

# Long-Term Renoprotective Effect of Nisoldipine and Lisinopril in Type 1 Diabetic Patients With Diabetic Nephropathy

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GFR of a long-acting dihydropyridine calcium antagonist, nisoldipine, with a long-acting ACE inhibitor, lisinopril, in hypertensive type 1 diabetic patients with diabetic nephropathy.

**OBJECTIVE** — To compare the long-term effect on kidney function of a long-acting calcium antagonist (nisoldipine) versus a long-acting ACE inhibitor (lisinopril) in hypertensive type 1 diabetic patients with diabetic nephropathy.

**RESEARCH DESIGN AND METHODS** — We performed a 4-year prospective, randomized, double-dummy controlled study comparing nisoldipine (20–40 mg once a day) with lisinopril (10–20 mg once a day). The study was double-blinded for the first year and single-blinded thereafter. The study included 51 hypertensive type 1 diabetic patients with diabetic nephropathy. Three patients dropped out during the first month; results for the remaining 48 patients are presented.

**RESULTS** — At baseline, the two groups were comparable: glomerular filtration rate (GFR) was  $85 \pm 5$  and  $85 \pm 6$   $\text{ml} \cdot \text{min}^{-1} \cdot [1.73 \text{ m}]^{-2}$ ; mean 24-h ambulatory blood pressure was  $108 \pm 3$  and  $105 \pm 2$  mmHg, and albuminuria was 1,554 mg/24 h (95% CI 980–2,465) and 1,033 mg/24 h (760–1,406) in the lisinopril and nisoldipine groups, respectively. Mean 24-h arterial blood pressure during the study did not differ between the lisinopril and nisoldipine groups ( $100 \pm 2$  and  $103 \pm 1$  mmHg, respectively). The time-course of albuminuria differed between groups ( $P < 0.001$ ). Whereas initiation of treatment with lisinopril resulted in a reduction from baseline albuminuria by 52% (95% CI 14–73), albuminuria in the nisoldipine group did not change throughout the study. GFR declined in a biphasic manner with an initial (0–6 months) reduction of  $1.3 \pm 0.3$   $\text{ml} \cdot \text{min}^{-1} \cdot \text{month}^{-1}$  in the lisinopril group compared with  $0.2 \pm 0.4$   $\text{ml} \cdot \text{min}^{-1} \cdot \text{month}^{-1}$  in the nisoldipine group ( $P < 0.01$ ). The subsequent sustained decline (6 to 48 months or the end of treatment) was identical in the two groups:  $0.5 \pm 0.1$   $\text{ml} \cdot \text{min}^{-1} \cdot \text{month}^{-1}$  (NS). Two patients in the lisinopril group and three patients in the nisoldipine group entered therapy for end-stage renal failure.

**CONCLUSIONS** — Long-term treatment with lisinopril or nisoldipine has similar beneficial effects on progression of diabetic nephropathy in hypertensive type 1 diabetic patients.

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Several studies have demonstrated that effective antihypertensive treatment diminishes the rate of decline in kidney function and postpones end-stage renal failure in diabetic nephropathy (1,2). However, the long-term effect of calcium antagonists

on the rate of decline in glomerular filtration rate (GFR) as a principal end point in type 1 diabetic patients with diabetic nephropathy remains to be clarified.

Therefore, the aim of the present study was to compare the long-term effect on

## RESEARCH DESIGN AND

**METHODS** — Our study was planned to run for 4 years and was double-blinded for the first year. For the remaining 3 years, the study was unblinded for clinical investigators and single-blinded for patients. An interim report of the first year of the study, including enrollment criteria and randomization procedures, has been published previously (3).

Originally, 52 type 1 diabetic patients with diabetic nephropathy were randomized (lisinopril,  $n = 25$ ; nisoldipine,  $n = 27$ ). A kidney biopsy of one nisoldipine-treated patient with a rapid decline in GFR revealed epimembranous glomerulonephritis; this patient consequently was excluded from all analyses. For the long-term evaluation of decline in GFR, a minimal observation period of 1 year was required. Three patients who dropped out during the first month of the intervention period were excluded: one because of palpitations (nisoldipine), one because of peripheral edema (nisoldipine), and one because of nausea/hypotension (lisinopril). Thus, 48 patients were included in the final analysis of decline in GFR. The mean follow-up time was comparable in the lisinopril and nisoldipine groups (45 vs. 42 months, respectively).

