

Progression of Carotid Artery Intima-Media Thickness During 12 Years in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study

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OBJECTIVE—This study investigated the long-term effects of intensive diabetic treatment on the progression of atherosclerosis, measured as common carotid artery intima-media thickness (IMT).

RESEARCH DESIGN AND METHODS—A total of 1,116 participants (52% men) in the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, a long-term follow-up of the Diabetes Control and Complications Trial (DCCT), had carotid IMT measurements at EDIC years 1, 6, and 12. Mean age was 46 years, with diabetes duration of 24.5 years at EDIC year 12. Differences in IMT progression between DCCT intensive and conventional treatment groups were examined, controlling for clinical characteristics, IMT reader, and imaging device.

RESULTS—Common carotid IMT progression from EDIC years 1 to 6 was 0.019 mm less in intensive than in conventional ($P < 0.0001$), and from years 1 to 12 was 0.014 mm less ($P = 0.048$); but change from years 6 to 12 was similar (intensive – conventional = 0.005 mm, $P = 0.379$). Mean A1C levels during DCCT and DCCT/EDIC were strongly associated with progression of IMT, explaining most of the differences in IMT progression between DCCT treatment groups. Albuminuria, older age, male sex, smoking, and higher systolic blood pressure were significant predictors of IMT progression.

CONCLUSIONS—Intensive treatment slowed IMT progression for 6 years after the end of DCCT but did not affect IMT progression thereafter (6–12 years). A beneficial effect of prior intensive treatment was still evident 13 years after DCCT ended. These differences were attenuated but not negated after adjusting for blood pressure. These results support the early initiation and continued maintenance of intensive diabetes management in type 1 diabetes to retard atherosclerosis. *Diabetes* 60:607–613, 2011

The incidence of cardiovascular events in patients with type 1 diabetes is high for their age (1,2), with a prevalence of cardiovascular disease similar to that in nondiabetic individuals who are 10 to 20 years older (3). Patients with type 1 diabetes have increased levels of subclinical cardiovascular disease, as measured by carotid intima-media thickness (IMT), a measure of atherosclerosis. Carotid IMT is increased in children, adolescents, and adults with type 1 diabetes compared with those without diabetes (4–9).

Intensive diabetes therapy aimed at achieving glycemic control as close to the nondiabetic range as safely possible reduced the rate of microvascular complications in the Diabetes Control and Complications Trial (DCCT) (10). A trend favoring the intensive treatment group regarding macrovascular disease ($P = 0.08$) (11) prompted the addition of examinations to study earlier signs of cardiovascular disease during the long-term observational follow-up of the DCCT cohort (Epidemiology of Diabetes Interventions and Complications or EDIC) (12). Coronary artery calcification (CAC) was measured with computed tomography during EDIC years 7 to 9. Prior intensive treatment during DCCT was associated with lower prevalence of CAC >200 in the combined cohort ($P = 0.026$) (13).

We initially reported that intensive diabetes therapy did not appear to influence carotid IMT measured in EDIC year 1 (14), at a time when IMT measurements were not significantly different from those of age-matched and gender-matched nondiabetic individuals. IMT measurement at EDIC year 6 demonstrated that the progression of carotid IMT was reduced in the intensive compared with the conventional treatment group, despite comparable A1C levels during EDIC follow-up (15). These findings suggested that a durable effect of the differences in metabolic control during DCCT might play a role in atherosclerosis, as has been shown for microvascular complications of diabetes (“metabolic memory”) (16–18). The duration of this effect on atherosclerosis is unknown.

We report the 12-year follow-up of carotid IMT in the EDIC cohort to determine the effects of glycemic control on atherosclerosis progression in type 1 diabetes over time. Specifically, we compared IMT progression between the original intensive and conventional treatment groups in the observational EDIC follow-up between years 1 and 6, 6 and 12, and during the entire 12-year period, and assessed the association of mean A1C with IMT progression. We also examined the risk factors for IMT progression.

