Decreasing Incidence of Severe Diabetic Microangiopathy in Type 1 Diabetes

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OBJECTIVE — Conflicting evidence of a decline in incidence of microvascular complications in type 1 diabetes during the last decades has been reported. To assess recent trends in the cumulative incidence of diabetic microangiopathy in type 1 diabetes, we analyzed data from long-term prospective observational studies lasting ≥20 years.

RESEARCH DESIGN AND METHODS — A total of 600 Caucasian patients with onset of type 1 diabetes between 1965 and 1984 were followed until death or until the year 2000. Patients were divided into four groups based on the year of diabetes onset: group A, 1965–1969 (n = 113); group B, 1970–1974 (n = 130); group C, 1975–1979 (n = 113); and group D, 1979–1984 (n = 244). Group A, B, and C are prevalence cohorts identified in 1984; group D is an inception cohort.

RESULTS — In patients followed for ≥20 years, the cumulative incidence (95% CI) of diabetic nephropathy after 20 years of diabetes (urinary albumin excretion >300 mg/24 h) was reduced in patients with more recent diabetes onset (groups A–D): 31.1% (22.5–39.7) vs. 28.4% (19.8–37.0) vs. 18.9% (10.9–26.9) vs. 13.7% (6.2–21.2) (P = 0.015). Similarly, the cumulative incidence of proliferative retinopathy was as follows: 31.2% (22.2–39.8) vs. 30.3% (22.2–38.4) vs. 19.3% (11.2–27.4) vs. 12.5% (5.2–19.8) ($P < 0.01$). In the latter groups, antihypertensive treatment was started earlier, blood pressure and HbA_{1c} were lower, and fewer patients smoked.

CONCLUSIONS — Our study demonstrates a decrease in the cumulative incidence of diabetic microangiopathy in type 1 diabetes over the past 35 years. Improved glycemic control, lower blood pressure (in part due to early aggressive antihypertensive treatment), and reduced prevalence of smoking rates were associated with the improved prognosis.

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In type 1 diabetic patients, microvascular lesions of the kidney and eye lead to increased morbidity and mortality (1). Relative cardiovascular mortality in proteinuric type 1 diabetic patients is 37-fold that in the general population (2). In addition, type 1 diabetic patients suffering from diabetic nephropathy have a sixfold increased risk of developing proliferative diabetic retinopathy than normoalbuminuric patients (3), and visual impairment and blindness are also much more common (4). In type 1 diabetes, previous studies have demonstrated a cumulative incidence of diabetic nephropathy and proliferative retinopathy of 20–40% after 20–25 years of disease duration (1,5–8). Clinical trials aiming at improved glycemic and blood pressure control have documented a beneficial effect on the development and progression of diabetic kidney and eye complications (1,9–14). A reduction in incidence of diabetic microangiopathy (diabetic nephropathy, proliferative retinopathy, and maculopathy) might be expected to result from improved clinical management of glycemia and blood pressure. However, reported data on clinical outcome over recent decades have been inconsistent (3,5,15,16). We assessed recent trends in the cumulative incidence of diabetic microangiopathy in a prospective observational study lasting ≥20 years in 600 Caucasian patients cared for at the Steno Diabetes Center until death or until the year 2000.

RESEARCH DESIGN AND METHODS

Study design and patients

Our study comprised 600 Caucasian patients with onset of type 1 diabetes between 1965 and 1984. Patients were divided into four groups based on year of onset of diabetes, as shown in Table 1. Groups A, B, and C are prevalence cohorts identified in 1984 for a clinic-based follow-up study and have been described in detail previously (3,5). In brief, all type 1 diabetic patients at Hvidöre Hospital with onset of diabetes between 1965 and 1979, and before the age of 41 years, and who were >18 years of age at the time of study were included. Patients from groups A, B, and C were followed until death or until the year 2000, and data were compared with data from group D. After 20 years of diabetes, two patients from group A were lost to follow-up (median follow-up of 18.2 years), five patients from group B (median follow-up of 16.7 years), and 24 patients from group C (median follow-up of 15.6 years) before death or an event occurred.

