The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group*

Effect of Intensive Diabetes Therapy on the Progression of Diabetic Retinopathy in Patients With Type 1 Diabetes: 18 Years of Follow-up in the DCCT/EDIC

Diabetes 2015;64:631–642 | DOI: 10.2337/db14-0930

The Diabetes Control and Complications Trial (DCCT) demonstrated that a mean of 6.5 years of intensive therapy aimed at near-normal glucose levels reduced the risk of development and progression of retinopathy by as much as 76% compared with conventional therapy. The Epidemiology of Diabetes Interventions and Complications study (EDIC) observational follow-up showed that the risk of further progression of retinopathy 4 years after the DCCT ended was also greatly reduced in the former intensive group, despite nearly equivalent levels of HbA_{1c}, a phenomenon termed metabolic memory. Metabolic memory was shown to persist through 10 years of follow-up. We now describe the risk of further progression of retinopathy, progression to proliferative diabetic retinopathy, clinically significant macular edema, and the need for intervention (photocoagulation or anti-VEGF) over 18 years of follow-up in EDIC. The cumulative incidence of each retinal outcome continues to be lower in the former intensive group. However, the year-to-year incidence of these outcomes is now similar, owing in large part to a reduction in risk in the former conventional treatment group.

In the Diabetes Control and Complications Trial (DCCT, 1983–1993), intensive diabetes therapy that lowered glycemic levels, compared with conventional therapy, reduced the development and progression of diabetes microvascular complications in both adults (1) and adolescents (2). Thereafter, subjects were followed observationally in the Epidemiology of Diabetes Interventions and Complications study (EDIC, 1994 to present) (3). Over the first 4 years of EDIC, the former DCCT intensive therapy group (INT) experienced a lower incidence of further progression of retinopathy than did the former conventional group (CONV), despite similar HbA_{1c} levels in both groups (4). This benefit was observed in both the adult (4) and adolescent (5) subsets of the DCCT. The slower progression of retinopathy, nephropathy, and neuropathy (4,6,7) with INT versus CONV, despite similar EDIC HbA_{1c} levels, has been called "metabolic memory." At 10 years of EDIC follow-up, metabolic memory persisted in adults (7) but was less apparent in the participants enrolled as adolescents during DCCT (8). The long-term benefit with INT is closely associated with lower HbA_{1c} during the DCCT (8,9). Recent reports review the prolonged benefits of DCCT INT during the DCCT/EDIC (10,11), including retinopathy (12).

We now describe the progression of retinopathy over a total of 18 years of EDIC follow-up. A companion paper (13) describes the progression of nephropathy.

RESEARCH DESIGN AND METHODS

Design and Subjects

The DCCT (1) was a randomized trial comparing the effects of intensive versus conventional diabetes therapy on diabetes complications, including retinopathy (the

Corresponding author: John M. Lachin, jml@bsc.gwu.edu.

Received 13 June 2014 and accepted 2 September 2014.

Clinical trial reg. nos. NCT00360893 and NCT00360815, clinicaltrials.gov.

This article contains Supplementary Data online at http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db14-0930/-/DC1.

*A complete list of participants and industry contributors for the DCCT/EDIC research group can be found at http://www.nejm.org/doi/full/10.1056/NEJMoa1111732.

See accompanying article, p. 341.

DCCT primary outcome), nephropathy, and neuropathy. During 1983–1989, 1,441 subjects 13–39 years old were enrolled (195 adolescents were at least Tanner stage II), 726 subjects into the primary prevention cohort (diabetes duration 1–5 years, no retinopathy, and urinary albumin excretion <40 mg/day) and 715 into the secondary intervention cohort (1–15 years duration, early [microaneurysms] to mild nonproliferative retinopathy, and microalbumin excretion <200 mg/day). Intensive therapy (n = 711) aimed to achieve nondiabetic levels of glycemia as safely as possible, whereas conventional therapy (n = 730) aimed to maintain clinical well-being with no specific glucose targets. DCCT follow-up included annual standard ophthalmoscopic exam with measures of best-corrected visual acuity and seven-field color stereo fundus photography every 6 months (14).

At DCCT end (1993), CONV subjects were taught and initiated intensive diabetes therapy, and all subjects were transferred to their own health care providers for diabetes care. In 1994, 1,375 of the 1,428 surviving subjects (96%) joined the EDIC observational study (3).

The annual EDIC evaluation included a history, physical, and HbA_{1c}, with a fasting lipid profile and urinary microalbumin every other year (one-half the cohort each year). An ophthalmologic evaluation (as during DCCT, including best-corrected visual acuity) was conducted in all participants at EDIC years 4 and 10 (1997 and 2003), and on every fourth anniversary of entry into the DCCT, e.g., 1996, 2000, etc., for a patient randomized in 1984 (14). Photographs were graded centrally masked to treatment assignment. The severity of retinopathy and macular edema were assessed separately in each eye using the final Early Treatment Diabetic Retinopathy Study (ETDRS) scale (15).

Of the 1,375 EDIC subjects, 50 died before the scheduled ophthalmologic evaluation during EDIC years 15–18, and 111 did not have the evaluation at years 15–18. Outcome data were available for 1,214 EDIC participants, 1,209 who had evaluable fundus photographs completed during EDIC years 15–18 and 5 without photographs but known to have had prior laser therapy. This represents 84% of the original DCCT cohort, 92% of those surviving to years 15–18, and 88% of those enrolled in EDIC. The DCCT and the EDIC protocols were approved by the institutional review boards at all participating clinical sites and the Coordinating Center.

Statistical Methods

Quantitative or ordinal characteristics were compared using the Wilcoxon rank sum test and categorical variables using the contingency χ^2 test. Retinopathy outcomes were further three or more–step retinopathy progression (or just "progression") from the level at DCCT closeout, new severe nonproliferative diabetic retinopathy (SNPDR), and new proliferative diabetic retinopathy (PDR) among those without SNPDR or PDR, respectively, during the DCCT. Pan-retinal photocoagulation therapy was counted as worsening for each outcome if not previously observed. Additional outcomes included clinically significant macular edema (CSME) and either focal photocoagulation or anti-VEGF therapy.

Incidence analyses used Weibull proportional hazards regression models for interval-censored data (16) adjusted for baseline factors. The Weibull model was verified against the Turnbull empirical estimate (17) (see Supplementary Data). Natural cubic splines with 4 *df* generated a smoothed Turnbull estimate of the associated hazard function (18). P values were obtained from likelihood ratio tests.

Prevalence analyses were stratified by retinopathy severity at DCCT closeout, with a Mantel-Haenszel stratified-adjusted odds ratio estimate and test-based confidence limits (19).

A Weibull model also assessed the effects of time-dependent covariates (20) on incidence. Mediation of the treatment group effect was assessed by the change in the group effect after adjustment for a given time-dependent covariate (21). All analyses were performed using SAS 9.3 or the R-package.

