 12 patients on conventional therapy, with macroalbuminuria developing in two of them. Renal function was preserved by both types of treatment in both patient groups. Long-term treatment with either conventional therapy or captopril did not alter metabolic variables. We conclude that captopril alone or in combination decreases albuminuria and prevents the development of macroalbuminuria in hypertensive type II diabetics with persistent microalbuminuria. The renoprotective effect of this agent, however, remains to be demonstrated with longer term data on renal function. Aggressive antihypertensive treatment with either captopril or conventional therapy appears to be effective in preventing the onset of microalbuminuria in most normoalbuminuric patients. In contrast, with previous short-term studies, the use of converting enzyme inhibitors or conventional therapy did not cause adverse metabolic effects. (Hypertension 1993;21:786-794)

Recent cross-sectional studies have revealed a prevalence of microalbuminuria between 27% and 40% in patients with non-insulin-dependent diabetes mellitus (NIDDM) or type II diabetes attending diabetic clinics. Mogensen reported that patients with microalbuminuria most often developed progressive renal injury over time. In addition, follow-up studies have demonstrated that microalbuminuria is a strong predictor of all-cause mortality, mainly of cardiovascular origin, in NIDDM patients. Moreover, in the presence of hypertension, the evolution of macrovascular and microvascular disease is accelerated in diabetic patients.

A recent study suggested that intervention with angiotensin converting enzyme (ACE) inhibitors or calcium antagonists modified the evolution of urinary albumin excretion (UAE) in hypertensive insulin-dependent diabetic patients and NIDDM patients. However, to the best of our knowledge, the effects of long-term antihypertensive treatment with ACE inhibitors compared with those of conventional therapy on UAE are unknown. The present prospective randomized trial aimed to evaluate the influence of long-term blood pressure (BP) reduction on UAE and renal function with the ACE inhibitor captopril versus conventional antihypertensive therapy in borderline to moderately hypertensive NIDDM patients with normal serum creatinine. An interim report published in 1991 after 9 months of treatment showed that overall UAE was significantly reduced by captopril as single therapy or combined with hydrochlorothiazide but was unaffected by an equally effective reduction in BP with metoprolol, hydrochlorothiazide, or both. We now report on the long-term differential effects of captopril alone or in combination and conventional treatment on UAE and renal function in patients with and without microalbuminuria at study inclusion. In addition, we examined the 36-month effects of captopril and conventional drugs on carbohydrate and lipid profiles.

Methods

Patients and Study Protocol

This study was a prospective, double-blind, randomized investigation with parallel groups of non-insulin-dependent diabetic Caucasian patients referred to the hypertension research unit. Men and women, aged 45–75 years, with mild-to-moderate hypertension and normal serum creatinine (≤120 μmol/L) were consid-
Methods

BP was measured in the hypertension unit between 8 and 10 AM by the same trained nurse with a standard mercury sphygmomanometer after the patient had rested for 15 minutes in the supine position. Systolic BP was recorded at Korotkoff phase I (first appearance of pulse sound) and diastolic BP at Korotkoff phase V (disappearance of the pulse sound). The mean of three readings on each occasion was used.

Laboratory tests of blood and urine were done by routine clinical chemistry methods. UAE was measured on two timed overnight (8–12 hours) urine collections within a week. Patients were strongly advised to have minimal physical activity. Clear instructions were given on how to collect urine samples, and patients were asked to bring complete samples to the clinic with them. The urine volume was recorded and aliquots stored at −20°C until analysis of albumin concentration was made by radioimmunossay (Pharmacia Albinum RIA, Pharmacia Diagnostic AB, Uppsala, Sweden). Between-batch coefficient of variation was 5% for a mean value of 37 μg/mL. Urine specimens had to be negative on culture. The mean of the two samples was calculated. Glomerular filtration rate was estimated by the plasma disappearance of 125I-ethylenediaminetetraacetic acid (EDTA).11–13 The values were standardized for a body surface area of 1.73 m². Glycosylated hemoglobin (Hb A₁c) was measured by high performance liquid chromatography.14 Lipids and lipoproteins were measured in the morning from venous blood samples obtained after a 12-hour fast in tubes containing 0.1% EDTA. The tubes were immediately centrifuged at 1,000 g for 10 minutes. Plasma cholesterol and triglyceride levels were determined after extraction with isopropanol and treatment with zeolite, according to the Technicon Auto Analyzer II procedure.15 Lipoproteins were analyzed by ultracentrifugation and precipitation (phosphotungstate and magnesium chloride).16,17 Plasma apolipoproteins A₁ and B were measured by rocket immunoelectrophoresis. The lyophilized serum standards for apolipoprotein measurements were prepared in the laboratory at our Lipid Research Unit and calibrated with reference standards obtained from the Centers for Disease Control, Atlanta, Ga. The variation coefficient in our laboratory is <2%.18

