

Coronary Calcium in Adults With Type 1 Diabetes

A Stronger Correlate of Clinical Coronary Artery Disease in Men Than in Women

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We studied the relationship of coronary artery calcification (CAC), a marker of coronary atherosclerosis, with prevalent clinical coronary artery disease (CAD) and established cardiovascular disease (CVD) risk factors in a type 1 diabetic population. At the 10-year follow-up examination of the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study cohort, 302 adults (mean age 38.1 ± 7.8 years) received electron beam tomography (EBT) scanning of the heart and a clinical examination. Clinical CAD was defined as a confirmed history of myocardial infarction (MI), angiographic stenosis $\geq 50\%$, Pittsburgh EDC Study physician-diagnosed angina, or ischemic electrocardiogram (ECG). CAC correlated with most CVD risk factors. CAC had 84 and 71% sensitivity for clinical CAD in men and women, respectively, and 100% sensitivity for MI or obstructive CAD. A CACS cut point of 400 was the most efficient coronary calcium correlate of CAD. In subjects with angina only, CAC sensitivity was 83% in men and 46% in women. In logistic regression, CAC, ECG R-R variation, peripheral vascular disease, and Beck Depression Inventory independently correlated with prevalent CAD in men and overall. Except for CAC, the same variables independently correlated with CAD in women, and age also entered the model. CAC was an independent correlate of MI or obstructive CAD in both sexes and was the strongest independent correlate in men, but CAC was not independently associated with angina and ischemic ECG in either sex. It is concluded that EBT-detected CAC is strongly correlated with CAD in type 1 diabetes—particularly in men. *Diabetes* 49:1571–1578, 2000

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ABD, ankle-brachial difference; ABI, ankle-brachial index; BDI, Beck Depression Inventory; CAC, coronary artery calcification; CACS, CAC score; CAD, coronary artery disease; cal400, CACS cut point of 400; CHP, Children's Hospital of Pittsburgh; CVD, cardiovascular disease; DSP, distal symmetric polyneuropathy; EBT, electron beam tomography; ECG, electrocardiogram; EDC, Epidemiology of Diabetes Complications; E/I, expiration/inspiration; LEAD, lower-extremity arterial disease; MI, myocardial infarction; ON, overt nephropathy; PAC, peripheral arterial calcification; PVD, peripheral vascular disease; ROC, receiver operating characteristic; sBP, systolic blood pressure; WHR, waist-to-hip ratio.

Cardiovascular disease (CVD) mortality risk in type 1 diabetes is up to 10-fold higher than in the general population and accounts for the majority of deaths in middle-aged type 1 diabetic patients (1). Angiographically mild lesions may spontaneously rupture and/or progress to severe stenoses or occlusions over a period of a few months (2). A large fraction of coronary artery disease (CAD) thus first comes to clinical attention through acute events. Coronary artery calcification (CAC) has been found to be specific for atherosclerosis (3,4), except for a single case report (5). The degree of CAC also correlates with coronary plaque burden (6).

Electron beam tomography (EBT) is a noninvasive technique for the detection and quantification of CAC. The American Heart Association (7) concluded in their Scientific Statement that "reproducibility varies from excellent to moderate." However, they also state that "unless the calcific area is greater than 2 mm, reproducibility appears to be insufficient for serial assessment of coronary calcium levels in individual patients," an opinion consistent with a report from Wang et al. (8). Nonetheless, the American Heart Association statement also concludes, EBT is "sufficiently accurate to predict angiographic stenoses somewhere in the coronary arteries and to predict clinical end points in symptomatic patients." Because partial volume effects play a key role in the variability of calcium scores, some investigators advise averaging the results of duplicate scans (9).

Although coronary artery calcification score (CACS) is predicted by CVD risk factors (7,10,11), it is in many studies an independent predictor of obstructive CAD (11–13). According to a study that used 4 meta-analyses (one for each testing modality: EBT, treadmill, stress-echocardiography, or stress thallium), CACs, whether based on sensitivity, specificity, or maximum combined sensitivity and specificity, provided the most cost-effective pathway for diagnosing obstructive CAD, whereas negative and positive predictive values were similar to other testing modalities (14).

CAC has >90% sensitivity for history of myocardial infarction (MI) (10,15). A study involving age-matched type 2 diabetic patients found that CACS and nephropathy, but not other CVD risk factors, were significantly associated with symptomatic CAD and >75% stenosis (16).

Whether and in what populations CACS predicts events independent of established CVD risk factors has not been determined (17–22). In the only published prognostic study

of CACS in diabetes (type 2), calcification score predicted events, but patients in the second tertile of scores experienced the most events. No adjustment was made for other risk factors (23). Because of the very high risk of CAD in type 1 diabetes and its frequent unheralded appearance, the early detection of CAD would be particularly valuable so that intensive therapy can be initiated. Little, however, is currently known about CAC in type 1 diabetes.

Accordingly, we used EBT to study the relationship of CAC and prevalent clinical CAD in adults with type 1 diabetes to determine if similar relationships are seen to those in the general population. Further objectives were to determine the most efficient cut point in terms of identifying prevalent CAD and the major predictors of CAC in type 1 diabetes.

RESEARCH DESIGN AND METHODS

Study population. Subjects were participants in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study. The Pittsburgh EDC Study is a 10-year prospective follow-up study of risk factors for complications of childhood-onset type 1 diabetes. Pittsburgh EDC Study participants were recruited from the Children's Hospital of Pittsburgh (CHP) registry of type 1 diabetes, which has been shown to be representative of the Allegheny County population (24). Subjects diagnosed with type 1 diabetes at CHP (or seen at CHP within 1 year of diagnosis) before age 17 years between 1950 and 1980 were eligible for the Pittsburgh EDC Study. Recruitment was described previously (25).

Of the subjects, 658 met eligibility criteria and participated in the first biennial Pittsburgh EDC Study examination in 1986–1988. In the sixth Pittsburgh EDC Study cycle in 1996–1998 (10-year follow-up), 407 subjects were examined in the clinic.

Beginning in June 1997, EBT was offered during the weekday clinic to Pittsburgh EDC Study participants aged ≥ 30 years. After further approval from the Institutional Review Board, EBT was also made available to study participants aged 18–29 years, and subjects who had already completed the cycle 6 examination were invited to return for EBT screening if they had not received it. A total of 302 Pittsburgh EDC Study subjects completed EBT screening and a full cycle 6 visit.

