# Effect of Intensive Diabetes Treatment on Carotid Artery Wall Thickness in the Epidemiology of Diabetes Interventions and Complications

**Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group**

**The Epidemiology of Diabetes Interventions and Complications (EDIC) is a multicenter longitudinal observational study of the Diabetes Control and Complications Trial (DCCT) cohort. One of the major objectives of EDIC is to study the development and progression of atherosclerotic cardiovascular disease in type 1 diabetes. In this study, we evaluated the role of cardiovascular risk factors and antecedent therapy in the DCCT on carotid intima-media wall thickness (IMT) in type 1 diabetes. At ~18 months after the end of the DCCT, high-resolution B-mode ultrasonography was used to assess the carotid arteries of 1,325 patients with type 1 diabetes, 19–51 years of age, with duration of diabetes ranging from 6.3 to 26.1 years. An age- and sex-matched nondiabetic population ($n$ = 153) was studied with the same protocol. The ultrasound protocol was carried out in 28 EDIC clinics by centrally trained and certified sonographers using one of three scanning systems. Determination of IMT from videotaped images was performed by a single reader at the Central Ultrasound Reading Unit. Univariate associations with greater IMT were strongest for older age and longer diabetes duration, greater waist-to-hip ratio (men only), higher blood pressure, higher LDL cholesterol, and smoking. The DCCT therapy group (intensive versus conventional) and $HbA_{1c}$, measured at the time of the ultrasound or the mean $HbA_{1c}$ during the DCCT, were not significantly related to IMT. Multivariate analyses suggest that age, height, smoking, and BMI were the major predictors of common carotid IMT, whereas age, smoking, and LDL cholesterol predicted internal carotid IMT. There were significant differences between the IMT values of the internal carotid artery in the EDIC male cohort and similarly aged male nondiabetic control subjects. There were no significant differences between the IMT values in the EDIC female cohort and similarly aged female nondiabetic control subjects. At this point in the planned 10-year follow-up of the DCCT cohort, neither intensive therapy nor $HbA_{1c}$ level appears to influence the early signs of atherosclerosis. Traditional risk factors, including age, smoking, and LDL cholesterol, were related to IMT. As the cohort is only now entering the age interval during which rapid progression and clinical expression of atherosclerosis are expected, further follow-up will help to determine the role of hyperglycemia, and its interaction with other risk factors, on the development of atherosclerosis. *Diabetes* 48:383–390, 1999**



Type 1 diabetes is well recognized as a risk factor for early cardiovascular disease (CVD), leading to a more than 10-fold increase in risk in young adults (1–3) and greatly reducing the sex differential in CVD seen in the general population. The mechanism that underlies this effect of diabetes is unclear, and whether type 1 diabetes initiates the atherosclerotic process early or merely hastens the process once started is controversial (2,4). Furthermore, few studies have delineated the risk factors for CVD in type 1 diabetes, although data confirm a strong relationship with renal disease (5), particularly in men (6). Other risk factors of interest include the lipoprotein profile, blood pressure (BP), fibrinogen level, waist-to-hip ratio (WHR), and depressive symptomatology, particularly in women (6).

Carotid ultrasonography, measuring both the presence of stenosis and intima-media wall thickness (IMT), has provided a powerful noninvasive technique to determine atherosclerosis (7–13). IMT has been extensively used as an outcome measure in clinical trials (14–20). Strong correlations between IMT and cardiovascular risk factors and coronary artery disease (CAD) have been demonstrated in the general population (21,22). However, few studies have been performed in diabetes, particularly in type 1 diabetic populations. The Atherosclerosis Risk in Communities Study demonstrated greater IMT in both diabetic subjects (mainly those with type 2 diabetes) and nondiabetic participants with moderate hyperglycemia compared with subjects with normal glucose levels (23). Similarly, IMT was demonstrated to be increased in type 1 and type 2 diabetic Japanese subjects compared with those without diabetes (24). Two studies from Italy (25,26) have also reported increased IMT and a higher presence of carotid plaques and stenoses in type 2 diabetes (25). More relevant to the current study, young type 1 diabetic subjects (10–25 years of age) in Japan have increased IMT compared with control subjects (27).

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AER, albumin excretion rate; BP, blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; dBP, diastolic blood pressure; DCCT, Diabetes Control and Complications Trial; ECG, electrocardiogram; EDIC, Epidemiology of Diabetes Interventions and Complications; GFR, glomerular filtration rate; IMT, intima-media wall thickness; sBP, systolic blood pressure; WHR, waist-to-hip ratio.

Data concerning determinants of IMT in type 1 diabetes are also limited. In a Japanese population (27), lipoproteins, BP, and $HbA_{1c}$ were not related to IMT in 105 type 1 diabetic subjects. In contrast, in an even smaller study of type 1 diabetes ($n = 31$), age and $HbA_{1c}$ predicted IMT (28). The role of hyperglycemia (or glycemic control) as a risk factor for CVD or atherosclerosis in type 1 diabetes is poorly understood. Recent data in type 1 diabetes suggest little, if any, effect of $HbA_{1c}$ on CVD (6,8,29). In long-term follow-up of the original 102 subjects in the Stockholm Diabetes Intervention Study, the patients originally assigned to intensive therapy had decreased IMT of the left but not the right common carotid artery, compared with the patients originally assigned to conventional treatment (30).

