Effect of Prior Intensive Therapy in Type 1 Diabetes on 10-Year Progression of Retinopathy in the DCCT/EDIC: Comparison of Adults and Adolescents

Neil H. White,[1] Wanjie Sun,[2] Patricia A. Cleary,[2] William V. Tamborlane,[3] Ronald P. Danis,[4] Dean P. Hainsworth,[5] and Matthew D. Davis,[4] for the DCCT-EDIC Research Group*

OBJECTIVE—The aim of this study was to examine differences between adolescents and adults in persistence of the benefits of intensive therapy 10 years after completion of the Diabetes Control and Complications Trial (DCCT).

RESEARCH DESIGN AND METHODS—During the Epidemiology of Diabetes Interventions and Complications (EDIC) study, progression of retinopathy from DCCT closeout to EDIC year 10 was evaluated in 1,055 adults and 156 adolescents.

RESULTS—During 10 years of follow-up, HbA_{1c} (A1C) was similar between original intensive (INT) and conventional (CON) groups and between former adolescents and adults. At EDIC year 10, adults in the former INT group continued to show slower progression of diabetic retinopathy than those in the CON group (adjusted hazard reduction 56%, $P < 0.0001$), whereas in adolescents this beneficial effect had disappeared (32%, $P = 0.13$). Seventy-nine percent of observed differences in the prolonged treatment effect between adults and adolescents at year 10 were explained by differences in mean A1C during DCCT between adolescents and adults (8.9 vs. 8.1%), particularly between INT adolescents and adults (8.1 vs. 7.2%).

CONCLUSIONS—Prior glycemic control during DCCT is vital for the persistence of the beneficial effects of INT therapy 10 years later. Lowering A1C to as close to normal as safely possible without severe hypoglycemia and starting as early as possible should be attempted for all subjects with type 1 diabetes. These results underscore the importance of maintaining A1C at target values for as long as possible because the benefits of former INT treatment wane over time if A1C levels rise. ***Diabetes*** **59: 1244–1253, 2010**

From [1]Washington University, St. Louis, Missouri; [2]The George Washington University, The Biostatistics Center, Rockville, Maryland; the [3]the School of Medicine, Yale University, New Haven, Connecticut; the [4]University of Wisconsin–Madison, Madison, Wisconsin; and the [5]University of Missouri, Columbia, Missouri.

Corresponding author: Neil H. White, white_n@kids.wustl.edu.

Received 14 August 2009 and accepted 1 February 2010. Published ahead of print at http://diabetes.diabetesjournals.org on 11 February 2010. DOI: 10.2337/db09-1216. Clinical trial registry nos. NCT00360815 and NCT00360893, clinicaltrials.gov.

*A complete list of the participants in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group can be found at Arch Ophthalmol 2008;126:1713.

The Diabetes Control and Complications Trial (DCCT) clearly demonstrated the benefits of intensive diabetes therapy aimed at lowering blood glucose and HbA_{1c} (A1C) as near to the normal range as safely possible (1). A marked reduction in retinopathy onset, retinopathy progression, and microalbuminuria was demonstrated in both the adult (18–39 years old at enrollment) and adolescent (13–17) cohorts (2) treated with intensive therapy for a mean of 6.5 years. The Epidemiology of Diabetes Interventions and Complications (EDIC) study, the observational follow-up of the DCCT cohort (3), demonstrated that the differences in complication occurrence and progression between former intensive (INT) and conventional (CON) treatment groups continued in adolescent and adult cohorts during the first 4 years of EDIC (4,5) despite similar A1C in the treatment groups during this time period. This phenomenon has been termed "metabolic memory."

The demonstration of metabolic memory suggests that hyperglycemia contributes to the development of diabetes complications over a long period of time and that halting or reversing prior effects of hyperglycemia or prior benefits of improved glycemic control would also take an extended period of time (6). Indeed, although the difference in retinopathy progression between former DCCT INT and CON groups was recently shown to persist at least 10 years after the DCCT, the differences between the two groups appeared to be waning (79% hazard reduction in further retinopathy progression at EDIC year 4 vs. 53% at year 10) (7).

We now present analyses of the EDIC year-10 retinopathy data that were undertaken to determine whether persistence of metabolic memory differed based on age at the time of randomization in the DCCT (adults: 18–39 years vs. adolescents: 13–17) and, if so, what factors contribute to this difference. Specifically, retinopathy results at year 10 of the EDIC study for the adult DCCT cohort were compared with those of the adolescent cohort. The results from EDIC year 4 have previously been reported for both the entire DCCT cohort (4) and for the adolescent cohort (5) as have the retinopathy results for the entire cohort at EDIC year 10 (7).

RESEARCH DESIGN AND METHODS

The design and methods of the DCCT have been reported previously (1). In brief, the DCCT was a multicenter, randomized controlled trial comparing the occurrence and progression of diabetes complications in subjects with type 1 diabetes randomized to INT or CON therapy. Eligible subjects between 13 and 39 years of age were randomized to INT or CON in either the primary prevention arm (diabetes duration 1–5 years, no retinopathy, urine albumin

<40 mg/day) or the secondary intervention arm (duration 1–15 years, at least early background retinopathy but no severe retinopathy, urine albumin ≤200 mg/day). When the DCCT ended in 1993, all subjects were instructed on INT methods. In 1994, 1,375 of the DCCT participants enrolled in the EDIC study, an observational follow-up study of the DCCT. A1C was determined by high-performance liquid chromatography (8), in the same central laboratory during DCCT and EDIC. Nephropathy evaluation, including serum creatinine and a 4-h timed urine collection (to determine albumin excretion rate and creatinine clearance) and fasting lipoprotein profiles were performed every other year. Other annual evaluations included a standardized medical history and physical examination, electrocardiogram, and a lower extremity neuropathy examination.

Ophthalmologic examination, visual acuity, and seven-field fundus photography were scheduled for each subject every four years and for the entire cohort at EDIC years 4 and 10. Seven-field stereoscopic fundus photography was performed by trained and certified photographers and the photographs were graded at a central reading center using the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale by graders masked to previous DCCT treatment group assignment and A1C levels (9,10). Further 3-step progression during EDIC, defined as a ≥3-step progression from the ETDRS level at DCCT closeout, is the primary outcome reported in this article.

Statistical analyses. To test for differences between groups, Wilcoxon rank-sum tests were used for quantitative or ordinal data (11), and χ^2 tests/Fisher exact tests were used for categoric data (12). The Mantel-Haenszel method was used to calculate unadjusted odds ratios (ORs), as well as stratified, adjusted ORs, with test-based confidence limits (13). The percentage reduction in the odds with INT versus CON therapy was computed as $(1 - \text{OR}) \times 100$. Generalized estimating equations (GEEs) with unstructured working correlation matrix (14) were used to test for differences in odds reduction in further ≥3-step progression between EDIC years 4 and 10. All the analyses were performed in the adult and adolescent cohorts (as enrolled at DCCT baseline).

