Low Prevalence of Subclinical Atherosclerosis in Asymptomatic Patients With Type 1 Diabetes in a European Mediterranean Population

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OBJECTIVE

To evaluate the presence of early carotid and coronary atherosclerosis in asymptomatic patients with type 1 diabetes with no history of ischemic heart disease.

RESEARCH DESIGN AND METHODS

One hundred and fifty patients with type 1 diabetes (58% males; 38.6 ± 8.1 years, 20.4 ± 8.1 years of evolution; HbA_{1c} 8.1 ± 2.3%; 52% nonsmokers; 26% retinopathy; 9% microalbuminuria) and 50 nondiabetic control subjects age and sex matched were studied. Carotid ultrasonography to determine common carotid artery intima-media thickness (c-IMT) and the presence of atheroma plaques and cardiac computed tomography for calcium analysis and quantification (coronary artery calcium score [CACS]) were performed.

RESULTS

Most patients with type 1 diabetes and control subjects displayed a CACS of 0 (82 vs. 92%). Patients with type 1 diabetes with CACS ≥1 were older and had higher HbA_{1c} (44.5 ± 5.1 vs. 36.7 ± 8.1 years [$P < 0.001$] and 8.5 ± 1.1 vs. 7.8 ± 1.0% [$P < 0.003$], respectively) and longer evolution of diabetes (25.4 ± 9.2 vs. 19.3 ± 7.4 years, $P < 0.005$) and mean c-IMT (0.67 ± 0.18 vs. 0.53 ± 0.11 mm, $P < 0.001$) compared with patients with CACS of 0. Smoking ($P < 0.02$), nephropathy ($P < 0.05$), retinopathy ($P < 0.05$), and male sex ($P < 0.03$) were significantly and positively associated with CACS ≥1. Mean c-IMT was significantly higher in patients with type 1 diabetes (0.55 ± 0.14 vs. 0.48 ± 0.14 mm, $P < 0.01$), and 11% of them presented atheroma plaques (8% of control subjects). Multivariant logistic regression analysis showed that c-IMT was related to CACS ($\beta = 6.87$, $P < 0.001$).

CONCLUSIONS

A small percentage of patients with type 1 diabetes showed data suggestive of subclinical atherosclerosis. Universal screening of coronary disease in this population is not justified. Carotid ultrasonography may be useful for screening in the subset of patients with cardiovascular risk factors and long disease evolution.

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Cardiovascular disease, especially coronary heart disease (CHD), is the leading cause of death in type 2 diabetes (1–3). Different studies have shown that changes in vascular structure, such as coronary intimal thickening, changes in arterial compliance and stiffness, and endothelial dysfunction also occur early in the course of type 1 diabetes, leading to an accelerated atherosclerosis (4,5).

Remarkably, type 1 diabetes is associated with an even higher CHD risk of at least a 10-fold increase compared with age-matched nondiabetic subjects (6,7). Most of the clinical trials regarding prevention of CHD in diabetic patients have only included patients with type 2 diabetes, and their conclusions have been applied to patients with type 1 diabetes. However, it is unclear whether asymptomatic patients with type 1 diabetes benefit from the current preventive treatment strategies for type 2 patients. Current guidelines do not recommend active screening of CHD and consider type 1 diabetes as a high-risk state only when microalbuminuria is present (8), even though microalbuminuria may not reliably reflect nephropathy (9).

Coronary artery calcium score (CACS) is a well-established index of atherosclerosis and is feasible to be performed in the clinical practice (10). CACS has been shown to predict both future CHD and all-cause mortality in nondiabetic subjects (11,12). Type 2 diabetes is associated with higher CACS than the general population, independently of other cardiovascular risk factors (13).

In the Pittsburgh Epidemiology of Diabetes Complications Study cohort, CACS was strongly correlated with CHD, particularly in men (14), but there is scarce information of CACS in asymptomatic type 1 diabetes. A positive relationship between glycemic control and CACS has been described by the Epidemiology of Diabetes Interventions and Complications (EDIC) study, showing that intensive treatment is associated with lower CACS (15). Another study has also reported increased coronary calcification in women with type 1 diabetes compared with control subjects (16).