To address the limited studies and contradictory results with regard to the course of CVD in type 1 diabetes and the role of risk factors for atherosclerosis in type 1 diabetes, carotid ultrasonography was performed on prior participants of the Diabetes Control and Complications Trial (DCCT) (31) who are taking part in a longitudinal follow-up study called the Epidemiology of Diabetes Interventions and Complications (EDIC) (31a). The DCCT cohort (31), which excluded patients with hypertension, hyperlipidemia, and known CAD at baseline, provides an excellent opportunity to examine a large population of patients with type 1 diabetes without obvious CVD risk at baseline who have had careful prospective measurements of many of the putative risk factors for CVD previously established in type 2 diabetes and in nondiabetic populations. The DCCT cohort also provides the opportunity to examine the effects of diabetes treatment on CVD. The randomized interventions during the DCCT might influence the development of CVD, either directly by altering glucose levels or indirectly by altering lipid levels, the development of nephropathy or other risk factors. In addition, other side effects of intensive therapy documented in the DCCT, such as weight gain and increased rates of hypoglycemia, might also affect CVD risk.

Here we present the results of carotid arterial sonographic measurements of 1,325 patients during the baseline data collection of the EDIC study. The primary aims of this baseline analysis are to *1*) determine the feasibility of implementing the protocol in 28 sites; *2*) compare the EDIC cohort results with normative data from individuals matched for age and sex; *3*) examine the intercorrelations of IMT with demographic, clinical, and biochemical covariates that have been reported previously by other investigators; and *4*) determine whether the antecedent DCCT therapy (intensive versus conventional) and the different levels of glycemia achieved resulted in differences in IMT.

## RESEARCH DESIGN AND METHODS

**Subject population.** The original cohort of the DCCT consisted of 1,441 men and women who were 13–40 years of age and had type 1 diabetes for 1–15 years at entry (31). They entered the DCCT between 1983 and 1989 and were studied for an average of 6.5 years. A total of 730 patients were randomly assigned to conventional diabetes treatment and 711 to intensive diabetes treatment. In 1993, the DCCT was stopped because of evidence of a powerful salutary effect of intensive therapy on retinal, renal, and neurological long-term complications (31). At study close-out, DCCT subjects were informed of and invited to join EDIC, a multicenter longitudinal observational study. Of the 1,425 living members of the original cohort, 1,388 (96%) elected to participate in some or all aspects of EDIC. The carotid ultrasound protocol was carried out in 1,325 patients (92% of the original DCCT cohort) as part of the EDIC baseline examination. Table 1 presents the clinical characteristics of these 1,325 patients at EDIC baseline, stratified by original treatment group and sex.

TABLE 1
Baseline clinical characteristics of EDIC participants by sex and original treatment group assignment during the DCCT

| | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | Intensive | Conventional | *P* value | Intensive | Conventional | *P* value |
| *n* | 321 | 313 | — | 340 | 351 | — |
| Attained age (years) | 35 ± 7 | 34 ± 7 | 0.042 | 36 ± 7 | 36 ± 7 | 0.912 |
| Attained duration of type 1 diabetes (months) | 168 ± 58 | 170 ± 61 | 0.722 | 167 ± 59 | 159 ± 55 | 0.096 |
| Height (cm) | 165 ± 6 | 165 ± 6 | 0.682 | 178 ± 7 | 179 ± 7 | 0.076 |
| BMI (kg/m$^2$) | 26.5 ± 4.6 | 25.1 ± 3.6 | <.001 | 26.8 ± 4.2 | 25.9 ± 3.2 | 0.016 |
| BMI >27 (%) | 39.7 | 27.5 | 0.001 | 41.2 | 34.5 | 0.069 |
| Natural WHR | 0.76 ± 0.07 | 0.76 ± 0.07 | 0.731 | 0.88 ± 0.08 | 0.87 ± 0.09 | 0.101 |
| sBP (mmHg) | 114 ± 12 | 114 ± 13 | 0.739 | 119 ± 11 | 120 ± 12 | 0.186 |
| dBP (mmHg) | 74 ± 9 | 72 ± 10 | 0.101 | 77 ± 9 | 77 ± 8 | 0.446 |
| Hypertensive (%) | 9.7 | 12.9 | 0.210 | 21.2 | 17.6 | 0.240 |
| Total cholesterol (mg/dl) | 188 ± 36 | 188 ± 39 | 0.495 | 187 ± 35 | 184 ± 36 | 0.166 |
| HDL cholesterol (mg/dl) | 59 ± 14 | 59 ± 14 | 0.737 | 49 ± 13 | 50 ± 12 | 0.742 |
| LDL cholesterol (mg/dl) | 113 ± 29 | 113 ± 32 | 0.542 | 119 ± 30 | 115 ± 31 | 0.145 |
| Triglycerides (mg/dl) | 84 ± 74 | 82 ± 73 | 0.427 | 98 ± 77 | 97 ± 78 | 0.756 |
| AER (mg/24 h) | 21.1 ± 63.2 | 63.5 ± 313.9 | 0.003 | 28.6 ± 112.9 | 46.1 ± 123.2 | 0.038 |
| AER ≥40 mg/24 h (%) | 6.9 | 16.0 | <.001 | 7.4 | 17.9 | <0.001 |
| GFR | 117.5 ± 23.5 | 119.3 ± 26.1 | 0.069 | 115.3 ± 19.7 | 116.1 ± 24.8 | 0.335 |
| Insulin dose (U · kg$^{-1}$ · day$^{-1}$) | 0.63 ± 0.21 | 0.64 ± 0.19 | 0.801 | 0.67 ± 0.24 | 0.65 ± 0.20 | 0.269 |
| Cigarette smoking (current) (%) | 19.7 | 18.1 | 0.605 | 19.3 | 18.4 | 0.750 |
| $HbA_{1c}$ | 7.9 ± 1.4 | 8.2 ± 1.5 | 0.009 | 7.9 ± 1.2 | 8.4 ± 1.3 | <0.001 |
| Mean $HbA_{1c}$ during DCCT | 7.3 ± 0.9 | 9.0 ± 1.4 | <0.001 | 7.2 ± 0.9 | 9.0 ± 1.1 | <0.001 |
| Framingham score | 0.018 ± 0.025 | 0.017 ± 0.028 | 0.037 | 0.039 ± 0.038 | 0.037 ± 0.035 | 0.704 |