RESULTS

Subject Characteristics and HbA_{1c}

Table 1 presents the characteristics of the initially enrolled 1,441 DCCT subjects, of the 1,423 survivors evaluated at the close of the DCCT, and of the 1,214 with a retinal examination during years 15–18 of EDIC. The mean age at DCCT enrollment was 27 years. At EDIC years 15–18, mean age was minimally, albeit significantly, higher in the former INT than CONV (51 vs. 50 years, P = 0.015). The mean duration of diabetes was 5.7 years at DCCT baseline and 29 years at EDIC years 15–18. The mean HbA_{1c} at DCCT baseline was 9.1% (76 mmol/mol) and at DCCT closeout was 7.2% (55 mmol/mol) in INT and 9.1% (76 mmol/mol) in CONV. Over the first few years of EDIC, the HbA_{1c} level in INT rose while that in CONV fell, resulting in mean levels of ~8% (64 mmol/mol) over the years 15–18 of EDIC. Figure 1 shows the yearly quartiles of the distributions of HbA_{1c} levels over DCCT and EDIC.

Three-Step Progression of Retinopathy

During years 15–18 of EDIC follow-up, 39% of the 684 INT subjects at risk had further progression from DCCT closeout (incidence) vs. 56% of the 674 CONV subjects, with a 46% adjusted risk reduction (CI 36, 54; $P <$ 0.0001) (Table 2 and Supplementary Table 1). In prior analyses over 4 and 10 years of EDIC follow-up, the risk reductions were 71% (56, 81; $P < 0.0001$) and 51% (36, 63; $P < 0.0001$) with INT, respectively. Thus, the beneficial effects of DCCT INT on the risk of further retinopathy progression have persisted for up to 18 years after the close of the DCCT, although with smaller effects over time.

Table 1—Clinical characteristics of the former DCCT INT and CONV participants at DCCT baseline, DCCT closeout, and EDIC years 15–18

	DCCT baseline (1983–1989) (*n* = 1,441)		End of DCCT (1993) (*n* = 1,423)		EDIC years 15–18 (2007–2012) (*n* = 1,214)	
	INT	CONV	INT	CONV	INT	CONV
n	711	730	701	722	606	608
Medical history						
Age (years)	27.2 (7.1)	26.7 (7.1)	33.6 (7.0)	33.0 (7.0)	50.9 (7.2)	49.9 (7.0)†
Female (%)	48.5	45.9	48.9	46.0	48.8	46.9
Diabetes duration (years)	5.8 (4.2)	5.5 (4.1)	12.3 (4.9)	11.9 (4.8)	29.3 (5.3)	28.7 (5.4)†
DCCT primary cohort (%)	49.0	51.8	49.2	51.7	48.4	50.8
Hypertension (%)§	3.1	2.1	4.4	3.9	62.4	66.0
Hyperlipidemia (%)‖	22.8	23.4	25.8	29.9	64.5	66.8
Current cigarette smoking (%)	18.6	18.4	20.3	19.8	12.2	12.2
Medical treatment						
Glucose management						
Pump or multiple daily injections (≥3) (%)	0	0	97.2	5.1‡	98.2	96.1‡
Glucose monitoring ≥4 times a day (%)	0	0	52.6	3.7‡	66.8	70.2
Use of ACE inhibitor or ARB (%)¶	0	0	—	—	53.0	57.6
Physical examination						
BMI (kg/m^2)	23.4 (2.7)	23.5 (2.9)	26.5 (4.2)	25.0 (3.1)‡	28.9 (5.6)	28.2 (5.0)
Obese (BMI ≥30 kg/m^2) (%)	1.3	1.9	18.5	5.7‡	35.6	31.4
Systolic blood pressure (mmHg)	114.5 (11.3)	114.6 (11.4)	116.3 (11.7)	115.3 (12.0)	121.1 (14.5)	120.4 (14.7)
Diastolic blood pressure (mmHg)	73.1 (8.2)	72.9 (8.7)	74.4 (8.8)	74.2 (8.8)	71.7 (9.0)	71.3 (8.8)
Mean arterial pressure (mmHg)	86.9 (8.2)	86.8 (8.6)	88.3 (8.9)	87.9 (8.9)	88.1 (9.5)	87.7 (9.4)
Laboratory values						
HbA_{1c} (%)#	9.1 (1.6)	9.1 (1.6)	7.2 (0.9)	9.1 (1.3)‡	8.0 (1.1)	8.0 (1.0)
mmol/mol	76 (17.5)	76 (17.5)	55 (9.8)	76 (14.2)	64 (12.0)	64 (10.9)
Plasma lipids (mg/dL)						
Total cholesterol	177.1 (32.8)	175.7 (33.6)	178.9 (31.3)	183.7 (36.9)†	175.4 (36.2)	172.5 (38.5)
HDL cholesterol	50.8 (12.3)	50.3 (12.3)	50.8 (12.8)	51.6 (12.9)	61.3 (19.4)	61.6 (18.3)
LDL cholesterol	110.3 (28.7)	109.1 (29.4)	111.7 (27.3)	114.6 (31.5)	97.3 (29.5)	94.4 (30.5)†
Triglycerides	80.8 (43.3)	81.8 (51.3)	81.9 (51.5)	88.3 (54.5)‡	84.4 (54.9)	83.4 (76.7)
Complications						
Eye						
Retinopathy levels (%)				‡		‡
No retinopathy (10/10)	48.9	51.8	28.3	17.2	10.8	4.8
MA only (20/<20)	35.1	27.8	39.7	32.1	36.9	26.2
Mild NPDR (35/<35)	11.6	15.2	21.3	28.5	20.2	18.1
Moderate NPDR (43/<43 – 53/53)	4.5	5.1	8.3	14.4	16.5	19.7
SNPDR or worse (53/<53 +)	0	0.1	2.6	7.8	15.5	31.2
Renal						
Sustained AER >30 mg/24 h	5.2	4.3	7.6	14.5‡	13.5	20.6‡
AER >300 mg/24 h	0	0	1.4	3.2†	4.0	7.4‡
Sustained eGFR <60 mL/min/1.73 m^2 (%)	0	0	0.1	0.4	3.9	5.4

Data presented as mean (SD) or percent. Retinopathy or CSME assessments by fundus photography were completed for 1,423 subjects at DCCT closeout and 1,259 subjects between EDIC years 15 and 18. Each subject was assessed once every 4 years timed to the year of entry into the DCCT and all subjects assessed at 4 and 10 years. †$P < 0.05$ by the Wilcoxon rank sum test for quantitative outcomes, χ^2 test for categorical outcomes, or Armitage trend test for ordinal outcomes (retinopathy) comparing conventional and intensive treatment. ‡$P < 0.01$ by the Wilcoxon rank sum test for quantitative outcomes, χ^2 test for categorical outcomes, or Armitage trend test for ordinal outcomes (retinopathy) comparing conventional and intensive treatment. §Hypertension was defined by systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medications. ‖Hyperlipidemia was defined by an LDL cholesterol level ≥130 mg/dL (3.4 mmol/L) or the use of lipid-lowering agents. ¶Medication usage was not recorded during the DCCT. Use of ACE inhibitors was proscribed during the DCCT. At EDIC year 1, ACE inhibitor use was 5.6% in INT and 6.9% in CONV. ARBs were not available until later during EDIC. #End of DCCT HbA_{1c} is the mean HbA_{1c} throughout the DCCT; EDIC years 15–18 HbA_{1c} values are time-averaged values through EDIC to the years 15–18 visit. The time-averaged mean (SD) HbA_{1c} levels through DCCT and EDIC combined were 7.8% (0.9) and 8.3% (1.0) (62 [9.8] and 67 [10.9] mmol/mol) among participants assigned to intensive and conventional diabetes therapy, respectively. ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; MA, microaneurysms; NPDR, nonproliferative diabetic retinopathy.

