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 DCCT 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

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Received 1 March 2010 and accepted 16 November 2010.

DOI: 10.2337/db10-0296. Clinical trial reg. nos. NCT003609893, NCT00360815, clinicaltrials.gov.

*The writing group of the DCCT/EDIC Research Group takes responsibility for the contents of this article. A complete list of the members of the DCCT/EDIC Research Group can be found in Arch Ophthamol 2008,126:1713.

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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 30 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, urinary 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 ultrasonography 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 group, to ensure current interobserver reliability on central 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 emipiric knowledge about overall imaging characteristics. A total of 8 mtx of multiple 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 reader (RP) of these ultrasound images and had previously read year 1 and 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 measurements (>0.93 and >0.98, 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 the DCCT and annual EDIC year 6. 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 cova-riates 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 χ² test for categoric 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 in- teraction 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 AIC 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 AIC at eligibility (9.0 ± 1.6% for participants and 9.4 ± 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 ± 1.0% vs. 9.0 ± 1.7% for women, 7.4 ± 1.0% vs. 9.1 ± 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 = 0.053). 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 AIC 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 AIC 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 AIC over years 1 to 6, and the DCCT/EDIC mean through year 6 had lesser effects. Likewise, the DCCT mean AIC and that over each subsequent EDIC period had a significant effect on the change in IMT over year 1 to 12. The DCCT mean AIC 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.
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.

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**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 |   |   |
|------------------------------------------------------|-----------------------|---|---|
|                                                      | Intensive             | Conventional | Intensive | Conventional |
|                                                      | Women                 |   |   |
|                                                      | Conventional |   |   |
| N                                                    | 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 $\geq 30$ 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])                                | 2.5 ± 0.9*            | 2.6 ± 1.3 | 2.5 ± 1.1* | 2.9 ± 1.4 |
| $\geq 40$ mg/24 h (%)                                | 4.6*                  | 15.2 | 10.7* | 19.3 |
| AER $\geq$40 or dialysis/transplant (ever)           | 27.7                  | 30.8 | 17.6* | 26.1 |
| DCCT/EDIC to years 1–2                               | 30.7                  | 38    | 22.3* | 34.8 |
| DCCT/EDIC to years 5–6                               | 37.1                  | 44    | 30.4* | 40.4 |
| AER $\geq$300 or dialysis/transplant (ever)          | 3                    | 6     | 3    | 4.9 |
| DCCT/EDIC to years 1–2                               | 3.0*                  | 8.3   | 3.7*  | 10.1 |
| DCCT/EDIC to years 5–12                              | 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) | (0.443–0.922) | (0.455–1.065) |
| IMT year 6                                           |                       |   |   |
| Common carotid IMT (mm)                              |                       |   |   |
| Mean ± SD                                           | 0.615 ± 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) | (0.440–1.333) | (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 $\chi^2$ test for categorical variables comparing conventional and intensive treatment. Hypertension was defined by a systolic blood pressure $\geq 140$ mmHg, a diastolic blood pressure $\geq 90$ 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 $\geq 130$ mg/dL or the use of lipid-lowering agents (physicians were alerted to the presence of hyperlipidemia during the DCCT and the EDIC study).
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 ± 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 ± 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 ± 0.007 mm (P = 0.044) among those with microalbuminuria up to year 6, and by 0.020 ± 0.006 mm (P = 0.002) with microalbuminuria up to year 12 versus not; and by 0.022 ± 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 ≥30 kg/m² (obesity) at year 1 was not associated with 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. 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, 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.
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† | P | β-coefficient† | P | β-coefficient† | P |
| 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 | 0.0057 ± 0.0028 | 0.0006 |
| EDIC years 1 to 6, mean | 0.0042 ± 0.0021 | 0.0497 | 0.0071 ± 0.0027 | 0.0775 | 0.0084 ± 0.0030 | 0.0049 |
| DCCT/EDIC to year 6‡ | 0.0082 ± 0.0023 | 0.0003 | 0.0068 ± 0.0028 | 0.175 | 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 readers and machine devices. Change from years 1 to 6 and years 1 to 12 model 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 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‡ | P | β-coefficient‡ | P |
| Model R²                   | 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 | 0.2928 | 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/m² (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.
CAROTID ARTERY IMT PROGRESSION IN DCCT/EDIC

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.

ACKNOWLEDGMENTS

The DCCT/EDIC project is supported by contracts with the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, National Eye Institute, National Institute of Neurologic Disorders and Stroke, the General Clinical Research Centers Program and the Clinical and Translation Science Centers Program, National Center for Research Resources, and by Genentech through a Cooperative Research and Development Agreement with the National Institute of Diabetes and Digestive and Kidney Diseases.

The following companies were contributors of free or discounted supplies and/or equipment: LifeScan, Roche, Aventis, Eli Lilly, OmniPod, Can-Am, BD Biosciences, Animas, Medtronic, Medtronic Minimed, Bayer (donation one time in 2008), and Omron. No other potential conflicts of interest relevant to this article were reported.

J.F.P. participated in protocol development, implementation of image acquisition, supervision of image analysis, and drafted and edited the manuscript. J.-Y.C.B. performed analysis, wrote statistical methods and results, and reviewed and edited the manuscript. A.P.H. shared inception of the manuscript, contributed to data collection and analysis, and performed critical review. D.H.O. assisted in the design of the study, the collection and analysis of the data, and reviewed and edited the manuscript. J.M.L. participated in procuring funding, directed the statistical analysis, and performed critical review. D.H.O. assisted in the design of the study, the collection and analysis of the data, and reviewed and edited the manuscript. J.M.L. participated in procuring funding, directed the statistical analysis, and substantially edited and revised the manuscript. D.M.N. helped to procure funding, contributed to data collection and discussion, and reviewed and edited the manuscript.

The authors acknowledge the technical editorial assistance of Mary Hawkins and the technical assistance of...
WanYu Hsu, both of the Biostatistics Center, The George Washington University, in placement and construction of tables/figure.

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