Diabetic Retinopathy and Other Ocular Findings in the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications Study

*Lloyd Paul Aiello, for the DCCT/EDIC Research Group**

OBJECTIVE

To evaluate whether intensive treatment (INT) with the goal of achieving blood glucose levels as close to the nondiabetic range as safely possible reduced the risk of onset and progression of diabetic retinopathy (DR) in subjects with type 1 diabetes (T1D) compared with conventional therapy (CON).

RESEARCH DESIGN AND METHODS

The Diabetes Control and Complications Trial (DCCT) (1982–1993) was a multicenter, controlled clinical trial comparing INT with CON for onset and progression of DR. The Epidemiology of Diabetes Interventions and Complications (EDIC) study (1994–present) is an observational follow-up of the DCCT cohort.

RESULTS

Of the 1,441 DCCT subjects, 726 had no DR (primary prevention cohort) and 715 had mild DR (secondary intervention cohort) at baseline. Subjects were followed for a mean of 6.5 years. INT median HbA_{1c} was 7% compared with CON median of 9%. INT reduced the adjusted mean risk for the development of DR by 76% and slowed progression of DR by 54% compared with CON. Following DCCT, the HbA_{1c} levels in the original INT and CON groups converged (year 8, INT 7.98%; CON 8.07%); nevertheless, the groups continued to have a durable effect of initial assigned therapy with significantly lower incidence of further DR progression in the INT group (hazard reduction 53–56%). Severe retinal outcomes and procedures to treat them were reduced by 50% in the original INT group.

CONCLUSIONS

INT delays the onset and slows the progression of DR. Furthermore, the early effects of metabolic control continue to accrue over many years despite subsequent comparable glycemic control (metabolic memory). These results emphasize the need for optimizing glycemic control as early as possible in patients with diabetes.

Diabetes Care 2014;37:17–23 | DOI: 10.2337/dc13-2251

Beetham Eye Institute, Joslin Diabetes Center, and Department of Ophthalmology, Harvard Medical School, Boston, MA

Corresponding author: Lloyd Paul Aiello, lpaiello@joslin.harvard.edu.

Received 24 September 2013 and accepted 3 October 2013.

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

**A complete list of participants in the DCCT/EDIC Research Group can be found in N Engl J Med 2011;365:2366–2376.*

See accompanying articles, pp. 5, 8, 9, 24, 31, 39, and 44.

In 1916, despite the absence of data or the means of effectively controlling glucose levels, Elliott P. Joslin recommended diet, exercise, and medical blood glucose control as the three avenues to live well and reduce the risk of complications from diabetes (1). In the postinsulin era, controversy surrounded the recommendation to reduce the risk of diabetes complications by maintaining intensive control of blood glucose levels until 1993 when the Diabetes Control and Complications Trial (DCCT) conclusively demonstrated that intensive control of blood glucose levels significantly reduced the risk of microvascular complication for persons with type 1 diabetes (T1D) (2).

The DCCT was designed to evaluate whether intensive treatment (INT), with the goal of achieving blood glucose levels as close to the nondiabetic range as safely possible, reduced the risk of onset and progression of microvascular complications of T1D compared with conventional therapy (CON). At the conclusion of the DCCT, participants were invited to participate in the Epidemiology of Diabetes Interventions and Complications (EDIC) study to assess long-term microvascular and macrovascular outcomes.

This article details the key findings of DCCT and EDIC with regard to diabetic eye disease outcomes as reported to date.

RESEARCH DESIGN AND METHODS

The DCCT was conducted from 1983 to 1993 and enrolled 1,441 subjects. At baseline, all subjects were aged 13–39 years, had T1D for 1–15 years, and had no diabetic retinopathy (DR) (primary prevention cohort) or mild nonproliferative DR (NPDR) with at least one microaneurysm in either eye, but no more than moderate NPDR (secondary intervention cohort). Participants were randomly assigned to INT, requiring three or more insulin injections per day or use of an insulin pump, with doses adjusted based on frequent self-monitoring of blood glucose (SMBG), meal size and content, and exercise levels, or to CON, with one or two insulin injections per day (3). INT was goal-driven, aiming for preprandial SMBG between 70 and 120 mg/dL, postprandial levels $<$180, and HbA_{1c}, measured monthly, $<$6.05%. CON did not have specific SMBG targets and was aimed at being free of symptoms of hyperglycemia. Avoidance of frequent or severe hypoglycemia was a goal of both treatment arms. At the conclusion of the DCCT, 97% (n = 1,394) of the original DCCT cohort joined the EDIC study. A more detailed description of the methods for both the DCCT and EDIC is presented in the article by Nathan (4).

