The Beneficial Effects of Earlier Versus Later Implementation of Intensive Therapy in Type 1 Diabetes

*John M. Lachin,[1] Ionut Bebu,[1] and David M. Nathan,[2] for the DCCT/EDIC Research Group**

Diabetes Care 2021;44:2225–2230 | https://doi.org/10.2337/dc21-1331

OBJECTIVE

The principal aim is to estimate the benefits of earlier versus later implementation of intensive therapy in type 1 diabetes with respect to the long-term risks of progression of a renal (microvascular) and cardiovascular (macrovascular) complication in the Epidemiology of Diabetes Interventions and Complications (EDIC) study.

RESEARCH DESIGN AND METHODS

Cox proportional hazards regression models estimated the 20-year cumulative incidence (absolute risk) and the 20-year relative risk of cardiovascular disease (CVD) and reduced estimated glomerular filtration rate (eGFR) over the first 20 years of EDIC follow-up as a function of the mean HbA_{1c}.

RESULTS

A hypothetical patient treated earlier with 10 years of intensive therapy and a mean HbA_{1c} of 7% (53 mmol/mol) followed by 10 years with a mean of 9% (75 mmol/mol) would have a 33% reduction in the risk of CVD and a 52% reduction in reduced eGFR compared with a patient with a mean HbA_{1c} of 9% (75 mmol/mol) over the first 10 years followed by later intensive therapy over 10 years with an HbA_{1c} of 7% (53 mmol/mol). Despite both patients having the same average glycemic exposure over the 20 years, the patient with the lower HbA_{1c} over the first 10 years had a lower risk of progression of complications over the 20 years than the patient who had the higher value initially.

CONCLUSIONS

While implementation of intensive therapy at any time in type 1 diabetes will be beneficial, within the 20-year period modeled, earlier relative to later implementation is associated with a greater reduction in the risks of kidney and cardiovascular complications.

The Diabetes Control and Complications Trial (DCCT) (1983–1993) conclusively demonstrated that improved glycemic control achieved by intensive therapy, compared with higher glycemic levels provided by conventional therapy, reduces the risk of onset and progression of microvascular complications in type 1 diabetes (1). Statistically, the beneficial effects of intensive therapy were completely explained by the ~2% absolute difference in the level of HbA_{1c} between the treatment

[1]*The Biostatistics Center, George Washington University, Rockville, MD*
[2]*Massachusetts General Hospital Diabetes Center, Harvard Medical School, Boston, MA*

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

Received 25 June 2021 and accepted 19 July 2021

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

**A complete list of the members of the DCCT/EDIC Research Group can be found in N Engl J Med 2017;376:1507–1516.*

This article is part of a special article collection available at https://care.diabetesjournals.org/collection/long-term-effects-of-earlier-glycemic-control.

See accompanying articles, pp. 2212, 2216, and 2231.

groups during DCCT (2). In both the intensive and the conventional groups, the risk of retinopathy progression decreased by ~43% per 10% reduction in the mean HbA_{1c} within each treatment group during DCCT (3).

Following the conclusion of the DCCT, the conventional group patients were trained in intensive therapy, and all patients were referred to their personal health care provider for diabetes care. Subsequently, 98% of the surviving patients enrolled in the Epidemiology of Diabetes Interventions and Complications (EDIC) study and have been followed with annual assessments (1994 to date). Over the first few years of follow-up in EDIC, the HbA_{1c} levels in the original two treatment groups converged. Despite this, the patients in the original DCCT intensive therapy group continued to have a reduced risk of further progression of complications for at least 10 years after the end of DCCT (4), termed "metabolic memory." This phenomenon, and other observations during DCCT, suggested that initiating and maintaining intensive therapy earlier in the course of diabetes would have long-term benefits compared with doing so later in the course of diabetes. However, the magnitude of the benefit of earlier versus later implementation of intensive therapy has not been described.

Data from the first 20 years of EDIC follow-up (1994–2014) are used here to estimate the beneficial absolute and relative risks of progression of complications associated with different treatment scenarios to explore the impact of the order in which intensive therapy is initiated. In one scenario, a 10-year period of intensive therapy with an HbA_{1c} of 9% (75 mmol/mol) is followed by 10 years with an HbA_{1c} of 7% (53 mmol/mol). In the complementary scenario, 10 years with an HbA_{1c} of 7% (53 mmol/mol) is followed by 10 years at 9% (75 mmol/mol).