Additionally, increased common carotid artery (CCA) intima-media thickness (c-IMT) has been found to also be associated with diabetes in other chronic diseases where atherosclerosis is present (17).

Prediction and early diagnosis of CHD allows an appropriate intervention in the initial stages of the disease. Therefore, the aim of the current study was to evaluate the presence of early atherosclerosis in asymptomatic patients with type 1 diabetes with a lengthy evolution of the disease (>10 years) living in a Mediterranean country, with no previous history of ischemic heart disease.

RESEARCH DESIGN AND METHODS

A group of 150 asymptomatic patients with type 1 diabetes followed in our outpatient clinic were consecutively recruited between 2010 and 2012. Inclusion criteria were age between 20 and 50 years and an evolution of disease >10 years. Exclusion criteria included a previous history of clinical macrovascular disease or CHD. Current smoking and previously smoking condition for <5 years were included in the same category. A group of nondiabetic subjects matched for age, sex, and smoking condition were recruited from the relatives, and staff from our hospital were also included in the control group. All patients were under intensive insulin treatment, with 15% using pump devices.

The study was approved by the local ethics committee, in accordance with the Declaration of Helsinki; all participants provided their written informed consent prior to inclusion.

Demographic and clinical data, including age, sex, history of clinical macrovascular disease and microvascular diabetes complications, family history of early CHD in first-degree relatives (defined as CHD occurring before 55 years of age in men and before 65 years of age in women), and medical treatment (antihypertensive agents, statins, and acetylsalycilic acid) were recorded for all subjects. BMI was calculated as weight in kilograms divided by height per square meter.

Diabetic nephropathy was evaluated according to urinary albumin excretion. Normal urinary albumin excretion was considered <30 mg/24 h, microalbuminuria from 30 to 299 mg/24 h, and proteinuria >300 mg/dL. These results were confirmed on at least two out of three consecutive determinations. Diabetic retinopathy was defined by fundus oculi performed by a specialized ophthalmologist.

Biochemical Measurements

Blood samples were drawn by venipuncture at between 0800 and 0830 h after overnight fast. Plasma glucose, total cholesterol, HDL and LDL cholesterol, and triglycerides were measured by routine clinical chemistry immediately after extraction. HbA_{1c} was measured in blood samples with EDTA by high-performance liquid chromatography using a fully automated Adams Menarini HI-AUTO A1c 8160 analyzer manufactured by Arkray (Kyoto, Japan) with an interassay coefficient of variation of 1.8 and 1.5% at HbA_{1c} levels of 4.8 and 9.0%, respectively (reference range 4–5.8%). This method is a cation exchange high-performance liquid chromatography method certified by the National Glycohemoglobin Standardization Program of traceability to the Diabetes Control and Complications Trial (DCCT) reference method. Mean HbA_{1c} was calculated as an average of three determinations in the previous year before inclusion in the study.

Cardiac Computed Tomography Protocol

Multidetector cardiac computed tomography (CT) was performed using a 16-slice high-resolution CT electrocardiogram synchronized, with retrospective reconstruction and with special attention to the coronary arteries (SOMATOM Sensation 16 and Syngo Calcium Scoring software for analysis and calcium calcification). CACS was identified as a dense area in the coronary artery exceeding the threshold of 130 Hounsfield units. A total Agatston score was determined for each patient. The results were expressed according to the classification previously described by Shaw et al. (18). Scans were read by a single radiologist.

