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THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*

Abstract *Background.* Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (IDDM). We examined whether intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range could decrease the frequency and severity of these complications.

Methods. A total of 1441 patients with IDDM — 726 with no retinopathy at base line (the primary-prevention cohort) and 715 with mild retinopathy (the secondary-intervention cohort) were randomly assigned to intensive therapy administered either with an external insulin pump or by three or more daily insulin injections and guided by frequent blood glucose monitoring or to conventional therapy with one or two daily insulin injections. The patients were followed for a mean of 6.5 years, and the appearance and progression of retinopathy and other complications were assessed regularly.

Results. In the primary-prevention cohort, intensive therapy reduced the adjusted mean risk for the development of retinopathy by 76 percent (95 percent confidence interval, 62 to 85 percent), as compared with conventional therapy. In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54 percent (95 percent confidence interval, 39 to 66 percent) and reduced the development of proliferative or severe nonproliferative retinopathy by 47 percent (95 percent confidence interval, 14 to 67 percent). In the two cohorts combined, intensive therapy reduced the occurrence of microalbuminuria (urinary albumin excretion of ≥40 mg per 24 hours) by 39 percent (95 percent confidence interval, 21 to 52 percent), that of albuminuria (urinary albumin excretion of ≥300 mg per 24 hours) by 54 percent (95 percent confidence interval, 19 to 74 percent), and that of clinical neuropathy by 60 percent (95 percent confidence interval, 38 to 74 percent). The chief adverse event associated with intensive therapy was a two-to-threefold increase in severe hypoglycemia.

Conclusions. Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with IDDM. (N Engl J Med 1993;329:977-86.)

INSULIN-dependent diabetes mellitus (IDDM) is accompanied by long-term microvascular, neurologic, and macrovascular complications. Although the daily management of IDDM is burdensome and the specter of metabolic decompensation ever-present, long-term complications, including retinopathy, nephropathy, neuropathy, and cardiovascular disease, have caused the most morbidity and mortality since the introduction of insulin therapy.[1,2] The prevention and amelioration of these complications have been major goals of recent research.

Although studies in animal models of diabetes[3-5] and epidemiologic studies[6-8] implicate hyperglycemia in the pathogenesis of long-term complications, previous clinical trials have not demonstrated a consistent or convincing beneficial effect of intensive therapy on them.[9-11] A recent publication from the Stockholm Diabetes Intervention Study demonstrated a more uniform beneficial effect of intensive therapy in patients with established complications, despite the apparent crossover of most conventionally treated patients to intensive therapy during the trial.[12]

The Diabetes Control and Complications Trial was a multicenter, randomized clinical trial designed to compare intensive with conventional diabetes therapy with regard to their effects on the development and progression of the early vascular and neurologic complications of IDDM.[13-15] The intensive-therapy regimen was designed to achieve blood glucose values as close to the normal range as possible with three or more daily insulin injections or treatment with an insulin pump. Conventional therapy consisted of one or two insulin injections per day. Two cohorts of patients were studied in order to answer two different, but related, questions: Will intensive therapy prevent the development of diabetic retinopathy in patients with no retinopathy (primary prevention), and will inten-

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*A complete list of the persons and institutions participating in the Diabetes Control and Complications Trial Research Group appears in the Appendix.

sive therapy affect the progression of early retinopathy (secondary intervention)? Although retinopathy was the principal study outcome, we also studied renal, neurologic, cardiovascular, and neuropsychological outcomes and the adverse effects of the two treatment regimens.

Methods

Study Design

The trial design and methods have been described elsewhere.[13-25] Neither the investigators nor the patients were aware of the outcome data unless predetermined criteria, such as the development of severe retinopathy requiring laser therapy, were met. The physician and the patient were then made aware of the specific condition, and appropriate management was arranged.

A total of 1441 patients were recruited at 29 centers from 1983 through 1989.[15] In June 1993, after an average follow-up of 6.5 years (range, 3 to 9), the independent data monitoring committee[16] determined that the study results warranted terminating the trial.

Eligibility Criteria and Base-Line Characteristics

The major criteria for eligibility included insulin dependence, as evidenced by deficient C-peptide secretion; an age of 13 to 39 years; and the absence of hypertension, hypercholesterolemia, and severe diabetic complications or medical conditions.[13,15,25] To be eligible for the primary-prevention cohort, patients were required to have had IDDM for one to five years, to have no retinopathy as detected by seven-field stereoscopic fundus photography, and to have urinary albumin excretion of less than 40 mg per 24 hours. To be eligible for the secondary-intervention cohort, the patients were required to have had IDDM for 1 to 15 years, to have very-mild-to-moderate nonproliferative retinopathy,[13,26] and to have urinary albumin excretion of less than 200 mg per 24 hours. A multicomponent process of informed consent was used to promote the patients' understanding of the study objectives and procedures, emphasizing the necessity of accepting random assignment to either intensive or conventional treatment.[17] Randomization was stratified according to the primary-prevention and secondary-intervention cohorts at each center.[27] The base-line characteristics of the study cohorts are shown in Table 1.

Table 1. Base-Line Characteristics of the Two Study Cohorts.*

Characteristic	Primary Prevention		Secondary Intervention	
	Conventional therapy (N = 378)	Intensive therapy (N = 348)	Conventional therapy (N = 352)	Intensive therapy (N = 363)
Age (yr)	26±8	27±7	27±7	27±7
Adolescents, 13–18 yr (%)	19	16	9	10
Male sex (%)	54	49	54	53
White race (%)	96	96	97	97
Duration of IDDM (yr)	2.6±1.4	2.6±1.4	8.6±3.7	8.9±3.8
Insulin dose (U/kg of body weight/day)	0.62±0.26	0.62±0.25	0.71±0.24	0.72±0.23
Glycosylated hemoglobin (%)†	8.8±1.7	8.8±1.6	8.9±1.5	9.0±1.5
Mean blood glucose (mg/dl)‡	229±80	234±86	232±78	234±81
Blood pressure (mm Hg)				
Systolic	114±12	112±11	116±12	114±12
Diastolic	72±9	72±9	73±9	73±9
Body weight (% of ideal)	103±14	103±13	105±13	104±12
Current smokers (%)	17	19	19	18
Serum cholesterol (mg/dl)	173±35	176±33	179±32	178±33
Serum triglycerides (mg/dl)	77±57	75±41	87±44	87±45
Serum HDL cholesterol (mg/dl)	51±13	52±13	49±11	49±12
Serum LDL cholesterol (mg/dl)	106±30	109±29	112±28	112±29
Absence of retinopathy (%)	100	100	0	0
Microaneurysms only (%)§	0	0	58	67
NPDR(%)¶				
Mild	0	0	23	18
Moderate	0	0	19	15
Urinary albumin excretion (mg/24 hr)	12±8	12±9	19±24	21±25
Creatinine clearance (ml/min)	127±28	128±30	130±30	128±31
Clinical neuropathy (%)‖	2.1	4.9	9.4	9.4