Data are means ± SD, *n*, or %. Baseline is that at EDIC baseline (1994–1995) after an average of 6.5 years of intensive treatment in DCCT. Hypertensive is defined as sitting sBP ≥140 mmHg and/or dBP ≥90 mmHg or the use of antihypertensive medication. Framingham score is defined as described by Anderson et al. (An Updated Coronary Risk Profile. *Circulation* 83:355–365, 1991).

**Ultrasonography and image analysis.** Carotid ultrasonography was performed between June 1994 and April 1995 (1–2 years after the close of the DCCT) at 28 clinical centers using one of three machines (Toshiba, American Medical Systems, Tustin, CA; ATL Ultra Mark 9; Advanced Technology Laboratory, Bothell, WA; and Acuson XT 128; Mt. View, CA). The criteria used to select these machines included the following:

- Accurate delineation of near and far wall boundaries,
- Accurate plaque detection and sizing,
- Simultaneous Doppler, preferably with color,
- Detection and quantification of early subintimal change,
- Accurately reproduced images on videotape using S-VHS recorders.

The EDIC Ultrasound Scanning Protocol was adapted from procedures used in the Cardiovascular Health Study (7), the Insulin Resistance Atherosclerosis Study (32), and the Mexican-American Heart Study (33).

The imaging protocol involved obtaining a single longitudinal lateral view of the distal 10 mm of the right and left common carotid arteries and three longitudinal views in different imaging planes of each internal carotid artery. The internal carotid artery was defined as including both the carotid bulb, identified by the loss of the parallel wall present in the common carotid artery, and the 10-mm segment of the internal carotid artery distal to the tip of the flow divider that separates the external and internal carotid arteries (Fig. 1).

Centrally trained and certified sonographers conducted the studies. Studies were recorded on S-VHS tapes and sent weekly to the Central Ultrasound Reading Unit. The maximum IMT of the common carotid artery was defined as the mean of the maximum IMT for near and far walls in both right and left sides. The maximum IMT of the internal carotid artery was defined in the same way, and the results from the three scans were averaged (anterior, lateral, and posterior views on both sides).

**Normative data.** During the first year of the EDIC, each of the 28 clinics performed six carotid ultrasounds on nondiabetic subjects who were between the ages of 20 and 50 years with no history of CVD, hypertension, or stroke ($n$ = 153). The mean age (35.3 ± 8.5) and percentage of women (49.7%) were not significantly different than those of the EDIC cohort.

**Other procedures.** On the anniversary of enrolling in the DCCT, each EDIC subject has a standardized annual history and physical examination, including a detailed evaluation of overall health, diabetes management, occurrence of diabetic complications, development of new disease, and medications used. Annual evaluations also include resting electrocardiograms (ECGs), Doppler ultrasound measurements of ankle/arm BP ratios, and arm BPs. Serum creatinine and $HbA_{1c}$ are determined as they were in the DCCT (34). Lipid profiles and 4-h urine collections for measurement of albumin excretion rate and creatinine clearance are obtained in alternate years using the same methods as in the DCCT (35).

**Statistical analysis.** Quality scores for carotid ultrasound scans were based on the number of lines visualized from the eight views. The proportion of lines with quality scores of good or excellent were compared across the 28 clinics.

To evaluate the possible association with other covariates, multiple linear regression models were fit to the average maximum IMTs of the common and internal carotid arteries. Both models were fit by ordinary least squares, but a reciprocal transformation had to be applied to internal IMT to obtain a homoscedastic and approximately normal residual distribution. The semipartial $R^2$ for each variable measures the increase in $R^2$ obtained by introducing that variable into a model already including all the others.