Carotid Ultrasonography

Ultrasonographic images were acquired using high resolution B-mode ultrasound (Siemens Acuson Sequoia 512) with an electric linear array 13-5 MHz transducer. Acquisition, processing, and storage of B-mode images were computer-assisted with the version of the software provided by the manufacturer. All measurements were performed by the same trained radiologist. The CCA segment was defined as the distal 1 cm of the CCA, immediately proximal to the onset of increased spatial separation of the walls of the CCA. Both near and far walls of these arterial segments were scanned longitudinally and transversely to assess the presence of plaques. The protocol involved scanning of the CCA, carotid bifurcations, and origins (first 2 cm) of internal carotid arteries. The presence of carotid plaques was defined as focal echo structures encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding c-IMT value, or when c-IMT was >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface. Quantification of plaque thickness was made at the site of the maximum encroachment perpendicular to the vessel wall by measuring the distance between the media-adventitia interface and the lesion surface facing the lumen. CCA-IMT was measured in a longitudinal view at a site free of plaques along a 10-mm-long segment on the far wall of the CCA in agreement with the carotid IMT consensus (2004–2006) (19). Composite right and left c-IMT were calculated as the average of the four readings in each artery segment, and the mean of the left and right c-IMT measurements was used in the analysis.

Statistical Methods

Continuous variables were expressed as mean ± SD or median (interquartile range) and categorical variables as frequency and/or percentage. Differences between groups were tested by the Student *t* test or the nonparametric Mann-Whitney *U* test, where appropriate. A *P* value <0.05 was considered statistically significant. Categorical variables were compared with a χ^2 test. Separate multivariate regression analyses with backward elimination were performed, correcting for all baseline clinical characteristics, including as confounders age, male sex, BMI, smoking, positive family history of CHD, dyslipidemia, hypertension, and mean HbA_{1c} to identify independent predictors of each coronary atherosclerosis variable on multidetector cardiac CT. All statistical analyses were performed using the Statistical Package for Social Science (SPSS, Chicago, IL) for personal computers, version 12.0.

RESULTS

The clinical characteristics of the 150 patients and the 50 control subjects are shown in Table 1. All patients had normal creatinine levels and a glomerular filtration rate >60 mL/min.

CACS

CACS results are shown in Table 2. A high proportion of subjects in both the control group and patient group displayed a CACS of 0 (92 vs. 82%), and the differences between groups were not statistically significant. For all patients, mean and median CACS were 19.5 ± 102 and <1, respectively. When a CACS of moderate severity of >100 was considered, it was found only in a low proportion of type 1 diabetes (6/150, 4%). When patients were categorized using a lower CACS of ≥1, those showing values higher than this cutoff had significantly higher age and a longer duration of the disease compared with patients with a CACS of 0 (Fig. 1*A*). There were more men than women with CACS ≥1 ($P < 0.02$). In relation to metabolic control, patients with CACS ≥1 also showed significantly higher HbA_{1c} (Fig. 1*B*).

Thirteen out of the 150 patients (9%) presented nephropathy, and 10 of them also presented retinopathy. Eight of the 13 patients with nephropathy had a CACS of 0, and 5 of them had a CACS >50 (with values of 58, 99, 227, 523, and 1,062). These five patients also presented proliferative retinopathy. The highest CACS (1,062) was found in a type 1 diabetic patient (female, 47 years old, current smoker, and with a positive family history of CHD) (Supplementary Fig. 1).

Carotid Ultrasonography

Patients with type 1 diabetes showed a significantly higher c-IMT compared with the control group (0.55 ± 0.14 vs. 0.48 ± 0.14 mm, $P < 0.01$). A low proportion of subjects in both groups presented atheroma plaques (16 patients and 4 control subjects, 11 vs. 8%), in all cases, conditioning stenosis of <50%.

