

# The Effect of Intensive Glycemic Treatment on Coronary Artery Calcification in Type 1 Diabetic Participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study

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**The Epidemiology of Diabetes Interventions and Complications (EDIC) study, an observational follow-up of the Diabetes Control and Complications Trial (DCCT) type 1 diabetes cohort, measured coronary artery calcification (CAC), an index of atherosclerosis, with computed tomography (CT) in 1,205 EDIC patients at ~7–9 years after the end of the DCCT. We examined the influence of the 6.5 years of prior conventional versus intensive diabetes treatment during the DCCT, as well as the effects of cardiovascular disease risk factors, on CAC. The prevalences of CAC >0 and >200 Agatston units were 31.0 and 8.5%, respectively. Compared with the conventional treatment group, the intensive group had significantly lower geometric mean CAC scores and a lower prevalence of CAC >0 in the primary retinopathy prevention cohort, but not in the secondary intervention cohort, and a lower prevalence of CAC >200 in the combined cohorts. Waist-to-hip ratio, smoking, hypertension, and hypercholesterolemia, before or at the time of CT, were significantly associated with CAC in univariate and multivariate analyses. CAC was associated with mean HbA<sub>1c</sub> (A1C) levels before enrollment, during the DCCT, and during the EDIC study. Prior intensive diabetes treatment during the DCCT was associated with less atherosclerosis, largely because of reduced levels of A1C during the DCCT. *Diabetes* 55: 3556–3565, 2006**

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CAC, coronary artery calcification; CT, computed tomography; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; IMT, intima-media thickness; ROC, receiver operating characteristics.

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**P**atients with type 1 diabetes have a high risk of developing cardiovascular disease (CVD), which in young adulthood can be 10-fold higher than in the general population (1,2). The reasons for this increased risk have not been fully elucidated and can only be partly explained by standard cardiovascular risk factors. Surprisingly, cumulative hyperglycemia has not been shown consistently to be a risk factor for cardiovascular events in type 1 diabetes (3–8).

The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study provides an opportunity to explore the complex relationships among traditional CVD risk factors, glycemia, and CVD outcomes (9). The DCCT demonstrated the importance of glycemic control in preventing or delaying microvascular complications (10), but it did not reach a clear conclusion with respect to macrovascular complications, owing to the low prevalence of macrovascular disease in the relatively young cohort (11). The long-term EDIC follow-up included assessments of subclinical CVD with measurement of carotid intima-media thickness (IMT) (12,13) and with computerized tomography (CT) of the heart to detect and quantitate calcification in the coronary arteries, a marker of atherosclerosis (14). The EDIC study demonstrated a significant protective effect of prior intensive diabetes therapy, compared with conventional therapy, on the progression of IMT over a 6-year period that was associated with the level of HbA<sub>1c</sub> (A1C) (13). Progression of IMT was associated with the level of glycemia (A1C) over time, consistent with some (15), but not all (16,17), reports in type 1 diabetes.

The association of glycemia with coronary artery calcification (CAC) in type 1 diabetes is unclear. Two studies (18,19) failed to demonstrate a relationship between glycemia and CAC in type 1 diabetes, whereas one did (20). These studies showed relationships with traditional CVD risk factors, but a smaller sex difference in CAC than is usual for the nondiabetic population, consistent with the reduction in the difference between sexes for CAD in type 1 diabetes.

The DCCT/EDIC study has recently reported (21) that

DCCT intensive therapy significantly reduced the long-term risk of clinical CVD by 42%; however, the cumulative incidence of such events remains low, precluding multivariate analyses at this time. Measurement of CAC provides an opportunity to assess the effects of putative and established CVD risk factors on the progression of atherosclerosis in type 1 diabetes that may ultimately translate into effects on risk of clinical events.

Herein we assess the long-term effects of original DCCT (conventional versus intensive) treatment assignment on the degree of CAC measured 8 years after the completion of the DCCT. We also examine the association of CAC with history of glycemia, with other risk factors and markers of CVD, and with clinically prevalent CVD.

## RESEARCH DESIGN AND METHODS

Between 1983 and 1989, the DCCT enrolled 1,441 subjects with type 1 diabetes who, at baseline, were 13–39 years of age, had type 1 diabetes for 1–15 years, and were in generally good health (10). The DCCT consisted of two cohorts: the primary prevention cohort had type 1 diabetes for 1–5 years, no retinopathy, and urinary albumin excretion <40 mg per 24 h at baseline; the secondary intervention cohort had type 1 diabetes for 1–15 years, very mild to moderate nonproliferative retinopathy, and urinary albumin excretion  $\leq$ 200 mg per 24 h at baseline. At the end of the DCCT in 1993, after 6.5 years of mean follow-up, intensive therapy was recommended for all subjects, and they returned to their own health care providers for diabetes care. In 1994, 1,375 (96%) of the 1,425 surviving members volunteered to participate in the EDIC observational follow-up study (9).

**Computed tomography of coronary calcification.** Computed tomography (CT) was performed between November 2000 and March 2003 (11–20 years after enrolment into the DCCT, 7–9 years after its end) in 1,205 (86%) of the surviving 1,404 participants, with specific patient consent. CT was performed in 19 scanning sites (see APPENDIX) using a C-150 cardiac-gated electron beam CT scanner ( $n = 9$ ; Imatron, San Francisco, CA), a Lightspeed ( $n = 7$ ; General Electric Medical Systems, Waukesha, WI) or a Volume Zoom (Siemens, Erlanger, Germany) multidetector CT system, a Lightspeed Marconi MX-8000 (GE), or a Somatom 4+ (Siemens) ( $n = 3$ ). All participants were scanned twice over calibration phantoms of known physical calcium concentration.

