Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up

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OBJECTIVE

Early initiation of intensive diabetes therapy aimed at achieving near-normal glycemia reduces the early development of vascular complications in type 1 diabetes. We now assess whether intensive therapy compared with conventional therapy during the Diabetes Control and Complications Trial (DCCT) affected the incidence of cardiovascular disease over 30 years of follow-up.

RESEARCH DESIGN AND METHODS

The DCCT randomly assigned 1,441 patients with type 1 diabetes to intensive versus conventional therapy for a mean of 6.5 years, after which 93% were subsequently monitored during the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study. Cardiovascular disease (nonfatal myocardial infarction and stroke, cardiovascular death, confirmed angina, congestive heart failure, and coronary artery revascularization) was adjudicated using standardized measures.

RESULTS

During 30 years of follow-up in DCCT and EDIC, 149 cardiovascular disease events occurred in 82 former intensive treatment group subjects versus 217 events in 102 former conventional treatment group subjects. Intensive therapy reduced the incidence of any cardiovascular disease by 30% (95% CI 7, 48; P = 0.016), and the incidence of major cardiovascular events (nonfatal myocardial infarction, stroke, or cardiovascular death) by 32% (95% CI −3, 56; P = 0.07). The lower HbA_{1c} levels during the DCCT/EDIC statistically account for all of the observed treatment effect on cardiovascular disease risk. Increased albuminuria was also independently associated with cardiovascular disease risk.

CONCLUSIONS

Intensive diabetes therapy during the DCCT (6.5 years) has long-term beneficial effects on the incidence of cardiovascular disease in type 1 diabetes that persist for up to 30 years.

Cardiovascular disease (CVD), the leading cause of death for men and women, is accelerated in type 1 diabetes (1–3). The effect of hyperglycemia on microvascular and macrovascular complications is well documented in longitudinal studies of patients with type 1 and type 2 diabetes (4–7). Early interventions designed to

optimize glycemic control have been shown to reduce the development and progression of these complications (6,8,9). Participants in the Diabetes Control and Complications Trial (DCCT) with further follow-up in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (DCCT/EDIC) demonstrated that intensive diabetes therapy aimed at near-normal blood glucose levels compared with conventional therapy during the DCCT reduced the subsequent development and progression of retinopathy, nephropathy, and neuropathy during EDIC (6,8,10). These beneficial effects from a period of intensive glycemic control persisted beyond the completion of the intervention trial and despite similar levels of glycemic control in the two former treatment groups during EDIC. We referred to this phenomenon as metabolic memory (11,12). In 2005, ~10 years after the completion of the DCCT, we first reported that the period of initial intensive diabetes therapy also reduced the risk of developing CVD (i.e., nonfatal myocardial infarction and stroke, cardiovascular death, confirmed angina, and coronary artery revascularization) in EDIC, although the number of CVD events was relatively low (13).

In the long-term follow-up of the DCCT/EDIC study, with more than 2 decades of diabetes management that was no longer prescribed by study protocol, we have noted that the treatment group specific effects on microvascular complications, although declining, remain clinically significant (3,6,10). We now report the 30-year risk of CVD in the DCCT/EDIC cohort and evaluate treatment group differences and the association of HbA$_{1c}$ and albuminuria measures with this life-threatening complication of type 1 diabetes. We also examine the suggestion in the literature that HbA$_{1c}$ may relate more strongly to fatal rather than nonfatal CVD events (14–17).

RESEARCH DESIGN AND METHODS

The methods of the DCCT and EDIC follow-up study have been described in detail (11,18–20). The DCCT (1983 and 1993) was designed to compare the effects of a randomly assigned intensive versus conventional diabetes treatment regimen on the development of microvascular complications.

Subjects

The DCCT randomized 1,441 volunteers with type 1 diabetes, age 13 to 39 years, to intensive (n = 711) versus conventional (n = 730) therapy. Participants with diabetes duration of 1 to 5 years without evidence of microvascular complications comprised the primary prevention cohort, and those with diabetes duration of 1 year up to 15 years with minimal retinopathy or nephropathy comprised the secondary cohort. Of these, 1,423 participants completed the study after a mean follow-up of 6.5 years. Subjects with a history of CVD or with hypertension (blood pressure ≥140/90 mmHg) or hypercholesterolemia (fasting serum cholesterol ≥3 SDs above age- and gender-specific means) were not eligible to participate (18). After the end of the DCCT, 1,394 of the surviving cohort (96% of the original DCCT cohort) joined the long-term EDIC follow-up study starting in 1994. Participants previously randomized to conventional therapy were taught intensive therapy, and ongoing care was returned to their usual health care team.

