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ORIGINAL RESEARCH

Coronary Artery Disease Events and Carotid Intima-Media Thickness in Type 1 Diabetes in the DCCT/EDIC Cohort

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BACKGROUND: Carotid artery intima-media thickness (IMT) is associated with the risk of subsequent cardiovascular events in the general population. This association has not been established in type 1 diabetes.

METHODS AND RESULTS: We studied if carotid IMT is associated with the risk of a first coronary artery disease event in participants with type 1 diabetes in the EDIC (Epidemiology of Diabetes Interventions and Complications) study, the long-term observational follow-up of the DCCT (Diabetes Control and Complications Trial). Between 1994 and 1996, common carotid artery and internal carotid artery IMT were measured with high-resolution ultrasound in 1309 study participants with a mean age of 35 years and diabetes duration of 13.8 years; 52% were men. Cox proportional hazards models evaluated the association of standardized common carotid artery IMT and internal carotid artery IMT with subsequent cardiovascular events over the next 17 years. Models were adjusted for age, sex, mean hemoglobin A1c levels, and traditional cardiovascular risk factors. Associations of common carotid artery IMT with subsequent CAD were significant after adjustment for imaging device, sex, and age (hazard ratio [HR], 1.23 per 0.09 mm [95% CI, [1.04–1.45]; P=0.0141), but did not remain significant after further adjustment for traditional risk factors and hemoglobin A1c (HR, 1.14 per 0.09 mm [95% CI, 0.97–1.33]; P=0.1206). No significant associations with subsequent coronary artery disease events were seen for internal carotid artery IMT.

CONCLUSIONS: In the DCCT/EDIC cohort with type 1 diabetes, common carotid artery IMT, but not internal carotid artery IMT, is weakly associated with subsequent coronary artery events, an association eliminated after adjusting for coexistent traditional cardiovascular risk factors.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT00360815 and NCT00360893.

Key Words: carotid intima-media thickness ■ coronary artery disease ■ type 1 diabetes

The rate of cardiovascular events is higher in individuals with type 1 diabetes (T1D) than in those without.[1,2] Prevalent cardiovascular disease in individuals with T1D shows a distribution by age corresponding to additional aging of 10 to 20 years in the nondiabetic population.[2] Carotid intima-media thickness (IMT), a surrogate marker of cardiovascular disease, is also increased in individuals with T1D as compared with those without T1D.[3–9]

Findings from the DCCT (Diabetes Control and Complications Trial) in T1D have shown that improved glycemic control (ie, lowering of hemoglobin A1c [HbA1c] levels) in those randomized to the intensive treatment group reduced the rate of microvascular complications

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*A complete list of participants in the DCCT/EDIC Research Group can be found in the Supplemental Material.

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CLINICAL PERSPECTIVE

What Is New?

- Ultrasound measurements of the common and internal carotid artery wall intima-media thickness (IMT) are associated with first-time coronary artery disease events in the general population.
- In this longitudinal study (EDIC [Epidemiology of Diabetes Interventions and Complications]), the long-term observational follow-up of the DCCT (Diabetes Control and Complications Trial) of patients with type 1 diabetes, this association held for common carotid artery IMT when age and sex were taken into consideration, attenuated by individual traditional Framingham cardiovascular risk factors, and was absent when all risk factors were included.
- Unexpectedly, there was no positive association between coronary artery disease events and internal carotid artery IMT, likely because of the young age of the cohort and the low prevalence of carotid plaque at baseline.

What Are the Clinical Implications?

- Assessment of subclinical cardiovascular disease risk with carotid artery IMT measurements has limited applicability in young patients with type 1 diabetes.
- The lack of association of maximum internal carotid artery IMT, a measure of plaque height, in these patients may be because of the low prevalence of plaque in this age group.
- If carotid artery markers of subclinical disease are to be used in young patients with type 1 diabetes, consideration should be given to their age.

Nonstandard Abbreviations and Acronyms

CHS	Cardiovascular Health Study
DCCT	Diabetes Control and Complications Trial
EDIC	Epidemiology of Diabetes Interventions and Complications
ICA	internal carotid artery
IMT	intima-media thickness
MESA	Multi-Ethnic Study of Atherosclerosis
T1D	type 1 diabetes

(microalbuminuria and retinopathy) compared with those randomized to the standard treatment group.[10] Moreover, during the long-term observational follow-up after the end of DCCT, the EDIC (Epidemiology of Diabetes Interventions and Complications) study,[11] lower HbA1c levels during the DCCT were associated with reduced rates of carotid IMT progression in participants having previously been in the intensive versus the conventional treatment group.[12] This decreased carotid IMT progression rate in the former intensive treatment arm of the DCCT was observed, although the between group difference in HbA1c levels seen during DCCT dissipated during the EDIC study.[12]

An association between increased IMT and cardiovascular events has not been established in patients with T1D. Consequently, the current analyses were undertaken to examine the association of increased carotid IMT with subsequent coronary artery disease (CAD) in the EDIC cohort. We also evaluated whether traditional risk factors have an effect on the association between IMT and coronary heart disease events.