Scans were read centrally at the Harbor-UCLA (University of California, Los Angeles) Research and Education Institute (Torrance, CA) to identify and quantify CAC, calibrated according to the readings of the phantom using the method of Agatston et al. (22). The average score from the two scans was used in the analysis. Readers were masked to subject identity and prior treatment assignment.

Scans were evaluated by the staff at the reading center on seven criteria: motion artifact, streak artifact, phantom placement, slice registration, lack of noise, axis coverage, and  $xy$  axis coverage. The 19 scanning centers were monitored monthly on these criteria. The intra- and interreader precision was evaluated with the use of a set of standard scans that were reread by the same reader and another reader at the reading center. The kappa measure of intrareader agreement beyond chance for the presence or absence of calcification was 0.81, and the interreader kappa was 0.86. The coefficient of reliability for the calcification scores was 0.99 for both inter- and intrareader.

**Other procedures.** Each EDIC subject had an annual history, physical examination, electrocardiogram, and laboratory testing, including serum creatinine and A1C, determined as they were during the DCCT (9,10,23). Fasting lipid profiles and 4-h urine collections for measurement of albumin excretion rate and creatinine clearance were obtained in alternate years during the EDIC study (9). Carotid IMT was measured by B-mode ultrasonography in 1994 and again in 2000–2001 (12,13). Combined IMT was defined as the sum of the standardized intima-media measurements of the common and internal carotid arteries. Standardized IMT was defined as: (variable – mean)  $\div$  SD, as described by O’Leary et al. (24).

Hypertension was defined as systolic blood pressure  $\geq$ 140 mmHg or diastolic blood pressure  $\geq$ 90 mmHg, documented hypertension, or use of antihypertensive agents. Hypercholesterolemia was defined as LDL cholesterol  $\geq$ 130 mg/dl or use of lipid-lowering agents. Cardiovascular clinical outcomes included fatal and nonfatal myocardial infarctions, stroke, revascularization (bypass surgery or angioplasty), angina confirmed with a positive exercise tolerance test or angiogram, or silent myocardial infarctions identified using criteria applied to the follow-up electrocardiogram. For classification of cardiovascular clinical outcomes, information from death certificates; medical records from hospitalizations; autopsy reports, if available; and interviews with the participants were reviewed by the EDIC mortality and

morbidity committee, masked to treatment assignment, and the event was classified according to specified guidelines (25).

**Statistical analyses.** Analyses were conducted using SAS (26). Clinical characteristics were compared using Wilcoxon’s rank-sum test for continuous quantitative variables and  $\chi^2$  or Fisher’s exact tests for categorical variables. Analyses used the prevalence of CAC scores of >0 and >200 Agatston units; the latter has been a predictor of CVD events in other studies (18,20,27). The Mantel-Haenszel  $\chi^2$  test of nonzero correlation was used to test for a linear trend in proportions (28). The stratified adjusted Mantel-Haenszel analysis adjusted for other qualitative covariate effects on the OR or test of trend (28). Homogeneity of treatment effect over strata was assessed by the Breslow-Day test (28). Logistic regression examined the relationship between covariates and the prevalence of CAC (28,29). The entropy  $R^2$  coefficient was used to describe the proportion of variation in risk explained by the model (29).

Tobit-censored regression models (30) assessed covariate effects on the observed CAC score, which is a mixture of a discrete random variable (any measurable calcification, yes/no) and a quantitative random variable (the amount of CAC, if measurable). The Tobit regression coefficient represents the log ratio of the geometric mean CAC score per unit increase in the covariate, assuming some true measurable calcification for all subjects, including those with undetectable levels. Ordinary multiple regression of the observed measurable values is biased, whereas logistic regression of the prevalence of measurable calcification is inefficient (31). The Tobit model was fit using the LIFEREG procedure in SAS (26), where the natural logarithm of the nonzero CAC scores was reduced by subtracting the natural logarithm of the lowest detectable CAC score (the lower limit of quantification of CAC). Goodness of fit was assessed by applying the Hosmer-Lemeshow test to the estimated probabilities from the Tobit model as a predictor for presence of CAC, and by the Spearman correlation coefficient between the measured score of CAC and that predicted from the Tobit model (32).

The intent-to-treat effects of prior DCCT conventional versus intensive therapy were assessed in basic logistic and Tobit models, adjusted for baseline age, type 1 duration, sex, scanning site, and DCCT baseline retinopathy cohort (primary versus secondary). Additional multivariate models explored effects of covariates measured up to the time of CAC measurement. The most significant factor among similar variables (e.g., systolic and diastolic blood pressure) was used. Backward elimination was used to select two-way interactions with treatment group (28,29), retaining those nominally significant at  $P \leq 0.05$ . In models with an interaction, the overall treatment effect was assessed using a test of both the group and the group by covariate interaction on 2 degrees of freedom (df) (29). Receiver operating characteristics (ROC) plots were used to describe the sensitivity and specificity of CAC for prevalent CVD (21,33–35).

## RESULTS

**Clinical characteristics.** Table 1 shows the clinical characteristics of the participants in the CT study at DCCT baseline and at the exam immediately before, or at time of, the CT scan, stratified by sex and original DCCT treatment group. Of the 1,205 participants, 95% were Caucasian, and 53% were male. In both male and female subjects, blood pressure and lipids were not significantly different between the former DCCT conventional- and intensive-treatment groups at the time of the CT scans. In men only, prevalence of hypertension and aspirin use were significantly lower in the intensive group. The A1C level before CT was similar in the treatment groups in both sexes, but mean A1C level during the  $\sim$ 9 years of EDIC follow-up before the CT scan was slightly higher in the conventional than in the intensive group in men (8.2 vs.  $8.0 \pm 1.1\%$ ,  $P < 0.01$ ). Albumin excretion rates were significantly lower in the intensive than in the conventional-treatment group ( $P < 0.01$ ). Measurements of adiposity were not different between the treatment groups. A comparison of the EDIC subjects who participated in the CT study with those who did not participate revealed similar distributions of sex, race, and treatment group. However, the participants who did not have CT scans were younger (25 vs. 27 years at DCCT entry) and had higher mean A1C (8.5 vs.  $8.2\%$ ,  $P < 0.003$ ) during the DCCT.