Statistical Analysis

Data are presented as mean±SEM unless otherwise indicated. Calculations of UAE rates were done on log-transformed values to correct for distribution skewness, and data for each group or subgroup are presented as the geometric means. To better assess the effect of ACE inhibition on UAE and glomerular filtration rate, we divided the study population into patients having microalbuminuria at baseline (UAE between 20 and 200 μg/min) and those without microalbuminuria (UAE <20 μg/min). Comparisons were then established within each group between patients treated with captopril and those not receiving this drug by a two-way analysis of variance on repeated measures. Because the equality of the slopes was rejected, the comparison of each treatment time to baseline in each group was established by paired t test with Bonferroni correction.19 The association between changes in BP and changes in UAE was examined with the Pearson's product-moment correlation coefficient. Lipid and lipoprotein profiles were analyzed by comparing baseline and final data by paired t test also using the Bonferroni correction for interpretation. Statistical significance was set at a value of p<0.05.
TABLE 1. Patients Withdrawn From Captopril or Conventional Treatment During the Study

<table>
<thead>
<tr>
<th>Reason for withdrawal</th>
<th>Captopril treatment (n=16)</th>
<th>Conventional treatment (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal reasons and/or poor drug compliance</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Diastolic blood pressure ≥100 mm Hg</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>3</td>
<td>...</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>...</td>
<td>2</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Decrease in libido</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>...</td>
</tr>
</tbody>
</table>

Results

Population Characteristics

Of the 109 hypertensive NIDDM patients who entered the double-blind phase of the study, 35 were withdrawn during the 3-year follow-up period (Table 1). These patients were equally distributed between the captopril (n=16) and the conventional (n=19) treatment groups. Four patients of the captopril group died, three from myocardial infarction during the first 9 months of the study and one from colon cancer. Table 2 gives the data for the clinical characteristics of the 74 patients who completed the 36-month study protocol. Patients treated with captopril (n=34) had higher body weight and height than patients treated with conventional therapy (n=40), but the body mass index was comparable between groups. All other variables were similar in the two groups.

By the end of 36 months of active treatment, 36 patients were under monotherapy, whereas 38 patients required combination therapy. Ten patients were treated with hydrochlorothiazide (mean daily dose, 35 mg), 11 patients with captopril (68.2 mg), and 15 patients with metoprolol (140 mg). Twenty-three patients received a combination of captopril (97.8 mg) and hydrochlorothiazide (40.2 mg), and 15 patients were given a combination of metoprolol (200 mg) and hydrochlorothiazide (36.7 mg). There was no significant change in body weight as well as in dietary protein consumption in the treatment groups during the trial. Patient compliance was good, as >95% of the tablets were consumed by all participants.

Blood Pressure

In patients with microalbuminuria, BP dropped from 168±4/100±3 at baseline to 159±3/87±3 mm Hg (p<0.05 for systolic and p<0.001 for diastolic BP) after 36 months of therapy with metoprolol, hydrochlorothiazide, or both, and from 161±3/97±2 to 148±7/85±3 mm Hg (p<0.05 for systolic BP and p<0.001 for diastolic BP). With captopril as monotherapy or combined with hydrochlorothiazide, BP decreased from 157±3/96±1 to 145±3/85±2 mm Hg (p<0.001 for both systolic and diastolic BPs). There were no differences in BP at baseline or at 36 months between groups with or without microalbuminuria, and BP reduction was identical in all groups. With the exception of a lower systolic BP at 15 months in microalbuminuric patients treated with captopril, sustained BP control of a comparable degree was observed in both groups treated with either captopril or conventional therapy throughout the 3 years (Figure 1).

![Figure 1. Line graphs show effect of 36 months of treatment with captopril or conventional therapy on systolic and diastolic blood pressures in patients with (top panel) and without (bottom panel) microalbuminuria. *p<0.05 vs. conventional therapy.](http://hyper.ahajournals.org/content/21/6/788)
TABLE 3. Effects of Treatment on Kidney Function and Diabetes Control in Patients Without Microalbuminuria