METHODS

Data Sharing

Data collected for the DCCT/EDIC study through June 30, 2017 are available to the public through the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository (https://repository.niddk.nih.gov/studies/edic/). Data collected in the current cycle (July 2017–June 2022) will be available within 2 years after the end of the funding cycle.

Additional Statement for Collaborators

Additional support for this DCCT/EDIC collaborative study was provided by grants N01 DK062204-007/DK/NIDDK NIH HHS/United States.

Patients

The DCCT enrolled 1441 patients between 1983 and 1989. Participants were 13 to 39 years old, had T1D for 1 to 15 years, were in generally good health, were free of hypertension, hyperlipidemia, or cardiovascular disease at baseline, and were randomly assigned to either intensive or conventional treatment of their diabetes and followed for an average of 6.5 years.[10] Following the end of the DCCT, participants randomized to the conventional treatment group were taught intensive treatment methods, and all participants returned to their health care providers for ongoing diabetes care. Ninety-six percent (1375) of the 1425 surviving participants of the original cohort volunteered to participate in the EDIC study, the observational follow-up study to the DCCT cohort.[11] A detailed description of the EDIC study procedures and baseline characteristics has been published.[11] Carotid ultrasonography was performed locally, at each of the 28 clinical centers throughout the United States and Canada between June 1994 and April 1996, 1 to 2 years after EDIC

began.[11] Institutional review board approval was obtained at each clinical center, and all patients gave informed consent to participate in the EDIC study, including carotid ultrasonography.

Out of the 1441 patients seen at the EDIC study year 1, a total of 1325 participants underwent ultrasound imaging at the EDIC study year 1. Sixteen participants who had CAD events before the time of ultrasound imaging were excluded from these analyses. Consequently, a total of 1309 participants are included in the current analyses (Figure 1).

Clinical Risk Factors

Each EDIC study subject had an annual evaluation that included smoking history, a physical examination, sitting blood pressure measurement, body mass index measurement in the patient's weight in kilograms divided by the patient's height in meters squared, an ECG, and laboratory testing including HbA1c levels. HbA1c levels were measured quarterly during the DCCT and yearly during the EDIC study. The DCCT/EDIC time-weighted mean HbA1c, with weights of 0.25 for the DCCT and 1 for the EDIC values, represents the total glycemic exposure during the DCCT/EDIC. Fasting lipids and urinary albumin excretion rates were measured in alternate years during the EDIC study. Microalbuminuria was defined as an albumin excretion rate of >30 mg per 24 hours on at least 2 consecutive annual visits. We also report on the baseline insulin doses taken by the patients, stratified by presence of incident CAD events.

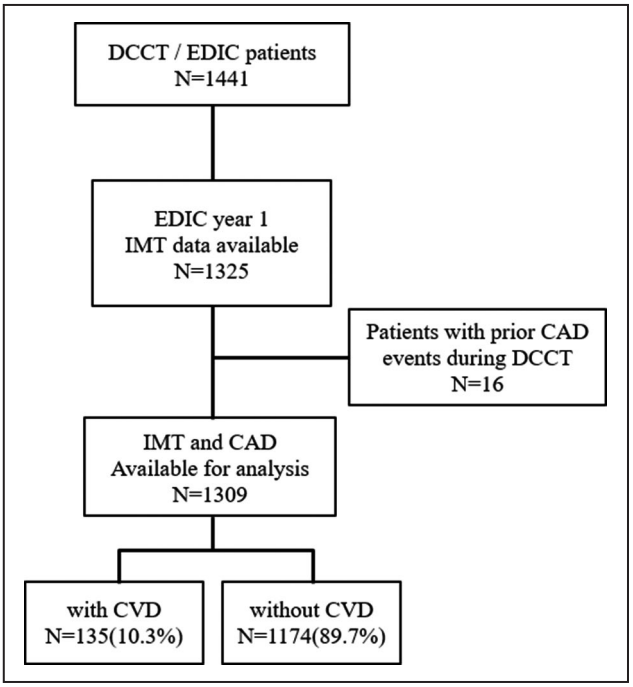

Figure 1. EDIC (Epidemiology of Diabetes Interventions and Complications) participants flowchart.
CAD indicates coronary artery disease; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; and IMT, intima-media thickness.