The risk reduction with INT was somewhat greater among those with microaneurysms alone or mild nonproliferative retinopathy at DCCT closeout (~55%) than among those with no retinopathy (30%), virtually all from the original primary prevention cohort (Table 2). However, the risk reductions within all strata were nominally significant.

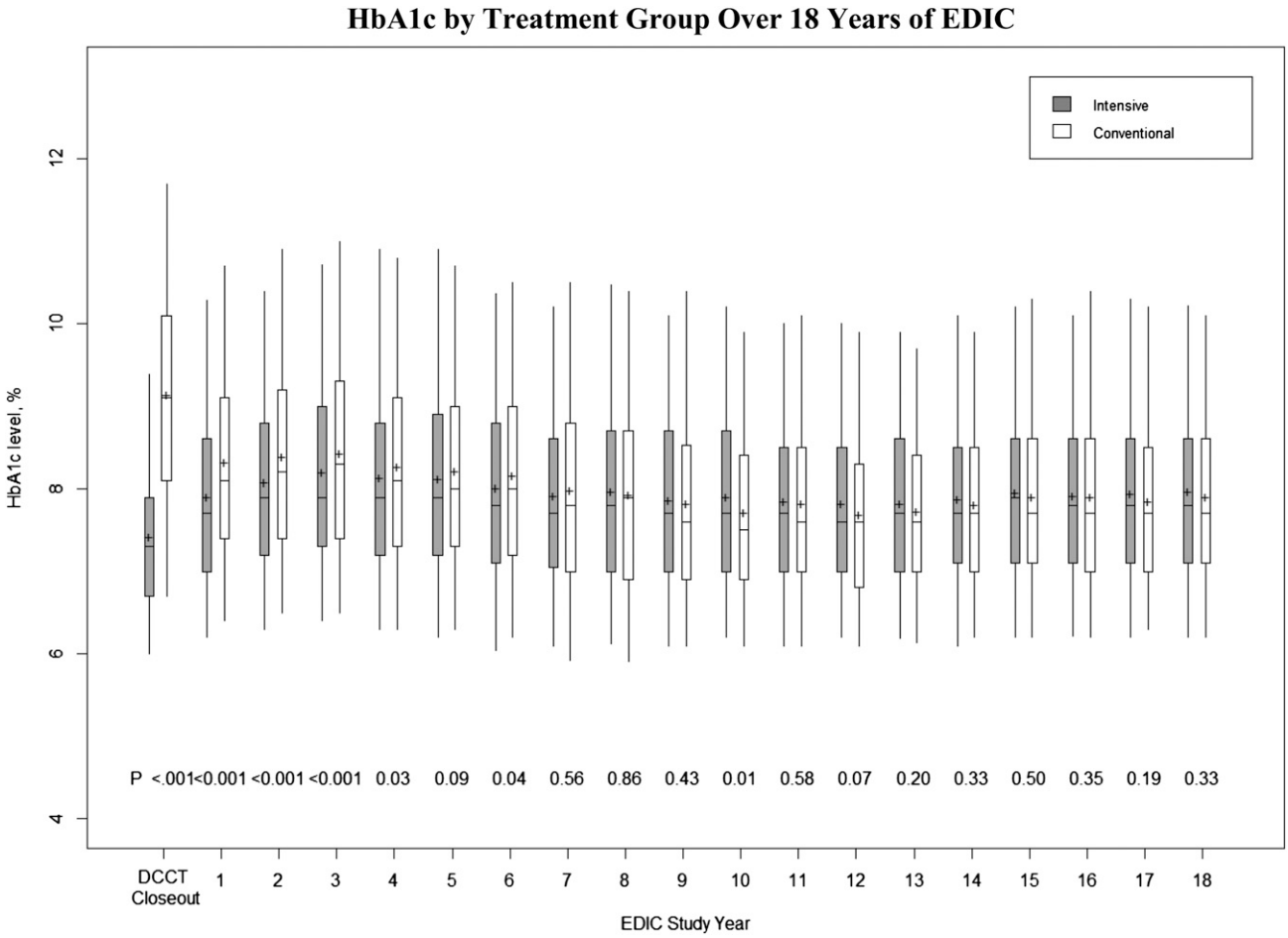

Figure 1— Box plots of the distribution of glycosylated hemoglobin (HbA_{1c}) values in the DCCT treatment group at the end of the DCCT and at each of the first 18 years of EDIC. Each box shows the quartiles, + denotes the mean, and whiskers show the range.

The cumulative incidence of retinopathy progression in the two groups has increased in parallel in recent years (Fig. 2*A*). Figure 3*A* shows that the underlying year-to-year incidence (risk or hazard rate) of further progression with INT has not continued to increase over the 18 years, whereas that with CONV was higher over years 1–9 but then fell to a level similar to INT beyond 10 years. Thus, over EDIC years 1–10, the risk with INT versus CONV was reduced by 52% (42, 60; $P < 0.0001$), whereas over 11–18 years, it was reduced by only 12% (−25, 39; $P = 0.47$) and was not significant.

The prevalence of a three or more–step change from DCCT baseline increased over time while the odds reduction declined (Table 3). Relative to the retinopathy level at DCCT closeout, further three or more–step retinopathy progression at EDIC years 15–18 was present in 189 (32%) in INT vs. 272 (47%) in CONV (not shown in tables), for a 43% adjusted odds reduction (27, 55; $P < 0.0001$).

More Advanced Stages of Retinopathy

Table 3 shows the prevalence and adjusted odds reductions at DCCT closeout, EDIC year 10, and EDIC years 15–18 for SNPDR, PDR, CSME, and a history of photocoagulation therapy for either proliferative retinopathy or CSME or anti-VEGF therapy. At DCCT closeout, the prevalences of these outcomes with CONV were 7–9% and were significantly lower with INT, with odds reductions of 46–76%. After 10 years of EDIC, the prevalences with CONV were 20–26%, and the adjusted odds reductions with INT ranged from 44 to 63% and remained highly significant.

At EDIC years 15–18, the prevalences with CONV were higher by ~5% than those at year 10 of follow-up, whereas those with INT were almost twice as great as at year 10. As a result, the adjusted odds reductions for INT versus CONV were lower than at year 10, 42% (20, 58; $P = 0.001$) for SNPDR, 43% (21, 59; $P = 0.001$) for PDR, 23% (−4, 44; $P = 0.09$) for CSME, and 33% (9, 51; $P = 0.01$) for photocoagulation or anti-VEGF therapy.

