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Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes

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

Abstract

BACKGROUND—Intensive diabetes therapy aimed at achieving near normoglycemia reduces the risk of microvascular and neurologic complications of type 1 diabetes. We studied whether the use of intensive therapy as compared with conventional therapy during the Diabetes Control and Complications Trial (DCCT) affected the long-term incidence of cardiovascular disease.

METHODS—The DCCT randomly assigned 1441 patients with type 1 diabetes to intensive or conventional therapy, treating them for a mean of 6.5 years between 1983 and 1993. Ninety-three percent were subsequently followed until February 1, 2005, during the observational Epidemiology of Diabetes Interventions and Complications study. Cardiovascular disease (defined as nonfatal myocardial infarction, stroke, death from cardiovascular disease, confirmed angina, or the need for coronary-artery revascularization) was assessed with standardized measures and classified by an independent committee.

RESULTS—During the mean 17 years of follow-up, 46 cardiovascular disease events occurred in 31 patients who had received intensive treatment in the DCCT, as compared with 98 events in 52 patients who had received conventional treatment. Intensive treatment reduced the risk of any cardiovascular disease event by 42 percent (95 percent confidence interval, 9 to 63 percent; P = 0.02) and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57 percent (95 percent confidence interval, 12 to 79 percent; P = 0.02). The decrease in glycosylated hemoglobin values during the DCCT was significantly associated with most of the positive effects of intensive treatment on the risk of cardiovascular disease. Microalbuminuria and albuminuria were associated with a significant increase in the risk of cardiovascular disease, but differences between treatment groups remained significant (P≤0.05) after adjusting for these factors.

CONCLUSIONS—Intensive diabetes therapy has long-term beneficial effects on the risk of cardiovascular disease in patients with type 1 diabetes.

Type 1 Diabetes Mellitus Is Associated with long-term complications that affect the eyes, kidneys, and peripheral and autonomic nervous systems.[1] Although the pathophysiological basis of these complications remains uncertain, hyperglycemia appears to play a central role. Epidemiologic studies have demonstrated a strong association between the level of glycemia and the occurrence of these diabetic complications.[2] The Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study, DCCT's long-term follow-up study, have demonstrated a consistent salutary effect of

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intensive therapy, aimed at achieving glucose control as close to the nondiabetic range as safely possible, on the development and progression of retinopathy, nephropathy, and neuropathy.[3,4] The DCCT/EDIC study has established a causal role of hyperglycemia in the development and progression of the microvascular complications of type 1 diabetes.

Although cardiovascular disease is not specific to diabetes, it is more prevalent among patients with type 1 or type 2 diabetes than among those without diabetes.[5,6] Type 1 diabetes is associated with at least a 10-fold increase in cardiovascular disease as compared with an age-matched nondiabetic population.[6,7] An association between hyperglycemia and cardiovascular disease has been suggested by some,[8] but not all,[9] studies of patients with type 1 diabetes. However, controlled clinical trials of patients with type 1 or type 2 diabetes have not demonstrated a reduction in the occurrence of cardiovascular disease with long-term intensive diabetes therapy. During the DCCT, fewer cardiovascular events occurred in the intensive-treatment group than in the conventional-treatment group, but the small number of events in the relatively young cohort precluded a determination of whether the use of intensive diabetes therapy affected the risk of cardiovascular disease.[10] Using long-term follow-up data on the DCCT/EDIC cohort, we evaluated whether intensive therapy reduces the risk of cardiovascular events among patients with type 1 diabetes.

METHODS

Detailed descriptions of the methods of the DCCT and EDIC follow-up study have been published previously.[3,4,11,12] The DCCT, a randomized, controlled clinical trial conducted between 1983 and 1993, was designed to compare the effects of an intensive diabetes treatment regimen with those of conventional therapy.

STUDY POPULATION

Of the 1441 patients with type 1 diabetes who were 13 to 40 years old at the time of randomization, 1422 completed the DCCT; the mean follow-up was 6.5 years. At baseline, eligibility criteria excluded patients with a history of cardiovascular disease or with hypertension (defined by a blood pressure of 140/90 mm Hg or more) or hypercholesterolemia (defined by a serum cholesterol level obtained after an overnight fast that was at least 3 SD above age- and sex-specific means).[11] Of the surviving cohort, 1394 — representing 97 percent of the original cohort — agreed to join the long-term EDIC follow-up study in 1994. The current report includes follow-up data obtained through February 1, 2005, at which point 93 percent of the original cohort (96 percent of 1397 surviving participants) remained in the study. The DCCT/EDIC study was approved by the institutional review boards of all participating centers, and all participants provided written informed consent.