Carotid IMT

IMT measurements of the common and internal carotid arteries were obtained according to a standardized protocol used in both the CHS (Cardiovascular Health Study) and the MESA (Multi-Ethnic Study of Atherosclerosis).[13] Single longitudinal views of the distal right and left common carotid arteries (CCAs) were taken with the ultrasound transducer held at 45° to the horizontal and placed to include the beginning of the carotid bulb (divergence of the common carotid outer wall). Three longitudinal views of each internal carotid artery (ICA) were obtained with the probe held sequentially in the anterior, lateral, and posterior projections. The ICA included both the carotid bulb and the 10-mm segment distal to the tip of the flow divider that separates the internal from external carotid artery. Studies were performed by certified EDIC technicians at the clinical centers, recorded on S-Video Home System tapes, and read at the Ultrasound Reading Center (Tufts Medical Center, Boston, MA) by a single reader. Reproducibility analysis of 50 replicate measures was performed by the same reader. Ultrasound devices were divided into 3 categories based on manufacturer and model. IMT measurements were made in the phase of the cardiac cycle when the artery diameter was the smallest (diastole) using a customized software program that processed the line tracings of the lumen-intima and the media-adventitia interfaces made by the reader.[14] The mean far wall IMT (in millimeters) of the right and left common carotid arteries were used as the CCA IMT variable, whereas the maximum ICA IMT was determined as the maximum value from either the near and far walls on both right and left sides.[13]

Reproducibility was assessed with 50 replicate measurements performed by the same reader. The intraclass correlations between the original maximal wall thickness and the measurement obtained on rereading were 0.87 and 0.99 for CCAs and ICAs, respectively. The IMT variables were analyzed as standardized values (value/standard deviation of the distribution; 0.09 mm for CCA IMT and 0.16 mm for ICA IMT).

CAD Outcome

CAD outcomes were adjudicated by the EDIC Mortality and Morbidity Review Committee, who were masked to the DCCT treatment assignment, HbA1c, and glucose levels.[15,16] Mortality and Morbidity Review Committee was also unaware of the CCA and ICA IMT measurements, because these were not included with the medical records reviewed by the Mortality and Morbidity Review Committee. CAD was a composite

outcome defined as the time to the first of either death secondary to cardiovascular disease or any sudden death judged not to be caused by hypoglycemia or other known reason (n=6), acute myocardial infarction (n=35), silent myocardial infarction appearing as a major new Q-wave abnormality on routine ECG follow-up (n=36), CAD requiring bypass surgery or angioplasty (n=42), or CAD confirmed by angiography or by a combination of angina and ischemia documented with noninvasive testing (n=16) for participants with at least 1 such event, or the time of the last known event-free time (censoring time) for participants without any of these individual events. The analyses reported here only include adjudicated qualifying CAD events occurring through December 31, 2013, ≈17 years after the IMT measurements.

Statistical Analysis

Continuous variables are described as mean and SD values, whereas categorical variables are presented as percentages. Comparisons between patients with and without CAD events were made using the Wald statistics from unadjusted Cox proportional hazards models. Associations between the 2 IMT variables and the risk of subsequent CAD events were assessed using separate Cox proportional hazards models with 95% CIs and *P* values using robust (sandwich) standard errors, which are robust with respect to departures from model assumptions.[17] The minimally adjusted model was adjusted for ultrasound device, age, and sex. Given the relative low number of CAD events, we were not powered to reliably build multivariable risk models using variable selection methods (such as lasso). Instead, based on clinical input, 4 prespecified models were considered by separately adding (ie, 1 at a time) systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and history of smoking. A final multivariable model included all these variables. The DCCT/EDIC study has 94.5% of person-years active participation out of expected follow-up, and values were carried forward in the case of intermittent missing data.

We then repeated the analyses by adding mean HbA1c to all of the models described above. The final models included age, sex, ultrasound device, mean HbA1c, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, current smoking, and the respective IMT variables. Model goodness of fit was assessed using the Akaike information criteria values (smaller values are preferable). The risk factors (such as age or systolic blood pressure) used in the Cox proportional hazards models were entered as fixed covariates using their values at the time of the IMT measurements.

Kaplan-Meier curves were constructed for quartiles of ultrasound device-adjusted IMT values (Q1: 0.245–<0.415 mm, Q2: ≥0.415–<0.470 mm, Q3: ≥0.470–<0.530 mm, and Q4: ≥0.530–0.955 mm for CCA IMT; and Q1: 0.28–<0.45 mm, Q2: ≥0.45–<0.52 mm, Q3: ≥0.52–<0.60 mm, and Q4: ≥0.60–2.10 mm for ICA IMT). Two-sided $P \leq 0.05$ was considered statistically significant. Statistical analyses used SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

The DCCT baseline characteristics were similar between IMT participants (N=1309) and IMT nonparticipants (N=132), except for smoking and HbA1c (data not shown). Compared with participants, nonparticipants were more likely to be current smokers and had higher HbA1c levels at DCCT baseline (data not shown). At the time of the ultrasound imaging (EDIC years 1–2), 52% of the participants were men, and the mean age was 35 years (SD, 6.9 years). The mean duration of T1D was 13.8 years (SD, 4.8 years), the mean HbA1c was 8.1% (SD, 1.4%), the mean CCA IMT was 0.48 mm (SD, 0.09 mm), and the mean ICA IMT was 0.55 mm (SD, 0.16 mm) (Table 1).