Interval censoring was observed because of the large intervals between visits at which photographs were collected. Weibull proportional hazard regression model was used because of its robustness in the presence of heavily interval censored data (15,16). This model evaluated the effects of prior treatment and other risk factors on the cumulative incidence of further retinopathy progression from DCCT closeout through EDIC years 4 and 10. It also evaluated the difference in treatment effect (metabolic memory) between adults and adolescents by including the interaction term of treatment and adult/adolescent in the model after adjustment for the other risk factors. The Weibull model used all fundus photographs over all EDIC years in all patients. Hazard ratios and P values were obtained from the Wald test. The overall treatment effect and adult/adolescent effect were calculated using a 2 degrees of freedom (df) likelihood ratio test. The proportion reduction in the magnitude of Madalla R^2 based on the value of the χ^2 from the likelihood ratio test was used to describe the proportion of variation in risk (difference in metabolic memory between adults and adolescents) explained by the A1C levels (13,17,18). All analyses were performed using SAS Version 9.1.

RESULTS

Subject follow-up. Of the 1,441 subjects (195 adolescents) originally enrolled in the DCCT, 1,375 (175 adolescents) were available at the conclusion of DCCT and enrolled in the EDIC study; 1,208 subjects (170 adolescents) were evaluated for retinopathy at EDIC year 4; and 1,211 subjects (156 adolescents) were evaluated at EDIC year 10. The prevalence analyses reported here are limited to the 1,211 subjects (156 adolescents) with a year-10 retinopathy evaluation.

The characteristics of these 1,211 subjects are summarized in Table 1. Compared with adults, at DCCT baseline adolescents were more likely to be from the primary prevention cohort, have higher A1C, and have milder retinopathy. They also had longer DCCT follow-up, higher DCCT mean A1C, more severe retinopathy, and higher albumin excretion rate (AER) levels at DCCT closeout. At DCCT entry, there were no significant differences between INT and CON groups in any of the risk factors reported in Table 1 in either the adult or adolescent cohort. At DCCT closeout (equivalent to EDIC entry), treatment group differences were seen in adults for the distribution of retinopathy severity, the need for photocoagulation, and microalbuminuria (AER >40 mg/24 h). In adolescents, there was a similar (but nonsignificant) shift toward milder levels in overall distribution of retinopathy severity in the INT group (the risk of sustained 3-step progression was significantly reduced in the INT group in adolescents during DCCT as reported earlier [2]), but there was no difference in rates of photocoagulation, or AER levels. Mean A1C levels during DCCT and across DCCT and EDIC combined were significantly lower in the INT group in both adults and adolescents.

Treatment and metabolic outcomes. During the 10 years of EDIC follow-up, diabetes management was similar between former DCCT CON and INT groups. At EDIC year 10, the majority of patients were using intensive therapy, either continuous subcutaneous insulin infusion or multiple daily insulin injections (Table 1). In addition, more than half of the patients were self-monitoring blood glucose more than three times a day except in the CON adolescents (39%).

As shown in Table 1, there was no difference in A1C at DCCT baseline between INT and CON groups in either adolescents or adults, but the DCCT baseline A1C was higher in the adolescents (9.6 vs. 9.0% in adults, $P < 0.0001$). As previously reported, the A1C was reduced in the INT compared with the CON group during DCCT in both age groups. However, adolescents had higher DCCT mean A1C levels than the adult cohort in both the INT and the CON group (Table 1, $P < 0.0001$). During the EDIC follow-up, mean A1C was similar between adults and adolescents and between former INT and CON subjects (INT adult: 8.0 ± 1.1%; CON adult: 8.1 ± 1.1%; INT adolescent: 8.2 ± 1.3%; CON adolescent: 8.2 ± 2.1%, each $P > 0.05$).

Metabolic memory at EDIC years 4 and 10: prevalence analysis. As previously reported for both the entire DCCT/EDIC cohort (4) and for the adolescent cohort (5), the prevalence of further 3-step progression of retinopathy from end of DCCT at EDIC year 4 was significantly lower in the former INT group than in the former CON group despite similar A1C during this period; this was referred to as metabolic memory. Figure 1 compares the metabolic memory effect on further 3-step progression at 4 and 10 years of EDIC follow-up between adolescents and adults who were free of scatter photocoagulation during DCCT and had retinopathy evaluations at EDIC years 4 and 10. At EDIC year 10, prolonged beneficial treatment effect continued to be observed in the adult cohort. The prevalence of further 3-step progression was 22% in the INT adults and 41% in the CON adults, with odds reduction of 57% (CI: 43–67%) in INT versus CON ($P < 0.0001$); this is attenuated compared with that at EDIC year 4 (odds reduction: 72%; 95% CI: 57–82%; $P < 0.0001$). In the adolescent cohort, however, there was no longer evidence of metabolic memory. After 10 years of EDIC follow-up, 40% of both the INT and CON adolescents had further retinopathy progression (odds reduction: 0%; 95% CI: −88 to 49%; $P = 0.9500$) compared with 23% in CON and 8% in INT 4 years after DCCT closeout (odds reduction: 72%; 95% CI: 17–90%, $P = 0.0165$). GEE analysis verified that the odds reduction was significantly different between EDIC years 4 and 10 in both the adults ($P = 0.0329$) and adolescents ($P = 0.0071$).

Similar analyses were performed for the other retinopathy outcomes in the adolescents (Table 2) and adults (Table 3). In the adult cohort, the odds for each of these outcomes were significantly lower in the INT group com-

TABLE 1
Characteristics of the 1,211 patients evaluated for retinopathy after 10 years of EDIC follow-up by age (adults vs. adolescents) and DCCT treatment group (INT vs. CON)