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Conventional therapy (n=28)</th>
<th>Captopril therapy (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 9 months 36 months</td>
<td>Baseline 9 months 36 months</td>
</tr>
<tr>
<td>Glomerular filtration rate (mL/min per 1.73 m²)*</td>
<td>93 (64-127) 92 (59-126) 92 (64-126)</td>
<td>96 (66-132) 92 (70-133) 93 (58-132)</td>
</tr>
<tr>
<td>Creatinine (mmol/L)*</td>
<td>78.2±2.7 85.2±3.1 83.7±3.2</td>
<td>77.4±3.4 86.7±2.7 85.5±3.3</td>
</tr>
<tr>
<td>Urinary albumin excretion (µg/min)</td>
<td>5 (1-18) 6 (1-81) 5 (1-31)</td>
<td>6 (1-17) 4 (1-22) 6 (1-28)</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)*</td>
<td>8.7±0.6 9.0±0.5 9.5±0.6</td>
<td>7.9±0.6 8.0±0.5 8.6±0.6</td>
</tr>
<tr>
<td>A₁c glycosylated hemoglobin (%)†</td>
<td>9.2±0.4 9.4±0.4 9.3±0.4</td>
<td>9.3±0.4 8.7±0.3 9.3±0.4</td>
</tr>
</tbody>
</table>

*Values are mean (range). †Values are mean±SEM. §p<0.05, |p<0.01 vs. baseline. ¶Values are geometric mean (range).

Effects on Kidney Function and Metabolic Control

Renal function parameters for patients who completed the protocol are summarized in Tables 3 and 4. None of the patients had hyperfiltration, defined as a baseline glomerular filtration rate exceeding 135 mL/min per 1.73 m². Although not statistically significant, patients in the conventional therapy group had a lower baseline glomerular filtration rate. Neither therapy influenced the glomerular filtration rate significantly during the study in subjects either with or without microalbuminuria (Figure 2). Furthermore, when the values of dropout patients at their last treatment point were added, there was no significant difference in glomerular filtration rate from baseline to 9 and 36 months in microalbuminuric patients treated with either captopril (97.1±4.8 versus 97.7±8.7 versus 92.5±8.2 mL/min per 1.73 m²) or conventional therapy (86.2±6.1 versus 89.8±8.2 versus 91.2±9.6 mL/min per 1.73 m²). Serum creatinine increased slightly but significantly in both groups of patients without microalbuminuria. No significant changes were observed in UAE at 9 and 36 months (Table 3) and over the entire course of the study (Figure 3) in patients without microalbuminuria treated with conventional therapy. A significant but transient decrease in UAE was seen at 9 months in patients on captopril therapy. Moreover, only one of the ACE inhibitor-treated and two of the non-ACE inhibitor-treated patients progressed to a modest range of microalbuminuria (20-40 µg/min) during the course of the study (Table 4). On the other hand, UAE decreased significantly at 9 and 36 months in patients with microalbuminuria treated by captopril as single therapy or combined with hydrochlorothiazide (Table 4). In those treated with conventional therapy, UAE was reduced significantly at 9 months but rose significantly thereafter. The fall in UAE during captopril therapy (Figure 3) occurred within 3 months of treatment and remained significant during the entire course of the study except at 15 months. Furthermore, as shown in Figure 4, UAE decreased in eight of the nine patients treated with captopril alone (n=1) or combined with hydrochlorothiazide (n=8), whereas it rose in eight of the 12 patients treated with conventional therapy. Two patients of the latter group treated with hydrochlorothiazide progressed to macroalbuminuria (UAE >200 µg/min), although glomerular filtration rate was not significantly modified during the study period (from 52 and 114 mL/min per 1.73 m² at baseline to 50 and 118 mL/min per 1.73 m², respectively, at 36 months). However, one of these patients had severe progression of the proliferative retinopathy documented at baseline, and the other developed intermittent claudication and multiple foot ulcers. The reduction in albuminuria in most patients treated with captopril and in a few patients treated with conventional therapy was not correlated with the reduction in systolic and diastolic BP as well as with the mean arterial pressure (Figure 5). Glycemic control as assessed by fasting blood glucose and Hb A₁c concentration did not differ between groups at baseline nor after 36 months of treatment (Tables 3 and 4).

