Prolonged Effect of Intensive Therapy on the Risk of Retinopathy Complications in Patients With Type 1 Diabetes Mellitus:

10 Years After the Diabetes Control and Complications Trial

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Abstract

Objective—To examine the persistence of the original treatment effects 10 years after the Diabetes Control and Complications Trial (DCCT) in the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study. In the DCCT, intensive therapy aimed at near-normal glycemia reduced the risk of microvascular complications of type 1 diabetes mellitus compared with conventional therapy.

Methods—Retinopathy was evaluated by fundus photography in 1211 subjects at EDIC year 10. Further 3-step progression on the Early Treatment Diabetic Retinopathy Study scale from DCCT closeout was the primary outcome.

Results—After 10 years of EDIC follow-up, there was no significant difference in mean glycated hemoglobin levels (8.07% vs 7.98%) between the original treatment groups. Nevertheless, compared with the former conventional treatment group, the former intensive group had significantly lower incidences from DCCT close of further retinopathy progression and proliferative retinopathy or worse (hazard reductions, 53%-56%; *P*<.001). The risk (hazard) reductions at 10 years of EDIC were attenuated compared with the 70% to 71% over the first 4 years of EDIC (*P*<.001). The persistent beneficial effects of former intensive therapy were largely explained by the difference in glycated hemoglobin levels during DCCT.

Conclusion—The persistent difference in diabetic retinopathy between former intensive and conventional therapy ("metabolic memory") continues for at least 10 years but may be waning.

The Diabetes Control and Complications Trial (DCCT) was designed to determine whether intensive therapy with the aim of maintaining glycemic levels as close to the nondiabetic range as possible would prevent or delay the long-term complications of type 1 diabetes mellitus.[1] The DCCT demonstrated substantial reductions in the risk of development and progression of the early microvascular complications of diabetes over an average of 6.5 years of intensive therapy as compared with conventional therapy. At the close of the DCCT in 1993, patients in the conventional therapy group were offered intensive therapy and instructed in its use. All patients subsequently returned to their health care providers for further diabetes care and 97% of the original DCCT cohort (n=1394) was enrolled in the Epidemiology of Diabetes Interventions and Complications (EDIC), a long-term observational study.[2] An earlier report showed that the ongoing risk of all levels of retinopathy remained significantly reduced in the

intensive compared with the conventional group during the first 4 years of EDIC, despite similar glycated hemoglobin (HbA_{1c}) levels over this period (called "metabolic memory").[3] Determining the duration of metabolic memory is important to quantify the long-term clinical effects of intensive diabetes therapy. The current report describes the continuing differences between the 2 original treatment groups in retinal complications 10 years after the close of the DCCT.

METHODS

SUBJECTS

At baseline, the 1441 patients enrolled in the DCCT during 1983-1989 were 13 to 39 years of age, had type 1 diabetes mellitus for 1 to 15 years, and were in generally good health. The primary prevention (726 patients with no retinopathy, albumin excretion rates <28 μg/min [<40 mg/24 hours], and 1-5 years' diabetes duration) and secondary intervention (715 patients with diabetes duration of 1-15 years, minimal to moderate nonproliferative diabetic retinopathy [NPDR], and urinary albumin excretion rates <139 μg/min [≤200 mg/24 hours]) cohort participants were randomly assigned to either intensive therapy, with the goal of achieving glycemic levels as close to the nondiabetic range as safely possible, or to conventional therapy, as previously described.[1] Intensive therapy included at least 3 injections of insulin daily or continuous subcutaneous insulin infusion with pumps, with insulin dose adjustments based on frequent self-monitoring of capillary glucose levels, meal size and composition, and physical activity levels. Mean duration of follow-up in the DCCT was 6.5 years.

ASSESSMENT OF RETINOPATHY

During EDIC, retinopathy was assessed by 7-field stereo fundus photography in approximately one-quarter of the cohort each year and in the entire cohort at years 4 and 10. Photography was not conducted if a patient had previously undergone panretinal photocoagulation in both eyes. Retinopathy status was determined in 1211 patients at EDIC year 10, 1045 based on fundus photography and 166 living patients with a known history of panretinal photocoagulation in either eye during DCCT (35 patients) or EDIC (131 patients). All photographs were graded centrally, with graders masked to therapy assignment, using the final Early Treatment Diabetic Retinopathy Study (ETDRS) grading scale[4] and DCCT methods.[5] The primary outcome was the time to the first occurrence of further retinopathy progression during EDIC, defined as a 3-step or more progression from the level of retinopathy at DCCT closeout,[3] representing a reproducible measure of clinically important worsening. The secondary retinopathy outcome was the time to the first occurrence of proliferative diabetic retinopathy (PDR) or worse during EDIC. Other retinopathy outcomes were the prevalence of a 3-step or more progression from DCCT entry, severe NPDR (ETDRS leve l53/<53) or worse, clinically significant macular edema (CSME),[6] and photocoagulation therapy (focal or scatter). Patients who received panretinal scatter photocoagulation (laser) therapy in either eye were counted as having worsened retinopathy for all of these outcomes thereafter, and patients who received focal photocoagulation for macular edema were counted as having CSME thereafter. Visual acuity was assessed by ETDRS methods.[7]

Interreader reliability during EDIC was evaluated by having different graders reread the same 50 fundus photographs at each EDIC year and comparing the results with the primary double reading at DCCT closeout. The individual weighted κ measure[8] of interrater agreement beyond chance ranged from 0.82 to 0.92 for ordinal ETDRS scores and from 0.71 to 0.90 for ordinal CSME scores over 10 years of measurements. The overall weighted κ[9] stratified for EDIC year was 0.91 for ETDRS scores and 0.84 for CSME scores.

