The Effect of Intensive Diabetes Treatment on the Progression of Diabetic Retinopathy in Insulin-Dependent Diabetes Mellitus

The Diabetes Control and Complications Trial

The Diabetes Control and Complications Trial Research Group

Objective: To determine the magnitude of the decrease in the risk of retinopathy progression observed with intensive treatment and its relationship to baseline retinopathy severity and duration of follow-up.

Design: Randomized clinical trial, with 3 to 9 years of follow-up.

Setting and Patients: Between 1983 and 1989, 29 centers enrolled 1441 patients with insulin-dependent diabetes mellitus aged 13 to 39 years, including 726 patients with no retinopathy and a duration of diabetes of 1 to 5 years (primary prevention cohort) and 715 patients with very mild to moderate nonproliferative diabetic retinopathy and a duration of diabetes of 1 to 15 years (secondary intervention cohort). Ninety-five percent of all scheduled examinations were completed.

Interventions: Intensive treatment consisted of the administration of insulin at least three times a day by injection or pump, with doses adjusted based on self–blood glucose monitoring and with the goal of normoglycemia. Conventional treatment consisted of one or two daily insulin injections.

Outcome Measures: Change between baseline and follow-up visits on the Early Treatment Diabetic Retinopathy Study retinopathy severity scale, assessed with masked gradings of stereoscopic color fundus photographs obtained every 6 months.

Results: Cumulative 8.5-year rates of retinopathy progression by three or more steps at two consecutive visits were 54.1% with conventional treatment and 11.5% with intensive treatment in the primary prevention cohort and 49.2% and 17.1% in the secondary intervention cohort. At the 6- and 12-month visits, a small adverse effect of intensive treatment was noted ("early worsening"), followed by a beneficial effect that increased in magnitude with time. Beyond 3.5 years of follow-up, the risk of progression was five or more times lower with intensive treatment than with conventional treatment. Once progression occurred, subsequent recovery was at least two times more likely with intensive treatment than with conventional treatment. Treatment effects were similar in all baseline retinopathy severity subgroups.

Conclusion: The results of the Diabetes Control and Complications Trial strongly support the recommendation that most patients with insulin-dependent diabetes mellitus use intensive treatment, aiming for levels of glycemia as close to the nondiabetic range as is safely possible.

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THE DIABETES Control and Complications Trial (DCCT), a multicenter randomized clinical trial, was designed to determine whether intensive treatment, with the goal of achieving blood glucose levels as close to the nondiabetic range as safely possible, would reduce the risk of development and/or progression of diabetic retinopathy and other long-term complications in patients with insulin-dependent diabetes mellitus (IDDM) and to assess the risks of such treatment compared with conventional treatment.[1] Two separate groups of patients were enrolled: a primary prevention cohort comprising 726 patients with IDDM of 1 to 5 years' duration who were free of retinopathy and a secondary intervention cohort comprising 715 patients with IDDM of 1 to 15 years' duration who had very mild to moderate nonproliferative diabetic retinopathy (NPDR). Retinopathy was assessed in seven-field stereoscopic color fundus photographs, which were graded with use of the Early Treatment Diabetic Retinopathy Study (ETDRS) modification of the Airlie House Classification.[2,3]

From the Diabetes Control and Complications Trial. A complete list of participants in this study appears at the end of this article.

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DESIGN AND METHODS

ELIGIBILITY

Design and methods have been presented in detail[8-10] and summarized[1] previously. Briefly, major eligibility criteria were insulin dependence as evidenced by deficient *c*-peptide secretion, age 13 to 39 years, and general good health without hypertension or hypercholesterolemia. Participants in the primary prevention cohort had a duration of diabetes of 1 to 5 years, no retinopathy observed on color photographs, best corrected visual acuity in each eye of 20/25 or better (ETDRS charts), and urinary albumin excretion lower than 40 mg/24 h. Participants in the secondary intervention cohort had a duration of diabetes of 1 to 15 years, very mild (microaneurysms only) to moderate NPDR, visual acuity in each eye of 20/32 or better, and urinary albumin excretion of 200 mg/24 h or lower.

TREATMENT

Participants were randomly assigned to receive either conventional or intensive treatment. The former consisted of one or two daily insulin injections, daily self-monitoring of urine or blood glucose levels, and diet and exercise education. The goals of treatment were freedom from symptoms of hyperglycemia and from severe or frequent hypoglycemia, as well as maintenance of normal growth and development and ideal body weight. Intensive treatment consisted of insulin administered three or more times daily by injection or an external pump, with doses adjusted according to self-monitored blood glucose levels measured at least four times per day, as well as anticipated dietary intake and exercise. The goals were preprandial blood glucose levels between 3.9 and 6.7 mmol/L (70 and 120 mg/dL), postprandial levels lower than 10.0 mmol/L (<180 mg/dL), a weekly 3 AM measurement higher than 3.6 mmol/L (>65 mg/dL), and a monthly glycosylated hemoglobin (HbA_{1c}) level within the nondiabetic range (<6.05%).

ASSESSMENT OF RETINOPATHY

Seven-field stereoscopic color fundus photographs were taken by certified photographers every 6 months and were graded (with graders masked to treatment) centrally according to the ETDRS protocol,[2] which provides a grade for the severity of each lesion of diabetic retinopathy for each eye. Photographs from baseline and annual follow-up visits were graded independently by two graders, with grades that differed by one step averaged and those that differed by two or more steps adjudicated by a senior grader, who assigned the final grade. Photographs from nonannual follow-up visits underwent a single grading. Grades for the various lesions were used to derive overall retinopathy severity levels for each patient according to the ETDRS interim and final scales.[3] An abbreviated summary of the final scale used in this report is shown in **Table 1** and **Table 2**. The reproducibility of the double grading system was assessed by regrading about 100 sets of photographs periodically throughout the study, with graders unaware that these were regradings. Seven comparisons were conducted during the course of the study, with degrees of agreement in the following ranges: complete agreement, 53.3% to 67.6%; agreement within one step, 84.3% to 95.0%; and agreement within two steps, 96.2% to 98.3%. Unweighted κ values ranged from 0.44 to 0.61. Weighted κ values with 1 for complete agreement, 0.75 for disagreement by one step, 0.5 for disagreement by two steps, and 0 for all other disagreements ranged from 0.72 to 0.84.

Change along the retinopathy severity scale over time was the principal outcome analyzed. One important outcome measure was the cumulative incidence of progression by three or more steps on the scale at two consecutive visits, termed *sustained progression* and defined as occurring at the first of the two consecutive visits. Recovery from progression by three or more steps (sustained or at a single visit) was also analyzed. To be defined as "recovering," a patient had to progress by at least three steps and then recover to less than three steps from the baseline level at any single visit after the progression had been observed. For example, a patient who progressed from step 3 at baseline to step 7 (four steps) at one visit, but at a later visit had a retinopathy grade at step 5 (two steps from baseline), would be considered to have recovered at that visit from the previous progression of at least three steps. To be eligible for such analyses, adequate fundus photographs had to have been obtained during at least one visit subsequent to the visit(s) at which progression was observed.

STATISTICAL METHODS

The life-table method was used to estimate the cumulative incidence of events,[11] with adjustments for periodically timed assessments.[12] Event rates are presented as number per 100 patient-years based on the ratio of the observed number of patients experiencing the event (cases) to the total patient years of exposure (at risk). The average relative risk (RR) comparing the two treatment groups within each cohort during the complete period of observation was estimated by a proportional hazards analysis,[11] with stratification adjustment for the baseline grade of retinopathy, and used to test the difference between cumulative incidence curves. The adjusted percentage change in risk for intensive therapy vs conventional therapy was calculated from the average adjusted RR of intensive vs conventional treatment as $(RR-1)\times 10$. For assessment of change in RRs over time, the 9 years of follow-up were divided into four intervals: the first year, when early worsening had its principal effect; years 2 to 5 (divided into two equal intervals), during which most patients (n=1088) were followed up; and the period beyond 5 years.

The prevalence of progression by three or more steps on the scale and the entire distribution of change on the scale between baseline and follow-up visits were also analyzed. The multivariate analysis of differences in proportions was used to compare the treatment groups with respect to the proportions of subjects with a characteristic present (prevalence) at each visit.[13] The overall test of group differences over time employed the Wei-Lachin Test with equal weights for each 6-month evaluation.[14] The Wilcoxon Rank-Sum Test was used to compare the treatment groups with respect to the distributions of ordinal or numerical variables, and the contingency χ^2 test was used for categorical variables.[15] For the analysis of repeated measurements over time of an ordinal or a numerical variable, the multivariate Mann-Whitney (Wilcoxon) analysis[14] was employed in conjunction with an overall test of differences between groups, with equal weights used for each

Continued on next page

6-month evaluation.[14] In these analyses, the Mann-Whitney difference between treatments (intensive minus conventional treatments) was used to quantify the magnitude of the difference between treatment groups. This is the difference in the estimated probabilities that a patient would have a more favorable outcome (ie, less progression of retinopathy) with intensive treatment vs conventional treatment. When the probabilities of more favorable outcome are the same in the two treatment groups, this difference is zero. If all patients in the intensive treatment group fared better than all patients in the conventional treatment group, the difference would be 1.0. In addition to the test of an average difference over time, a test of linear trend was conducted. The latter test is based on the slope of Mann-Whitney difference as a function of study time, estimated by weighted least squares based on the covariance matrix of the Mann-Whitney differences over time.[14] All outcomes were analyzed based on original random assignment of each patient. All results nominally significant at $P<.05$ are indicated.