The current report includes follow-up through 31 December 2013, with 85.8% of the original cohort (93.2% of 1,327 surviving participants) remaining in the study (Supplementary Fig. 1). Apart from those who died or developed CVD, the remaining subjects participated in 96% of the possible follow-up period. DCCT/EDIC was approved by the institutional review boards of all participating centers, and all volunteers provided written informed consent.

Study Procedures

During the DCCT, HbA$_{1c}$ levels were measured quarterly, and fasting lipids, serum creatinine, albumin excretion rate (AER), and other CVD risk factors were measured annually in a central laboratory (18,20). Annual electrocardiograms were centrally read while masked to treatment assignment. DCCT methods were continued during EDIC follow-up; however, the frequency of assessment differed. HbA$_{1c}$ was measured annually in EDIC, and fasting lipids and renal function were measured in alternate years in EDIC (yearly in DCCT). The time-weighted mean HbA$_{1c}$ represented the total glycemic exposure during DCCT/EDIC with weights of 0.25 and 1 for quarterly DCCT and annual EDIC values, respectively, up to the measure immediately preceding the event or censoring for those without an event.

To be consistent with contemporary guidelines, sustained microalbuminuria was defined as an AER of at least 30 on two consecutive occasions and albuminuria as ≥300 mg/24 h, and each was counted as present if end-stage renal disease (ESRD) occurred. ESRD included kidney transplantation or dialysis (18). Kidney failure was defined as ESRD or the development of an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation.

Diabetes Therapy

During the DCCT, intensive therapy consisted of three or more daily insulin injections or use of an external insulin infusion pump, with dose adjustments based on at least four self-monitored glucose measurements per day. Daily glucose goals were 70–120 mg/dL before meals and <180 mg/dL peak levels after meals. The HbA$_{1c}$ goal was a value of <6.05% (42.6 mmol/mol), 2 SDs above the nondiabetic mean. Conventional therapy used one or two daily injections of insulin and had no glucose goals beyond prevention of hyper- and hypoglycemia.

Outcomes

The primary outcome was the time to the first of any of the following types of cardiovascular events: nonfatal myocardial infarction or stroke; death judged to be secondary to CVD; subclinical ("silent") myocardial infarction detected on an annual electrocardiogram (21); angina confirmed by ischemic changes with exercise tolerance testing or by clinically significant obstruction on coronary angiography; congestive heart failure (CHF) with paroxysmal nocturnal dyspnea, orthopnea, or marked limitation of physical activity caused by heart disease; or revascularization with angioplasty and/or coronary artery bypass (22).

The occurrence of any CVD event was routinely documented during annual participant study visits, with additional medical records sought to verify all self-reported events. To ensure complete capture of all known CVD

events before year end, staff efforts were escalated in early 2013 to ensure full reporting of all known CVD events irrespective of completion of the annual visit. Medical records describing cardiovascular events, including electrocardiograms and cardiac enzymes, were obtained and centrally adjudicated by a Mortality and Morbidity Review Committee masked to DCCT treatment assignment, HbA_{1c}, and glucose levels. Only events adjudicated as definite cardiovascular events were included in these analyses (21).

Statistical Analysis

Previous analyses of CVD events through year 11 of EDIC were conducted after 50 DCCT conventional treatment group subjects had experienced a cardiovascular event (13). The research group also prespecified that analyses of risk factors for CVD events would be embargoed until 100 such conventional cases were observed. That landmark was reached near the end of 2013. In this report we present updated analyses of the incidence of CVD through 31 December 2013, the differences between former DCCT treatment groups, and the association of CVD events with HbA_{1c} and renal outcomes. Results nominally significant at $P < 0.05$ (two-sided) are cited.