*Plus–minus values are means ±SD. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol to millimoles per liter, multiply by 0.02586.

†Mean value in nondiabetic persons, 5.05±0.5 percent.

‡Based on the mean value of seven determinations during a 24-hour period.

§P = 0.01 by the Wilcoxon rank-sum test for the difference in the level of retinopathy at base line between the treatment groups in the secondary-intervention cohort.

¶NPDR denotes nonproliferative diabetic retinopathy. Mild NPDR was defined by the presence of microaneurysms plus mild-to-moderate retinal hemorrhages or hard exudates.[3,16] Moderate NPDR was defined by the presence of microaneurysms plus any of the following: cotton-wool spots, mild intraretinal microvascular abnormalities or venous beading, or severe retinal hemorrhages.[3,16]

‖Defined as peripheral sensorimotor neuropathy on physical examination by the study neurologist plus either abnormal nerve conduction in two different peripheral nerves or unequivocally abnormal autonomic test results.[9,10] P = 0.04 for the difference between groups in the primary-prevention cohort with respect to the base-line prevalence of clinical neuropathy.

Treatment and Follow-up

Conventional therapy consisted of one or two daily injections of insulin, including mixed intermediate and rapid-acting insulins, daily self-monitoring of urine or blood glucose, and education about diet and exercise.[13,25] Conventional therapy did not usually include daily adjustments in the insulin dosage. The goals of conventional therapy included the absence of symptoms attributable to glycosuria or hyperglycemia; the absence of ketonuria; the maintenance of normal growth, development, and ideal body weight; and freedom from severe or frequent hypoglycemia. Women who became pregnant or were planning a pregnancy received intensive therapy until the time of delivery, after which they resumed conventional treatment. Patients in the conventional-therapy group were examined every three months.

Intensive therapy included the administration of insulin three or more times daily by injection or an external pump. The dosage was adjusted according to the results of self-monitoring of blood glucose performed at least four times per day, dietary intake, and anticipated exercise. The goals of intensive therapy included preprandial blood glucose concentrations between 70 and 120 mg per deciliter (3.9 and 6.7 mmol per liter), postprandial concentrations of less than 180 mg per deciliter (10 mmol per liter), a weekly 3-a.m. measurement greater than 65 mg per deciliter (3.6 mmol per liter), and hemoglobin A_{1c} (glycosylated hemoglobin), measured monthly, within the normal range (less than 6.05 percent). The patients initially chose either multiple injections or pump therapy and could subsequently change to the other method if their glycemic goals were not achieved or if such was their preference. The patients in the intensive-therapy group visited their study center each month and were contacted even more frequently by telephone to review and adjust their regimens.

Outcome Measures

Seven-field stereoscopic fundus photographs were taken by certified photographers every six months and were centrally assessed by graders unaware of the treatment-group assignments. The graders used the protocol of the Early Treatment Diabetic Retinopathy Study (ETDRS).[28] The overall levels of severity of retinopathy were determined for each patient according to the ETDRS interim scale,[26] in which a scale of 25 steps is used to represent the overall extent of retinopathy in both eyes. In the primary-prevention co-

hort, the development of clinically important retinopathy was defined as a change of at least three steps from base line that was sustained for at least six months. Similarly, a sustained three-step change was used to define progression of retinopathy in the secondary-intervention cohort. This definition was chosen because of its reproducibility and because it represented a measure of clinically important worsening. Proliferative retinopathy and severe nonproliferative retinopathy were chosen as additional outcomes, because they indicate the need for frequent follow-up and possibly photocoagulation.[29] The measures of nephropathic, neuropathic, neuropsychological, macrovascular, and quality-of-life outcomes have been described in detail elsewhere.[13,18-25]

Statistical Analysis

The Wilcoxon rank-sum test was used to compare the two treatment groups within each cohort with regard to ordinal and numerical variables, and the contingency chi-square test was used for comparisons of categorical variables.[30] For a stratified analysis of proportions, the adjusted log relative risk comparing the results in the two treatment groups within each cohort was calculated by least-squares analysis.[31] Event rates are presented as the number of events per 100 patient-years based on the ratio of the observed number of events to the total number of patient-years of exposure. The life-table method was used to estimate the cumulative incidence of events,[32] with adjustment for periodically timed assessments.[33] The difference between cumulative incidence curves was tested by the Mantel (log-rank) test.[32] The average relative risks for the two treatment groups within each cohort over the entire observation period were estimated by proportional-hazards analysis,[32] with stratification or adjustment of the model for base-line variables. The imbalance in the base-line distribution of categories of retinopathy (Table 1) was adjusted for in the estimates of the reduction in the risk of retinopathy in the secondary-intervention cohort. The adjusted percentages of reduction in risk with intensive therapy were calculated by subtracting the average adjusted relative risk of intensive as compared with conventional therapy from 1 and multiplying by 100. The relative risk in the combined cohort was estimated by stratification according to the primary and the secondary cohorts. In the case of recurrent events, the relative risk was computed as the ratio of the crude event rates. The variance of the event rate and of the log relative risk included an adjustment for overdispersion.[34] A log-linear Poisson regression model was used to assess the relation between the risk of events and the time-dependent covariate measured periodically during the trial.[34] The time-dependent covariate values were also grouped according to decile, and the crude rate of the event was computed within the categories of the covariate. All outcomes were analyzed on the basis of the original treatment assignments. All results nominally significant at $P<0.05$ are indicated.