	Adolescents (n = 156)			Adults (n = 1,055)		
	CON	INT	P*	CON	INT	P*
n	83	73		532	523	
At DCCT entry						
Women (%)	56.6	46.6	0.2099	44.9	49.9	0.1053
Age (year)	14.8 ± 1.4†	15.1 ± 1.3†	0.0894	28.4 ± 5.6†	28.9 ± 5.7†	0.1957
Primary prevention cohort (%)	67.5†	54.8†	0.1044	48.7†	48.4†	0.9199
Duration of diabetes (year)	4.8 ± 3.4	5.5 ± 3.5	0.1481	5.9 ± 4.2	6.1 ± 4.3	0.4880
AER >40 mg/24 h (%)	7.2	8.2	0.8168	4.7	4.6	0.9321
Severity of retinopathy (%)						
None	67.5†	54.8†	0.1765	48.7†	48.4†	0.0661
Microaneurysms only	21.7	37.0		29.0	34.8	
Mild nonproliferative retinopathy	7.2	6.9		16.9	12.2	
Moderate or severe nonproliferative retinopathy	3.6	1.4		5.5	4.6	
At EDIC entry‡						
DCCT follow-up (year)	7.2 ± 1.9†	7.5 ± 1.9†	0.2088	6.2 ± 1.6†	6.2 ± 1.6†	0.4639
Severity of retinopathy (%)						
None	8.4†	16.4†	0.1004	19.3†	30.2†	**<0.0001**
Microaneurysms only	37.4	42.5		30.8	39.4	
Mild nonproliferative retinopathy	27.7	28.8		27.7	20.5	
Moderate or severe nonproliferative retinopathy	26.5	12.3		22.3	9.9	
Photocoagulation during DCCT (%)						
Scatter, for severe retinopathy	4.8	4.1	0.8308	4.0	1.3	**0.0084**
Focal, for macular edema	1.2	1.4	0.9272	6.0	2.3	**0.0025**
AER >40 mg/24 h (%)	20.7†	20.8†	0.9876	10.8†	5.6†	**0.0021**
AER >300 mg/24 h (%)	4.9†	5.6†	1.0000	2.7†	1.0†	0.0613
Mean blood pressure (mmHg)	87.0 ± 7.8	87.1 ± 9.4	0.7572	88.4 ± 8.8	88.9 ± 8.5	0.3461
Elevated lipid (%)§	12.1	5.5	0.1521	10.3	7.5	0.1005
Treatment at EDIC year 10 (%)						
Continuous subcutaneous insulin infusion (pump) or multiple daily injections	91.0	94.4	0.4223	92.4	96.9	**0.0016**
Self-monitoring of blood glucose ≥4 times/day	38.9	64.5	**0.0018**	61.1	55.8	0.0866
Glycemic control						
A1C at DCCT eligibility (%)	9.5 ± 1.8†	9.6 ± 1.7†	0.4367	8.9 ± 1.6†	9.0 ± 1.5†	0.3439
DCCT mean A1C (%)	9.7 ± 1.2†	8.1 ± 1.1†	**<0.0001**	8.9 ± 1.2†	7.2 ± 0.8†	**<0.0001**
EDIC mean A1C up to year 10 (%)	8.2 ± 2.1	8.2 ± 1.3	0.8892	8.1 ± 1.1	8.0 ± 1.1	0.0713
DCCT-EDIC mean A1C up to year 10 (%)	8.8 ± 1.0	8.2 ± 1.1	**0.0005**	8.4 ± 1.0	7.7 ± 0.9	**<0.0001**

Data are means ± SD unless otherwise indicated. *P values were based on Wilcoxon rank-sum test for quantitative or ordinal variables, or χ^2/Fisher exact test for categoric variables. †$P < 0.05$ for comparison between adolescents and adults as a whole. ‡The baseline data in the EDIC study were the same as the data at the end of the DCCT. §Elevated lipid is defined as two consecutive reports of hypercholesterolemia (LDL cholesterol >160 mg/dl) and/or hypertriglyceridemia (triglycerides >500 mg/dl) within 1 month during DCCT. Data in boldface are statistically significant.

pared with the CON group at DCCT closeout, at EDIC year 4, and at EDIC year 10 (odds reduction: 59–79%, 64–94%, and 48–74%, respectively; all $P < 0.002$), reflecting a strong persistence of metabolic memory all the way through EDIC year 10. In the adolescent cohort, however, metabolic memory did not appear to be present for any of these outcomes at EDIC year 10 and was present only for ≥3-step progression and severe nonproliferative diabetic retinopathy at year 4.

Metabolic memory through EDIC years 4 and 10: cumulative incidence analysis. To further assess metabolic memory, we compared the cumulative incidence of further ≥3-step progression during EDIC from the level at DCCT closeout between former INT and CON treatment groups in adolescents and adults. Separate Weibull proportional hazards regression models were constructed in adolescent and adult groups after adjustment for DCCT primary prevention and secondary intervention cohort, diabetes duration, A1C at DCCT entry, and retinopathy severity at DCCT closeout. The models used evaluations from all years in all eligible subjects, excluding 29 adults and 7 adolescents who underwent scatter photocoagulation in either eye during DCCT. Figure 2 shows the estimated cumulative incidence for each treatment group in adults and adolescents during the first 4 years of EDIC (*A* and *B*) and for the first 10 years of EDIC follow up (*C* and *D*). The Weibull model (Fig. 2) revealed a highly significant beneficial effect of former INT in both adults and adolescents 4 years after the end of DCCT (adjusted hazard reduction 72%, $P < 0.0001$ and 67%, $P = 0.01$, respectively). At EDIC year 10, this highly significant beneficial effect of the former INT therapy was still apparent (adjusted hazard reduction 56%, $P < 0.0001$), although attenuated compared with EDIC year 4, in the adult cohort. In the adolescent cohort, the difference in 10-year cumulative incidence between INT and CON