Clinical characteristics were compared using Wilcoxon rank sum tests for quantitative variables and χ^2 tests for categorical variables (23). The Kaplan-Meier method estimated the cumulative incidence of the first cardiovascular event (24). The Cox proportional hazards model estimated covariate effects (hazard ratio [HR] and 95% CI) on CVD risk that were tested using the Wald test (25). The corresponding risk reduction was calculated as $100 (1 - HR)$. The Kaplan-Meier estimate of the underlying incidence (hazard) function within groups was computed, and a smooth estimate was obtained using natural cubic splines with 2 degrees of freedom (26). Event rates, including all (i.e., multiple) events in all subjects, are presented as the number per 100 patient-years, and the difference was tested using robust Poisson regression analysis (24). Cox models also assessed the effects of time-dependent covariates on CVD risk such as the updated mean HbA_{1c}.

RESULTS

Cohort characteristics at DCCT baseline, DCCT close-out, year 10–11 of EDIC, and year 19–20 are described in Supplementary Table 1. Owing to exclusion criteria, no participants had hypertension or hypercholesterolemia at DCCT baseline, and only 5% had microalbuminuria. The only significant group difference was a minimally higher systolic blood pressure in the conventional treatment group. At DCCT study end, the conventional and intensive treatment groups had diverged with regard to several established and putative CVD risk factors (e.g., BMI and triglycerides) and differed in the levels of microvascular outcomes. By EDIC year 11, the prevalence of microalbuminuria and albuminuria remained higher in the former conventional treatment group. However, there were small differences between groups in other traditional CVD risk factors and a negligible difference in HbA_{1c}. Additional differences emerged by year 20, albeit small (e.g., a lower LDL cholesterol in the conventional therapy group). The prevalence of cardioprotective medication use increased by year 11 and increased further by year 20, with no major differences in medication use or type between groups.

Mean HbA_{1c} during the average 6.5 years of DCCT intensive therapy was ~2% (20 mmol/mol) lower than that during conventional therapy (7.2 vs. 9.1% [55.6 vs. 75.9 mmol/mol], $P < 0.001$). Subsequently during EDIC, HbA_{1c} differences between the treatment groups dissipated. At year 11 of EDIC follow-up and most recently at 19–20 years of EDIC follow-up, there was only a trivial difference between the original intensive and conventional treatment groups in the mean level of HbA_{1c} (Supplementary Table 1). However, after a mean of 26 years of follow-up (maximum 30 years), differences in weighted mean HbA_{1c} during the DCCT/EDIC follow-up remained significant between the former intensive and conventional treatment groups (weighted mean HbA_{1c} of 7.8 ± 0.9 vs. 8.2 ± 0.9% [61.3 ± 10.0 vs. 66.3 ± 10.1 mmol/mol], respectively, $P < 0.0001$).

By year end 2013, 366 adjudicated cardiovascular events occurred in 184 subjects, 149 among 82 former intensive treatment group subjects and 217 among 102 former conventional treatment group subjects (Table 1). The event rates in the intensive and conventional treatment groups were 0.81 and 1.18 per 100 patient-years, respectively ($P = 0.06$). The rates of specific clinical events were also consistently lower in the original intensive treatment group, but not significantly owing to the smaller numbers of events.

Overall, 115 of the 715 subjects (16.1%) in the secondary intervention cohort experienced 223 CVD events vs. 69 of 726 (9.5%) in the primary prevention cohort who experienced 143 events (HR 1.45; 95% CI 1.08, 1.96; $P = 0.0143$), and 96 of 761 males (12.6%) had 184 CVD events compared with 88 of 680 females (12.9%) who experienced 182 CVD events (HR 0.99; 95% CI 0.74, 1.32; $P = 0.9337$).

Figure 1A shows the Kaplan-Meier estimated cumulative incidence of the first occurrence of any cardiovascular event within each DCCT treatment group. The incidence within the original DCCT intensive group is 30% lower than that of the conventional group (95% CI 7, 48; $P = 0.016$). The incidence of the first occurrence of a nonfatal myocardial infarction, stroke, or cardiovascular death (major adverse cardiac events [MACE]) was reduced 32% with intensive compared with conventional therapy (95% CI −3, 56; $P = 0.07$) (Fig. 1B).

The effects on cardiovascular events (i.e., excluding stroke) were similar, with a 31% risk reduction in the former intensive group compared with the conventional group (95% CI 6, 49; $P = 0.020$). Furthermore, there is the suggestion of a greater reduction in the risk of less frequent fatal events with intensive versus conventional therapy (6 vs. 16, HR 0.33) than nonfatal events (71 vs. 85, HR 0.73).