TABLE 1  
Clinical characteristics of participants in CT scan study by sex and DCCT treatment assignment

	Female subjects		Male subjects	
	Intensive	Conventional	Intensive	Conventional
<i>n</i>	297	275	300	333
Age at entry into DCCT (years)	27 ± 7*	26 ± 7	28 ± 7	28 ± 7
DCCT follow-up (years)	6.4 ± 1.7	6.3 ± 1.7	6.4 ± 1.7	6.1 ± 1.6
EDIC follow-up (years)	9.2 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	9.2 ± 0.5
DCCT baseline				
Retinopathy (negative by fundus photographs) (%)	51	49	46	54
Albumin excretion rate (mg/24 h)	16 ± 20	15 ± 13	17 ± 21	15 ± 20
Diabetes duration (months)	69 ± 50	71 ± 51	70 ± 50†	60 ± 46
Visit prior to or at time of CT scan				
Age (years)	43 ± 7*	42 ± 7	43 ± 7	43 ± 7
Current smokers (%)	15	14	18	15
Diabetes Duration (years)	21 ± 5	21 ± 5	21 ± 5π	20 ± 5
BMI (kg/m <sup>2</sup> )	28 ± 5	27 ± 5	28 ± 4	28 ± 4
Natural waist-to-hip ratio	0.79 ± 0.07	0.78 ± 0.06	0.91 ± 0.06	0.90 ± 0.06
Ankle-to-arm blood pressure ratio <0.9 (%)	15	12	7	8
Systolic BP (mmHg)	120 ± 14	120 ± 15	123 ± 13	125 ± 15
Diastolic BP (mmHg)	75 ± 9	74 ± 9	78 ± 9	78 ± 10
Hypertensive (%)§	29	36	35¶	46
Aspirin ≥14 tablets per month (%)	22	25	26§	33
Menopause (%)	26	21	—	—
One or both parents with diabetes (%)	20	15	17	19
Carotid IMT year 6	0.60 ± 0.11	0.59 ± 0.10	0.63 ± 0.10	0.65 ± 0.14
Lipids				
Total cholesterol (mmol/l)	4.94 ± 0.95	4.83 ± 0.84	4.81 ± 0.90	4.73 ± 0.85
HDL cholesterol (mmol/l)	1.59 ± 0.38	1.62 ± 0.38	1.31 ± 0.35	1.32 ± 0.30
LDL cholesterol (mmol/l)	2.89 ± 0.76	2.81 ± 0.69	2.98 ± 0.76	2.92 ± 0.74
LDL-to-HDL ratio	1.9 ± 0.8	1.8 ± 0.6	2.4 ± 0.9	2.3 ± 0.8
Triglycerides (mmol/l)	0.95 ± 0.64	0.89 ± 0.58	1.15 ± 0.88	1.06 ± 0.61
Hypercholesterolemia (%)‡	30	29	44	40
Renal				
Albumin excretion rate (mg/24 h)	36 ± 194†	84 ± 370	105 ± 731†	234 ± 863
Albumin excretion rate >40 mg/24 h (%)	9	18	13	26
A1C				
At DCCT eligibility	9.2 ± 1.6	9.1 ± 1.7	9.0 ± 1.6	8.8 ± 1.6
Mean during DCCT	7.3 ± 0.9	9.1 ± 1.4	7.2 ± 0.9	8.9 ± 1.1
At DCCT closeout	7.3 ± 1.0	9.1 ± 1.8	7.4 ± 1.1	9.1 ± 1.3
Mean during EDIC	8.1 ± 1.2	8.1 ± 1.2	8.0 ± 1.1†	8.2 ± 1.1
Mean at visit prior to CT	8.0 ± 1.4	7.9 ± 1.5	7.9 ± 1.2	7.9 ± 1.3
Mean during combined DCCT/EDIC	7.8 ± 0.9	8.5 ± 1.1	7.7 ± 1.0	8.5 ± 1.0

Data are the means ± SD unless otherwise indicated. \* $P < 0.05$ , † $P < 0.01$ , and || $P < 0.001$  for intensive vs. conventional. ‡LDL ≥130 or using anti-lipid agents; §defined as systolic ≥140 or diastolic ≥90 mmHg, or hypertension has been documented, or using antihypertensive agents.

**CAC distributions.** Figure 1 shows the distribution of CAC scores, including the prevalence of CAC = 0, 1–200, and >200 Agatston units by treatment group stratified by primary prevention and secondary intervention cohorts. These analyses showed differences between treatment groups in the primary cohort ( $P = 0.03$ ), but not in the secondary cohort ( $P = 0.41$ ), not adjusted for scanning site or other baseline factors.

Figure 2A–D shows the prevalences of CAC >0 and >200 Agatston units within each treatment group, stratified by sex and also by decade of age at the time of the scan. The overall prevalences for CAC >0 and >200 Agatston units were 31.0 and 8.5%, respectively. The prevalences of CAC >0 and >200 Agatston units increased linearly by decade of age within each sex ( $P < 0.01$  for each). Within both sexes, and within each treatment group, the prevalence of calcification increased significantly with age, except for CAC >200 Agatston units in the intensive group among women, for which the overall

incidence was lower than for men or conventional group women, especially among those ≥50 years.