STUDY PROCEDURES

During the DCCT, participants were examined annually. Glycosylated hemoglobin values were measured quarterly,[13] and fasting lipid levels, serum creatinine values, and other risk factors for cardiovascular disease were measured annually in a central laboratory.[11] Microalbuminuria and albuminuria were defined by urinary albumin excretion of at least 40 mg in a 24-hour period and of at least 300 mg in a 24-hour period, respectively.[11] Renal disease was defined by the development of a serum creatinine level of at least 2 mg per deciliter (177 μmol per liter) or the need for dialysis or kidney transplantation. Electrocardiograms were obtained and examined annually by readers who were unaware of patients' treatment assignments. During the EDIC follow-up study, the methods used in the DCCT were continued, but glycosylated hemoglobin was measured annually and fasting lipid levels and renal function were measured in alternate years.[12]

TREATMENT

Intensive therapy consisted of three or more daily injections of insulin or treatment with an external insulin pump, with dose adjustments based on at least four self-monitored glucose measurements per day. Daily glucose goals were 70 to 120 mg per deciliter (3.9 to 6.7 mmol per liter) before meals and peak levels of less than 180 mg per deciliter (10.0 mmol per liter) after meals. The goal for glycosylated hemoglobin was less than 6.05 percent — 2 SD above the mean value for persons without diabetes. Conventional therapy had no glucose goals beyond those needed to prevent symptoms of hyperglycemia and hypoglycemia and consisted of one or two daily injections of insulin. The absolute difference between groups in the mean glycosylated hemoglobin value at the end of the mean 6.5 years of the DCCT was approximately 2 percentage points (7.4 percent in the intensive-treatment group vs. 9.1 percent in the conventional-treatment group, $P<0.01$). At the end of the DCCT, the conventional-treatment group was offered intensive treatment and all participants returned to their own health care providers for diabetes care. Subsequently, differences in treatment dissipated, with only a trivial, nonsignificant difference between groups in the fraction of patients using three or more daily injections of insulin or an insulin pump (Table 1). Differences in the mean (±SD) glycosylated hemoglobin value also narrowed in the intensive-treatment and conventional-treatment groups over the entire 11 years of the EDIC follow-up study (8.0±1.2 percent and 8.2±1.2 percent, respectively; $P = 0.03$).

OUTCOMES

The primary outcome was the time to the first of any of the following cardiovascular events: nonfatal myocardial infarction or stroke; death judged to be due to cardiovascular disease; subclinical myocardial infarction; angina, confirmed by ischemic changes on exercise tolerance testing or by clinically significant obstruction on coronary angiography; or the need for revascularization with angioplasty or coronary-artery bypass.[14] Subclinical (“silent”) myocardial infarctions were identified on the annual electrocardiograms.[15]

Medical records describing cardiovascular events, including electrocardiographic findings and cardiac enzyme levels, were submitted for adjudication to a committee whose three members were unaware of patients' treatment assignments. Only cardiovascular events that were considered definite were counted.[16]

STATISTICAL ANALYSIS

The DCCT/EDIC Study Research Group specified in 1996 that no analyses comparing the cardiovascular events between groups would be performed until 50 patients in the original conventional-treatment group had had a cardiovascular event, providing the study with a statistical power of 85 percent to detect a 50 percent reduction in the risk of cardiovascular events between groups. No interim analyses were performed until that milestone was reached at the beginning of 2005. This article is based on all events that had occurred as of February 1, 2005. Analyses were conducted according to the intention-to-treat principle on the basis of the original DCCT treatment assignment. Results that were nominally significant (two-sided $P<0.05$) are cited.