Over a follow-up of 17 years, 1309 participants experienced 135 initial CAD events for an event rate of 4.1 events per 1000 patient-years. The largest categories of initial events were coronary revascularizations (n=42, 31%), silent myocardial infarction (n=36, 27%) and nonfatal myocardial infarction (n=35, 26%), with the remaining being new onset angina (n=16) and death from CAD (n=6). The Kaplan-Meier curves for quartiles of CCA IMT values show that individuals in the fourth quartile have distinctly greater risk of events than those in the lower quartiles (Figure 2A). Participants in the highest quartile CCA IMT had an increased risk of CAD compared with the participants in the lower 3 quartiles combined (P=0.04; data not shown). This was not the case for ICA IMT, where differences between quartiles were not significant (Figure 2B).

In minimally adjusted models (age, sex, ultrasound device), CCA IMT was associated with subsequent CAD events, whereas ICA IMT was not (Table 2). The associations between CCA IMT and the risk of subsequent CAD events remained significant after separately adding smoking history, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol to the baseline model. However, CCA IMT did not remain significantly associated with the subsequent risk of CAD in the fully adjusted model for all of these factors (hazard ratio [HR], 1.15 [95% CI, 0.98–1.35]). ICA IMT was not significantly associated with subsequent CAD events in any of the models.

The effect of adding HbA1c to the models listed in Table 2 was to minimally reduce the associations between CCA IMT variables and CAD events (Table 3). When added to the minimally adjusted models (age, sex,

Table 1. Characteristics at the Time of IMT Measurements at EDIC Year 1 for Patients With and Without Incident CAD

Characteristics at EDIC year 1*	All participants	CAD		*P* value‡
		Yes	No	
No. of participants	1309	135	1174	
Women, %	48.0	50.4	47.7	0.5098
Race, % White	96.3	95.6	96.4	0.6201
Intensive group, %	50.2	46.7	50.6	0.3344
Age, y	35.0±6.9	38.2±6.3	34.7±6.9	<0.0001
Duration of IDD, y	13.8±4.8	15.0±5.1	13.6±4.8	0.0032
Current cigarette smokers, %	18.1	25.2	17.3	0.0160
Body mass index, kg/m^2	26.1±4.0	26.6±4.5	26.0±4.0	0.1019
Systolic blood pressure, mm Hg	117±12	122±14	116±12	<0.0001
Diastolic blood pressure, mm Hg	75±9	78±9	75±9	0.0005
Insulin dose, units/kg per d	0.67±0.21	0.69±0.21	0.66±0.21	0.0958
HbA1c, %	8.1±1.4	8.5±1.4	8.1±1.3	<0.0001
Weighted mean HbA1c, %	8.1±1.4	8.4±1.5	8.1±1.3	0.0033
HDL cholesterol, mg/dL	52±13	53±14	52±13	0.9375
Non-HDL cholesterol, mg/dL	131±36	145±32	130±36	<0.0001
LDL cholesterol, mg/dL	114±30	126±28	113±30	<0.0001
Total cholesterol, mg/dL	184±35	197±33	182±35	<0.0001
Triglycerides, mg/dL	87±66	95±51	86±67	0.1129
IMT measurements				
Common IMT, mm	0.48±0.09	0.51±0.10	0.47±0.09	0.0001
Internal IMT, mm	0.55±0.16	0.59±0.25	0.55±0.15	0.0012

CAD indicates coronary artery disease; EDIC, Epidemiology of Diabetes Interventions and Complications; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IDD, insulin-dependent diabetes; IMT, intima-media thickness; and LDL, low-density lipoprotein.

*Number (%) for categorical variables or mean±SD for continuous variables.

‡*P* values were based on Wald statistics in unadjusted Cox models.

ultrasound device), mean HbA1c did not significantly decrease the association of CCA IMT with CAD events, the HRs decreasing from 1.23 (95% CI, 1.04–1.45) to 1.20 (95% CI, 1.01–1.41). CCA IMT was no longer significantly associated with risk of CAD after separate addition of systolic blood pressure to the baseline model with HbA1c. The addition of HbA1c to the fully adjusted model did not significantly change the HR of CCA IMT for CAD events: 1.15 (95% CI, 0.98–1.35) for the fully adjusted model without HbA1c (Table 2, model C) and 1.14 (95% CI, 0.97–1.33) with HbA1c added (Table 3, model C). ICA IMT was not significantly associated with CAD events in any of the models. Similar findings were obtained in models further adjusted for insulin dose (data not shown). The fully adjusted models (models C in Tables 2 and 3) provided the best fit (as evidenced by the lowest Akaike Information Criteria value) for both CCA IMT and ICA IMT.