**DCCT treatment group differences.** In the primary cohort, compared with the conventional-treatment group, the intensive-treatment group had a significantly lower prevalence of CAC >0 Agatston units (21.7 vs. 29.8%, respectively), with an adjusted odds ratio (OR) for conventional versus intensive therapy of 1.59 (95% CI 1.06–2.39,  $P = 0.024$ ). By contrast, there was no treatment effect in the secondary cohort (OR 0.94). The difference in ORs between cohorts (i.e., group by cohort interaction) was barely significant ( $P = 0.049$ ).

The adjusted effect of conventional versus intensive therapy on the prevalence of CAC >200 Agatston units within the primary prevention cohort (OR 2.13) was not significantly different from that in the secondary intervention cohort (1.50,  $P = 0.474$  for test of interaction). For the two cohorts combined, the adjusted treatment group effect had an OR of 1.65 (95% CI 1.06–2.58,  $P = 0.026$ ).

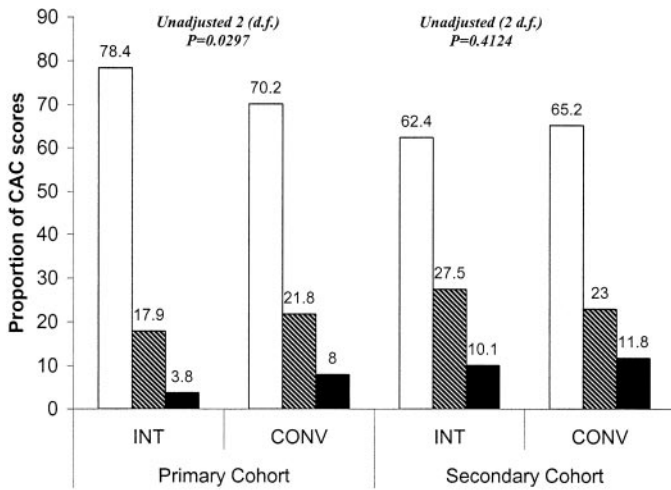


FIG. 1. Distribution of CAC scores (Agatston units) by cohort and treatment group. □, CAC = 0; ▨, CAC 1-200; ■, CAC >200. CONV, conventional treatment; INT, intensive treatment.

In a Tobit regression analysis of the log(CAC) score in the primary prevention cohort, allowing for nonmeasurable values, the conventional-treatment group on average had a 3.7-fold higher CAC score than the intensive group (95% CI 1.3-10.5,  $P = 0.014$ ). However, there was no treatment group difference within the secondary intervention cohort, the geometric mean ratio being 1.00 (0.4-2.5,  $P = 0.87$ ). The difference between the primary versus secondary cohorts (i.e., the 3.7 vs. 1.0 treatment group effect) approached statistical significance ( $P = 0.060$  for the test of interaction). Further analyses in the secondary

intervention cohort revealed a significant group by diabetes duration interaction effect ( $P = 0.0008$ ) and the overall treatment group effect with 2 df was significant ( $P = 0.003$ ). The treatment effect increased with longer duration of diabetes at DCCT baseline, with the geometric mean ratio 1.4-fold higher for each additional year of diabetes duration (Fig. 3). This interaction was diminished after adjusting for A1C at DCCT entry, smoking, hypertension, and waist-to-hip ratio at the time of CT scan, but it remained significant ( $P = 0.0097$ ).

A further analysis adjusting for the differences in the log mean A1C between treatment groups during the DCCT explained virtually all of the treatment group effect within the primary prevention cohort. For the Tobit model, the treatment group effect ( $P = 0.01$ ) became nonsignificant ( $P = 0.69$ ) after adjustment for A1C. In the Tobit model within the primary prevention cohort, and with the above baseline factors, a 10% increase in the DCCT mean A1C was associated with a 1.85-fold increase in the geometric mean CAC score ( $P < 0.0001$ ); within the secondary intervention cohort, it was associated with a 1.32-fold increase ( $P = 0.051$ ). The difference between cohorts (test of interaction) was not significant ( $P = 0.21$ ).

**Correlation between CAC and CAD risk factors.** Univariate rank correlations, partially adjusted for DCCT baseline age and sex, assessed the association between the prevalence of CAC >0 Agatston units, CAC >200 Agatston units, and the log CAC, with covariates (Table 2). The results were similar across all of the CAC outcomes. Attained age ( $r = 0.34$ ), male sex ( $r = 0.21$ ), waist-to-hip ratio ( $r = 0.14$ ), combined common and internal carotid IMT at year 6 ( $r = 0.17$ ), hypercholesterolemia ( $r = 0.14$ ),