RESEARCH DESIGN AND METHODS

The methods of DCCT and EDIC have been previously described in detail (1,5). In brief, DCCT enrolled 1,441 patients who were randomly assigned to receive intensive therapy aiming for glycemic levels as close to the nondiabetic range as safely possible or to conventional insulin therapy using one to two insulin injections per day with the goal of avoiding symptoms of hyper- or hypoglycemia. Approximately one-half were enrolled in a primary prevention cohort with 1–5 years' duration of diabetes, no retinopathy, and an albumin excretion rate $<$40 mg/24 h and one-half in a secondary intervention cohort with 1–15 years' duration, mild retinopathy, and albumin excretion rate $<$200 mg/24 h.

The DCCT was closed in 1993 after an average 6.5 years of treatment and follow-up. Annual follow-up visits in EDIC commenced in 1994. The DCCT closeout in 1993 constituted the EDIC baseline. The analyses herein are based on the 1,396 (98% of the survivors) who enrolled in EDIC. At the start of EDIC in 1994, the participants had a mean age of 35 years, diabetes duration of 12 years, and HbA_{1c} of 8.2%, and 48% were female.

The current analyses describe the differences between patients with different patterns of glycemia over the first and second 10-year intervals of follow-up with respect to the incidence of any cardiovascular disease (CVD) and reduced estimated glomerular filtration rate (eGFR) ($<$60 mL/min/1.73 m^2). Any CVD included the first of either fatal or nonfatal myocardial infarction or stroke, confirmed angina, silent myocardial infarction, revascularization, or congestive heart failure (6). For each outcome, patients with that event during DCCT were excluded in these analyses (15 with CVD and 6 with reduced eGFR).

During the 20 years of EDIC follow-up, 160 patients experienced a CVD event (60 during years 1–10 and 100 during years 11–20). Likewise, 140 patients reached a reduced eGFR (41 during years 1–10 and 99 during years 11–20). The cumulative incidence of each outcome at 20 years of EDIC follow-up was estimated from a Cox proportional hazards (PH) regression model (7) in conjunction with the Breslow estimate of the background risk (7). Subjects with an outcome after 20 years of follow-up were administratively right censored at 20 years.

HbA_{1c} was measured by high-performance liquid chromatography annually during EDIC. Models included the updated mean HbA_{1c} during EDIC as a time-varying covariate defined at each time point as the average of the HbA_{1c} values up to (and including) that time point. The PH assumption was verified. The updated mean HbA_{1c} had a stronger association with the risk of each outcome than did the current HbA_{1c}.

For the analysis of CVD, there was no interaction between the updated mean HbA_{1c} and either original treatment group, primary versus secondary cohort, or first versus second 10-year period. For reduced eGFR, the HbA_{1c} coefficient differed significantly between the first and second 10-year periods. Thus, the updated mean HbA_{1c} is the only independent variable in the Cox models used to estimate the cumulative incidence of outcomes (CVD and reduced eGFR), with a single coefficient for CVD and separate coefficients for each 10-year period for reduced eGFR.

For a hypothetical patient with HbA_{1c} values of a and b over the first and second 10-year periods, the cumulative incidence at 20 years was obtained by numerical integration over the estimated hazard (incidence) function. The computations used an updated mean HbA_{1c} value of a at all event or censoring times of all patients over the first 10 years of EDIC follow-up. During the second 10-year period, an HbA_{1c} value at time t in the interval $10 < t \leq 20$ would have an updated mean computed as $([a \times 10] + [b \times (t - 10)])/t$.

RESULTS

A smoothed (model-free) estimate of the log of the risk (hazard rate) of CVD and reduced eGFR (Fig. 1) showed a near-linear relationship with the updated mean HbA_{1c}. The cumulative incidence estimated from the regression model was nearly identical to the empirical (model-free) estimate for each outcome (Fig. 2). To simplify the presentation, the reduced eGFR panel in Fig. 1 is based on computations with the updated mean HbA_{1c} alone over 20 years, whereas those for Fig. 2 and Table 2 used separate computations with HbA_{1c} within each 10-year period. These figures show that the models should provide accurate estimates of the absolute and relative risks for CVD and reduced eGFR over the 20-year period.