After a 4-week run-in period without any antihypertensive medication, patients were randomized to receive either lisinopril (10 mg once a day) and placebo nisoldipine or nisoldipine (20 mg once a day) and placebo lisinopril. Antihypertensive treatment was adjusted according to office blood pressure measurements. The study's aim was to obtain and maintain either a diastolic blood pressure  $< 90$  mmHg or a reduction in diastolic blood pressure of at least 10 mmHg. These blood pressure goals were not altered during the trial. If a study subject's blood pressure goal was not achieved,

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**Abbreviations:** GFR, glomerular filtration rate.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

lisinopril was increased to 20 mg or nisoldipine was increased to 40 mg once a day. Additional antihypertensive medication, mainly furosemide, was added if therapeutic goals were not achieved or as needed to control peripheral edema. The use of other ACE inhibitors, calcium-channel blockers, or angiotensin II receptor blockers was avoided. Office blood pressure was measured (using the average of two measurements) after 15 min resting in the supine position with a Hawksley random zero device and appropriate cuff size. Measurements were performed at 1, 2, 4, and 6 months and every 3 months thereafter.

The 24-h blood pressure was measured with the Takeda TM2420 device (4), versions 6 and 7 (A&D, Tokyo), at baseline; after 4, 6, 9, and 12 months; every 6 months thereafter. Blood pressure was measured every 15 min during the day (7:00 A.M. to 11:00 P.M.) and every 30 min during the night (11:00 P.M. to 7:00 A.M.). Values were averaged for each hour before the calculation of the average 24-h blood pressure. Daytime and nighttime were defined individually based on actual sleeping hours.

At baseline and every 6 months thereafter, clinical investigations were carried out between 8:00 A.M. and 1:00 P.M. Patients were studied after an overnight fast. After the collection of fasting plasma samples, patients had morning doses of insulin and breakfast. Antihypertensive medication was given as usual. During the clinical investigations, patients rested supine while drinking 150–200 ml of tap water per hour and rose only to pass urine.

As part of the clinical investigations, study subjects were administered a single injection of edetic acid labeled with 3.7 MBq  $^{51}\text{Cr}$ -EDTA at 9:00 A.M. GFR was measured in the 4-h period that followed by determination of the radioactivity in venous blood samples taken at 180, 200, 220, and 240 min after the injection (5–7). During the 4-h clearance period, urinary excretion of albumin and IgG were determined by enzyme immunoassay methods (8,9). Urine volume was corrected for the presence of residual urine as determined by ultrasound at the beginning and end of the clearance period. To correct urinary protein excretion for changes in plasma protein concentration and in GFR, the fractional clearances of albumin and IgG were determined.

All patients were asked to collect three 24-h urine specimens at baseline; at 1, 2, 4, and 6 months; and every 3 months thereafter for measurements of albumin, IgG,

retinol binding protein (10), sodium, and urea. From the nitrogen content of the excreted urea and an estimated value of nonurea nitrogen of 31 mg/kg a day, protein intake was calculated (11).

Serum albumin, electrolytes, creatinine, urate, hemoglobin, bilirubin, aspartate aminotransferase, total cholesterol, HDL cholesterol, triglyceride concentrations, and leukocyte and platelet counts were measured by standard laboratory techniques. HbA<sub>1c</sub> was measured by high-performance liquid chromatography (Diamat; Bio-Rad, Richmond, CA) (normal range 4.1–6.4%). Compliance was assessed by tablet counting and by measurement of plasma renin concentration. Postural blood pressure response was performed by measurement of lying blood pressure after a 10-min rest in the supine position; subsequently, the systolic blood pressure response to standing was recorded from 1 to 7 min while standing. Retinopathy was scored from fundus photography after pupillary dilatation as none, background, or proliferative. Smokers were defined as subjects smoking >1 cigarette a day; all others were classified as nonsmokers. At baseline and every 6 months thereafter, patients were interviewed concerning the following side effects: tiredness, headache, dizziness, flushing, gastrointestinal problems, nightmares, cough, breathlessness, palpitations, reduced physical activity, cold extremities, and skin and taste disturbances.