Table 5 provides information on renal function at the last treatment point for patients withdrawn from the study. Ten patients were excluded within the first 3 months and therefore had no values while under ther-

TABLE 4. Effects of Treatment on Kidney Function and Diabetes Control in Patients With Microalbuminuria

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Conventional therapy (n=12)</th>
<th>Captopril therapy (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 9 months 36 months</td>
<td>Baseline 9 months 36 months</td>
</tr>
<tr>
<td>Glomerular filtration rate (mL/min per 1.73 m²)*</td>
<td>87 (53-115) 86 (38-125) 86 (40-129)</td>
<td>99 (69-124) 94 (60-122) 93 (52-118)</td>
</tr>
<tr>
<td>Creatinine (mmol/L)*</td>
<td>80.4±7.4 92.1±5.4 91.0±7.5</td>
<td>81.5±3.8 90.4±4.6 91.2±4.1</td>
</tr>
<tr>
<td>Urinary albumin excretion (µg/min)*</td>
<td>46 (22-108) 25 (7-88)</td>
<td>60 (21-158) 14 (3-73) 21 (3-57)</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)*</td>
<td>9.4±1.2 9.1±0.5 9.4±0.8</td>
<td>9.1±0.9 7.2±0.3 8.1±1.0</td>
</tr>
<tr>
<td>A₁c glycosylated hemoglobin (%)†</td>
<td>9.3±0.7 8.7±0.3 9.2±0.3</td>
<td>9.2±0.5 8.4±0.3 8.9±0.4</td>
</tr>
</tbody>
</table>

*Values are mean (range). †Values are mean±SEM. §Values are geometric mean (range). ¶p<0.01, |p<0.05 vs. baseline.
The main purpose of this long-term double-blind study was to assess the effect of the ACE inhibitor captopril as a single therapy or combined with hydrochlorothiazide, compared with conventional therapy, on UAE in hypertensive NIDDM patients with and without microalbuminuria. Our results indicate that with a similar fall in BP, only the ACE inhibitor induced a persistent decrease in UAE during the entire 36-month treatment in patients with microalbuminuria. In contrast, mean UAE decreased significantly at 9 months with conventional therapy, but it returned to baseline values after 36 months of treatment. Furthermore, whereas an increase in UAE was prevented in every patient treated with captopril, two of the 12 patients treated with conventional therapy progressed to macroalbuminuria defined by UAE >200 µg/min.

Our data confirm and extend those of other short- and medium-term studies showing a reduction in UAE in normotensive or hypertensive insulin-dependent diabetic patients or NIDDM patients with persistent microalbuminuria treated with ACE inhibitors. Changes in UAE were probably not caused by protein restriction or improved metabolic control, as these parameters were not modified during the present study. The beneficial effect on UAE in patients treated with captopril was not induced by a reduction in the glomerular filtration rate, as usually seen in diabetic patients with hyperfiltration. The lower glomerular filtration rate in the conventional therapy group may suggest a greater degree of renal impairment and thus greater potential for progression of microalbuminuria. However, because BP reduction was similar in patients treated with either captopril or conventional therapy and because the reduction in UAE was not correlated with the reduction in BP, it is likely that the reduction in UAE was related to the specific renal hemodynamic effects of ACE inhibition. This is supported by the findings that further activating the renin-angiotensin system augments both the renal hemodynamic effect and the antiproteinuric effect of ACE inhibition. It is noteworthy that of the eight patients with microalbuminuria exhibiting a decreased UAE with ACE inhibition during the present study, seven were treated with the combination of captopril and hydrochlorothiazide. The BP-independent effect of ACE inhibition on UAE has been previously reported in other studies carried out in insulin-dependent diabetic patients or NIDDM patients treated with ACE inhibitors alone or in combination.
Permeability to proteins. Although calcium antagonist therapy has been shown to diminish proteinuria in some reports, other studies have shown no effect or even a worsening of the proteinuria. On the other hand, the results of a recent study contrast with our data in showing comparable effects of the \( \beta \)-blocker atenolol and of enalapril on UAE in NIDDM patients. However, the short duration of that study may explain the effects of atenolol on proteinuria. Indeed, such an effect on UAE observed in patients with microalbuminuria treated with metoprolol in our study was only transient and has been demonstrated in earlier studies in which BP has been reduced by \( \beta \)-blockers combined with other antihypertensive drugs.

In a recent study, the presence of proliferative retinopathy, coronary heart disease, and peripheral vascular disease was significantly associated with increased albuminuria. These pathophysiological events could explain the progression to macroalbuminuria without reduction in glomerular filtration rate in two of our microalbuminuric patients treated with conventional therapy. The identical known duration of either diabetes mellitus or hypertension observed in our two groups of patients tends to support a recent suggestion that albuminuria is an indicator of widespread vascular damage, possibly reflecting a genetically determined abnormality independent of hypertension and poor metabolic control. In a recent study, it was suggested that treatment with enalapril reduced the rate of decline in kidney function in patients with diabetic nephropathy more than equally effective antihypertensive treatment with metoprolol. However, it is noteworthy that 1) this study was unblinded; 2) the mean daily dose of furosemide was 120 mg in the metoprolol group and 50 mg in the enalapril group; 3) dropouts were not analyzed, including one patient treated with enalapril who had a rise in creatinine; and 4) the average of recumbent and upright mean diastolic pressures was not decreased significantly in the metoprolol group. Conventional treatment in the present study appeared to be as effective as captopril in maintaining baseline renal function. Consequently, the renoprotective effects of ACE inhibitors in hypertensive NIDDM patients remain to be demonstrated with longer term data on renal function and probably renal biopsy material. Furthermore, because there have been no studies indicating that the lowering of BP without reducing UAE should be less protective against cardiovascular morbidity, longer term follow-up studies are thus mandatory before ACE inhibitors can be advocated for these patients.