As recently reported, in each cohort, intensive treatment substantially reduced the risk of retinopathy progression and the risks of development of diabetic neuropathy and nephropathy.[1] Adverse effects of intensive treatment included a threefold increase in the occurrence of severe hypoglycemia (62 vs 19 episodes per 100 patient-years) and a tendency for weight gain. The benefits of intensive treatment were judged to be clearly greater than its adverse effects, and intensive treatment

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was recommended for most patients with IDDM.[1] The goal of the present report is to provide a comprehensive assessment of the decreased risk of retinopathy progression observed in the DCCT with intensive treatment, particularly (1) the magnitude of this effect, (2) the degree to which it changes with time, and (3) its relationship to the severity of baseline retinopathy.

The primary outcomes specified in the trial design were (1) in the primary prevention cohort, persistent development of any retinopathy, defined as the presence of at least one microaneurysm in either eye at two consecutive visits (scheduled at 6-month intervals), and (2) in the secondary intervention cohort, progression (worsening) of retinopathy by three or more steps on the ETDRS interim scale of retinopathy severity,[3] which was considered to be a clinically important change. The primary analytic method was a comparison of the cumulative incidence of these events between the treatment groups. During the trial, it became apparent to the independent data review group that these outcomes were subject to variability within patients and from visit to visit. A more conservative measure, progression by three or more steps evident at two consecutive 6-month visits, termed *sustained progression,* was adopted. This measure is emphasized herein. Results of the originally specified analyses will be provided in another report that is currently being prepared.

Table 1. Abbreviated Summary of the Final Version of the Early Treatment Diabetic Retinopathy Study Scale of Diabetic Retinopathy Severity for Individual Eyes*

Level	Severity	Definition
10	No retinopathy	Diabetic retinopathy absent
20	Very mild NPDR	Microaneurysms only
35	Mild NPDR	Microaneurysms plus hard exudates, cotton-wool spots, and/or mild retinal hemorrhages
43	Moderate NPDR	Microaneurysms plus mild IRMA or moderate retinal hemorrhages
47	Moderate NPDR	More extensive IRMA, severe retinal hemorrhages, or venous beading in one quadrant only
53	Severe NPDR	Severe retinal hemorrhages in four quadrants, or venous beading in at least two quadrants, or moderately severe IRMA in at least one quadrant
61	Mild PDR	NVE<0.5 disc area in one or more quadrants
65	Moderate PDR	NVE≥0.5 disc area in one or more quadrants or NVD<0.25-0.33 disc area
71-75	High-risk PDR	NVD≥0.25-0.33 disc area and/or vitreous hemorrhage
81-85	Advanced PDR, fundus partially obscured	. . .

**NPDR indicates nonproliferative diabetic retinopathy; IRMA, intraretinal microvascular abnormalities; PDR, proliferative diabetic retinopathy; NVE, new vessels elsewhere; and NVD, new vessels on or within 1 disc diameter of optic disc.*

Table 2. Abbreviated Final Version of the Early Treatment Diabetic Retinopathy Study Scale of Diabetic Retinopathy Severity for Persons

Step	Level (Worse Eye/Better Eye)
1	10/10
2	20/<20
3	20/20
4	35/<35
5	35/35
6	43/<43
7	43/43
8	47/<47
9	47/47
10	53/<53
11	53/53
12-23	≥61/<61

Two other developments subsequent to the design and initiation of the DCCT were also taken into consideration in determining analytic methods. First, analyses of the various component lesions of diabetic retinopathy as predictors of the development of proliferative diabetic retinopathy led to revision of the ETDRS scale of retinopathy severity from its interim to its final form.[3] Second, several small randomized trials demonstrated

Table 3. Baseline Characteristics of the Two Study Cohorts*

	Primary Prevention Cohort		Secondary Intervention Cohort	
	Conventional (n=378)	Intensive (n=348)	Conventional (n=352)	Intensive (n=363)
Age, y	26±8	27±7	27±7	27±7
% Male	54	49	54	53
Race (% W)	96	96	97	97
Duration of insulin-dependent diabetes mellitus, y	2.6±1.4	2.6±1.4	8.6±3.7	8.9±3.8
Hemoglobin A_{1c}, %†	8.8±1.7	8.8±1.6	8.9±1.5	9.0±1.5
Systolic blood pressure, mm Hg	114±12	112±11	116±12	114±12
Diastolic blood pressure, mm Hg	72±9	72±9	73±9	73±9
Body mass index, kg/m²				
Male	24±3	23±3	24±3	23±3
Female	23±3	23±3	24±3	24±3
Retinopathy level, %‡				
10/10	100	100	0	0
20/<20	0	0	28.1	38.3
20/20	0	0	29.3	30.0
35/<35	0	0	20.2	13.5
35/35	0	0	11.4	8.8
43/<43	0	0	7.1	5.8
43/43	0	0	1.7	1.4
47/<47	0	0	1.7	1.7
53/<53	0	0	0.3	0

*Values are mean±SD, except where percent is specified.
†Nondiabetic mean is 5.05%±0.5%.
‡See Table 1 for explanation of retinopathy levels. The difference in the level of retinopathy at baseline between intensive and conventional treatment groups in the secondary intervention cohort, P=.02 by Wilcoxon Rank-Sum Test.

early, transient worsening of diabetic retinopathy to be an unexpected consequence of intensive treatment, resulting in an adverse effect during the initial year of treatment.[4-7] Therefore, this report emphasizes analytic methods that take into account change in treatment effect over time with use of the final version of the ETDRS scale.

RESULTS

BASELINE CHARACTERISTICS, FOLLOW-UP, AND COMPLIANCE

Table 3 presents selected baseline characteristics by cohort and treatment group. There were no substantial or statistically significant differences, except that the retinopathy severity level in the secondary cohort was slightly greater in the conventional treatment group (P=.02). Analyses of outcome were stratified according to baseline retinopathy severity. Levels 47/<47 and higher were combined into one stratum. As previously reported, follow-up was nearly complete and compliance was excellent; 98% of all scheduled fundus photographs were completed and patients spent 97% of study time administering assigned treatment. The intensive and conventional treatment groups maintained a separation in mean glycosylated hemoglobin level of about two percentage points throughout the follow-up period of 3 to 9 years (about 7.2% and 9.1%, respectively; P<.001).[1]

CUMULATIVE INCIDENCE OF SUSTAINED PROGRESSION

Figure 1 presents cumulative incidence rates of sustained progression by three or more steps on the final version of the ETDRS retinopathy severity scale for the two cohorts. As summarized in **Table 4**, of the 378 participants in the primary prevention cohort who were assigned to receive conventional treatment, 87 experienced progression during 1929 person-years at risk, yielding an average hazard rate of 4.51 per 100 person-years and an estimated 8.5-year cumulative incidence rate of 54.1%. Of the 348 participants in this cohort assigned to receive intensive treatment, 20 experienced progression during 1874 person-years, yielding a hazard rate of 1.07 per 100 person-years and an estimated 8.5-year cumulative incidence of 11.5%.

Of the 352 participants in the secondary intervention cohort who were assigned to receive conventional treatment, 116 experienced progression during 1953 person-years at risk, yielding a hazard rate of 5.94 per 100 person-years and an 8.5-year cumulative incidence rate of 49.2%. Of the 363 participants in this cohort assigned to receive intensive treatment, 48 experienced progression during 2229 person-years, yielding a hazard rate of 2.15 per 100 person-years and an 8.5-year cumulative incidence of 17.1%. Proportional hazards analyses of the entire follow-up period yielded average RRs for intensive vs conventional treatments of 0.21 and 0.36 (P<.0001 in each case) in the primary prevention and secondary intervention cohorts, respectively, corresponding to reductions in risk of 78.5% and 64.5% with intensive treatment (**Table 5**).