At the completion of 48 months of treatment with the study medication, all antihypertensive medication was withdrawn for 4 weeks in all patients except two, whose GFR was below 10 ml · min<sup>-1</sup> · [1.73 m]<sup>-2</sup>. One other patient was excluded from this part of the study because of severe hypertension. Office blood pressure, GFR, and albuminuria were determined in the remaining 18 and 15 patients in the lisinopril and nisoldipine groups who completed the trial.

### Statistical analysis

An intention-to-treat strategy in the statistical analysis was applied with an evaluation of clinical outcome during the entire study period in all 52 randomized patients. Urinary excretion of albumin and IgG and the fractional clearances of these proteins were logarithmically transformed before statistical analysis and are given as geometric means (95% CI). All other data are given as means ± SEM. All comparisons of normally or log-normally distributed parameters were performed with a Student's *t* test. Inter-

group comparisons were made by using an unpaired design, and intragroup comparisons were made by using a paired design. A  $\chi^2$  test was used to evaluate frequencies. For the parameters of interest, the changes in the two groups during the investigation period were analyzed by analysis of variance for repeated measurements with structured covariance matrices. In addition, the rate of kidney function decline was analyzed by regression lines for GFR over individually determined times during the treatment period. Linear regression and stepwise linear regression analysis were used to evaluate the correlation between putative predictors and the rate of decline in GFR. Correlations were calculated either with absolute values at baseline and during treatment or with initial changes (0–6 months).

A prestudy sample size calculation was performed. Based on data from 40 hypertensive type 1 diabetic subjects with diabetic nephropathy and GFR >40 ml · min<sup>-1</sup> · [1.73 m]<sup>-2</sup>, the observed SD on rate of decline in GFR was 2.5 ml · min<sup>-1</sup> · year<sup>-1</sup> during ongoing antihypertensive treatment. To detect a difference in rate of decline in GFR of 2 ml · min<sup>-1</sup> · year<sup>-1</sup> ( $\alpha$  = 5% [two-sided],  $\beta$  = 20%), at least 48 patients were required. Results were analyzed with commercially available programs: SPSS (SPSS, Chicago) and SAS (SAS Institute, Cary, NC). *P* ≤ 0.05 was considered significant (two-tailed).

**RESULTS** — At baseline, the two groups were comparable with regard to sex and duration of diabetes, but patients in the lisinopril group were, on average, 6 years younger (Table 1). The lisinopril and nisoldipine groups were further comparable with respect to the following: GFR, 85 ± 5 and 85 ± 6 ml · min<sup>-1</sup> · [1.73 m]<sup>-2</sup>; 24-h blood pressure, 155 ± 4/86 ± 2 and 152 ± 3/83 ± 2 mmHg; and office blood pressure, 152 ± 2 over 95 ± 1 and 157 ± 3 over 94 ± 1 mmHg, respectively. Additionally, albuminuria at baseline did not differ significantly between the lisinopril group (1,554 mg/ 24 h [95% CI 980–2,465]) and the nisoldipine group (1,033 mg/ 24 h [760–1,406]).

The office diastolic blood pressure was reduced significantly and to the same extent in the two groups (NS). For office systolic blood pressure, there was no significant difference in the time course of the two groups, although the reduction was slightly more pronounced in the lisinopril group (data not shown). At the end of the study period, 14 patients (58%) in the

lisinopril group and 10 patients (42%) in the nisoldipine group were treated with low-dose study medication; the remaining patients received high-dose medication. A total of 14 patients in each group received diuretics: 40 mg/day (range 40–500) in the lisinopril group versus 160 mg/day (range 40–2,000) in the nisoldipine group ( $P = 0.12$ ). One nisoldipine- and three lisinopril-treated patients were taking hydralazine; one patient in the lisinopril group was taking a cardioselective  $\beta$ -blocker.