Clinical characteristics were compared with the use of the Wilcoxon rank-sum test for quantitative variables and the chi-square test for categorical variables.[17] The cumulative incidence of a cardiovascular event (the first of any) within groups was estimated according to the Kaplan-Meier method, the difference between groups was evaluated by means of the log-rank test, and the hazard ratio comparing intensive with conventional treatment and 95 percent confidence intervals were estimated by means of a Cox proportional-hazards model. The corresponding risk reduction was calculated as 100 × (1 - the hazard ratio). Event rates, including multiple events in the same patient, are presented as the number per 100 patient-

years, and the difference was evaluated, with allowance for repeated events and over-dispersion.[18] Proportional-hazards models were used to assess the effects of time-dependent covariates (mean glycosylated hemoglobin value updated to the time of the cardiovascular event during the DCCT or, if no event occurred during the DCCT, to the end of the DCCT; or the development of renal disease, microalbuminuria, or albuminuria) and the effect of the treatment group, after adjustment for such covariates.[19] The effect of the glycosylated hemoglobin value during the EDIC trial was not assessed in these analyses.

The DCCT and EDIC studies were designed entirely by the DCCT/EDIC Study Research Group, which collected the data. The writing committee prepared the article and vouches for its completeness and accuracy.

RESULTS

The major characteristics relevant to cardiovascular disease are described at baseline, at the end of the DCCT, and at year 11 of the EDIC study (Table 1). At baseline, no patients in the DCCT had hypertension or hypercholesterolemia, on the basis of the standards at the time, and only 5 percent had microalbuminuria (urinary albumin excretion of at least 40 mg per 24 hours). There were no significant differences between the intensive-treatment and conventional-treatment groups in any risk factors for cardiovascular disease at baseline, except for a minimally higher systolic blood pressure in the conventional-treatment group. At the end of the DCCT, the two groups had diverged with regard to the prevalence of several established and putative risk factors for cardiovascular disease. Microalbuminuria and albuminuria were more prevalent (13 percent vs. 7 percent, $P < 0.01$, and 3 percent vs. 1 percent, $P<0.05$, respectively) in the conventional-treatment group than in the intensive-treatment group, and the glycosylated hemoglobin value was higher (9.1±1.5 percent vs. 7.4±1.1 percent, $P<0.01$) in the conventional-treatment group. By year 11 of the EDIC study, the prevalences of microalbuminuria and albuminuria remained greater in the former conventional-treatment group and the prevalence of a serum creatinine value of at least 2 mg per deciliter was also significantly greater in this group (2 percent vs. 0 percent, $P<0.05$). There were only trivial or nonsignificant differences between the groups in the prevalence of other conventional risk factors for cardiovascular disease at the end of the DCCT and at year 11 of the EDIC study; the absolute difference in the glycosylated hemoglobin value between groups was only 0.1 percent at year 11 of the EDIC study ($P = 0.38$) (Table 1).

A total of 144 cardiovascular events occurred in 83 patients during the mean 17 years of follow-up, 46 among 31 patients originally assigned to intensive treatment and 98 among 52 patients originally assigned to conventional treatment (Table 2). The respective event rates were 0.38 and 0.80 per 100 patient-years ($P = 0.007$). Although the rates of individual clinical events that made up the main outcome were not significantly different between groups, they were consistently lower, usually by at least 50 percent, in the intensive-treatment group than in the conventional-treatment group.

A life-table analysis of the cumulative incidence of a first cardiovascular event showed that intensive treatment was associated with a 42 percent reduction in risk, as compared with conventional treatment (95 percent confidence interval, 9 to 63 percent; $P = 0.02$) (Fig. 1A). The risk of the first occurrence of nonfatal myocardial infarction, stroke, or death from cardiovascular disease was reduced 57 percent with intensive treatment, as compared with conventional treatment (95 percent confidence interval, 12 to 79 percent; $P = 0.02$) (Fig. 1B).

Proportional-hazards models, adjusted for selected baseline factors, were used to assess the association of time-dependent covariates with the risk of cardiovascular disease in the combined cohort and the effect of the DCCT treatment group before and after adjustment for

each factor (Table 3). The hazard ratio for intensive as compared with conventional treatment, adjusted only for baseline factors, was 0.53 (P = 0.005). A history of renal disease did not have a significant effect on the risk of cardiovascular disease or on the treatment-group effect, perhaps because of the small number of such patients (35). A history of microalbuminuria or of albuminuria was significantly associated with an increase in the risk of cardiovascular disease by a factor of more than 2.5 and explained part of the treatment-group effect, as reflected by the increase in the hazard ratio and P value. The difference in cardiovascular disease outcomes between groups remained significant after adjustment for these factors.