In the DCCT, DR was monitored by 7-field stereoscopic fundus photographs taken by certified photographers every 6 months and graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol (5). Graders at a centralized reading center, masked to treatment group assignment, assessed the photographs for severity level of DR according to ETDRS scales, with a 25-step scale representing the range of DR in each eye (6).

In both the primary prevention group and the secondary intervention group, the development of DR was defined as a three-step or greater change of retinopathy from baseline, sustained for 6 or more months. Additional outcomes included the development of severe or worse NPDR and proliferative DR (PDR) (2,7). In the EDIC study, DR was evaluated as in the DCCT, albeit with a reduced frequency of examinations (8,9). Approximately 25% of the EDIC cohort was photographed each year and the entire EDIC cohort was photographed at years 4 and 10, except for those participants who had previous scatter (panretinal) laser photocoagulation (PRP) in both eyes. The primary outcome was initial occurrence of a three-step or more progression of DR from the termination of the DCCT through the EDIC follow-up using the ETDRS grading scale (5) and DCCT methods (10). Secondary outcomes included the initial occurrence of PDR during EDIC; a three-step or greater progression from DCCT baseline; development of severe NPDR (ETDRS level 53) or worse; development of clinically significant macular edema (CSME); and either PRP or focal laser photocoagulation.

RESULTS

DCCT

Of the 1,441 subjects in the DCCT, at baseline 726 had no DR (primary prevention cohort) and 715 had mild DR (secondary intervention cohort). Subjects were followed for a mean of 6.5 years. At the conclusion of the DCCT, the INT group had a median HbA_{1c} of 7.2% compared with CON median HbA_{1c} of 9.1%. A more detailed description of the participant characteristics for both the DCCT and EDIC has been presented by Nathan (4).

Over the first 3 years of DCCT follow-up, there was little difference between the INT and CON groups in the primary prevention cohort (Fig. 1). In subsequent years, the INT group had delayed onset of DR, and at the conclusion of the DCCT the INT group had a 76% ($P < 0.001$) risk reduction for the development of DR compared with the CON group. In the secondary intervention group (Fig. 2), although there was an initial worsening of DR, by study completion INT reduced the risk of DR progression by 54% ($P < 0.001$) as compared with the CON group (2).

The benefits of INT extended beyond DR progression alone. There were also marked risk reductions in development of PDR (47%), onset of macular edema (26%), and application of laser therapy (56%) (2). There was a 61% risk reduction in the development of severe NPDR in the secondary intervention cohort (Fig. 3). This beneficial effect was evident by year 4 and continued to increase throughout the study. The development of neovascularization of the optic disk or elsewhere was also benefitted by INT during DCCT, with a 48% risk reduction compared with the group receiving CON in the secondary intervention cohort. Again, the benefit of INT became evident by year 4 and continued through study end. INT was also associated with a 23% reduction in risk of developing CSME in the secondary intervention cohort, with observed benefit accruing after year 5.

In the DCCT, the rate of retinopathy progression was highly associated with HbA_{1c} as shown in Fig. 4. For each 10% decrease in HbA_{1c} (e.g., 9.0–8.1%), there is approximately a 44% decreased risk of