The 24-h mean arterial blood pressure was significantly reduced in both groups during the investigation period. In the lisinopril group, it was lowered from  $108 \pm 3$  mmHg at baseline to an average of  $100 \pm 2$  mmHg during treatment; in the nisoldipine group, it was lowered from  $105 \pm 2$  to  $103 \pm 1$  mmHg (Fig. 1). Between the lisinopril and nisoldipine groups, there was no overall significant difference in the time course of mean arterial blood pressure between the lisinopril and nisoldipine groups ( $P = 0.33$ ). The decrease over time in 24-h diastolic blood pressure did not differ statistically between groups, whereas the reduction in 24-h systolic blood pressure tended to be more pronounced in the lisinopril group ( $P = 0.06$ ).

No overall significant difference in the time-course of GFR was observed in the two groups. There was a significant decline in GFR in both groups ( $P < 0.001$ ) and no overall significant difference between the GFR levels of the two groups. GFR declined in a biphasic manner with an initial (0–6 months) faster reduction ( $1.3 \pm 0.3$  ml  $\cdot$  min $^{-1}$   $\cdot$  month $^{-1}$ ) in the lisinopril group compared with a  $0.2 \pm 0.4$  ml  $\cdot$  min $^{-1}$   $\cdot$  month $^{-1}$  reduction in the nisoldipine group ( $P < 0.01$ ). The subsequent sustained decline (6 to 48 months or end of treatment) was similar in the two groups:  $0.5 \pm 0.1$  ml  $\cdot$  min $^{-1}$   $\cdot$  month $^{-1}$  (NS). Similarly, the rate of decline in GFR during the entire observation period was  $0.5 \pm 0.1$  ml  $\cdot$  min $^{-1}$   $\cdot$  month $^{-1}$  in both groups (NS). The mean difference between the two groups in decline of GFR was  $0.08 \pm 0.17$  ml  $\cdot$  min $^{-1}$   $\cdot$  month $^{-1}$  ( $1.0 \pm 2.0$  ml  $\cdot$  min $^{-1}$   $\cdot$  year $^{-1}$ ). Inclusion of ambulatory blood pressure as a covariate revealed no differences between the lisinopril and nisoldipine group in the analysis of GFR over time (NS).

Two patients in the lisinopril group and three patients in the nisoldipine group entered therapy for end-stage renal failure (NS). In univariate analyses, significant cor-

**Table 1—Baseline clinical characteristics of 48 hypertensive type 1 diabetic patients with diabetic nephropathy**

	Lisinopril	Nisoldipine	P
Sex (M/F)	17/7	15/9	NS
Age (years)	$35 \pm 6$	$41 \pm 9$	$<0.01$
Duration of diabetes (years)	$24 \pm 1$	$25 \pm 1$	NS
BMI (kg/m $^2$ )	$24.6 \pm 0.6$	$25.3 \pm 0.8$	NS
Insulin dose (U $\cdot$ kg $^{-1}$ $\cdot$ day $^{-1}$ )	$0.72 \pm 0.16$	$0.63 \pm 0.20$	NS
Retinopathy background (simplex/proliferative)	8/16	9/15	NS
Smokers	14	13	NS
Postural blood pressure testing			
Maximal decrease (mmHg)	12 (0–55)	17 (0–73)	0.05
Maximal decrease $\geq 20$ mmHg (n)	4	9	NS