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RESEARCH DESIGN AND METHODS

Participants. The 1,441 patients enrolled in the DCCT between 1983 and 1989 were aged 13 to 39 years, had had type 1 diabetes for 1 to 15 years, and were in generally good health at baseline (10). At baseline, the primary prevention cohort ($n = 726$) had no retinopathy, urine albumin excretion <40 mg/24 h, and diabetes duration of 1 to 5 years. The secondary intervention cohort ($n = 715$) had minimal to moderate nonproliferative retinopathy, urinary excretion of albumin ≤ 200 mg/24 h, and duration of diabetes of 1 to 15 years. At the end of the DCCT, after 6.5 years of mean follow-up, 1,375 of the 1,425 surviving members (96%) of the original cohort volunteered to participate in EDIC (12). During EDIC, all therapy was provided by the patients' own physicians, and intensive therapy was recommended for all patients. A detailed description of EDIC procedures and baseline characteristics has been published (12).

Carotid ultrasound imaging was first performed between June 1994 and April 1996 (1 to 2 years after initiation of EDIC and ~ 8 years after the beginning of the DCCT; range 4–11 years) (15). It was repeated between October 1998 and November 2000 in 1,229 EDIC participants. A third ultrasound study was performed between October 2004 and April 2006. We compared IMT progression rates between EDIC visits at years 1, 6, and 12 in participants who had all three IMT measurements, comprising 1,116 of 1,240 participants who completed the annual EDIC year 12 examination.

Assessment of carotid IMT. IMT measurement has been described in detail (15). A single longitudinal lateral view of the distal 10 mm of the right and left common carotid arteries (CCAs) and three longitudinal views in different imaging planes of each internal carotid artery (ICA) were obtained by certified technicians at the clinical centers, recorded on S-VHS tapes, and read in a central unit (Tufts Medical Center, Boston, MA) by two readers, masked to treatment assignment. The current study focuses on CCA IMT measurements because progression is more consistently measured for CCAs than for the ICA (19,20). The three ultrasound studies for each participant were read by the same reader within 1 month in a batch fashion (21) to guard against reader drift in measurements. The Coordinating Center assigned the order of readings. Ultrasound devices were grouped by manufacturer, model, probe imaging frequency, and empiric knowledge about overall imaging characteristics. A total of 27 combinations of imaging devices summarized equipment differences for the three study time points and the 28 centers. The maximum IMT (millimeter) of the CCA was defined as the mean of the maximum IMT for near and far walls on both right and left sides.

Quality control procedures for IMT. Either of two readers contemporaneously read the EDIC year 1, 6, and 12 carotid ultrasound studies, the year 1 and 6 exams being reread to ensure that the same reader read all three exams. One read 83% of these ultrasound images and had previously read year 1 and 6 ultrasound studies for prior publications. For the common carotid IMT, the primary reader had an intrareader coefficient of reliability (intraclass correlation) of >0.93 (over different periods, $n = 142$ pairs), and the interreader reliability was >0.81 ($n = 206$ pairs). The coefficients were similar for the ICA measures (>0.93 and >0.90 , respectively).

Other procedures. An annual history, physical examination, and electrocardiogram were obtained for each participant, as well as laboratory testing that included determination of serum creatinine and A1C levels, as occurred during the DCCT (10,22). The time-weighted mean A1C was computed during the duration of the DCCT and up to specific EDIC years, with the quarterly DCCT and annual EDIC values weighted by 3 and 12 months, respectively. Lipid profiles and 4-h urine collections for measurement of albumin excretion rate (AER; mg/24 h) and creatinine clearance were obtained in alternate years during EDIC (12). Microalbuminuria and albuminuria were defined as AER ≥ 40 mg/24 h and AER ≥ 300 mg/24 h, respectively, at any visit during DCCT, including at DCCT baseline, and through EDIC year 1, 6, or 12. Year 6 covariates were obtained from the EDIC year 6 history and physical examination and from the laboratory data (fasting lipids and renal function) collected in year 5 or 6.

Statistical analyses. Groups were compared using the Wilcoxon rank sum test for quantitative variables and the χ^2 test for categorical variables. A single general linear mixed model for repeated measurements (23–25) assessed differences between the DCCT intensive versus conventional groups in the CCA IMT at EDIC years 6 and 12 using an unstructured covariance matrix for the within-subject correlation. The model adjusted for the EDIC year 1 IMT, age, ultrasound equipment, reader, sex, and study cohort and included interaction terms for treatment group by EDIC year (6 or 12 as a class effect). Contrasts of the model coefficients then provided estimates and tests of the differences between groups in the change in carotid IMT from years 1 to 6, 1 to 12, and 6 to 12.