Results

Adherence and Metabolic Control

The entire cohort of 1441 patients was followed for a mean of 6.5 years (range, 3 to 9), a total of more than 9300 patient-years. Ninety-nine percent of the patients completed the study, and more than 95 percent of all scheduled examinations were completed. Eleven patients died, and 32 patients, 8 of whom were lost to follow-up, were assigned to inactive status for some time during the trial because of unavailability for study or the investigator's decision that continuation of their treatment would be hazardous. Overall, the average percentage of time spent receiving the assigned treatment was 97 percent. This includes 95 women assigned to conventional therapy who received intensive therapy during pregnancy or while planning a pregnancy.

The adherence to assigned treatment and the effectiveness of intensive therapy in lowering blood glucose concentrations are reflected in the substantial difference over time between the glycosylated hemoglobin values of the intensive-therapy group and those of the conventional-therapy group (Fig. 1A). Glycosylated hemoglobin reached a nadir at six months in the patients receiving intensive therapy. A statistically significant difference in the average glycosylated hemoglobin value was maintained after base line between the intensive-therapy and conventional-therapy groups in both cohorts ($P<0.001$). Although 44 percent of the patients receiving intensive therapy achieved the goal of a glycosylated hemoglobin value of 6.05 percent or less at least once during the study, less than 5 percent maintained an average value in this range. The blood glucose concentrations achieved with each treatment, as measured with quarterly seven-point capillary-blood glucose profiles, are shown in Figure 1B. The mean (±SD) value for all glucose profiles in the intensive-therapy group was 155±30 mg per deciliter (8.6±1.7 mmol per liter), as compared with 231±55 mg per deciliter (12.8±3.1 mmol per liter) in the conventional-therapy group ($P<0.001$).

Retinopathy

Primary-Prevention Cohort

The cumulative incidence of retinopathy, defined as a change of three steps or more on fundus photography that was sustained over a 6-month period, was similar in the two treatment groups until approximately 36 months, when the incidence curves began to separate (Fig. 2A). From five years onward, the cumulative incidence of retinopathy in the intensive-therapy group was approximately 50 percent less than in the conventional-therapy group. During a mean of six years of follow-up, retinopathy as defined above developed in 23 patients in the intensive-therapy group and 91 patients in the conventional-therapy group. Intensive therapy reduced the adjusted mean risk of retinopathy by 76 percent (95 percent confidence interval, 62 to 85 percent) (Table 2). The reduction in risk increased with time. Too few patients in the primary-prevention cohort had proliferative or severe nonproliferative retinopathy (two in the intensive-therapy group and four in the conventional-therapy group) or clinically important macular edema (one and four, respectively), or required photocoagulation (three and two patients, respectively) for reliable conclusions to be drawn.

Secondary-Intervention Cohort

The patients in the intensive-therapy group had a higher cumulative incidence of sustained progression of retinopathy by three steps or more during the first year than did those in the conventional-therapy group, but a lower cumulative incidence beginning at 36 months and continuing for the rest of the study (Fig. 2B). Intensive therapy reduced the average risk of such progression by 54 percent (95 percent confi-

dence interval, 39 to 66 percent) during the entire study period (77 patients in the intensive-therapy group and 143 patients in the conventional-therapy group). Intensive therapy reduced the adjusted risk of proliferative or severe nonproliferative retinopathy by 47 percent (P = 0.011) and that of treatment with photocoagulation by 56 percent (P = 0.002) (Table 2).

Consistency of Retinopathy Results

The cumulative incidence of sustained progression of retinopathy by three steps or more was analyzed within subgroups of patients to determine whether the reduction in risk with intensive therapy was consistent among subgroups. The subgroups were defined on the basis of base-line covariates, including age (adults vs. adolescents), sex, duration of IDDM, percentage of ideal body weight, level of retinopathy, mean blood pressure, presence of clinical neuropathy, screening glycosylated hemoglobin value, and albuminuria. A consistent reduction in the risk of retinopathy with intensive therapy was evident in all subgroups in both the primary-prevention and the secondary-intervention cohorts. The difference in retinal outcome between intensive and conventional therapy was also consistent among clinics.

Nephropathy

In both cohorts, microalbuminuria (defined as urinary albumin excretion, measured annually, of ≥40 mg per 24 hours) or albuminuria (urinary albumin excretion of ≥300 mg per 24 hours) developed in fewer patients in the intensive-therapy group than in the conventional-therapy group (Fig. 3). Intensive therapy reduced the mean adjusted risk of microalbuminuria by 34 percent (P = 0.04) in the primary-prevention cohort and by 43 percent (P = 0.001) in the secondary-intervention cohort (Table 2). The risk of albuminuria was reduced by 56 percent (P = 0.01) in the secondary-intervention cohort. Advanced nephropathy, as defined by urinary albumin excretion of 300 mg or more per 24 hours and a rate of creatinine clearance below 70 ml per minute per 1.73 m^2 of body-surface area, developed in very few patients (two in the intensive-therapy group and five in the conventional-therapy group).

The cumulative incidence of microalbuminuria was analyzed among selected subgroups in the 1368 patients in both cohorts in whom urinary albumin excretion was less than 40 mg per 24 hours at base line. The effect of intensive treatment in reducing risk was maintained within the subgroups defined according to age, sex, duration of IDDM, mean blood pressure, base-line glycosylated hemoglobin value, dietary protein intake, and history of smoking.