Table 1—Basal characteristics of patients with type 1 diabetes and control group

	Type 1 diabetes	Control
n	150	50
Age (years)	38.6 ± 8.1	38.1 ± 7.2
Sex (male/female %)	58/42	56/44
Evolution of type 1 diabetes (years)	20.4 ± 8.1	—
Family history of CHD (%)	20	22
BMI (kg/m^2)	25.1 ± 3.6	25.3 ± 4.3
Systolic blood pressure (mmHg)	117.3 ± 13.5	—
Diastolic blood pressure (mmHg)	70.9 ± 7.7	—
Retinopathy (%)	26	—
Nephropathy (%)	9	—
HbA_{1c} (%, mmol/mol)	8.1 ± 2.3 (64.89 ± 11.48)	—
Total cholesterol (mg/dL)	182.7 ± 25.1	191.1 ± 34.1
HDL (mg/dL)	60.3 ± 15.1	61.8 ± 16.6
LDL (mg/dL)	105.3 ± 21.9	111.3 ± 33.5
Smoke (% yes/no)	48/52	42/58
Statins (%)	21	—
Antihypertensive (%)	15	—
Acetylsalycilic acid (%)	16	—

Continuous variables are expressed as mean ± SD and categorical variables as percentages.

Table 2—CACS results

	Type 1 diabetes	Control
Score 0: no plaques (very low risk)	123 (82%)	46 (92%)
Score 1–10: minimal plaques (low risk)	12 (8%)	1 (2%)
Score 11–100: mild calcification (moderate risk)	9 (6%)	2 (4%)
Score 101–400: moderate calcification (high risk)	4 (2.6%)	1 (2%)
Score >400: significant calcification (very high risk)	2 (1.3%)	0

Patients with nephropathy showed a higher c-IMT compared with patients without nephropathy (0.59 ± 0.14 vs. 0.54 ± 0.14 mm, $P < 0.08$). There were no differences regarding c-IMT in relation to retinopathy.

Patients with type 1 diabetes with plaques had a significantly higher HbA_{1c} and c-IMT (Fig. 1*C*) compared with those patients without plaques. Four out the 16 patients with plaques (25%) presented retinopathy, and only 1 patient had both proliferative retinopathy and nephropathy.

Associations Between Study Variables

When univariate correlation analyses were performed in diabetic subjects, we found that previous and active smoking habit ($P < 0.02$), nephropathy ($P < 0.05$), retinopathy ($P < 0.05$), and male sex ($P < 0.03$) were significantly and positively associated with CACS ≥1 ($P < 0.01$ and $P < 0.004$). No relationships were found regarding family history of CHD. The presence of carotid plaques was only associated with smoking condition ($P < 0.02$) but not with the rest of the study variables. Those patients with type 1 diabetes with a CACS ≥1 showed a significantly higher c-IMT compared with patients with a CACS of 0 (Fig. 1*B*). A positive correlation was found between values of CACS and c-IMT ($r_s = 0.36$, $P < 0.001$).

A multivariant logistic regression analysis was performed in the type 1 diabetic group in order to identify those factors independently influencing CACS, including all variables that showed a statistically significant association in the univariate analysis. The step forward methodology was applied, including the following variables: age, sex, duration of disease, smoking status, HbA_{1c}, retinopathy, nephropathy, treatment for hypertension, statin use, CHD family history, and aspirin treatment. After elimination of confounders, the final model included the following covariates: duration of diabetes, statin treatment, and c-IMT ($R^2 = 0.44$). In all the models generated, we found that c-IMT was related to the CACS ($\beta = 6.87$, $P < 0.001$), duration of diabetes ($\beta = 0.09$, $P < 0.008$), and statin treatment ($\beta = 1.43$, $P < 0.02$).

CONCLUSIONS

Most clinical guidelines do not recommend active screening in apparently healthy patients with type 1 diabetes (20–22), but a debate regarding this has been ongoing for years. In our study, we found that a small percentage of type 1 diabetic individuals who had been diagnosed >10 years previously presented data suggestive of subclinical atherosclerosis. Most of our patients displayed a CACS of 0, slightly lower than in the control group. Only a very low 4% of patients showed a CACS >100, suggesting moderate or significant calcification, with most of them also presenting associated microvascular complications. Moreover, c-IMT information was quite concordant with CACS data.