DISCUSSION

In this longitudinal follow-up of patients with T1D, we found that CCA IMT is associated with the risk of subsequent CAD events, that the addition of individual cardiovascular risk factors reduces the strength of this association, and that the association was no longer significant in models fully adjusted for all risk factors. No association was seen between ICA IMT and CAD events. We further note that, by itself, HbA1c does not seem to be a mediator of the association between IMT and CAD events.

Our study offers some insights on the limited use of carotid artery IMT as a biomarker of CAD risk in T1D. The observation that common carotid artery IMT is an independent predictor of CAD events in minimally adjusted models, but loses significance after traditional cardiovascular risk factors are taken into account, confirms observations made in a large meta-analysis in type 2 diabetes.[18] However, the lack of an association between ICA IMT and CAD events was unexpected. Many cohorts have reported that increased ICA IMT has similar if not greater value than CCA IMT as a predictor of future CAD events.[19–22] It is not clear why this association is not demonstrated in this study of T1D. One possibility is that glycemic exposure affects carotid plaque development and morphology, thereby modifying the association with CAD events. Another possibility is that ICA IMT only becomes a predictor of CAD when it reaches a certain size threshold (ie, 1.5 mm). Using this definition of plaque, only 3 (0.2%)

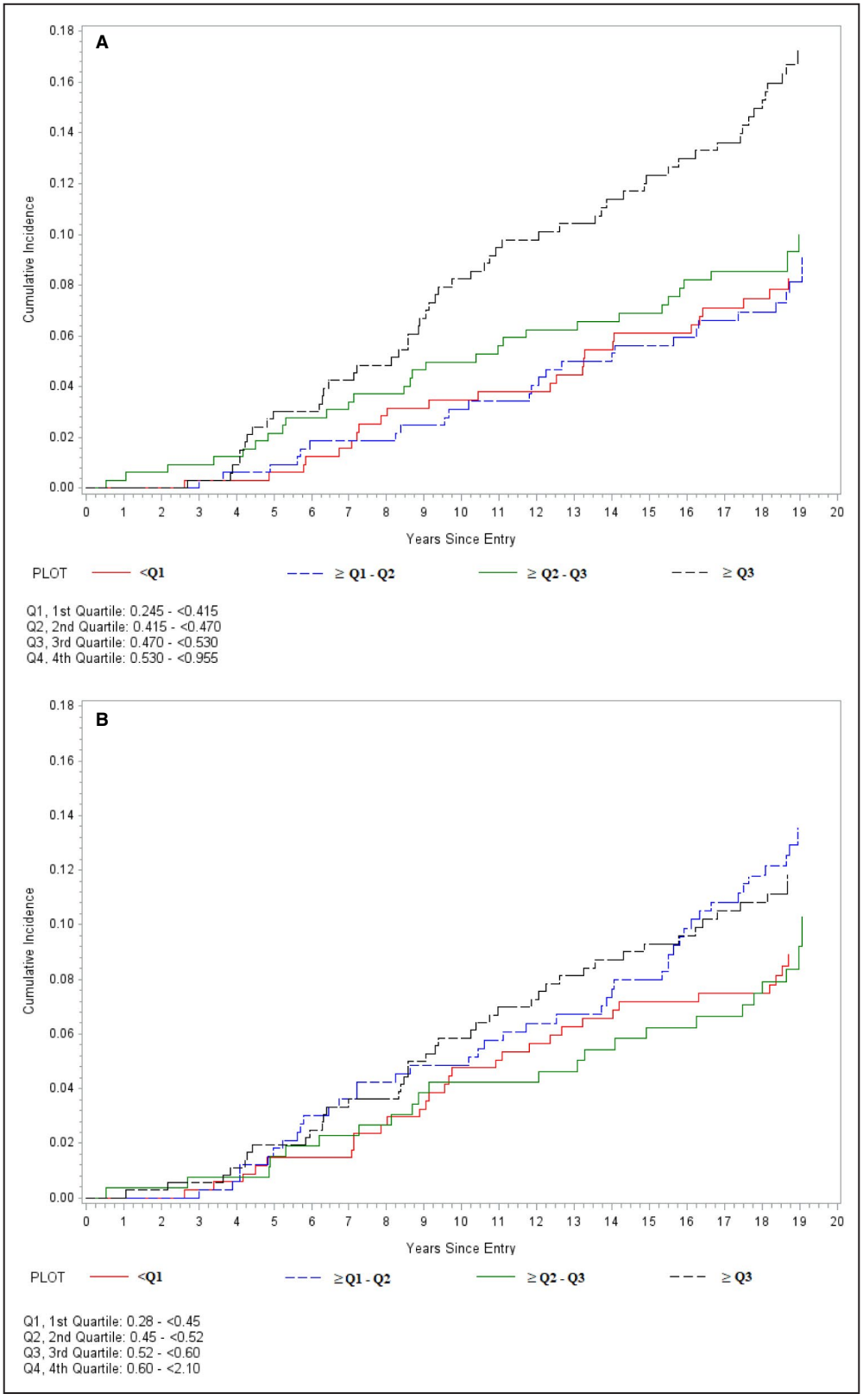

Figure 2. Cumulative incidence of cardiovascular disease by quartiles (Q) of common carotid artery (CCA) and internal carotid artery (ICA) intima-media thickness (IMT).
A, Cumulative incidence of coronary artery disease (CAD) separately by quartiles of CCA IMT at EDIC (Epidemiology of Diabetes Interventions and Complications) year 1. **B**, Cumulative incidence of CAD separately by quartiles of ICA IMT at EDIC year 1.

Table 2. Associations of CCA and ICA IMT at EDIC Year 1 With the Risk of Subsequent Coronary Artery Disease

Subclinical	CCA IMT, per 0.09 mm			ICA IMT, per 0.16 mm		
	Hazard ratio (95% CI)	*P* value	AIC	Hazard ratio (95% CI)	*P* value	AIC
IMT, year 1						
A*	1.23 (1.04–1.45)	0.0141	1873.78	1.13 (0.97–1.31)	0.1161	1876.70
B1‡	1.20 (1.03–1.41)	0.0230	1872.43	1.11 (0.97–1.29)	0.1367	1874.81
B2§	1.18 (1.00–1.40)	0.0476	1865.53	1.09 (0.93–1.28)	0.2831	1867.80