Neuropathy

Clinical neuropathy was defined as an abnormal neurologic examination that was consistent with the presence of peripheral sensorimotor neuropathy plus

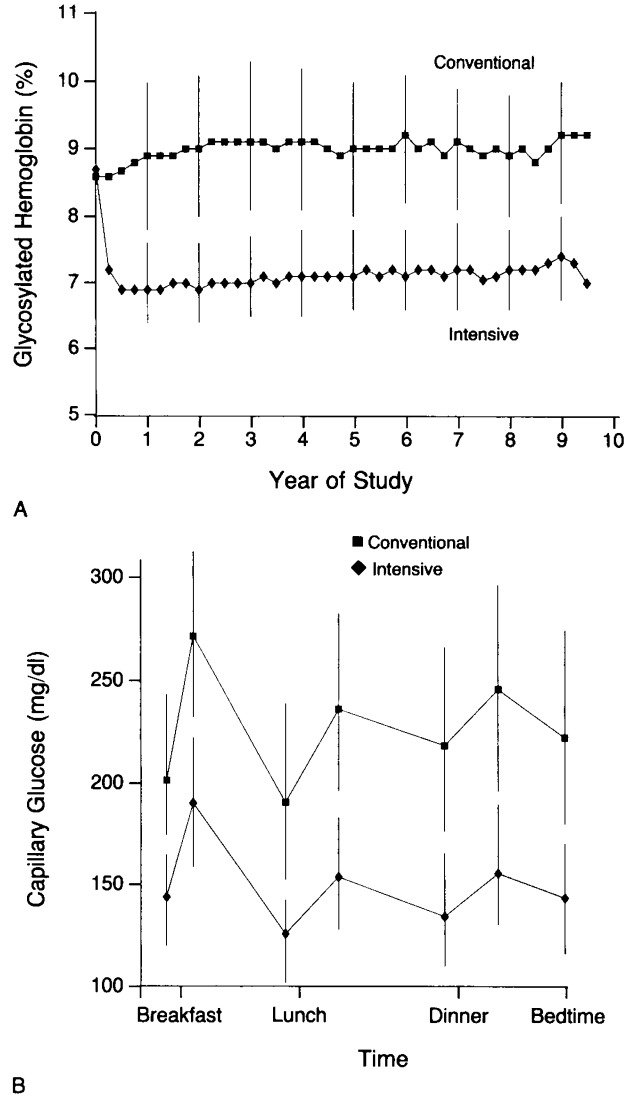

Figure 1. Measurements of Glycosylated Hemoglobin and Blood Glucose in Patients with IDDM Receiving Intensive or Conventional Therapy.

Panel A shows the medians of all quarterly glycosylated hemoglobin values, with the 25th and 75th percentiles of the yearly values indicated by the vertical lines. The differences between treatments were statistically significant (P<0.001) from three months until the end of the study. Panel B shows the medians of the quarterly mean values for the seven capillary-blood glucose measurements in a 24-hour period in each patient, with the 25th and 75th percentiles indicated by the vertical lines. The differences between treatments were statistically significant (P<0.001) at each of the seven testing times.

either abnormal nerve conduction in at least two peripheral nerves or unequivocally abnormal autonomic-nerve testing.[9,10] In the patients in the primary-prevention cohort who did not have neuropathy at base line, intensive therapy reduced the appearance of neuropathy at five years by 69 percent (to 3 percent, vs. 10 percent in the conventional-therapy group; P = 0.006) (Table 2). Similarly, in the secondary-intervention cohort, intensive therapy reduced the appearance of clinical neuropathy at five years by

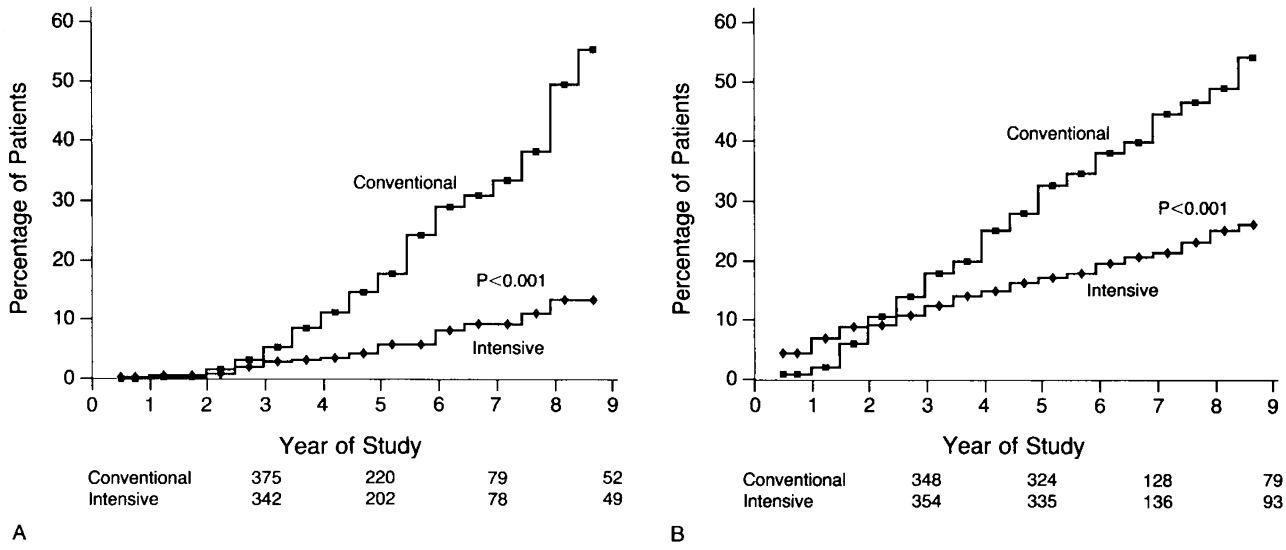

Figure 2. Cumulative Incidence of a Sustained Change in Retinopathy in Patients with IDDM Receiving Intensive or Conventional Therapy.

A sustained change in the severity of retinopathy was defined as a change observed by fundus photography of at least three steps from base line that was sustained for at least six months. In the primary-prevention cohort (Panel A), intensive therapy reduced the adjusted mean risk of the onset of retinopathy by 76 percent during the course of the study, as compared with conventional therapy ($P<0.001$). In the secondary-intervention cohort (Panel B), intensive therapy reduced the adjusted mean risk of progression of retinopathy by 54 percent as compared with conventional therapy ($P<0.001$). The numbers of patients in each therapy group who were evaluated at years 3, 5, 7, and 9 are shown below the graphs.