A multiple linear regression model (26) assessed covariate effects, including different A1C variables, on the change in IMT from years 1 to 6 adjusted for year 1 IMT and other factors. Another model assessed change from years 6 to 12 adjusted for year 6 IMT and risk factors; and another assessed change from

years 1 to 12 adjusted for year 1 values. In multivariate risk factor models (years 1 to 6 and 6 to 12 only), the most significant factor for the multivariate association among similar variables (e.g., systolic [sBP] and diastolic blood pressure) was used. Results nominally significant at two-sided $P < 0.05$ were cited.

RESULTS

The baseline characteristics of the 1,116 EDIC participants and 325 nonparticipants (without all three IMT measurements) were similar except for A1C at eligibility ($9.0 \pm 1.6\%$ for participants and $9.4 \pm 1.7\%$ for nonparticipants, $P < 0.0001$). The clinical characteristics at EDIC year 6 were not significantly different between the original DCCT treatment groups, with the exception of albumin excretion rates (Table 1), reflecting the persistent benefit of intensive treatment during DCCT. At DCCT close out, mean A1C levels were lower in the intensive treatment group ($7.3 \pm 1.0\%$ vs. $9.0 \pm 1.7\%$ for women, $7.4 \pm 1.0\%$ vs. $9.1 \pm 1.3\%$ for men, $P < 0.0001$). Annual A1C levels were minimally different (0.1–0.4 A1C %), albeit nominally significant, between treatment groups during the first 6 years of EDIC but not during years 7 to 12 (data not shown). However, the weighted average over DCCT and EDIC up to EDIC years 1, 6, and 12 each remained significantly different between treatment groups (Table 1). A nominally significant difference between treatment groups was noted in the year 6 IMT among men but not women; however, the group by gender interaction was not statistically significant ($P = 0.13$). Thus, further analyses were conducted for the men and women combined.

Table 2 and Fig. 1 show the least squares means of carotid IMT progression from EDIC year 1 to years 6 and 12 from longitudinal regression models for repeated measurements, adjusted for baseline factors. The progression of IMT from EDIC years 1 to 6 was significantly less in the intensive compared with the conventional treatment group (-0.019 mm, $P < 0.0001$), as was the change from year 1 to 12 (-0.014 mm, $P = 0.048$; Table 2, Fig. 1). However, the difference between treatment groups in the change in IMT from year 6 to 12 was not significant ($+0.005$ mm, $P = 0.379$). Similar results were obtained after adjusting for the current sBP and LDL, but the difference between groups in the change of carotid IMT from years 1 to 12 was no longer nominally significant ($P = 0.083$).

In the conventional treatment group, the mean change from year 1 to 6 (0.036 mm) was nominally lower than from year 6 to 12 (0.051 mm), but the difference was not significant (0.015 ± 0.012 mm, $P = 0.211$). In the intensive treatment group, the change in IMT from years 1 to 6 was very minimal (0.016 mm), but the change from years 6 to 12 (0.057 mm) was significantly greater (0.040 ± 0.012 mm, $P < 0.0006$) and similar to the change in the conventional treatment group during the same time period.

Table 3 describes in the treatment groups combined the association of the mean A1C over DCCT and during different periods of DCCT and EDIC, with the IMT progression adjusted for the same factors as in Table 2. The mean A1C in DCCT and through EDIC year 1 had similar significant effects on the progression of IMT from year 1 to 6, whereas the EDIC mean A1C over years 1 to 6, and the DCCT/EDIC mean through year 6 had lesser effects. Likewise, the DCCT mean A1C and that over each subsequent EDIC period had a significant effect on the change in IMT over year 1 to 12. The DCCT mean A1C had a lesser effect on the change in IMT from years 6 to 12 relative to its effects on the changes from years 1 to 6 or years 1 to 12, in keeping with the pattern of treatment group differences

TABLE 1

Clinical characteristics of 1,116 EDIC participants with common carotid IMT measurements at years 1, 6, and 12 according to sex and original treatment assignment

