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Effect of improved metabolic control on loss of kidney function in Type 1 (insulin-dependent) diabetic patients: an update of the Steno studies

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Summary. We re-examined 69 of the 70 patients entering the two independent Steno Studies of effects of improved metabolic control on progression of late diabetic complications. They were analysed according to an intent to treat after follow-up for 8 years (Steno Study 1) and 5 years (Steno Study 2). The glycaemic control had improved in the insulin infusion group compared with the conventional treatment group (mean HbA_{1c}) by $2.0 \pm 0.6\%$ vs 0.7 ± 1.2 in Steno Study 1 and by $1.8 \pm 1.2\%$ vs 0.4 ± 1.3 ($p < 0.01$) in Steno Study 2. In the insulin infusion groups three patients had died during episodes of ketoacidosis. These were not caused by malfunction of the insulin infusion pumps. In the conventional treatment groups, three patients suffered five cardiovascular events causing two deaths. From the sixth month of Steno Study 1 the annual change of the glomerular filtration rate was -3.7 (-5.4 to -2.0) $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ vs -1.0 (-2.1 to -0.1) (conventional vs insulin infusion group, mean (95% confidence interval, $p < 0.01$)). The change in urinary albumin excretion was associated with the glycaemic control ($n = 69, r = 0.49, p < 0.0002$). No progression was observed among 32 patients with low range microalbuminuria (30 to 99 mg/24 h). Among the 19 patients with an initial albumin excretion between 100 and 300 mg/24 h, progression of complications was more frequent during conventional treatment ($n = 10$) vs insulin infusion ($n = 9$): Clinical nephropathy (10 of 10 vs 2 of 9, $p < 0.01$) and arterial hypertension (7 of 10 vs 1 of 9, $p < 0.01$). The glomerular filtration rate declined during conventional treatment by -23 (-42 to -4) $ml \cdot mm^{-1} \cdot 1.73\,m^{-2}$ ($p < 0.05$) but not during insulin infusion (-13 (-31 to 5) NS). These results suggest that patients at risk of nephropathy should be offered near normal glycaemic control in order to preserve their kidney function.

Key words: Type 1 (insulin-dependent) diabetes mellitus, HbA_{1c}, microalbuminuria, insulin infusion pumps, continuous subcutaneous insulin infusion, blood pressure.

The effects of improved metabolic control on the development and progression of microvascular complications in Type 1 (insulin-dependent) diabetic patients have been studied in a number of prospective randomized trials. Only some of these have been in progress for one year or more [1–11]. If the lesions in question were not too advanced at entry [5, 7], these studies have demonstrated beneficial effects of improved metabolic control on various morphological and physiological markers of microangiopathy and neuropathy [1–4, 6, 8–11]. Such effects are likely also to delay or prevent loss of kidney function and vision but this was never demonstrated because of small numbers of patients studied and study periods too short for significant clinical progression to occur in either intensive treatment or control groups. Attaching the greatest importance to kidney function we have re-addressed this important question and re-examined 69 of the 70 Type 1 diabetic patients who entered one of the two independent Steno Studies of improved vs unchanged metabolic control in 1980 [1] or in 1983 [2].

Subjects and methods

Subjects

The subjects were 70 patients with Type 1 diabetes who fulfilled the following criteria: Age 18–51 years, postprandial C-peptide level < 0.2 nmol/l, history of diabetes 5–35 years, diabetes onset before age 30, serum creatinine < 150 μmol/l and no history of non-diabetic renal disease. In 1980 34 entered the Steno Study 1 [1] and in 1983 36 entered the Steno Study 2 [2]. The patients gave their informed consent and the protocols were approved by the regional scientific ethical committee. Steno Study 1 [1] had the additional entrance criterion of presence of background retinopathy. Shortly after randomization, one patient in each group turned out to have minor proliferative changes. One in the insulin infusion group had well regulated hypertension treated with hydroflumethiazide, 25 mg daily. No other patients took any medication besides insulin. All were included in the present study.