Clinical evaluation and procedures. Before attending the clinic, participants completed a questionnaire concerning demographic information, medical history, depressive symptoms (Beck Depression Inventory [BDI] [26]), and physical activity. An ever-smoker was defined as 100+ lifetime cigarettes. Height was measured with the clinic stadiometer. BMI was calculated as weight (kg)/height² (m²). Two waist measurements were made midway between the upper iliac crest and lower costal margin, and 2 hip measurements were made at the maximum hip circumference. Averages of each were used to derive the waist-to-hip ratio (WHR).

Sitting blood pressures were measured according to the Hypertension Detection and Follow-up Program protocol (27) using a random zero sphygmomanometer. The mean of the second and third readings was used. Hypertension was defined as blood pressure $>140/90$ mmHg or taking antihypertensive medication.

Resting ankle/arm pressures were taken with the subject supine using a Doppler blood flow detector. The right and left tibialis posterior and dorsalis pedis arterial pressures were compared with the arm pressure. Ankle-brachial pressures were calculated using the arm pressure taken closest in time to the ankle pressure. Any subject with an ankle-brachial index (ABI) of <0.8 for any of the 4 vessels or a history of claudication or of amputation for vascular cause was considered positive for lower-extremity arterial disease (LEAD). Subjects with an ankle-brachial difference (ABD) of ≥ 75 mmHg for any of the 4 vessels were considered positive for peripheral arterial calcification (PAC) (28). A 12-lead electrocardiogram (ECG) was obtained. The expiration/inspiration (E/I) ratio was calculated from ECG R-R intervals according to an office-based method, using the mean of 2 tests, separated by a 1-min rest. An E/I ratio <1.10 was considered evidence of autonomic neuropathy (29).

Fasting blood samples were taken. HbA_{1c} was measured using automated high-performance liquid chromatography (Diamat; Bio-Rad, Hercules, CA). Cholesterol and triglycerides were measured enzymatically (30,31). HDL cholesterol was determined using a modification of the Lipid Research Clinics method by a heparin and manganese procedure (32). LDL cholesterol was calculated using the Friedewald equation (33), which has been previously validated in this type 1 diabetic population.

Distal symmetric polyneuropathy (DSP) was determined according to the Diabetes Control and Complications Trial protocol (34). Subjects with the presence of 2 or more symptoms, signs, and absent tendon reflexes were considered positive.

Overt nephropathy (ON) was defined as having an albumin excretion rate >200 $\mu\text{g}/\text{min}$ in ≥ 2 of 3 timed urine collections (24-h, overnight, and post-clinic), renal dialysis, or a kidney transplant. If 2 timed urine specimens were not available or complete, a previously validated urinary albumin-to-creatinine (mg/mg) ratio >0.31 was used to define ON. Urinary albumin was determined immuno-nephelometrically (35). If no specimens were available, serum creatinine >2 mg/dl was considered evidence of ON.

Clinical CAD was defined as a history of MI (confirmed by ECG Q-waves or hospital records, using standardized criteria) (36), coronary artery occlusion $\geq 50\%$ by angiography, ischemic ECG (Minnesota codes 1.1–1.3, 4.1–4.3, 5.1–5.3, or 7.1) (37) at the 10-year examination, or diagnosis of angina by the Pittsburgh EDC Study physician during any cycle visit.

CAC was measured by EBT using an Imatron C-150 ultrafast computed tomography scanner (Imatron, South San Francisco, CA). Threshold calcium determination was set using a density of 130 Hounsfield units in a minimum of 2 contiguous pixels. While supine subjects held their breath, ~ 30 scans were obtained in 3-mm contiguous sections of the heart. Scans were triggered by ECG signals at 80% of the R-R interval. CACS was calculated according to the method of Agatston et al. (38). A high reproducibility of coronary scans has been reported in a previous study in our facility with an intraclass correlation of 0.99, partially reflecting the wide range of calcification noted in this study (39).

Statistical analysis. Analysis was performed using SPSS for VMS/VAX (40). Receiver operating characteristic (ROC) curves were produced using Epistat (41). Differences between subjects were evaluated using Student's *t* test for continuous variables and χ^2 test for dichotomous variables. Non-normally distributed variables were transformed by natural log if possible (triglycerides); the Mann-Whitney *U* test was used to compare continuous variables that could not be log-normalized (CACS, BDI, pulse, and E/I ratio). $P < 0.05$ was considered statistically significant. Sub-analysis focused on cases of CAD with hard evidence, i.e., myocardial infarction or angiographic stenosis of $\geq 50\%$ ($n = 20$).

Linear regression was used to evaluate potential predictors of CACS. Variables that were correlated with CACS at the $P < 0.10$ level were made available for forward stepwise multiple linear regression models. Significance of $P < 0.05$ was required to enter the model, and $P > 0.10$ was required for exclusion from the model of a variable that had entered.

Logistic regression was used to evaluate potential risk factors for prevalent clinical CAD. The same entrance and exclusion criteria were used for model building.

The following calcium variables were evaluated: calcium present/absent; total calcium score; $3+/-<3$ calcified vessels; CACS cut points in intervals of 100, from 100 to 900; and an age-related CACS cut point (400 for age 50+ years, 100 for age <50 years). From preliminary analyses, it was believed that the CACS cut point of 400 (cal400) was the most efficient predictor of clinical CAD. Multivariate models were thus developed using the cal400 variable. The other calcium variables were each in turn substituted for cal400 in the full multivariate models. However, none of the other calcium variables was as statistically significant as cal400 nor did any improve model fit or the proportion of variance explained.

Because of collinearity with age ($r = 0.69$), the duration variable was not used in multivariate analyses. Results were virtually identical if duration was used, except that, unlike age, duration did not enter the final models for CAD prediction in women (Table 3). The lowest ABI and highest ABD of the 4 taken on each subject were used for analyses. In all final models, a single variable—peripheral vascular disease (PVD) (indicating the presence of LEAD and/or PAC)—was a stronger correlate of CAD than either the LEAD or PAC variable and was used in place of them.

RESULTS

The 105 cycle-6 participants without EBT screening were significantly younger (35.5 years) than the 302 cycle-6 participants with EBT screening (38.1 years, range 18–55; $P < 0.001$), reflecting the initial selection criteria, but did not differ significantly in sex distribution or prevalence of clinical CAD.