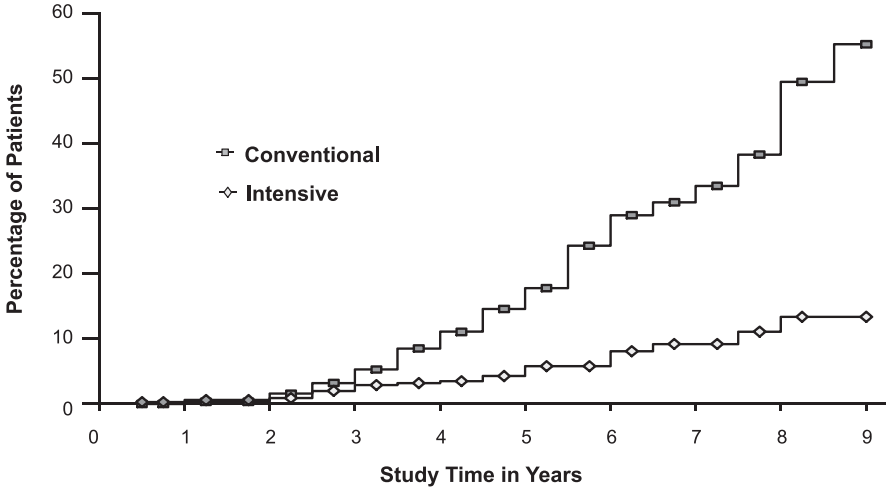

Figure 1—Cumulative incidence of DR progression (three-step or greater by ETDRS criteria [6]) in the DCCT primary prevention cohort. There was little difference in percentage of patients with retinopathy progression between the INT and CON groups over the first 3 years; however, there was a 76% risk reduction for DR progression evident at the conclusion of the DCCT after mean follow-up of 6.5 years (14).

DR progression over the range of HbA_{1c} levels studied (11,12).

Early Worsening

While INT resulted in long-term risk reduction in the progression of DR, increased progression of DR did occur in the first year of follow-up after initiation of INT for some subjects (13). This phenomenon, termed "early worsening," underlies the crossing of the cumulative retinopathy progression curves for INT and CON between 2 and 3 years in the secondary intervention group (Fig. 2). Early worsening occurred most frequently in subjects with more advanced baseline DR, and was predominantly driven by the development of cotton wool spots and intraretinal microvascular abnormalities. Risk factors for early worsening included higher HbA_{1c} levels at entrance to the study, magnitude of HbA_{1c} reduction, duration of diabetes, and the baseline level of DR (13). Early worsening occurred within 12 months in 13.1% of 711 subjects assigned to INT and in 7.6% of 728 subjects assigned to CON. Crossover occurred at 18 months, with 51% of the INT group and 55% of the CON group showing recovery (13). The long-term benefit of INT and the limited risk associated with early worsening in most subjects strongly support the initiation of INT in most cases. Careful retinal monitoring during the initiation of INT, especially in individuals with significant retinopathy or high HbA_{1c} at baseline, may be indicated.

EDIC

During EDIC, all subjects were instructed to use INT, and HbA_{1c} values for the original INT and CON groups converged as described in previous articles in this series (4). Despite the nearly identical mean HbA_{1c} levels between INT and CON during EDIC (~8.0%), the EDIC demonstrated a continued durable effect of initial assigned therapy with significantly lower incidence of further progression of DR and PDR in the INT group. This phenomenon, whereby a

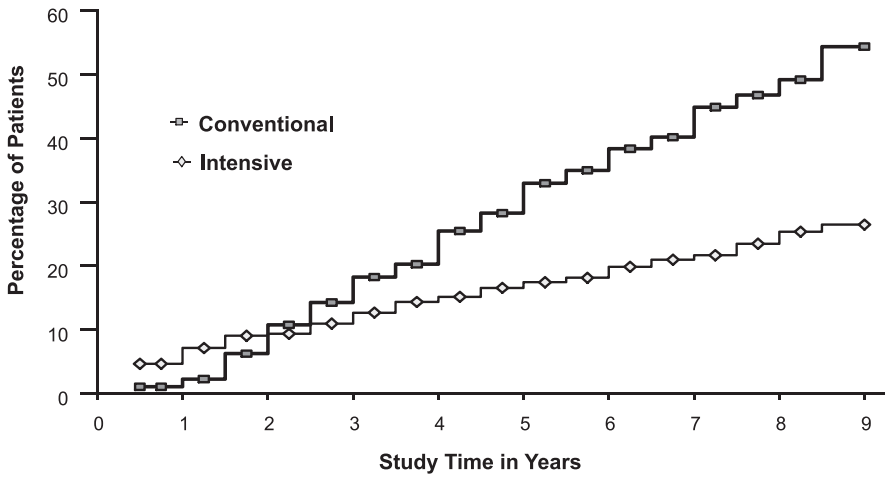

Figure 2—Cumulative incidence of DR progression in the DCCT secondary intervention cohort. By the conclusion of the DCCT, there was a 54% reduction in the risk of retinopathy (≥ three-step) progression in the secondary intervention cohort for those in the INT group as compared with the CON group (11,14).