Group D is an inception cohort of all newly diagnosed type 1 diabetic patients referred to the Steno Memorial Hospital between 1 September 1979 and 31 August 1984. The inception cohort comprised 286 patients; 7 mentally ill patients could not be studied. Group D comprised 244 patients who had an age of onset of diabetes before the age of 41 years. Of these patients, 216 (88.5%) were followed from the onset of diabetes until the year 2000 or time of death (n = 13) or to exclusion due to other serious competing

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Abbreviations: HPLC, high-performance liquid chromatography; UAE, urinary albumin excretion.

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

Table 1—*Patient characteristics and clinical and laboratory data during 20 years of follow-up in 600 patients with type 1 diabetes*

	Group A (onset from 1965 to 1969)	Group B (onset from 1970 to 1974)	Group C (onset from 1975 to 1979)	Group D (onset from 1979 to 1984)	*P*
n	113	130	113	244	—
Sex (M/F)	62/51	72/58	65/48	144/100	NS
Age at onset of diabetes (years)*	19.8 ± 10.6	20.9 ± 9.8	23.1 ± 8.6	23.2 ± 8.8	0.003
Smoking (%)	69	54	65	45	<0.001
During follow-up					
HbA_{1c} (%)†	8.9 ± 0.1	8.8 ± 0.1	8.9 ± 0.1	8.5 ± 0.1	0.006
Systolic blood pressure (mmHg)†	138.1 ± 1.2	134.6 ± 1.3	131.9 ± 1.3	127.9 ± 0.8	<0.001
Diastolic blood pressure (mmHg)†	84.7 ± 0.7	82.9 ± 0.7	81.7 ± 0.7	79.2 ± 0.5	<0.001
Mean arterial blood pressure (mmHg)†	102.5 ± 0.8	100.1 ± 0.8	98.4 ± 0.8	95.4 ± 0.6	<0.001
Class of antihypertensive treatment (ACE inhibitor/non–ACE inhibitor)	15/24	29/17	28/6	55/6	<0.001
Time from diabetes onset to start of antihypertensive treatment (years)	16.9 ± 0.4	14.8 ± 0.5	13.9 ± 0.8	13.3 ± 0.6	<0.001

Data are *means ± SD or †means ± SE unless otherwise indicated.

medical or psychosocial conditions (n = 6). There is an overlap in onset of diabetes between group C and D; however, because patients at recruitment were attending only one of the two different hospitals, no patient was enrolled in both group C and D.

In the Copenhagen area, all type 1 diabetic patients were randomly referred to either the Hvidöre Hospital or the Steno Memorial Hospital (tertiary referral centers for diabetes) for lifelong treatment and diabetes control, irrespective of the development of late complications. No other treatment facilities for type 1 diabetic patients were available, and treatment at both hospitals always has been free of charge. The Steno Memorial Hospital had a patient capacity twice that of Hvidöre Hospital. In 1991, Hvidöre Hospital and Steno Memorial Hospital were merged into the Steno Diabetes Center.

Procedures, measurements, and outcome

All patients visited the outpatient clinic every 3–4 months, irrespective of the development of late complications, as part of the routine follow-up. At each visit, postprandial blood glucose and urinary glucose concentrations were measured, body weight was recorded, and insulin doses were adjusted. All patients were treated with at least two daily injections of insulin. A diet containing 45–55% carbohydrate, 30–35% fat, and 15–20% protein was recommended. No sodium or protein restrictions were applied during the study. In addition, from 1983, HbA_{1c} was measured at each visit. For each patient, the average yearly HbA_{1c} was used as the estimate of the mean metabolic control of that year. The method used for measurement of HbA_{1c} from venous blood samples has changed over the years: from 1983 to 1988, high-performance liquid chromatography (HPLC) ion exchange (17) and isoelectric focusing (18) were used. These methods have a normal range of 4.1–6.1% and 4.1–6.4%. From 1989, HbA_{1c} was measured with HPLC (Bio-Rad Diamat; Bio-Rad, Richmond, CA) with a normal range of 4.1–6.4%. The correlation between this method and the two previous methods were as follows: r = 0.983 (n = 194) and r = 0.931 (n = 119), respectively. Finally, from 1994, another HPLC-based method was used (Bio-Rad Variant; Bio-Rad). The normal range remained unchanged (4.1–6.4%), and the coefficient of correlation between the latter and present method was r = 0.993 (n = 161).