Twenty-five of 146 men (17.1%) and 31 of 156 women (19.9%; a nonsignificant difference) had clinical CAD. Subjects were classified according to their highest CAD type as follows: MI (4 men and 4 women), $\geq 50\%$ stenosis or coronary bypass surgery (5 men and 7 women), angina with ischemic ECG (1 man and 2 women), angina only (11 men and 11 women), and ischemic ECG only (4 men and 7 women). The first 2 categories (hereafter referred to as MI/stenosis) were

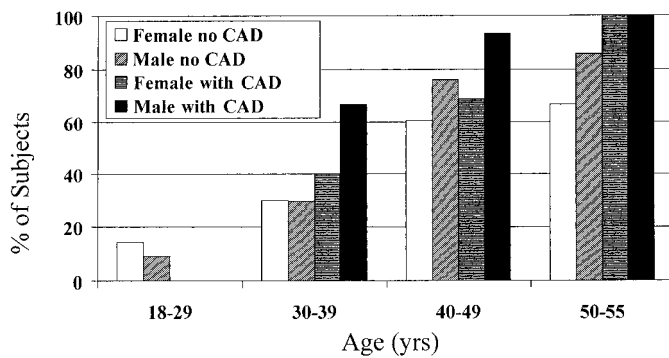


FIG. 1. Prevalence of CAC by age, sex, and clinical CAD status.

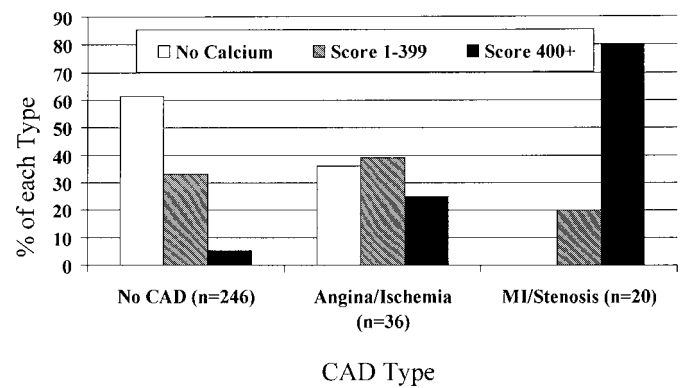


FIG. 2. Distribution of CACS within CAD status.

grouped for analysis, as were the last 3 (hereafter referred to as angina/ischemia). Ten of the subjects with histories of MI/stenosis also had histories of angina. Thus, 9 men and 11 women were classified as having “hard” cardiac end points (MI/stenosis), whereas 16 men and 20 women were classified as angina/ischemia.

The prevalence of any CAC increased with age from 11% before age 30 years to 88% in individuals aged 50–55 years (Fig. 1). Calcification was more common in subjects with clinical CAD (77%) than in those without CAD (39%; $P < 0.0001$). CAC was detected in all subjects with CAD aged ≥ 50 years. In subjects with the same CAD status, there was little sex difference in CAC prevalence at every age.

The odds ratio of clinical CAD increased from 1.0 in men without calcification (referent) to 4.3 and 50.9 in men with CACS 1–399 and 400+, respectively. In women, the odds ratio increased from 2.2 to 3.8 and 28.8 in the same CACS categories.

Figure 2 shows the distribution of CAC within CAD status. Of the subjects without clinical CAD, 61% had no detectable

CAC compared with 36% of subjects with angina/ischemia and no subjects with MI/stenosis. Of the subjects who were free of clinical CAD, 5% had a CACS of 400+, as did 25% of subjects with angina/ischemia and 80% of subjects with MI/stenosis. However, more subjects with angina/ischemia had a CACS of 1–399 ($n = 14$) than of 400+ ($n = 9$).

The sensitivity and specificity of CAC for clinical CAD varied by sex, CACS cut point, and type of CAD, as shown in Table 1. Overall, the presence of any calcification had 77% sensitivity and 61% specificity for CAD. Sensitivity was higher in men (84%) than women (71%), whereas specificity was comparable. Positive predictive values were low (31%), whereas negative predictive values were 90% in women and 95% in men.

The sensitivity and specificity of any CAC for MI/stenosis were 100 and 58%, with little sex difference. The maximum accuracy, using a cut point of 151–168, resulted in sensitivity of 95% and specificity of 84%. At the CACS cut point of 400, overall sensitivity and specificity were 80 and 92%, respectively, and were higher in men than women.

TABLE 1 Accuracy of coronary artery calcium for clinical CAD in type 1 diabetes

CAD type	<i>n</i>	CACS	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All CAD	Both sexes	Any CAC	77	61	31	92
		CACS 400+	45	95	66	88
	Men	Any CAC	84	61	31	95
		CACS 400+	44	97	73	89
	Women	Any CAC	71	62	31	90
		CACS 400+	45	93	61	87
MI/stenosis	Both sexes	Any CAC	100	58	15	100
		CACS 400+	80	92	42	99
	Men	Any CAC	100	57	13	100
		CACS 400+	89	95	53	99
	Women	Any CAC	100	59	16	100
		CACS 400+	73	90	35	98
Angina/ischemia	Both sexes	Any CAC	64	57	17	92
		CACS 400+	25	89	24	90
	Men	Any CAC	75	57	18	95
		CACS 400+	19	91	20	90
	Women	Any CAC	55	57	16	90
		CACS 400+	30	88	26	90

NPV, negative predictive value; PPV, positive predictive value.

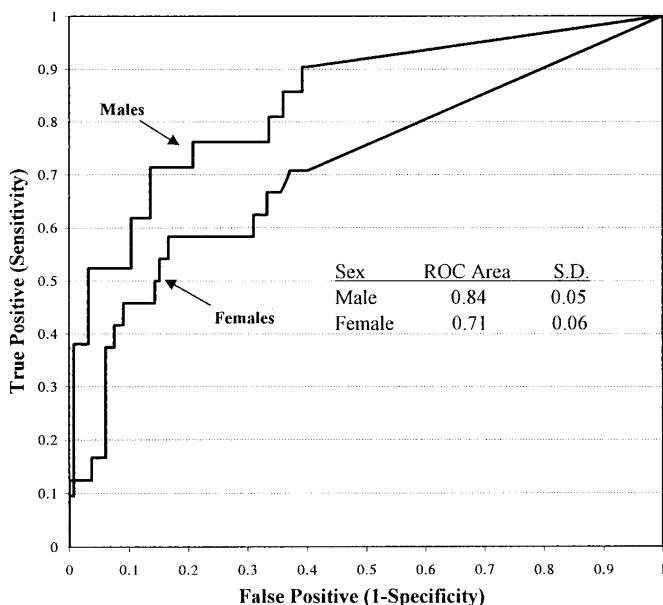


FIG. 3. ROC curves for CACS and evidence of MI, $\geq 50\%$ angiographic stenosis, or angina.