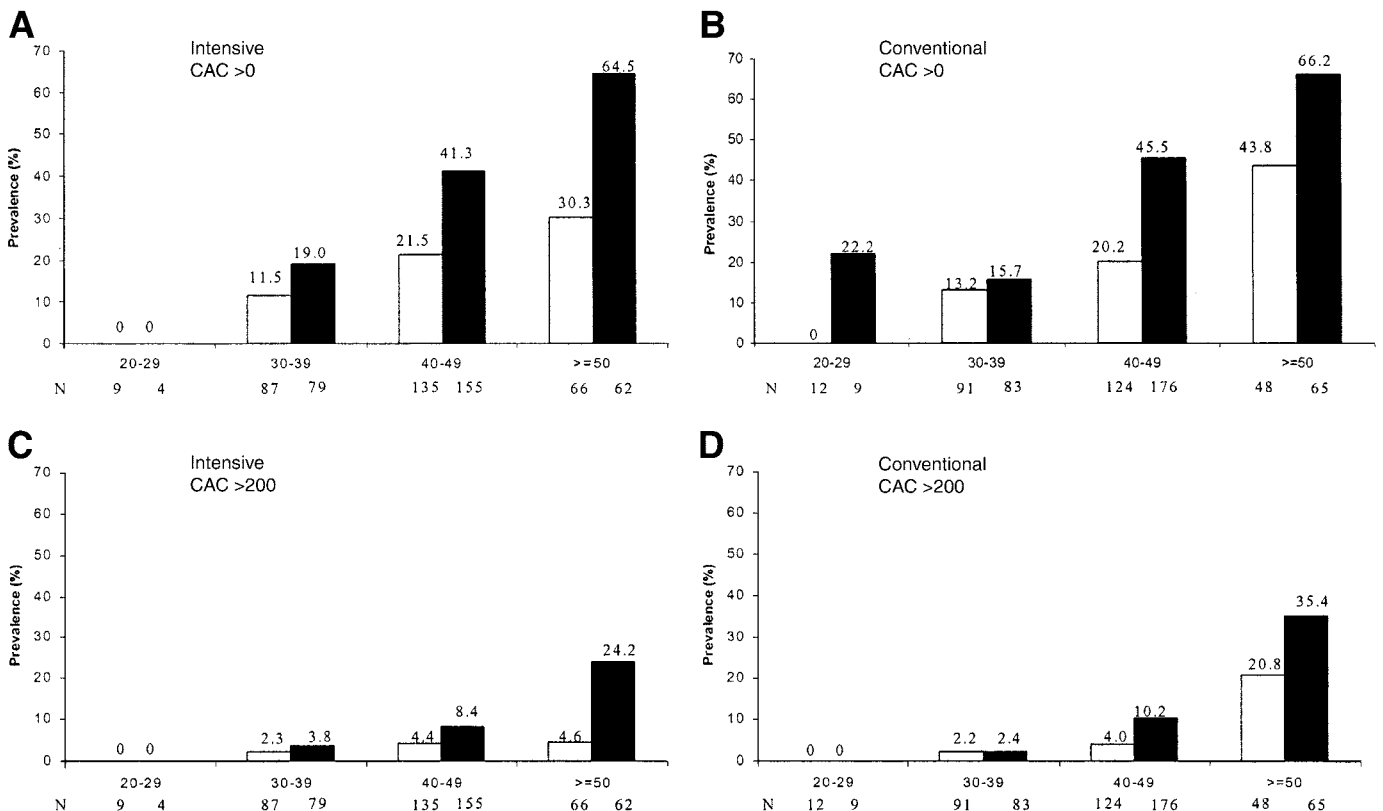
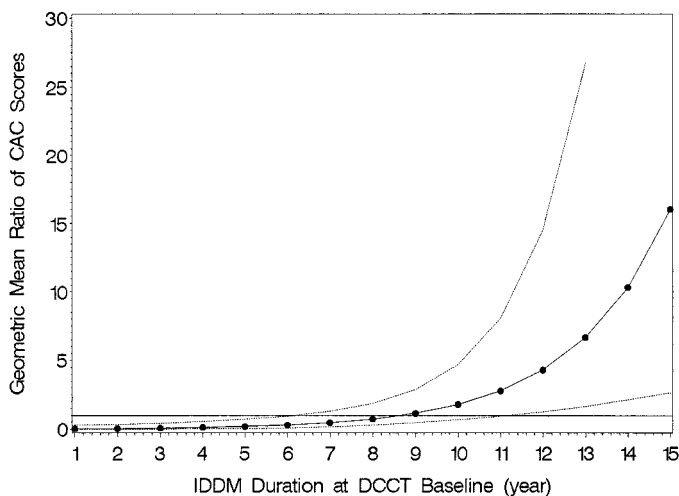


FIG. 2. Unadjusted prevalence of CAC >0 and CAC >200 Agatston units within each treatment group, separately stratified by sex and age at the time of the scan. A: CAC >0 intensive treatment. B: CAC >0 conventional treatment. C: CAC >200 intensive treatment. D: CAC >200 conventional treatment. The number of subjects evaluated in each age category is noted. □, female subjects; ■, male subjects.



**FIG. 3.** Estimated geometric mean ratio of CAC scores for conventional- versus intensive-treatment groups as a function of type 1 duration, using the Tobit model, at DCCT baseline in the secondary cohort. Dotted lines represent 95% CIs. The overall treatment group difference was significant ( $P = 0.003$ ). Overall age effect was also significant ( $P < 0.0001$ ).  $P$  values for durations of 1–15 years, respectively, are 0.002, 0.003, 0.004, 0.007, 0.015, 0.043, 0.154, 0.535, 0.756, 0.235, 0.061, 0.019, 0.008, 0.004, and 0.002.  $P$  values are a test that the ratio = 1 at each year of duration. IDDM, type 1 diabetes.

and hypertension ( $r = 0.15$ ) had the strongest association with the log CAC. There was no significant correlation with ankle-to-arm blood pressure ratio. Other weaker or less consistent correlates were with smoking, DCCT baseline retinopathy status, microalbuminuria, menopausal status, and a parental history of type 2 diabetes. Neither total cholesterol nor LDL cholesterol levels were significant correlates, whereas triglyceride level was positively and HDL cholesterol level was negatively correlated with CAC. A1C before the DCCT, the mean levels during the DCCT, at DCCT closeout, before the CAC scan, mean during EDIC, and mean during DCCT and EDIC all correlated with CAC ( $P < 0.01$ ).