Each patient had a 24-h urinary albumin excretion (UAE) rate estimated at least once a year. Before 1984, the UAE rate was estimated by the use of reagent-impregnated strips (Albustix; Ames, Bridgend, U.K.; detection limit ~150 mg albumin/l). In general, patients with an UAE rate >300 mg/24 h had a positive Albustix test. Albuminuria was quantitated using the Laurell method before 1974 (19), the automated immunotopical nephelometric analysis from 1974 to 1984 (20), radioimmunoassay from 1984 to 1990 (21) (sensitivity: 0.5 mg/l, coefficient of variation: 9%), and enzyme immunoassay from 1990 on (22) (sensitivity 1.1 mg/l, coefficient of variation 8%). A close correlation between radial immunodiffusion and radioimmunoassay (r = 0.98) (23) and radioimmunoassay and enzyme immunoassay (r = 0.99) (22) was documented before changing the methods. From 1997, the DAKO Turbidimetric method was used to measure UAE. This method is closely correlated with enzyme immunoassay (r = 0.99) and has a coefficient of variation of 5%. Persistent microalbuminuria and albuminuria was defined as an UAE rate between 30 and 300 mg/24 h and >300 mg/24 h in at least two of three consecutive samples, respectively, as recommended in a consensus report (24). Sterility of urine was checked by culture (Uricult; Orion, Helsinki, Finland), and urine was collected after treatment if bacterial growth had been detected. Diabetic nephropathy was diagnosed clinically if the following criteria were fulfilled: persistent albuminuria, duration of diabetes >10 years, presence of diabetic retinopathy, and absence of clinical or laboratory evidence of other kidney or renal tract disease (12). If these criteria were not fulfilled, a diagnostic kidney biopsy was performed. Time of onset of diabetic nephropathy was defined as the first recorded positive urine sample in at least two of three consecutive samples.

Blood pressure was measured at least once a year with a standard mercury

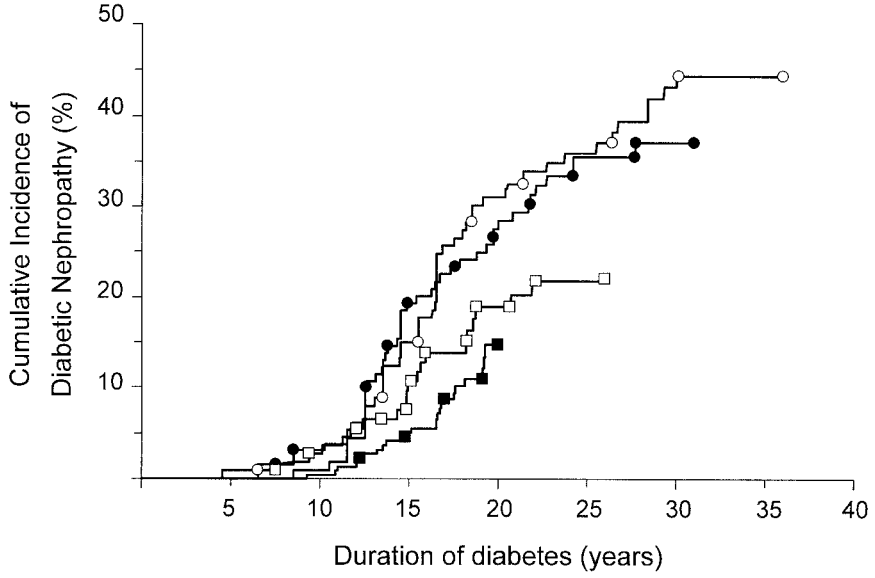

Figure 1—*Cumulative incidence of diabetic nephropathy in 600 type 1 diabetic patients with onset of diabetes from 1965 to 1969* (n = *113, group A [○]), 1970 to 1974* (n = *130, group B [●]), 1975 to 1979* (n = *113, group C [□]), and 1979 to 1984* (n = *244, group D [■]*). P < *0.001, log-rank test, pooled over strata. Not all patients in group D have yet been followed for 20 years. For pairwise log-rank test over strata after 20 years of diabetes, see* RESULTS.

sphygmomanometer and appropriate cuff size. The measurements were performed with the patient in the sitting position after ~10 min rest. Arterial hypertension was diagnosed according to the World Health Organization criteria (≥160/95 mmHg) until 1995 and thereafter according to the American Diabetes Association criteria (≥140/90 mmHg) (25). Patients were classified as smokers if they were smoking more than one cigarette per day.