57 percent (to 7 percent, vs. 16 percent; $P<0.001$) (Table 2). All three components of the definition of clinical neuropathy were reduced similarly by intensive therapy (Fig. 4).

Macrovascular Disease

The relative youth of the patients made the detection of treatment-related differences in rates of macrovascular events unlikely. However, intensive therapy reduced the development of hypercholesterolemia, defined as a serum concentration of low-density lipoprotein cholesterol greater than 160 mg per deciliter (4.14 mmol per liter), by 34 percent (95 percent confidence interval, 7 to 54 percent) in the combined cohort ($P = 0.02$). When all major cardiovascular and peripheral vascular events were combined, intensive therapy reduced, albeit not significantly, the risk of macrovascular disease by 41 percent (to 0.5 event

Table 2. Development and Progression of Long-Term Complications of Diabetes in the Study Cohorts and Reduction in Risk with Intensive as Compared with Conventional Therapy.*

Complications	Primary Prevention			Secondary Intervention			Both Cohorts†
	Conventional therapy	Intensive therapy	Risk reduction	Conventional therapy	Intensive therapy	Risk reduction	Risk reduction
	rate/100 patient-yr		*% (95% CI)*	*rate/100 patient-yr*		*% (95% CI)*	*% (95% CI)*
≥3-Step sustained retinopathy	4.7	1.2	76 (62–85)‡	7.8	3.7	54 (39–66)‡	63 (52–71)‡
Macular edema§	—	—	—	3.0	2.0	23 (−13–48)	26 (−8–50)
Severe nonproliferative or proliferative retinopathy§	—	—	—	2.4	1.1	47 (14–67)¶	47 (15–67)¶
Laser treatment§‖	—	—	—	2.3	0.9	56 (26–74)‡	51 (21–70)¶
Urinary albumin excretion (mg/24 hr)							
≥40	3.4	2.2	34 (2–56)¶	5.7	3.6	43 (21–58)‡	39 (21–52)‡
≥300	0.3	0.2	44 (−124–86)	1.4	0.6	56 (18–76)¶	54 (19–74)¶
Clinical neuropathy at 5 yr**	9.8	3.1	69 (24–87)¶	16.1	7.0	57 (29–73)‡	60 (38–74)‡

*Rates shown are absolute rates of the development and progression of complications per 100 patient-years. Risk reductions represent the comparison of intensive with conventional treatment, expressed as a percentage and calculated from the proportional-hazards model with adjustment for base-line values as noted, except in the case of neuropathy. CI denotes confidence interval.

†Stratified according to the primary-prevention and secondary-prevention cohorts.

‡$P\leq 0.002$ by the two-tailed rank-sum test.

§Too few events occurred in the primary-prevention cohort to allow meaningful analysis of this variable.

¶$P<0.04$ by the two-tailed rank-sum test.

‖Denotes the first episode of laser therapy for macular edema or proliferative retinopathy.

**Excludes patients with clinical neuropathy at base line.

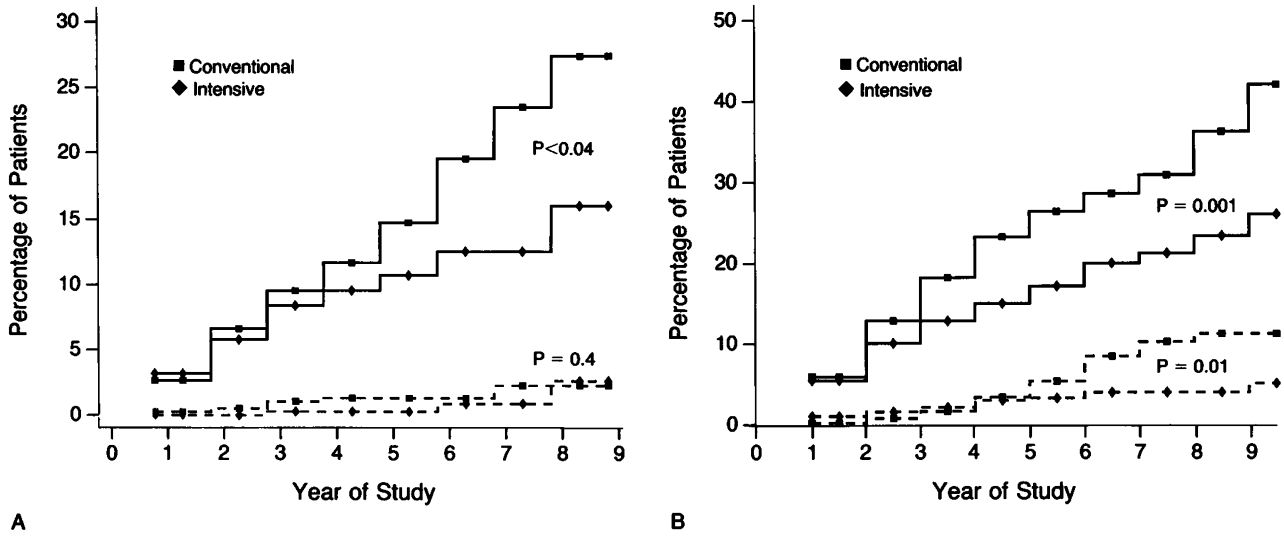

Figure 3. Cumulative Incidence of Urinary Albumin Excretion ≥300 mg per 24 Hours (Dashed Line) and ≥40 mg per 24 Hours (Solid Line) in Patients with IDDM Receiving Intensive or Conventional Therapy.

In the primary-prevention cohort (Panel A), intensive therapy reduced the adjusted mean risk of microalbuminuria by 34 percent (P<0.04). In the secondary-intervention cohort (Panel B), patients with urinary albumin excretion of ≥40 mg per 24 hours at base line were excluded from the analysis of the development of microalbuminuria. Intensive therapy reduced the adjusted mean risk of albuminuria by 56 percent (P = 0.01) and the risk of microalbuminuria by 43 percent (P = 0.001), as compared with conventional therapy.

per 100 patient-years, vs. 0.8 event; 95 percent confidence interval, −10 to 68 percent).