B3‖	1.20 (1.02–1.41)	0.0259	1861.42	1.11 (0.95–1.29)	0.1877	1863.99
B4¶	1.23 (1.04–1.45)	0.0140	1875.24	1.12 (0.97–1.30)	0.1280	1878.32
C#	1.15 (0.98–1.35)	0.0933	1856.20	1.07 (0.91–1.25)	0.4211	1857.94

AIC indicates Akaike information criteria; CCA, common carotid artery; EDIC, Epidemiology of Diabetes Interventions and Complications; ICA, internal carotid artery; and IMT, intima-media thickness.

*A: adjusted for device, sex, and age at EDIC year 1.

‡B1: adjusted for device, sex, age, and smoking at EDIC year 1.

§B2: adjusted for device, sex, age, and systolic blood pressure at EDIC year 1.

‖B3: adjusted for device, sex, age, and total cholesterol at EDIC year 1.

¶B4: adjusted for device, sex, age, and high-density lipoprotein at EDIC year 1.

#C: adjusted for device, sex, age, smoking, systolic blood pressure, total cholesterol, and high-density lipoprotein at EDIC year 1.

patients in this study had plaque forming at their carotid bifurcations, and 2 of these 3 patients had subsequent CAD events. This may simply reflect the relatively young age of our cohort at the time of the carotid ultrasound examination. Therefore, this study is underpowered to detect an association between ICA IMT/plaque and events. Pathologic differences are described between coronary and carotid artery plaques in types 1 and 2 diabetes and may in part explain this effect.[23] For example, in cases of sudden death, individuals with types 1 and 2 diabetes show a lower rate of intracoronary thrombosis than people without diabetes.[23] In addition, carotid artery plaques in individuals with diabetes are less likely to show evidence of thrombosis.[24]

Adjusting for mean HbA1c levels did not considerably reduce the strength of the association of CAD risk with common carotid IMT and most individual risk factors. We would have expected a stronger effect change based on the association of HbA1c with carotid IMT seen in EDIC[12] and in women with diabetes.[25,26]

Limitations

One limitation of our study is the use of a single reader. As such, although we might have eliminated interreader effects, there might still be an inherent variability in the measurements performed by this reader. Some of the negative findings in our analyses may be attributable to

Table 3. Associations of CCA and ICA IMT at EDIC Year 1 With the Risk of Subsequent Coronary Artery Disease Further Adjusted for Mean Hemoglobin A1c