ASSESSMENT OF GLYCEMIC CONTROL

Hemoglobin A_{1c} was measured annually in a central laboratory by high-performance liquid chromatography.[10] The mean HbA_{1c} value was calculated as the time-weighted average during the DCCT and EDIC.[11]

STATISTICAL ANALYSES

To test for differences between groups, the Wilcoxon rank sum test was used for quantitative or ordinal observations[12] and the χ^2 test, for categorical data.[13] Generalized estimating equations with an unstructured working correlation matrix[14] were used to assess the aggregate HbA_{1c} level difference between groups over EDIC years and to test for differences in odds reduction in further 3-step or more progression and PDR between EDIC years 4 and 10.

Analyses of progression of retinopathy were stratified by, or included adjustment for, retinopathy severity at the end of DCCT, defined as no retinopathy (ETDRS grade 10/10), microaneurysms only (ETDRS grade 20), mild NPDR (ETDRS grade 30), moderate NPDR or greater (≥ETDRS grade 40), and any previous laser therapy (focal or scatter). The Mantel-Haenszel method provided a stratified adjusted odds ratio,[15] with test-based confidence intervals (CIs). Logistic regression models assessed the effects of covariates on the prevalence (odds) of a particular retinopathy outcome at a specific EDIC year.[15] *P* values were obtained from likelihood ratio tests. The percentage of reduction in the odds with intensive vs conventional therapy was computed as (1-odds ratio)×100.

The Weibull proportional hazards regression model for interval-censored data[16] evaluated the treatment group effects on the cumulative incidence of further retinopathy progression during EDIC adjusted for other covariates. The model used all photographs in all patients. The Weibull assumption was verified by empirical estimation of the survival function.[17] Risk (hazard) reduction with intensive vs conventional therapy was calculated as (1-hazard ratio)×100. *P* values were obtained from likelihood ratio tests. The proportion reduction in -log likelihood (R_r^2) was used to describe the proportion of variation in risk explained by the HbA_{1c} levels.[15] All analyses were performed using SAS (SAS Institute Inc, Cary, North Carolina).

RESULTS

SUBJECTS

Table 1 shows the characteristics at DCCT baseline and at the end of the DCCT (EDIC baseline) of the 1211 subjects with retinopathy status determined at EDIC year 10. At DCCT baseline, there were no significant differences between the intensive and conventional treatment groups. However, treatment group differences reflecting the beneficial effects of intensive therapy were seen at DCCT end for HbA_{1c} level, prevalence of hyperlipidemia, retinopathy level, and need for photocoagulation.

TREATMENT AND METABOLIC OUTCOMES

During 6.5 years of treatment in DCCT, intensive and conventional therapy groups adhered to their assigned therapies 98% and 97% of the time, respectively. At EDIC year 4, 95% of the former intensive therapy group were still being treated with multiple daily injections of insulin or an infusion pump, compared with 75% of the former conventional therapy group (*P*<.001). At EDIC year 10, the differences between the 2 groups had narrowed further with regard to insulin therapy and self-monitoring (Table 1).

At entry to the DCCT, the mean HbA_{1c} level in each treatment group was 9% (to convert to proportion of total hemoglobin, multiply by 0.01) (Table 1). Following 6.5 years of DCCT follow-up, the mean HbA_{1c} levels were 7.3% and 9.0% in the intensive and conventional

therapy groups, respectively. At the first EDIC evaluation, 1 year after DCCT end, HbA_{1c} values in the 2 groups had converged (Figure 1). Over 10 years in EDIC, the mean HbA_{1c} levels in the 2 former treatment groups were almost the same (8.07% in the conventional therapy group vs 7.98% in the intensive therapy group; P=.20).

OPHTHALMOLOGIC OUTCOMES FROM DCCT BASELINE TO EDIC YEARS 4 AND 10

The prevalences of various levels of retinopathy and CSME were lower in the former intensive therapy group than in the former conventional therapy group at the end of DCCT and also at years 4 and 10 of EDIC (Table 2). The likelihood (odds) of a 3-step or more progression in retinopathy from DCCT baseline, the principal DCCT outcome, was 76% lower in the intensive than in the conventional therapy group at the end of DCCT (10.7% vs 33.2%). After 4 years of follow-up in EDIC, 48.9% of the former conventional therapy group had a 3-step or more progression in retinopathy from DCCT baseline compared with 17.8% of the former intensive therapy group; after 10 years, 60.6% had progressed in the conventional group vs 35.8% in the intensive group.

The overall prevalences during EDIC reflect, in part, retinopathy differences associated with intensive vs conventional therapy during DCCT. To eliminate the carryover of the treatment group differences at the end of the DCCT into EDIC, we performed logistic regression analysis adjusted for the level of retinopathy at the end of the DCCT. The adjusted odds of retinopathy progression from DCCT entry were reduced by 74% with intensive vs conventional therapy at 4 years of EDIC and 57% at 10 years (each P<.001). Continued significant reductions at 4 and 10 years of EDIC follow-up were also observed in the adjusted odds of severe NPDR or worse, PDR or worse, CSME, and photocoagulation. However, the odds reductions at 10 years were less than that observed at 4 years, except for those for photocoagulation (Table 2).