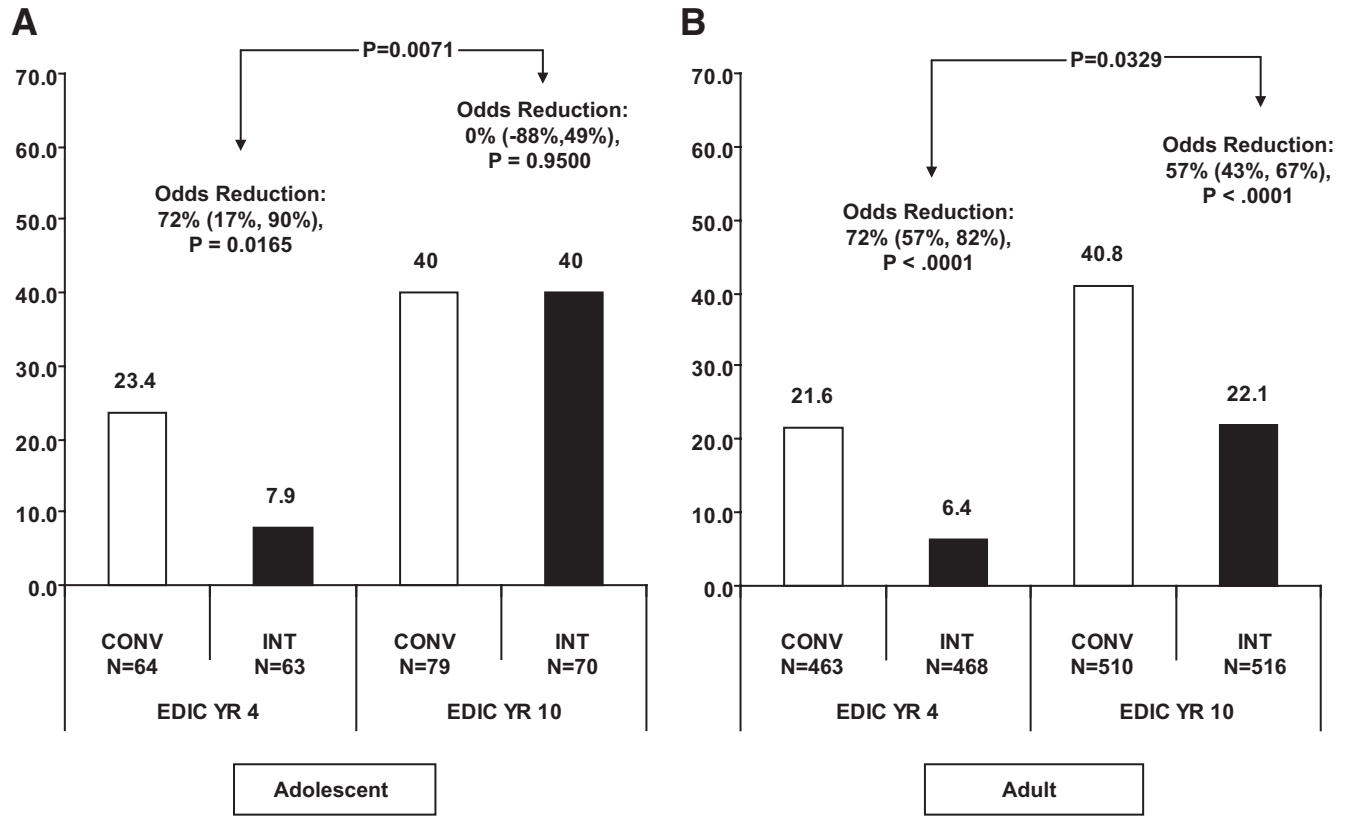

FIG. 1. Prevalence of further 3-step progression of retinopathy from the level at DCCT closeout at years 4 and 10 of EDIC, among patients free of scatter laser photocoagulation during the DCCT and evaluated for retinopathy at EDIC year 10, by DCCT treatment group, for adolescents (*A*) and for adults (*B*). Patients with prior scatter photocoagulation during DCCT (7 adolescents and 29 adults) were excluded. Odds reduction was for intensive therapy (INT) compared with conventional therapy (CON). *P* values are from Mantel-Haenszel test and GEE models.

groups was still in favor of the former INT group, but the adjusted hazard reduction was less pronounced and no longer significant (32%, $P = 0.1399$).

Risk factors for further retinopathy progression. Table 4 examines the risk factors for further retinopathy progression from DCCT closeout in a multivariate Weibull regression model after combining the adult and adolescent cohorts, and including the interaction of treatment (INT/CON) and age (adult/adolescent). The model demonstrates that the risk of further progression of retinopathy increased significantly with higher A1C level at DCCT baseline ($P < 0.0001$) and with higher mean blood pressure and blood lipids at DCCT closeout ($P < 0.0001$). Risk was also associated with retinopathy severity at DCCT closeout; patients with no retinopathy were at greater risk of progression than those with microaneurysms only or mild nonproliferative retinopathy but at lesser risk than those with moderate or severe retinopathy.

As expected from previous results, after controlling for other risk factors, the interaction between DCCT treatment group (INT vs. CON) and age cohort (adolescent vs. adult) remained significant ($P = 0.0381$), indicating that the prolonged treatment effect on metabolic memory differed by age. Likewise, this also indicates that the age effect differed by treatment group. In the former INT group, the hazard ratio (HR) of adolescent versus adult was 1.7 ($P = 0.0078$), indicating that INT adolescents had 70% higher risk of developing further 3-step progression in retinopathy than the INT adults after adjustment for the other risk factors. In the former CON group, however, the HR was 1.0, indicating that CON adolescents had the same risk of further retinopathy progression as CON adults. The overall age (adolescent vs. adult) effect ($P < 0.0001$; df = 2) and the overall treatment (INT vs. CON) effect ($P = 0.0290$; df = 2) on retinopathy progression are both significant.

Relationship of hyperglycemia (A1C) to metabolic memory difference between adults and adolescents. To determine how much of the metabolic memory difference between adolescents and adults could be attributed to the mean A1C levels achieved during DCCT and during EDIC, separate Weibull models (as in Table 4) were constructed with and without further adjustment for mean A1C during DCCT or across DCCT and EDIC combined (Table 5). These models show that 79% of the metabolic memory difference between adults and adolescents ($P = 0.0385$) is attributed to the difference in mean A1C level during DCCT (8.1 vs. 8.9 for the combined INT and CON adults vs. adolescents, respectively), and 86% is attributed to mean A1C difference across DCCT and EDIC combined (8.0 vs. 8.4 for the combined INT and CON adults vs. adolescents, respectively). Furthermore, given the difference in effect of age in the two treatment groups, as shown in Table 4, similar Weibull models were constructed in the INT and CON groups separately. In the INT group, 93% of the observed difference in further retinopathy progression between INT adults and adolescents ($P = 0.0155$) was explained by their mean A1C difference in DCCT (7.2 vs. 8.1%). However, in the CON group, the age effect was not significant ($P = 0.8848$), indicating that CON adults and CON adolescents had similar risk of further retinopathy

TABLE 2
Retinopathy outcomes during the first 4 and 10 years of EDIC follow-up among adolescents free of that outcome at DCCT closeout who had retinopathy evaluated at EDIC year 10

	DCCT closeout				EDIC year 4				EDIC year 10			
Retinopathy outcome*	INT†	CON†	Odds reduction (95% CI)‡	*P*	INT	CON	Odds reduction (95% CI)‡	*P*	INT	CON	Odds reduction (95% CI)‡	*P*
≥Three-step progression from DCCT baseline (%)	26.0	48.2	62 (23–81)	**0.0044**	19.2	45.5	71 (23–90)	**0.0144**	50.9	53.4	10 (−104 to 60)	0.8395
n	73	83			47	33			53	43		
SNPDR+ (%)	5.5	7.2	23 (−177 to 80)	0.6572	1.6	16.1	91 (31–98)	**0.0085**	11.6	19.5	46 (−37 to 79)	0.2560
n	73	83			62	62			69	77		
PDR+ (%)	5.5	7.2	23 (−177 to 80)	0.6562	1.6	9.7	85 (−32 to 98)	0.1143	11.6	18.2	41 (−52 to 77)	0.3550
n	73	83			62	62			69	77		
CSME (%)	5.5	2.7	−108 (−1,076 to 63)	0.8986	3.2	1.7	−96 (−2,122 to 83)	1.000	11.6	6.9	−75 (−488 to 45)	0.3932
n	73	74			62	60			69	72		
Photocoagulation therapy (focal or scatter) (%)	5.5	4.8	−15 (−376 to 72)	0.8520	0.0	5.1	NA	0.1233	7.3	17.7	64 (−11 to 88)	0.0834
n	73	83			69	79			69	79		

*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. †INT is the former DCCT intensive group and CON is the former DCCT conventional group. ‡The odds reduction is for intensive therapy compared with conventional therapy. CSME, clinically significant macular edema; PDR+, proliferative diabetic retinopathy or worse; SNPDR+, severe nonproliferative retinopathy or worse. Data in boldface are statistically significant.

progression despite a significant difference in the DCCT mean A1C (9.7 vs. 8.9%).