Figure 2 shows the underlying instantaneous (day-to-day) incidence (HR) functions. For any CVD and for MACE, the incidence function in the former conventional group was higher than that in the intensive group over the first ~17 years of follow-up, but the curves became equal in later years. The estimates beyond 25 years, however, are imprecise because the number at risk declines due to the staggered entry of subjects into the DCCT during 1983–1989.

Table 1—Cardiovascular events in each original treatment group of the DCCT

Event	Intensive-treatment group				Conventional-treatment group			
	Patients* n (%)	Events† n	Initial events‡ n	Secondary events§ n	Patients* n (%)	Events† n	Initial events‡ n	Secondary events§ n
Any CVD events	82 (11.5)	149	82	67	102 (14.0)	217	102	115
1. Nonfatal acute MI	24 (3.4)	26	19	7	29 (4.0)	35	23	12
2. Nonfatal cerebrovascular event	8 (1.1)	9	7	2	12 (1.6)	13	11	2
3. Death from CVD	9 (1.3)	9	5	4	16 (2.2)	16	8	8
4. Silent MI	20 (2.8)	21	19	2	33 (4.5)	36	24	12
5. Confirmed angina	20 (2.8)	20	11	9	22 (3.0)	33	11	22
6. Revascularization	40 (5.6)	62	20	42	48 (6.6)	71	22	49
7. CHF	2 (0.3)	2	1	1	10 (1.4)	13	3	10
MACE	39 (5.5)	44	39	5	49 (6.7)	64	49	15
1. Nonfatal acute MI	24 (3.4)	26	24	2	29 (4.0)	35	28	7
2. Nonfatal cerebrovascular event	8 (1.1)	9	8	1	12 (1.6)	13	11	2
3. Death from CVD	9 (1.3)	9	7	2	16 (2.2)	16	10	6

MI, myocardial infarction. *Number of patients with each type of event, regardless of whether it is the initial event for that subject. †The total number of events of each type in all subjects. ‡If a patient had multiple initial events on the same day, then only the most severe initial event is tabulated according to the following order of severity: nonfatal acute MI, CHF, revascularization, and confirmed angina. §The number of additional events of other types experienced by the subjects with a specific event. For example, 24 subjects experienced a total of 26 acute nonfatal MIs, of which it was the initial event for 19 subjects and a subsequent (secondary) event for 7 subjects.

Proportional hazards models, adjusted for selected baseline factors, also assessed the association of selected time-dependent covariates with CVD risk and the effect of DCCT treatment group before and after adjustment for each of these limited factors (Table 2). The HR of intensive versus conventional treatment, adjusted only for baseline factors, was 0.70 (P = 0.015). The five subjects with a history of kidney failure had a 4.8-fold risk of CVD than did those without antecedent kidney failure, but adjustment for kidney failure did not materially alter the treatment group effect, perhaps because of the small number of affected subjects. A history of sustained microalbuminuria (71 subjects) or albuminuria (27 subjects) was each significantly associated with about a twofold increased risk of CVD versus those without and explained a sufficient part of the treatment group effect to render it no longer significant (P = 0.10 and P = 0.06, respectively).

A 10% lower updated mean HbA$_{1c}$ during DCCT/EDIC (e.g., 8 vs. 7.2%) was associated with an HR of 0.72, representing a 28% reduction in the risk of a cardiovascular event (95% CI 19, 37; P < 0.0001). The updated log mean DCCT/EDIC HbA$_{1c}$ explained all of the treatment group effect on risk of CVD, the treatment group HR being

exactly 1 and no longer significant (P = 0.99) after adjustment for HbA$_{1c}$.

CONCLUSIONS

We have previously demonstrated the beneficial effects of an average of 6.5 years of intensive versus conventional diabetes therapy on the risk of any CVD and also on the standardized MACE outcome (13). This was based on analysis of events when at least 50 conventional subjects had experienced a CVD event (mean of 17 years of follow-up). The current analysis (mean of 26 years of follow-up) was performed after at least 100 cases (184 total events) in the former conventional group had occurred. The cumulative incidence curves for any CVD and MACE within the former intensive and conventional groups continue to demonstrate a treatment effect with a continuing difference in cumulative incidence over time. However, the risk reduction of any CVD with intensive therapy through 2013 is now less than that reported previously through 2004 (30% [P = 0.016] vs. 47% [P = 0.005]), and likewise, the risk reduction per 10% lower mean HbA$_{1c}$ through 2013 was also somewhat lower than previously reported but still highly statistically significant (17% [P = 0.0001] vs. 20% [P = 0.001]).