Subclinical	CCA IMT, per 0.09 mm			ICA IMT, per 0.16 mm		
	Hazard ratio (95% CI)	*P* value	AIC	Hazard ratio (95% CI)	*P* value	AIC
IMT (year 1)						
A*	1.23 (1.04–1.45)	0.0141	1873.78	1.13 (0.97–1.31)	0.1161	1876.70
B‡	1.20 (1.01–1.41)	0.0286	1862.68	1.12 (0.97–1.29)	0.1308	1864.80
B1§	1.18 (1.00–1.39)	0.0436	1861.86	1.10 (0.96–1.27)	0.1575	1863.56
B2‖	1.17 (0.99–1.38)	0.0645	1856.62	1.09 (0.93–1.26)	0.2918	1858.50
B3¶	1.18 (1.01–1.39)	0.0427	1854.58	1.10 (0.95–1.28)	0.1906	1856.52
B4#	1.20 (1.02–1.41)	0.0286	1864.05	1.11 (0.96–1.28)	0.1504	1866.34
C**	1.14 (0.97–1.33)	0.1206	1850.96	1.06 (0.91–1.24)	0.4394	1852.41

AIC indicates Akaike information criteria; CCA, common carotid artery; EDIC, Epidemiology of Diabetes Interventions and Complications; ICA, internal carotid artery; and IMT, intima-media thickness.

*A: adjusted for device, sex, and age at EDIC year 1.

‡B: adjusted for device, sex, age, and mean hemoglobin A1c at EDIC year 1.

§B1: adjusted for device, sex, age, mean hemoglobin A1c, and smoking at EDIC year 1.

‖B2: adjusted for device, sex, age, mean hemoglobin A1c, and systolic blood pressure at EDIC year 1.

¶B3: adjusted for device, sex, age, mean hemoglobin A1c, and total cholesterol at EDIC year 1.

#B4: adjusted for device, sex, age, mean hemoglobin A1c, and high-density lipoprotein at EDIC year 1.

**C: adjusted for device, sex, age, mean hemoglobin A1c, smoking, systolic blood pressure, total cholesterol, and high-density lipoprotein at EDIC year 1.

the young age of the DCCT cohort at the time of the ultrasound imaging and to the low statistical power with 135 CAD events. Given the exploratory nature of our analyses and the relatively low number of CAD events (n=135), no adjustment for multiplicity was conducted. Therefore, our results should be interpreted with care.

The lack of association between ICA IMT and CAD events was surprising, because ICA IMT was expected to give a stronger statistical signal than CCA IMT.[19–22] This might simply be because only 3 patients (0.2%) had an ICA IMT ≥1.5 mm, a threshold used to define carotid plaque.

It should also be noted that the association between CCA IMT and CAD events did not reach a statistically significant threshold in fully adjusted models (Tables 2 and 3).

Our definitions of the CAD outcomes have not changed over time. However, as with any other clinical study with a long follow-up, the ascertainment of the coronary disease in our cohort reflects the standard of medical care at the time. This may have led to underestimating the burden of CAD in our cohort, reducing our ability to detect associations with the carotid IMT.

In conclusion, we have not found that carotid IMT is associated with the risk of subsequent CAD events in individuals with T1D when putative cardiovascular risk factors such as smoking and cholesterol levels are taken into consideration.

ARTICLE INFORMATION

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Dr Lachin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Lachin and Polak designed study. J.-Y.C Backlund performed analyses, Dr Polak and J.-Y.C Backlund drafted the article, Dr Polak, J.-Y.C Backlund, and Drs Bebu, Lachin, Budoff, and Raskin revised article for critical content and approved the final version.

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Disclosures

Dr Polak reports receiving grants from the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Neurological Disorders and Stroke. The remaining authors have no disclosures to report.