To further examine the relationship of DCCT mean A1C and retinopathy progression between the treatment groups and adult/adolescent cohorts, separate Weibull models were constructed in the INT and CON groups, after further adjusting for A1C and the interaction of age (adult vs. adolescent) and A1C. In each treatment group of each age cohort, the risk of further retinopathy progression increases with the DCCT mean A1C (adjusted HR per 10% increase in A1C, e.g., 8–8.8, 1.5 or greater in each of the four categories, $P < 0.003$ in each).

Interestingly, in the INT group, but not in the CON group, the association between DCCT mean A1C and risk of retinopathy progression between DCCT closeout and EDIC year 10 was stronger in adults than in adolescents (Fig. 3). In the INT group, HRs per 10% increase in A1C were 2.2 in adults and 1.5 in adolescents (and per 10% decrease were 0.42 and 0.62, respectively) ($P = 0.0140$). In the CON group, corresponding HRs were 1.6 (increase) and 0.59 (decrease), respectively, for adults and adolescents.

DISCUSSION

The EDIC study demonstrated the surprising and unexpected phenomenon that the benefits of improving glycemic control on the development and progression of retinopathy (4,5) persisted for 4 years after completion of the DCCT, despite A1C levels that were similar in the two former treatment groups (metabolic memory). The benefits of INT therapy and improved glycemic control were substantial and similar in both adults and adolescents during and for up to 4 years after the end of DCCT, although adolescents had higher A1C as well as higher rates of hypoglycemia (4,5) during DCCT.

In contrast, after 10 years of EDIC follow-up, the different metabolic memory effect between adults and adolescents presented here indicates that lower A1C during INT intervention is an important determinant of the long-term durability of its benefits. Indeed, the difference in DCCT mean A1C between adults and adolescents (8.1 vs. 8.9%) explains 79% of the observed difference in the metabolic memory effect on further retinopathy progression between adults and adolescents after 10 years of EDIC follow-up. Examining the A1C information further (Table 1), adolescents started with a higher mean A1C level than adults at DCCT enrollment in both the INT (9.6 vs. 9.0%) and CON (9.5 vs. 8.9%) groups, and A1C remained higher in both groups during the entire DCCT period (8.1 vs. 7.2% in INT; 9.7 vs. 8.9% in CON). It was only during the EDIC follow-up that the mean A1C between adolescents and adults, as well as between former INT and CON groups, converged.

Interestingly, although the CON adolescents had higher A1C levels than the CON adults at DCCT enrollment (9.5 vs. 8.9%) and during the entire DCCT period (9.7 vs. 8.9%), the hazard of further retinopathy progression did not differ between CON adolescents and adults (adjusted hazard reduction 1.0) 10 years after the end of DCCT after adjustment for the other risk factors. However, with a similar trend of higher A1C in INT adolescents than in INT adults at DCCT enrollment (9.6 vs. 9.0%) and during DCCT (8.1 vs. 7.2%), INT adolescents had significantly higher risk of retinopathy progression at 10 years compared with the INT adults (adjusted hazard reduction 1.7, $P = 0.0078$), and 93% of the observed difference between the two age

TABLE 3
Retinopathy outcomes during the first 4 and 10 years of EDIC follow-up among adults free of that outcome at DCCT closeout who had retinopathy evaluated at EDIC year 10

	DCCT closeout				EDIC year 4§				EDIC year 10§			
Retinopathy outcome*	INT†	CON†	Odds reduction (95% CI)‡	*P*	INT	CON	Odds reduction (95% CI)‡	*P*	INT	CON	Odds reduction (95% CI)‡	*P*
≥Three-step progression from DCCT baseline (%)	8.6	30.8	79 (70–85)	**<0.0001**	11.4	26.7	64 (47–76)	**<0.0001**	29.3	44.3	48 (31–61)	**<0.0001**
n	523	532			431	330			475	368		
SNPDR+ (%)	2.1	7.0	71 (43–86)	**0.0002**	2.2	10.2	81 (62–90)	**<0.0001**	6.3	19.6	73 (58–82)	**<0.0001**
n	523	532			464	449			512	495		
PDR+ (%)	2.1	6.8	71 (41–85)	**0.0002**	1.7	9.3	83 (63–92)	**<0.0001**	6.1	19.6	74 (59–83)	**<0.0001**
n	523	532			464	450			512	496		
CSME (%)	3.7	8.4	59 (28–76)	**0.0014**	0.4	7.5	94 (77–99)	**<0.0001**	5.2	14.1	66 (46–79)	**<0.0001**
n	516	510			450	429			497	468		
Photocoagulation therapy (focal or scatter) (%)	3.1	8.5	66 (38–81)	**0.0002**	1.0	6.4	85 (61–94)	**<0.0001**	4.9	16.8	74 (59–84)	**<0.0001**
n	523	532			507	487			507	487		

*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. †INT is the former DCCT intensive group and CON is the former DCCT conventional group. ‡The odds reduction is for intensive therapy compared with conventional therapy. §*n* at EDIC years 4 and 10 is limited to those free of particular events at DCCT closeout. Data in boldface are statistically significant.

groups in the former INT therapy was explained by their difference in DCCT mean A1C. Further analysis reveals that INT adults are more sensitive to the A1C in DCCT than the INT adolescents. Because INT adults have lower A1C levels than the INT adolescents (7.2 vs. 8.1), a higher sensitivity means a greater hazard reduction (58 vs. 38% per 10% decrease in A1C) and a better treatment effect in the INT adults. Therefore, the lower A1C during DCCT and the higher sensitivity of retinopathy progression to the DCCT mean A1C in the INT adults than in the INT adolescents are likely the driving force of the long-term durability of the benefits of intensive therapy. That is, the reduced ability to maintain glycemic levels as close to normal as possible during DCCT in the INT adolescents compared with INT adults and the lower sensitivity of the INT adolescents to the A1C level during DCCT account for the differing duration of metabolic memory in retinopathy progression between adolescents and adults 10 years after the end of DCCT. These data provide further compelling evidence that the metabolic memory phenomenon is largely driven by the prior levels of glycemic control achieved. However, the mechanism for the metabolic memory phenomenon is not well understood.