In Steno Study 2 [2] the additional entrance criterion was a urinary albumin excretion rate in the range of 30–300 mg/24 h in two of three 24 h urine specimens collected at home over a 3-month period, supine systolic blood pressure < 160 mm Hg and diastolic blood

pressure < 95 mm Hg. One patient with anorexia nervosa did not recover before moving to another part of the country and was the only patient excluded from this follow-up. The study, therefore, comprised 69 patients.

Random assignment

In both studies, the 69 patients had been assigned randomly to either continuous subcutaneous insulin infusion or to remain on conventional insulin treatment. The two groups were well matched in key demographic and clinical data [1, 12], apart from differences explained by the different entrance criteria. After the two-year reports [1, 2] the patients could freely choose between conventional insulin treatment with one or two insulin injections per day, multiple injections with four injections per day, and continuous subcutaneous insulin infusion by means of portable insulin infusion pumps.

Diabetic control

The metabolic control was monitored by measuring glycosylated haemoglobin (haemoglobin HbA_{1c}, reference range 5.4–6.3% [13]) every other month during study and at least four times a year throughout the follow-up period. The long-term (years) glycaemic control of each patient was estimated by first calculating the annual median of all HbA_{1c} measurements through that year, and then calculating for each patient the mean of these values, (hereafter called the mean of all HbA_{1c} values). Patients on the intensified treatment regimens adjusted their insulin dose according to blood glucose measurements at home using blood glucose stix (BM-Test-Glycemic 1–44 Boehringer Mannheim GmbH, FRG), or Haemo-Glukotest 1–44, (Boehringer). After two years of study the patients continued their regular visits at the outpatients' clinic of the Steno Memorial Hospital, but the check-up on the frequency of blood glucose measurements at home was not continued. In case of acute illness or high blood glucose the use of ketostix were strongly and repeatedly recommended and in case of doubt the patients were asked to contact the hospital.

Laboratory measurements and ophthalmoscopy

Urinary albumin concentration was initially measured by a radial immunodiffusion technique [14] to examine one or two sterile 24 h urine specimens collected at home every other month. Since 1985 an ELISA technique tested against the previous technique [15] was used.

Blood pressure in the right arm was measured every second month with a standard sphygmomanometer (25 by 12 cm cuff) after 20 min of lying at rest. The diastolic blood pressure was recorded at disappearance of the Korotkoff sounds (phase 5). The glomerular filtration rate was assessed at 0, 6, 12, 24 months and at re-examination five or eight years after randomization by measuring plasma disappearance of a single i. v. injection of (^{51}Cr) edetic acid (given at 09.00 hours) over a period of 4 h [16]. Patients were examined with an ophthalmoscope through the dilated pupilla at entry to the study and at re-examination.

Endpoints

These were death, major cardiovascular events, decline in glomerular filtration rate, blood pressure increase persistently above 160/95 mm Hg (with subsequent start of antihypertensive treatment), urinary albumin excretion rate above 300 mg/24 h in two out of three 24 h urine collections and development of proliferative retinopathy. Results are given at re-examination or as the last reading before death. If antihypertensive treatment was started, the data on blood pressure and urinary albumin excretion rates are given as median of the last three readings prior to treatment.

Analysis of patients with microalbuminuria

An analysis was performed on the 51 patients from the two studies who at entry had no nephropathy but an elevated urinary albumin excretion rate ranging from 30 to 300 mg/24 h in at least two out of three 24 h urine samples (microalbuminuria). They were subdivided according to presence of low range (30 to 99 mg/24 h, $n = 32$) or high range (100 to 300 mg/24 h, $n = 19$) microalbuminuria and were analysed according to the original randomization of Steno Study 1 and 2 (Table 4). This subdivision was made because our previous prospective study of the discriminative level of urinary albumin excretion had shown that all patients with a urinary albumin excretion above 70 µg/min ≈ 100 mg/24 h progressed to nephropathy within seven years [17] whereas few patients with microalbuminuria in the low range of 30 to 99 mg/24 h progressed. Patients in the subgroups were similar with respect to age, diabetes duration and at entry had similar HbA_{1c}, glomerular filtration rate and blood pressure (Table 4).