Adverse Events and Safety

Mortality did not differ significantly between the treatment groups (seven deaths in the intensive-treatment group and four in the conventional-treatment group) and was less than expected on the basis of population-based mortality studies.[35] As reported elsewhere,[36] the incidence of severe hypoglycemia, including multiple episodes in some patients, was approximately three times higher in the intensive-therapy group than in the conventional-therapy group (P<0.001). In the intensive-therapy group, there were 62 hypoglycemic episodes per 100 patient-years in which assistance was required in the provision of treatment, as compared with 19 such episodes per 100 patient-years in the conventional-therapy group. This included 16 and 5 episodes of coma or seizure per 100 patient-years in the respective groups. There were no deaths, myocardial infarctions, or strokes definitely attributable to hypoglycemia, and no significant differences between groups with regard to the number of major accidents requiring hospitalization (20 in the intensive-therapy group and 22 in the conventional-therapy group). However, there were two fatal motor vehicle accidents, one in each group, in which hypoglycemia may have had a causative role. In addition, a person not involved in the trial was killed in a motor vehicle accident involving a car driven by a patient in the intensive-therapy group who was probably hypoglycemic. There were 54 hospitalizations, usually brief, to treat severe hypoglycemia in 40 patients in the intensive-therapy group, as compared with 36 hospitalizations in 27 patients in the conventional-therapy group, including 7 and 4 hospitalizations, respectively, to treat hypoglycemia-related injuries.

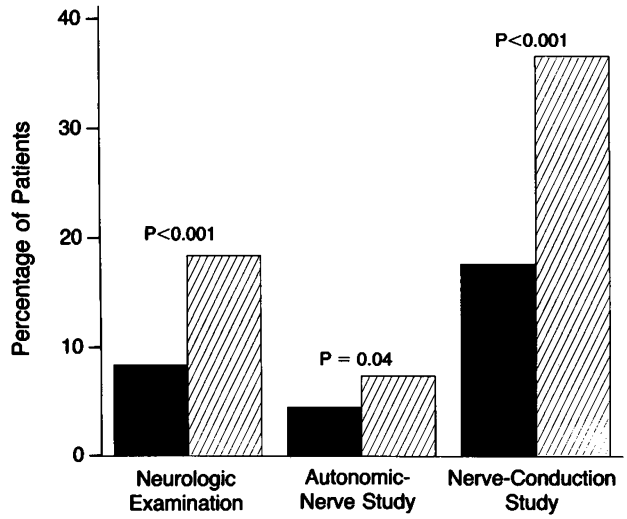

Figure 4. Prevalence of Abnormal Clinical Neurologic Examinations, Abnormal Results of Nerve-Conduction Studies, and Abnormal Autonomic-Nerve Studies at Five Years in Patients Receiving Intensive (Solid Bars) or Conventional (Hatched Bars) Therapy.

Abnormal results of nerve-conduction studies were defined as abnormal results of neurophysiologic tests in at least two peripheral nerves. The analysis included all patients from either cohort who did not have the abnormality in question at base line.

Despite the higher risk of severe hypoglycemia with intensive therapy, there was no difference between the two therapy groups in the occurrence of clinically important changes in neuropsychological function.[12] In addition, there were no significant differences in the mean total scores on the trial's quality-of-life questionnaire,[13] despite the added demands of intensive thera-

py. Weight gain was a problem with intensive therapy,[37] with an increase of 33 percent in the mean adjusted risk of becoming overweight, a condition defined as a body weight more than 120 percent above the ideal (12.7 cases of overweight per 100 patient-years in the intensive-therapy group vs. 9.3 in the conventional-therapy group). At five years, patients receiving intensive therapy had gained a mean of 4.6 kg more than patients receiving conventional therapy. The event rates for diabetic ketoacidosis were 1.8 and 2.0 episodes per 100 patient-years in the conventional-therapy and intensive-therapy groups, respectively ($P>0.7$).

Discussion

Intensive therapy of patients with IDDM delays the onset and slows the progression of clinically important retinopathy, including vision-threatening lesions, nephropathy, and neuropathy, by a range of 35 to more than 70 percent. The large number of patients studied, the inclusion of a primary-prevention cohort, and the long follow-up period in this study provided the opportunity to demonstrate the effects of treatment in patients with a range of ages, durations of diabetes, degrees of severity of retinopathy, and baseline glycosylated hemoglobin values.

The most consistent finding in previous trials was transient worsening of retinopathy with intensive therapy,[9,38,39] a result now confirmed by this trial. This early worsening, consisting of the development of soft exudates or intraretinal microvascular abnormalities, occurred mainly in the secondary-intervention cohort during the first year of therapy (22 percent of the patients in the intensive-therapy group and 13 percent of those in the conventional-therapy group). The abnormalities often disappeared by 18 months (Fig. 2B). Early worsening should not deter clinicians from using intensive therapy, because the patients with early worsening who were so treated ultimately had a 74 percent reduction (95 percent confidence interval, 46 to 88 percent) in the risk of subsequent progression as compared with patients with early worsening who received conventional therapy ($P<0.001$).

Intensive insulin therapy reduced the risk of albuminuria and microalbuminuria by 54 percent and 39 percent, respectively, in the combined cohort. A reduction in the progression to albuminuria was suggested by a previous study of 36 patients with IDDM who had generally higher levels of urinary albumin excretion at base line than the patients in the present trial.[40] Whether the decrease in the development of both microalbuminuria and albuminuria will result in a decrease in the development of renal insufficiency will be clarified by follow-up of the entire study cohort. The ability of intensive therapy to reduce the development of neuropathy suggests that neuropathy may be preventable. Finally, the tantalizing possibility that intensive therapy may reduce macrovascular disease requires further investigation.