It should be noted that the persistent adverse effects of hyperglycemia and the long-term beneficial effects of lowering glycemia on the development and progression of complications have also been shown in animal models of diabetes (19), in which it has also been termed metabolic memory. One possible explanation for the metabolic memory phenomenon is the slow accumulation, and subsequent slow degradation, of advanced glycation end products (AGEs) (20). Indeed, DCCT patients in the INT group had lower concentrations of these AGEs in skin collagen than did patients in the CON group (21). The levels of these skin collagen AGEs were also shown to be associated with the subsequent increase in progression of retinopathy (and nephropathy) over the first 10 years of EDIC (22). The finding that the metabolic memory effect appears to be waning between EDIC years 4 and 10 in the entire cohort (7) and in the adult cohort (data reported here) and is no longer present in the adolescent cohort may be the result of a combination of clearance of the long-lasting AGEs in the former CON group and the accumulation of AGEs in the former INT group. There are currently no direct data to prove this speculation, and comparison of AGEs between adult and adolescent cohorts of DCCT/EDIC is not currently available. However, in the near future, measurements of skin fluorescence may provide data related to this speculation.

Another possible, but equally speculative, mechanism by which prior glycemic control could have persistent effects on development and progression of diabetes complications is by epigenetic mechanisms. The phenomenon of epigenetics refers to the chemical modification of cellular DNA or nuclear histones by factors in the internal environmental milieu of the individual. Persistent changes in key chromatin histone methylation could be induced by hyperglycemia and result in sustained dysregulation (expression or repression) of gene expression for long periods of time. Epigenetic chromatin regulation of cellular transcription can operate at both the local (that is, single gene) level and at a global level over a period of time, affecting multiple chromosomal domains. With the initiation of the EDIC Epigenetics study, epigenetic modifications of chromatin and alterations of gene expression that could persist for a long period of time are being evaluated.

Despite the demonstrated differences in metabolic memory at 10 years between adult and adolescent cohorts, a few limitations must be acknowledged. First, the sample size of the adolescent cohort is small relative to the adult cohort, providing less power to demonstrate a significant effect should it exist in this age group. The small sample size of the adolescent cohort will not affect our conclusion related to the primary outcome of this study, further 3-step progression from DCCT closeout, because the odds reduction at EDIC year 10 for adolescents was 0% (Fig. 1). We cannot, however, rule out a type 2 error in other retinopathy outcomes, such as severe nonproliferative diabetic retinopathy or worse, proliferative diabetic retinopathy, or photocoagulation therapy (odds reduction: 46, 41, and

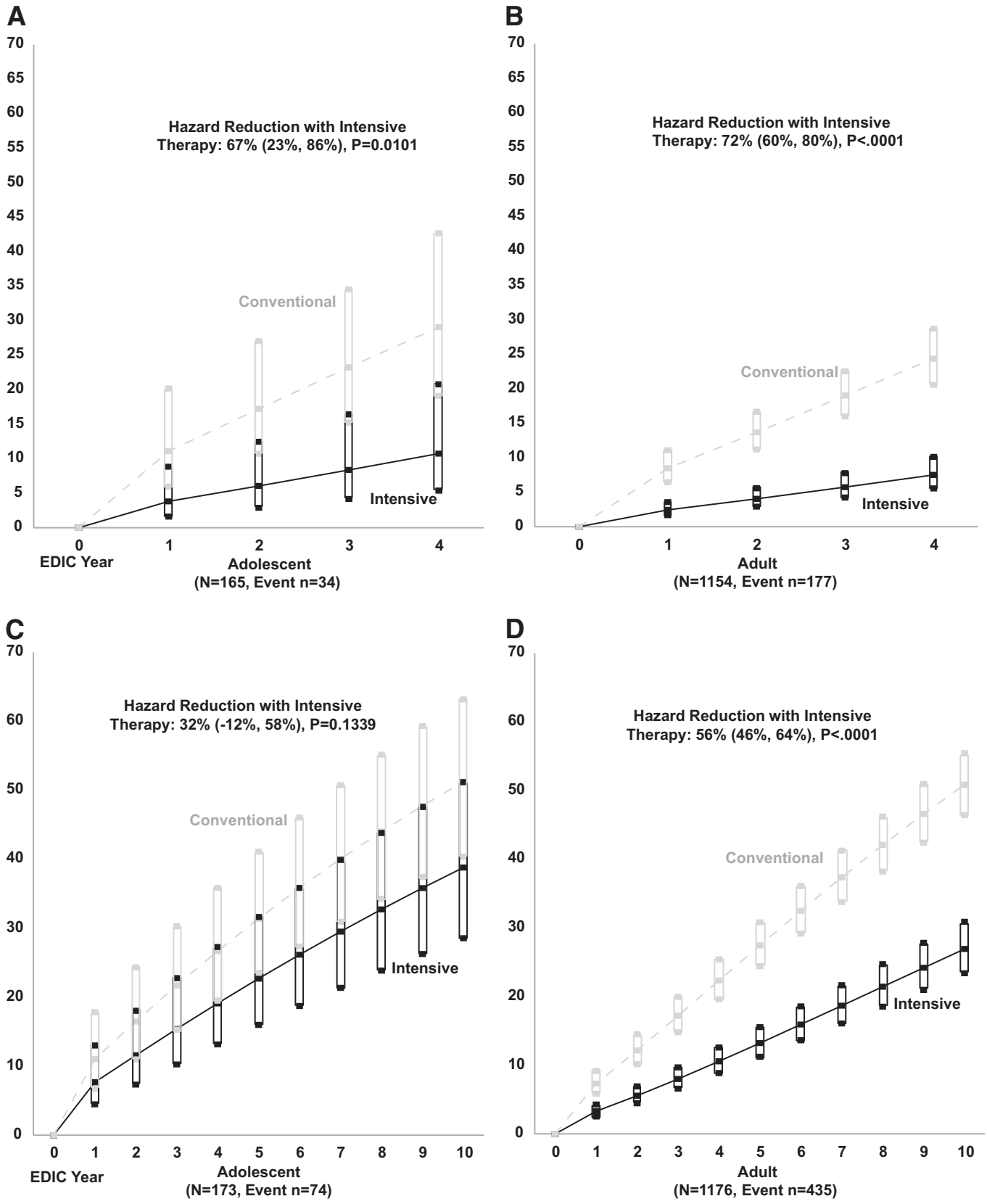

FIG. 2. Estimated cumulative incidence of further 3-step progression of retinopathy from DCCT closeout, by DCCT treatment group, through EDIC year 4, for adolescents (*A*) and for adults (*B*); through EDIC year 10, for adolescents (*C*) and for adults (*D*). Subjects with prior scatter photocoagulation during DCCT (7 adolescents and 29 adults) were excluded from analyses. Based on Weibull regression models adjusted for the level of retinopathy at the end of the DCCT, primary vs. secondary cohort, the A1C value on entry to the DCCT, and diabetes duration at DCCT baseline. Hazard reduction was for intensive therapy compared with conventional therapy.