Statistical methods

Data are given as mean with SD or 95% confidence interval. Urinary albumin excretion were log transformed before analyses and given as geometric mean with 95% confidence interval. Paired and unpaired Student's *t*-test and Fisher's exact test were used for comparisons within and between the groups. Multiple stepwise regression analysis including all patients were performed with a commercially available program (Statgraphic, STSC, Rockvill, Md., USA). Levels of significance were set to $p < 0.05$ (two tailed).

Results

Glycaemic control

The glycaemic control is given as the mean of all HbA_{1c} values measured in each patient during the entire study and follow-up period. It had significantly improved in the original insulin infusion groups compared with the conventional treatment groups (Table 1). Eighteen patients had changed their form of treatment during the third to fourth year of follow-up, and metabolic control during the last three years prior to the re-examination was no longer distinguishable between the original groups (Table 1). An overall trial effect was observed. Thus, the 33 patients in the conventional treatment groups improved their mean HbA_{1c} during the entire study by 0.6% (95% confidence

Table 1. Steno studies 1 and 2. A five and eight years follow-up. Metabolic control, actual treatment

	Steno 1		Steno 2	
Original treatment	CSII	CIT	CSII	CIT
Numbers studied	18	16	18	17
HbA_{1c} (%)				
At entry	9.6 ± 1.6	8.8 ± 1.4	9.6 ± 2.0	9.1 ± 1.2
Mean of all HbA_{1c}	7.6 ± 0.9	8.1 ± 1.1	7.9 ± 1.1	8.8 ± 1.0
ΔHbA_{1c}	2.0[a] ± 0.6	0.7 ± 1.2	1.8[a] ± 1.2	0.4 ± 1.3
Mean during last 3 years	7.9 ± 1.0	7.9 ± 1.3	8.2 ± 1.2	8.7 ± 1.3
Insulin dose (U/kg) at last examination	0.53 (0.30–0.85)	0.53 (0.39–0.70)	0.50 (0.33–1.21)	0.55 (0.23–1.10)
Form of treatment[b] at re-examination CSII/MIT/CIT	13/5/0	4/4/8	16/2/0	0/3/14

Mean ± 1 SD or range in parentheses.
[a] Different from the CIT group ($2p < 0.01$); [b] CSII: Continuous subcutaneous insulin infusion. MIT: Multiple injection treatment. CIT: Conventional insulin treatment

Table 2. Steno Studies 1 and 2. A five and eight years follow-up. Major endpoints

	Steno 1		Steno 2	
Original treatment	CSII	CIT	CSII	CIT
Numbers studied:	18	16	18	17
Nephropathy: (normal/microalbuminuria/clinical nephropathy)				
At entry	8/9/1	6/7/3	0/18/0	0/17/0
At re-examination	10/6/2	7/1/8	6/11/1	6/6/5
Retinopathy: (nil/background/proliferative)				
At entry	0/17/1	0/15/1	5/12/1	5/11/1
At re-examination	0/12/6	0/7/9	4/12/2	2/12/3
Antihypertensive treatment:				
At entry	1	0	0	0
At re-examination	5	8	2	3

CSII: Continuous subcutaneous insulin infusion. CIT: Conventional insulin treatment

interval −1 to −0.1%, $p = 0.013$). The insulin dose was similar in the four groups (Table 1).

Hypoglycaemia and ketoacidosis

In the insulin infusion groups the overall frequencies of ketoacidotic (0.09 per patient-year) and hypoglycaemic episodes (0.10 per patient-year) requiring medical intervention during the last year were similar to our previous reports.

Three patients had died during diabetic ketoacidosis confirmed biochemically upon post mortem.

Case no. 1. (Steno Study 2). A 36-year-old male with a diabetes duration of 16 years, a mean HbA_{1c} of 8.0% and an initial and last urinary albumin excretion rate of 63 and 96 mg/24 h. He apparently developed pneumonia and was treated with antibiotics by a general practitioner. The hospital was not informed. The patient persistently informed the family and various doctors on house calls that the diabetes was under control, until he acutely deteriorated and died in respiratory failure (presumably Kussmauls respiration) in an ambulance. Autopsy revealed not pneumonia but an enlarged heart with increased amounts of connective tissue, indicating cardiomyopathy. The insulin infusion pump was operating impeccably.