In contrast to the clear-cut efficacy of intensive insulin therapy in reducing long-term complications, the risk of severe hypoglycemia was three times higher with such therapy. Relatively few patients required hospitalization or medical attention for hypoglycemia or resultant injuries, and serial neuropsychological testing showed no changes in cognitive function. Although we are mindful of the potential for severe injury, we believe that the risk of severe hypoglycemia with intensive therapy is greatly outweighed by the reduction in microvascular and neurologic complications.

Was the benefit of intensive therapy a result of the lowered glycemia, and can we choose a glycemic target that will preserve the benefits of intensive therapy but reduce the risk of severe hypoglycemia? We cannot answer these questions directly, because it was not practical to assign patients to multiple treatment groups with different levels of glycemia. Nevertheless, because of the clinical importance of the question, we analyzed the relation between the rate of development of retinopathy and glycemic exposure, expressed as the glycosylated hemoglobin value over time. These secondary analyses showed a continuously increasing risk of sustained progression by three steps with increasing mean glycosylated hemoglobin values (Fig. 5A), even after adjustment for temporal effects and potential confounding factors. Similarly, the risk of severe hypoglycemia increased continuously with lower monthly glycosylated hemoglobin values (Fig. 5B). These secondary analyses do not support the existence of a specific target value for glycosylated hemoglobin at which the benefits of intensive therapy are maximized and the risks minimized.

On the basis of these results, we recommend that most patients with IDDM be treated with closely monitored intensive regimens, with the goal of maintaining their glycemic status as close to the normal range as safely possible. Because of the risk of hypoglycemia, intensive therapy should be implemented with caution, especially in patients with repeated severe hypoglycemia or unawareness of hypoglycemia. The risk–benefit ratio with intensive therapy may be less favorable in children under 13 years of age and in patients with advanced complications, such as end-stage renal disease or cardiovascular or cerebrovascular disease. Patients with proliferative or severe nonproliferative retinopathy may be at higher risk for accelerated progression of their retinopathy after the start of intensive therapy[41] and should be followed closely by their ophthalmologists. Finally, although we did not study patients with non-insulin-dependent diabetes mellitus (NIDDM), hyperglycemia is associated with the presence or progression of complications in NIDDM,[42,43] as it is in IDDM. If the main conclusions of this trial with regard to the benefits of reducing glycemia are extended to patients with NIDDM, careful regard for age, capabilities, and coexisting diseases will be necessary. We therefore advise caution in the use of therapies other than diet that are aimed at achieving euglycemia in patients with NIDDM.

Intensive therapy was successfully carried out in the present trial by an expert team of diabetologists,

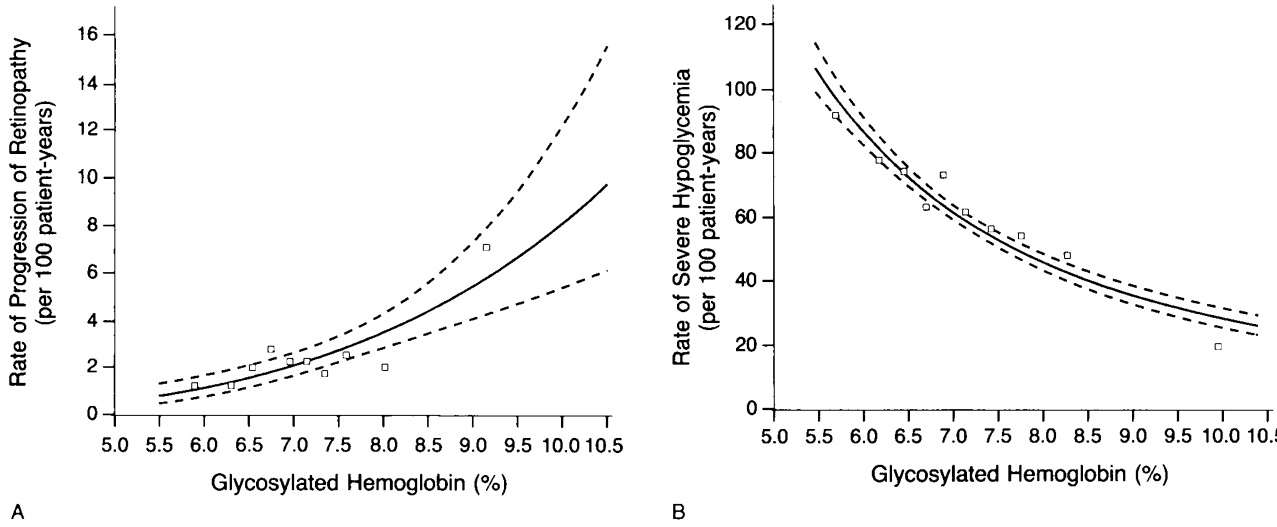

Figure 5. Risk of Sustained Progression of Retinopathy (Panel A) and Rate of Severe Hypoglycemia (Panel B) in the Patients Receiving Intensive Therapy, According to Their Mean Glycosylated Hemoglobin Values during the Trial.

Progression of retinopathy was defined as in the legend to Figure 2. In Panel A, the glycosylated hemoglobin values used were the mean of the values obtained every six months. In Panel B, the mean of the monthly values was used. Squares indicate the crude rates within deciles of the mean glycosylated hemoglobin values during the trial; each square corresponds to more than 400 patient-years. The solid lines are regression lines estimated as a function of the log of the mean glycosylated hemoglobin value in Panel A and the log of the glycosylated hemoglobin value in Panel B; the dashed lines are 95 percent confidence intervals.

nurses, dietitians, and behavioral specialists, and the time, effort, and cost required were considerable. Because the resources needed are not widely available, new strategies are needed to adapt methods of intensive treatment for use in the general community at less cost and effort. Meanwhile, the health care system should provide the support necessary to make intensive therapy available to those patients who will benefit.