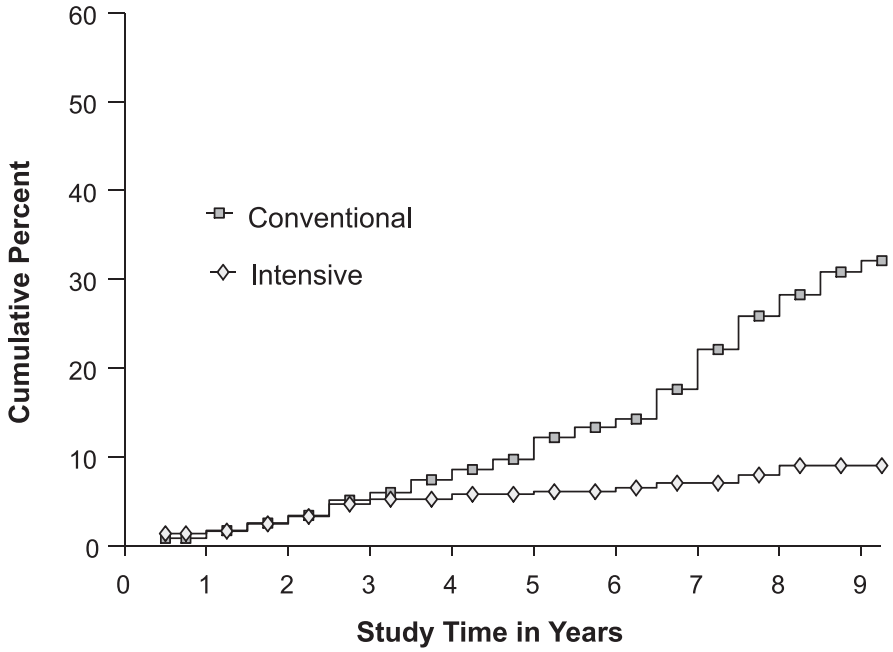

Figure 3—Cumulative incidence for onset of severe NPDR in the DCCT secondary intervention cohort. There was a 61% risk reduction in the development of severe NPDR in the INT cohort compared with the CON cohort.

period of previous glycemic control continues to affect future development of diabetes complications despite subsequent equivalency of HbA_{1c} between groups, was termed "metabolic memory" (8,14).

In the first 4 years of the EDIC observational study, those subjects from the INT group did progressively better than those from the CON group. Starting from the adjusted retinopathy severity present at DCCT closeout, there was a 70% ($P < 0.0001$) risk reduction in DR progression in the initial INT group as compared with those subjects in the CON group (14). This finding represented the first conclusive demonstration of the metabolic memory phenomenon.

In addition, at EDIC year 4, in those subjects free of complications at the end of DCCT, there were also marked risk reductions in development of PDR (55%), onset of macular edema (73%), and application of laser therapy (62%) in the original INT group compared with CON group. The percent of these effects explained by the difference in HbA_{1c} levels between the treatment groups during DCCT was nearly complete, accounting for 99.9% of new-onset PDR, 98.8% of new-onset severe NPDR, 98.0% of new-onset diabetic macular edema, 97.7% of DR severity progression, and 94.3% of new laser surgery (14).