Case no. 2. (Steno Study 2). A 32-year-old male with a diabetes duration of 16 years, a urinary albumin excretion rate of 33 to 25 mg/24 h and a mean HbA_{1c} of 9.2%. He had recently been divorced and was receiving psychiatric therapy after having attempted suicide. He was living alone and was found dead in his bed with signs of previous excitation. The insulin infusion pump was operating impeccably with the connecting tubes seemingly intact. Post mortem examination did not reveal the cause of death.

Case no. 3. (Steno Study 1) A 25-year-old male with a diabetes duration of 24 years who was living alone. The urinary albumin excretion rate at entry and during the study were 179 to 200 mg/24 h, the mean HbA_{1c} was 6.4%. The patient suffered from proliferative retinopathy with a progressive loss of vision and had, in consequence, recently lost his job. He was found dead without objective signs of convulsions. The pump was operating impeccably but had been disconnected and was neatly placed on a table beside the bed. Biochemical examination of blood and urine was performed but no post mortem examination.

Cardiovascular events

Three patients in the conventional treatment group of Steno Study 2 and one initially receiving insulin infusion in Steno Study 1 suffered six severe cardiovascular events during which two of the patients died.

Case no. 1. A 44-year-old female with diabetes for 23 years, a urinary albumin excretion rate of 68–85 mg/24 h, a mean HbA_{1c} of 8.6% and receiving antihypertensive treatment had a lethal pulmonary embolism of unknown origin.

Case no. 2. A 46-year-old male with diabetes for 31 years, a urinary albumin excretion rate of 180 to 313 mg/24 h, a mean HbA_{1c} of 8.6% and receiving antihypertensive treatment had three cerebro-vascular accidents within one year and died during the last episode.

Case no. 3. A 52-year-old male with diabetes for 23 years, a urinary albumin excretion rate of 66 to 41 mg/24 h, a mean HbA_{1c} of 8.6% and a blood pressure of 145/90 mmHg, receiving no antihypertensive treatment. A minor cerebro-vascular accident of the left cerebral hemisphere caused a partial hemiparesis with almost complete remission after 4 weeks.

Case no. 4. (Steno Study 1) A 55-year-old female with diabetes for 27 years and a urinary albumin excretion rate over 1000 mg/24 h at entry, declining to persistently below 300 mg/24 h after introduction of antihypertensive treatment. She received insulin infusion for two years (HbA_{1c} 7.3%) but then changed to multiple injections (HbA_{1c} 10.1%). The patient survived a subendocardial infarction in 1985.

Nephropathy, blood pressure and retinopathy

In both studies, Steno 1 and 2, the number of patients progressing to clinical nephropathy, proliferative retinopathy or developing hypertension were higher in the conventional treatment groups compared with the insulin infusion groups (Table 2). None of these differences, however, reached statistical significance when analysing the two studies separately.

The systolic blood pressure increased significantly ($p < 0.05$) in the conventional treatment groups of both studies but not during insulin infusion (Table 3). In both studies more than half of the patients had a stable urinary albumin excretion rate or even normalized a slightly elevated one (Steno 2, six patients in each treatment group, Table 2). Only one patient progressed from normal to microalbuminuria and progression from normoalbuminu-