The cumulative incidence curves (Fig. 1A and B) are a function of past differences

between former treatment groups that are perpetuated into the future and of differences in the day-to-day incidences (current risks) over time. The latter may be a more direct measure of the long-term metabolic memory effects. Plots of these incidence functions (Fig. 2A and B) for any CVD and MACE show that the incidences (risk of an event at each day) in both former treatment groups were increasing with time, that in the conventional group higher than intensive, and that beyond ~17 years of follow-up, the incidences in the two groups were similar. As noted, the incidence estimates beyond 25 years are less precise owing to the declining numbers at risk. These suggest that the beneficial metabolic memory effect on the underlying incidence of any CVD and MACE may be diminishing with longer follow-up.

The treatment group effect for any CVD in the 2005 report through 20 years of follow-up was 42%, whereas through 30 years, it has declined to 30% (P = 0.016) (13). The actual decline may be greater because the latter estimate includes CHF, whereas the former does not, and there is now a fivefold difference in the few cases of CHF between treatment groups (2 intensive vs. 10 conventional cases). However, it is unlikely there were many heart failure events at the 2005
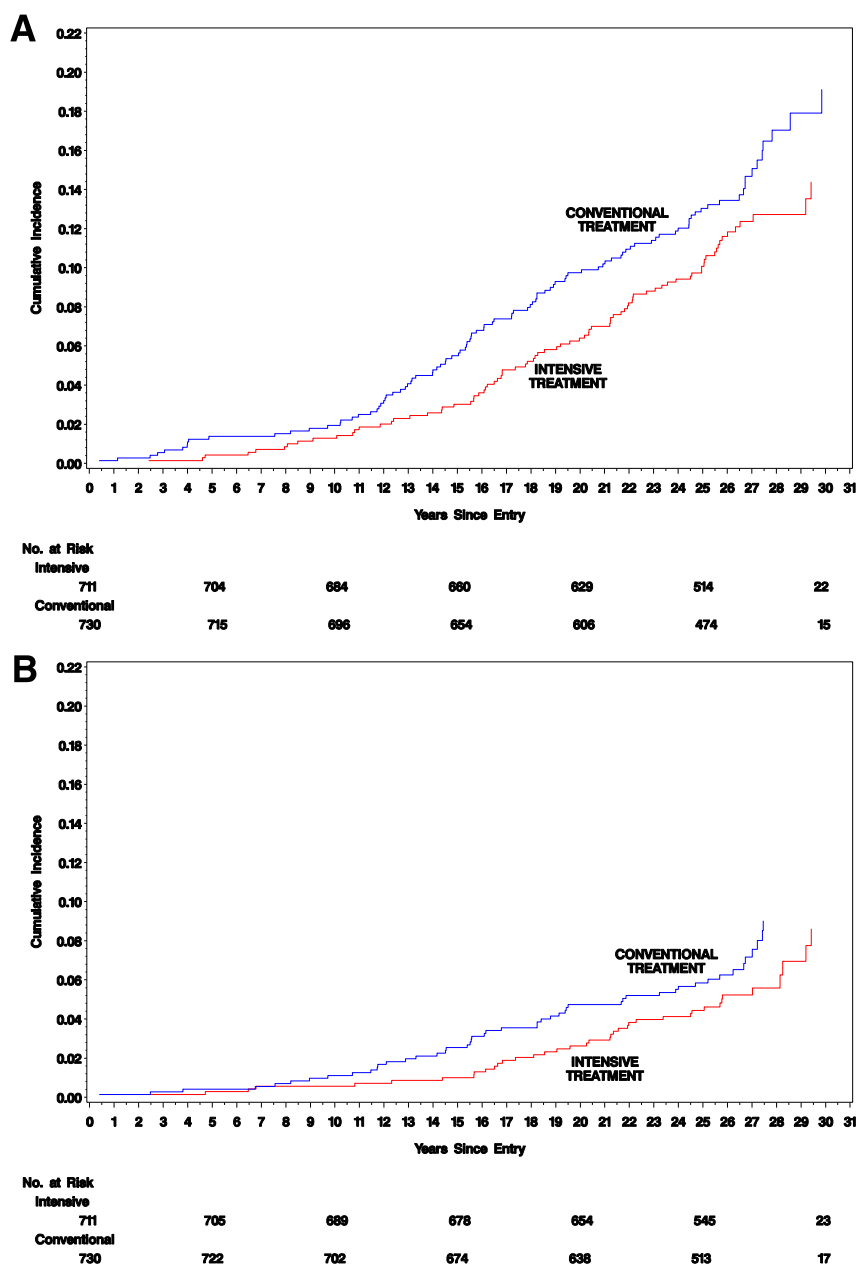
Figure 1—Cumulative incidence of cardiovascular outcomes in the conventional treatment and intensive treatment groups during up to 30 years of DCCT/EDIC treatment and follow-up. *A*: The first of any of the predefined CVD outcomes. The risk reduction with intensive therapy was 30% (95% CI 7, 48; *P* = 0.016). *B*: The first occurrence of MACE. The risk reduction with intensive therapy was 32% (95% CI −3, 56; *P* = 0.07).