OPHTHALMIC OUTCOMES FROM EDIC BASELINE TO EDIC YEARS 4 AND 10

To assess metabolic memory further, we examined the prevalence of further 3-step or more progression of retinopathy from the level of retinopathy at DCCT closeout, adjusted for the level at closeout, among those free of panretinal scatter laser therapy during the DCCT. There was a 71% (95% CI, 56%-81%) odds reduction (P<.001) with intensive vs conventional therapy at EDIC year 4 (6.6% and 21.8% prevalence, respectively) and 50% (95% CI, 35%-62%) reduction (P<.001) at EDIC year 10 (24.2% and 40.8% prevalence for intensive and conventional treatment groups, respectively). Generalized estimating equations analysis showed that the beneficial treatment effect in further 3-step or more progression waned (P=.003). We also examined the prevalence of PDR or worse among those free of PDR during the DCCT. The odds reduction with intensive therapy after adjustment for the retinopathy levels at DCCT closeout was 76% (95% CI, 45%-89%) at EDIC year 4 (P<.001), with prevalences of 1.5% and 8.9% in the intensive and conventional treatment groups, respectively. At year 10, the odds reduction of PDR or worse was 59% (95% CI, 37%-73%; P<.001), with prevalences of 6.5% and 19.2% in the intensive and conventional treatment groups, respectively. However, for PDR or worse, the generalized estimating equations analysis showed that the odds reduction was not significantly different between years 4 and 10 (P=.12).

An additional analysis examined the cumulative incidence of further 3-step or more progression during EDIC from the level at DCCT closeout in multivariate Weibull proportional hazards regression models using evaluations at all years in subjects, after excluding 36 participants who had scatter photocoagulation in either eye during DCCT (Table 3) (n=1349). The Weibull model revealed a highly significant beneficial effect of DCCT intensive therapy up to 10 years after the end of DCCT. **Figure 2**A presents the estimated cumulative incidence of retinopathy further progression in each group derived from the Weibull model, reaching 51% at 10 years in the former conventional and 29% in the intensive treatment groups. The risk (hazard) of

further retinopathy progression over the 10 years of EDIC was reduced by 53% ($P<.001$; 95% CI, 43%-61%). However, this beneficial effect was attenuated compared with the results over the first 4 years after the end of DCCT[3] (Figure 2B), when there was a 70% risk (hazard) reduction (95% CI, 59%-79%; $P<.001$) with intensive therapy. The Weibull model was further fit for the interval between EDIC year 4 and EDIC year 10 (Figure 2B) among those patients who were free of further 3-step progression from DCCT closeout as of EDIC year 4 (n=1105). The risk reduction between EDIC years 4 and 10 verified the persistent and highly significant, albeit attenuated, beneficial effect of the former intensive therapy over this 6-year period (38% risk reduction; 95% CI, 22%-51%; $P<.001$).

A Weibull model analysis of the cumulative incidence of PDR or worse among patients who were free of PDR or worse during DCCT had similar results (Figure 3). The risk (hazard) of PDR during the 10 years of EDIC follow-up was reduced by 56% (95% CI, 37%-70%; $P<.001$), 71% during the first 4 years of EDIC (95% CI, 44%-85%; $P<.001$), and 46% from EDIC year 4 to 10 (95% CI, 16%-65%; $P<.001$).

Table 3 presents separate Weibull models of the incidence of further 3-step progression and PDR over the 10 years of EDIC follow-up within the strata defined by retinopathy levels at DCCT closeout (EDIC baseline). For all DCCT closeout retinopathy levels, there was an overall benefit over the 10 years, but as the severity of retinopathy increased at DCCT closeout, the relative benefits of DCCT intensive therapy decreased. Whereas Table 3 examines the prolonged protective effect of intensive vs conventional treatment at each retinopathy level, Table 4 examines whether the inclusion of other risk factors attenuates the effects of intervention group. After adjusting for other DCCT baseline and DCCT closeout covariates, the differences between DCCT treatment groups in the risk of further progression of retinopathy remained highly significant (Table 4) ($P<.001$). Risk of further progression of retinopathy increased significantly with higher HbA_{1c} level at DCCT baseline (19% increase in risk per 1% increase in HbA_{1c} level; $P<.001$), higher mean blood pressure at DCCT closeout (11% increase in risk per 5 mm Hg-increase in the mean blood pressure; $P < .001$), and hyperlipidemia at DCCT closeout (70% increase in risk for those with hyperlipidemia vs those without; $P=.001$).

RELATION OF PROGRESSION OF RETINOPATHY TO HYPERGLYCEMIA

Another Weibull model assessed the effect of the combined DCCT and EDIC mean HbA_{1c} levels on the risk of further progression of retinopathy among those free of scatter photocoagulation during DCCT. Within each former therapy group, the hazard of further 3-step or more progression of retinopathy during EDIC increased as the mean HbA_{1c} values during the DCCT and EDIC increased, adjusting for cohort, diabetes duration, HbA_{1c} level at DCCT entry, and the level of retinopathy at the end of the DCCT. In the former conventional and intensive therapy groups, there was a 1.9 times greater risk and 2.0 times greater risk, respectively, of further progression of retinopathy for every 10% increase in HbA_{1c} level (eg, from 8.0% to 8.8%) during the DCCT and EDIC (95% CI, 1.8-2.2; $P<.001$ and 95% CI, 1.8-2.3; $P<.001$, respectively). The HbA_{1c} level effects on further progression of retinopathy were not significantly different for the 2 former DCCT treatment groups ($P=.40$).

In additional models that combined both treatment groups and adjusted for mean HbA_{1c} levels during DCCT or for mean HbA_{1c} levels during EDIC separately, 89% of the prolonged effect (R^2) of DCCT intensive therapy on further retinopathy progression was explained by the differences in the DCCT mean HbA_{1c} levels, whereas the EDIC mean HbA_{1c} levels explained only 1.6% of the prolonged intensive therapy effect.