TABLE 4
Risk factor analysis for further retinopathy progression from DCCT closeout through EDIC year 10 Weibull model with interval censoring

Covariate	χ^2	*P*	HR (95% CI)*
At DCCT entry			
Type 1 diabetes duration (year)†	3.2	0.0762	0.97 (0.94–0.02)
Primary vs. secondary cohort	0.0	0.9494	1.01 (0.77–1.32)
A1C level at DCCT eligibility (%)	38.0	**<0.0001**	1.19 (1.12–1.25)
At EDIC entry‡			
Retinopathy level			
Microaneurysms only vs. no retinopathy	24.3	**<0.0001**	0.53 (0.41–0.68)
Mild nonproliferative vs. no retinopathy	13.2	**0.0003**	0.58 (0.43–0.78)
Moderate or severe vs. no retinopathy	3.9	**0.0496**	1.41 (1.33–2.24)
Mean blood pressure (mmHg)†§	18.6	**<0.0001**	1.12 (1.06–1.17)
Elevated lipid (yes vs. no)‖	16.6	**<0.0001**	1.72 (1.33–2.24)
Age (adolescent vs. adult) at DCCT enrollment	7.1	**0.0079**	—
DCCT treatment group (CT vs. INT)	1.7	0.1928	—
DCCT treatment group by age (adolescent vs. adult)	4.3	**0.0381**	—
Treatment effect (CON vs. INT)			
In adult cohort: CON vs. INT (df = 1)	64.3	**<0.0001**	2.3 (1.9–2.9)
In adolescent cohort: CON vs. INT (df = 1)	1.7	0.1927	1.4 (0.9–2.2)
Overall treatment effect: CON vs. INT (df = 2)	7.1	**0.0290**	
Age effect (adolescent vs. adult)			
In INT group: adolescent vs. adult (df = 1)	7.1	**0.0078**	1.7 (1.1–2.5)
In CT group: adolescent vs. adult (df = 1)	0.0	0.9737	1.0 (0.7–1.4)
Overall age effect (adolescent vs. adult) (df = 2)	65.3	**<0.0001**	
Model log likelihood	−1,445.2		

*HR is the ratio of hazard of retinopathy progression for a 1-unit increase in quantitative variables or change in status for dichotomous variables if without notation. †HR is based on a 5-unit increase in type 1 diabetes duration (year)/mean blood pressure (mmHg). ‡The EDIC entry data are the same as DCCT closeout data. §Mean blood pressure = 2/3 diastolic blood pressure + 1/3 systolic blood pressure. ‖Elevated lipid is defined as two consecutive reports of hypercholesterolemia (LDL cholesterol >160 mg/dl) and/or hypertriglyceridemia (triglycerides >500 mg/dl) within 1 month during DCCT. Data in bold face are statistically significant.

64%, respectively) (Table 2), due to the low power (20–40%) engendered by the small sample size of adolescents. Second, 18% of the adults and 25% of the adolescents who enrolled in the DCCT did not have a retinopathy assessment after 10 years of EDIC follow-up. Among these nonparticipants, 5 adolescents and 33 adults died prior to EDIC year 10. Further analyses (supplementary Table 1, available in an online appendix at http://diabetes.diabetesjournals.org/cgi/content/full/db09-1216/DC1) indicated that participants and nonparticipants are similar in treatment group, age, sex, diabetes duration, A1C, retinopathy levels, blood pressure, and lipids in the adult cohort, and similar in the majority of characteristics in the adolescent cohort except that the 10-year adolescent participants were slightly older at DCCT entry (14.9 vs. 14.2 years; $P = 0.0034$) and had worse retinopathy ($P = 0.0301$) at DCCT closeout. A possible reason may be that patients with milder retinopathy pay less attention to the monitoring of their retinopathy levels. How-

TABLE 5
Proportion of difference in metabolic memory between adults and adolescents after 10 years of EDIC follow-up explained by DCCT and EDIC mean A1C

Model*	Effect	χ^2	*P*	Proportion explained (%)†
Overall				
Unadjusted for A1C	DCCT treatment group by age (adolescent vs. adult) interaction effect‡	4.2	0.0385	
Adjusted for DCCT mean A1C	DCCT treatment group by age (adolescent vs. adult) interaction effect	0.9	0.3448	79
Adjusted for DCCT-EDIC mean A1C	DCCT treatment group by age (adolescent vs. adult) interaction effect	0.6	0.4412	86
INT only§				
Unadjusted for A1C	Age effect (adolescent vs. adult)	5.9	0.0155	
Adjusted for DCCT mean A1C	Age effect (adolescent vs. adult)	0.4	0.5071	93
CON only§				
Unadjusted for A1C	Age effect (adolescent vs. adult)‖	0.0	0.8848	

*All the models (unadjusted and adjusted) were from Weibull model after adjustment for all the risk factors in Table 3. A1C during DCCT or across DCCT and EDIC combined was further adjusted in the adjusted models. †Proportion explained; see "Statistical analyses" section. ‡The interaction term of DCCT treatment group and age (adolescent vs. adult) measures the difference in prolonged treatment effect (metabolic memory) between adults and adolescents. §Model used was from the same Weibull model in Table 3 but constructed within the INT and CON group, respectively. ‖Because there is no age (adolescent vs. adult) effect in the unadjusted model, there is no need to further adjust for A1C.