CAC sensitivity for MI/stenosis (100%) was significantly higher than that for angina/ischemia (64%) ($P < 0.002$, 1-tailed). The difference between CACS 400+ sensitivity for MI/stenosis (80%) and angina/ischemia (25%) was significant

($P < 0.0001$). The sex difference in sensitivity for angina (men, 83%; women, 46%) approached statistical significance ($P = 0.06$, 1-tailed).

The ROC area curves for CACS and evidence of MI, stenosis, and/or angina are shown by sex in Fig. 3. The area under the curve for both sexes was 0.77. The area was greater for men (0.84) than for women (0.71), although the difference was not significant ($P = 0.11$, 2-tailed).

CVD risk factor distributions are shown in Table 2 for subjects with and without clinical CAD. Subjects with CAD were on average 7–8 years older and had had diabetes 8 years longer (both $P < 0.001$) than subjects free of CAD. Traditional CVD risk factors were generally worse in subjects with CAD. Mean HbA_{1c} levels were significantly higher in men with CAD (10.7%) than without CAD (9.8%) but differed little in women.

The mean CACSs in subjects with no CAD, angina/ischemia, or MI/stenosis were 37, 6, and 302 for ages 30–39 years; 135, 204, and 1,085 for ages 40–49; and 401, 827, and 956 for ages 50–55 years, respectively.

In multivariate modeling, the significant independent correlates of clinical CAD were E/I ratio, BDI, PVD, and (except in women) cal400 (Table 3). Age also entered the model for women. In all models, PVD was the strongest correlate of prevalent CAD, although overall, BDI was equally strong. Sex was not an independent CAD correlate. If coronary calcium was not available, age entered the model for both sexes, whereas systolic blood pressure (sBP) (but not E/I ratio) entered the model for men.

TABLE 2
Risk factors in type 1 diabetes by sex and prevalent clinical CAD status: EDC 10-year examination

Characteristic	Men		Women	
	No CAD	CAD	No CAD	CAD
<i>n</i>	121	25	125	31
Age (years)	36.2 \pm 6.1	42.9 \pm 6.3*	37.1 \pm 7.5	45.4 \pm 6.3*
Duration (years)	27.5 \pm 6.7	35.5 \pm 6.5*	28.4 \pm 7.3	36.4 \pm 7.3*
HbA _{1c} (%)	9.8 \pm 1.6	10.7 \pm 1.6†	9.8 \pm 1.8	10.2 \pm 1.3
CACS	67.0 \pm 174.0	568.6 \pm 853.3*‡	83.2 \pm 220.2	452.6 \pm 542.2*‡
CACS (% 1+)	38.8	84.0*	38.4	71.0§
CACS (% 400+)	3.3	44.0*	7.2	45.2*
BMI (kg/m ²)	25.8 \pm 3.2	24.7 \pm 3.9	24.8 \pm 4.1	24.7 \pm 5.0
WHR	0.91 \pm 0.06	0.93 \pm 0.06§	0.80 \pm 0.07	0.83 \pm 0.08†
Triglycerides (mmol/l)	3.0 \pm 1.8	3.3 \pm 1.7	2.3 \pm 1.1	3.3 \pm 2.0†§
LDL cholesterol (mmol/l)	3.1 \pm 0.7	3.1 \pm 0.9	3.0 \pm 0.9	3.2 \pm 0.9
HDL cholesterol (mmol/l)	1.2 \pm 0.3	1.4 \pm 0.3†	1.6 \pm 0.4	1.5 \pm 0.4
Hypertension (%)	19.8	60.0*	27.2	54.8
sBP (mmHg)	115.9 \pm 14.8	130.6 \pm 20.8	114.5 \pm 16.7	125.9 \pm 20.2
dBp (mmHg)	73.8 \pm 9.8	76.0 \pm 13.3	66.5 \pm 9.8	65.5 \pm 10.7
Ever smoked (%)	37.1	48.0	34.4	38.7
Pulse (per minute)	71.7 \pm 11.0	71.2 \pm 10.2	70.5 \pm 9.7	74.3 \pm 13.7
LEAD (%)	7.7	32.0*	7.4	48.3*
PAC (%)	12.5	48.0*	5.6	23.3
PVD (%)	13.8	64.0*	11.5	57.1*
BDI	4.2 \pm 5.3	11.1 \pm 10.7*‡	7.1 \pm 7.2	11.9 \pm 8.9†‡
ON (%)	16.8	50.0*	17.1	32.3
DSP (%)	33.1	72.0*	33.9	64.5*
E/I ratio	1.20 \pm 0.16	1.12 \pm 0.14‡	1.17 \pm 0.13	1.06 \pm 0.11‡
E/I ratio (% <1.10)	36.7	56.0	39.8	70.0

Data are *n*, means \pm SD, or prevalence (%). * $P < 0.001$; † $P < 0.05$; ‡Mann-Whitney *U* test; §log-transformed before *t* test; || $P < 0.01$. Comparisons by CAD status. dBp, diastolic blood pressure.