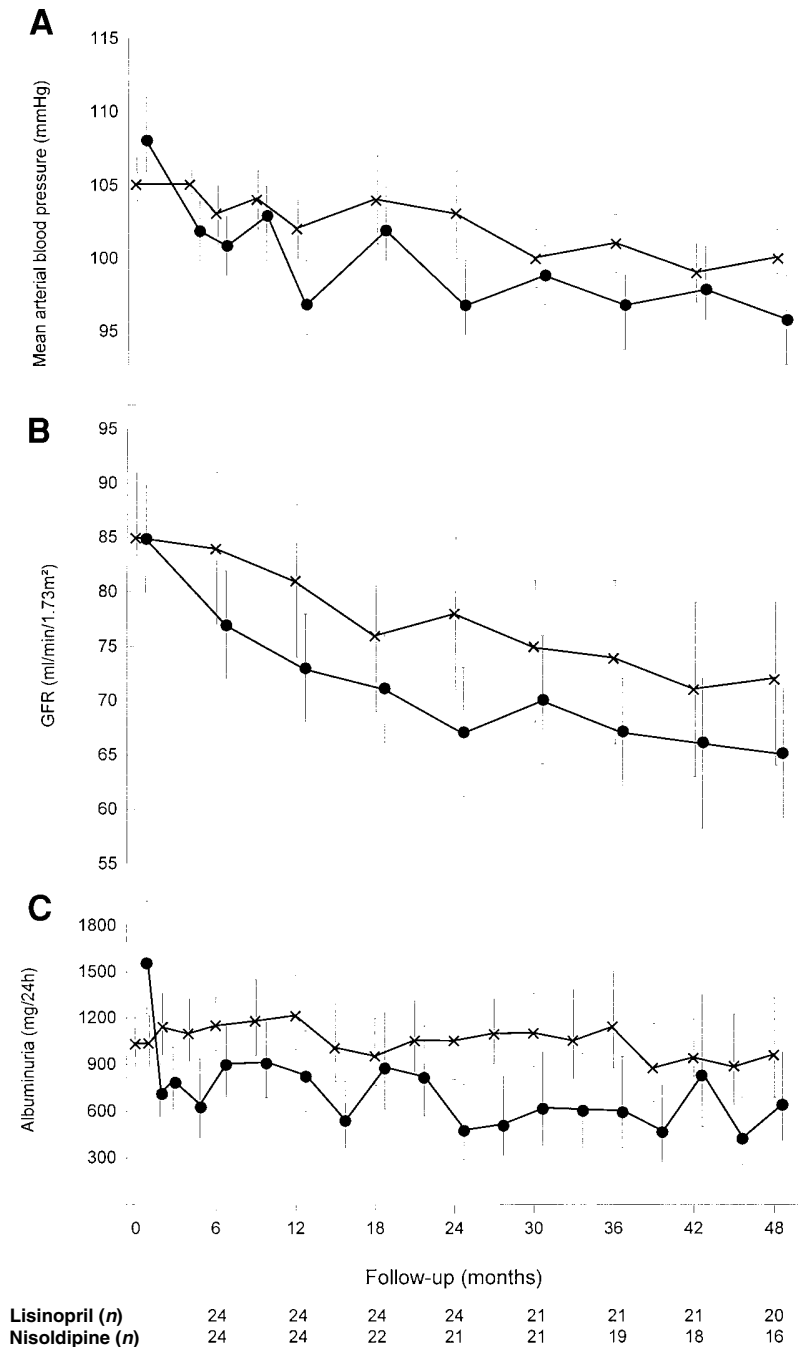
Data are n, means  $\pm$  SD, or median (range).

relations were found between the rate of decline in GFR and the values at baseline and during follow-up of the following: 24-h blood pressure, HbA $_{1c}$ , serum cholesterol, and albuminuria. However, age, baseline GFR, average urinary sodium excretion, protein intake during follow-up, and initial changes in GFR, blood pressure, or albuminuria were not correlated to the rate of decline in GFR. In a multivariate model, high values during the observation period of 24-h diastolic blood pressure, HbA $_{1c}$ , and albuminuria were associated with increased rate of decline in GFR, independently of the randomization group ( $r^2$  [adjusted] = 0.42).

There was a significant difference in the time-course of albuminuria between groups ( $P < 0.001$ ). Whereas initiation of treatment with lisinopril reduced baseline albuminuria by 52% (95% CI 14–73), albuminuria increased insignificantly by 12% (–10 to 40) in the nisoldipine group throughout the study (Fig. 1). Geometric mean of albuminuria during treatment was 747 mg/24 h (95% CI 415–1,348) in the lisinopril group and 1,129 mg/24 h (777–1,640) in the nisoldipine group (NS). Fractional clearance of albumin did not differ between groups at baseline and was reduced in the lisinopril group from  $380 \times 10^{-6}$  (95% CI 217–648) to  $236 \times 10^{-6}$  (111–501) compared with an increase from  $212 \times 10^{-6}$  (95% CI 136–330) to  $337 \times 10^{-6}$  (193–588) in the nisoldipine group ( $P = 0.005$  between groups). A similar pattern was seen for fractional clearance of IgG, which declined insignificantly from  $129 \times 10^{-6}$  (95% CI 62–240) to  $92 \times 10^{-6}$  (43–195) and rose from  $68 \times 10^{-6}$  (95% CI 37–108) to  $106 \times 10^{-6}$  (59–188) ( $P = 0.01$ ) during treatment with lisinopril and nisoldipine, respectively ( $P = 0.02$ ).