An updated glycosylated hemoglobin value during the DCCT (mean glycosylated hemoglobin value updated to the time of the cardiovascular event during the DCCT or, if no event occurred during the DCCT, to the end of the DCCT) that was 10 percent lower in one patient than in another (e.g., 7.2 percent vs. 8.0 percent) was associated with a hazard ratio of 0.80, representing a 20 percent reduction in the risk of a cardiovascular event (95 percent confidence interval, 9 to 30 percent; P<0.001). The use of the updated log mean glycosylated hemoglobin value during the DCCT explained a large part of the treatment-group effect on the risk of cardiovascular disease, the treatment-group hazard ratio being closer to 1 and no longer significant (P = 0.61) after adjustment. There were no significant differences between groups in the use of medications known to affect the risk of cardiovascular disease, except for the use of beta-blockers, which was more common in the conventional-treatment group than in the intensive-treatment group (7 percent vs. 3 percent, P<0.05) at year 11 of the EDIC study (Table 1).

We determined which baseline characteristics of the entire cohort in the DCCT were associated with the occurrence of the cardiovascular disease outcome independent of treatment assignment (Table 4). At baseline, older age (31 vs. 27 years), a longer duration of diabetes (7 vs. 6 years), the presence of retinopathy, current smoking, a higher body-mass index (24.0 vs. 23.3), higher total and low-density lipoprotein cholesterol levels (194 vs. 175 mg per deciliter [5.0 vs. 4.5 mmol per liter] and 127 vs. 109 mg per deciliter [3.3 vs. 2.8 mmol per liter], respectively), higher glycosylated hemoglobin levels (9.5 percent vs. 9.0 percent), and a higher albumin excretion rate (19.3 vs. 15.7 mg per 24 hours), and assignment to conventional treatment were all associated with the development of cardiovascular disease.

DISCUSSION

Controlled clinical trials involving patients with type 1 diabetes and those with type 2 diabetes have conclusively demonstrated that intensive diabetes therapy aimed at lowering glycemic levels reduces the risk of diabetic retinopathy, nephropathy, and neuropathy.[3,20] In addition, the DCCT/EDIC study demonstrated that a period of approximately 6.5 years of intensive diabetes therapy had a long-term, sustained effect on the subsequent risk of microvascular complications.[4] The pathophysiological mechanisms responsible for the improvement in outcomes and for the prolonged effects of early intervention remain unclear; we have referred to the latter phenomenon as “metabolic memory.” It is in this context that we evaluated the effect of intensive diabetes therapy on the long-term risk of cardiovascular disease.

The primary outcome was defined as a cardiovascular event that included clinical findings or the need for revascularization. As compared with conventional therapy, intensive diabetes therapy reduced the risk of a cardiovascular event by 42 percent and reduced the risk of severe clinical events, including nonfatal myocardial infarction, stroke, or death from cardiovascular disease, by 57 percent. The risk of each of the individual cardiovascular events was reduced to a similar degree. These findings extend our previous observations that intensive as compared with conventional therapy reduces the progression of atherosclerosis, measured by carotid intima-media thickness, and the prevalence of coronary-artery calcification.[21,22]

There are several potential explanations for the effectiveness of a period of intensive diabetes management on the long-term risk of cardiovascular disease outcomes. First, the same glycemic mechanisms that reduce the incidence of microvascular disease may also apply to the development of atherosclerosis and resulting cardiovascular disease. Patients who had a cardiovascular event were more likely to have had retinopathy and had higher albumin excretion rates at baseline. Epidemiologic evidence has shown that any elevation in glycemia, even within the subdiabetic range, increases the risk of cardiovascular disease.[23] Thus, a reduction in the glycosylated hemoglobin value might be expected to have beneficial effects on cardiovascular disease. The long-term effect of hyperglycemia on the risk of microvascular complications may be mediated by the generation of advanced glycation end products, which have been implicated in cardiovascular disease.[24-26]

Alternatively, the beneficial effect of intensive therapy on the risk of cardiovascular disease may be a result of the reduction in the incidence of microvascular disease. Both renal disease and autonomic neuropathy have been proposed as risk factors for cardiovascular disease.[27-29] To the extent that intensive therapy reduces these risk factors,[3,30] cardiovascular disease may also be reduced.