Table 5 presents rates of sustained progression by three or more steps in each of four subdivisions of the follow-up period, as well as average RRs and percent reductions in risk over the entire follow-up period, for each cohort and for subgroups of the secondary intervention cohort. During the

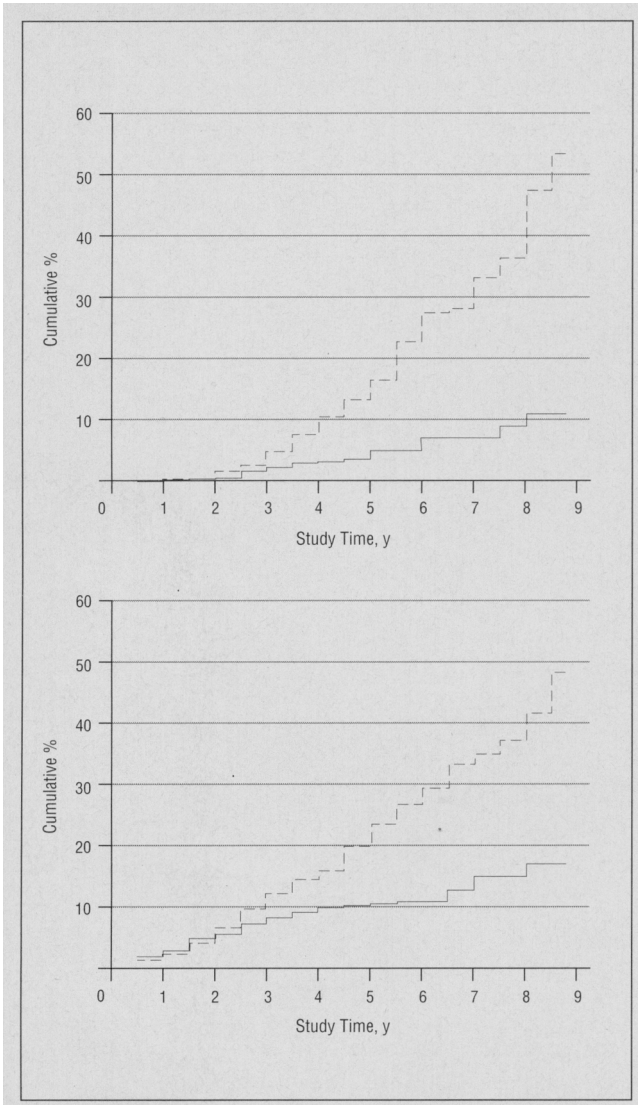

Figure 1. *Cumulative incidence of sustained progression by three or more steps on the final version of the Early Treatment Diabetic Retinopathy Study scale in the conventional (broken lines) and intensive (solid lines) treatment groups (P<.001) of the primary prevention (top) and secondary intervention (bottom) cohorts. Numbers of patients at risk in conventional and intensive treatment groups for the primary prevention cohort were 255 and 245, respectively, in the 4.0- to 4.5-year interval and 27 and 38, respectively, in the 8.0- to 8.5-year interval. Numbers of patients at risk in the conventional and intensive treatment groups for the secondary intervention cohort were 291 and 322, respectively, in the 4.0- to 4.5-year interval and 44 and 81, respectively, in the 8.0- to 8.5-year interval.*

first year of follow-up, rates in the two treatment groups within each cohort were essentially the same. Thereafter, rates increased substantially in the conventional treatment group of each cohort, while changing relatively little in the intensive treatment group, so that RRs for the intensive compared with the conventional treatment group decreased over time (*P* for time trend, .0384 and <.0001 in the primary prevention and secondary intervention cohorts, respectively). This analysis suggests that the average RRs of 0.21 and 0.36 in the primary prevention and secondary intervention, respectively, may underestimate the long-range benefit of intensive treatment. In each of the baseline retinopathy severity subgroups, except the most severe (level 43/<43 or worse), the temporal pattern was similar, with a substantial increase in rates between earlier and later time periods in the conventional treatment group, relatively little change in the intensive treatment group, and consequently a decrease in RR over time. In the small subgroup with moderate NPDR (level 43/<43 or worse), rates tended to be markedly higher and similar in both treatment groups during the first 3 years, with decreases thereafter only modestly greater in the intensive treatment group and the RR close to 1.0 in each time interval.

RECOVERY FROM PROGRESSION BY THREE OR MORE STEPS ON THE RETINOPATHY SEVERITY SCALE

Analyses of cumulative incidence ignore subsequent recovery from the event, as well as its recurrence, and thus differences in rates of recovery or recurrence between treatment groups are not reflected in life-table estimates of treatment effect. Analyses of recovery from progression revealed rates of recovery after sustained or nonsustained progression that were substantially greater with intensive treatment than with conventional treatment (**Table 6**). The chance of recovery after sustained progression, estimated over all the remaining follow-up time, was about twice as great with intensive treatment as opposed to conventional treatment in the primary prevention cohort and almost three times as great in the secondary intervention cohort. A greater chance of recovery in the intensive group was present within each of the baseline retinopathy severity subgroups. Further analyses employing methods in which recovery and recurrence are reflected (prevalence) were therefore performed.

Table 4. Summary of Life-Table Analyses of Sustained Progression by Three or More Steps

	Primary Prevention Cohort		Secondary Intervention Cohort	
	Conventional	Intensive	Conventional	Intensive
Total No. at baseline	378	348	352	363
No. with progression	87	20	116	48
Person-years at risk	1929	1874	1953	2229
Average rate, cases per 100 person-years at risk	4.51	1.07	5.94	2.15
Crude relative risk of intensive vs conventional treatment	0.24		0.36	
Average relative risk (95% confidence interval)*	0.21† (0.13-0.35)		0.36† (0.25-0.50)	
Cumulative incidence at 8.5 y, %	54.1	11.5	49.2	17.1

**From proportional hazards model, adjusted (secondary cohort only) for baseline retinopathy level (levels 47/<47 and above combined).*
†P<.0001.

Table 5. Rates of Sustained Progression by Three or More Steps From Baseline, Relative Risks (RRs), and Percent Change in Risk by Follow-up Time Period

Baseline Retinopathy Level	No. at Baseline (C+I)	Time Period, y	Conventional (C), Rate (Cases/ Person-Years)*	Intensive (I), Rate (Cases/ Person-Years)*	Crude RR, I:C	Entire Follow-up Period RR†	Entire Follow-up Period % Change in Risk From C (95% Confidence Interval)‡
Primary prevention cohort (10/10)	726	0-1	0.26 (1/378)	0.29 (1/348)	1.09	0.21	−78.5 (−64.9 to −86.9)
		1.5-3	2.28 (17/746)	1.16 (8/690)	0.51		
		3.5-5	6.44 (36/559)	1.11 (6/541)	0.17		
		5.5-8.5	13.41 (33/246)	1.69 (5/295)	0.13		
Secondary intervention cohort	715	0-1	2.29 (8/349)	2.50 (9/360)	1.09	0.36	−64.5 (−49.8 to −74.8)
		1.5-3	5.30 (35/661)	3.06 (21/687)	0.58		
		3.5-5	6.78 (39/576)	1.25 (8/642)	0.18		
		5.5-8.5	9.26 (34/367)	1.85 (10/541)	0.20		
Subgroups of secondary intervention cohort							
20/<20	240	0-3	1.67 (5/299)	2.47 (10/406)	1.47	0.39	−61.4 (−26.4 to −79.7)
		3.5-8.5	6.95 (19/274)	1.25 (6/481)	0.18		
20/20	212	0-3	4.75 (14/295)	1.88 (6/320)	0.40	0.21	−79.1 (−57.9 to −89.6)
		3.5-8.5	8.56 (25/292)	1.10 (4/363)	0.13		
35/≤35	193	0-3	4.42 (14/317)	1.65 (4/242)	0.38	0.24	−76.2 (−48.4 to −89.1)
		3.5-8.5	7.43 (22/296)	1.48 (4/271)	0.20		
43/<43 or worse	70	0-3	10.10 (10/99)	12.50 (10/80)	1.24	1.04	3.6 (114.1 to −49.9)
		3.5-8.5	8.64 (7/81)	5.88 (4/68)	0.68		

*Rate in cases per 100 person-years at risk.

†Average RR (I:C) from proportional hazards model, adjusted (secondary cohort only) for baseline retinopathy level (levels 47/<47 and above combined).

‡Percent change in risk was obtained as follows: 100×[RR(I:C)−1]. Negative values represent percent decrease in risk from C; positive values, percent increase.