Wilcoxon rank-sum tests were used to make separate comparisons of the distributions of common IMT and internal IMT between EDIC patients and nondiabetic control subjects within strata defined by age and sex. Separate linear models for each segment were used to adjust for covariance with age before testing; EDIC patients and control subjects were adjusted jointly but stratified by sex. Comparison of IMTs between the DCCT randomized treatment groups was made using the Wei-Lachin test of stochastic ordering (36), which has greatest power against alternatives in which both segments tend to be thicker in the same treatment group. Tests were stratified by sex and decade of age, and an overall test adjusted for between-strata differences (36) was also performed. Based on the results of the multiple linear regression models, the EDIC patients' IMT values were first adjusted for covariance with age and cumulative pack-years of cigarette smoking. All $P$ values are reported at their nominal levels, without adjustment for multiple comparisons.

## RESULTS

**Data quality.** Baseline reproducibility analyses of 140 replicate measures resulted in absolute mean differences of 0.04 mm for both the common carotid and the intimal carotid. Intraclass correlation between original and re-readings of maximum wall thickness were 0.71 and 0.89 for the common and for internal carotid arteries, respectively.

Carotid artery data by clinic were generally of uniform high quality. The percentage of scans of the common carotid artery in which all six lines were legible and graded as good or excellent ranged from 90 to 100% across clinics. Visualization of the internal carotid artery was less uniform, with the percentage of scan with all six lines legible ranging from 15 to 94% of scans. Scans that did not meet the criteria (mainly segments of the internal carotid) had only four or five lines legible. A process for continuous quality control was instituted so that information was fed back to each center in an effort to improve scan quality.

**Comparison of nondiabetic control subjects with EDIC subjects.** Table 2 presents the IMT data including the average maximum of the common and internal carotid arteries stratified by sex and age decades for nondiabetic and type 1 diabetic subjects. A Wilcoxon test of the difference between sexes for both diabetic and nondiabetic groups indicates highly significant ($P \leq 0.0001$) differences, with men having greater IMT mean thickness. Adjusting for covariance with height reduces but does not eliminate the significance ($P$ =



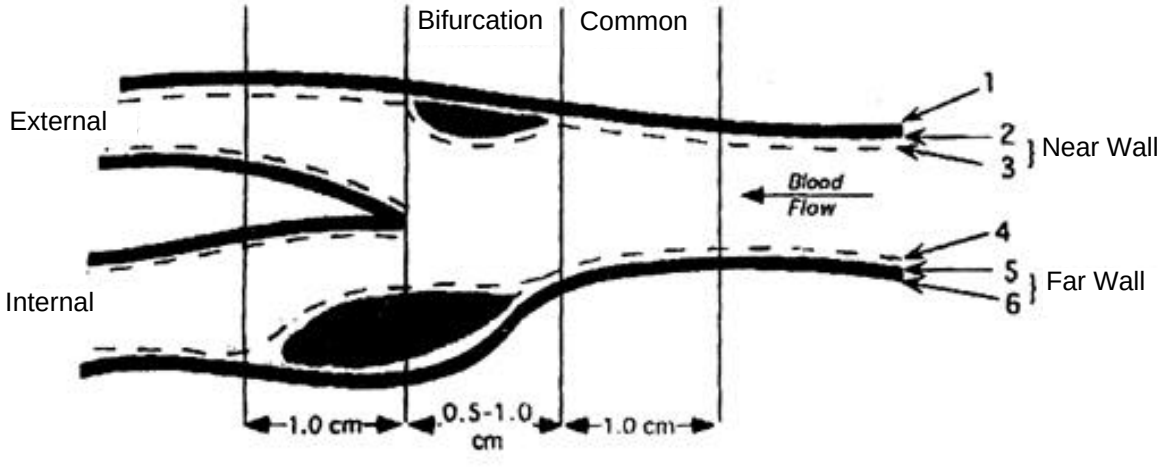


**FIG. 1. Schematic drawing of the carotid artery: the bifurcation of the common into the internal and external carotid arteries, the location of the segments scanned in the EDIC, and the six lines to be measured in the sonographic images.**

TABLE 2
Comparison of IMT in nondiabetic subjects with EDIC type 1 diabetes cohort