Retinopathy was assessed at least yearly through dilated pupils by ophthalmoscopy in all patients from 1965 to 1988 (by the same trained observer in groups A–C; by other trained observers in group D). From 1988, 60° color fundus photographs (CF-60UV; Canon, Tokyo) of fields 1 and 2 of both eyes were taken after maximal dilation of the pupils in all patients, as defined by the Diabetic Retinopathy Study (26). In case of abnormal findings, additional photos of the periphery were taken. Whenever maculopathy was suspected, two stereo photographs were taken with the macula in the center. All fundus photographs were read by ophthalmologists. Proliferative retinopathy was characterized by neovascularization with or without connective tissue formation. Maculopathy was diagnosed when the patient fulfilled at least two of the following criteria: loss of visual acuity, hard exudates, and/or edema of the macula. Time of onset of proliferative retinopathy and maculopathy was defined as the first eye examination where the lesions were observed. The criteria for the different stages of diabetic retinopathy were kept sustained during the whole study period. The change in method from ophthalmoscopy to fundus photography in 1988 has been evaluated, and no change in the rate of progression of diabetic retinopathy was noted (3).

Findings from the better eye were used to define best corrected visual acuity. Until 1988, visual acuity was measured using a Snellen's chart. with the patients own spectacles where necessary. If a visual acuity <1.0 was obtained, a pinhole was added. After 1988, an autorefractometer incorporating a Snellen's chart (Autorefractometer NR-7000; Nikon, Nippon Kogaku, Japan) was used after dilation of the pupils. The level of agreement between visual acuity measured by Snellen's chart and the autorefractometer was determined in 98 patients (mean difference between visual acuity [95% CI]: 0.0061 [−0.015 to 0.025, limits of agreement −0.29 to 0.20]) (3). All measurements >1.0 were set to 1.0. Blindness was defined as a corrected visual acuity ≤0.1 in the better eye. Patients visited the eye clinic at least once a year if diabetic retinopathy was present and every second year if retinopathy was absent. Argon or xenon laser treatment was initiated from the mid-1970s if proliferative retinopathy or maculopathy was present. The local ethical committee approved the experimental design.

Statistical analysis

The cumulative incidences of diabetic nephropathy, proliferative retinopathy, and maculopathy were calculated based on the entire follow-up period ending in 2000, with a life-table method taking into account differences in the interval of follow-up. The method makes proper allowances for those observations that are censored and makes use of information from all subjects during follow-up to the time to event or censoring. The four groups were compared using the log-rank test. Results are expressed as means and SD or SE. In each patient, all measurements performed during the entire follow-up period were used to calculate mean values. In normally distributed variables, comparison between groups was performed by one-way ANOVA. In nonnormally distributed continuous variables, a Kruskal-Wallis test was used for comparison between groups. A χ^2 test was used to compare frequencies. A P value of ≤0.05 (two-sided) was considered statistically significant. All calculations were performed with a commercially available program (SPSS 10.0; SPSS, Chicago).

RESULTS — Group A, B, C, and D consisted of 113, 130, 113, and 244 patients, respectively. A small male predominance was observed in all groups, and the mean age at onset of diabetes was slightly higher in the latter cohorts (Table 1). In those patients followed for ≥20 years, thus restricting group D to patients with onset of diabetes before 1981, the cumulative incidence (95% CI) of diabetic nephropathy after 20 years of diabetes was 31.1% (22.5–39.7) in group A (1965–1969), 28.4% (19.8–37.0) in group B (1970–1974), 18.9% (10.9–26.9) in group C (1975–1979), and 13.7% (6.2–21.2) in group D (1979–1984) (P = 0.015, pooled over strata). Result from the pairwise log-rank test over strata were as follows: group A vs. B: P = 0.7, group A vs. C: P = 0.06, group A vs. D: P = 0.004, group B vs. C: P = 0.10, group B vs. D: P = 0.01, and group C vs. D: P = 0.3. A declining cumulative incidence of