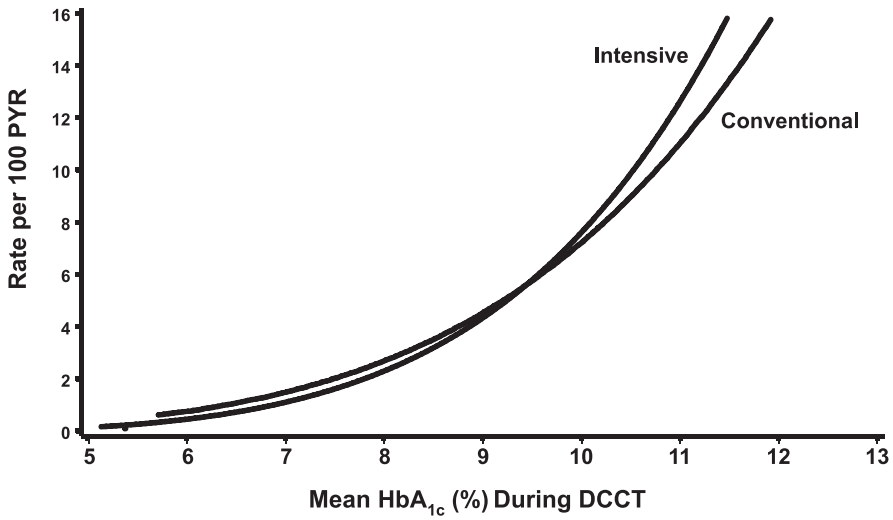

Figure 4—The risk of DR progression as related to mean HbA_{1c} during DCCT. The rate of DR progression per 100 patient-years (100 PYR) was similar and highly associated with HbA_{1c} in the DCCT for both the INT and the CON groups (12).

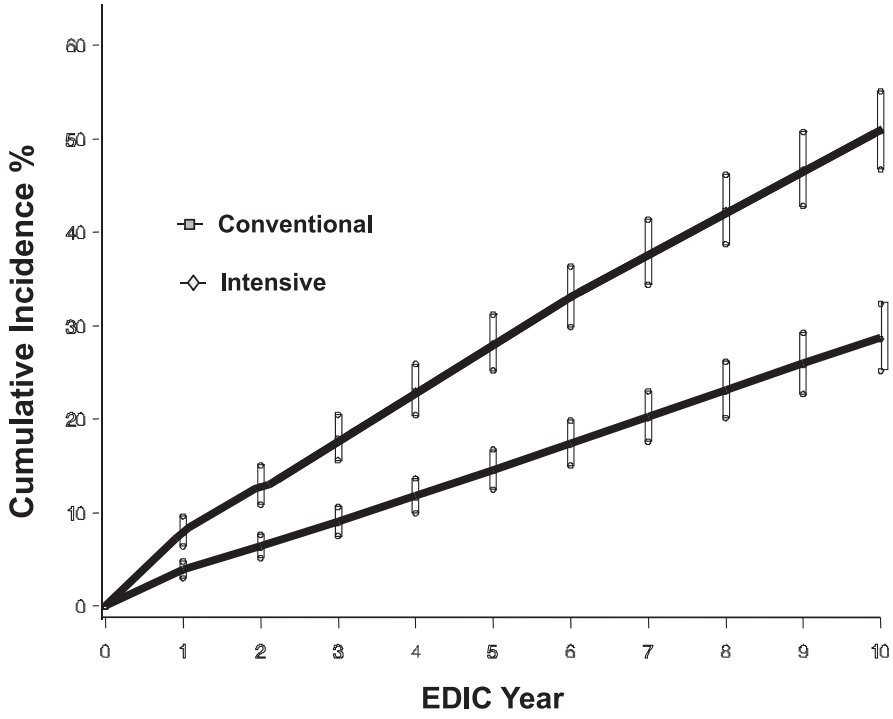

Figure 5—After adjustment for DR severity at DCCT closeout, the cumulative incidence of further DR progression during the first 10 years of EDIC follow-up is shown (8).

INT benefit continued during subsequent follow-up such that at EDIC year 8 the INT group experienced a 63% ($P < 0.0001$) risk reduction in retinopathy progression adjusted for DCCT closeout level as compared with CON. Risk reductions associated with INT exceeded those observed in DCCT for onset of CSME and application of laser.