Characteristics	DCCT treatment groups			
	Women		Men	
	Intensive	Conventional	Intensive	Conventional
<i>N</i>	267	266	296	287
Demographic, year 6				
Attained age (years)	40 ± 7*	39 ± 7	41 ± 7	41 ± 6
Attained type 1 duration (years)	19 ± 5	19 ± 5	19 ± 5	18 ± 5
Smoking (%)	16.5	15.3	18.6	13.3
Medical, year 6				
Body mass index ≥30 kg/m ² (%)	24.3*	15.6	21.8	18.6
Systolic blood pressure (mmHg)	118 ± 14	117 ± 14	122 ± 12	123 ± 13
Diastolic blood pressure (mmHg)	74 ± 9	73 ± 10	77 ± 9	77 ± 8
Hypertension (%)†	24.9	28.6	30.5	35.1
Lipids, year 5 or 6‡				
Total cholesterol (mg/dL)	190 ± 33	187 ± 34	192 ± 38	187 ± 33
HDL cholesterol (mg/dL)	63 ± 16	62 ± 14	51 ± 13	51 ± 11
LDL cholesterol (mg/dL)	111 ± 30	109 ± 29	119 ± 30	117 ± 29
Triglycerides (mg/dL)	77 ± 42	76 ± 47	103 ± 73	98 ± 73
Hyperlipidemia (%)§	30.3	26.3	36.6	35.8
AER (mg/24 h), year 5 or 6‡				
Median (1st, 3rd quartile)	10* (6, 17)	10 (6, 21)	10* (7, 16)	12 (7, 29)
Log (value [mg/24 h])	2.3 ± 0.9*	2.6 ± 1.3	2.5 ± 1.1*	2.9 ± 1.4
≥40 mg/24 h (%)	4.6*	15.2	10.7*	19.3
AER ≥40 or dialysis/transplant (ever)				
DCCT/EDIC to years 1–2	27.7	30.8	17.6*	26.1
DCCT/EDIC to years 5–6	30.7	38	22.3*	34.8
DCCT/EDIC to years 11–12	37.1	44	30.4*	40.4
AER ≥300 or dialysis/transplant (ever)				
DCCT/EDIC to years 1–2	3	6	3	4.9
DCCT/EDIC to years 5–6	3.0*	8.3	3.7*	10.1
DCCT/EDIC to years 11–12	4.5*	11.7	5.1*	15.7
Weighted mean A1C (%)				
DCCT A1C	7.3 ± 0.8*	9.1 ± 1.3	7.2 ± 0.8*	8.9 ± 1.1
DCCT/EDIC to year 1	7.3 ± 0.8*	8.9 ± 1.2	7.3 ± 0.9*	8.8 ± 1.0
DCCT/EDIC to year 6	7.6 ± 0.9*	8.6 ± 1.1	7.6 ± 1.0*	8.6 ± 1.0
DCCT/EDIC to year 12	7.7 ± 1.0*	8.3 ± 1.0	7.7 ± 0.9*	8.3 ± 1.0
IMT year 1				
Common carotid IMT (mm)				
Mean ± SD	0.601 ± 0.080*	0.582 ± 0.073	0.633 ± 0.088	0.637 ± 0.105
Median	0.592	0.578	0.627	0.625
Range	(0.440–0.846)	(0.414–0.787)	(0.444–0.922)	(0.455–1.065)
IMT year 6				
Common carotid IMT (mm)				
Mean ± SD	0.613 ± 0.087	0.610 ± 0.096	0.647 ± 0.101*	0.677 ± 0.141
Median	0.602	0.6	0.636	0.646
Range	(0.411–0.928)	(0.417–1.121)	(0.440–1.133)	(0.425–1.772)

Data are means ± SD unless noted otherwise. IMT, common intima-media thickness. * $P < 0.05$ by Wilcoxon rank-sum test for continuing variables and χ^2 test for categorical variables comparing conventional and intensive treatment. †Hypertension was defined by a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, documented hypertension, or the use of antihypertensive agents. ‡Renal function and lipid levels were determined from the biennial evaluation conducted at year 5 or 6 of the EDIC study. §Hyperlipidemia was defined by an LDL cholesterol level ≥130 mg/dL or the use of lipid-lowering agents (physicians were alerted to the presence of hyperlipidemia during the DCCT and the EDIC study).

in Table 2. Further, the EDIC mean A1C from years 1 to 6 and for years 1 to 12 had a stronger effect than that of the DCCT mean A1C alone. Averaging the A1C over DCCT and EDIC periods did not increase the effect of the EDIC mean A1C alone on progression from years 6 to 12. These results indicate that mean A1C during DCCT and EDIC up to the year of each assessment has the strongest association with the rate of progression in IMT up to that year.