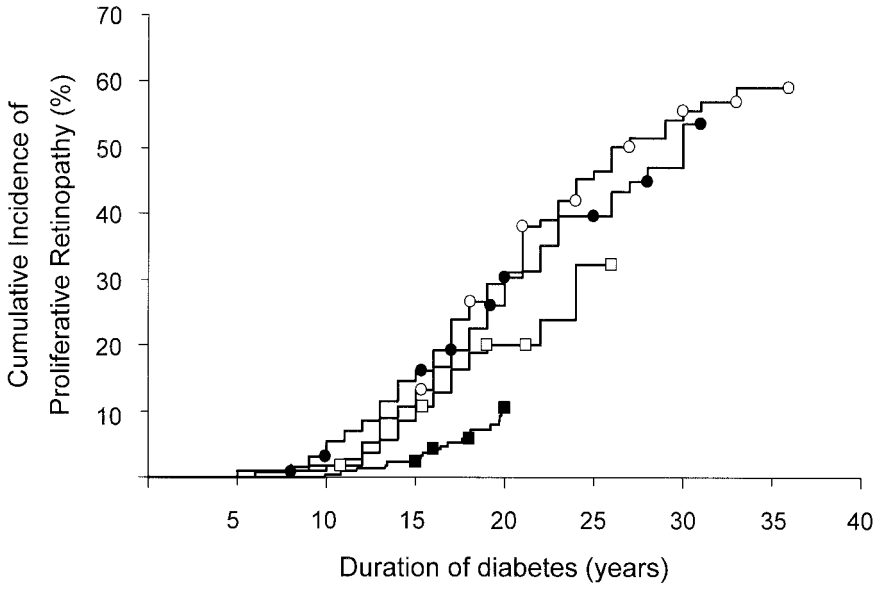

Figure 2—*Cumulative incidence of proliferative retinopathy in 600 type 1 diabetic patients with onset of diabetes from 1965 to 1969* (n = *113, group A [○]), 1970 to 1974* (n = *130, group B [●]), 1975 to 1979* (n = *113, group C [□]), and 1979 to 1984* (n = *244, group D [■]*). P < *0.001, log-rank test, pooled over strata. Not all patients in group D have yet been followed for 20 years. For pairwise log-rank test over strata after 20 years of diabetes, see* RESULTS.

diabetic nephropathy after 20 years of diabetes with increasing calendar year of diabetes onset was demonstrated ($P < 0.015$, pooled over strata). Figure 1 shows the cumulative incidence of diabetic nephropathy in all four groups based on data from the entire follow-up period from onset of diabetes to 2000. The yearly incidence rate was lower in group D compared with the previous groups. The cumulative incidence of diabetic nephropathy reached a plateau after 30 years of diabetes in groups A and B (Fig. 1).

The number of patients with normo-/micro-/macroalbuminuria was 52/24/37 in group A, 53/40/37 in group B, 71/23/19 in group C, and 179/40/25 in group D after 20 years of diabetes. Patients were assigned albuminuric status based on information from their most recent visit to the clinic. The cumulative incidence of combined micro- and macroalbuminuria after 20 years of diabetes was 31.1% in group D. Testing for microalbuminuria was not available for groups A, B, and C.

In patients followed for ≥20 years, thus restricting group D to patients with onset of diabetes before 1981, the cumulative incidence (95% CI) of proliferative retinopathy after 20 years of diabetes was 31.2% (22.2–39.8) in group A, 30.3% (22.2–38.4) in group B, 19.3% (11.2–27.4) in group C, and 12.5% (5.2–19.8) in group D ($P < 0.01$, pooled over strata). Results from the pairwise log-rank test over strata were as follows: group A vs. B: $P = 0.91$, group A vs. C: $P = 0.07$, group A vs. D: $P = 0.002$, group B vs. C: $P = 0.07$, group B vs. D: $P = 0.003$, and group C vs. D: $P = 0.16$. A declining cumulative incidence of proliferative retinopathy after 20 years of diabetes with increasing calendar year of onset of diabetes was demonstrated. The yearly incidence rate was lower in group D than in the previous groups. Figure 2 shows the cumulative incidence of proliferative retinopathy in all four groups based on data from the entire follow-up period from onset of diabetes to 2000. There was no suggestion of a plateau in incidence in any group (Fig. 2).