Appendix

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References

1. National Diabetes Data Group. Diabetes in America: diabetes data compiled 1984. Bethesda, Md.: National Institutes of Health, 1985. (NIH publication no. 85-1468.)
2. Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one. Diabetologia 1978;14:363-77.
3. Engerman R, Bloodworth JM Jr, Nelson S. Relationship of microvascular disease in diabetes to metabolic control. Diabetes 1977;26:760-9.
4. Engerman RL, Kern TS. Progression of incipient diabetic retinopathy during good glycemic control. Diabetes 1987;36:808-12.
5. Cohen AJ, McGill PD, Rossetti RG, Guberski DL, Like AA. Glomerulopathy in spontaneously diabetic rat: impact of glycemic control. Diabetes 1987;36:944-51.
6. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 1984;102:520-6.
7. *Idem.* Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. JAMA 1988;260:2864-71.
8. Chase HP, Jackson WE, Hoops SL, Cockerham RS, Archer PG, O'Brien D. Glucose control and the renal and retinal complications of insulin-dependent diabetes. JAMA 1989;261:1155-60.
9. Kroc Collaborative Study Group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria: a preliminary multicenter trial. N Engl J Med 1984;311:365-72.
10. Lauritzen T, Frost-Larsen K, Larsen H-W, Deckert T. Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. Diabetes 1985;34:Suppl:74-9.
11. Brinchmann-Hansen O, Dahl-Jorgensen K, Hanssen KF, Sandvik L. The response of diabetic retinopathy to 41 months of multiple insulin injections, insulin pumps, and conventional insulin therapy. Arch Ophthalmol 1988; 106:1242-6.
12. Reichard P, Nilsson B-Y, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 1993;329:304-9.
13. DCCT Research Group. The Diabetes Control and Complications Trial (DCCT): design and methodologic considerations for the feasibility phase. Diabetes 1986;35:530-45.
14. *Idem.* Diabetes Control and Complications Trial (DCCT): results of feasibility study. Diabetes Care 1987;10:1-19.
15. *Idem.* Diabetes Control and Complications Trial (DCCT): update. Diabetes Care 1990;13:427-33.
16. Siebert C, Clark DM Jr. Operational and policy considerations of data monitoring in clinical trials: the Diabetes Control and Complications Trial experience. Controlled Clin Trials 1993;14:30-44.
17. DCCT Research Group. Implementation of a multicomponent process to obtain informed consent in the Diabetes Control and Complications Trial. Controlled Clin Trials 1989;10:83-96.
18. *Idem.* Color photography vs fluorescein angiography in the detection of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1987;105:1344-51.
19. *Idem.* Factors in development of diabetic neuropathy: baseline analysis of neuropathy in feasibility phase of Diabetes Control and Complications Trial (DCCT). Diabetes 1988;37:476-81.
20. Schumer M, Burton G, Burton C, Crum D, Pfeifer MA. Diabetic autonomic neuropathy — part I: autonomic nervous system data analysis by a computerized central unit in a multicenter trial. Am J Med 1988;85:137-43.
21. DCCT Research Group. Feasibility of centralized measurements of glycated hemoglobin in the Diabetes Control and Complications Trial: a multicenter study. Clin Chem 1987;33:2267-71.
22. *Idem.* A screening algorithm to identify clinically significant changes in neuropsychological function in the Diabetes Control and Complications Trial. J Clin Exp Neuropsychol (in press).
23. *Idem.* Reliability and validity of a diabetes quality-of-life measure for the Diabetes Control and Complications Trial (DCCT). Diabetes Care 1988; 11:725-32.

24. *Idem.* DCCT protocol. Springfield, Va.: Department of Commerce, National Technical Information Service, 1988. (Publication no. 88-116462-AS.)
25. *Idem.* DCCT manual of operations. Springfield, Va.: Department of Commerce, National Technical Information Service, 1993. (Publication no. 93-183382.)
26. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS report no. 12. Ophthalmology 1991;98:823-33.
27. Wei LJ, Lachin JM. Properties of the urn randomization in clinical trials. Controlled Clin Trials 1988;9:345-64.
28. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs — an extension of the modified Airlie House classification: ETDRS report no. 10. Ophthalmology 1991;98:786-806.
29. *Idem.* Early photocoagulation for diabetic retinopathy: ETDRS report number 9. Ophthalmology 1991;98:Suppl:766-85.
30. Snedecor GW, Cochran WG. Statistical methods. 6th ed. Ames: Iowa State University Press, 1967.
31. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research: principles and quantitative methods. Belmont, Calif.: Lifetime Learning, 1982: 359.
32. Lee ET. Statistical methods for survival data analysis. Belmont, Calif.: Lifetime Learning, 1980:88-92, 127-9, 306-12.
33. Tygstrup N, Lachin JM, Juhl E, eds. The randomized clinical trial and therapeutic decisions. New York: Marcel Dekker, 1982:174.
34. McCullagh P, Nelder JA. Generalized linear models. 2nd ed. New York: Chapman & Hall, 1989:194-200, 429-30.
35. Dorman JS, Laporte RE, Kuller LH, et al. The Pittsburgh insulin-dependent diabetes mellitus (IDDM) morbidity and mortality study: mortality results. Diabetes 1984;33:271-6.
36. DCCT Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. Am J Med 1991;90:450-9.
37. *Idem.* Weight gain associated with intensive therapy in the Diabetes Control and Complications Trial. Diabetes Care 1988;11:567-73.
38. Lauritzen T, Frost-Larsen K, Larsen HW, Deckert T. Effect of 1 year of near-normal blood glucose levels on retinopathy in insulin-dependent diabetics. Lancet 1983;1:200-4.
39. Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. BMJ 1985;290:811-5.
40. Feldt-Rasmussen B, Mathiesen ER, Deckert T. Effect of two years of strict metabolic control on progression of incipient nephropathy in insulin-dependent diabetes. Lancet 1986;2:1300-4.
41. Lawson PM, Champion MC, Canny C, et al. Continuous subcutaneous insulin infusion (CSII) does not prevent progression of proliferative and preproliferative retinopathy. Br J Ophthalmol 1982;66:762-6.
42. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol 1984;102:527-32.
43. Nathan DM, Singer DE, Godine JE, Harrington CH, Perlmuter LC. Retinopathy in older type II diabetics: association with glucose control. Diabetes 1986;35:797-801.