There are no previous long-term studies in hypertensive NIDDM patients with normal UAE comparing ACE inhibitors with conventional antihypertensive drugs. The results of the present study did not show a specific advantage of the ACE inhibitor captopril over the thiazide diuretic and the \( \beta \)-adrenergic receptor antagonist alone or in combination that are often used as drugs of first choice in antihypertensive treat-
TABLE 6. Influence of Antihypertensive Agents on Upld and Lipoprotein Subtractions in Plasma

<table>
<thead>
<tr>
<th>Measurement</th>
<th>With microalbuminuria</th>
<th>Without microalbuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n=2)</td>
<td>End (n=7)</td>
</tr>
<tr>
<td></td>
<td>Baseline (n=12)</td>
<td>End (n=3)</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>79 (42-117)</td>
<td>92 (67-118)</td>
</tr>
<tr>
<td>(mL/min per 1.73 m²)</td>
<td>97 (65-116)</td>
<td>101 (75-94)</td>
</tr>
<tr>
<td>Creatinine†</td>
<td>97.6±8.8</td>
<td>100.5±4.5</td>
</tr>
<tr>
<td>Urinary albumin excretion (μg/min)‡</td>
<td>37 (35-39)</td>
<td>42 (10-143)</td>
</tr>
</tbody>
</table>

*Values are mean (range).
†Values are mean±SEM.
‡Values are mean±SEM.

Indeed, with a similar reduction in BP, conventional therapy appeared to be as effective as captopril in preventing the rise in UAE and in preserving renal function over the 3-year period. These results may suggest that aggressive treatment of elevated BP, irrespective of the type of antihypertensive agent, may be beneficial in NIDDM patients without microalbuminuria. However, the long-term consequences of each type of treatment on kidney function and mortality remain to be established.

The choice of an antihypertensive agent in the management of hypertensive patients with diabetes mellitus depends not only on its potential renoprotective effect but must also include consideration of other factors that could be deleterious to the diabetic patient. It is important to consider the metabolic effects of drugs that can aggravate the carbohydrate intolerance or the lipid abnormalities that are common in diabetic patients with hypertension. In accordance with other studies carried out in hypertensive NIDDM patients,46-47 treatment with the ACE inhibitor during the present study did not adversely influence glycemic control and lipid profile. On the other hand, our results do not confirm previous observations48-51 that treatment with diuretics in NIDDM patients worsens glycemic control or plasma lipid profile. However, the short duration of these studies may be the explanation, as most long-term studies showed no overall changes or short-term adverse effects that waned with time, occasionally to values below baseline.52 Data concerning the effects of β-blockers in hypertensive NIDDM patients vary to a great extent. Some studies have reported deleterious effects on glycemic control and on lipoprotein metabolism,47,49-50 whereas other studies found no difference.51-54 In the present investigation, the cardioselective β-blocker metoprolol had no detrimental effect on glycemic control as estimated by fasting plasma glucose and Hb A1c and appeared to have no untoward effects on lipid profile. Because the advantage of using the ACE inhibitor as regards biochemical abnormalities has not been demonstrated during 3 years of treatment, our results cannot advocate avoiding diuretics and β-blockers in hypertensive diabetic patients, as earlier suggested.55

To conclude, in this long-term study, treatment with captopril decreased UAE and prevented the development of macroalbuminuria in hypertensive NIDDM patients with microalbuminuria at baseline more effectively than treatment with conventional drugs. On the other hand, captopril and conventional treatment were equally effec-
tive in preventing an abnormal decrease in UAE in normoalbuminuric patients. Both ACE inhibition and conventional therapy maintained baseline renal function in either microalbuminuric or normoalbuminuric patients. Our findings also suggest that long-term antihypertensive treatment with either conventional therapy or an ACE inhibitor does not cause aggravation in glycemic control or deleterious effects on plasma lipid profile in hypertensive NIDDM patients.

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Captopril or conventional therapy in hypertensive type II diabetics. Three-year analysis.
Y Lacourcière, A Nadeau, L Poirier and G Tancrède

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