TABLE 3
Multivariate correlates of prevalent CAD

	Sex	β	SE	Odds ratio*	<i>P</i>	
Overall						
BDI	Both	0.101	0.024	2.1	0.0000	
PVD		2.21	0.430	9.2	0.0000	<i>n</i> = 273
Cal400		1.61	0.509	5.0	0.0015	-2LL = 155.3
E/I ratio		-4.84	1.94	0.5	0.013	
PVD	Male	2.39	0.646	10.9	0.0002	
Cal400		3.18	0.981	24.0	0.0012	<i>n</i> = 132
BDI		0.108	0.033	2.2	0.0092	-2LL = 68.6
E/I ratio		-4.70	2.36	0.5	0.046	
PVD	Female	2.12	0.631	8.4	0.0008	
BDI		0.115	0.034	2.4	0.0008	<i>n</i> = 141
Age		0.009	0.004	2.4	0.023	-2LL = 73.5
E/I ratio		-9.71	4.80	0.3	0.043	
MI/stenosis						
Cal400	Both	3.53	1.02	34.0	0.0005	
Hypertension		3.27	1.14	26.4	0.0041	<i>n</i> = 267
Triglycerides		0.021	0.008	3.7	0.0056	-2LL = 35.3
PVD		2.48	1.21	11.9	0.041	
Age		0.017	0.009	5.0	0.046	
Cal400	Male	5.00	1.13	148.4	0.0000	<i>n</i> = 146
						-2LL = 32.5
Triglycerides	Female	0.024	0.008	4.5	0.0027	
Age		0.018	0.008	5.5	0.027	<i>n</i> = 140
Cal400		1.89	1.03	6.6	0.067	-2LL = 31.9
Angina/ischemic ECG						
PVD	Both	2.02	0.493	7.6	0.0000	
BDI		0.105	0.026	2.2	0.0001	<i>n</i> = 236
E/I ratio		-7.47	2.85	0.3	0.0088	-2LL = 122.4
LDL cholesterol		-0.018	0.009	0.6	0.049	
PVD	Male	2.41	0.739	11.1	0.0011	
BDI		0.118	0.043	2.4	0.0057	<i>n</i> = 124
E/I ratio		-5.93	2.92	0.4	0.043	-2LL = 59.1
BMI		-0.225	0.112	0.4	0.045	
PVD	Female	2.04	0.651	7.7	0.0017	
BDI		0.098	0.034	2.1	0.0043	<i>n</i> = 133
Age		0.010	0.004	2.5	0.021	-2LL = 69

*Odds ratio yes/no or per SD change (7.8 years, 1.6 mmol/l [triglycerides], 0.8 mmol/l [LDL cholesterol], 3.9 kg/m² [BMI], 7.5 U [BDI], or 0.15 [E/I ratio]). LL, log likelihood.

Prevalent MI/stenosis independently correlated with cal400, hypertension, triglycerides, age, and PVD in both sexes, with cal400 being the strongest correlate. In men, cal400 was the only significant independent MI/stenosis correlate. In women, triglycerides and age were stronger than cal400, but all 3 variables were significant. Sex was not an independent MI/stenosis correlate. If the CAC variable was not available, no other variables entered the models for women or for both sexes, whereas PVD entered the model for men.

After excluding subjects with MI/stenosis, univariately, cal400 was strongly correlated with angina/ischemia ($P < 0.02$ in all sex-specific comparisons, $P < 0.0003$ for both sexes). The independent correlates of prevalent angina/ischemia (PVD, BDI, E/I ratio, and, in women, age) were similar to the correlates of clinical CAD, except that CAC was not significant.

Table 4 shows CVD risk factor distributions by sex and presence or absence of coronary calcification. Among both men and women, age, diabetes duration, sBP, BDI, and WHR were significantly higher in subjects with CAC, whereas E/I ratio

was lower. Triglycerides were also higher ($P < 0.05$) in women with CAC. The prevalence of hypertension, nephropathy, DSP, and LEAD were significantly higher in subjects with CAC. PAC and a smoking history were more common in the presence of CAC (significantly so in men).

CACS was correlated with most of the CVD risk factors studied (Table 5). The strongest correlations were with age, diabetes duration, sBP, and E/I ratio in both men and women. As a reflection of the associations of LEAD and PAC with low and high ankle blood pressure, respectively, ABI was negatively correlated with CACS for ABI < 1.10 , but this association was positive for ABI > 1.20 (not shown). Conversely, ABD was positively correlated with CAC at ABD values > 0 , but less strongly over its entire range. Glycosylated hemoglobin was not correlated with coronary calcium.

In stepwise multiple linear regression, diabetes duration (or age) was the strongest independent correlate of calcium score in both men and women ($P \leq 0.0002$). In men, hypertension also entered the model ($P < 0.003$). In women, PVD and DSP also entered the model. If CAD was made available

TABLE 4
Risk factors in type 1 diabetes by sex and coronary calcification: EDC 10-year examination

Characteristic	Men		Women	
	No CAC	CAC	No CAC	CAC
<i>n</i>	78	68	86	70
Age (years)	33.4 ± 6.1	41.8 ± 6.7*	35.5 ± 7.1	42.9 ± 7.0*
Duration (years)	25.4 ± 5.6	32.9 ± 7.0*	26.7 ± 7.0	34.1 ± 7.2*
HbA _{1c} (%)	10.1 ± 1.6	9.8 ± 1.7	9.8 ± 1.7	10.0 ± 1.8
BMI (kg/m ²)	25.3 ± 3.1	26.0 ± 3.6	24.7 ± 3.6	24.9 ± 5.1
WHR	0.90 ± 0.05	0.94 ± 0.06*	0.79 ± 0.06	0.82 ± 0.07†
Triglycerides (mmol/l)	2.9 ± 1.8	3.2 ± 1.8‡	2.3 ± 1.0	2.8 ± 1.7‡
LDL cholesterol (mmol/l)	3.0 ± 0.8	3.2 ± 0.7	3.0 ± 0.9	3.1 ± 0.8
HDL cholesterol (mmol/l)	1.3 ± 0.3	1.3 ± 0.3	1.6 ± 0.4	1.5 ± 0.4
Hypertension (%)	9.0	47.1*	22.1	45.7§
sBP (mmHg)	112.9 ± 11.6	124.6 ± 19.6*	111.6 ± 14.2	123.0 ± 20.2*
dBp (mmHg)	73.4 ± 8.3	75.0 ± 12.6	67.4 ± 8.4	64.9 ± 11.6
Ever smoked (%)	28.9	50.8§	29.4	42.6
Pulse (per minute)	72.1 ± 11.0	71.0 ± 10.6	71.1 ± 10.4	71.4 ± 11.1
LEAD (%)	2.6	23.4*	2.4	31.3*
PAC (%)	6.4	32.8*	5.9	13.0
PVD (%)	9.0	39.7*	7.1	36.4*
BDI	4.2 ± 6.2	6.7 ± 7.6†	7.6 ± 8.2	8.6 ± 7.2
ON (%)	10.5	35.8*	14.0	27.9†
DSP (%)	26.9	54.4*	28.2	54.3§
E/I ratio	1.22 ± 0.15	1.16 ± 0.15*	1.18 ± 0.13	1.11 ± 0.12*
E/I ratio (% <1.10)	29.9	51.5§	32.1	62.3*

Data are *n*, means ± SD, or prevalence (%). **P* < 0.001; †*P* < 0.05; ‡log-transformed before *t* test; §*P* < 0.01; ||Mann-Whitney *U* test. Comparisons by CAC status. dBp, diastolic blood pressure.

to predict calcification score, duration (or age) and CAD were equally strong, and PVD also entered the model.