Microalbuminuria and albuminuria were each strongly associated with an increased risk of cardiovascular disease, and each explained some, but not all, of the DCCT treatment-group effect. The treatment-group effect remained significant after adjustment for these factors, suggesting that other effects of intensive therapy are at work. Adjusting for the updated mean glycosylated hemoglobin value during the DCCT explained the majority of the effect of intensive as compared with conventional therapy on the risk of cardiovascular disease. The results demonstrate that differences in glycosylated hemoglobin values during the DCCT accounted for much of the cardiovascular benefit accompanying intensive therapy, mediated in part by the reduction in the incidence of microalbuminuria or albuminuria.

We believe that the DCCT/EDIC study is unique in its long-term objective documentation of glycemic control, established and putative risk factors for cardiovascular disease, and the status of microvascular and cardiovascular complications. The virtually complete follow-up for more than two decades of the DCCT/EDIC cohort, whose members at baseline had no or minimal microvascular disease, no hypertension or hypercholesterolemia (by the standards at the time), and no clinical evidence of cardiovascular disease at baseline, facilitated the study of incident cardiovascular disease. However, several caveats apply to our data. First, the total number of events remains relatively low, precluding definitive assessment of treatment effects on the risks of the different types of cardiovascular events. Second, some of the cardiovascular events, such as the need for revascularization, are dependent on clinicians' judgment and are subject to application bias. Third, the fraction of silent myocardial infarctions was relatively high as compared with that in other studies.[9] Finally, the interventions were unmasked during the DCCT and EDIC study, thus possibly introducing bias in the ascertainment of cardiovascular events or in the application of therapies that may have affected the risk of cardiovascular disease.

Although we cannot entirely discount these sources of potential bias, the uniform collection of historic data, the clinical severity of the cardiovascular outcomes, the masked adjudication of events, and the treatment of the DCCT/EDIC participants predominantly by non-DCCT clinicians for most of their follow-up substantially diminish the risk of bias. Although the relatively large fraction of silent myocardial infarctions is noteworthy, other studies have demonstrated that their outcome may be as severe as that of symptomatic infarctions.[31] In addition, the difference between the treatment groups in the frequency of silent infarctions, detected on electrocardiograms obtained annually by graders who were unaware of patients' study assignments, paralleled the other outcomes. The only difference in medications between

groups that may have confounded the outcome was the more common use of beta-blockers in the conventional-treatment group. This would have decreased the relative benefits of intensive therapy on the risk of cardiovascular disease.

The salutary effect of a mean of 6.5 years of intensive therapy on the risk of cardiovascular events is evidence that intensive diabetes management reduces the incidence of cardiovascular disease. This benefit reinforces the original DCCT message that intensive therapy should be implemented as early as possible in people with type 1 diabetes. The relative reduction in the risk of nonfatal myocardial infarctions, stroke, and death from cardiovascular disease, of 57 percent — the most clinically compelling outcome — exceeds the reductions in risk achieved with other proven interventions, such as medications that lower cholesterol and blood pressure. The large reduction in the risk of cardiovascular events will further improve the projected long-term health and economic benefits of intensive therapy for diabetes.[32]