**Multivariate regression models.** Expanded multivariate regression models assessed the association of additional risk factors, measured either at DCCT baseline or close to the time of the CT scan during EDIC, with CAC. In a logistic model, hypercholesterolemia, increased waist-to-hip ratio, and smoking were significantly associated with prevalence of CAC  $>0$  Agatston units. As observed in the intent-to-treat analysis of the DCCT treatment group effect, there was a significant interaction between treatment group and baseline retinopathy strata (primary versus secondary cohort). Overall, the model explained 20% ( $R^2$ ) of the variation in risk. A logistic regression model with the prevalence of CAC  $>200$  Agatston units produced similar results.

The multivariate Tobit regression model (Table 3) provided results similar to the two logistic regression models. The CAC score increased 1.3-fold per year of age, was 3.4-fold more for men than women, was 7.1-fold greater among current smokers, and increased 1.3-fold per 10 mg per 24 increase in albumin excretion rate, 2.6-fold per 10% increase in waist-to-hip ratio, 2.8-fold among those with hypercholesterolemia, 2.8-fold among those with hypertension, and 1.4-fold per 10% increase in DCCT mean A1C. The Hosmer-Lemeshow test ( $P = 0.14$ ), comparing the Tobit model predicted probability of having CAC to the detected presence of CAC, and the significant Spearman

correlation coefficient (0.4781,  $P < 0.0001$ ) between the predicted and observed CAC scores both suggest that this model fits the observed data.

**Sensitivity and specificity.** The sensitivities and specificities of CAC  $>0$  and  $>200$  Agatston units for nonfatal myocardial infarction ( $n = 10$ ) were 80 and 69.4% and 70 and 92.1%, respectively. The sensitivities and specificities for all CVD events (see RESEARCH DESIGN AND METHODS,  $n = 44$ ) for CAC  $>0$  and  $>200$  Agatston units were 72.7 and 70.5% and 47.7 and 93.0%, respectively. The ROC curve (Fig. 4) reflects the characteristics of the CAC score with discriminating power for CVD. CAC  $>0$  Agatston units showed the highest (29%) false-positive rate and highest (73%) true-positive rate. The false- and true-positive rates for CAC  $>200$  Agatston units were 7 and 44%, respectively. The area under the ROC curve was 0.78 (95% CI 0.69–0.86).

## DISCUSSION

The most important and new observation of this study is that the prevalence of CAC, and the CAC scores, in the DCCT/EDIC type 1 diabetes cohort are significantly lower in the former intensive treatment compared with the former conventional-treatment group. The prevalence of a clinically significant CAC score of  $>200$  Agatston units was 7.0% in the former intensive-treatment group and 9.9% in the former conventional-treatment group.

The beneficial effect of prior intensive therapy during the 6.5 years of the DCCT was greater among those entered into the primary prevention cohort with 1–5 years' diabetes duration on entry, among other factors, than among those entered into the secondary intervention cohort with 1–15 years' duration. The beneficial effect of intensive therapy is largely attributable to the differences between groups in the level of A1C during the DCCT.

The lesser treatment effect in the secondary intervention cohort appeared to be the result of an interaction between baseline diabetes duration and treatment group (Fig. 3). The beneficial treatment effect at longer durations was washed out by the negative treatment effect at shorter durations, mainly 1–5 years. The absence of a treatment effect among those in the secondary intervention cohort with only 1–5 years' duration could be an artifact of the selection criteria. Prior epidemiological modeling (36) suggests that subjects who have retinopathy present after only 1–5 years' duration tend to have higher preexisting levels of A1C that could in turn diminish the long-term effectiveness of intensive therapy on other outcomes, such as CAC. In addition, there were some imbalances between treatment groups in the subcohort of the secondary intervention cohort with 1–5 years' diabetes duration. Most importantly, compared with the conventional-treatment patients, intensive-treatment patients had higher A1C levels at DCCT entry (9.6 vs. 8.8%).

The 31% prevalence of CAC  $>0$  Agatston units in the DCCT/EDIC cohort is lower than in other reports of type 1 diabetic cohorts (18–20,37). This may reflect a substantially lower CVD risk, based on eligibility criteria and lower mean A1C, than in other studies. In addition, unlike some (18–20) but not all (37) reports, female subjects in the DCCT/EDIC study had a lower prevalence of CAC level in all age-groups. The male-to-female OR of 2.7 for CAC  $>0$  Agatston units in our cohort is similar to the OR of 2.5 reported in a previous study of type 1 diabetes (37).