DISCUSSION

Coronary calcium increases with age (42). Coronary calcium has been found more often and in larger quantities in diabetic patients with CAD compared with patients without CAD (43,44). Whereas there is conflicting evidence as to whether CAC is more common in type 2 diabetes patients than nondiabetic subjects (10,42,45), there is almost no evidence concerning CAC in type 1 diabetes. In this study, we have shown that CAC relates to clinical CAD independent of other risk factors; however, overall, this association is stronger in men than in women. CAC shows similar risk factor associations to clinical CAD. The CACS dose response for CAD observed by us agrees with a cross-sectional report in nondiabetic subjects (44) but was not seen in one prospective study (23).

Our CAC prevalence results in type 1 diabetic subjects who were free of known CAD are comparable to those of Rewers et al. (46) and Colhoun et al. (47) for subjects aged 40 years and above for each sex, but differ markedly in younger ages (being much lower in the current study). This difference may be a result of small sample sizes for the age-group <30 years. We also used a minimum calcium threshold of 1 mm area compared with 0.63 mm (M. Rewers, personal communication) and 0.52 mm (H. Colhoun, personal communication).

Rewers et al. (46), Colhoun et al. (47), and the present study all found that the sex difference in prevalence of calcium, which is quite large in nondiabetic subjects, is attenuated or abolished in type 1 diabetes. A study involving both type 1 and type 2 diabetic subjects obtained similar results

(43). These observations are compatible with the loss of protection against CVD seen in type 1 diabetic women (48).

A variety of coronary calcium score cut points have been used by others (12,14,15,20). The present study is the first to our knowledge to report cross-sectional associations of coronary calcium and clinical CAD in type 1 diabetes. In univariate analysis, CAC and CACS 400+ were strongly associated with CAD. A score of 400+ was the best coronary calcium correlate of CAD in multivariate modeling. Additional calcium markers such as square root and log transformations were also investigated but did not improve on the 400 cut point. CACS >400 is considered a high level of cardiovascular risk in recent guidelines for EBT use in asymptomatic individuals (49).

Using EBT, Goel et al. (10) found coronary calcium in 74% of men with chest pain but only 32% of women (10). This finding, together with the sex difference in EBT sensitivity in the present study (83 vs. 46% for angina), supports the impression that the clinical expression of CAD differs between men and women (50).

Studies comparing CAC by type of CAD do not agree whether coronary calcification is more (4), less (51), or equally (45,52–53) strongly associated with MI compared with angina. CAC prevalence may differ between stable and unstable angina (54). In the present study, calcification was more strongly associated with a history of MI or MI/stenosis than of angina alone, with the sex differences noted previously.

A potential confounder of CAC's association with CAD type is the time between coronary event and calcium detection. A longer interval allows for increased calcification of lesions. Survival and selection biases are also likely. There was evidence in our study that subjects with "angina only" had a first event at an earlier time than subjects with MI/stenosis

TABLE 5
Spearman correlation coefficients of CACS in men and women with type 1 diabetes

Variable	Men	Women
Age	0.61*	0.56*
Duration	0.56*	0.54*
HbA _{1c}	-0.05	0.06
BMI	0.05	-0.09
WHR	0.29*	0.16†
Triglycerides	0.16†	0.17†
LDL cholesterol	0.18†	0.15†
HDL cholesterol	0.05	-0.12
sBP	0.35*	0.30*
dBP	0.05	-0.17†
ABI	0.06	-0.14†
ABI <1.10	-0.26	-0.28‡
ABD	0.30*	0.12
ABD >0	0.32*	0.22‡
Pulse	-0.07	-0.00
BDI	0.20†	0.10
E/I ratio	-0.29*	-0.37*

* $P < 0.001$; † $P < 0.05$; ‡ $P < 0.01$. dBP, diastolic blood pressure.

(suggesting differential survival), but the difference disappeared when subjects with ischemic ECG at the cycle-6 visit were grouped with subjects with angina.

One previous study (53) investigated patient characteristics predominantly in men with CAD and negative EBT scans. Subjects without CAC were younger, and none had hypertension. The present study also found that among subjects with angina/ischemia, negative scans were associated with younger age. Among women with angina, CAC was always associated with LEAD, and absence of CAC was associated with absence of LEAD.

Our lower correlation between CACS and angina, particularly in women, raises the possibility of inappropriate diagnosis. An additional possibility is that angina in diabetes has a different pathogenesis than MI/stenosis. Consistent with this argument is the finding in our 6-year incidence data that BDI is more predictive of morbidity (MI and angina) than mortality, whereas traditional CVD risk factors such as blood pressure and lipids are more closely related to CHD mortality (55). Further follow-up is needed to resolve this critical issue.

The cross-sectional associations between CVD risk factors and CAD at the 10-year follow-up of the Pittsburgh EDC Study cohort were similar to those found at baseline (56). Like Rewers et al. (46), but unlike Colhoun et al. (47), we did not find BMI to be associated with calcification. Although the mean BMI was similar in the present study and that of Colhoun et al., there were substantial differences in diabetes duration, sBP, HDL cholesterol, and prevalence of albuminuria, even within subjects aged 30–45 years and free of previously known CAD or kidney failure.

The Pittsburgh EDC Study will continue to follow subjects for coronary events. An estimated 13% of study subjects who were free of clinical CAD at the 10-year follow-up visit will experience a first event (angina, MI, or fatal CHD) in the years 1998–2002. If the risk for an event is 3.6 times as great (19) in subjects with CAC, we project that the event rate in the subjects with negative EBT scans will be 6.4%, and the

event rate will be 22.9% in subjects with positive scans. The projected event rate in subjects with negative scans is by no means negligible and suggests that they too need appropriate cardiovascular risk factor management. Although the subjects with high CACSs may be at higher risk of a first event, further follow-up data are needed before EBT screening can be recommended for type 1 diabetic patients. The enormous CVD risk faced by these subjects makes early intervention critical, especially in subjects with subclinical disease.