Table 6. Cumulative Incidence of Recovery From a Three-Step Progression or Greater (Life-Table Rates)

No. of Visits With ≥3-Step Progression	Cohort	Conventional (C) No.*	Conventional (C) At Next Visit (6 mo), %	Conventional (C) Within 3 Visits (18 mo), %	Intensive (I) No.*	Intensive (I) At Next Visit (6 mo), %	Intensive (I) Within 3 Visits (18 mo), %	Remaining Follow-up Time RR, I:C†	Remaining Follow-up Time % Change in Risk From C (95% Confidence Interval)‡
1	Primary prevention	135	57.8	77.0	61	80.3	94.6	2.56	158.9 (42.6-370.0)
	Secondary intervention	149	44.3	61.1	102	67.6	86.5	2.44	141.7 (60.1-264.9)
2 consecutive (sustained)	Primary prevention	68	29.4	47.1	18	44.4	72.2	2.04	105.5 (−12.0-380.2)
	Secondary intervention	101	19.8	32.0	45	35.6	59.9	2.70	168.4 (51.9-374.3)
...	Subgroups of secondary intervention cohort at baseline								
	20/<20	21	14.3	26.7	14	35.7	59.8	5.56	462.7 (34.8-2248.4)
	20/20	30	33.3	53.7	9	44.4	77.8	1.85	84.0 (−40.4-468.1)
	35/≤35	33	12.1	19.7	8	50.0	50.0	4.35	326.9 (13.7-1502.7)
	43/<43+	17	17.6	24.5	14	21.4	52.9	3.57	261.1 (8.4-1102.6)

*Number at risk, ie, patients with progression and at least one subsequent visit with gradable photographs.

†Adjusted relative risk (RR) and percent change in risk are stratified for retinopathy severity level at the visit at which a three-step progression or greater was observed.

‡Percent change in risk was obtained as follows: 100×[RR(I:C)−1]. Negative values represent percent decrease in risk from C; positive values, percent increase.

PREVALENCE OF PROGRESSION BY THREE OR MORE STEPS ON THE RETINOPATHY SEVERITY SCALE

Figure 2 presents the percentage of participants with progression by three or more steps at each semiannual follow-up visit in the two cohorts. Unlike the analysis of cumulative incidence shown in Figure 1, in this analysis of prevalence, the status of a patient at a given visit is recorded without respect to the status at other visits. In each cohort, there was an increasingly steep rise from baseline in the conventional treatment group compared with a somewhat larger early rise followed by a more gradual subsequent increase in the intensive treatment group.

The 1-, 4-, 6-, and 9-year prevalence rates in Figure 2 are given in **Table 7**. In Table 7, this information is presented for baseline retinopathy severity subgroups as well. The 1-year visit was selected for presentation to al-

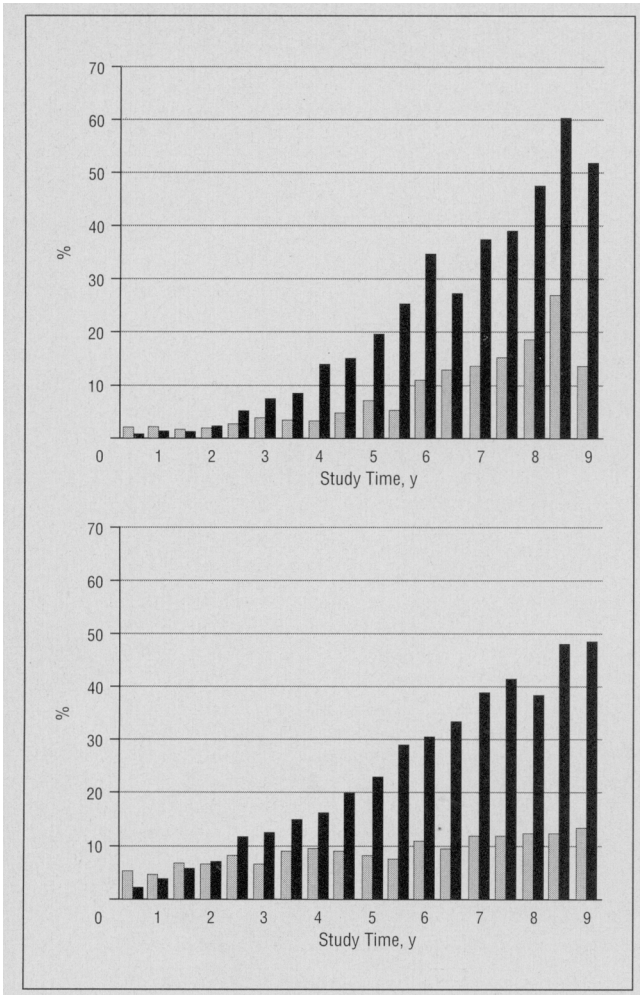

Figure 2. *Percent of participants with progression by three or more steps at each semiannual follow-up visit for the conventional (solid bars) and intensive (shaded bars) treatment groups in the primary prevention (top) and secondary intervention (bottom) cohorts (P<.001 for intensive vs conventional treatment).*

low evaluation of early worsening, the 4-year visit because nearly all participants completed this visit, the 9-year visit because it provides the longest follow-up available, and the 6-year visit because it comprises the time between 4 and 9 years, when numbers of participants were still fairly large. In the conventional treatment group of the primary prevention cohort, prevalence of progression by three or more steps increased from 1.3% at the 1-year visit to 14.1%, 35.1%, and 52.2% at the 4-, 6-, and 9-year visits, respectively. Corresponding percentages in the intensive treatment group were 2.0, 3.5, 11.3, and 14.3, representing a trend for a small adverse treatment effect at 1 year followed by an approximately threefold reduction at and after 4 years. The average difference between treatment groups (conventional minus intensive) with three or more steps of progression over all 6-month visits was 13.8% ($P<.001$). Results were similar for the secondary intervention cohort as a whole and for its three mildest subgroups (levels 20/<20, 20/20, and 35/≤35), except that the beneficial treatment effect was less apparent at the 4-year visit. In the level 43/<43 or worse subgroup, the prevalence of progression was already about 15% at 1 year in both treatment groups, and the treatment effect appeared to be somewhat less.

DISTRIBUTION OF CHANGE FROM BASELINE

Analyses to this point have addressed either the cumulative incidence or the point prevalence of worsening by at least three steps on the retinopathy severity scale. These analyses do not describe the actual number of steps of worsening, nor do they allow for differences between groups in extent of improvement. **Table 8** presents the percent distribution and the mean number of steps of change for better or worse on the scale between the baseline and the 1-, 4-, 6-, and 9-year visits separately for each cohort. Also shown for each of these visits in each cohort is the difference between intensive and conventional treatment groups in the estimated probability that participants in that group would have more favorable outcome (fewer steps of worsening or more steps of improvement) compared with participants in the other group (the Mann-Whitney difference). The Mann-Whitney difference is an appropriate statistic for use with the ordinal retinopathy severity scale, because no assumption is made about the equality of the intervals between steps along the scale. Thus, it does not consider the number of steps of difference between treatment groups. Analysis of the mean number of steps worse reflects distance along the scale under the assumption of equal intervals between steps, but because the intervals cannot be assumed to be equal, statistical tests were not performed on the differences between the means. In the primary prevention cohort at 1 year, worsening was slightly more frequent in the intensive treatment group, whatever cutpoint is chosen in the distribution of number of steps worse. This is reflected in the slightly higher mean, 0.32 steps worse vs 0.24 steps in the conventional treatment group, and in the slightly negative Mann-Whitney difference. At 4, 6, and 9 years, worsening was more common in the conventional treatment group. The difference in mean number of steps worse between treatment groups and the Mann-Whitney difference (ie, the probability of a more favorable outcome in the intensive treatment group) grew larger with time, reaching about 1.5 steps (3.15 steps with conventional minus 1.64 steps with intensive therapy) and 0.492, respectively, at 9 years.

In the secondary intervention cohort, improvement as well as worsening could occur. In the conventional treatment group at the 1-year visit, worsening was almost completely balanced by improvement, resulting in a mean worsening of 0.01 steps. In the intensive treatment group, however, mean worsening was 0.33 steps. The Mann-Whitney difference at 1 year was −0.121. At 4, 6, and 9 years, worsening was more frequent and improvement less frequent in the conventional treatment group. The difference in mean worsening and the probability of a more favorable outcome in the intensive treatment group increased with time, reaching about 2.3 steps (3.35 minus 1.09) and .448, respectively, at 9 years. The slopes of the Mann-Whitney differences at 6-month visits over time were 0.076 and 0.078 per year in the two cohorts ($P<.001$ in each cohort for a test of difference from 0). These slopes are shown in **Figure 3**. In each cohort, the probability of a more favorable outcome in the intensive treatment group reached .2 by about 5 years and .4 by about 8 years.