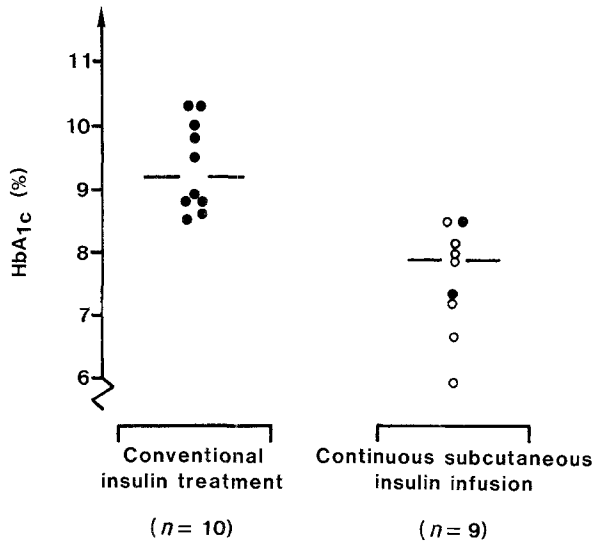

Fig. 1. Metabolic control during a mean of seven years of observation in 19 Type 1 (insulin-dependent) diabetic patients who had a urinary albumin excretion between 100 and 300 mg/24 h when entering one or other of the two Steno studies. The HbA_{1c} value for each patient is given as the mean of annual medians of all measurements during study. Closed circles: Patients progressing to clinical nephropathy. Significant difference between groups ($p < 0.001$). All nine patients randomized to receive continuous subcutaneous insulin treatment remained on this treatment. Among the ten in the original conventional treatment group, one had changed to continuous insulin infusion (mean HbA_{1c} 8.5%) and two received multiple insulin injections (HbA_{1c} 8.9% and 9.4%)

ria to clinical nephropathy was not observed. The differences in urinary albumin excretion between the insulin infusion and the conventional treatment groups at re-examination were not significant (Table 3). The glomerular filtration rate declined significantly in both treatment groups of Steno Study 1 (Table 3). In the insulin infusion group of Steno Study 1 a decline in the glomerular filtration rate had been observed during the first 6 months of study (124 ± 28 ml·min^{-1}·1.73 m^{-2} to 114 ± 24 ($p < 0.05$) as a response to the improvement of the metabolic control, with a mean reduction of HbA_{1c} of 2%. The glomerular filtration rate thereafter remained stable for the following 7 years and six months. In the conventional treatment group no change was observed at 6 months (113 ± 15 ml·min^{-1}·1.73 m^{-2} to 115 ± 15 (NS)). When, therefore, using the glomerular filtration rate at six months as the initial value, a difference between the groups was observed: The reduction was -28 (-41 to -15) ml·min^{-1}·1.73 m^{-2} in the conventional treatment group and -8 (-16 to 0) in the insulin infusion group ($p < 0.01$ between groups). The annual change was -3.7 (-5.4 to -2.0) ml·min^{-1}·1.73 m^{-2} vs -1.0 (-2.1 to -0.1) ($p < 0.01$). No significant change in the glomerular filtration rate was observed during 5 years follow-up in Steno Study 2 (Table 3).

A multiple regression analysis of all 69 patients was performed with the urinary albumin excretion rate at re-examination as the dependent variable. Independent variables of significance were the initial urinary albumin excretion rate ($p < 0.0001$) and the mean HbA_{1c} during study ($p < 0.01$). Of no influence were age, diabetes duration and initial values of HbA_{1c}, glomerular filtration rate and systolic as well as diastolic blood pressure. Mean HbA_{1c} was the major determinant when testing the change in urinary albumin excretion rates ($p < 0.01$) and this change was also associated with the glomerular filtration rate at entry ($p < 0.05$). The change in glomerular filtration rate (at re-examination vs at entry) was also dependent on the initial glomerular filtration rate ($p < 0.0001$), urinary albumin excretion rate ($p < 0.01$) and on diastolic blood pressure ($p < 0.05$). An association with HbA_{1c} was not expressed.

Combined analysis of 51 patients with microalbuminuria at entry demonstrated that only one of 32 with low range microalbuminuria (65 mg/24 h, mean HbA_{1c} 8.3%) progressed to clinical nephropathy (Table 4). In contrast, a significant progression was observed among the 19 patients at severe risk of nephropathy with an initial urinary albumin excretion rate ranging from 100 to 300 mg/24 h at entry to Steno Study 1 ($n = 8$) and to Steno Study 2 ($n = 11$). Nine patients had been randomized to receive insulin infusion and 10 to the conventional treatment groups (Table 4). In the insulin infusion group 2 of the 9 developed clinical nephropathy vs 10 of 10 in the control group ($p < 0.001$, Table 4). In the conventional treatment group the urinary albumin excretion rate was increasing ($p < 0.05$) and the glomerular filtration rate declining ($p < 0.05$, Table 4 and Fig. 2). Also, in that group the systolic blood pressure increased significantly and arterial hypertension was diagnosed more frequently ($p < 0.01$, Table 4). In the insulin infusion group no significant changes took place. The long-term glycaemic control given as individual HbA_{1c} values (mean of 7 years) of these 19 patients are shown in Figure 1.