Few studies on CACS measurement in the asymptomatic type 1 diabetic population have been performed (15,16,23–25). Data concerning the Mediterranean population are even scarcer and our results clearly differ from previously published reports that showed higher CACS in comparison with our findings (see Table 3). In those studies, patients were younger but with a higher HbA_{1c} (24) or the prevalence of hypertension and dyslipidemia was higher (25) than in our cohort. The EDIC cohort follow-up showed a loss of protective effect assigned to women and that intensive glucose treatment was also associated with a better CACS (15). Other studies by Colhoun et al. (16) and Dabelea et al. (23) displayed a smaller proportion of patients with CACS of 0 than our study despite that mean age and duration of type 1 diabetes were similar. Long duration of disease and the presence of autonomic cardiovascular neuropathy are also associated with high CACS (26). None of our patients presented clinical signs of dysautonomia, although no specific procedures were performed to rule it out.

In the current study, patients with type 1 diabetes showed a higher c-IMT when compared with the control population but there were no differences in the presence of plaques. Our patients did not show a particular metabolic instability, and hypoglycemia was not severe or very frequent. However, metabolic instability may also worsen c-IMT, and for this reason, another study performed in Spain with such patients presented a higher c-IMT compared with our cohort (27).

The fact that our cohort is living in a geographical area with a low prevalence of CHD (28–30) may have influenced our findings. This general population background with specific dietary factors, such as Mediterranean lifestyle, may be of importance, especially when comparing with Northern European diets (30). Actually, a recent randomized, controlled intervention trial conducted in a population from our region showed that a Mediterranean diet reduced the incidence of major cardiovascular events (31). Finally, the genetic background of the cohort was also relevant as there was a low CHD family history.

In addition, and possibly of much importance, it has to be taken into account that our patients with type 1 diabetes have all been treated in the era of universal intensive glycemic treatment (15% were under pump treatment), as well as the use of cardiovascular protective drugs immediately when indicated according to international guidelines. Therefore, our data on CACS are very close to those found in the intensive arm of the EDIC cohort (15). This intensive glycemic treatment could have a positive impact