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VISUAL ACUITY 10 YEARS AFTER THE END OF THE DCCT

After 10 years of EDIC follow-up, 4 former intensive therapy patients had a visual acuity worse than 20/200 in 1 eye. None was so affected in both eyes. Only 1 of these 4 patients lost vision owing to diabetic retinopathy. One former conventional therapy group patient had a visual acuity worse than 20/200 in 1 eye at EDIC year 10 owing to PDR.

COMMENT

During the first 10 years of follow-up in the EDIC, the level of glycemic control in the former DCCT therapy groups converged. Based on previous epidemiologic assessments, the small difference in HbA_{1c} values between the former therapy groups would be expected to reduce the relative benefit of intensive therapy that occurred during the DCCT.[18] However, progression of retinopathy during the first 4 years of post-DCCT follow-up remained markedly less frequent in the former intensive therapy group, despite an increase in median HbA_{1c} value from 7.2% during the DCCT to 7.9% during the EDIC, than in the former conventional therapy group. Conversely, in the former conventional therapy group, the risk of progression of retinopathy during the first 4 years of EDIC[3] remained about the same as during the first 4 years of the DCCT,[19] despite a decrease in the median HbA_{1c} value from 9.1% during DCCT to 8.2% during EDIC. The continued separation in retinopathy of the former treatment groups was not merely a reflection of the differences in the severity of retinopathy between the 2 groups at the end of the DCCT, since the reductions in risk of further progression persisted after adjusting for the differences in complications between the 2 therapy groups at DCCT end. DCCT/EDIC has shown a similar prolonged effect of prior intensive therapy on microalbuminuria and albuminuria[11] and neuropathy.[20]

The likelihood of further progression of retinopathy in both groups was strongly associated with the mean HbA_{1c} value during the DCCT and EDIC combined, with a stronger effect of the mean HbA_{1c} value during the DCCT. In the Stockholm Diabetes Intervention Study, the prevalence of severe retinopathy after 7.5 years of follow-up was related to the mean HbA_{1c} value during the first 5 years of follow-up.[21]

Intensive therapy that maintains near-normal glycemic levels for an average of 6.5 years has a beneficial impact on long-term complications that extends at least 10 years beyond the actual period of such therapy. Moreover, therapy that maintains higher HbA_{1c} levels has adverse effects on complications that persist beyond the period of high HbA_{1c} levels. However, the DCCT/EDIC results should not be interpreted to mean that intensive therapy need only be applied for a limited period. Rather, the results support the implementation of intensive treatment as early in the course of the disease as possible. Stratified Weibull models fitted separately in the 4 retinopathy strata at DCCT closeout (Table 3) reveal that the metabolic memory is waning faster in patients with more severe retinopathy than in those with milder

retinopathy, which reinforces the importance of implementing intensive glycemia control as early in the course of the disease as possible.

One potential limitation of the current study is that we did not adjust for other medication use, which might have confounded the results. However, we have shown in previously published analyses that the use of other medications, such as angiotensin-converting enzyme inhibitors and aspirin, was not significantly different between the treatment groups.[22]

The persistent adverse effects of hyperglycemia and the long-term beneficial effects of lowering glycemia on the development and progression of complications, also shown in animal models of diabetes,[23] has been termed *metabolic memory*. One possible explanation for this phenomenon is the slow accumulation, and subsequent slow degradation, of advanced glycation end products (AGEs).[24] DCCT patients in the intensive therapy group had lower concentrations of these substances in skin collagen than did patients in the conventional therapy group.[25] The levels of skin collagen AGEs were also associated with the subsequent incidence of progression of retinopathy (and nephropathy) over the first 10 years of EDIC.[26] Although the metabolic memory effect is present 10 years after the DCCT, the apparent waning of metabolic memory ("metabolic amnesia") between EDIC years 4 and 10 may be secondary to a combination of clearance of the long-lasting AGEs in the former conventional group and the accumulation of AGEs in the former intensive treatment group. There are currently no direct data to prove this speculation, and alternative explanations include epigenetic effects of hyperglycemia or a combination of effects.

Acknowledgements

Biography

Ophthalmological Numismatics

Johann Gottlieb Fabini (Theofil Janos) (1791-1847) was one of the first Hungarian professors of ophthalmology. Fabini, a native of Transylvania, studied medicine in Vienna, Austria, where for 2 years he was assistant to George Beer. While in Vienna, he also had the opportunity to work with Carl von Graefe and William MacKenzie. Returning to Hungary in 1817, he was appointed chair of Ophthalmology at the University of Budapest, where he was to remain for the rest of his career. His primary interests were the diseases of the cornea, which is reflected in his publications in 1830 and 1831, respectively, of *Doctrina de morbus oculorum* and *Praecipius corneae morbis*.

In Hungary in 1982, a commemorative medal by Eszter Miro was cast in bronze, 105 mm in diameter. The medal is uniface and depicts Fabini's clothed facing bust, three-quarters to the left; within the curve at left: FABINI TEOFIL; and within the curve at lower right, the artist's initials: ME.

Courtesy of: Jay M. Galst, MD, clinical associate professor, New York Medical College, and Peter van Alfen, PhD, associate curator, American Numismatic Society.