follow-up. Likewise, the risk reduction for MACE has declined from 57 to 32%, the latter no longer being statistically significant (*P* = 0.07). The difference in CHF between groups is of interest, but the numbers are too small to permit any definitive statement or analysis of additional, potentially confounding, factors.

Adjusting for the effects of microalbuminuria and albuminuria individually, both reduce the HR for the treatment group effect on any CVD such that it is no longer statistically significant (*P* = 0.10 and *P* = 0.06, respectively). A greater effect is apparent, however, when adjustment is made for the updated mean HbA$_{1c}$ from DCCT and EDIC combined, such that the HR becomes 1.00 (*P* = 0.98). It is thus likely that the better glycemia experienced during DCCT with intensive therapy has

CVD benefits beyond the subsequent development of microalbuminuria.

Although the pathogenesis of coronary artery disease (CAD) in type 1 diabetes is still poorly understood and there are morphologic and risk factor differences, as reviewed elsewhere, atherosclerosis is clearly a slowly progressive state that starts in childhood and is likely to be accelerated in the presence of diabetes (16). This acceleration is likely to result from many pathways, including renal disease and lipid and blood pressure changes (16). We previously showed a lower incidence of hypertension in the former intensive therapy group (27) as well as decreased glucose-based atherosclerosis mechanisms, including glyco-oxidative stress (5), inflammation (28), and advanced glycosylated end-product formation (29). Thus this acceleration of atherosclerosis that is apparent in type 1 diabetes appears to have been reduced by a 6-year period of DCCT intensive therapy, a benefit that has continued to be evident many years later. This is consistent with the chronicity of the atherosclerotic process; as such, individuals will be subsequently progressing from a lower degree of glycemic damage. Thus, seeing a strong continuing—although somewhat reduced—treatment effect many years after the randomized treatment phase stopped (and after which both groups had similar glucose control) is consistent with the natural history of atherosclerosis itself and with the DCCT metabolic memory observations with all other complications (3,19).