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REFERENCES

- Portuese E, Orchard T: Mortality in insulin-dependent diabetes. In *Diabetes in America*. 2nd ed. Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, Eds. Washington, DC, U.S. Govt. Printing Office, 1995, p. 221–232 (NIH publ. no. 95-1468)
- Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, Santamore WP: Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 78:1157–1166, 1988
- Blankenhorn DH: Coronary calcification: a review. *Am J Med Sci* 242:1–9, 1961
- Frink RJ, Mehar RW, Brown AL Jr, Kincaid OW, Brandenburg RO: Significance of calcification of the coronary arteries. *Am J Cardiol* 26:241–247, 1970
- Lachman AS, Spray TL, Kerwin DM, Shugoll GI, Roberts WC: Medial calcinosis of Monckberg. *Am J Med* 63:615–622, 1977
- Sangiori G, Rumberger JA, Severson A, Edwards WD, Greegoire J, Fitzpatrick LA, Schwartz RS: Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using noncalcifying methodology. *J Am Coll Cardiol* 31:126–133, 1998
- Wexler L, Brundage B, Crouse J, Detrano R, Fuster V, Maddahi J, Rumberger J, Stanford W, White R, Taubert K: Coronary artery calcification: pathophysiology, epidemiology, imaging, methods, and clinical implications. *Circulation* 94:1175–1192, 1996
- Wang S, Detrano RC, Secci A, Tang W, Doherty TM, Puentes G, Wong N, Brundage BH: Detection of coronary calcification with electron-beam computed tomography: evaluation of interexamination reproducibility and comparison of three image-acquisition protocols. *Am Heart J* 132:550–558, 1996
- Kajinami K, Seki H, Takekoshi N, Mabuchi H: Quantification of coronary artery calcification using ultrafast computer tomography: reproducibility of measurements. *Coron Artery Dis* 4:1103–1108, 1993
- Goel M, Wong ND, Eisenberg H, Hagar J, Kelly K, Tobis JM: Risk factor correlates of coronary calcium as evaluated by ultrafast computed tomography. *Am J Cardiol* 70:977–980, 1992
- Schwartz RS, Rumberger JA, Sheedy PF II, Kaufmann R, Peyser P: Identification of patients at risk for coronary artery disease using electron-beam CT. In *Atherosclerosis X* Woodford FP, Davignon J, Sniderman A, Eds. Amsterdam, Elsevier, 1995, p. 1018–1023
- Kennedy J, Shavelle R, Wang S, Budoff M, Detrano RC: Coronary calcium and standard risk factors in symptomatic patients referred for coronary angiography. *Am Heart J* 135:696–702, 1998
- Guerci AD, Spadaro LA, Goodman KJ, Lledo-Perez A, Newstein D, Lerner G, Arad Y: Comparison of electron beam computed tomography scanning and conventional risk factor assessment for the prediction of angiographic coronary artery disease. *J Am Coll Cardiol* 32:673–679, 1998
- Rumberger JA, Behrenbeck T, Breen JF, Sheedy PF: Coronary calcification by electron beam computed tomography and obstructive coronary artery disease: a model for costs and effectiveness of diagnosis as compared with conventional cardiac testing methods. *J Am Coll Cardiol* 33:453–462, 1999
- Mahmarijan JJ, Hedrick TD, He Z-X, Edmundowicz D, Lundergan CF, Verani MS, Wolfkiel CJ, Roberts R: High incidence of coronary artery calcification among patients with a first acute myocardial infarction: results of a multicenter trial using electron beam tomography (Abstract). *J Am Coll Cardiol* 31:209A, 1999
- Sato T, Hosoi M, Hasegawa T, Hasegawa T, Yamakita T, Miyamoto M, Tanaka S, Sudo Y, Itagane H, Ueda N, Haze K, Fujii S: Highly calcified coronary artery detected by electron beam computed tomography in diabetic patients with ischemic heart disease (Abstract). *Diabetes* 48 (Suppl. 1):A374, 1999
- Woo P, Mao S, Wang S, Detrano RC: Left ventricular size determined by elec-