Table 1 presents the cumulative incidence of any initial CVD event by 20 years of EDIC follow-up estimated from

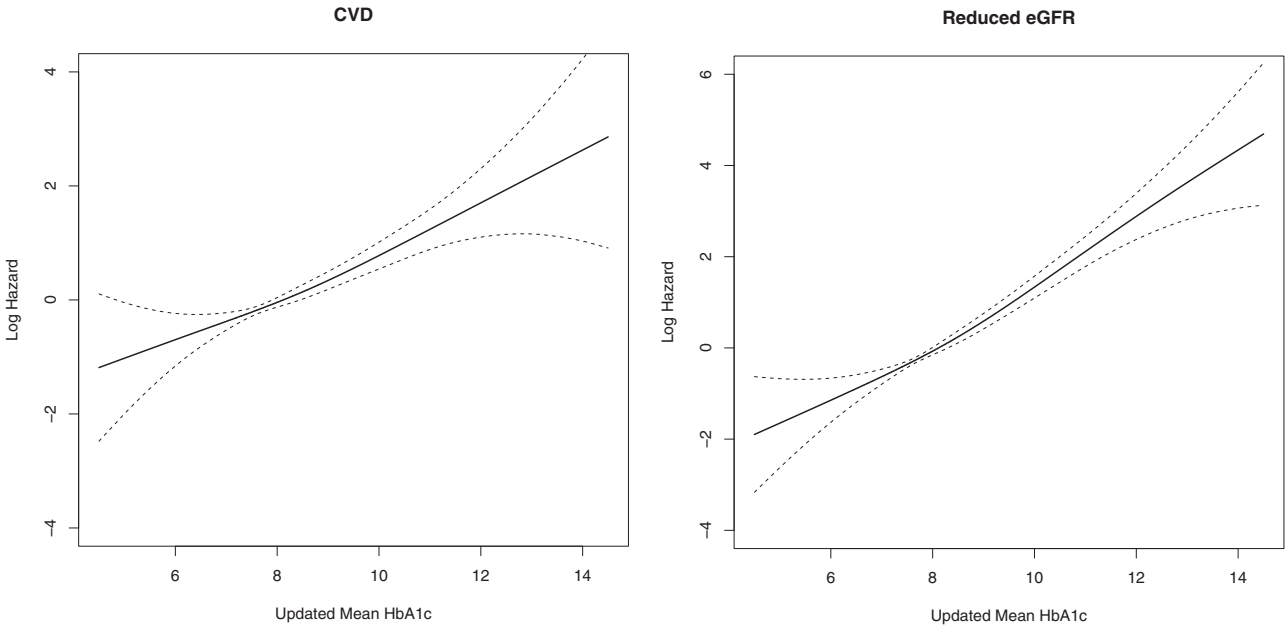

Figure 1—The smoothed empirical (model-free) estimate of the underlying relationship between the log hazard (risk) of CVD and reduced eGFR ($<$60 mL/min/1.73 m^2) with the updated weighted mean HbA_{1c} that represents virtually a linear relationship that would be represented by a linear term in the Cox PH model. The reduced eGFR panel is based on the full cohort over 20 years.

the Cox PH model for four hypothetical patients with specified values of HbA_{1c} for years 1–10 and years 11–20. Consider the first hypothetical patient with an HbA_{1c} of 9% (75 mmol/mol) over the full 20 years who would have a cumulative incidence (absolute risk) of CVD by year 20 of 0.153 (15.3%). Then consider the second patient with an HbA_{1c} of 9% (75 mmol/mol) over years 1–10 who then switches to an HbA_{1c} of 7% (53 mmol/mol) over years 11–20. That patient would have an absolute risk of 0.134, or a risk difference (reduction) of −0.019. Taking the ratio of the cumulative incidence for the second versus the first patient, this represents a 12.4% reduction in the 20-year cumulative incidence (95% CI 8.0, 17.2).