The extent to which metabolic memory reflects delayed progression and the carrying forward of a reduced degree of glycemic damage or a long-term alteration of future risk remains unclear. Mechanistically, this may reflect a complex balance of alterations in tissue-destructive and potential protective factors. Another possible explanation for the equilibration of the current risks beyond year 17, principally due to a stabilization of the risk in the conventional group, is the possible "exhaustion of susceptible" subjects in the conventional group, more so than the intensive group, whereby subjects who are predisposed (genetically or otherwise) experience a CVD event early in follow-up, and those remaining at risk
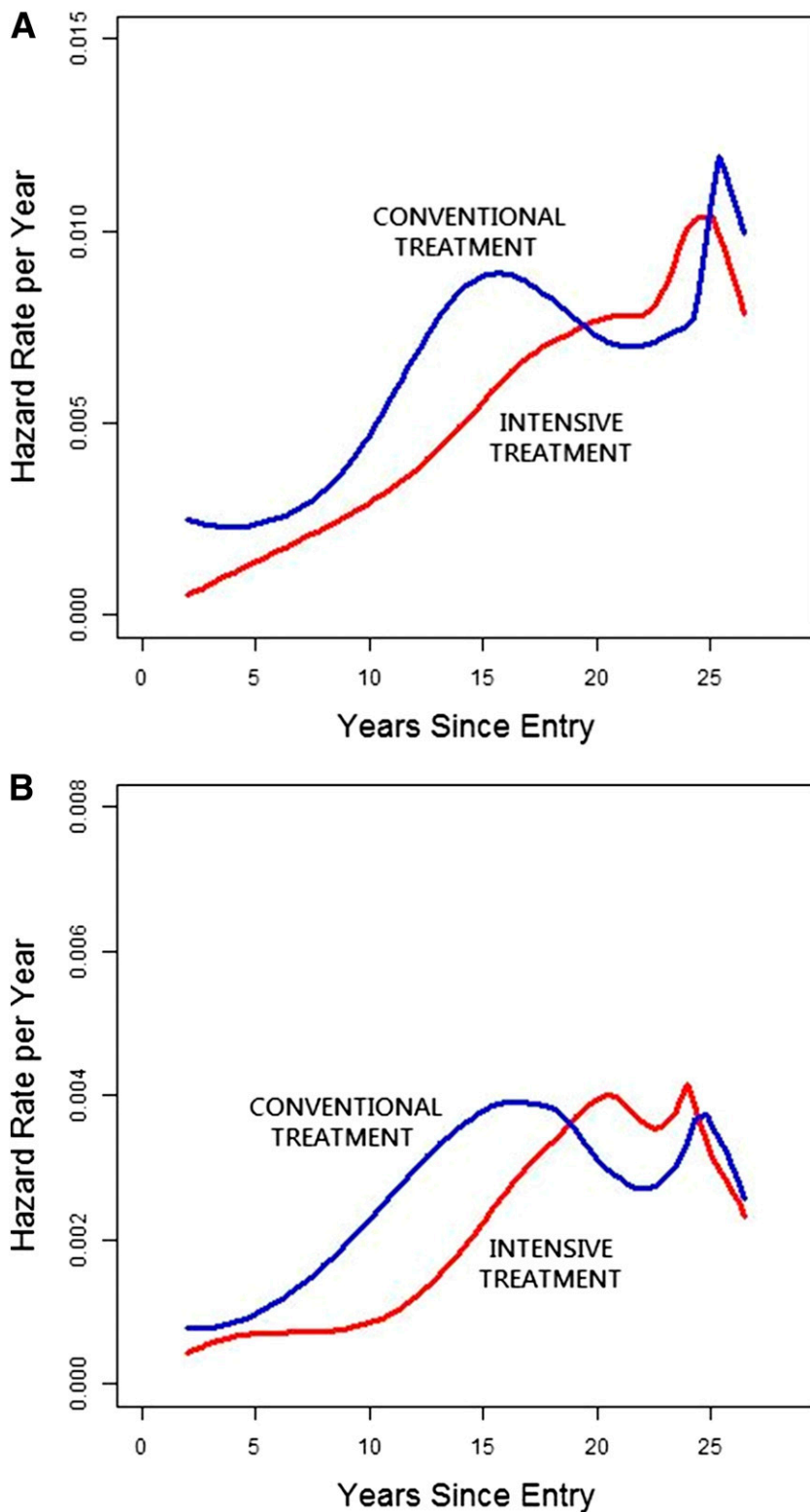
Figure 2—Underlying HR function representing the risk of a new event among those remaining at risk at every point in time. Note that the number of subjects at risk declines beyond year 24 owing to staggered entry of subjects during 1983–1989. *A*: Any CVD. *B*: MACE.

benefit of early intensive therapy intervention in young adults with recent-onset type 1 diabetes, when the atherosclerotic process can be attenuated in its relatively early stage, but does not necessarily apply to subjects with older-onset type 2 diabetes with more advanced CVD. For instance, in the extended follow-up of the Veterans Affairs Diabetes Trial (VADT), although the time to the first major CVD event increased with intensive glycemic control, there was no significant difference in cardiovascular mortality (30). Similar to the inclusion criteria and study follow-up of the DCCT/EDIC study, the UK Prospective Diabetes Study (UKPDS), with its inclusion of younger patients with newly diagnosed diabetes and an absence of recent CVD events, demonstrated significant reductions in myocardial infarction and mortality in the former intensive treatment patient cohort, unlike the results of other studies of type 2 diabetes, including the VADT, involving older individuals with longer duration of diabetes and a greater incidence of preexisting CVD and/or CVD risk factors at baseline (7,30–32).