Adjustment for the current levels of sBP and LDL over each period (mean over 1–6, 1–12, and 6–12 years)

attenuated the association of the different DCCT and/or EDIC A1C measures with the change in IMT over each period, the associations with the EDIC mean A1C measures no longer being significant. However, the associations of the DCCT mean and the DCCT/EDIC combined mean A1C with the changes from years 1 to 6 and years 1 to 12 remained significant, whereas the associations with the change in IMT from years 6 to 12 were nonsignificant. In these models, sBP was significantly associated with IMT progression ($P < 0.0001$) not LDL.

TABLE 2
Change in least squares means* of common IMT over EDIC years 1, 6, and 12 by treatment group

EDIC period	Change in least squares		Mean IMT difference (mm \pm SE) (Intensive – Conventional)	P
	Intensive	Conventional		
Years 1 to 6	0.016 \pm 0.010	0.036 \pm 0.010	–0.019 \pm 0.005	<0.0001
Years 6 to 12	0.057 \pm 0.005	0.051 \pm 0.005	0.005 \pm 0.006	0.379
Years 1 to 12	0.072 \pm 0.011	0.086 \pm 0.010	–0.014 \pm 0.007	0.048

*From a single general linear mixed model with effects for treatment group, age, sex, study cohort, IMT at year 1, IMT reader, image device, EDIC year 6 or 12, and group by EDIC year interactions. Changes from years 1 to 6, 6 to 12, and 1 to 12 were estimated by contrasts among the model coefficients.

When the effect of intensive versus conventional therapy in Table 2 is also adjusted for the DCCT mean A1C, the *F* test of the treatment group effects on progression from years 1 to 6 and years 1 to 12 are reduced by 87 and 96%, respectively. Thus, virtually all of these long-term treatment group differences in IMT progression are explained by the differences in A1C during the DCCT.

In models adjusting for the same factors as in Table 3, the progression of IMT from years 1 to 6 was greater by 0.013 \pm 0.006 mm (*P* = 0.031) among those with microalbuminuria at any time up to EDIC year 1 versus not, but the difference among those with versus without microalbuminuria up to year 6 was smaller (*P* = 0.07). Progression from years 1 to 6 was also greater by 0.021 \pm 0.01 mm (*P* = 0.043) among those with albuminuria up to year 6 versus not, but not among those with albuminuria versus not up to year 1 (*P* = 0.08). IMT progression from years 6 to 12 was greater by 0.014 \pm 0.007 mm (*P* = 0.044) among those with microalbuminuria up to year 6, and by 0.020 \pm 0.006 mm (*P* = 0.002) with microalbuminuria up to year 12 versus not; and by 0.022 \pm 0.011 mm (*P* = 0.034) among those with albuminuria up to year 12, but not up to year 6 (*P* = 0.06) versus not. However, none of these differences in IMT progression remained significant when also adjusted for the DCCT/EDIC weighted mean A1C.

The multivariable risk factor models of common carotid IMT progression from years 1 to 6 and from years 6 to 12 (Table 4), adjusted for treatment group, explained approximately 51 and 57% of the variation in CCA IMT, respectively. Lipids (LDL, HDL, total cholesterol) did not add significantly to the models (*P* > 0.10). Smoking and an interaction of SBP and sex had significant effects on the change in IMT within both periods. In both models, the male-female difference increased as SBP at the beginning of the period increased, the difference being 0 at 104 mmHg for IMT progression from 1 to 6 years, and 109 for IMT progression from 6 to 12 years. In both models, men with sBP >120 mmHg (approximately) had significantly higher IMT progression (*P* = 0.05).

A BMI \geq 30 kg/m² (obesity) at year 1 was not associated with IMT progression from years 1 to 6, but BMI \geq 30 kg/m² at year 6 was significantly associated with greater IMT progression from years 6 to 12. Because BMI differed between treatment groups, especially among women (Table 1), the two effects may be confounded. However, these BMI effects were similar in additional models adjusted for treatment group, or that adjusted for the DCCT/EDIC mean A1C up to the beginning of each period. Conversely, after adjustment for the prevalence of obesity, the effect of the DCCT/EDIC mean A1C up to year 1 on IMT progression from years 1 to 6 was unchanged, but the effect of

the mean A1C to year 6 on IMT progression from years 6 to 12 was no longer significant (*P* = 0.23).