| | Women | | | | | Men | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Nondiabetic | | Type 1 diabetes | | | Nondiabetic | | Type 1 diabetes | | |
| Age (years) | *n* | IMT (mm) | *n* | IMT (mm) | *P* | *n* | IMT (mm) | *n* | IMT (mm) | *P* |
| Common carotid artery | | | | | | | | | | |
| 20–29 | 25 | 0.603 ± 0.062 | 172 | 0.616 ± 0.073 | 0.471 | 21 | 0.648 ± 0.098 | 125 | 0.636 ± 0.059 | 0.971 |
| 30–39 | 27 | 0.663 ± 0.074 | 278 | 0.657 ± 0.081 | 0.453 | 25 | 0.657 ± 0.076 | 350 | 0.684 ± 0.083 | 0.103 |
| 40–49 | 25 | 0.704 ± 0.078 | 178 | 0.696 ± 0.079 | 0.622 | 30 | 0.741 ± 0.094 | 211 | 0.745 ± 0.104 | 0.925 |
| Internal carotid artery | | | | | | | | | | |
| 20–29 | 25 | 0.547 ± 0.053 | 172 | 0.583 ± 0.092 | 0.065 | 21 | 0.588 ± 0.085 | 125 | 0.629 ± 0.083 | 0.032 |
| 30–39 | 27 | 0.632 ± 0.153 | 278 | 0.632 ± 0.147 | 0.859 | 25 | 0.645 ± 0.104 | 350 | 0.684 ± 0.114 | 0.071 |
| 40–49 | 25 | 0.655 ± 0.074 | 178 | 0.719 ± 0.226 | 0.704 | 30 | 0.741 ± 0.147 | 211 | 0.806 ± 0.261 | 0.437 |

Data are means ± SD or *n*. Nondiabetic data were obtained from six normal subjects without diabetes at each of the 29 clinics using the EDIC ultrasound scanning protocol and read at the Central Ultrasound Reading Unit. Data exclude six EDIC patients who were 19 years old when scanned and five who were aged 50 or 51 years old. *P* values are from Wilcoxon rank-sum test after linear adjustment for covariance with age. $P < 0.0001$ for both common and internal IMT, type 1 men versus type 1 women; $P = 0.59$ for common IMT, $P = 0.004$ for internal IMT, type 1 men versus nondiabetic men; $P = 0.89$ for common IMT, $P = 0.11$ for internal IMT, type 1 women versus nondiabetic women.

0.0007). A test of trend of the increasing maximum wall thickness over the age decades is significant in all strata (e.g., nondiabetic men, type 1 diabetic men, etc.).

Comparing the nondiabetic population with the sex-matched control subjects revealed that overall the type 1 diabetic men had greater IMT thickness for the internal carotid (0.713 ± 0.184 vs. 0.664 ± 0.130 mm, $P = 0.004$) but not for the common carotid (0.694 ± 0.10 vs. 0.686 ± 0.10 mm, $P = 0.59$). Within the different age-groups, only the youngest group of men had significantly different internal carotid IMT than their age-matched control subjects (0.629 vs. 0.588, $P = 0.03$). The type 1 diabetic women's mean IMT thickness was similar to the nondiabetic women's for both the common and internal carotid.

**Univariate correlation.** Table 3 presents univariate Spearman correlations of various clinical characteristics with average maximum wall thickness for the common and internal carotid arteries. Attained age and Framingham risk scores were the variables most strongly associated with IMT in both the common and internal carotid arteries. Attained duration of type 1 diabetes had a weaker, but statistically significant, association with wall thickness that, in men, persisted after adjusting for age. Current $HbA_{1c}$ was not correlated with wall thickness; however, $HbA_{1c}$ at the time of carotid studies did not reflect glycemic exposure during the DCCT, since all subjects were encouraged to adopt intensive therapy at the end of the DCCT. Therefore, correlations between mean $HbA_{1c}$ during the DCCT and IMTs were also computed. Mean $HbA_{1c}$ during the DCCT was not significantly correlated with either common or internal carotid IMT among men or with internal IMT among women. The correlation of mean $HbA_{1c}$ with common IMT in women, while nominally significant, was weak ($r = –0.11$, $P = 0.008$) and indicated an inverse relationship. Total and LDL cholesterol levels were correlated with wall thickness, but HDL cholesterol and triglyceride levels were not. Systolic blood pressure (sBP) was associated with IMT in both men and women, and diastolic blood pressure (dBP) was associated with IMT in men only. WHR correlated with IMT in men, but not women, while total pack-years of cigarette smoking was correlated with both common and internal carotid IMT in both sexes. Correlations were similar in the two treatment groups.

**Multivariate analyses.** Table 4 shows the multiple linear regression analysis. Apart from age, the major predictors of common carotid IMT in women were height, glomerular filtration rate (GFR), BMI, and smoking, while in men, height, smoking, BMI, sBP, duration of type 1 diabetes, and average LDL cholesterol during the DCCT were independent predictors. Overall, 29 and 20% of the variance was explained in men and women, respectively. For internal carotid IMT, age, sBP, and LDL were the major predictors in both sexes, and smoking had a significant but reduced effect compared with the model for the common carotid, especially in men. GFR was also a predictor in men. Again, more of the variance was explained in men (24%) than in women (17%).

**Tests for treatment group difference.** Table 5 presents IMT by sex, age, and treatment group. There are no strata in which intensive treatment group patients had significantly different age- and smoking-adjusted wall thicknesses than conventional treatment group patients. The difference between intensive and conventional treatment from the N-weighted test of stochastic ordering for the combined strata was not statistically significant ($P = 0.39$).

## DISCUSSION

The current report confirms the feasibility of using carotid ultrasonography in a large multicenter study with excellent reproducibility for common carotid and acceptable reproducibility for internal carotid IMT measurements (37,38). The quality of scans was good or excellent for the vast majority of centers, especially for the common carotid artery.