Figure 2*B* presents the cumulative incidence of new PDR during the years 15–18 of EDIC. The adjusted risk of PDR with INT versus CONV was reduced by 47% (30, 60; $P < 0.001$) (Table 2). The hazard reductions for those with some degree of retinopathy at DCCT closeout (strata 2, 3, and 4 in Table 2) ranged from 44 to 53%, each being significant. However, among those with no retinopathy at DCCT closeout (stratum 1) (316 of 1,318 subjects at risk,

Table 2—Incidence of further three or more–step progression of retinopathy and new PDR between the end of the DCCT and after 18 years of the EDIC study overall and stratified by the level of retinopathy at the end of DCCT

	Further ≥3-step progression				PDR			
Retinopathy levels at DCCT closeout	*n* at risk*	No. with event (%)	Adjusted risk reduction (%, CI)†	*P* value	*n* at risk‡	No. with event (%)	Adjusted risk reduction (%, CI)†	*P* value
All levels	1,358		46 (36, 54)	<0.0001	1,318		47 (30, 60)	<0.0001
Intensive	684	267 (39.0%)			668	86 (12.9%)		
Conventional	674	380 (56.4%)			650	172 (26.5%)		
Stratified by retinopathy levels at DCCT closeout								
Stratum 1: no retinopathy			30 (5, 49)	0.021			8 (−186, 70)	0.89
Intensive	194	100 (51.6%)			194	8 (4.1%)		
Conventional	123	74 (60.2%)			122	5 (4.1%)		
Stratum 2: microaneurysm only								
Intensive	275	88 (32.0%)	54 (38, 65)	<0.0001	274	23 (8.4%)	53 (19, 73)	0.007
Conventional	220	112 (50.9%)			220	32 (14.6%)		
Stratum 3: mild nonproliferative retinopathy			55 (33, 70)	<0.0001			52 (23, 70)	0.002
Intensive	149	44 (29.5%)			149	31 (20.8%)		
Conventional	200	101 (50.5%)			199	64 (32.2%)		
Stratum 4: moderate or severe nonproliferative retinopathy			45 (17, 63)	0.004			44 (9, 65)	0.018
Intensive	65	35 (53.9%)			50	24 (48.0%)		
Conventional	126	93 (73.8%)			104	71 (68.3%)		

*Analysis includes all subjects who were free of scatter photocoagulation during DCCT, alive at the initiation of EDIC, and had at least one retinal evaluation in EDIC. The stratified analysis was limited to those with retinopathy measurements at DCCT closeout. Analyses were stratified by retinopathy severity at the end of DCCT, defined as no retinopathy (ETDRS grade 10/10), microaneurysms only (grade 20), mild nonproliferative diabetic retinopathy (NPDR) (grade 30), or greater or equal to moderate NPDR (≥grade 40 or scatter laser). †A separate Weibull model was performed for each strata and for all levels combined, after adjustment for primary/secondary cohort, HbA_{1c} value at entry to the DCCT, and diabetes duration at DCCT baseline. Analysis of all levels combined was also adjusted for the level of retinopathy at the end of the DCCT. Risk reduction is for intensive therapy as compared with conventional therapy. The *P* value is obtained from a Wald test of the group coefficient in the model. ‡Analysis includes all subjects who were free of PDR during DCCT, alive at the initiation of EDIC, and either had an EDIC retinal assessment or reported pan-retinal laser treatment for retinopathy during EDIC.

principally from the primary prevention cohort), the risk reduction was only 8% and not significant. In both groups, only 4.1% of those without retinopathy at DCCT closeout had developed PDR 15–18 years later despite a diabetes duration of ~29 years.

The year-to-year incidence of progression to PDR (Fig. 3*B*) showed a pattern similar to that for three or more–step retinopathy progression. The incidence with CONV fell more in recent years, whereas with INT, it was level over time so that the risk reduction over 11–18 years (26%) was no longer significant (−15, 57; $P = 0.18$) between groups, whereas that up to EDIC year 10 (55%) was significant (36, 69; $P < 0.0001$).

Whereas the prevalence of CSME at years 15–18 was not significantly different between INT and CONV (23% reduction in odds, $P = 0.09$) (Table 3), the cumulative incidence of CSME up to years 15–18 was reduced by 35% (16, 50; $P < 0.0001$) with INT versus CONV (Fig. 2*C*). Figure 3*C* shows a narrowing incidence by year 10 so that the risk reduction over the first 10 years (55%) was significant (35, 69; $P < 0.0001$), whereas that over years 11–18 (−5%) was not.

Finally, the cumulative incidence of any new photocoagulation during EDIC showed a 39% risk reduction with INT versus CONV (19, 53; $P < 0.0001$) (Fig. 2*D*). By EDIC years 15–18, there was a narrowing in the differences in incidences between INT and CONV, resulting in a significant 60% risk reduction (41, 73; $P < 0.0001$) over years 1–10 but becoming nonsignificant over years 11–18 (−3%; P = NS) (Fig. 3*D*).

During DCCT and EDIC combined, best-corrected visual acuity worse than 20/100 was observed in 20 INT vs. 21 CONV patients (23 vs. 22 eyes), and worse than 20/200 in 14 vs. 12 patients (15 vs. 12 eyes), not counting one patient with loss of vision due to an accident.

Risk Factors and Mediation of the Treatment Group Differences

Table 4 describes time-dependent covariate associations with further retinopathy progression and new PDR during years 15–18 of EDIC follow-up. Adjusted for DCCT baseline covariates and the level of retinopathy at DCCT closeout (Table 4 and Supplementary Table 1), the risk of retinopathy progression was reduced by 46% with INT versus CONV (36, 54; $P < 0.0001$). Additional time-dependent covariates were then added to this baseline-adjusted model one at a time, and the percentage reduction in the treatment group χ^2 value computed (Table 4). This equals the percentage of the treatment group effect on retinopathy progression that was mediated or explained by treatment group differences in that covariate. Time-varying indicator variables for a history of hyperlipidemia,