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Appendix

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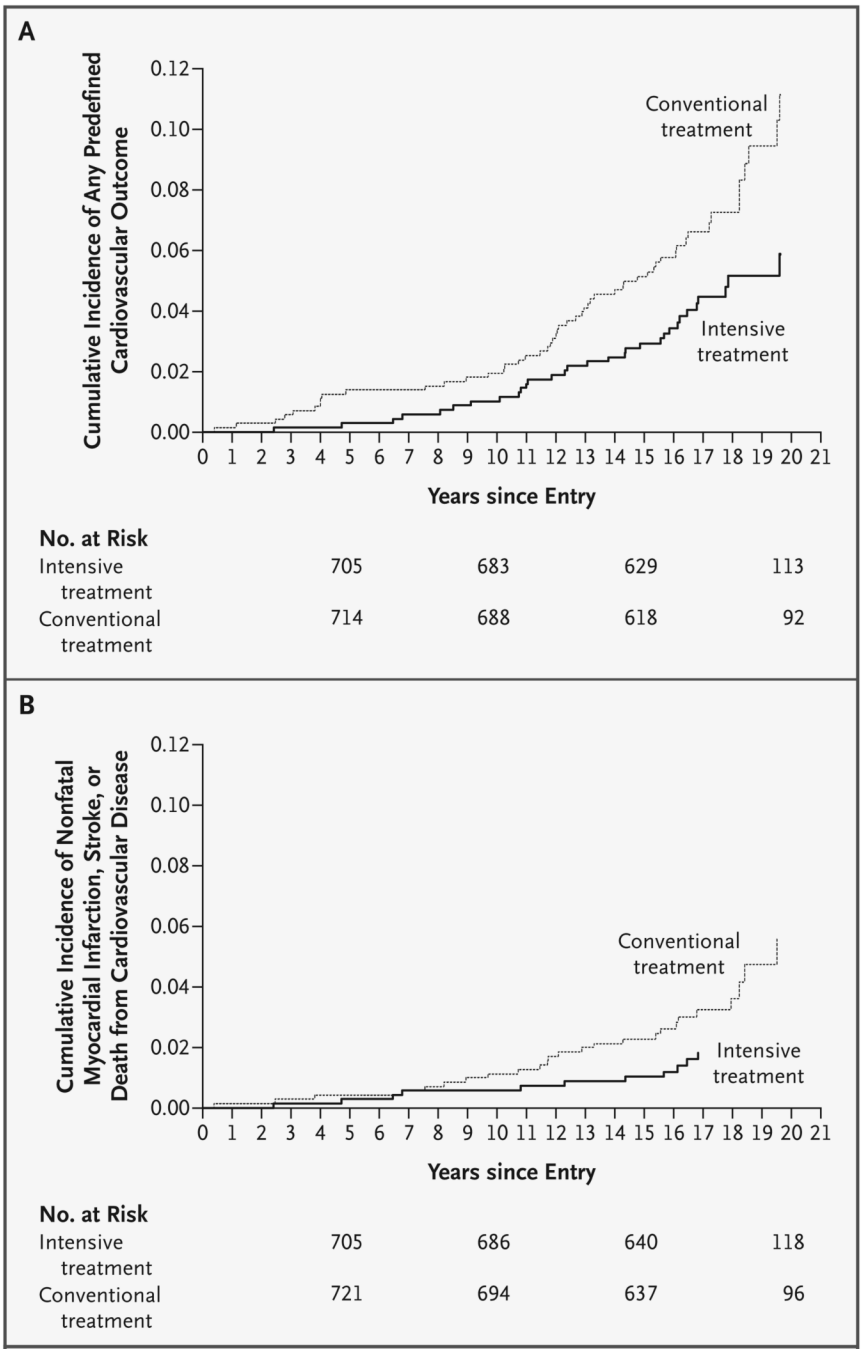

Figure 1. Cumulative Incidence of the First of Any of the Predefined Cardiovascular Disease Outcomes (Panel A) and of the First Occurrence of Nonfatal Myocardial Infarction, Stroke, or Death from Cardiovascular Disease (Panel B)

As compared with conventional treatment, intensive treatment reduced the risk of any predefined cardiovascular disease outcome by 42 percent (95 percent confidence interval, 9 to 63 percent; P = 0.02) (Panel A) and reduced the risk of the first occurrence of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57 percent (95 percent confidence interval, 12 to 79 percent; P = 0.02) (Panel B).