Supplementary Material

Appendix S1

REFERENCES

1. Swerdlow AJ, Jones ME. Mortality during 25 years of follow-up of a cohort with diabetes. *Int J Epidemiol*. 1996;25:1250–1261. doi: 10.1093/ije/25.6.1250
2. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992–1999. *Diabetologia*. 2006;49:660–666. doi: 10.1007/s00125-005-0120-4
3. Atabek ME, Kurtoglu S, Pirgon O, Baykara M. Arterial wall thickening and stiffening in children and adolescents with type 1 diabetes. *Diabetes Res Clin Pract*. 2006;74:33–40. doi: 10.1016/j.diabres.2006.03.004
4. Dalla Pozza R, Bechtold S, Bonfig W, Putzker S, Kozlik-Feldmann R, Netz H, Schwarz H. Age of onset of type 1 diabetes in children and carotid intima medial thickness. *J Clin Endocrinol Metab*. 2007;92:2053–2057. doi: 10.1210/jc.2006-2868
5. Distiller LA, Joffe BI, Melville V, Welman T, Distiller GB. Carotid artery intima-media complex thickening in patients with relatively long-surviving type 1 diabetes mellitus. *J Diabetes Complications*. 2006;20:280–284. doi: 10.1016/j.jdiacomp.2005.07.012
6. Kawasumi M, Tanaka Y, Uchino H, Shimizu T, Tamura Y, Sato F, Mita T, Watada H, Sakai K, Hirose T, et al. Strict glycemic control ameliorates the increase of carotid IMT in patients with type 2 diabetes. *Endocr J*. 2006;53:45–50. doi: 10.1507/endocrj.53.45
7. Krantz JS, Mack WJ, Hodis HN, Liu CR, Liu CH, Kaufman FR. Early onset of subclinical atherosclerosis in young persons with type 1 diabetes. *J Pediatr*. 2004;145:452–457. doi: 10.1016/j.jpeds.2004.06.042
8. Peppa-Patrikiou M, Scordili M, Antoniou A, Giannaki M, Dracopoulou M, Dacou-Voutetakis C. Carotid atherosclerosis in adolescents and young adults with IDDM. Relation to urinary endothelin, albumin, free cortisol, and other factors. *Diabetes Care*. 1998;21:1004–1007. doi: 10.2337/diacare.21.6.1004
9. Yavuz T, Akcay A, Omerolu RE, Bundak R, Sükür M. Ultrasonic evaluation of early atherosclerosis in children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab*. 2002;15:1131–1136.
10. Diabetes Control Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, Rand L, Siebert C. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;14:977–986.
11. Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. *Diabetes Care*. 1999;22:99–111.
12. Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, O'Leary DH, Genuth S; Diabetes Control and Complications Trial; Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med*. 2003;348:2294–2303. doi: 10.1056/NEJMoa022314
13. Polak JF, Szklo M, O'Leary DH. Carotid intima-media thickness score, positive coronary artery calcium score, and incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2017;6:e004612. doi: 10.1161/JAHA.116.004612
14. Polak JF, Pencina MJ, Herrington D, O'Leary DH. Associations of edge-detected and manual-traced common carotid intima-media thickness

measurements with Framingham risk factors: the Multi-Ethnic Study of Atherosclerosis. *Stroke*. 2011;42:1912–1916. doi: 10.1161/STROKEAHA.110.603449
15. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. *Diabetes Care*. 2016;39:686–693. doi: 10.2337/dc15-1990
16. Lachin JM, Orchard TJ, Nathan DM; DCCT/EDIC Research Group. Update on cardiovascular outcomes at 30 years of the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care*. 2014;37:39–43. doi: 10.2337/dc13-2116
17. Lachin J. *The Assessment of Relative Risks*. 2nd ed. John Wiley and Sons; 2011.
18. den Ruijter HM, Peters SAE, Groenewegen KA, Anderson TJ, Britton AR, Dekker JM, Engström G, Eijkemans MJ, Evans GW, de Graaf J, et al. Common carotid intima-media thickness does not add to Framingham Risk Score in individuals with diabetes mellitus: the use-IMT initiative. *Diabetologia*. 2013;56:1494–1502. doi: 10.1007/s00125-013-2898-9
19. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, Volcik K, Boerwinkle E, Ballantyne CM. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk in Communities) Study. *J Am Coll Cardiol*. 2010;55:1600–1607. doi: 10.1016/j.jacc.2009.11.075
20. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med*. 2011;365:213–221. doi: 10.1056/NEJMoa1012592
21. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med*. 1999;340:14–22. doi: 10.1056/NEJM199901073400103
22. Polak JF, Szklo M, Kronmal RA, Burke GL, Shea S, Zavodni AE, O'Leary DH. The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2013;2:e000087. doi: 10.1161/JAHA.113.000087
23. Yahagi K, Kolodgie FD, Lutter C, Mori H, Romero ME, Finn AV, Virmani R. Pathology of human coronary and carotid artery atherosclerosis and vascular calcification in diabetes mellitus. *Arterioscler Thromb Vasc Biol*. 2017;37:191–204. doi: 10.1161/ATVBAHA.116.306256
24. Spagnoli LG, Mauriello A, Palmieri G, Santeusanio G, Amante A, Taurino M. Relationships between risk factors and morphological patterns of human carotid atherosclerotic plaques. A multivariate discriminant analysis. *Atherosclerosis*. 1994;108:39–60. doi: 10.1016/0021-9150(94)90036-1
25. Kupfer R, Larrubia MR, Bussade I, Pereira JRD, Lima GAB, Epifanio MA, Schettino CDS, Momesso DP. Predictors of subclinical atherosclerosis evaluated by carotid intima-media thickness in asymptomatic young women with type 1 diabetes mellitus. *Arch Endocrinol Metab*. 2017;61:115–121. doi: 10.1590/2359-3997000000255
26. Larsen JR, Brekke M, Bergengen L, Sandvik L, Arnesen H, Hanssen KF, Dahl-Jorgensen K. Mean HbA1c over 18 years predicts carotid intima media thickness in women with type 1 diabetes. *Diabetologia*. 2005;48:776–779. doi: 10.1007/s00125-005-1700-z

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