There were no significant changes in visual acuity within or between groups at re-examination. During conventional treatment 23 of 33 patients had a normal visual

Table 3. Steno studies 1 and 2. A five and eight years follow-up. Effects of improved metabolic control on urinary albumin excretion rate, glomerular filtration rate and blood pressure

	Steno 1		Steno 2	
Original treatment	CSII	CIT	CSII	CIT
Urinary albumin excretion (mg/24 h):				
At entry	43 (21–91)	73 (30–134)	73 (51–104)	65 (45–95)
At re-examination	33 (15–72)	122 (33–444)	62 (38–102)	72 (27–186)
Glomerular filtration rate (GFR): (ml·min^{-1}·1.73 m^{-2})				
At entry	124 ± 28	113 ± 15	109 ± 19	113 ± 21
At re-examination	106 ± 27[b]	87 ± 26[b]	108 ± 22	113 ± 22
GFR (last-first)	-18 (-28 to -8)	-26 (-40 to -12)	-1 (-9 to $+9$)	0 (-7 to $+5$)
Blood pressure (mmHg)				
At entry				
systolic	132 ± 14	126 ± 13	128 ± 13	128 ± 12
diastolic	85 ± 6	85 ± 9	83 ± 5	82 ± 8
At re-examination				
systolic	137 ± 22	137 ± 24[a]	132 ± 18	136 ± 14[a]
diastolic	83 ± 11	87 ± 9	81 ± 11	86 ± 11

CSII: Continuous subcutaneous insulin infusion. CIT: Conventional insulin treatment. Mean ± SD or logarithmic mean with 95% confidence interval.

[a] Significant deterioration compared with initial examination, $2p < 0.05$; [b] Significant deterioration compared with initial examination, $2p < 0.01$

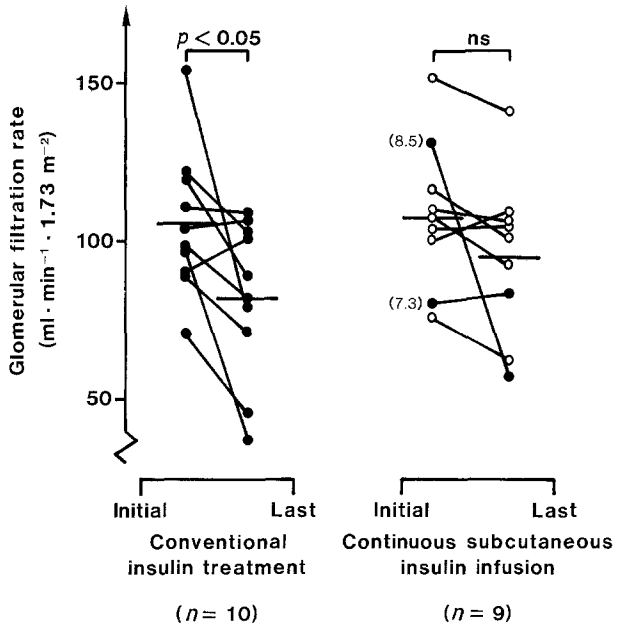

Fig. 2. Glomerular filtration rate at entry and at re-examination. Same 19 patients as in Figure 1. Closed circles: Patients progressing to clinical nephropathy. Horisontal bars: Mean values. In parentheses: mean HbA_{1c} during study, given for the two patients progressing to nephropathy

acuity of 6/6 on both eyes. Three eyes of two patients had a visual acuity worse than 6/60. The numbers during insulin infusion were 27 out of 36 and four eyes of two patients worse than 6/60.