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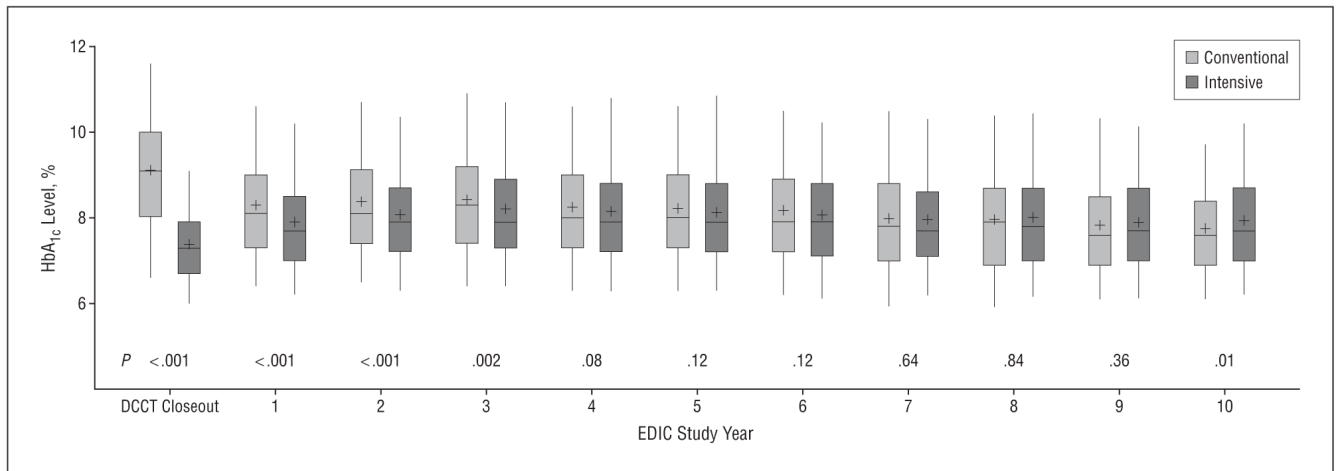
Figure 1.
Distribution of glycated hemoglobin (HbA$_{1c}$) values by Diabetes Control and Complications
Trial (DCCT) treatment group at the end of the DCCT and at each of the first 10 years of the
Epidemiology of Diabetes Interventions and Complications (EDIC) study among 1211 subjects
evaluated for retinopathy at year 10 of the EDIC study. The box presents the quartiles of the
distribution, the vertical lines show the 95th and fifth percentiles, the horizontal line is the
median, and the mean is shown as +.
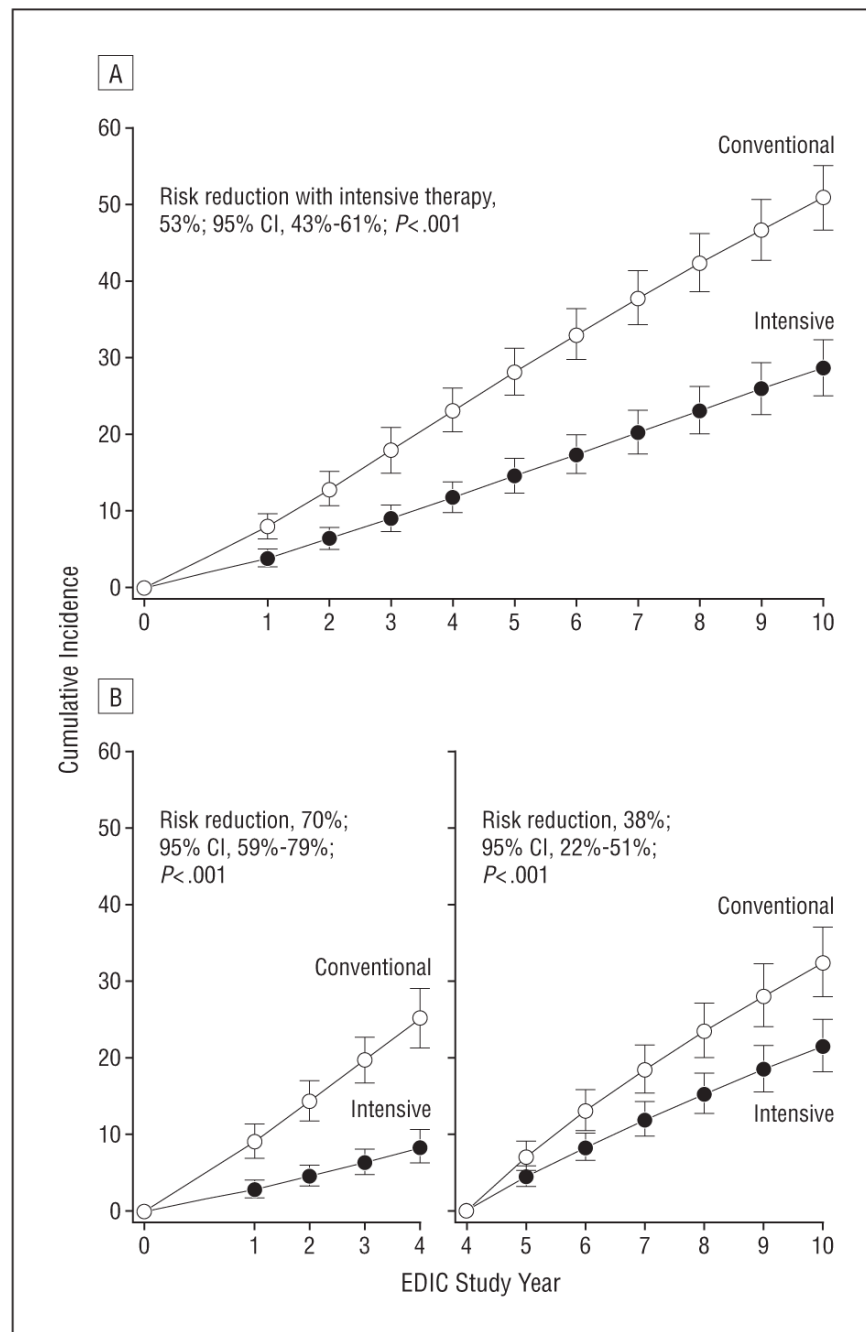
Figure 2.
Estimated cumulative incidence of further 3-step progression of retinopathy from Diabetes
Control and Complications Trial (DCCT) closeout to Epidemiology of Diabetes Interventions
and Complications (EDIC) study year 10 (n=1349) (A) and from DCCT closeout to EDIC year
4 (n=1320) and from EDIC year 4 to EDIC year 10 (n=1105) (B) based on Weibull regression
models adjusted for the level of retinopathy at the end of the DCCT, primary vs secondary
cohort, glycated hemoglobin value on entry to the DCCT, and diabetes mellitus duration at
DCCT baseline. Retinopathy was evaluated in 369 patients during EDIC year 1, 448 in year
2, 430 in year 3, 1225 in year 4 (1997), 338 in year 5, 440 in year 6, 406 in year 7, 204 in year
8, 233 in year 9, and 1211 in year 10 (2003). Subjects with prior scatter photocoagulation during