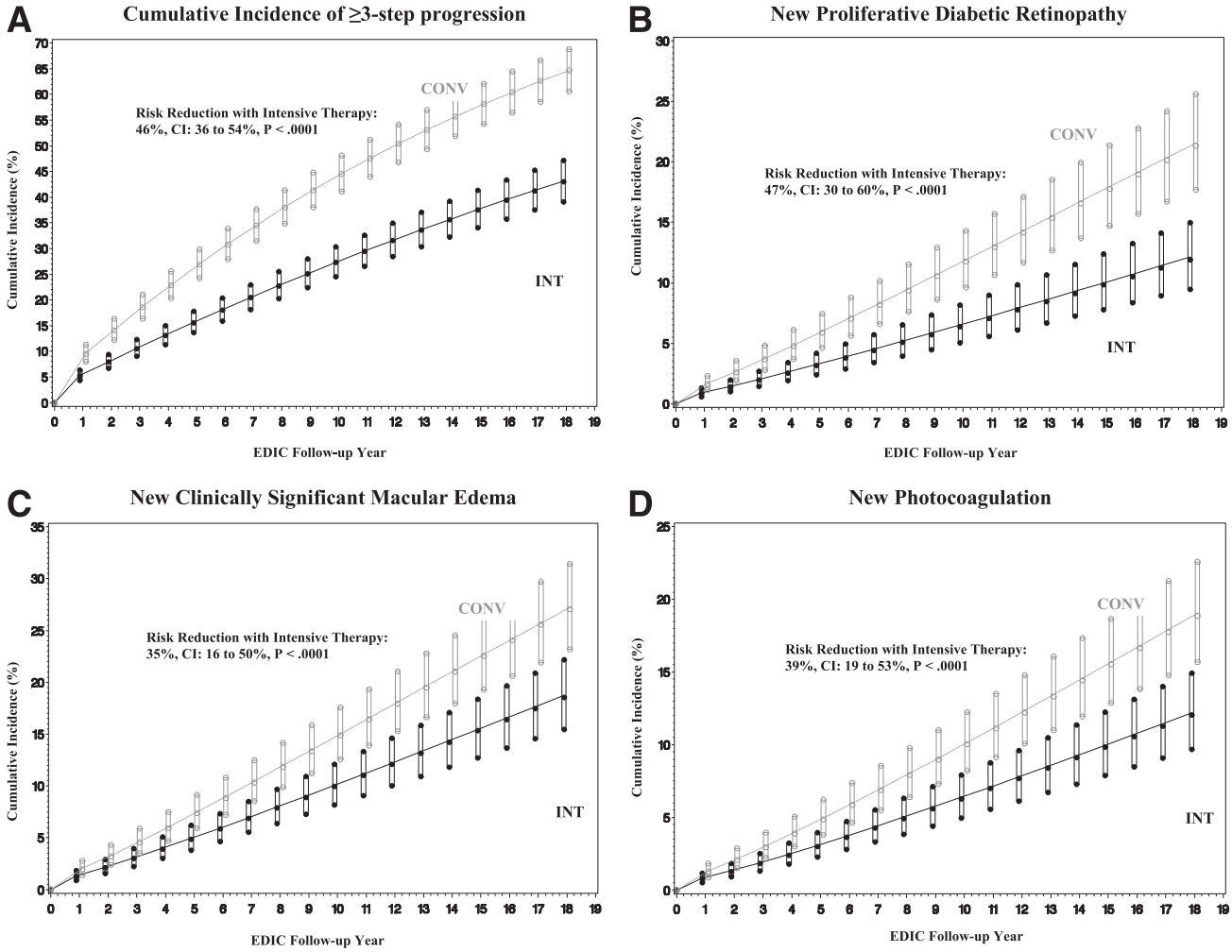

Figure 2—Estimated cumulative incidence of further progression of retinopathy from DCCT closeout to EDIC year 18 within the former DCCT INT and CONV. *A*: Further three-step progression from the level at DCCT closeout (n = 1,358). *B*: New onset of PDR (n = 1,318). *C*: New onset of CSME (n = 1,277). *D*: New photocoagulation (pan-retinal or focal laser or anti-VEGF use) based on fundus photography grading and/or patient reporting (n = 1,335). Estimated cumulative incidence was based on the 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 duration at DCCT baseline. Subjects who had prior scatter photocoagulation during the DCCT (n = 36), who died during the DCCT (n = 11), or who had no EDIC measurements (n = 36) were excluded from all the analyses. Subjects with prior PDR during the DCCT (n = 78) excluded from *B*, prior CSME during the DCCT (n = 120) excluded from *C*, and prior treatment during the DCCT (n = 74) excluded from *D*.

microalbuminuria (albumin excretion rate [AER] >30 mg/24 h), current smoking, and the updated mean arterial pressure level (mmHg) were all strongly positively associated with the risk of further retinopathy progression, but none explained >38% of the INT versus CONV difference in risk. Smoking and blood pressure explained none of the risk. Renin-angiotensin-aldosterone system (RAAS) inhibitor use was not associated with progression and did not explain the difference between groups.

An additional model assessed the association of the DCCT mean HbA_{1c} (a fixed covariate) and the updated mean HbA_{1c} during EDIC. Each was significantly positively associated with risk of retinopathy progression, and when adjusted for both, the effect of treatment group on retinopathy progression was virtually eliminated, indicating that the DCCT and EDIC mean HbA_{1c} levels completely mediated the treatment group metabolic memory effect. That is, the INT versus CONV differences in HbA_{1c} during the DCCT and EDIC account for nearly all of the group differences in retinopathy progression during the years 15–18 of EDIC follow-up.

Similar analyses showed that the DCCT baseline duration of diabetes, retinopathy levels at DCCT closeout, and treatment group were significantly associated with risk of progression to PDR during EDIC follow-up (Table 4 and Supplementary Table 1). In additional models, hyperlipidemia, microalbuminuria, and blood pressure were significantly positively associated with the risk of PDR, but smoking and RAAS inhibitor use were not. However, none of these explained >40% of the effect of treatment group on PDR risk. On the other hand, DCCT mean HbA_{1c} and updated EDIC mean HbA_{1c} were strongly associated with

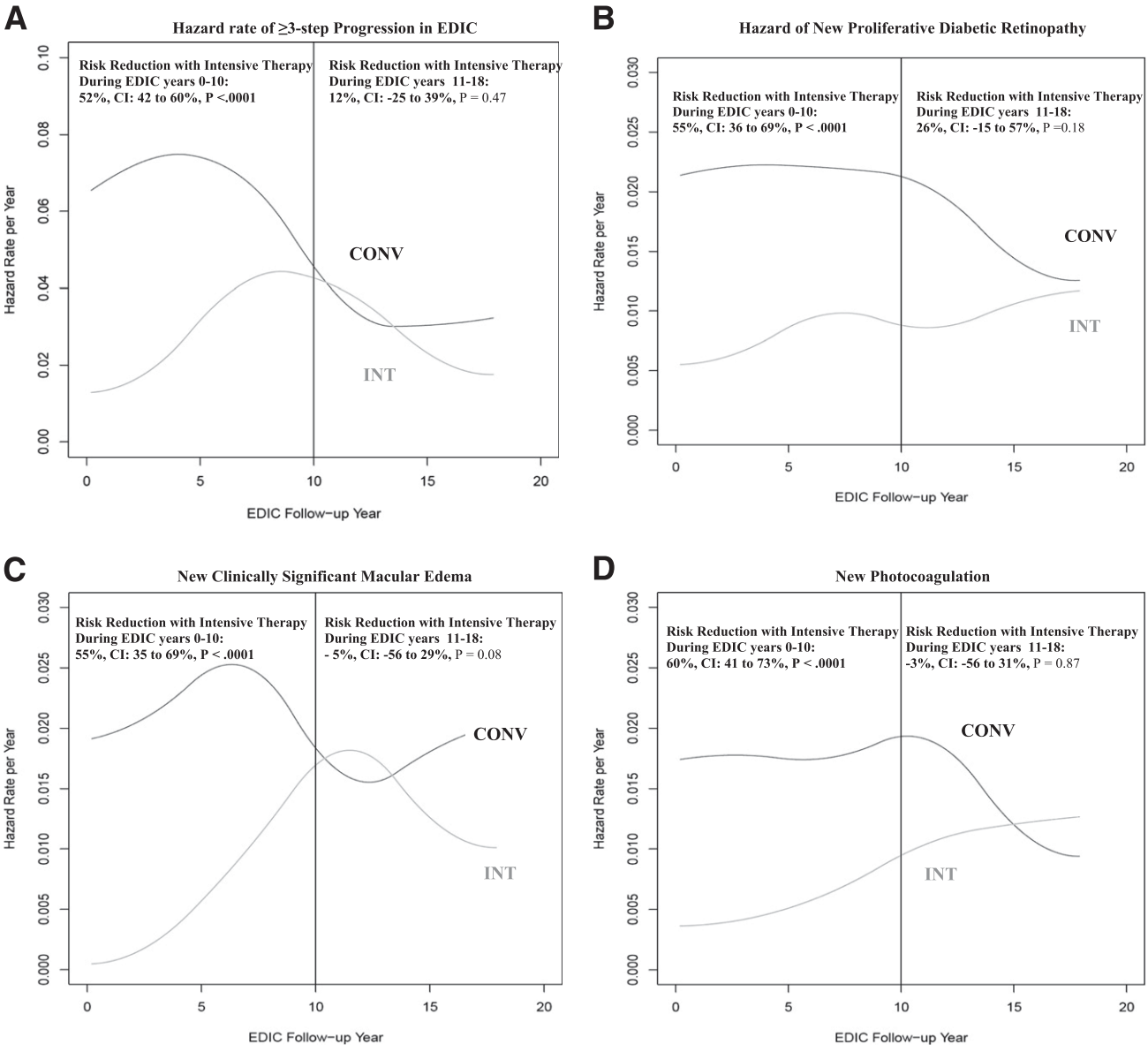

Figure 3—Estimated hazard rate (incidence) function of further progression of retinopathy from DCCT closeout to EDIC year 18 within the former DCCT INT and CONV. *A*: Further three-step progression from the level at DCCT closeout. *B*: New onset of PDR. *C*: New onset of CSME. *D*: New photocoagulation (pan-retinal or focal laser or anti-VEGF use) based on fundus photography grading and/or patient reporting. Estimated hazard rate was based on a smoothed Turnbull nonparametric estimate of the survival function, without adjustment for other factors. Risk reductions from DCCT closeout to EDIC year 10 and from EDIC year 10 to EDIC year 18 were obtained from separate Weibull regression models of those at risk during each period.