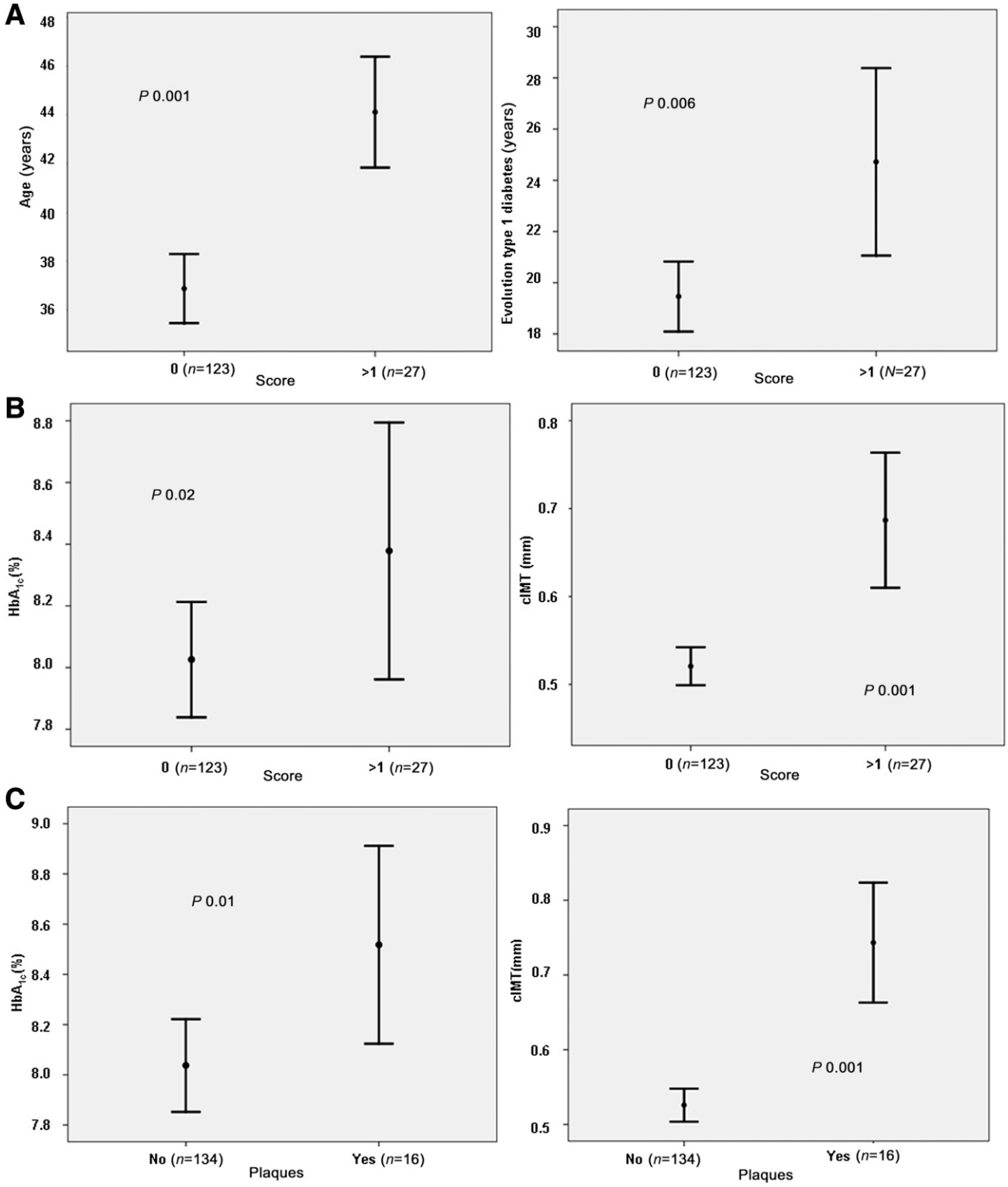

Figure 1—*A*: Association of CACS with age and type 1 diabetes evolution. *B*: Association of CACS with metabolic control and carotid ecography. *C*: Association of carotid plaques with metabolic control and c-IMT.

in the prevention of cardiovascular disease as well as better control of blood pressure and lipids in the current era of diabetes management.

In summary, our data indicate that a small percentage of patients with type 1 diabetes living in Catalonia with a mean disease duration of 20 years showed data suggestive of subclinical atherosclerosis. For this reason, universal screening of coronary disease in this Mediterranean type 1

Table 3—CACS in asymptomatic patients with type 1 diabetes

	Cleary et al. (15)	Colhoun et al. (16)	Dabelea et al. (23)	Salem et al. (24)	Djaberi et al. (25)	Present study
n	1,205 Int/Conv*	199	656	60	65	150
Mean age (years)	43	38	37	16	46	38
Evolution type 1 diabetes (years)	21	24	23	12	23	20
Retinopathy/nephropathy (%)	50	—	—	30/63	—	26/9
HbA_{1c} (%)	7.9	8.6	7.8	9.7	7.6	8.1
Hypertension/dyslipidemia (%)	29/30	21/—	14/—	—	49/63	15/21
Mean CACS	—†	—†	—†	44	217	19
CACS = 0						
(% total)	78/70	—	—	80	—	82
(% men/women)	—	48/53	52/72	—	—	67/91

*Int, intensive treatment; Conv, conventional treatment. †In these studies, CACS was reported categorized as 0 or >0.

diabetic population is not justified. CACS is expensive, and our data support that alternative and cheaper techniques that are readily available in the clinical practice, such as carotid ultrasonography, may be useful for CHD screening in patients with type 1 diabetes when associated classic cardiovascular risk factors, microvascular complications, or very long disease durations are present. In this subset of subjects, as CHD mortality is higher than expected, attention should be given to detecting macrovascular disease in the same way as it is done for microvascular disease, provided that the screening procedure is sufficiently robust.

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