There was no significant difference in mean IMT between EDIC subjects and age- and sex-matched control subjects, except for internal carotid IMT among men. Because two major determinants of IMT are age and BP, the similarity in IMT may reflect the young age of the EDIC subjects and the

TABLE 3
Spearman correlation coefficients of clinical characteristics with average maximum IMT

| | | Common carotid artery | | Internal carotid artery | |
|---|---|---|---|---|---|
| | Sex | Correlation | *P* value | Correlation | *P* value |
| Attained age (years) | M | 0.46 | <0.001 | 0.38 | <0.001 |
| | F | 0.42 | <0.001 | 0.35 | <0.001 |
| Attained duration of type 1 diabetes (months) | M | 0.13 | <0.001 | 0.12 | 0.002 |
| | F | 0.08 | 0.04 | 0.12 | 0.004 |
| Height (cm) | M | 0.17 | <0.001 | 0.05 | 0.19 |
| | F | 0.12 | 0.003 | –0.04 | 0.36 |
| BMI (kg/m$^2$) | M | 0.15 | <0.001 | 0.09 | 0.02 |
| | F | 0.06 | 0.12 | 0.02 | 0.56 |
| WHR | M | 0.22 | <0.001 | 0.14 | <0.001 |
| | F | 0.01 | 0.89 | 0.01 | 0.85 |
| sBP (mmHg) | M | 0.21 | <0.001 | 0.14 | <0.001 |
| | F | 0.14 | <0.001 | 0.11 | 0.007 |
| dBP (mmHg) | M | 0.11 | 0.004 | 0.13 | <0.008 |
| | F | 0.07 | 0.08 | 0.07 | 0.09 |
| Total cholesterol (mg/dl) | M | 0.21 | <0.001 | 0.23 | <0.001 |
| | F | 0.09 | 0.04 | 0.13 | 0.002 |
| HDL cholesterol (mg/dl) | M | –0.03 | 0.37 | 0.00 | 0.92 |
| | F | 0.00 | 0.96 | 0.03 | 0.41 |
| LDL cholesterol (mg/dl) | M | 0.24 | <0.001 | 0.26 | <0.001 |
| | F | 0.08 | 0.06 | 0.13 | 0.001 |
| Triglycerides (mg/dl) | M | 0.07 | 0.06 | 0.05 | 0.19 |
| | F | 0.06 | 0.14 | 0.00 | 0.94 |
| Smoking (total pack-years) | M | 0.21 | <0.001 | 0.09 | 0.02 |
| | F | 0.15 | <0.001 | 0.16 | <0.001 |
| Insulin dose (U · kg$^{-1}$ · day$^{-1}$) | M | –0.06 | 0.10 | –0.10 | 0.02 |
| | F | –0.08 | 0.06 | –0.05 | 0.20 |
| $HbA_{1c}$ | M | 0.07 | 0.07 | 0.02 | 0.56 |
| | F | –0.02 | 0.62 | 0.02 | 0.68 |
| Mean $HbA_{1c}$ during the DCCT | M | 0.06 | 0.12 | –0.02 | 0.57 |
| | F | –0.11 | 0.008 | –0.07 | 0.07 |
| Framingham risk score | M | 0.47 | <0.001 | 0.38 | <0.001 |
| | F | 0.42 | <0.001 | 0.35 | <0.001 |
| AER (mg/24 h) | M | 0.10 | 0.01 | 0.07 | 0.09 |
| | F | –0.01 | 0.76 | 0.01 | 0.85 |
| GFR | M | –0.01 | 0.76 | 0.02 | 0.54 |
| | F | –0.05 | 0.25 | –0.02 | 0.65 |

initial exclusion of hypertensive subjects in the DCCT. These data are in contrast to those of Yamasaki et al. (27), who reported significantly greater IMT for 10- to 25-year-old type 1 diabetic subjects compared with nonmatched control subjects, despite the smaller number of type 1 diabetic patients and control subjects (<10% and 30%, respectively) in the Japanese study. The discrepancy between the Japanese and EDIC studies may be secondary to the unmatched control group in the Japanese study, racial differences in the pathogenesis of atherosclerosis, or other factors. The finding of increased IMT in type 2 diabetic subjects (23,26) may be secondary to older age or the high prevalence of other CVD risk factors found in type 2 diabetes that were not present in the EDIC population.

Another possible explanation of the lack of a marked difference in IMT in our type 1 diabetic subjects is the possibility that IMT does not reflect the aspects, or stages, of atherosclerosis that are enhanced or exacerbated by type 1 diabetes. Although IMT is thought to be an intermediate biological marker of atherosclerosis and correlates with the presence of plaque or clinical events (39), it does not provide a direct measure of occlusive disease or plaque stability. Nor does it directly measure the hemostatic (and possibly inflammatory) disturbances that may play a vital role in atherosclerotic disease and that are disturbed in diabetes, such as abnormal fibrinogen levels (40) and platelet function (41). The true predictive power of IMT for future events is uncertain, and the data supporting a correlation with existent disease, while encouraging, are still limited (21,22,39,42,43). These potential limitations, however, do not negate the value of carotid ultrasonography in diabetes, which may throw more light on the pathogenesis of artherosclerotic disease generally, as well as on the specific enhanced risk in diabetes. Only careful follow-up with repeated sonography and assessment of clinical outcomes will allow definitive determination of the effect of diabetes on the overall natural history of atherosclerotic CVD.