PDR risk and together explained virtually all of the treatment group difference in PDR risk.

HbA_{1c} and Crossing Hazards

A further analysis of retinopathy progression shows that the 52% risk reduction with intensive therapy during the first 10 years (Fig. 3*A*) is significantly different from the 12% reduction in years 11–18 ($P = 0.039$). Preliminary analyses show that the acute change in HbA_{1c} between DCCT closeout and EDIC year 1 alone does not explain this group by period interaction; however, it is partially mediated by the history of HbA_{1c} levels over DCCT and over EDIC (interaction $P = 0.28$ after HbA_{1c} adjustments).

Adults Versus Adolescents

Among the 195 adolescents, DCCT intensive therapy reduced the risk of sustained retinopathy progression by 61% (30, 78; $P < 0.01$) (2). Of these, 188 entered EDIC. Among the 178 who were at risk for further retinopathy progression during EDIC, there was no difference in risk with INT versus CONV over the years 15–18 of EDIC follow-up (6% risk reduction [−42, 38]; $P = 0.77$). During years 1–10 there was no significant benefit with INT (25%

Table 3—Prevalence of various retinopathy complications in the former DCCT INT and CONV at DCCT closeout, EDIC year 10, and EDIC years 15–18 among 1,214 patients evaluated for retinopathy or CSME during EDIC years 15–18

	DCCT closeout (n = 1,214)				EDIC year 10 (n = 1,133)				EDIC years 15–18 (n = 1,214)			
Retinopathy complications†	INT*	CONV	Odds reduction (%, CI)‡	*P*	INT	CONV	Adjusted odds reduction (%, CI)§	*P*	INT	CONV	Adjusted odds reduction (%, CI)§	*P*
n	606	608			559	574			606	608		
≥3 step progression from DCCT baseline	9.2	31.5	78 (69, 84)	<0.0001	34.3	60.6	60 (49, 69)	<0.0001	41.1	58.7	41 (25, 54)	<0.0001
SNPDR or worse (SNPDR+) (%)	2.2	8.3	76 (55, 87)	<0.0001	8.8	25.8	62 (43, 75)	<0.0001	15.9	31.5	42 (20, 58)	0.001
PDR or worse (PDR+) (%)	2.0	7.0	73 (48, 86)	<0.0001	8.6	25.4	63 (43, 75)	<0.0001	15.7	31.5	43 (21, 59)	0.001
n	581	562			533	521			581	562		
CSME (%)	3.8	6.8	46 (7, 68)	0.024	9.4	20.4	44 (17, 63)	0.004	17.0	26.0	23 (−4, 44)	0.09
n	606	608			559	574			606	608		
Photocoagulation therapy (%)‖	3.3	7.7	59 (30, 76)	0.0007	9.3	25.4	58 (37, 72)	<0.0001	17.2	30.9	33 (9, 51)	0.010

*Each subject was assessed once every 4 years during years 15–18 of EDIC timed to the year of entry into the DCCT. All subjects (consenting) were assessed at years 4 and 10. †Owing to staggered retinal assessments, patients could have completed an EDIC retinal examination that did not show progression, but later received treatment due to progression during the interim. Accordingly, such patients with scatter photocoagulation after the last retinal examination were counted as worsening for retinopathy (SNPDR or PDR); those with focal photocoagulation or on anti-VEGF were counted as worsening for macular edema (CSME). The *n* for CSME does not include patients who received pan-retinal photocoagulation for retinopathy. ‡The odds reduction is for intensive therapy as compared with conventional therapy. The percent reduction in the odds for the INT versus CONV was computed as (1 − odds ratio) × 100. §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 analysis is limited to the 1,214 patients with retinopathy evaluated at years 15–18, the risk reduction at EDIC year 10 is slightly different from that previously published (8). ‖Prior photocoagulation therapy is based on fundus photography grading and/or patient reporting. Photocoagulation includes pan-retinal laser for retinopathy or focal laser or use of anti-VEGF for CSME.

Table 4—Associations of time-dependent covariates with risk of further three or more–step progression from DCCT closeout or new PDR in EDIC and the impact of adjusting for each covariate on the DCCT intensive diabetes treatment effect

	Further ≥3-step progression					PDR				
	Risk associated with the covariate		Effect of DCCT intensive diabetes therapy			Risk associated with the covariate		Effect of DCCT intensive diabetes therapy		
Time-dependent covariate(s)	Hazard ratio (95% CI)†	*P* value	Risk reduction (%) (95% CI)	*P* value	% explained by covariate	Hazard ratio (95% CI)†	*P* value	Risk reduction (%) (95% CI)‡	*P* value	% explained by covariate
Baseline adjusted model*			46 (36, 54)	<0.0001	—			46 (29, 59)	<0.0001	—
HbA_{1c} (per 10% increase)‡			0 (−28, 22)	0.9821	100%			−1 (−51, 32)	0.9555	100%
DCCT mean	1.17 (1.07, 1.29)	0.0006				1.22 (1.06, 1.42)	0.0063			
Updated EDIC mean	1.57 (1.46, 1.68)	<0.0001				1.66 (1.49, 1.85)	<0.0001			
Hyperlipidemia vs. not§	1.39 (1.16, 1.67)	0.0003	42 (31, 52)	<0.0001	37%	1.39 (1.06, 1.82)	0.018	44 (24, 58)	0.0001	24%
Sustained AER >30 mg/24 h vs. not	1.79 (1.42, 2.25)	<0.0001	44 (34, 53)	<0.0001	10%	2.54 (1.93, 3.34)	<0.0001	39 (19, 53)	0.0006	40%
Currently smoking vs. not	1.34 (1.10, 1.61)	0.0028	46 (36, 54)	<0.0001	0%	1.27 (0.94, 1.71)	0.12	46 (29, 59)	<0.0001	1.6%
Mean arterial blood pressure	1.02 (1.01, 1.03)	<0.0001	47 (37, 55)	<0.0001	0%	1.04 (1.02, 1.05)	<0.0001	46 (30, 59)	<0.0001	0%
RAAS inhibitor use	0.96 (0.76, 1.21)	0.70	46 (36, 54)	<0.0001	0.1%	1.34 (1.00, 1.81)	0.052	45 (28, 59)	<0.0001	2.8%