The third patient with an HbA_{1c} of 7% (53 mmol/mol) followed by 9% (75 mmol/mol) would have a 20-year cumulative incidence of 0.090. Compared with the second patient above, initiating intensive therapy earlier results in a risk difference of 0.044 or a 32.8% reduction (95% CI 22.9, 41.9) in the cumulative incidence. Finally, the fourth patient maintains an HbA_{1c} of 7% (53 mmol/mol) over the entire 20-year period and would have a 20-year cumulative incidence of 0.077, representing a difference of 0.013 or a 14.5% reduction compared with the third patient.

Table 2 shows like calculations for reduced eGFR. The percent reductions accompanying the hierarchy of four scenarios yield a greater range of 20-year cumulative incidence for reduced eGFR (0.049–0.181) than CVD (0.077–0.153). The corresponding successive risk reductions of 19.8%, 51.9%, and 28.5% for reduced eGFR were even greater than those for CVD.

CONCLUSIONS

The risks (log hazard rate) of CVD and reduced eGFR have virtually linear associations with the updated mean HbA_{1c}, and the resulting model-based estimated cumulative incidence functions for CVD and reduced eGFR over time are virtually identical to the empirical estimates that are model free. Thus, the model provides precise estimates of the cumulative incidence of CVD and reduced eGFR over a 20-year period of follow-up as a function of HbA_{1c}. Since the cohort had a mean duration of 12 years and a mean age of 35 years at the start of EDIC in 1994, these results apply to a population with type 1 diabetes over a mean of 32 years' duration and 55 years of age.

These analyses show that the cumulative incidence (absolute risk) of CVD and reduced eGFR over a 20-year period depend not only on the mean HbA_{1c} over time but also on the sequence with which higher or lower values of HbA_{1c} are maintained. In particular, a patient with 10 years of an HbA_{1c} of 7% (53 mmol/mol) followed by 10 years of 9% (75 mmol/mol) has a 33% lower risk of CVD by 20 years of follow-up than a patient with the opposite HbA_{1c} pattern of 9% (75 mmol/mol) and then 7% (53 mmol/mol). Not surprisingly, patients with 20 years at an HbA_{1c} of 9% (75 mmol/mol) have even higher risks, and those with 20 years at 7% (53 mmol/mol) have lower risks.

Also, note that the patient with 10 years of an HbA_{1c} of 7% (53 mmol/mol) followed by 10 years of 9% (75 mmol/mol) and the patient with the opposite HbA_{1c} pattern of 9% (75 mmol/mol) initially followed by 7% (53 mmol/mol) have the same mean HbA_{1c} over 20 years. Nevertheless, they will have a different eventual cumulative incidence at 20 years, with the patient with the lower HbA_{1c} values early in follow-up having a 33% lower risk of CVD at 20 years.

These findings are concordant with the empirical observation that a period of intensive therapy with a mean HbA_{1c} of ∼7% (53 mmol/mol) during DCCT vs. 9% (75 mmol/mol) with conventional therapy resulted in a substantial continuing