The changes in urinary excretion of retinol-binding protein did not differ significantly between groups ( $P = 0.14$ ). However, this marker of tubular function only increased significantly (from 752  $\mu$ g/24 h [95% CI 377–1,500] to 1,274  $\mu$ g/24 h [629–2,578]) in nisoldipine-treated patients, whereas no change from baseline (684  $\mu$ g/24 h [293–1,597]) to follow-up (729  $\mu$ g/24 h [321–1,658]) was seen in the lisinopril group. Table 2 shows the biochemical data at baseline and during the study period.

Four patients in the lisinopril group withdrew from the study: two developed ischemic heart disease simultaneously with end-stage renal failure, one withdrew because of angina pectoris (without subsequent myocardial infarction), and one had severe orthostatic hypotension. Eight patients in the nisoldipine group did not complete the study because of the following: death (cerebrovascular disease,  $n = 2$ ; diabetic ketoacidosis,  $n = 1$ ), end-stage renal failure ( $n = 3$ ), nonfatal myocardial infarction ( $n = 1$ ), and a hypertensive crisis ( $n = 1$ ). Furthermore, two nisoldipine-treated patients had a nonfatal major stroke that did not require permanent discontinuation of study medication, and one patient in each group experienced a transitory cerebral ischemic event. One woman in the nisoldipine group, who ceased randomized treatment within the first month, had a breast cancer diagnosed during the 4-year follow-up period. The intention-to-treat analysis of major clinical events in 52 randomized patients revealed no significant difference in fatal and nonfatal cardiovascular events, end-stage renal failure, or death between groups (NS); a per-protocol analysis gave similar results. Finally, in the lisinopril group, eight patients reported persistent cough, and three reported edema despite ongoing diuretic treatment, as com-



**Figure 1**—Mean course of 24-h ambulatory mean arterial blood pressure (A), GFR (B), and albuminuria (C) in hypertensive type 1 diabetic patients before and during antihypertensive treatment with lisinopril (●) or nisoldipine (X). Analysis of repeated measurements evaluating arterial blood pressure and GFR revealed a significant effect of time but not of treatment group. There was a significant difference in the time course of albuminuria between groups ( $P < 0.001$ ). The vertical bars represent SEM (albuminuria, geometric mean  $\times/\div$  antilog SEM).

pared with four and seven nisoldipine-treated patients, respectively (NS).

Plasma renin was increased in all lisinopril-treated patients to a median of 108 mU/l (range 23–1,415), whereas it remained unchanged in the nisoldipine

group ( $P < 0.001$ ) (Table 2). Furthermore, tablet counting revealed a compliance of 96% (76–102) in the lisinopril group and 98% (73–108) in the nisoldipine group.

In patients whose antihypertensive treatment was withdrawn at the end of the

study, baseline mean arterial blood pressure, GFR, and albuminuria, respectively, were  $106 \pm 2$  mmHg,  $94 \pm 5$  ml  $\cdot$  min $^{-1}$   $\cdot$  [1.73 m] $^{-2}$ , and 1,093 mg/24 h (691–1,728) in the lisinopril group versus  $108 \pm 3$  mmHg,  $93 \pm 6$  ml  $\cdot$  min $^{-1}$   $\cdot$  [1.73 m] $^{-2}$ , and 787 mg/24 h (579–1,071) in the nisoldipine group (NS). An initial decline in GFR (to  $85 \pm 6$  ml  $\cdot$  min $^{-1}$   $\cdot$  [1.73 m] $^{-2}$ ) was observed during the first 6 months of treatment with lisinopril, whereas GFR remained unchanged after initiation of nisoldipine therapy. After 4 weeks of withdrawal from long-term antihypertensive treatment, the rise in blood pressure was similar in the lisinopril and nisoldipine groups (NS; between-group data not shown). GFR rose in the lisinopril group from  $70 \pm 5$  to  $77 \pm 6$  ml  $\cdot$  min $^{-1}$   $\cdot$  [1.73 m] $^{-2}$  ( $P < 0.005$ ), whereas kidney function remained unchanged ( $78 \pm 6$  to  $79 \pm 6$  ml  $\cdot$  min $^{-1}$   $\cdot$  [1.73 m] $^{-2}$ ) in nisoldipine-treated patients (NS). In the lisinopril group, albuminuria was reduced during treatment and increased to pretreatment levels after 4 weeks without antihypertensive treatment, which is not different from the unchanged urinary albumin excretion rate in the nisoldipine group (NS; data not shown).