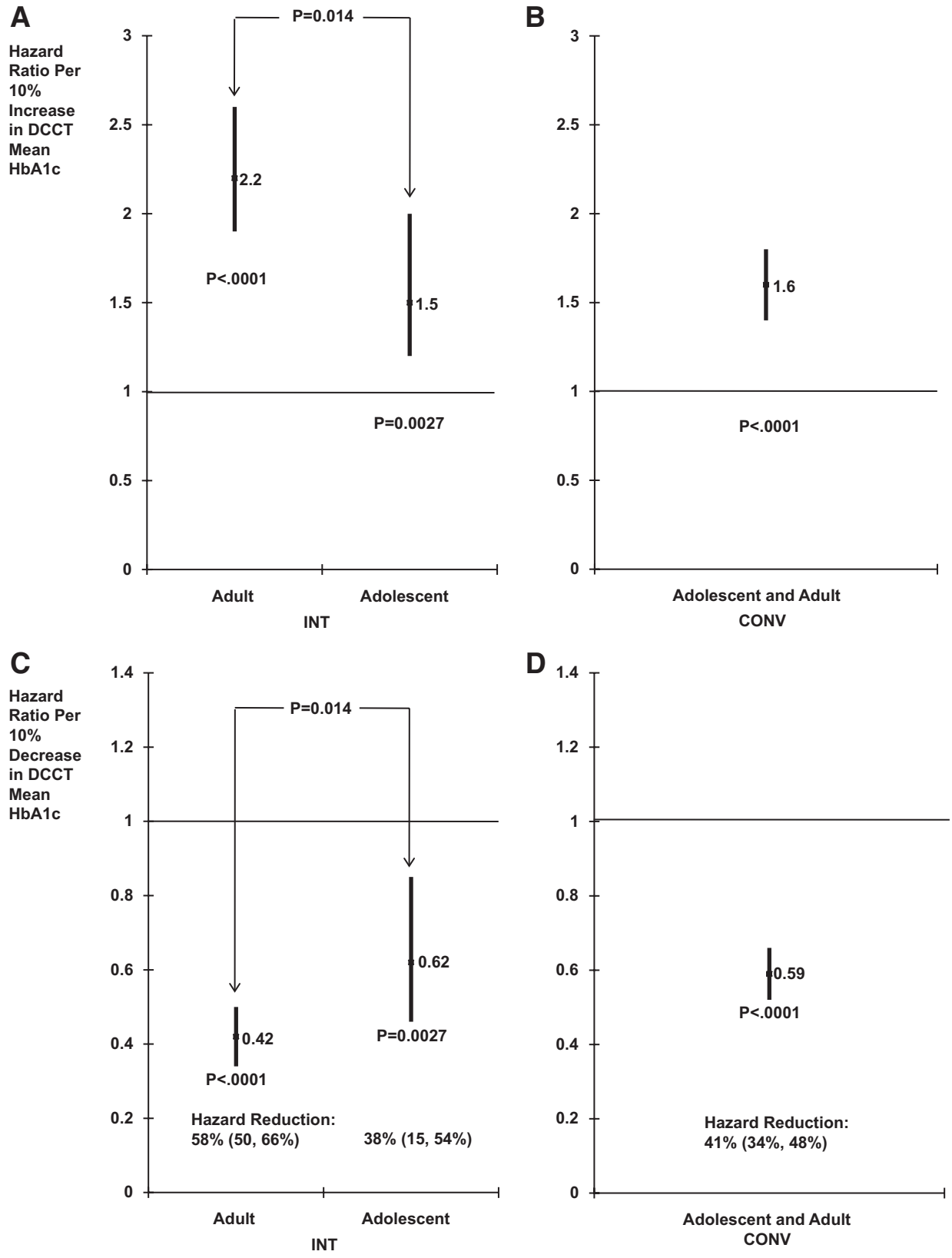

FIG. 3. Sensitivity of further retinopathy progression in EDIC to difference in DCCT mean A1C for adolescents and adults, for a 10% increase in A1C in INT (*A*) and CON (*B*), and a 10% decrease in A1C in INT (*C*) and CON (*D*). Based on separate Weibull regression models in INT and CON, adjusted for the level of retinopathy at the end of the DCCT, primary vs. secondary cohort, A1C value on entry to the DCCT, diabetes duration at DCCT baseline, log transformation of DCCT mean A1C, age (adult vs. adolescent), and interaction of DCCT mean A1C and age.

ever, because the treatment group is balanced between participants and nonparticipants, this observed slight imbalance should not bias the conclusion in this study.

The DCCT/EDIC studies have shown that intensive treatment directed at achieving blood glucose and A1C levels as close to normal as safely possible without severe hypoglycemia, and starting as early in the course of diabetes as safely possible, is vital for achieving sustained reductions of diabetic retinopathy. The results of the present analyses reinforce the need to maintain A1C at target values for as long as possible and demonstrate the waning benefits over time in the face of higher A1C levels.

ACKNOWLEDGMENTS

The DCCT/EDIC project is supported by contracts with the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) the National Eye Institute, the National Institute of Neurological Disorders and Stroke, the General Clinical Research Centers Program and Clinical and Translational Science Awards Program, National Center for Research Resources, and Genentech through a Cooperative Research and Development Agreement with the NIDDK.

Contributors of free or discounted supplies and/or equipment: Lifescan, Roche, Aventis, Eli Lilly, OmniPod, Can-Am, B-D, Animas, Medtronic, Medtronic Minimed, Bayer (one-time donation, 2008), Omron.

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

REFERENCES

1. 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. EDIC Research Group. 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. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. 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 among adolescents: 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. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA 2003;290:2159–2167
7. White NH, Sun W, Cleary PA, Danis RP, Davis MD, Hainsworth DP, Hubbard LD, Lachin JM, Nathan DM. Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes: 10 years after the Diabetes Control and Complications Trial. Arch Ophthalmol 2008;126:1707–1715
8. Steffes M, Cleary P, Goldstein D, Little R, Wiedmeyer HM, Rohlfing C, England J, Bucksa J, Nowicki M, the DCCT/EDIC research group. Hemoglobin A1c measurements over nearly two decades: sustaining comparable values throughout the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study. Clin Chem 2005;51:753–758
9. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial: Diabetes Control and Complications Trial Research Group. Ophthalmology 1995;102:647–661
10. The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus: The Diabetes Control and Complications Trial. Arch Ophthalmol 1995;113:36–51
11. Snedecor GW, Cochran WG. *Statistical Methods*. 6th ed. Ames, Iowa, Iowa State University Press, 1980
12. Agresti A. *Categorical Data Analysis*. New York, NY, John Wiley & Sons, 1990
13. Lachin JM. *Biostatistical Methods: The Assessment of Relative Risks*. New York, NY, John Wiley & Sons, 2000
14. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22
15. 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
16. Sparling YH, Younes N, Lachin JM, Bautista OM. Parametric survival models for interval-censored data with time-dependent covariates. Biostatistics 2006;7:599–614
17. Madalla, GS. *Limited-Dependent and Qualitative Variables in Econometrics*. Cambridge, U.K., Cambridge University Press, 1983
18. Magee L. R2 measures based on Wald and likelihood ratio joint significance tests. Am Statistician 1990;44:250–253
19. Engerman RL, Kern TS. Progression of incipient diabetic retinopathy during good glycemic control. Diabetes 1987;36:808–812
20. Vlassara H, Bucala R, Striker L. Pathogenic effects of advanced glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. Lab Invest 1994;70:138–151
21. Monnier VM, Bautista O, Kenny D, Sell DR, Fogarty J, Dahms W, Cleary PA, Lachin J, Genuth S, and the DCCT Skin Collagen Ancillary Study Group. Skin collagen glycation, glycoxidation, and crosslinking are lower in subjects with long-term intensive versus conventional therapy of type 1 diabetes: relevance of glycated collagen products versus HbA1c as markers of diabetic complications. Diabetes 1999;48:870–880
22. Genuth S, Sun W, Cleary P, Sell DR, Dahms W, Malone J, Sivitz W, Monnier VM, for the DCCT Skin Collagen Ancillary Study Group. Glycation and carboxymethyllysine levels in skin collagen predict the risk of future 10-year progression of diabetic retinopathy and nephropathy in the Diabetes Control and Complications Trial and epidemiology of diabetes interventions and complications participants with type 1 diabetes. Diabetes 2005;54:3103–3111