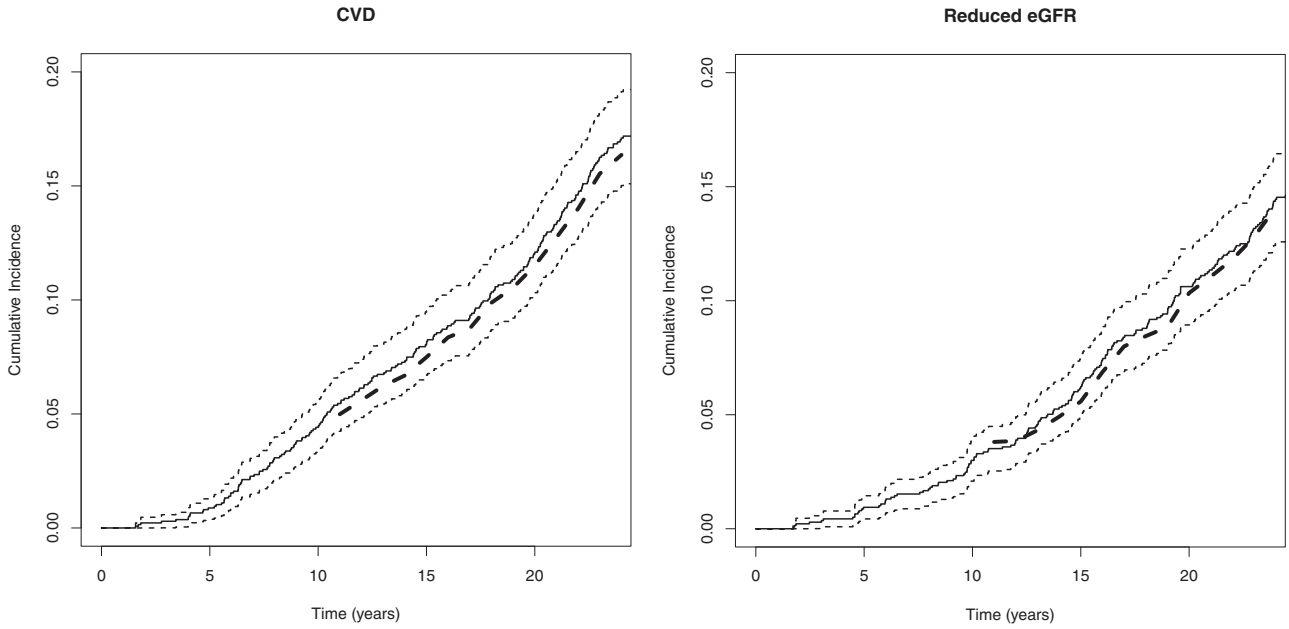

Figure 2—The cumulative incidence of any CVD and reduced eGFR over the first 20 years of follow-up in EDIC (solid line) and 95% CI estimated from the Cox PH model in conjunction with the Breslow estimate of the underlying hazard function compared with the empirical Kaplan-Meier estimate of the cumulative incidence function (dashed line), the two estimates being virtually identical. The model for reduced eGFR used a separate coefficient for the mean HbA_{1c} within each 10-year period.

benefit during EDIC, even though the HbA_{1c} levels during EDIC converged to ~8% in both groups. We have attributed this pattern to the phenomenon of metabolic memory (4,8,9) that is consonant with what others have described as a legacy effect (10) in type 2 diabetes.

In this study, we compared the 20-year cumulative incidence following periods with earlier versus later implementation of intensive therapy. We chose 20 years because there is a substantial density of events over this period. However, given that the cohort had a mean of 12 years' duration at EDIC baseline, technically these results may not apply to patients who are newly diagnosed or would have >30 years of diabetes. Nevertheless, we conjecture that these differences would also be evident if extended beyond 20 years, provided that the mean HbA_{1c} continues to affect the risk of these outcomes. As we describe in recent work (9), early reductions in the day-to-day risks will be perpetrated into the future so that the cumulative incidence will continue to increase at a higher rate among those with later implementation of intensive therapy.

This interpretation is also supported by recent results. Previously, Lind et al. (11) described a model that weights HbA_{1c} values according to their influence on the risk of future events. The model was used to assess the impact of a delay in implementing intensive therapy in the UK Prospective Diabetes Study (UKPDS) type 2 diabetes cohort

Table 1—Cumulative incidence of any initial CVD outcome by 20 years of EDIC follow-up

HbA_{1c} years 1–10*	HbA_{1c} years 11–20*	20-year cumulative incidence		Difference (95% CI)	Reduction, % (95% CI)†
9% (75 mmol/mol)	9% (75 mmol/mol)	0.153			
			}	−0.019 (−0.027, −0.011)	12.4 (8.0, 17.2)
9% (75 mmol/mol)	7% (53 mmol/mol)	0.134			
			}	−0.044 (−0.058, −0.029)	32.8 (22.9, 41.9)
7% (53 mmol/mol)	9% (75 mmol/mol)	0.090			
			}	−0.013 (−0.017, −0.009)	14.5 (8.8, 20.2)
7% (53 mmol/mol)	7% (53 mmol/mol)	0.077			

Estimated from a Cox PH model with Breslow estimate of the underlying hazard function for hypothetical patients with specified values of HbA_{1c} for years 1–10 and 11–20, the estimated difference and percent reduction in cumulative incidence, and the 95% CI compared with the patient above. *Analyses used a Cox PH model based on 60 cases of CVD during years 1–10 of EDIC and 100 CVD events during years 11–20, with the updated mean HbA_{1c} during the 20 years as the only covariate. †Other scenarios could be compared directly. For example, the 7%, 7% vs. the 9%, 9% scenario shows a difference in 20-year cumulative incidence of 0.153 − 0.077 = 0.076, or a 49.7% reduction (= 100 × [0.076 / 0.153]).