*Basic Weibull proportional hazards models evaluated the associations of DCCT treatment group with risk of further three or more–step progression or new PDR in EDIC, respectively, after adjustment for diabetes duration, HbA_{1c} at DCCT entry, and retinopathy level at DCCT closeout. Risk reduction associated with intensive diabetes therapy is calculated as (1 − hazard ratio of intensive vs. conventional diabetes therapy with or without adjustment for covariate) × 100%. †Separate Weibull models evaluated associations of each time-dependent covariate with risk of retinopathy progression or new PDR to generate each covariate hazard ratio. Hazard ratio for covariates is evaluated per 10% increase in DCCT or EDIC HbA_{1c} (e.g., from 8 to 8.8%), unit change in other quantitative covariates, or status change in binary covariates. DCCT mean HbA_{1c} (a fixed covariate) and EDIC mean HbA_{1c} (a time-dependent covariate) modeled together. Additional models assessed the interaction between the covariate and the DCCT/EDIC weighted mean HbA_{1c}. None was significant at the 0.05 level. ‡Separate Weibull models then evaluated the risk reduction with DCCT intensive vs. conventional diabetes therapy on risk of retinopathy progression or new PDR in EDIC, adjusting for each time-dependent covariate one at a time in addition to the covariates adjusted in the basic model (and modeling DCCT HbA_{1c} along with the EDIC HbA_{1c}). The percent of the DCCT treatment effect explained by group differences in each covariate is computed as the percentage change in the DCCT treatment group χ^2 test value from the basic treatment effect model to the model adjusted for the time-dependent covariate. Since each covariate is evaluated in a separate model, the proportions do not sum to 100%. §Hyperlipidemia was defined by an LDL cholesterol level ≥130 mg/dL (3.4 mmol/L) or the use of lipid-lowering agents.

risk reduction [−22, 64]; $P = 0.25$), and likewise over years 11–18 there was no benefit (79% risk increase [−24, 316]; $P = 0.19$). Among the 1,195 adults who entered EDIC, over the 18 years there was a significant 52% risk reduction with INT versus CONV (42, 60; $P < 0.001$), with a significant benefit during years 1–10 (56% [46, 64]; $P < 0.001$) but a lesser nonsignificant benefit during years 11–18 (27% [−9, 51]; $P = 0.13$).

Model Validation

The Supplementary Data demonstrates good agreement of the model-based versus model-free Turnbull (17) estimates.

DISCUSSION

Long-term follow-up for 15–18 years beyond the DCCT demonstrates a persistent beneficial effect of the initial mean of 6.5 years of DCCT intensive versus conventional therapy on retinopathy progression by three or more steps on the ETDRS scale, PDR, CSME, and photocoagulation or anti-VEGF therapy for retinopathy or CSME. For each outcome, the cumulative incidence function through years 15–18 was significantly lower in the former INT than CONV (Fig. 2). Thus, fewer former INT participants continue to be affected by these retinal complications 18 years after the close of the DCCT.

However, the risk reductions (hazard ratios) for these outcomes over 15–18 years of follow-up in the former INT versus CONV are less than previously reported. During the DCCT, the risk of retinopathy progression was reduced by 73% (95% CI 63, 80; $P < 0.0001$) with intensive versus conventional therapy (1). Among the 1,214 subjects with years 15–18 outcomes, the odds (prevalence) of further retinopathy progression from the level at DCCT closeout, adjusted for the closeout level, was reduced by 74% (65, 81; $P < 0.0001$) at EDIC year 4, and 59% (47, 68; $P < 0.0001$) at EDIC year 10, with intensive versus conventional therapy. At EDIC years 15–18, the adjusted odds of progression was reduced by 43% (27, 55; $P < 0.0001$). Previously reported results differ slightly, owing to larger sample sizes therein (4,8).

In addition, the year-to-year incidence (hazard rate) of new cases per year has narrowed for each outcome and is now similar within the original treatment groups beyond EDIC year 10. In fact, the risk reduction with former intensive therapy beyond year 10 is no longer statistically significant for any outcome (Fig. 3). As a result, the group differences in the prevalence of having a worse outcome at years 15–18 are less than previously observed. The prevalence of CSME was not significantly different (Table 3).

These findings are largely a function of a declining incidence in the former CONV beyond year 10, combined in some outcomes with an increasing incidence in the INT. Interestingly, for no retinal outcome was the narrowing of the difference in risk attributable solely to increasing incidence in the INT, although such an increase was suggested for CSME (Fig. 3*C*).

Since the HbA_{1c} in the former INT rose from ~7% (53 mmol/mol) at DCCT closeout to ~8% (64 mmol/mol) during EDIC, some rise in the incidence of further progression would be expected in this group during EDIC. However, for the most part, the incidence in the INT remained low and relatively level for most retinal outcomes. This is perhaps the major manifestation of the metabolic memory phenomenon.

Similarly, since the HbA_{1c} in the former CONV fell from ~9 to 8% (75 to 64 mmol/mol), some fall in the incidence of further progression would be expected. However, this expected fall, or the metabolic memory effect, was delayed until about 10 years after the close of the DCCT. This delay is analogous to the original effects of lowering glycemia with intensive therapy during the DCCT. Despite the rapid reduction of HbA_{1c} from ~9% (75 mmol/mol) to 7% (53 mmol/mol) during the first 6 months of the DCCT, there was virtually no difference in risk of retinopathy progression for the first 5 years of treatment. So the reduced incidence in the CONV later in EDIC follow-up could simply be another manifestation of the metabolic memory associated having a lower HbA_{1c} by ~1% (10.9 mmol/mol) during EDIC than during the DCCT.

Although baseline factors and other factors measured over time including hyperlipidemia, microalbuminuria, smoking, and blood pressure (but not RAAS inhibitor use) were significantly associated with retinopathy progression and progression to PDR, treatment group differences in these factors failed to account for or mediate the treatment group difference in risk of progression. Rather, as consistently observed in the past, the level of HbA_{1c} during DCCT and EDIC explains virtually all of the treatment group effects on risk of progression.

During the DCCT, the mean HbA_{1c} among the 195 subjects who entered as adolescents was significantly greater than that among the 1,246 adults within the INT (8.1 vs. 7.1%, 65 vs. 54 mmol/mol) and the CONV (9.8 vs. 9.0%, 84 vs. 75 mmol/mol) (each $P < 0.001$), resulting in a similar ~2% (21 mmol/mol) difference in HbA_{1c} in adults and adolescents. As a result, the reduction in the risk of retinopathy progression with intensive therapy was similar among adolescents (61% risk reduction) as in adults (63% risk reduction) (2). Among the 141 original adolescents assessed at year 4 of EDIC, the 77% odds reduction of retinopathy progression at year 4 (prevalence) with intensive therapy was similar to that observed in the full cohort (75%) (5). However, at year 10, among the 96 original adolescents evaluated and still at risk, there was only a 10% odds reduction (prevalence) with intensive versus conventional therapy (−104, 60; $P = 0.84$), whereas a significant benefit was observed among adults. Although the difference in metabolic memory effect among adults versus adolescents at 10 years appears to be explained by the higher HbA_{1c} during DCCT among adolescents, interpreting the results in the former adolescent subset must be tempered by the relatively small numbers of subjects.

Although the risk of new CSME was also reduced significantly by 35% over the total 18 years of EDIC, there was a smaller, nonsignificant difference in the prevalence of CSME at the years 15–18 evaluations. Further follow-up is needed to determine whether the former intensive treatment group will continue to enjoy a reduced risk of this outcome.