The current study has limitations, the major one being that the DCCT cohort was a selected trial population and not necessarily representative of type 1 subjects in the general population. However, the DCCT conventional treatment group was found to be generally comparable to a subset of a

TABLE 4
Summary of multiple linear regression models for common carotid IMT and 1/internal carotid IMT

| | Common | | | 1/Internal | | |
|---|---|---|---|---|---|---|
| | Slope | $P$ | Semipartial $R^2$ (%) | Slope | $P$ | Semipartial $R^2$ (%) |
| Women | | | | | | |
| Age | 0.00435 | <0.001 | 11.95 | –0.01176 | <0.001 | 7.02 |
| Type 1 diabetes duration (months) | 0.00006 | 0.267 | 0.21 | –0.00034 | 0.078 | 0.54 |
| Height | 0.00131 | 0.011 | 1.11 | 0.00188 | 0.315 | 0.18 |
| Smoking (pack-years) | 0.00076 | 0.062 | 0.60 | –0.00367 | 0.013 | 1.07 |
| BMI | 0.00155 | 0.050 | 0.67 | 0.00122 | 0.670 | 0.03 |
| sBP | 0.00028 | 0.307 | 0.18 | –0.00217 | 0.027 | 0.85 |
| LDL cholesterol (DCCT average) | 0.00009 | 0.507 | 0.08 | –0.00172 | <0.001 | 2.00 |
| GFR | 0.00025 | 0.053 | 0.65 | –0.00056 | 0.230 | 0.25 |
| $HbA_{1c}$ (DCCT average) | –0.00310 | 0.274 | 0.21 | 0.01192 | 0.247 | 0.23 |
| Intensive therapy | –0.00522 | 0.515 | 0.07 | 0.02407 | 0.407 | 0.12 |
| Men | | | | | | |
| Age | 0.00451 | <0.001 | 9.35 | –0.01167 | <0.001 | 7.19 |
| Type 1 diabetes duration (months) | 0.00018 | 0.001 | 1.53 | –0.00046 | 0.006 | 1.13 |
| Height | 0.00161 | <0.001 | 2.15 | –0.00051 | 0.684 | 0.03 |
| Smoking (pack-years) | 0.00149 | <0.001 | 2.52 | –0.00263 | 0.015 | 0.89 |
| BMI | 0.00322 | <0.001 | 2.06 | –0.00131 | 0.612 | 0.04 |
| sBP | 0.00085 | 0.002 | 1.38 | –0.00201 | 0.016 | 0.88 |
| LDL cholesterol (DCCT average) | 0.00033 | 0.009 | 1.03 | –0.00220 | <0.001 | 5.07 |
| GFR | 0.00025 | 0.072 | 0.49 | –0.00105 | 0.012 | 0.94 |
| $HbA_{1c}$ (DCCT average) | 0.00226 | 0.481 | 0.08 | 0.00894 | 0.350 | 0.13 |
| Intensive therapy | –0.00985 | 0.241 | 0.21 | 0.01190 | 0.635 | 0.03 |

Total women in the common group is 20.5%; total women in the 1/internal group is 17.4%; total men in the common group is 29.4%; total men in the 1/internal group is 24.3%.

population-based type 1 diabetes cohort (44). A further limitation to the study was the exclusion at baseline of patients with hypertension and hyperlipidemia. As noted, the relatively young age of the EDIC cohort and the exclusions noted above may have reduced the occurrence of CVD and the ability to detect risk factor associations and differences in IMT at the current time. It should also be noted that the current analysis is essentially cross-sectional (albeit with a well-documented and randomized historical prospective measure of glycemic exposure) and is subject to the limitations of these studies, in particular, the absence of baseline (carotid) studies. Cardiovascular risk profile, however, did not differ by DCCT treatment group at baseline (31).

An increased number of CVD events is very likely to occur in the DCCT cohort during the 10 years of the EDIC. By the end of the 10-year follow-up, the mean age of the study population, the major predictor of CAD, will approach 43 years, and type 1 diabetes duration will average 22 years. Based on