Table 2—Cumulative incidence of reduced eGFR (<60 mL/min/1.73 m^2) by 20 years of EDIC follow-up

HbA_{1c} years 1–10*	HbA_{1c} years 11–20*	20-Year cumulative incidence		Difference (95% CI)	Reduction, % (95% CI)†
9% (75 mmol/mol)	9% (75 mmol/mol)	0.181			
			}	−0.036 (−0.047, −0.024)	19.8 (13.2, 26.7)
9% (75 mmol/mol)	7% (53 mmol/mol)	0.145			
			}	−0.075 (−0.103, −0.053)	51.9 (44.5, 60.9)
7% (53 mmol/mol)	9% (75 mmol/mol)	0.069			
			}	−0.019 (−0.024, −0.014)	28.5 (21.2, 35.4)
7% (53 mmol/mol)	7% (53 mmol/mol)	0.049			

Estimated from a Cox PH model with Breslow estimate of the underlying hazard function for hypothetical patients with specified values of HbA_{1c} for years 1–10 and 11–20 and the estimated difference, percent reduction in cumulative incidence, and 95% CI compared with the patient above. *Analyses used a Cox PH model based on 41 cases of reduced eGFR during years 1–10 of EDIC and 99 cases of reduced eGFR during years 11–20, with the updated mean HbA_{1c} having a separate coefficient value within the first and second 10 years. †Other scenarios could be compared directly. For example, the 7%, 7% vs. the 9%, 9% scenario shows a difference in 20-year cumulative incidence of 0.181 − 0.049 = 0.132, or a 72.9% reduction (= 100 × [0.132 / 0.181]).

(12). A 1% HbA_{1c} reduction starting from the time of diagnosis resulted in a 19% reduction in the risk of all-cause mortality, whereas delaying the 1% reduction 10–15 years later resulted in only a 2.7% risk reduction. Likewise, the corresponding myocardial infarction risk reductions were 19.7% and 6.5% for an immediate and later HbA_{1c} reduction, respectively.

EDIC was preceded by 10 years of follow-up in DCCT (mean 6.5 years), and it would be possible to also include this period in the risk models. However, during DCCT, only 15 patients experienced a CVD event, and 6 experienced reduced eGFR. These small numbers are insufficient to accurately assess the relationship of each outcome with mean HbA_{1c} levels during DCCT. Thus, the DCCT period and these small numbers of events have been excluded.

We had also planned to present similar analyses of the cumulative incidence of proliferative diabetic retinopathy. However, the model-estimated cumulative incidence function for retinopathy differed from those for CVD and reduced eGFR in Fig. 2 in that it did not accurately fit the empirical cumulative incidence function. In part, this is likely a reflection of the substantial variation in the number of retinal assessments that were conducted every 4th year during EDIC (one-fourth annually) as well as in the entire EDIC cohort at years 4 and 10. As a result, there were ∼60% more retinal examinations during the first 10-year period of EDIC than during the second.

However, all the DCCT and EDIC outcomes, including proliferative diabetic retinopathy, have been shown to be strongly associated with the updated mean HbA_{1c} (2,3). Therefore, all these outcomes would likely be sensitive to the pattern of HbA_{1c} over time and would be expected to show different absolute risks for different HbA_{1c} patterns as shown for CVD and reduced eGFR. Also, while prior reports from DCCT and the early years of EDIC used progression of subclinical outcomes (e.g., microalbuminuria), with ≥20 additional years of follow-up in EDIC alone, we have now accrued sufficient numbers to use the hard clinical outcome of reduced eGFR.

The practical, clinical message of these findings is that earlier metabolic control has substantial long-term implications for the health of people with type 1 diabetes. This clinical message may be particularly challenging since type 1 diabetes usually presents during childhood and adolescence when patients, their families, and health care providers often struggle with the host of new treatments and lifestyle adjustments required to manage newly diagnosed diabetes. We hope that the clinical import of initiating intensive therapy as early in the course of type 1 diabetes as safely possible will provide motivation to patients, families, and their caregivers to achieve an HbA_{1c} in the target range as early and as long as possible.