Discussion

This study has confirmed our original observation after two years of an association between long-term glycaemic control (HbA_{1c}) and change in urinary albumin excretion in Type 1 diabetic patients with clinical signs of microangiopathy [2]. It has also confirmed that blood pressure, though significantly increasing in the conventional treatment group, remains unchanged during insulin infusion [2]. As a new observation, the present results suggest that the rate of decline of the glomerular filtration rate can be reduced during several years of improved metabolic control. This was indicated after eight years of follow-up in Steno Study 1 when analysing according to an intent to treat, i.e. with the patients in the original randomized treatment groups. The number of patients with a normal urinary albumin excretion rate, microalbuminuria or nephropathy were similar between the groups after randomization with no difference in the urinary albumin excretion at entry (Table 2). Despite the randomization patients in the insulin infusion group tended to have higher glomerular filtration rates at entry, possibly a glomerular hyperfiltration related to their (insignificantly) higher HbA_{1c} values at entry. Six months later when the glycaemic control had been improved, their glomerular filtration rate had been normalized to the level of the control group [18] and thereafter remained stable for 7 years and 6 months. If the results were reasonably analysed with the glomerular filtration rates at 6 months vs eight years the annual change was -3.7 (-5.4 to 2.0) $ml \cdot min^{-1} \cdot 1.73^{-2}$ in the conventional treatment group ($p < 0.01$) vs

Table 4. Combined analysis of all 51 Type 1 (insulin-dependent) diabetic patients with microalbuminuria (30–300 mg/24 h), at entry of the Steno Studies (5 to 8 years follow-up)

	Initial urinary albumin excretion rate (UAE)					
	30–99 mg/24 h			100–300 mg/24 h		
Original treatment:	CSII	CIT	*p*	CSII	CIT	*p*
Numbers:	17	15		9	10	
Age (years)	31 ± 8	31 ± 8	NS	34 ± 10	31 ± 7	NS
Diabetes duration (years)	16 ± 4	16 ± 6	NS	16 ± 5	18 ± 6	NS
HbA_{1c} (%)						
At entry	9.9 ± 2.0	8.9 ± 1.3	NS	9.6 ± 1.5	9.3 ± 0.8	NS
Mean of all	7.9 ± 1.0[a]	8.4 ± 0.9	NS	7.7 ± 0.8[a]	9.4 ± 0.7	0.001
UAE (mg/24 h)						
At entry	49 (38–64)	44 (33–60)	NS	163 (123–214)	181 (144–227)	NS
At re-examination	36 (31–42)	29 (14–61)	NS	167 (74–377)	713[a] (454–1119)	0.002
GFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)						
At entry	119 ± 23	116 ± 20	NS	113 ± 23	110 ± 23	NS
At re-examination	114 ± 20	116 ± 19	NS	100 ± 26	87[a] ± 24	NS
Blood pressure (mm Hg)						
At entry						
systolic	128 ± 13	129 ± 11	NS	132 ± 11	131 ± 11	NS
diastolic	83 ± 5	81 ± 9	NS	85 ± 6	89 ± 8	NS
At re-examination						
systolic	133 ± 18	132 ± 13	NS	133 ± 20	149 ± 22[a]	NS
diastolic	82 ± 12	83 ± 8	NS	83 ± 10	93 ± 11	NS
Progression to clinical nephropathy *(n)*:	1	0	NS	2	10	0.001
Receiving antihypertensive treatment *(n)*:	4	1	NS	1	7	0.01
Developing proliferative retinopathy *(n)*:	0	2	NS	1	5	0.07

Mean ± SD or logarithmic mean with 95% confidence interval. GFR: Glomerular filtration rate. [a] Significantly different from the initial value, $2p < 0.05$

– 1.0 (– 2.1 to 0.1) during insulin infusion (NS) ($p < 0.01$ between groups).

From both Steno Studies all 10 patients in the conventional treatment groups with an initial urinary albumin excretion rate of 100 to 300 mg/24 h progressed to clinical nephropathy whereas only one of the 46 patients included with an albumin excretion rate below 100 mg/24 h (65 mg/24 h) progressed, supporting previous observations by our group [17]. When separating the 51 patients who at entry had microalbuminuria (excluding those with normal albumin excretion ($n = 14$) or clinical nephropathy ($n = 4$) no significant progress of disease for a median of seven years in either treatment group could be demonstrated among patients with microalbuminuria in the low range. One patient developed clinical nephropathy (mean HbA_{1c} of 8.3%) but 15 normalized their albumin excretion rates. It is a new observation that the glomerular filtration rate and the blood pressure remain stable for so many years in patients with microalbuminuria ranging from 30 to 99 mg/24 h when observed and treated as in this trial, i.e. with a fair but not "near-normalized" metabolic control, frequent blood pressure readings and institution of antihypertensive treatment at readings persistently above 160/95 mm Hg.