**CONCLUSIONS**— In a 4-year randomized controlled study of 48 hypertensive type 1 diabetic patients with diabetic nephropathy, the long-acting calcium antagonist nisoldipin induced comparable reductions in mean arterial blood pressure and had a beneficial effect on the rate of decline in GFR similar to that of the ACE inhibitor lisinopril. The relatively large decline in GFR observed after initiation of treatment with lisinopril was reversible and regained after withdrawal of antihypertensive treatment for 1 month at the end of follow-up, suggesting a hemodynamic mechanism. No enhanced changes in kidney function were observed in the nisoldipine-treated patients at initiation or after withdrawal of therapy. Lisinopril induced a significant reduction in albuminuria, whereas albuminuria remained unchanged in nisoldipine-treated patients. The level of albuminuria and the 24-h mean arterial blood pressure were alike during the study period.

None of the previous studies comparing calcium antagonists with ACE inhibitors in type 1 diabetic patients with overt nephropathy lasted  $>1$  year (3,12,13); thus, they are not suitable for the study of principal renal end points (rate of decline in

**Table 2—Laboratory data in hypertensive type 1 diabetic patients before and during 4 years of antihypertensive treatment with lisinopril or nisoldipine**

	Lisinopril		Nisoldipine		P (intergroup changes)
	Baseline	Follow-up	Baseline	Follow-up	
Hb (mmol/l)	8.4 ± 0.2	8.0 ± 0.2*	8.3 ± 0.2	8.3 ± 0.2	0.10
HbA <sub>1c</sub> (%)	9.0 ± 0.3	9.5 ± 0.2†	9.1 ± 0.3	9.4 ± 0.2	0.47
Serum levels					
Albumin (μmol/l)	37 ± 1	36 ± 1	40 ± 1	37 ± 1‡	0.09
Creatinine (μmol/l)	107 (72–223)	116 (73–294)*	101 (73–191)	105 (71–318)*	0.64
Potassium (mmol/l)	4.1 ± 0.1	4.4 ± 0.1*	4.2 ± 0.1	4.1 ± 0.1	0.004
Sodium (mmol/l)	138 ± 1	139 ± 1	138 ± 1	139 ± 1‡	0.49
Urate (mmol/l)	0.33 ± 0.02	0.37 ± 0.02*	0.33 ± 0.03	0.33 ± 0.02	0.06
Plasma renin (mU/l)	32 (6–166)	108 (23–1,415)‡	33 (13–110)	32 (12–117)	<0.001
Total cholesterol (mmol/l)	5.5 ± 0.3	5.4 ± 0.2	5.8 ± 0.3	6.0 ± 0.3	0.20
HDL cholesterol (mmol/l)	1.4 ± 0.1	1.4 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.46
Triglycerides (mmol/l)	1.2 (0.5–11.6)	1.3 (0.5–12.0)	1.3 (0.6–2.6)	1.2 (0.6–4.1)	0.96
Protein intake (g · kg <sup>-1</sup> · [24 h] <sup>-1</sup> )	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	0.35
Urinary sodium excretion (mmol/24 h)	179 ± 15	177 ± 10	181 ± 13	157 ± 11	0.25
Extracellular volume (l/1.73 m <sup>2</sup> )	14.7 ± 0.4	13.4 ± 0.2‡	13.8 ± 0.3	13.4 ± 0.2	0.08

Data are means ± SEM or median (range). \* $P \leq 0.01$ ; † $P \leq 0.05$ ; ‡ $P \leq 0.001$ , as compared with baseline.

GFR, development of end-stage renal failure, or death due to renal disease).