A similar trend was demonstrated in those patients followed for ≥20 years (thus restricting group D to patients with onset of diabetes before 1981) with respect to the cumulative incidence (95% CI) of maculopathy after 20 years of diabetes: group A: 18.6% (11.4–25.8), group B: 18.6% (11.9–25.3), group C: 10.7% (4.4–17.0), and group D: 7.4% (1.7–13.1) ($P = 0.03$, pooled over strata). The results from the pairwise log-rank test over strata were as follows: group A vs. B: $P = 0.83$, group A vs. C: $P = 0.10$, group A vs. D: $P = 0.02$, group B vs. C: $P = 0.06$, group B vs. D: $P = 0.02$, and group C vs. D: $P = 0.43$.

Visual acuity 20 years after diabetes onset was significantly better in patients with increasing calendar year of diabetes onset. The geometric mean (95% CI) visual acuity was 0.83 (0.77–0.90) in group A, 0.91 (0.87–0.96) in group B, 0.94 (0.90–0.97) in group C, and 0.97 (0.95–0.99) in group D (overall, $P < 0.001$; group A vs. B: $P < 0.01$; group A vs. C: $P < 0.01$; group A vs. D: $P < 0.001$; group B vs. C: $P = 0.66$; group B vs. D: $P < 0.01$; group C vs. D: $P < 0.01$). The number of blind patients was small in all groups (group A: $n = 4$, group B: $n = 2$, group C: $n = 1$, group D: $n = 0$; $P = 0.01$ for trend).

The mean values of HbA_{1c} were similar in the first three groups. However, values were significantly lower in the last group (1979–1984) (Table 1).

With increasing calendar year of diabetes onset (1965–1969 vs. 1970–1974 vs. 1975–1979 vs. 1979–1984), the time from onset of diabetes to initiation of antihypertensive treatment was shortened ($P < 0.001$) and mean arterial blood pressure during follow-up was reduced ($P < 0.001$; Table 1). There was no difference in the cumulative incidence of use of antihypertensive treatment in the different cohorts after 20 years of diabetes. However, in those patients receiving antihypertensive treatment, the use of ACE inhibitors became more frequent with increasing calendar year of diabetes onset. Finally, the prevalence of smokers was lower in the last cohort ($P < 0.001$; Table 1).

CONCLUSIONS — In our prospective observational study of 600 Caucasian type 1 diabetic patients with diabetes onset between 1965 and 1984, followed until death or until 2000, we demonstrate a dramatic decrease in the cumulative incidences of diabetic nephropathy, proliferative retinopathy, and maculopathy, with increasing calendar year of diagnosis. Furthermore, patients from the most recent cohort had a significantly better visual acuity after 20 years of diabetes compared with the three earlier cohorts. Antihypertensive treatment was started earlier in the latter cohorts, contributing to the observed lower blood pressure levels; HbA_{1c} was lower; and the prevalence of smokers was reduced in the last cohort. The major decline in the incidence of

diabetic nephropathy and the vision-threatening diabetic eye diseases proliferative retinopathy and maculopathy demonstrated in our study indicates an important improvement in microvascular morbidity and, we presume, an eventual improvement in the macrovascular mortality associated with diabetic nephropathy.

The cumulative incidence of diabetic nephropathy after 25 years of diabetes has been reported to decrease between 1940 and 1950, from 40% to 25–30%, remaining stable until the 1980s (27,28). Subsequently, Bojestig et al. (15) reported a dramatic decline (from 28 to 6%) in the cumulative incidence of diabetic nephropathy in children with type 1 diabetes diagnosed before the age of 15 years, but was unable to demonstrate a decline in laser-treated retinopathy (16). Our previous study, based on a shorter follow-up period of the three prevalence cohorts (groups A–C), revealed no evidence of a declining incidence of diabetic nephropathy (5). The inception cohort with onset of diabetes from 1979 to 1984 made up the difference between our present and past study. Although our results from the present study are not as impressive as the results from the study by Bojestig et al., our study confirms the trend toward a decline in the cumulative incidence of diabetic nephropathy, and in contrast to the Swedish study, we extend the finding to include diabetic retinopathy (proliferative retinopathy as well as maculopathy) in type 1 diabetic patients with onset of diabetes at <41 years of age.