Table 9 presents 1-, 4-, and 9-year results for the four subgroups of the secondary intervention cohort. Results were similar in all subgroups, with treatment effect increasing substantially over time. The slopes of the

Table 7. Percent Prevalence of Three-Step Progression or Greater at the 1-, 4-, 6-, and 9-Year Follow-up Visits and Average Risk Difference Over All Visits by Baseline Retinopathy Severity Level

Baseline Retinopathy Level	Treatment Group	≥3-Step Progression at 1 y, No. (%)	≥3-Step Progression at 4 y, No. (%)	≥3-Step Progression at 6 y, No. (%)	≥3-Step Progression at 9 y, No. (%)	Average Risk Difference, C−I, % (95% CI)*
Primary prevention cohort (10/10)	Conventional	376 (1.3)	341 (14.1)	134 (35.1)	46 (52.2)	
	Intensive	344 (2.0)	313 (3.5)	133 (11.3)	42 (14.3)	13.8 (9.3-18.3)
	P	<.465	<.001	<.001	<.001	<.001
Secondary intervention cohort	Conventional	348 (3.7)	344 (16.3)	211 (30.8)	77 (49.4)	
	Intensive	362 (4.4)	348 (9.8)	234 (11.1)	86 (14.0)	14.6 (10.3-18.8)
	P	<.646	<.012	<.001	<.001	<.001
Subgroups of secondary intervention cohort						
20/<20	Conventional	100 (1.0)	99 (9.1)	56 (30.4)	17 (58.8)	
	Intensive	140 (3.6)	135 (7.4)	91 (9.9)	36 (19.4)	13.9 (6.3-21.6)
	P	<.167	<.647	<.004	<.005	<.001
20/20	Conventional	102 (4.9)	100 (16.0)	68 (23.5)	26 (42.3)	
	Intensive	109 (4.6)	105 (10.5)	70 (10.0)	24 (0.0)	15.5 (9.2-21.8)
	P	<.915	<.245	<.032	<.001	<.001
35/≤35	Conventional	108 (1.9)	108 (17.6)	63 (31.7)	23 (47.8)	
	Intensive	81 (1.2)	77 (6.5)	52 (7.7)	18 (16.7)	15.3 (7.1-21.5)
	P	<.731	<.017	<.002	<.023	<.001
43/<43 or worse	Conventional	38 (13.2)	37 (32.4)	24 (50.0)	11 (54.5)	
	Intensive	32 (15.6)	31 (25.8)	21 (28.6)	8 (25.0)	9.8 (−9.7-29.4)
	P	<.771	<.549	<.132	<.169	<.324

**Average risk difference in percentage with a three-step progression or worse (conventional minus intensive) over all eighteen 6-month follow-up visits and 95% confidence interval (CI).*

Mann-Whitney differences at 6-month visits over time were 0.070 per year or greater in each subgroup ($P<.001$ in each subgroup for a test of difference from 0).

MORE SEVERE OUTCOMES

Figure 4 presents cumulative incidence rates of severe NPDR or worse, neovascularization (new vessels on the disc or elsewhere), and clinically significant macular edema (CSME) for the secondary intervention cohort. As expected, because most patients with severe NPDR develop neovascularization within 1 to 2 years, the results for severe NPDR or worse and for neovascularization were similar. In each of these analyses, the curves for the conventional and intensive treatment groups were superimposed during the first 3 years, after which the slope tended to increase in the conventional treatment group and to remain the same or decrease slightly in the intensive treatment group. Nine-year rates for severe or worse NPDR were 32% and 9% in the conventional and intensive treatment groups, respectively ($P<.001$); comparable rates for neovascularization were 24% and 8%, respectively ($P<.020$). For CSME, the curves in both treatment groups rose somewhat more rapidly, reaching about 11% to 12% at 5 years, after which the slope decreased in the intensive treatment group but remained the same in the conventional treatment group. Nine-year rates were 27% and 15% in the conventional and intensive treatment groups, respectively ($P<.215$). In the primary cohort, these outcomes were too infrequent for analysis (severe NPDR or worse, four cases in the conventional treatment group and two cases in the intensive treatment group; neovascularization, two cases in the conventional treatment group and one case in the intensive treatment group; and CSME, four cases in the conventional treatment group and one case in the intensive treatment group).

Table 10 presents rates and crude RRs for these three outcome measures in each of four subdivisions of the follow-up period, as well as average RRs and percent reductions in risk during the entire study period. For severe NPDR or worse, rates in both treatment groups were close to two per 100 person-years during both of the first two time intervals, yielding RRs close to 1. Subsequently, rates in the conventional treatment group rose and those in the intensive treatment group declined, leading to RRs after 3 years between 0.1 and 0.2. For neovascularization, rates increased in the conventional treatment group but remained close to one per 100 person-years in all periods in the intensive treatment group, and the RR decreased to 0.17 in the 5.5- to 9-year interval. For CSME, the rate in the intensive treatment group during the first year tended to be slightly higher than that in the conventional treatment group, possibly reflecting early worsening. In the next two intervals, rates were about two to three per 100 person-years in each treatment group, with RRs close to 1. In the last time interval, the rates increased in the conventional treatment group and decreased in the intensive treatment group, leading to an RR of 0.22.

Table 11 presents similar analyses of the development of severe NPDR or worse within baseline retinopathy subgroups in each of two time intervals. In each of the three mildest subgroups (20/<20, 20/20, and 35/≤35), rates were low and about the same in the two treatment groups for the first 3 years of follow-up. In the 3.5- to 9-year interval in each of these subgroups, the rate increased in the conventional treatment group but remained about the same in the intensive

Table 8. Percent Distribution of Number of Steps of Change From Baseline, Mean Number of Steps Worse, and Difference in Probabilities of Less Worsening With Intensive Treatment at the 1-, 4-, 6-, and 9-Year Visits for Primary Prevention and Secondary Intervention Cohorts

Visit	Treatment Group	No.	Better			Same	Worse						
			3+	2	1		1	2	3	4	5	6	7+
Primary prevention cohort													
1 y	Conventional	376	...	...	...	80.9	16.0	1.9	1.3	0.0	0.0	0.0	0.0
	Intensive	344	...	...	...	76.5	18.3	3.2	1.7	0.0	0.0	0.3	0.0
4 y	Conventional	341	...	...	...	40.8	25.5	19.6	10.9	1.5	1.5	0.3	0.0
	Intensive	313	...	...	...	53.4	28.4	14.7	2.9	0.0	0.0	0.3	0.3
6 y	Conventional	134	...	...	...	25.4	14.9	24.6	21.6	6.7	3.0	3.0	0.7
	Intensive	133	...	...	...	40.6	27.8	20.3	9.0	0.8	0.0	0.8	0.8
9 y	Conventional	46	...	...	...	10.9	6.5	30.4	17.4	19.6	4.3	4.3	6.5
	Intensive	42	...	...	...	31.0	28.6	26.2	4.8	2.4	2.4	0.0	4.8
All visits combined†			...	...	...	...	...	...	...	...	...	...	...	...
Slope over time (per year)‡			...	...	...	...	...	...	...	...	...	...	...	...
Secondary intervention cohort													
1 y	Conventional	348	2.3	8.0	23.9	34.8	19.5	7.8	2.3	0.6	0.3	0.3	0.3
	Intensive	362	0.6	3.6	20.2	38.7	22.4	10.2	2.8	0.6	0.6	0.0	0.6
4 y	Conventional	344	1.7	4.4	11.0	27.3	20.3	18.9	4.7	3.2	2.0	1.7	4.7
	Intensive	348	1.4	2.9	17.0	30.2	29.3	9.5	5.5	1.7	0.9	1.1	0.6
6 y	Conventional	211	0.9	3.3	6.6	18.5	22.3	17.5	10.4	6.2	4.7	4.7	4.7
	Intensive	234	0.9	3.0	12.4	28.2	29.1	15.4	5.1	2.1	1.7	0.9	1.3
9 y	Conventional	77	0.0	1.3	3.9	14.3	15.6	15.6	14.3	9.1	2.6	3.9	19.5
	Intensive	86	2.3	1.2	16.3	27.9	18.6	19.8	5.8	2.3	2.3	0.0	3.5
All visits combined†			...	...	...	...	...	...	...	...	...	...	...	...
Slope over time (per year)§			...	...	...	...	...	...	...	...	...	...	...	...

**The difference in the estimated probabilities that a participant would experience fewer steps of worsening, or more steps of improvement, with intensive vs conventional treatment. I-C indicates intensive minus conventional treatment,*

†Average over all 6-month visits of the difference in estimated probabilities.

‡Intensive treatment minus conventional treatment.

§The slope of the Mann-Whitney differences at 6-month visits over time. The P value is for a test that the slope is equal to zero.

treatment group, so that crude RRs decreased to between 0.1 and 0.2; average RRs during the entire study period ranged from 0.1 to 0.3. In the most severe subgroup (level 43/<43 or worse), the rates were high in both treatment groups for the first 3 years of follow-up. In the 3.5- to 9-year interval, the rate in the conventional treatment group remained about the same as in the earlier period, while in the intensive treatment group, the rate decreased substantially (from 17.6 to 3.2 per 100 person-years) and the crude RR decreased to 0 28; average RR during the entire study period was close to 1. **Table 12** presents rates of neovascularization within the baseline retinopathy subgroups. Results were similar to those presented in Table 11, but no trend toward a beneficial treatment effect in the 43/<43 or worse subgroup was observed until the 5.5- to 9-year interval.