An interesting observation in DCCT/EDIC is the potentially stronger effect of intensive therapy on protecting against fatal ($n = 25$) rather than nonfatal CAD. This preliminary observation will require further confirmation when we have a larger number of fatal CAD events in the future. This was examined because of a suggestion in the literature that HbA_{1c} may be a stronger predictor of fatal than nonfatal CAD events (15,33). Taken together these data may explain some of the inconsistencies of the glycemia-CAD relationship in past studies and point toward mechanisms that may be particularly related to glycemia per se, for example, mechanisms underlying plaque erosion, thrombosis, and renal disease, all of which have been associated with a more fatal presentation of CAD (34,35).

The current analyses have strengths and weaknesses. The DCCT/EDIC includes a well-characterized cohort of individuals with type 1 diabetes monitored for up to 30 years, with entry criteria designed to address the development and progression of the complications of type 1 diabetes.

beyond some point in time are protected. This could be assessed if and when a suitable risk function based on genetic or other factors is established, which could be the subject of future reports. The current data support the

Table 2—Proportional hazards models of the effect of time-dependent covariates on the risk of CVD and of the effect of the treatment group after adjustment for the time-dependent covariate

	Effect of time-dependent covariate*		Treatment group adjusted for specific time-dependent covariate*	
Time-dependent covariate	HR (95% CI)	P value	HR (95% CI)	P value
None	—	—	0.70 (0.52, 0.93)	0.0151
Sustained microalbuminuria (yes vs. no)‡	2.28 (1.67, 3.11)	<0.0001	0.78 (0.58, 1.05)	0.1038
Macroalbuminuria (yes vs. no)§	2.22 (1.46, 3.38)	0.0002	0.75 (0.56, 1.01)	0.0594
Kidney failure (yes vs. no)¶	4.84 (1.93, 12.11)	0.0008	0.71 (0.53, 0.95)	0.0199
Mean HbA$_{1c}$ during DCCT/EDIC#				
Per 10% increase	1.35 (1.21, 1.51)	<0.0001	1.00 (0.72, 1.39)	0.9843
Per 10% decrease	0.72 (0.63, 0.81)			

*Each of the above five models was also adjusted for the following DCCT baseline characteristics: HbA$_{1c}$ value, age, cholesterol level, and smoking status. ‡Sustained microalbuminuria was defined by a history of microalbuminuria (AER ≥30 mg/24 h) on at least two consecutive visits, or ESRD (dialysis or transplant). §Macroalbuminuria was defined by a history of albuminuria (AER ≥300 mg/24 h) or ESRD. ¶Kidney failure was defined by a history of eGFR <15 mL/min/1.73 m^2 or ESRD. #The weighted mean HbA$_{1c}$ up to the time of each CVD event was calculated as the weighted mean of the quarterly values during DCCT plus the annual values during EDIC, weighted respectively by ¼ and 1 to reflect the interval between values during the DCCT and EDIC. The log mean HbA$_{1c}$ value was used so that the HR per c-fold change in risk is *c3.17155*, where 3.17155 is the estimated regression coefficient; a *c* of 1.1 corresponds to a 10% increase in the mean glycosylated hemoglobin value, and a *c* of 0.9 to a 10% decrease.

The CVD adjudication process ensures capture of valid and verifiable CVD events. Over time, the occurrence of CVD events has increased, reflective of the increasing duration of type 1 diabetes and advancing age of the cohort. However, the mean age (~56 years) of the cohort remains relatively young when considering CVD events. In addition, the exclusion of individuals with preexisting hypertension, hyperlipidemia, or CVD, coupled with the continued relatively small number of CVD events, may limit applicability of these results to the population with type 1 diabetes as a whole.

In summary, intensive diabetes therapy during the DCCT (6.5 years) has long-term, clinically beneficial effects on the incidence of CVD in this cohort with type 1 diabetes. Efforts to make intensive diabetes management attainable at a young age must continue so as to reduce the rates of life-threatening CVD over the life span for patients with diabetes.

Appendix

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