To reduce selection bias, only type 1 diabetic patients from the Copenhagen area were included in our study. Historically, all adult type 1 diabetic patients from Copenhagen have randomly been referred either to Hvidöre Hospital or the Steno Memorial Hospital. No other treatment facilities for type 1 diabetic patients were available, and treatment at both hospitals has always been free of charge. Consequently, selective referral based on diabetic late complications or socioeconomic status is unlikely. Furthermore, no referral of patients without complications back to the general practitioners occurs; thus, selective exclusion of patients is avoided. In previous studies, patients having less than seven to nine visits to a diabetic care unit during the first 15–20 years of diabetes duration (nonattenders) have been demonstrated to have a higher risk of diabetic nephropathy than more frequent attenders (27,29). In our prevalence cohorts, selective dropout of patients who died because of diabetic nephropathy before identification in 1984 could lead to an underestimation of the cumulative incidence of diabetic microangiopathy. The cumulative incidence observed in the inception cohort (group D) is closer to the true incidence of the microvascular complications. Thus, the decline in cumulative incidence of diabetic microangiopathy demonstrated in the present study possibly reflects a conservative estimate. However, to determine the true incidence of diabetic late complications, population-based studies are needed.

To avoid detection bias, the same definitions for diabetic nephropathy, proliferative retinopathy, and maculopathy were applied in all four groups. A major concern in the present study relates to the potential detection bias due to the change in 1988 of fundus grading and assessment of visual acuity. The change in procedure on retinal grading as well as assessment of visual acuity has previously been reported, and no impact of the change in methods was found (3).

Treatment strategies with the purpose of preventing diabetic late complications have changed substantially during the last decades (9,30,31). Consequently, the decreasing incidences of microvascular complications that we observed are probably due to a change in treatment, notably glycemic and blood pressure control. Bojestig et al. (15) achieved excellent metabolic control in their patients and ascribed the observed decline in the cumulative incidence of diabetic nephropathy to this improvement. In comparison, our HbA_{1c} values were 8.8% in the three first cohorts, a level comparable to the conventionally treated group in the Diabetes Control and Complications Trial (9). The significant reduction in long-term glycemic control observed in our most recent cohort with onset of diabetes between 1979 and 1984 is of the same order of magnitude as demonstrated in the Epidemiology of Diabetes Interventions and Complications study (10).

Previous long-term studies have demonstrated that the progression from microalbuminuria to overt nephropathy, as well as the progression of diabetic retinopathy, can be prevented or delayed in normotensive type 1 diabetic patients treated with ACE inhibitors (30–33). Prevention of diabetic nephropathy through ACE inhibition has been demonstrated to be associated with long-lasting preservation of kidney function (34). The criteria for the diagnosis of arterial hypertension was changed in 1995 from the World Health Organization's criteria (≥160/95 mmHg) to the American Diabetes Associations criteria (≥140/90 mmHg), with an even lower blood pressure target after initiation of antihypertensive treatment (25). To achieve the new blood pressure target, an increasing range of effective antihypertensive therapies are at hand. Accordingly, in the present study, we observed a shift in class of antihypertensive agent toward a widespread use of ACE inhibitors as well as a reduction in time from onset of diabetes to initiation of antihypertensive treatment in the latter groups. These findings suggest that the new indication for ACE inhibitors as well as the application of more strict criteria for the diagnosis and treatment of arterial hypertension have beneficial effects on the cumulative incidence of microvascular complications in type 1 diabetic patients.

At the Steno Diabetes Center, we performed several of the smaller studies advocating the concept of strict glycemic control and antihypertensive treatment using ACE inhibitors as a tool to prevent or delay the development and progression of diabetic kidney and eye disease (12,30,35–39). Consequently, we strived early on to adopt these treatment modalities (i.e., multiple daily insulin injection therapy and routine ACE inhibition) in the routine care of our type 1 diabetic patients. Although the present study was not designed to evaluate putative risk factors for the development and progression of diabetic nephropathy and retinopathy, our observations are in accordance with previous prospective studies of type 1 diabetic patients, which have identified poor glycemic control, blood pressure elevation, and smoking as risk factors for the development of microvascular complications (8,40–42).

In conclusion, the cumulative incidence of diabetic nephropathy, proliferative retinopathy, and maculopathy has decreased in type 1 diabetic patients attending the Hvidöre and Steno Memorial Hospitals during the past decades and, in the later cohorts, has been accompanied by a significantly improved visual acuity

after 20 years of diabetes. Improved glycemic control, early aggressive antihypertensive treatment, and the reduced prevalence of smoking rates were associated with the improved prognosis.

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