COMMENT

We conclude that the beneficial effect of intensive treatment in slowing the progression of retinopathy was very substantial, increased with time, was consistent across all outcome measures assessed, and was present across the spectrum of retinopathy severity enrolled in the DCCT, although not to the same degree in all analyses. Of these four conclusions, the most intriguing is the increase in treatment effect with time. This is well demonstrated in Figure 3, which depicts the fairly steady increase in the probability of a more favorable outcome for participants in the intensive treatment group during at least the first 6 years of follow-up, with continuing but perhaps less steep increases thereafter. Given that the probability would reach 1.0 only if every patient in the intensive treatment group had a more favorable outcome than every patient in the conventional treatment group, it is impressive that the treatment effect had increased to about half of this theoretical limit by the end of the follow-up period.

What explains this increase in treatment effect over time, and to what extent do estimates of treatment effect based on the entire follow-up time reflect long-range treatment benefit? Part of the reason for the increase in the beneficial effect of intensive treatment during follow-up was its initial adverse effect, previously documented by other investigators and termed *early worsening*.[4-7] This is best shown in Figures 2 and 3 and was more apparent in the secondary intervention cohort. Another factor was the more frequent recovery from progression in the intensive treatment group compared with the conventional treatment groups (Table 6). This difference in recovery is reflected in analyses of prevalence (Figures 2 and 3 and Tables 7 through 9) but not in life-table analyses (Figure 1 and Tables 4 and 5), which do not allow for subsequent recovery. However, the results of the life-table analyses in both treatment groups are brought more in line with other analyses of prevalence by defining the event as sustained progression rather than progression at a single visit.

Another factor that appears to be present in the sec-

Mean Steps Worse	Mann-Whitney Difference in Probabilities* I−C‡	SE	P<
0.24 0.32	−0.046	0.031	.131
1.12 0.71	0.189	0.042	.001
1.99 1.13	0.321	0.067	.001
3.15 1.64	0.492	0.116	.001
... ...	0.211 0.076	0.040 0.009	.001 .001
0.01 0.33	−0.121	0.042	.005
1.22 0.61	0.137	0.043	.002
1.93 0.87	0.262	0.053	.001
3.35 1.09	0.448	0.087	.001
... ...	0.162 0.078	0.037 0.007	.001 .001

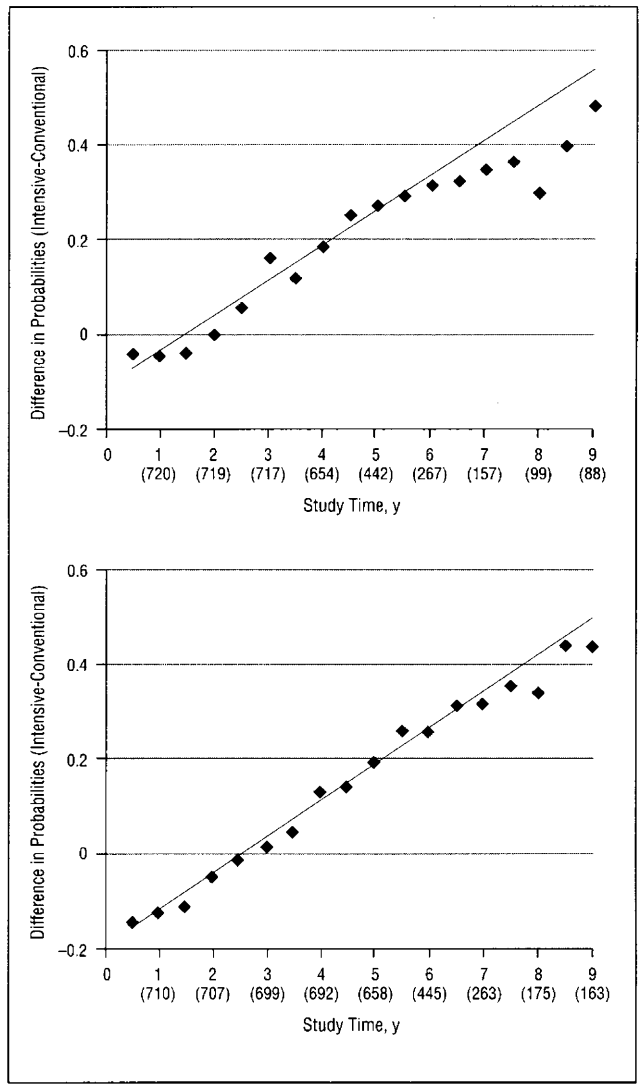

Figure 3. *Slopes of the Mann-Whitney differences at 6-month visits over time (differences in the estimated probabilities that participants in the intensive treatment group would have a more favorable outcome, ie, fewer steps of worsening or more steps of improvement, than those in the conventional treatment group) (P<.001) in the primary prevention (top) and secondary intervention (bottom) cohorts. Numbers in parentheses are numbers of patients.*

ondary intervention cohort is the inherent momentum of the retinopathic process, which has also been observed in experimental diabetic retinopathy.[16] This is best shown in Figure 1, bottom, and Table 5. In Figure 1, bottom, there is little difference between the treatment groups through the second year of follow-up; subsequently, the rates in the conventional treatment group increase while those in the intensive treatment group remain about the same for another year before decreasing in the 3.5- to 5-year interval (Table 5). The analyses of more severe outcome measures also support the notion that there are characteristics of the retinopathic process that can be stopped or reversed by intensive treatment only after a considerable delay. This retinopathic momentum appeared to extend through the first 3 years of follow-up for severe NPDR or worse and for neovascularization and through 5 years for macular edema (Figure 4 and Table 10).

Finally, perhaps the most important factor underlying the increase in treatment effect over time was the marked contrast between the progressive increase in the rates of progression observed in the conventional treatment groups and the stable or even decreasing rates of these events in the intensive treatment groups (Figures 1 and 4 and Tables 5 and 10). This contrast emphasizes the remarkable efficacy of intensive treatment, imperfect as it was in achieving its goal of normalizing glycemia. Taking all of these data into consideration, the best estimate of the long-term efficacy of intensive treatment would appear to be at least a fivefold reduction in risk of retinopathy progression, ie, a risk reduction of 80% or more. The Stockholm Study[17] also found a substantial increase in the beneficial effect of intensive treatment on the development of "serious retinopathy" (proliferative retinopathy or macular edema requiring immediate photocoagulation) after 7.5 years of follow-up (compare their Figure 1 with our Figure 4).

A comparison of treatment effects between subgroups defined by baseline retinopathy severity shows that the mildest three subgroups of the secondary intervention cohort are similar to each other and to the primary prevention cohort in all analyses, both in the magnitude of treatment effect and in its increase over time (Tables 5, 7, 8, 9, and 11). In the analyses that considered both worsening and improvement along the retinopathy severity scale (Tables 8 and 9), the level 43/<43 or worse subgroup appeared similar to the other

Table 9. Percent Distribution of Number of Steps Change From Baseline and Mean Number of Steps Worse and Difference in Probabilities of Less Worsening With Intensive Treatment at the 4- and 9-Year Follow-up Visits for Subgroups of the Secondary Intervention Cohort