- tron beam computed tomography predicts significant coronary artery disease and events. *Am J Cardiol* 79:1236-1238, 1997
18. Arad Y, Spadaro LA, Lledo A, Sherman S, Guerci AD: 3.6 years follow-up of 1136 asymptomatic adults undergoing electron beam CT (EBCT) of the coronary arteries (Abstract). *J Am Coll Cardiol* 31:209A, 1998
 19. Detrano RC, Tang W, Wong ND, Doherty TM, French W: Does age affect the accuracy of coronary calcium for predicting coronary events? (Abstract) *J Am Coll Cardiol* 33:415A, 1999
 20. Callister TQ, Raggi P, Lippolis NJ, Russo DJ: How should we use coronary artery calcium scores to predict events? (Abstract) *J Am Coll Cardiol* 33:414A, 1999
 21. Detrano RC, Wong ND, Doherty TM, Shavelle RM, Ginzton LE, Budoff MJ, Narahara KA: Coronary calcium does not accurately predict near-term future coronary events in high-risk adults. *Circulation* 99:2633-2638, 1999
 22. Secci A, Wong ND, Tang W, Wang S, Doherty T, Detrano R: Electron beam computed tomographic coronary calcium as a predictor of coronary events: comparison of two protocols. *Circulation* 96:1122-1129, 1997
 23. Le T, Detrano R, Charles MA: The relationship between clinical coronary events and coronary artery calcium as detected by the electron-beam ultrafast CT scan in diabetes (Abstract). *Diabetologia* 42 (Suppl. 1):A59, 1999
 24. Wagener DK, Sacks JM, LaPorte RE, MacGregor JM: The Pittsburgh study of insulin-dependent diabetes mellitus: risk for diabetes among relatives in IDDM. *Diabetes* 31:136-144, 1982
 25. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, LaPorte RE, Kuller LH: Prevalence of complications in IDDM by sex and duration: Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 39:1116-1124, 1990
 26. Beck AT, Garbin MG: Psychometric properties of the Beck Depression Inventory: 25 years of evaluation. *Clin Psychol Rev* 8:77-100, 1988
 27. Borhani NO, Kass EH, Langford HG, Payne GH, Remington RD, Stamler J: The hypertension detection and follow-up program. *Prev Med* 5:207-215, 1976
 28. Orchard TJ, Strandness DE: Assessment of peripheral vascular disease in diabetes. *Diabetes Care* 16:1199-1209, 1993
 29. Toyry J, Niskanen LK, Mantysaari MJ, Lansimies EA, Uusitupa MJ: Occurrence, predictors, and clinical significance of autonomic neuropathy in NIDDM. *Diabetes* 45:308-315, 1996
 30. Bucolo G, David H: Quantitative determination of serum triglycerides by use of enzymes. *Clin Chem* 19:476-482, 1973
 31. Allain C, Poon LS, Chan CSG, Richmond W, Fu PC: Enzymatic determination of total serum cholesterol. *Clin Chem* 20:470-475, 1974
 32. Warnick GR, Albers JJ: Heparin/Mn⁺⁺ quantitation of high-density-lipoprotein cholesterol: an ultrafiltration procedure for lipemic samples. *Clin Chem* 24:900-904, 1987
 33. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499-502, 1972
 34. DCCT Research Group: Manual of Operations for the Diabetes Control and Complications Trial. Washington, DC, U.S. Dept. of Commerce, 1987
 35. Ellis D, Buffone GJ: New approach to evaluation of proteinuria states. *Clin Chem* 23:666-670, 1977
 36. Orchard TJ, the CCSP Investigators: Validation of coronary heart disease mortality data: the Community Cardiovascular Surveillance Project pilot experience. *Am Heart Assoc Cardiovasc Dis Epidemiol Newslett* 157:46, 1985
 37. Marmot MG, Smith GD, Stansfield S, Patel C, North F, Head J, White I, Brunner E, Feeney A: Health inequalities among British civil servants: the Whitehall II Study. *Lancet* 337:1387-1393, 1991
 38. Agatston AS, Janowitz WH, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R: Quantitation of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 15:827-832, 1990
 39. Kuller LH, Matthews A, Sutton-Tyrrell K, Edmundowicz D, Bunker CH: Coronary and aortic calcification among women 8 years after menopause and their premenopausal risk factors: the Healthy Women Study. *Arterioscler Thromb Vasc Biol* 19:2189-2198, 1999
 40. SPSS: SPSS-X User's Guide. 3rd ed. Chicago, SPSS, 1988
 41. Epistat Services: *True Epistat Reference Manual*. Richardson, TX, Epistat Services, 1987
 42. Wong ND, Kouwabunpat D, Vo AN, Detrano RC, Eisenberg H, Goel M, Tobis JM: Coronary calcium and atherosclerosis by ultrafast computed tomography in asymptomatic men and women: relation to age and risk factors. *Am Heart J* 127:422-430, 1994
 43. Peters SR, Khaleeli E, Ko JY, Budoff MJ: The use of electron beam computed tomography to predict clinical significance of coronary calcification in diabetics (Abstract). *J Am Coll Cardiol* 33:415A, 1999
 44. Blair SN, Gibbons LW: Dose-response relation of coronary artery calcium scores by electron beam computed tomography to coronary heart disease (Abstract). *Circulation* 99:1105, 1999
 45. Tuzcu EM, Berkalp B, De Franco AC, Ellis SG, Goormastic M, Whitlow PL, Franco I, Raymond RE, Nissen SE: The dilemma of diagnosing coronary artery calcification: angiography versus intravascular ultrasound. *J Am Coll Cardiol* 27:832-838, 1996
 46. Rewers M, Ehrlich J, Jensen L, Seigel R, Barriga K, Garg S, Janowitz W, Eckel RH: High prevalence of asymptomatic coronary atherosclerosis detected by electron beam computed tomography in young adults with IDDM (Abstract). *Diabetes* 47 (Suppl. 1):A12, 1998
 47. Colhoun HM, Rubens MR, Chaturvedi N, Underwood SR, Fuller JH: Type 1 diabetes abolishes the sex difference in coronary artery calcification (Abstract). *Diabetes* 48 (Suppl. 1):A129, 1999
 48. Lloyd CE, Kuller LH, Ellis D, Wing RR, Orchard TJ: Coronary artery disease in IDDM: gender differences in risk factors but not risk. *Arterioscler Thromb Vasc Biol* 16:720-726, 1996
 49. Rumberger JA, Brundage BH, Rader DJ, Kondos G: Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. *Mayo Clin Proc* 74:243-252, 1999
 50. Douglas PS: Coronary artery disease in women. In *Heart Disease*. 5th ed. Braunwald E, Ed. Stamford, CT, Appleton & Lange, 1997, p. 1704-1718
 51. Shemesh J, Stroh CI, Tenenbaum A, Hod H, Boyko V, Fisman EZ, Motro M: Comparison of coronary calcium in stable angina pectoris and in first acute myocardial infarction utilizing double helical computerized tomography. *Am J Cardiol* 81:271-275, 1998
 52. Detrano RC, Wong ND, Tang W, French WJ, Georgiou D, Young E, Brezden OS, Doherty TM, Narahara KA, Brundage BH: Prognostic significance of cardiac cinefluoroscopy for coronary calcific deposits in asymptomatic high risk subjects. *J Am Coll Cardiol* 24:354-358, 1994
 53. Schmermund A, Baumgart D, Gorge G, Seibel R, Gronemeyer D, Ge Junbo, Haude M, Rumberger J, Erbel R: Coronary artery calcium in acute coronary syndromes. *Circulation* 96:1461-1469, 1997
 54. Hodgson JM, Reddy K, Suneja R, Nair RN, Lesnefsky EJ, Sheehan HM: Intracoronary ultrasound imaging: correlation of plaque morphology with angiography, clinical syndrome and procedural results in patients undergoing coronary angioplasty. *J Am Coll Cardiol* 21:35-44, 1993
 55. Forrest KY, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ: Are predictors of coronary heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study. *Atherosclerosis* 148:159-169, 2000
 56. Maser RE, Wolfson SK, Ellis D, Stein EA, Drash AL, Becker DJ, Dorman JS, Orchard TJ: Cardiovascular disease and arterial calcification in insulin-dependent diabetes mellitus: interrelations and risk factor profiles: Pittsburgh Epidemiology of Diabetes Complications Study-V. *Arterioscler Thromb* 11:958-965, 1991