the DCCT were excluded from analyses (26 in the conventional therapy group and 10 in the intensive therapy group). Patients who had further 3-step progression from DCCT closeout as of EDIC year 4 (n=212) and patients who were censored during the interval (n=32) were excluded from the analysis of incidence over years 4 to 10. CI indicates confidence interval.
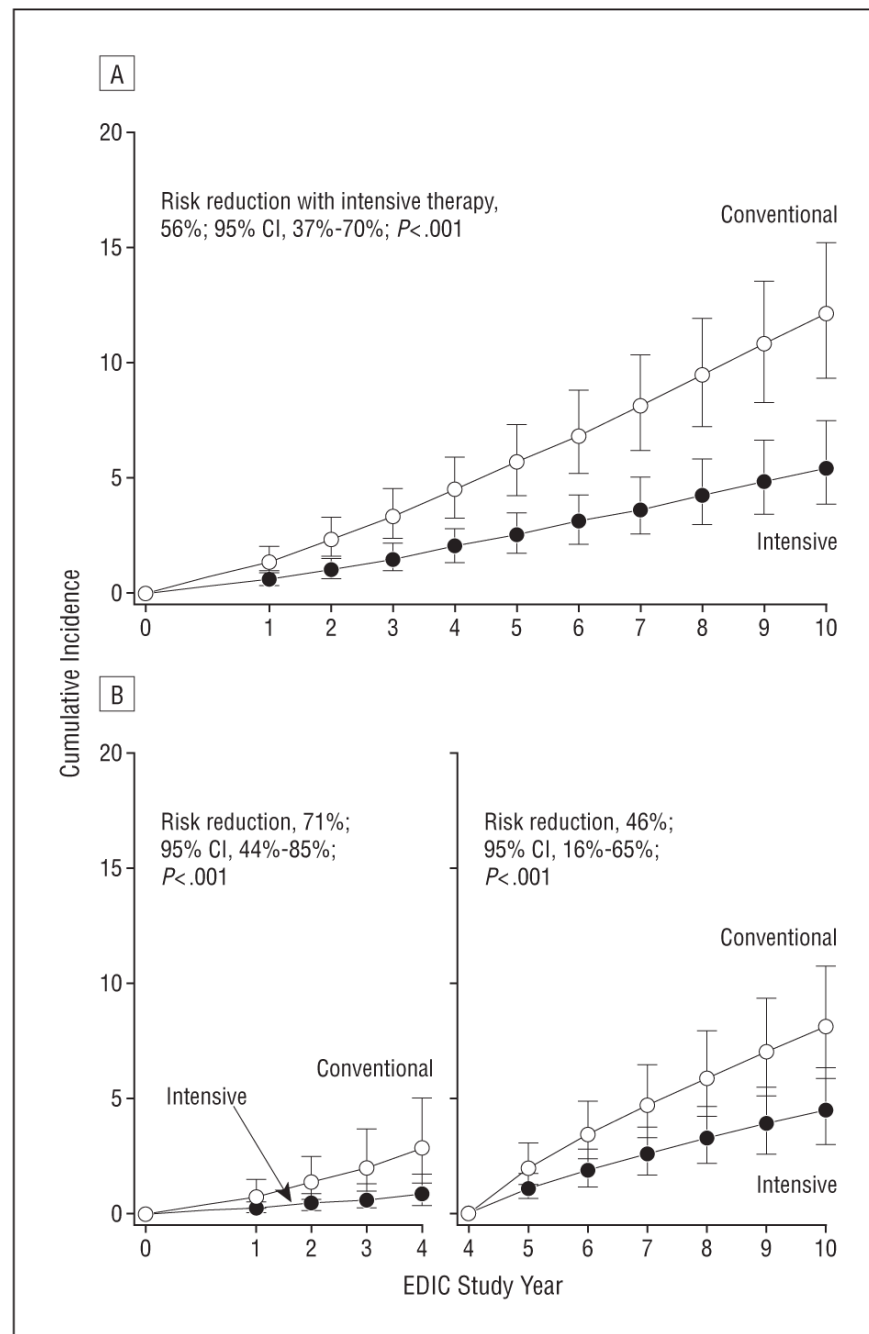
Figure 3.
Estimated cumulative incidence of proliferative diabetic retinopathy (PDR) or worse from Diabetes Control and Complications Trial (DCCT) closeout to Epidemiology of Diabetes Interventions and Complications (EDIC) year 10 (n=1314) (A) and from DCCT closeout to EDIC year 4 (n=1285) and from EDIC year 4 to EDIC year 10 (n=1215) (B) based on Weibull regression models adjusted for the level of retinopathy at the end of the DCCT, primary vs secondary cohort, glycated hemoglobin value on entry to the DCCT, and diabetes mellitus duration at DCCT baseline. The sample size is based on all EDIC evaluations in all subjects, including those at EDIC years 4 and 10, and those in a quarter of these subjects at other EDIC years. Patients with prior PDR or worse during the DCCT were excluded from all the analyses

(52 in the conventional therapy group and 26 in the intensive therapy group). Patients who had PDR during the first 4 years of EDIC follow-up (n=63) and patients who were censored during the interval (n=36) were excluded from the analysis of incidence over years 4 to 10. CI indicates confidence interval.