			Better				Worse						
Baseline Retinopathy Level	Group	No.	3+	2	1	Same	1	2	3	4	5	6	7+
20/<20													
1 y	Conventional	100			28.0	32.0	24.0	15.0	1.0	0.0	0.0	0.0	0.0
	Intensive	140			26.4	35.0	23.6	11.4	2.1	0.7	0.7	0.0	0.0
4 y	Conventional	99			13.1	24.2	29.3	24.2	6.1	1.0	2.0	0.0	0.0
	Intensive	135			15.6	23.0	41.5	12.6	5.9	1.5	0.0	0.0	0.0
9 y	Conventional	17			0.0	5.9	17.6	17.6	23.5	5.9	5.9	5.9	17.6
	Intensive	36			22.2	11.1	27.8	19.4	11.1	5.6	0.0	0.0	2.8
All visits combined†		...			...	...	...	...	...	...	...	...	...
Slope over time (per year)‡		...			...	...	...	...	...	...	...	...	...
20/20													
1 y	Conventional	102		2.9	12.7	47.1	25.5	6.9	4.9	0.0	0.0	0.0	0.0
	Intensive	109		6.4	7.3	46.8	27.5	7.3	3.7	0.9	0.0	0.0	0.0
4 y	Conventional	100		3.0	2.0	37.0	24.0	18.0	8.0	3.0	1.0	1.0	3.0
	Intensive	105		3.8	9.5	42.9	24.8	8.6	5.7	1.9	1.9	0.0	1.0
9 y	Conventional	26		0.0	0.0	23.1	11.5	23.1	15.4	7.7	3.8	3.8	11.5
	Intensive	24		0.0	8.3	41.7	25.0	25.0	0.0	0.0	0.0	0.0	0.0
All visits combined		...		...	...	...	...	...	...	...	...	...	...
Slope over time (per year)		...		...	...	...	...	...	...	...	...	...	...
35/<35 or 35/35													
1 y	Conventional	108	3.7	15.7	33.3	31.5	11.1	2.8	0.9	0.0	0.9	0.0	0.0
	Intensive	81	0.0	4.9	25.9	38.3	17.3	12.3	1.2	0.0	0.0	0.0	0.0
4 y	Conventional	108	2.8	8.3	18.5	23.1	12.0	17.6	1.9	6.5	0.9	2.8	5.6
	Intensive	77	1.3	2.6	35.1	27.3	19.5	7.8	5.2	1.3	0.0	0.0	0.0
9 y	Conventional	23	0.0	4.3	13.0	8.7	17.4	8.7	8.7	17.4	0.0	0.0	21.7
	Intensive	18	0.0	0.0	16.7	50.0	0.0	16.7	5.6	0.0	0.0	0.0	11.1
All visits combined		...	...	...	...	...	...	...	...	...	...	...	...
Slope over time (per year)‡		...	...	...	...	...	...	...	...	...	...	...	...
43/<43 or worse													
1 y	Conventional	38	10.5	21.1	15.8	18.4	15.8	5.3	2.6	5.3	0.0	2.6	2.6
	Intensive	32	6.3	6.3	21.9	28.1	12.5	9.4	6.3	0.0	3.1	0.0	6.3
4 y	Conventional	37	8.1	8.1	8.1	21.6	10.8	10.8	0.0	0.0	8.1	5.4	18.9
	Intensive	31	12.9	12.9	3.2	25.8	16.1	3.2	3.2	3.2	3.2	12.9	3.2
9 y	Conventional	11	0.0	0.0	0.0	18.2	18.2	9.1	9.1	0.0	0.0	9.1	36.4
	Intensive	8	25.0	12.5	12.5	12.5	0.0	12.5	0.0	0.0	25.0	0.0	0.0
All visits combined†		...	...	...	...	...	...	...	...	...	...	...	...
Slope over time (per year)‡		...	...	...	...	...	...	...	...	...	...	...	...

**The difference in the estimated probabilities that a participant would experience fewer steps of worsening, or more steps of improvement, with intensive vs conventional treatment. I-C indicates intensive minus conventional treatment,*

†Average over all 6-month visits of the difference in estimated probabilities.

‡The slope of the Mann-Whitney differences at 6-month visits over time. The P value is for a test that the slope is equal to zero.

groups, both in the difference in Mann-Whitney probabilities averaged over all visits and in the increase of these differences over time. In the analyses of cumulative incidence of sustained progression or of level 53/<53 or worse, treatment effect was not evident in this subgroup until after 3 years. During the first 3 years, events were substantially more frequent in this subgroup than in the others and about equally frequent in both treatment groups. These participants were near the upper boundary of the spectrum of retinopathy severity eligible for entry into the trial. The initial high progression rates may be due in part to this selection. These high rates continued through 3.5 years of follow-up in both treatment groups before declining in the intensive treatment group. The delay in the onset of a beneficial treatment effect may be attributable to an inherent momentum of retinopathy once it is initiated. The momentum might be expected to be greater when baseline retinopathy is more severe.

Although estimates of the magnitude of long-term treatment effect are clearly important, ours must be viewed with some caution because they are based on relatively small numbers of participants followed up for as long as 8 to 9 years. Numbers were particularly small in the level 43/<43 or worse subgroup. Moreover, more advanced levels of retinopathy were not included in the DCCT. Other investigators have suggested that early worsening, when it occurs in patients with severe NPDR or pro-

Mean Steps Worse	Mann-Whitney Difference in Probabilities* I–C	SE	P<
0.29	−0.002	0.073	.981
0.33			
0.97	0.093	0.073	.204
0.75			
4.12	0.541	0.144	.001
1.13			
. . .	0.213	0.061	.001
. . .	0.070	0.012	.001
0.35	−0.023	0.074	.762
0.37			
1.31	0.202	0.077	.009
0.70			
2.81	0.529	0.151	.002
0.67			
. . .	0.233	0.059	.001
. . .	0.086	0.012	.001
−0.52	−0.297	0.079	.001
0.10			
1.08	0.175	0.083	.035
0.12			
2.87	0.307	0.164	.062
1.50			
. . .	0.101	0.074	.173
. . .	0.076	0.013	.001
−0.13	−0.164	0.134	.221
0.75			
2.03	0.158	0.137	.251
0.94			
4.45	0.602	0.267	.025
0.38			
. . .	0.187	0.132	.156
. . .	0.080	0.019	.001

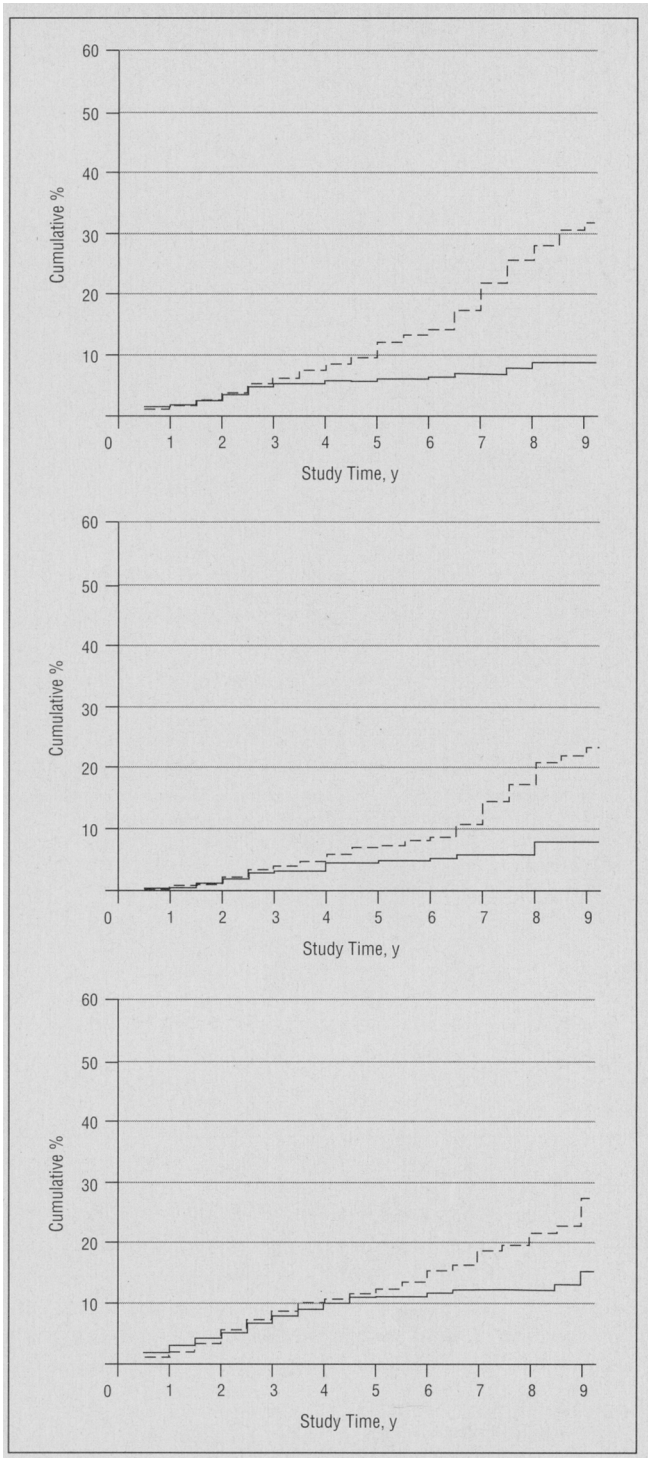

Figure 4. *Cumulative incidence of severe nonproliferative diabetic retinopathy or worse (top [P<.001]), new vessels of the disc or elsewhere (middle [P<.015]), and clinically significant macular edema (bottom) for conventional teatment (broken lines) and intensive treatment (solid lines) in the secondary intervention cohort. The 9-year rates in the conventional and intensive treatment groups were 32.1% and 9.0%, respectively, for severe or worse nonproliferative diabetic retinopathy, 23.6% and 8.1% for new vessels, and 27.4% and 15.3% for clinically significant macular edema.*

liferative diabetic retinopathy, may have a clinically important adverse effect. They have recommended particularly careful ophthalmologic surveillance of patients with retinopathy at these levels when intensive treatment is initiated, with lowering of the usual threshold for photocoagulation.[18-21]

In summary, analyses that allow assessment of change in treatment effect over time and that employ an improved retinopathy severity scale strengthen previously reported DCCT conclusions that intensive treatment provides a very substantial reduction in the risk of clinically important progression of retinopathy. Treatment benefit extended across the entire spectrum of retinopathy severity included in the DCCT. Ophthalmologists can and should use this information together with that presented in previous DCCT reports to help motivate most patients with IDDM to aim for levels of glycemia as near normal as considered safe for that patient.