Table 1

Clinical Characteristics of the DCCT/EDIC Cohort.*

Characteristic	DCCT at Baseline (1983-1989)		End of DCCT (1993)		Year 11 of EDIC (2004)†	
	Intensive Treatment (N = 711)	Conventional Treatment (N = 730)	Intensive Treatment (N = 698)	Conventional Treatment (N = 723)	Intensive Treatment (N = 593)	Conventional Treatment (N = 589)
Age (yr)	27±7	27±7	34±7	33±7	45±7	45±7
Female sex (%)	49	46	49	46	48	46
Retinopathy at baseline (%)	51	48	—	—	—	—
Duration of diabetes (yr)	6±4	5±4	12±5	12±5	24±5	23±5
Current cigarette smoker (%)	19	18	20	20	14	11
Body-mass index	23.3±2.7	23.4±2.9	26.6±4.2	25.1±3.2‡	28.4±6.9	27.6±4.5
Blood pressure (mm Hg)						
Systolic	113±12	115±12§	117±12	117±12	120±14	121±15
Diastolic	72±9	73±9	75±9	74±9	75±9	75±9
Hypertension (%)¶	0	0	3	4	38	41
Lipids //						
HDL cholesterol (mg/dl)	51±12	50±12	51±13	52±13	55±15	55±14
LDL cholesterol (mg/dl)	110±29	109±29	112±27	115±32	112±30	109±28
Total cholesterol (mg/dl)	177±33	176±34	180±31	184±38	186±35	181±32§
Triglycerides (mg/dl)	81±43	82±51	84±53	88±51§	93±60	86±54§
Hyperlipidemia (%)**	0	0	26	30	52	48
Renal function//						
Albumin excretion rate (mg/24 hr)	16.4±19.6	15.5±17.9	29.8±197.6	75.4±441.1‡	54.2±375.9	116.4±576.8‡
Albumin excretion rate (%)						
≥40 mg/24 hr	5	5	7	13‡	9	17‡
≥300 mg/24 hr	0	0	1	3§	2	6‡
Serum creatinine ≥2 mg/dl (177 μmol/liter) (%)	0	0	0	0	0	2§
Dialysis or transplantation ever (%)	0	0	0	0	1	1
Glycosylated hemoglobin (%)	9.1±1.6	9.1±1.6	7.4±1.1	9.1±1.5‡	7.9±1.3	7.8±1.3
Heart rate (beats/min)	68±11	68±11	69±11	71±12‡	70±12	70±12
Medication (%)††						
ACE inhibitors or ARBs (for any cause)	—	—	—	—	38	43

Characteristic	DCCT at Baseline (1983-1989)		End of DCCT (1993)		Year 11 of EDIC (2004)†	
	Intensive Treatment (N = 711)	Conventional Treatment (N = 730)	Intensive Treatment (N = 698)	Conventional Treatment (N = 723)	Intensive Treatment (N = 593)	Conventional Treatment (N = 589)
Hormone-replacement therapy	—	—	—	—	6	4
≥14 Aspirin tablets/mo	—	—	—	—	37	40
Beta-blocker	—	—	—	—	3	7‡
Statin	—	—	—	—	34	33
Intensive diabetes management (%)‡‡	0	0	98	10‡	97	94

*Plus-minus values are means ±SD. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, ACE angiotensin-converting enzyme, and ARB angiotensin-receptor blocker. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for trigylcerides to millimoles per liter, multiply by 0.1129.

†The annual EDIC examination at year 11 was completed for 1182 of the surviving patients at the time of data closeout for this study.

‡P<0.01 by the Wilcoxon rank-sum test or the chi-square test comparing conventional and intensive treatment.

§P<0.05 by the Wilcoxon rank-sum test or the chi-square test comparing conventional and intensive treatment.

¶Hypertension was defined by a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, documented hypertension, or the use of antihypertensive agents.

‖Renal function and lipid levels (HDL and LDL cholesterol) were determined from the biennial evaluation conducted at year 9 or 10 of the EDIC study on the basis of the year of entry into the DCCT.

**Hyperlipidemia was defined by an LDL cholesterol level of at least 130 mg per deciliter (3.4 mmol per liter) or the use of lipid-lowering agents. Physicians were alerted to the presence of hyperlipidemia during the DCCT and the EDIC study. Hypercholesterolemia was a DCCT exclusion criteria.

††Medication history was not obtained during the DCCT, but the use of ACE inhibitors was discouraged, and statins were not widely available or in use during the DCCT.

‡‡This category includes the use of multiple (three or more) daily injections or an insulin pump.

Table 2

Cardiovascular Events in Each Original Treatment Group of the DCCT.