Table 1

Characteristics of the 1211 Patients Evaluated for Retinopathy After 10 Years of EDIC Follow-up

| Characteristic | DCCT Treatment Group, %[a] | | P Value[c] |
	Conventional (n=615)[b]	Intensive (n=596)[b]	
At DCCT entry			
Women	49.2	50.8	.30
Age, y, mean (SD)	27 (7)	27 (7)	.13
Primary prevention cohort[d]	51.2	49.2	.47
Duration of diabetes mellitus, y, mean (SD)	5.7 (4.1)	6.0 (4.2)	.27
Glycated hemoglobin level, %, mean (SD)	9.0 (1.6)	9.1 (1.6)	.25
At DCCT closeout/EDIC baseline[e]			
Age, y, mean (SD)	33 (7)	34 (7)	.09
Duration of diabetes, y, mean (SD)	11.8 (4.9)	12.2 (4.9)	.14
DCCT follow-up, y, mean (SD)	6.3 (1.6)	6.4 (1.7)	.32
Glycosylated hemoglobin level, %, mean (SD)	9.0 (1.3)	7.3 (0.9)	<.001
Treatment			
Continuous subcutaneous insulin infusion (pump) or multiple daily injections	5.1	98.0	<.001
Self-monitoring of blood glucose level, ≥4 times/d	4.1	53.7	<.001
Arterial blood pressure,[f] mm Hg, mean (SD)	88.2 (8.7)	88.7 (8.6)	.30
Hyperlipidemia[g]	10.6	7.2	.04
Level of retinopathy			
None (10/10)	17.8	28.5	<.001
Microaneurysms only (20/[<]20)	31.7	39.8	
Mild nonproliferative retinopathy (35/[<]35)	27.7	21.5	
Moderate or severe nonproliferative retinopathy (43/[<]43)	22.8	10.2	
Photocoagulation during DCCT			
Scatter, for retinopathy	4.1	1.7	.01
Focal, for macular edema	5.4	2.2	.004
Treatment at EDIC year 10			
Continuous subcutaneous insulin infusion (pump) or multiple daily injections	92.2	96.6	.001
Self-monitoring of blood glucose level, ≥4 times/d	61.5	53.7	.007

Abbreviations: DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications.

SI conversion factors: To convert low-density lipoprotein cholesterol to micromoles per liter, multiply by 0.0259; triglycerides to micromoles per liter, multiply by 0.0113; hemoglobin to proportion of total hemoglobin, multiply by 0.01.

[a] Unless otherwise indicated.

[b] The numbers of patients who were alive, had gradable fundus photographs at EDIC year 10, or underwent scatter photocoagulation in one or both eyes during EDIC are included.

[c] P values were based on the Wilcoxon rank sum test for quantitative or ordinal variables or the χ^2 test for categorical variables.

[d] No retinopathy or microalbuminuria at baseline (see "Methods" section of the text).

[e] The baseline data in the EDIC study were the same as the data at the end of the DCCT.

[f]Arterial blood pressure=2/3 diastolic blood pressure + 1/3 systolic blood pressure.

[g]Hyperlipidemia is defined as 2 consecutive reports of hypercholesterolemia (low-density lipoprotein cholesterol level >160 mg/dL) or hypertriglyceridemia (triglyceride level >500 mg/dL) within 1 month during DCCT.

Table 2

Prevalence of Various Retinopathy Complications at DCCT Closeout and EDIC Years 4 and 10 Among 1211 Patients Evaluated for Retinopathy at EDIC Year 10

Retinopathy Complication[b]	DCCT Closeout (n=1211)				EDIC Year 4 (n=1094)				EDIC Year 10 (n=1211)			
	INT, %	CON, %	Odds Reduction[a] (95% CI), %	P Value	INT, %	CON, %	Adjusted Odds Reduction[b] (95% CI), %	P Value	INT, %	CON, %	Adjusted Odds Reduction[b] (95% CI), %	P Value
Sample size	596	615			541	553			596	615		
≥3-step progression from DCCT baseline	10.7	33.2	76 (67-82)	<.001	17.8	48.9	74 (64-80)	<.001	35.8	60.6	57 (45-66)	<.001
SNPDR or worse	2.5	7.0	66 (38-81)	<.001	4.6	17.4	68 (44-81)	<.001	9.1	25.0	58 (38-71)	<.001
PDR or worse	2.5	6.8	64 (35-81)	<.001	4.3	15.7	65 (39-80)	<.001	8.9	24.7	58 (38-71)	<.001
CSME[c]	3.9	7.7	51 (19-71)	.005	3.8	13.3	62 (35-78)	<.001	9.0	19.0	38 (9-59)	.009
Photocoagulation therapy (focal or scatter)[d]	3.4	8.0	60 (32-76)	<.001	4.2	13.7	54 (21-73)	.004	8.4	23.6	57 (38-71)	<.001

Abbreviations: CI, confidence interval; CON, former DCCT conventional therapy group; CSME, clinical significant macular edema; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; INT, former DCCT intensive therapy group; PDR, proliferative diabetic retinopathy; SNPDR, severe nonproliferative diabetic retinopathy.