Table 10. Rates of Severe Retinopathy Events in Secondary Intervention Cohort, Relative Risks (RRs), and Percent Change in Risk by Follow-up Time Period

Event	Time Period, y	Conventional (C), Rate (Cases/ Person-Years)*	Intensive (I), Rate (Cases/ Person-Years)*	Crude RR, I:C	Entire Study Time RR†	Entire Study Time % Change in Risk From C (95% Confidence Interval)‡
Severe or worse nonproliferative diabetic retinopathy (level 53/<53 or worse)	0-1	1.72 (6/350)	1.66 (6/361)	0.97	0.39	−60.8 (−37.7 to −75.3)
	1.5-3	2.21 (15/678)	1.86 (13/701)	0.83		
	3.5-5	3.33 (21/630)	0.45 (3/670)	0.13		
	5.5-9	5.57 (26/467)	0.70 (4/572)	0.13		
Neovascularization	0-1	0.86 (3/351)	0.55 (2/362)	0.65	0.54	−46.3 (−9.8 to −68.0)
	1.5-3	1.60 (11/688)	1.41 (10/711)	0.88		
	3.5-5	1.86 (12/646)	0.88 (6/681)	0.47		
	5.5-9	3.97 (20/504)	0.69 (4/580)	0.17		
Clinically significant macular edema	0-1	1.72 (6/350)	2.78 (10/360)	1.62	0.78	−22.1 (15.5 to −47.4)
	1.5-3	3.58 (24/671)	2.61 (18/690)	0.73		
	3.5-5	2.11 (13/618)	1.86 (12/645)	0.88		
	5.5-9	4.02 (20/498)	0.90 (5/559)	0.22		

*Rates in cases per 100 person-years at risk.
†Average RR (I:C) over entire study time, adjusted for baseline retinopathy level (levels 47/<47 and above combined).
‡Percent change in risk was obtained as follows: 100×[RR(I:C)−1]. Negative values represent percent decrease in risk from C; positive values, percent increase.

Table 11. Rates of Severe Nonproliferative Diabetic Retinopathy or Worse in Baseline Retinopathy Subgroups of the Secondary Intervention Cohort, Relative Risks (RRs), and Percent Change in Risk by Follow-up Time Period

Baseline Retinopathy Level	Time Period, y	Conventional (C) No.	Conventional (C) Rate (Cases/ Person-Years)*	Intensive (I) No.	Intensive (I) Rate (Cases/ Person-Years)*	Crude RR, I:C	Entire Study Time RR†	Entire Study Time % Change in Risk From C (95% Confidence Interval)‡
20/<20	0-3	100	. . . (0/300)	140	. . . (0/419)	. . .	0.12	−88.2 (1.8 to −98.6)
	3.5-9	100	1.52 (5/328)	138	0.19 (1/521)	0.13		
20/20	0-3	103	0.65 (2/308)	109	0.62 (2/322)	0.96	0.29	−70.6 (−9.6 to −90.5)
	3.5-9	100	3.05 (11/361)	105	0.53 (2/381)	0.17		
35/≤35	0-3	110	1.85 (6/325)	82	1.24 (3/241)	0.67	0.19	−80.7 (−49.7 to −92.6)
	3.5-9	103	6.77 (23/340)	79	0.72 (2/279)	0.11		
43/<43 or worse	0-3	38	13.68 (13/95)	32	17.61 (14/80)	1.29	0.86	−14.1 (69.0 to− 56.4)
	3.5-9	24	11.59 (8/69)	18	3.20 (2/63)	0.28		

*Rates in cases per 100 person-years at risk.
†Average RR (I:C) over entire study time.
‡Percent change in risk was obtained as follows: 100×[RR(I:C)−1]. Negative values represent percent decrease in risk from C; positive values, percent increase.

Table 12. Rates of Neovascularization in Baseline Retinopathy Subgroups of the Secondary Intervention Cohort, Relative Risks (RRs), and Percentage Change in Risk by Follow-up Time Period

Baseline Retinopathy Level	Time Period, y	Conventional (C) No.	Conventional (C) Rate (Cases/ Person-Years)*	Intensive (I) No.	Intensive (I) Rate (Cases/ Person-Years)*	Crude RR, I:C	Entire Study Time RR†	Entire Study Time % Change in Risk From C (95% Confidence Interval)‡
20/<20	0-3	100	. . . (0/300)	140	. . . (0/419)	. . .	0.14	−86.1 (26.1 to −98.5)
	3.5-9	100	1.20 (4/334)	138	0.19 (1/521)	0.16		
20/20	0-3	103	0.33 (1/308)	109	0.31 (1/324)	0.95	0.28	−72.2 (34.0 to −94.2)
	3.5-9	101	1.62 (6/372)	106	0.26 (1/386)	0.16		
35/≤35	0-3	110	1.53 (5/327)	82	0.82 (2/244)	0.54	0.24	−76.4 (−30.4 to 9−2.0)
	3.5-9	104	4.21 (15/356)	80	0.70 (2/285)	0.17		
43/<43 or worse	0-1	38	8.00 (3/38)	32	6.45 (2/31)	0.81	1.33	33.3 (179.9 to −36.5)
	1.5-3	35	7.52 (5/67)	30	12.73 (7/55)	1.69		
	3.5-5	29	7.77 (4/52)	23	12.05 (5/42)	1.55		
	5.5-9	18	8.11 (3/37)	12	3.57 (1/28)	0.44		

*Rates in cases per 100 person-years at risk.
†Average RR (I:C) over entire study time.
‡Percent change in risk was obtained as follows: 100×[RR(I:C)−1]. Negative values represent percent decrease in risk from C; positive values, percent increase.

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Reprint requests to DCCT Research Group, Box NDIC/DCCT, Bethesda, MD 20892.

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Office of the Chairman, Vanderbilt University, Nashville. O. Crofford.

Data Coordinating Center, George Washington University, Rockville, Md. J. Lachin, P. Cleary, D. Thompson, D. Kenny, S. Lan, G. Lan, A. Brenneman, W. Owen, J. Backlund, K. Adams, D. Arnold, R. Campanell, N. Loring, P. Scheirer, D. Becker, N. Janifer, D. Lamas, C. Dunegan, H. Atluri, C. Williams, S. Abdul-Baaqiy, S. Pakalapati, V. Yalamanchili, S. Ho, R. Friedman, B. McNaney, J. Givens, Y. Colaco, M. Jenifer, R. Osborne, V. Zell, and J. Young. *Former Members:* P. Gilbert, J. Knoke, A. Zbikowski, S. Sorlie, F. Eliopoulos, M. Foulkes, M. Tanenberg, M. Halperin, D. Kruger, R. Tanenberg, Q. Barros, W. Watson, H. Hollander, E. White, and D. Creveling.

Consultants. L. Rand, A. Kassoff, K. Adams, I. Grant, R. Heaton, J. Dorman, R. Spielman, R. Klein, and J. Dunbar.

National Institute of Diabetes and Digestive and Kidney Diseases Program Office, Bethesda, Md. C. Siebert, D. Beverly, S. Shores, L. Stecklein, and T. Pike. *Former Members:* R. Silverman, S. Heyse, D. Belcher, K. Newlin, R. Sherwin, L. Zalc, and J. Schlechter.

Central Units: Central Autonomic Coding Unit (Southern Illinois University), Springfield. M. Pfeiffer, M. Schumer, M. Moran, and J. Farquhar. *Former Members:* K. Hoskins and R. Hand.

Backup Glycosylated Hemoglobin Laboratory (University of Missouri), Columbia. J. England and H. Wiedmeyer. *Acknowledgments:* C. Rohlfing.

Central Fundus Photograph Reading Center (University of Wisconsin), Madison. M. Davis, L. Hubbard, Y. Magli, S. Thomas, J. Onofrey, K. Jensen, R. Brothers, S. Ansay, J. Armstrong, D. Badal, M. Vanderhoof-Young, B. Esser, P. Gelthman, D. Hurlburt, J. Reimers, K. Kewley, and K. Miner. *Former Members:* M. Harding, G. Boone, S. Meuer, V. Wipperfurth, P. Segal, A. Ganguly, P. Chinn-Sloan, L. Dold, and A. Temple.

Central Biochemistry Laboratory (University of Minnesota), Minneapolis—M. Steffes and J. Bucksa. *Former Glycosylated Hemoglobin Laboratory, Joslin Diabetes Center Inc:* S. Soeldner and M. Tanenberg.

Central Neurobehavioral Coding Unit (Western Psychiatric Institute and Clinic), Pittsburgh, Pa. C. Ryan and K. Adams. *Acknowledgments:* R. Catanzaro, A. Lukes, G. Bagovich, and T. Woodfill.

Central ECG Reading Unit (University of Minnesota). R. Crow, C. Johnson, and B. Carlson. *Former Members:* R. Prineas and M. MacDonald.

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