When analysing the patients with albumin excretion rates from 100–300 mg/24 h according to an intent to treat there was a significant difference between the metabolic control of the two treatment groups for a median of seven years. HbA_{1c}, urinary albumin excretion, glomerular filtration rate and blood pressure was similar at entry. The above indication of an effect on the rate of decline of the glomerular filtration rate received strong support. Two patients in the insulin infusion groups progressed to nephropathy but the glomerular filtration rate was significantly reduced only in the conventional treatment group and not during insulin infusion. In this small subset this significant deterioration within the conventional treatment group occurred without significant differences between the groups at re-examination. This may be due to the variability of the glomerular filtration rate within the small groups of only 10 and 9 patients (type 2 error). At re-examination, however, more patients in the conventional treatment group had developed clinical nephropathy and more patients were receiving antihypertensive treatment, compared with the insulin infusion group ($p < 0.01$).

More patients developed proliferative retinopathy in the conventional treatment groups but the difference did not reach statistical significance. The majority of patients had normal vision at follow-up and differences in visual acuity between the groups could not be demonstrated.

The effects of improved metabolic control were observed despite of no significant differences in HbA_{1c} between the groups during the past three years of follow-up. This indicates a long-term effect of the very good metabolic control during the first three to five years of study. However, a trial effect in the conventional treatment groups cannot be excluded. Among the 35 patients entering the control groups of the two trials there was an overall improvement in the metabolic control. This trial effect may explain why only one patient with a urinary albumin excretion rate below 100 mg/24 h progressed to nephropathy in contrast to previous reports [19, 20]. The observed trial effect is more clearly expressed in the multiple regression analyses of all 69 patients. Apart from the albuminuric level at entry, the most important determinant of changes in albumin excretion was glycaemic control (HbA_{1c}) during study. This association between long-term glycaemic control and progression of markers of microangiopathy supports previous observations [21–26]. Because of so many patients with microalbuminuria being stable or even normalizing their albumin excretion during five years observation no significant increase in urinary albumin excretion was observed in the control group of Steno Study 2. This may explain why this study did not add any new information from the second to the fifth year of follow-up.

The six cardiovascular events were all but one in patients receiving conventional treatment. The one patient from the insulin infusion group had changed to multiple injection treatment after two years and the metabolic control had been poor for the past six years with a mean HbA_{1c} of 10.1%. The study populations were, however, too small to allow for any conclusions regarding cardiovascular mortality and near-normal metabolic control.

Patients are at an increased risk of ketoacidosis during treatment with insulin infusion pumps [27, 28]. In this study three patients died during ketoacidosis while being treated with insulin infusion pumps. The cause of death could not be diagnosed exactly. All were males, two of them living alone. One was recently divorced and undergoing psychiatric therapy after an attempt to commit suicide. One had proliferative retinopathy with a rapidly reduced vision and had consequently lost his job. In the third case autopsy indicated severe cardiomyopathy. Pump failure was excluded by several tests on post mortem examination. All patients had been thoroughly educated in their treatment and were expected to be able to cope with any situation preceeding ketoacidosis. The fact that they eventually did not, calls for more intensive education and re-education of patients, families and doctors. It may also call for re-evaluations of the feasibility of this kind of intensified treatment. The observed frequency of ketoacidosis in our study is similar to that reported by other groups [29–33]. Despite an increased risk of ketoacidosis and of hypoglycaemia, the treatment with infusion pumps has been considered safe and not associated with excess mortality in 3500 patients selected for this treatment in the USA in 1982 [34].

Early antihypertensive treatment is of importance for the rate of decline of the glomerular filtration rate [36, 37] as well as for increasing the life expectancy of Type 1 diabetic patients with nephropathy [38, 39]. This study suggests that in the future patients at risk of nephropathy should also be offered near-normal metabolic control, if necessary by means of intensified insulin treatment regimens, in order to preserve their kidney function.

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