The longest DCCT/EDIC retinopathy follow-up data released to date reflects one decade of study after the close of the DCCT (8). After 10 years of EDIC observation, the benefit of early INT persisted with a 53% ($P < 0.0001$) reduction in the risk of further retinopathy progression (Fig. 5). Even after this decade of EDIC follow-up, and as observed at the conclusion of the DCCT and at EDIC year 4, the HbA_{1c} difference between the intervention groups during DCCT explained the majority of the retinopathy progression benefit (97.7% at EDIC year 4, 89.3% at EDIC year 10) (8).

While the primary outcome in EDIC was the initial occurrence of a 3-step or more progression of DR from the termination of the DCCT, during EDIC follow-up other important secondary outcomes were also assessed. Even after a decade of EDIC follow-up, these secondary outcomes reflect the benefit of INT as compared with CON during the earlier DCCT period (8). Similar to the effect on retinopathy progression, at EDIC year 10, there was a 56% ($P < 0.001$) risk reduction in the development of PDR in the INT group. As shown in Table 1, odds reduction at EDIC year 10 for other end points included onset of severe NPDR or worse (58%, $P < 0.001$), onset of PDR or worse (58%, $P < 0.001$), onset of CSME (38%, $P = 0.009$), and application of PRP (57%, $P < 0.001$). Although the magnitude of these reductions is not as great as observed at DCCT closeout and EDIC year 4, there is still substantial benefit for the original DCCT INT group for at least 10 years after the close of the DCCT. Finally, the benefit of INT for the cumulative incidence of major eye disease end points (PDR, CSME, application of laser, or development of blindness) is also clearly evident in relation to increasing diabetes duration. This is true when

Table 1—Effect of DCCT INT on odds ratios for prevalence of DR complications at DCCT closeout and EDIC years 4 and 10

	DCCT closeout (n = 1,211)		EDIC year 4 (n = 1,094)		EDIC year 10 (n = 1,211)	
	Odds reduction (%)	P	Odds reduction (%)	P	Odds reduction (%)	P
≥3-step DR progression	76	<0.001	74	<0.001	57	<0.001
Severe NPDR or worse	66	<0.001	68	<0.001	58	<0.001
PDR or worse	64	<0.001	65	<0.001	58	<0.001
CSME	51	0.005	62	<0.001	38	0.009
PRP	60	<0.001	54	0.004	57	<0.001

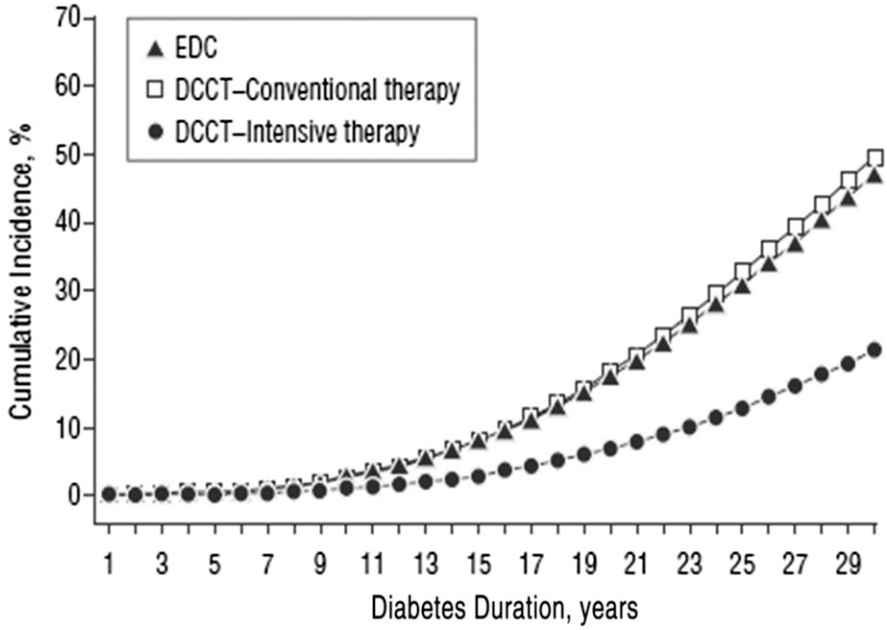

Figure 6—The cumulative incidence of any major eye disease end point (PDR, CSME, application of laser, or development of blindness) is shown in relation to diabetes duration. DCCT CON (open squares) and INT (solid circles) groups are presented. Also presented is the cumulative incidence of these major eye disease end points observed in the observational Pittsburgh Epidemiology of Diabetes Complications (EDC) study (solid triangles) (15).