Most previous studies in type 1 diabetes have not shown

TABLE 2  
Partial Spearman rank correlation between CAC and covariates\*

	CAC >0		CAC >200		Log CAC†	
	Coefficient	P value	Coefficient	P value	Coefficient	P value
Attained age	0.32	<0.0001	0.25	<0.0001	0.34	<0.0001
Sex (male versus female)‡	0.21	<0.0001	0.11	<0.0001	-0.21	<0.0001
Smoking (yes/no)	0.13	<0.0001	0.12	<0.0001	0.14	<0.0001
DCCT baseline						
Retinopathy (yes/no)	0.11	0.0001	0.09	0.003	0.12	<0.0001
Albumin excretion rate	0.09	0.003	0.07	0.012	0.09	0.001
Duration	0.11	0.0002	0.08	0.007	0.12	<0.0001
Age§	0.28	<0.0001	0.22	<0.0001	0.30	<0.0001
DCCT follow-up years	0.19	<0.0001	0.14	<0.0001	0.21	<0.0001
EDIC follow-up years	0.01	0.693	0.03	0.282	0.03	0.382
Most recent measure prior to CT scan						
Duration	0.16	<0.0001	0.13	<0.0001	0.17	<0.0001
Weight	0.02	0.512	-0.02	0.424	0.001	0.747
Height	-0.04	0.185	-0.08	0.005	-0.06	0.050
BMI	0.03	0.235	0.02	0.518	0.04	0.214
Waist-to-hip ratio	0.14	<0.0001	0.08	0.006	0.14	<0.0001
Ankle-to-arm ratio	-0.04	0.125	-0.09	0.002	0.07	0.024
HDL	-0.10	0.001	-0.06	0.056	-0.10	0.001
LDL	0.02	0.535	0.01	0.791	0.02	0.540
Total cholesterol	<0.01	0.981	0.01	0.627	0.004	0.900
LDL-to-HDL ratio	0.08	0.007	0.03	0.307	0.07	0.011
Triglyceride	0.07	0.015	0.07	0.012	0.08	0.005
Hypercholesterolemia (yes/no)	0.13	<0.0001	0.11	<0.0001	0.14	<0.0001
Systolic blood pressure	0.06	0.040	0.07	0.020	0.07	0.020
Diastolic blood pressure	-0.03	0.291	0.02	0.500	-0.02	0.400
Hypertension (yes/no)	0.12	<0.0001	0.12	<0.0001	0.15	<0.0001
Albumin excretion rate >40 (yes/no)	0.09	0.003	0.12	<0.0001	0.11	0.0001
Combined carotid IMT year 6	0.16	<0.0001	0.16	<0.0001	0.17	<0.0001
Aspirin use (yes/no)	0.11	<0.0001	0.11	0.0002	0.13	<0.0001
Menopause (yes/no)	0.11		0.06	0.140	0.02	0.070
One or both parents with type 2 diabetes (yes/no)	<0.01	0.881	0.09	0.005	0.01	0.785
A1C						
DCCT eligibility	0.12	<0.001	0.03	0.242	0.12	<0.0001
Mean during DCCT	0.09	0.001	0.10	0.001	0.11	0.0002
DCCT closeout	0.08	0.004	0.08	0.008	0.09	0.002
Mean during EDIC	0.09	0.001	0.04	0.155	0.09	0.001
At visit prior to CT	0.07	0.010	0.07	0.021	0.08	0.004
Mean during DCCT/EDIC	0.10	0.0003	0.08	0.007	0.11	<0.0001

\*Adjusted for DCCT baseline age and sex; †log CAC = 0 if CAC = 0; log CAC = log (CAC) - log (0.92) if CAC >0; ‡adjusted for baseline age only; §adjusted for sex only.

a significant association between glycemic control and CVD or CAD events, either cross-sectionally (3–5) or prospectively (6). Moreover, two previous studies have not shown a relationship between glycemic control and CAC (18,19). However, a recent report (20) showed a greater risk of progression of CAC over 3 years among those with A1C >7.5% than patients with A1C <7.5%. Perhaps owing to the small numbers who progressed (21 of 109), A1C was not a significant univariate risk factor. In contrast, the DCCT/EDIC study, with a much larger sample size and detailed longitudinal assessment of metabolic control, has shown that A1C measured before DCCT enrollment, mean A1C during the DCCT (which had the strongest correlation), and mean level during the EDIC study were each significantly correlated with CAC after adjustment for age and sex, and were independent of waist-to-hip ratio, smoking, hypertension, and hypercholesterolemia before CT scan. The DCCT cohort was selected to exclude patients with hypertension and hypercholesterolemia on entry to the DCCT, and the impact of hyperglycemia may

have become more apparent without the influence of these conventional CVD risk factors at baseline.

In univariate analyses, most of the known risk factors for coronary artery disease, including age, smoking, systolic blood pressure, hypertension, waist-to-hip ratio, hypercholesterolemia, HDL cholesterol and triglyceride levels, and microalbuminuria, were significantly associated with the presence of CAC in the DCCT/EDIC study. Although both microalbuminuria and hypertension were also reduced by prior intensive treatment (38), the effect of glycemic control on coronary artery calcium control was independent of these two risk factors. The LDL cholesterol level was not by itself a significant continuous risk factor for the prevalence of coronary artery calcium in the DCCT/EDIC study.

In the Tobit multivariate regression model, the mean CAC score was significantly greater in older individuals, men, and those with higher waist-to-hip ratios, retinopathy at DCCT baseline, and higher albumin excretion rates. The association of early signs of microvascular complications

TABLE 3  
Risk factor analysis for CAC

Covariates	Geometric mean ratio of CAC scores (95% CI)*	$\chi^2$	P value
Sex (male versus female)	3.4 (1.4–8.3)	6.8	0.0091
Scanning site (n = 19)	—	28.1	0.0611
DCCT baseline			
Age (year)	1.3 (1.2–1.4)	81.7	<0.0001
Diabetes duration (year)	1.3 (1.1–1.6)	4.1	0.0441
Albumin excretion rate (mg/24 h)†	1.3 (1.1–1.5)	7.3	0.0069
Cohort (primary versus secondary)	1.7 (0.7–4.4)	1.2	0.2651
EDIC year 7–9 (prior to CT scan)			
Smoking (yes versus no)	7.1 (3.0–16.9)	19.7	<0.0001
Waist-to-hip ratio (%)‡	2.6 (1.5–4.5)	11.5	0.0007
Hypercholesterolemia (yes versus no)	2.8 (1.4–5.7)	8.6	0.0033
Hypertension (yes versus no)	2.8 (1.4–5.7)	8.6	0.0034
DCCT mean A1C†	1.4 (1.1–1.7)	9.3	0.0022

Analysis was performed using Tobit regression:  $Y = \log CT - \log$  (lowest detectable CT score). \*Geometric mean ratio of CAC scores is the ratio of predicted CAC scores for a 1-unit increase in quantitative variables or change in status for dichotomous variables if without notation; †geometric mean ratio of CAC scores is based on 10 mg/24 h increase in albumin excretion rate, 10% increase in waist-to-hip ratio, and 10% increase in DCCT mean A1C.

with later CAC may reflect some common elements in their development and in the pathogenesis of atherosclerosis, such as hypertension or hyperglycemia.