TABLE 5
Average maximum IMTs by age and randomized treatment assignment

| | | Common carotid artery | | | | Internal carotid artery | | |
|---|---|---|---|---|---|---|---|---|
| Sex | Age (years) | $n$ | Intensive | $n$ | Conventional | Intensive | Conventional | $P$ |
| Women | | | | | | | | |
| | 20–29 | 78 | 0.626 ± 0.078 | 94 | 0.608 ± 0.068 | 0.576 ± 0.071 | 0.589 ± 0.107 | 0.809 |
| | 30–39 | 137 | 0.651 ± 0.086 | 141 | 0.663 ± 0.076 | 0.628 ± 0.129 | 0.636 ± 0.164 | 0.437 |
| | 40–49 | 102 | 0.698 ± 0.079 | 76 | 0.693 ± 0.080 | 0.704 ± 0.207 | 0.738 ± 0.250 | 0.954 |
| Men | | | | | | | | |
| | 20–29 | 65 | 0.637 ± 0.062 | 60 | 0.635 ± 0.056 | 0.636 ± 0.091 | 0.622 ± 0.072 | 0.743 |
| | 30–39 | 167 | 0.680 ± 0.079 | 183 | 0.687 ± 0.086 | 0.684 ± 0.107 | 0.685 ± 0.120 | 0.807 |
| | 40–49 | 104 | 0.728 ± 0.084 | 107 | 0.761 ± 0.118 | 0.791 ± 0.211 | 0.820 ± 0.302 | 0.149 |
| Combined (stratified-adjusted) | | | | | | | | 0.388 |

Data are means ± SD or $n$. $P$ values are from the Wei-Lachin test of stochastic ordering after adjustment of IMT values for covariance with age and pack-years of cigarette smoking. The "combined" test aggregates the within-stratum results while accounting for the differences between age-groups and sex. Means and SDs were calculated from the unadjusted IMTs. The table excludes 11 patients who were <20 or >49 years old when tested.

estimates derived from previous studies (1–6), the prevalence of CAD, as manifested clinically and/or as detected by ECG or exercise tolerance testing, is likely to be 15–40%. It seems likely that we shall have sufficient power to determine the relationship of IMT to CVD events occurring over the subsequent 10 years.

Documented risk factors for increased IMT include age, hypertension, lipid profile, and smoking. Our data suggest that these factors relate to IMT in type 1 diabetes. Among established lipid risk factors, only LDL level correlated with IMT. Some risk factors appeared to affect IMT in the common carotid, while others affected the internal carotid wall. For example, in multivariate analyses, smoking was more strongly related to common carotid IMT than to internal carotid, while LDL cholesterol was stronger for the internal carotid.

The large sample size in the current study allowed the multivariate analyses to establish a variety of factors including smoking, sBP, GFR, BMI, and LDL cholesterol as predictors of IMT. Some studies in type 2 diabetes have confirmed some of these associations, e.g., BP (24–26) and hyperlipidemia (24), while other studies in type 2 diabetes have failed to find such associations (27,28), possibly owing to their small sample size. The relationship between GFR and IMT may reflect the recognized association between renal disease and CVD in type 1 diabetes (5,6).

The role of glycemic control (or glycemic level) is of particular interest. The few data available relating glycemia to CVD in type 1 diabetes are controversial. The DCCT results suggested a borderline salutary effect of intensive treatment on combined macrovascular events (45). A follow-up report by the Stockholm Diabetes Intervention Study suggested that intensive treatment leads to reduced IMT thickness and less stiffening of the carotid arteries (30), although the results were not uniformly supportive. The current study does not support an association between $HbA_{1c}$ at the time of carotid ultrasonography or the mean $HbA_{1c}$ during the 6.5 years of the DCCT and IMT. In addition, treatment assignment during the DCCT did not have an apparent effect on IMT. It may be argued that the absence of a major difference in $HbA_{1c}$ at the time of ultrasonography between the two groups might explain the absence of an effect, and that 1.5 years of similar control after the DCCT may obliterate any benefit that 6.5 years of better control may have had. However, as much of the adverse effect of hyperglycemia in atherosclerosis is thought to be a chronic effect, e.g., cumulative advanced glycosylation end product formation (46), some differential effect of DCCT exposure might reasonably be expected. However, the current findings do not support an obvious association between glycemia and CVD in type 1 diabetes, consistent with several previous studies (3,6,28). Further follow-up will permit more definitive assessments as age, IMT, atherosclerosis, and clinical events all increase. Future studies will also help determine whether recent American Diabetes Association guidelines on the management of diabetic dyslipidemia in type 2 diabetes (47) should apply to type 1 diabetic subjects as well. The predictive power of LDL cholesterol for IMT in the current study provides some further support for aggressive cholesterol lowering (47). Intensive glycemic control in type 1 diabetes, nonetheless, remains the central component of diabetes management in view of its undoubted benefit in delaying or preventing microvascular complications and improving the CVD risk profile.

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Author Queries (please see Q in margin and underlined text)

Q1: Is "*w*" the correct symbol for equations such as "*w* = 153"? Does it need explanation at first mention?
Q2: The last line of the first footnote has been moved to Acknowledgments.
Q2a: Please supply a running title of ≤40 characters.
Q3: In Table 1, please supply title of article by Anderson et al.
Q4: Please list the name of the machine from Acuson.
Q5: In Table 2, last line of footnote, *P* = 11 correct?
Q6: Should CHD be changed to CAD or CVD?
Q7: Stockholm Diabetes Intervention "Society" in discussion vs. "Study" in introduction. OK as is or change needed?
Q8: Appendix—The term "(past)" appears after "A. Kowarski"; does this mean "past member"?
Q9: For ref. 33, please list volume, page range, and year of publication.
Q10: For ref. 35, please list location of publisher.

Table 1: First column, row six: should the number after ± begin with a decimal point (0.07)?