In conclusion, we examined patients enrolled in DCCT with established type 1 diabetes and followed during EDIC. Models estimated the risks of complications that would be incurred by a hypothetical patient with a mean HbA_{1c} at one value during the first 10 years of EDIC follow-up and a mean HbA_{1c} at another value during the second 10-year period. Computations then show that a patient with a mean HbA_{1c} of 7% (53 mmol/mol) over the first 10 years of EDIC followed by 9% (75 mmol/mol) over the next 10 years will experience a 33% lower risk of CVD and 52% lower risk of reduced eGFR at 20 years compared with a patient with the first 10 years at 9% (75 mmol/mol) followed by 10 years at 7% (53 mmol/mol). These benefits of earlier intensive therapy occur even though both patients have a mean HbA_{1c} of 8% over 20 years. These findings support implementing intensive therapy as early as safely possible in type 1 diabetes so as to reduce the risk of eventual progression of long-term complications.

Funding. The DCCT/EDIC has been supported by cooperative agreement grants (1982–1993, 2012–2017, 2017–2022) and contracts (1982–2012) 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 by the National Eye Institute, National Institute of Neurological Disorders and Stroke, General Clinical Research Centers Program (1993–2007), and Clinical Translational Science Center Program (2006–present). Additional support for this DCCT/EDIC collaborative study was provided by the National Institutes of Health through National Institute of Diabetes and Digestive and Kidney Diseases grant number 1-DP3-DK-104438.

Duality of Interest. The following industry contributors have provided free or discounted

supplies or equipment to support participants' adherence to the study protocols: Abbott Diabetes Care (Alameda, CA), Animas (Westchester, PA), Bayer Diabetes Care (North America Headquarters, Tarrytown, NY), Becton Dickinson (Franklin Lakes, NJ), Eli Lilly (Indianapolis, IN), Extend Nutrition (St. Louis, MO), Insulet Corporation (Bedford, MA), Lifescan (Milpitas, CA), Medtronic Diabetes (Minneapolis, MN), Nipro Home Diagnostics (Ft. Lauderdale, FL), Nova Diabetes Care (Billerica, MA), Omron (Shelton, CT), Perrigo Diabetes Care (Allegan, MI), Roche Diabetes Care (Indianapolis, IN), and Sanofi (Bridgewater, NJ). No other potential conflicts of interest relevant to this article were reported.

Industry contributors have had no role in the conduct of the DCCT/EDIC study.

Author Contributions. J.M.L. specified the study objectives, wrote elements of the manuscript, and had final responsibility for the decision to submit for publication. J.M.L., I.B., and D.M.N. wrote portions of the manuscript and reviewed and edited the manuscript. I.B. conducted the analyses. J.M.L. and I.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Nathan DM, Genuth S, Lachin J, et al.; 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. Lachin JM, Genuth S, Nathan DM, Zinman B; DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial–revisited. Diabetes 2008;57:995–1001

3. 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

4. Steffes MW, Chavers BM, Molitch ME, et al.; 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

5. 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

6. Lachin JM, Orchard TJ; DCCT/EDIC Research Group. Update on cardiovascular outcomes at 30 years of the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 2014;37:39–43

7. Lachin JM. *Biostatistical Methods: The Assessment of Relative Risks*. 2nd ed. Hoboken, NJ, John Wiley and Sons, 2011

8. Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM; The Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention 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

9. Lachin JM, Nathan DM; DCCT/EDIC Research Group. Understanding metabolic memory: the prolonged influence of glycemia during the Diabetes Control and Complications Trial (DCCT) on future risks of complications during the study of the Epidemiology of Diabetes Interventions and Complications (EDIC). Diabetes Care 2021;44: 2216–2224

10. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589

11. Lind M, Odén A, Fahlén M, Eliasson B. The shape of the metabolic memory of HbA_{1c}: re-analysing the DCCT with respect to time-dependent effects. Diabetologia 2010;53:1093–1098

12. Lind M, Imberg H, Coleman RL, Nerman O, Holman RR. Historical HbA_{1c} values may explain the type 2 diabetes legacy effect: UKPDS 88. Diabetes Care 2021;44:2231–2237