We previously reported that the rate of progression of carotid artery IMT from DCCT closeout to 6 years later

was reduced by prior intensive treatment (13). This effect was largely explained by the difference in A1C levels that existed between the two prior treatment groups. We have now shown that CAC correlates significantly with carotid IMT that was measured 1–3 years earlier (Table 2). Taken together, these prolonged effects of intensive treatment on both coronary artery calcium and carotid IMT support the interpretation that lowering glycemia with intensive treatment results in a slowing of atherosclerosis.

The mechanism(s) by which hyperglycemia causes atherosclerosis is incompletely understood but could involve long-lived advanced glycation end products (39,40) in vessel walls and their interactions with advanced glycation end product receptors (41). The demonstration of a delayed benefit from intensive treatment on atherosclerosis is also consistent with the persistent beneficial effect of prior intensive treatment on retinopathy and nephropathy during the EDIC study (38,42). The observation of a treatment effect principally within the primary prevention cohort with a preexisting mean duration of diabetes of 2.5 years on entry adds further weight to the recommendation that intensive treatment be started as early in the course of type 1 diabetes as safely and practically possible.

Certain limitations of this study should be noted. A baseline assessment of CAC was not obtained either at the beginning of the DCCT or at the beginning of EDIC study. Although such assessments are not necessary to document a treatment effect on CAC levels, without baseline levels it is not possible to describe the magnitude or rate of change in CAC over time. Theoretically, it is possible that these findings simply reflect a chance baseline imbalance in the CAC levels. However, this appears unlikely given the similarity of characteristics relevant to atherosclerosis in the conventional-treatment and intensive-treatment groups at DCCT baseline (9,10). Although CAC scores measured by electron-beam CT and multidetector CT correlate very well (43), the use of several different machines to measure CAC may have added variability to the measurements and interfered with our ability to establish correlations. However, even if we looked separately at the results from the nine electron-beam CT scanners and the results from the other scanners, the trend in differences between intensive- and conventional-treatment groups remained (data not shown).

The overwhelming majority of the subjects did not have any detectable levels of calcification, thus reducing the sensitivity of these analyses to detect an effect of intensive therapy, or to assess the relative effects of glycemia and known risk factors. The low prevalence of measurable CAC also limits the ability to assess the predictive value of CAC for future macrovascular events. Nevertheless, significant risk factor effects were observed, and an ROC analysis showed significant association between CAC score and prevalence of overt CVD at the time of assessment. A recent DCCT/EDIC analysis showed that intensive therapy reduced the risk of aggregate CVD events by 42% and the risk of major clinical events (fatal or nonfatal myocardial infarction or stroke) by 57% (each  $P < 0.02$ ) (21). However, the predictive value of a given level of CAC for the risk of a future CVD event cannot be definitively assessed, owing to the small number of such events that were observed after the measurement of CAC.

Finally, although coronary artery calcium is a quantitative marker of coronary atherosclerosis burden (44,45) and predicts coronary artery disease measured by angiography (46,47), it is not known whether the reduction in the

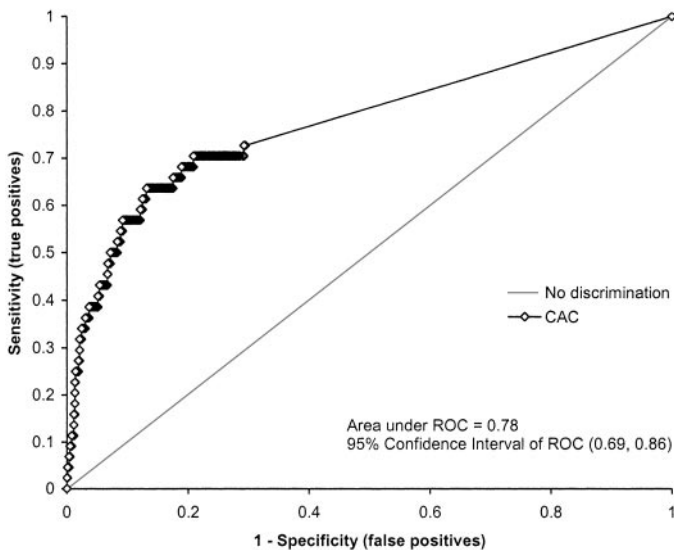


FIG. 4. ROC curve of CAC relative to cardiovascular events. True-positives are plotted on the y-axis and false-positives on the x-axis. The accuracy of the CAC is the area under the curve. An area of 1 represents a perfect test; an area of 0.5 represents a worthless test. An area under the curve of 0.78 implies that there is a 78% likelihood that a randomly selected affected case subject will have a higher CAC score than a randomly selected nonaffected control subject. The 95% CI (0.69–0.86) indicates that the lower end point is >0.50 and is better than random chance.

prevalence of CAC with intensive therapy will translate into a reduction in the incidence of coronary artery disease and other CVD events (48,49). The usefulness of screening asymptomatic patients with CT is controversial (50,51). The majority of DCCT/EDIC participants with a mean age of 43 years at the time of CAC measurement displayed no detectable coronary artery calcium. Further follow-up with assessment of clinical events will permit us to assess the predictive power of CAC for incident CVD events.

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#### APPENDIX

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