comparing INT to CON in the DCCT/EDIC, but is also evident in relation to large observational studies such as the Pittsburgh Epidemiology of Diabetes Complications (EDC) study of patients with T1D from Allegheny County, Pennsylvania (Fig. 6) (15).

CONCLUSIONS

Results from the DCCT clearly demonstrated that INT markedly delayed the onset and slowed the progression of DR. The EDIC study demonstrated the unexpected phenomenon of "metabolic memory," whereby a period of previous glycemic control continues to affect future development of diabetes complications despite subsequent equivalency of HbA_{1c} between groups. In EDIC, metabolic memory accounted for a profound reduction in risk of further disease progression that continues to be evident after more than a decade of follow-up. The observed benefits include many different diabetes-related ocular outcomes. Furthermore, the effects of metabolic memory observed in EDIC through year 10 appear to be almost entirely explained by the previous DCCT group difference in HbA_{1c}.

Nearly two decades of EDIC follow-up will be available soon, as will evaluation of the effect of glycemic control on the need for long-term surgical ocular intervention. These data will further extend the contributions of the DCCT/EDIC study and its already lasting legacy that guides therapy of T1D patients and provides marked reduction of the long-term burdens of eye disease and visual loss.

Acknowledgments. The author thanks Jerry D. Cavallerano, OD, PhD (Beetham Eye Institute, Joslin Diabetes Center, Boston, MA) for his contributions to the writing and review of the manuscript.

Funding. The DCCT/EDIC has been supported by U01 Cooperative Agreement grants (1982–93, 2011–2016) and contracts (1982–2011) with the Division of Diabetes Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (current grant numbers U01-DK-094176 and U01-DK-094157) and through support of the National Eye Institute, the National Institute of Neurological Disorders and Stroke, the Genetic Clinical Research Centers Program (1993–2007), and Clinical and Translational Science Center Program (2006–present), Bethesda, MD.

Industry contributors have had no role in the DCCT/EDIC but have provided free or discounted supplies or equipment to support participants' adherence to the study: Abbott Diabetes Care (Alameda, CA); Animas (West Chester, PA); Bayer Diabetes Care (Tarrytown, NY); Becton, Dickinson and Company (Franklin Lakes, NJ); CanAm (Atlanta, GA); Eli Lilly (Indianapolis, IN); LifeScan (Milpitas, CA); Medtronic Diabetes (Minneapolis, MI); Nova Diabetes Care (Bedford, MA); 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. L.P.A. researched and wrote the manuscript. L.P.A. 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. Joslin EP. *The Treatment of Diabetes Mellitus*. Philadelphia, PA, and New York, NY, Lea and Febiger, 1916
2. 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
3. The DCCT Research Group. The Diabetes Control and Complications Trial (DCCT). Design and methodologic considerations for the feasibility phase. Diabetes 1986;35: 530–545
4. Nathan DM. The Diabetes Control and Complications Trial/Epidemiology of

Diabetes Interventions and Complications study at 30 years: overview. Diabetes Care 2014;37:9–16

5. 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
6. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. Ophthalmology 1991;98 (Suppl):786–806
7. The Diabetes Control and Complications Trial Research Group. Color photography vs fluorescein angiography in the detection of diabetic retinopathy in the diabetes control and complications trial. Arch Ophthalmol 1987;105:1344–1351
8. White NH, Sun W, Cleary PA, et al.; Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications Research Group. 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. Epidemiology of Diabetes Interventions and Complications (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
10. Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial. Arch Ophthalmol 1995; 113:36–51
11. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 1995;44:968–983
12. 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
13. Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1998;116:874–886
14. 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
15. Nathan DM, Zinman B, Cleary PA, et al.; Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications experience (1983–2005). Arch Intern Med 2009;169:1307–1316