The natural history of diabetic nephropathy is characterized by a mean rate of decline in GFR of 10–15 ml · min<sup>-1</sup> · year<sup>-1</sup>, ranging from 0 to 25 ml · min<sup>-1</sup> · year<sup>-1</sup> (14–16) and a median survival time from onset of diabetic nephropathy of 5–7 years (17,18). During the present 4-year study, 3 patients died, and only 5 of the 48 patients required therapy for end-stage renal failure. No differences in the change of kidney function over time was observed between the lisinopril and nisoldipine groups, and by calculation of individual slopes for the sustained rate of decline in GFR, the annual loss of kidney function was 6 ml · min<sup>-1</sup> · year<sup>-1</sup> in both groups. A similar rate of decline in GFR was observed when office mean arterial blood pressure was reduced to a comparable level (103 mmHg) with metoprolol in the study by Björck et al. (19), whereas the loss in GFR was lower (2 ml · min<sup>-1</sup> · year<sup>-1</sup>) in the enalapril-treated group (office mean arterial blood pressure 102 mmHg). In the largest study of type 1 diabetic patients with diabetic nephropathy (20), average office mean arterial blood pressure was 96 mmHg in patients treated with captopril and 100 mmHg in patients treated with antihypertensive drugs other than ACE inhibitors or calcium-channel blockers. However, the average rate of decline in creatinine clearance was 13.4 ml · min<sup>-1</sup> · year<sup>-1</sup> (17%) in the placebo group and 9.2 ml · min<sup>-1</sup> · year<sup>-1</sup>

(11%) in the captopril group (21). The differences in rate of decline of kidney function between treatment groups was 3.9 and 4.2 ml · min<sup>-1</sup> · year<sup>-1</sup> in two previous studies (19,20). In our study, the mean difference between the two groups in rate of decline in GFR was 1.0 ± 2.0 ml · min<sup>-1</sup> · year<sup>-1</sup>.

Treatment with long-acting calcium-channel blockers or ACE inhibitors had the same beneficial effect on the rate of decline in creatinine clearance in hypertensive type 2 diabetic patients with proteinuria (22,23).

Additional renoprotective effects might be achieved by more aggressive blood pressure reduction, as suggested by a recent observational study (24) of 304 type 1 diabetic patients with overt diabetic nephropathy followed with annually GFR measurements for at least 3 years (median follow-up 7 years [range 3–20]). These data demonstrate an association between office blood pressure and rate of decline in GFR and suggest a target mean arterial blood pressure of 95 mmHg, at which level the annual change in GFR ranges between 1.4 and 3.5 ml · min<sup>-1</sup> · year<sup>-1</sup>. However, no significant differences in rate of decline in renal function were demonstrated in type 1 (25) or type 2 (23) diabetic patients randomized to intensive or moderate blood pressure control (the change in mean arterial blood pressure was 5–6 mmHg).

Furthermore, the beneficial effect of antihypertensive treatment increases with time in diabetic kidney disease (26). The

same progressive renoprotective effect has been demonstrated in patients with nondiabetic nephropathy (27).

In trials of blood pressure-lowering regimens, the duration of treatment is often relatively short, low-risk patients are included, and a considerable crossover between groups occurs; therefore, estimates of the full potential of treatment effects will be conservative. In hypertensive patients with diabetic nephropathy, treatment with several antihypertensive agents and diuretics is often required to obtain blood pressure control, as demonstrated in our observational study (24), in which >75% of patients received two or more antihypertensive drugs. In patients with more advanced diabetic kidney disease, three to four different antihypertensive agents are commonly used (28).

The short-term effects on albuminuria of different calcium antagonists versus ACE inhibitors in diabetic nephropathy has been evaluated in several studies, the results of which have been widely divergent, as reviewed by Parving et al. (29). Long-term studies have clearly demonstrated that ACE inhibitors are superior to calcium-channel blockers in reducing proteinuria (30).

Our study was powered and designed to evaluate the impact of different blood pressure-lowering agents on rate of decline in GFR in type 1 diabetic patients with diabetic nephropathy. The present study population is much too small to examine cardiovascular end points in relation to different antihypertensive treatment regimens.

In summary, long-term treatment with lisinopril or nisoldipine has similar beneficial effects on progression of diabetic nephropathy in hypertensive type 1 diabetic patients. High blood pressure, elevated albuminuria, and poor metabolic control act as progression promoters. The impact of more aggressive antihypertensive regimens or combination therapies remains to be investigated.

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