Event	Intensive-Treatment Group			Conventional-Treatment Group		
	No. of Events	No. of Patients*	No. of Initial Events†	No. of Events	No. of Patients*	No. of Initial Events†
Death from cardiovascular disease	3	3	3	9	9	4
Nonfatal acute myocardial infarction	7	7	6	16	15	11
Silent myocardial infarction	7	7	7	21	18	13
Revascularization	17	11	4	25	20	6
Confirmed angina	11	11	10	22	18	13
Nonfatal cerebrovascular event	1	1	1	5	5	5
All cardiovascular disease events	46		31	98		52
Nonfatal myocardial infarction or stroke or death from cardiovascular disease	11		11‡	30		25‡

*Patients could have multiple events.

†If patients had multiple first events on the same day, the initial events were ordered in the following way: confirmed angina, acute myocardial infarction, and the need for revascularization.

‡This category includes six patients who had angina as an antecedent event, one originally assigned to intensive treatment and five originally assigned to conventional treatment.

Table 3

Proportional-Hazards Models of the Effect of Time-Dependent Covariates on the Risk of Cardiovascular Disease and of the Effect of the Treatment Group after Adjustment for the Time-Dependent Covariate.

Time-Dependent Covariate	Effect of Time-Dependent Covariate*		Treatment Group Adjusted for Time-Dependent Covariate*	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
None	—	—	0.53 (0.34-0.83)	0.005
Renal disease (yes vs. no)†	2.99 (0.72-12.5)	0.20	0.54 (0.34-0.84)	0.006
Microalbuminuria (yes vs. no)‡	2.93 (1.85-4.65)	<0.001	0.62 (0.39-0.97)	0.04
Albuminuria (yes vs. no) §	2.57 (1.36-4.88)	0.009	0.58 (0.37-0.91)	0.02
Mean glycosylated hemoglobin value¶				
Per 10% increase	1.25 (1.10-1.43)	<0.001	0.84 (0.43-1.64)	0.61
Per 10% decrease	0.80 (0.70-0.91)	<0.001		

* All models were adjusted for the glycosylated hemoglobin value, age, cholesterol level, and smoking status at baseline in the DCCT.

† Renal disease was defined by a serum creatinine level of at least 2 mg per deciliter, a history of kidney transplantation, or the implementation of dialysis.

‡ Microalbuminuria was defined by a history of microalbuminuria or renal disease.

§ Albuminuria was defined by a history of albuminuria or renal disease.

¶ The log mean glycosylated hemoglobin value was used so that the hazard ratio per c-fold change in risk is $c^{2.26144}$, where 2.26144 is the estimated regression coefficient; a c of 1.1 corresponds to a 10 percent increase in the mean glycosylated hemoglobin value, and a c of 0.9 to a 10 percent decrease.

Table 4

Clinical Characteristics of EDIC Participants at Baseline in the DCCT According to the Presence or Absence of Cardiovascular Disease over the Course of the DCCT/EDIC Study.*

Characteristic	No Cardiovascular Disease (N = 1358)	Cardiovascular Disease (N = 83)	P Value
Intensive-treatment group (%)	50	37	0.02
Male sex (%)	53	48	0.39
Retinopathy at baseline (%)	49	63	0.014
Age (yr)	27±7	31±6	<0.001
Duration of diabetes (yr)	6±4	7±5	0.03
Body-mass index	23.3±2.8	24.0±2.8	0.05
Systolic blood pressure (mm Hg)	114±12	116±11	0.10
Diastolic blood pressure (mm Hg)	73±9	73±9	0.43
Serum creatinine (mg/dl)	0.81±0.15	0.78±0.14	0.08
Total cholesterol (mg/dl)	175±33	194±34	<0.001
HDL cholesterol (mg/dl)	51±12	50±13	0.78
LDL cholesterol (mg/dl)	109±29	127±29	<0.001
Triglycerides (mg/dl)	80.9±47.5	87.6±47.2	0.039
Albumin excretion rate (mg/24 hr)	15.7±18.5	19.3±22.8	0.02
Albumin excretion rate ≥40 mg/24 hr (%)	5	8	0.16
Glycoslated hemoglobin value at eligibility (%)	9.0±1.6	9.5±1.8	0.014
Current cigarette smoker (%)	18	33	<0.001
Autonomic nervous system-variation in RR (×1000)	47.9±22.2	43.3±19.0	0.17
Heart rate (beats/min)	68±11	70±12	0.07
Myocardial infarction in parents (%)	15	29	<0.001

* Plus-minus values are means ±SD. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein. To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.1129.