Another recent paper (13) describes similar analyses of albuminuria and renal function (estimated glomerular filtration rate) over 18 years of EDIC and showed nearly identical results. For each outcome, the groups continue to differ but the cumulative incidences are now increasing nearly in parallel. The underlying risks (hazard rates) in the former INT remain low and level over the 18 years, whereas those in the CONV are higher for the first 10 years but then drop after year 10 to match the level in the INT. Clinical neuropathy was not assessed with a frequency that permitted similar analyses of the patterns of incidence over time.

A fraction of subjects with diabetes may be protected from microvascular complications of diabetes. Thus, another possible explanation of the declining incidence of retinopathy progression in the CONV could be that those susceptible to such progression have now reached that outcome and those who have not may not be susceptible.

A major strength of EDIC is the high precision of the outcome assessments for retinopathy and other outcomes, and the remarkably high compliance of the subjects with the EDIC follow-up schedule. However, the compliance with the fundus photography examinations has not been quite as high as with other procedures. Of the 1,325 surviving subjects from the original cohort eligible to complete an examination during years 15–18, 1,214 (92%) did so. Although this level of long-term follow-up is exemplary, the less than complete adherence may still be considered a weakness. Similarly, the reliability of the long-term follow-up in the small adolescent subset is less, owing to the greater losses to follow-up.

Another weakness is the infrequently and unevenly timed retinal assessments. Given the young age of the original DCCT cohort and the low incidence of generally mild retinopathy during the DCCT, retinal examinations were only obtained in one-fourth of the subjects each year during EDIC, timed relative to the date of randomization, i.e., once every 4th year, except for years 4 and 10 when the entire cohort was assessed. This schedule of outcome assessments handicaps the ability of statistical methods to describe patterns of risk and covariate effects on risk. It is possible that the magnitude of covariate effects (though not their direction) would have differed if the retinal examinations had been conducted more frequently, e.g., annually. However, given the strong statistical effects reported, this weakness has clearly been mitigated by the large number of subjects now followed for up to 18 years during EDIC.

In conclusion, the initial period of 6.5 years of intensive therapy during the DCCT has resulted in a sustained beneficial reduction over up to 18 years of extended follow-up during EDIC in the cumulative incidence (total numbers) of subjects showing further retinopathy progression, and progression to more severe levels of retinopathy that require intervention. The benefit (risk reduction), however, is not as great as that observed in prior analyses up to 4 and up to 10 years of EDIC follow-up during which the phenomenon of metabolic memory applied. The diminished risk reduction during years 10–18 of EDIC follow-up is not explained by a rise in the risk of the former INT but rather by a decline in the risk after 10 years of follow-up in the CONV. The mechanisms for this fall are as yet undefined. Virtually all of the long-term benefits of former intensive versus conventional therapy are explained by the differences between the groups in the levels of HbA_{1c} during DCCT and EDIC.

APPENDIX

Writing Group: John M. Lachin (The George Washington University, Rockville, MD), Neil H. White (Washington University, St. Louis, MO), Dean P. Hainsworth (University of Missouri, Columbia, MO), Wanjie Sun (The George Washington University, Rockville, MD), Patricia A. Cleary (The George Washington University, Rockville, MD), and David M. Nathan (Massachusetts General Hospital, Boston, MA).

Funding. The DCCT/EDIC has been supported by U01 Cooperative Agreement grants (1982–1993 and 2011–2016) and contracts (1982–2011) with the Division of Diabetes, Endocrinology, & Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and through support by the National Eye Institute, the National Institute of Neurologic Disorders and Stroke, the Genetic Clinical Research Centers Program (1993–2007), and Clinical Translational Science Center Program (2006 to present) (Bethesda, MD). Industry contributors have had no role in the DCCT/EDIC study but have provided free or discounted supplies or equipment to support participant adherence to the study: Abbott Diabetes Care (Alameda, CA), Animas (Westchester, PA), Bayer Diabetes Care (North America Headquarters, Tarrytown, NY), Becton Dickinson (Franklin Lakes, NJ), CanAm (Atlanta, GA), Eli Lilly and Company (Indianapolis, IN), LifeScan (Milpitas, CA), Medtronic Diabetes (Minneapolis, MN), Omron (Shelton CT), OmniPod Insulin Management System (Bedford, MA), Roche Diabetes Care (Indianapolis, IN), and Sanofi (Bridgewater, NJ).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. J.M.L. obtained funding for the study, wrote the manuscript, and directed the statistical analyses. N.H.W. wrote sections of the manuscript and reviewed and edited the manuscript. D.P.H. contributed to the analysis plan specifications for the manuscript. W.S. conducted the statistical analyses, wrote sections of the manuscript, and reviewed and edited the manuscript. P.A.C. contributed to the analysis plan specifications for the manuscript and researched data. D.M.N. reviewed and made critical revisions to the manuscript. J.M.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term

complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329: 977–986

2. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. J Pediatr 1994;125:177–188

3. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care 1999;22:99–111

4. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381–389

5. White NH, Cleary PA, Dahms W, Goldstein D, Malone J, Tamborlane WV; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). J Pediatr 2001;139:804–812

6. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 2002;287:2563–2569

7. Martin CL, Albers J, Herman WH, et al.; DCCT/EDIC Research Group. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. Diabetes Care 2006;29:340–344

8. White NH, Sun W, Cleary PA, et al. 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. Arch Ophthalmol 2008; 126:1707–1715

9. White NH, Sun W, Cleary PA, et al.; DCCT-EDIC Research Group. Effect of prior intensive therapy in type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: comparison of adults and adolescents. Diabetes 2010;59:1244–1253

10. Nathan DM, Bayless M, Cleary P, et al.; DCCT/EDIC Research Group. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: advances and contributions. Diabetes 2013;62:3976–3986

11. Nathan DM; DCCT/EDIC Research Group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: overview. Diabetes Care 2014;37:9–16

12. Aiello LP; DCCT/EDIC Research Group. Diabetic retinopathy and other ocular findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2014;37:17–23

13. de Boer IH, Sun W, Gao P, et al.; for the DCCT/EDIC research group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. Lancet Diabetes Endocrinol. 17 July 2014 [Epub ahead of print]

14. Diabetes Control and Complications Trial Research Group. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Ophthalmology 1995;102:647–661

15. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Ophthalmology 1991;98(Suppl.):823–833

16. Odell PM, Anderson KM, D'Agostino RB. Maximum likelihood estimation for interval-censored data using a Weibull-based accelerated failure time model. Biometrics 1992;48:951–959

17. Turnbull BW. The empirical distribution function with arbitrarily censored and truncated data. J R Stat Soc [Ser B] 1976;38:290–295

18. Hastie TJ. Generalized additive models. In *Statistical Models in S*. Chambers JM, Hastie TJ, Eds. Pacific Grove, CA, Wadsworth & Brooks/Cole, 1992

19. Agesti A. *Categorical Data Analysis*. New York, John Wiley & Sons, 1990, p. 80–91, 235–236

20. Sparling YH, Younes N, Lachin JM, Bautista OM. Parametric survival models for interval-censored data with time-dependent covariates. Biostatistics 2006;7:599–614

21. MacKinnon DP. *Introduction to Statistical Mediation Analysis*. New York, Erlbaum, 2008