DISCUSSION

We have shown that intensive diabetes therapy during the DCCT had a beneficial effect on IMT progression during the entire 12 years of EDIC follow-up compared with conventional therapy. However, although the treatment groups differed in IMT progression from years 1 to 6 of EDIC, they progressed at similar rates from years 6 to 12. Thus, the beneficial effects of intensive therapy at 12 years are a reflection of the benefits previously observed at 6 years.

These differences in carotid IMT progression between the original DCCT treatment groups during a period when differences in A1C levels had largely disappeared show that a durable metabolic effect or “metabolic memory” exists for atherosclerosis, as has been demonstrated for microvascular disease (16,17). However, the similar IMT progression in the original treatment groups over EDIC years 6 to 12 support a waning of metabolic memory (“metabolic amnesia”) over time. Nevertheless, there is no evidence at this time of a “catch-up” effect, and the DCCT intensive group still has a significantly lower level of atherosclerosis over the entire 12 years of EDIC.

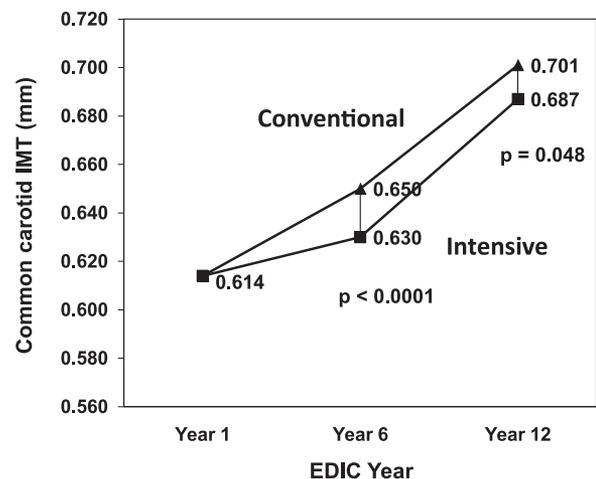


FIG. 1. Least squares means in common carotid artery IMT based on linear mixed model adjusted for age, sex, study cohort, IMT reader, image device, and mean baseline IMT value of 0.614 mm. A significant separation in mean IMT between treatment groups (intensive, ■; conventional, ▲) emerged between years 1 and 6 (*P* < 0.0001) that persisted to year 12 (*P* = 0.048). From years 6 to 12, the progression rates are similar for the two treatment groups.

TABLE 3

Association of mean A1C in combined treatment groups during DCCT and EDIC with change in common carotid IMT over EDIC years 1, 6, and 12*

Mean A1C	Change in carotid intima-media thickness					
	Years 1 to 6 (mm)		Years 6 to 12 (mm)		Years 1 to 12 (mm)	
	β -coefficient [†]	<i>P</i>	β -coefficient [†]	<i>P</i>	β -coefficient [†]	<i>P</i>
DCCT	0.0074 ± 0.0018	<0.0001	0.0038 ± 0.0023	0.1052	0.0087 ± 0.0026	0.0008
DCCT/EDIC to year 1‡	0.0079 ± 0.0020	<0.0001	0.0045 ± 0.0025	0.0694	0.0097 ± 0.0028	0.0006
EDIC years 1 to 6, mean	0.0042 ± 0.0021	0.0497	0.0071 ± 0.0027	0.0075	0.0084 ± 0.0030	0.0049
DCCT/EDIC to year 6‡	0.0082 ± 0.0023	0.0003	0.0068 ± 0.0028	0.0175	0.0115 ± 0.0032	0.0003
EDIC years 1 to 12	N/A	N/A	0.0083 ± 0.0029	0.0039	0.0103 ± 0.0032	0.0016
DCCT/EDIC to year 12‡	N/A	N/A	0.0086 ± 0.0031	0.0056	0.0132 ± 0.0035	0.0002

N/A, not applicable. *Separate multiple linear regression models for the change in IMT over each period adjusted for age, sex, study cohort, IMT reader, and image device. Change from years 1 to 6 and change from years 1 to 12 models also adjusted for the year 1 IMT. Change from years 6 to 12 model also adjusted for the year 6 IMT. Separate models with each different A1C measure were performed. †The β -coefficient (estimated ± SE) is the millimeter change in IMT progression per whole % greater A1C. ‡Weighted mean of DCCT and EDIC A1C values over time, each weighted by the interval of time between values 3 months for each DCCT quarterly A1C value, 12 months for each EDIC annual A1C value.