[a] The odds reduction is for INT as compared with CON.

[b] Adjusted odds reduction was computed after stratification by the level of retinopathy at the end of the DCCT as shown in Table 1. Since this Table is only limited to the 1121 patients with retinopathy evaluated at EDIC year 10 (except for CSME), the adjusted odds reduction at EDIC year 4 is slightly different from that previously published.[3]

[c] Based on 1174 patients who were evaluated for CSME at EDIC year 10, including 1173 at DCCT closeout (589 INT and 584 CON), 1068 at EDIC year 4 (534 INT and 534 CON), and 1174 at EDIC year 10 (589 INT and 585 CON).

[d] Patients with scatter photocoagulation after entry into the DCCT were counted as worse for retinopathy; those with focal photocoagulation were counted as worse for macular edema.

Table 3

Incidence of Further 3-Step Progression of Retinopathy and PDR Between DCCT Closeout and EDIC Year 10 Stratified by the Level of Retinopathy at DCCT Closeout

Retinopathy Level at DCCT Closeout	Further 3-Step Progression				PDR[a]			
	No. at Risk[b]	No. With Event	Adjusted Hazard Reduction[c] (95% CI), %	P Value[d]	No. at Risk[e]	No. With Event	Adjusted Hazard Reduction[c] (95% CI), %	P Value[d]
All levels	1349		53 (43 to 61)	<.001	1314		56 (37 to 70)	<.001
Intensive therapy	681	187			666	45		
Conventional therapy	668	322			648	121		
Stratum 1: no retinopathy			47 (26 to 62)	<.001			72 (42 to 87)	.001
Intensive therapy	194	71			194	1		
Conventional therapy	123	68			122	2		
Stratum 2: microaneurysm only			63 (47 to 74)	<.001				
Intensive therapy	274	53			273	9		
Conventional therapy	219	87			219	20		
Stratum 3: mild non-PDR			58 (34 to 73)	<.001			58 (19 to 78)	.009
Intensive therapy	148	31			148	15		
Conventional therapy	200	83			199	40		
Stratum 4: moderate or severe non-PDR			40 (9 to 60)	.02			39 (-3 to 64)	.06
Intensive therapy	65	32			50	20		
Conventional therapy	126	84			104	59		

Abbreviations: CI, confidence interval; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; PDR, proliferative diabetic retinopathy.

[a]For PDR, strata 1 and 2 were combined in stratified analysis and in adjustment for all-levels-combined analysis because of the low event rate in these 2 strata.

[b]The sample size for all levels is the same as in Figure 2A (n = 1349), based on all EDIC evaluations in all subjects, including those at EDIC years 4 and 10 and those in a quarter of these subjects at other EDIC years, among those patients who were free of scatter photocoagulation during DCCT.

[c]The Weibull model was performed for each stratum and for all levels combined after adjustment for primary/secondary cohort, glycated hemoglobin value at entry to the DCCT, and diabetes mellitus duration at DCCT baseline. Analysis of all levels combined was also adjusted for the level of retinopathy at the end of the DCCT. Hazard reduction is for intensive therapy as compared with conventional therapy.

[d]P values were based on the Wald χ^2 test from the Weibull model.

[e]The sample size for all levels is the same as in Figure 3A (n = 1314), based on all EDIC evaluations in all subjects, including those at EDIC years 4 and 10 and those in a quarter of these subjects at other EDIC years, among those patients who were free of PDR during DCCT. Among the 1314, 5 patients who did not have retinopathy evaluation at DCCT closeout were excluded from the stratified analysis.

Table 4

Weibull Proportional Hazards Regression Model of Risk Factors for Further 3-Step Progression of Retinopathy From DCCT Closeout Over 10 Years of EDIC Follow-up in 1349 Patients[a]

Covariate	χ^2	*P* Value	Hazard Ratio (95% CI)[b]
At DCCT entry			
Glycated hemoglobin level at DCCT eligibility	39.74	<.001	1.19 (1.13-1.26)
Cohort (primary vs secondary)	0.02	.88	1.02 (0.78-1.33)
Type 1 diabetes mellitus duration	3.25	.07	0.97 (0.94-1.00)
At DCCT closeout			
Mean blood pressure	17.50	<.001	1.11 (1.06-1.17)
Hyperlipidemia ever[c]	15.65	.001	1.70 (1.31-2.21)
DCCT treatment group, intensive vs conventional	62.44	<.001	0.46 (0.38-0.56)

Abbreviations: See Table 3.

SI conversion factors: See Table 1.

[a]The sample size is based on all EDIC evaluations in all subjects, including those at EDIC years 4 and 10 and those in a quarter of these subjects at other EDIC years, among those patients who were free of scatter photocoagulation during DCCT. The model was also adjusted for the retinopathy levels at the DCCT closeout (*P*<.001). Significance levels were not affected after adjustment for body mass index, albumin excretion rate, smoking, or neuropathy at DCCT closeout, none of which contributed meaningfully when added to this model (*P*>.053 for all).

[b]Hazard ratio is the ratio of hazard of retinopathy progression per 1-percentage point increase in glycated hemoglobin level, 1-year increased duration of diabetes mellitus, 5-mm Hg increase in mean blood pressure, or for the dichotomous variable as noted.

[c]Hyperlipidemia is defined as 2 consecutive reports of hypercholesterolemia (low-density lipoprotein cholesterol level >160 mg/dL) or hypertriglyceridemia (triglyceride level >500 mg/dL) within 1 month during DCCT.