Carotid IMT is a well-accepted marker of subclinical cardiovascular disease, based in part on the positive associations between carotid IMT and cardiovascular risk factors (27). Unfortunately, it is not yet possible to describe an association between changes in IMT during EDIC and the risk of cardiovascular events. Far too few participants ($n = 75$) have experienced a cardiovascular disease outcome event in the combined intensive and conventional groups since the year 6 IMT was measured to provide adequate statistical power to describe covariate effects on cardiovascular disease risk, especially within each group.

The associations of carotid IMT with cardiovascular risk factors in the intensive and conventional treatment groups were similar to those reported in other studies (28).

Carotid IMT has been used to determine the efficacy of lipid-lowering therapies in patients with cardiovascular disease, familial hyperlipidemia, and in those with moderately elevated lipid levels (29–31). Because the levels of traditional risk factors were similar in both treatment groups in our study, other nontraditional risk factors should be considered as having mediated the differences in carotid IMT. Blood glucose levels, A1C levels, and microalbuminuria are potential mediators of carotid IMT progression. Positive associations between blood glucose levels and IMT have been reported in nondiabetic individuals and in type 1 and type 2 diabetic populations (4,5,8,9,32).

A study of people with type 2 diabetes and metabolic syndrome suggested that the component factors of the

TABLE 4

Multivariate risk factor models* for progression of common IMT years 1 to 6 and 6 to 12

Risk factor (years 1 or 6)†	Change in carotid IMT (mm)			
	Years 1 to 6		Years 6 to 12	
	β -coefficient‡	<i>P</i>	β -coefficient‡	<i>P</i>
Model R^2	0.51		0.57	
Attained age (years)	0.0032 ± 0.0004	<0.0001	0.0019 ± 0.0005	0.0003
Sex (male vs. female)	0.0152 ± 0.0055	0.0053	0.0144 ± 0.0063	0.0227
Cohort (secondary vs. primary)	0.0064 ± 0.0050	0.2028	0.0122 ± 0.0062	0.0469
Common IMT (mm)	0.6847 ± 0.0343	<0.0001	0.8282 ± 0.0328	<0.0001
Treatment group (intensive vs. conventional)	−0.0199 ± 0.0051	<0.0001	0.0024 ± 0.0061	0.6921
Currently smoking (yes vs. no)	0.0173 ± 0.0066	0.0088	0.0288 ± 0.0084	0.0006
Systolic blood pressure (mmHg)	0.0002 ± 0.0003	0.486	0.0006 ± 0.0003	0.0693
Body mass index ≥ 30 kg/m ² (yes vs. no)	0.0101 ± 0.0076	0.1834	0.0224 ± 0.0078	0.0043
Systolic blood pressure* sex interaction	0.0010 ± 0.0004	0.0234	0.0014 ± 0.0005	0.0040
Male vs. female at 100 mmHg	−0.0041 ± 0.0087	0.6384	−0.0126 ± 0.0113	0.2642
Male vs. female at 110 mmHg	0.0056 ± 0.0059	0.3496	0.0009 ± 0.0079	0.9094
Male vs. female at 120 mmHg	0.0152 ± 0.0054	0.0053	0.0144 ± 0.0063	0.0227
Male vs. female at 130 mmHg	0.0249 ± 0.0078	0.0014	0.0280 ± 0.0079	0.0004
Male vs. female at 140 mmHg	0.0346 ± 0.0113	0.0023	0.0415 ± 0.0113	0.0003
Overall effect				
Sex	df = 2	0.0061	df = 2	0.0012
Systolic blood pressure	df = 2	0.0008	df = 2	<0.0001

*Separate multiple linear regression models for the change in IMT over each period adjusted for readers and machine devices. In additional models, LDL, HDL, and total cholesterol were not significantly associated with change in IMT over either period. †The model for IMT progression from years 1 to 6 was adjusted for risk factors evaluated or measured at EDIC year 1; the model for progression from years 6 to 12 was adjusted for factors evaluated or measured at EDIC year 6. ‡Coefficient (estimated ± SE) is the mm change in IMT progression per unit increase in the covariate, or the difference between covariate categories as stated.

metabolic syndrome, such as BMI and triglycerides, are more strongly associated with IMT than glucose levels (33). BMI ≥ 30 kg/m² at year 1 was not associated with greater IMT progression from years 1 to 6, but BMI ≥ 30 kg/m² at year 6 was significantly associated with greater IMT progression from years 6 to 12. The latter effect persisted after adjustment for treatment group and the DCCT/EDIC mean A1C up to year 6.

The prevalence of microalbuminuria was different between the groups, reflecting the long-term effects of the original DCCT interventions. Further, a history of microalbuminuria, and to a lesser extent albuminuria, was associated with the changes in IMT from years 1 to 6 and again from years 6 to 12 in the combined cohort. These effects were not as strong as those of A1C. A previous study of the general population showed no significant association between IMT and microalbuminuria (34). A study of type 2 diabetes suggested a minor effect (35).

We have previously reported that after 11 years of EDIC follow-up, intensive treatment therapy was associated with a 57% reduction in major cardiovascular disease events. This beneficial effect was virtually completely explained by the difference in A1C values between the treatment groups during DCCT (36). We also reported that coronary artery calcification in type 1 diabetes was significantly associated with mean A1C during DCCT (13). Here we have also shown that the A1C levels are associated with carotid IMT progression. Furthermore, the differences between groups in the DCCT mean A1C explain a large fraction of the long-term differences between groups in IMT progression from years 1 to 6 and from years 1 to 12.

DCCT mean A1C was significantly associated with IMT change for years 1 to 6 and 1 to 12, but not years 6 to 12. DCCT/EDIC A1C up to years 1 and 6 was strongly associated with IMT change over years 1 to 6; DCCT/EDIC mean A1C up to years 6 and 12 was strongly associated with IMT change over years 6 to 12; and DCCT/EDIC mean A1C up to years 1, 6, and 12 was strongly associated with IMT change from years 1 to 12.

As with other microvascular and cardiovascular outcomes in DCCT and EDIC, the cumulative glycemic exposure represented by the mean A1C since entry is strongly associated with IMT progression. A likely mechanism explaining the delayed effect of A1C on IMT progression may lie in the formation of long-lived advanced glycation end products (37,38). Because the half-life of collagen is up to 15 years, an effect on the artery wall might take years to be seen and then to dissipate as production of the glycation end products was affected by glycemic control (37,38). A previously published study in the DCCT cohort showed a predictive value for advanced glycation end products for future complications of retinopathy and nephropathy (39). A decrease in glycation of the collagen constituents of the artery wall due to prior differences in A1C levels during DCCT might explain the differences in IMT progression seen at EDIC years 1 to 6. Subcellular changes related to the differences in glycemia may have developed during the DCCT, but their expression as atherosclerosis and a change in IMT may have taken longer to develop, explaining the time course we observed. A full explanation of the pathophysiologic processes underlying IMT progression awaits future investigations.

Additional analyses described here also show that adjustments for the current levels of sBP and LDL attenuate the group difference in and DCCT/EDIC A1C associations with IMT progression, but do not negate them. In these

models, blood pressure, not LDL, was the significant factor. This indicates that the beneficial effects of intensive therapy and lower DCCT/EDIC A1C on carotid IMT during EDIC (40) are partly mediated by beneficial effects on blood pressure and hypertension.

Limitations of this study include less-than-complete follow-up of the entire DCCT cohort. In only 77% of the original 1,441 DCCT volunteers were all three IMT scans completed (84% of the 1,330 active EDIC participants). However, baseline characteristics of the participants were largely the same as those of the nonparticipants. The other limitation was the use of different ultrasound equipment among and within clinics over time. We included an adjustment for equipment in our model.

We conclude that during a period of 12 years after the end of the DCCT intervention, progression of atherosclerosis in patients with type 1 diabetes remains lower in the original intensive than the conventional treatment group. The beneficial effect of prior intensive treatment observed during the first 6 years of EDIC follow-up appears to wane during the second 6 years, although a benefit of intensive therapy persisted during the entire study period. The overall difference in IMT progression between the two treatment groups was observed despite similar exposure to traditional risk factors. These long-term benefits are largely explained by the differences in A1C during the DCCT, and the risk of progression in the entire cohort is associated with the cumulative mean A1C reflecting long-term glycemic exposure.

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