

Value of Coronary Artery Calcium Scanning by Computed Tomography for Predicting Coronary Heart Disease in Diabetic Subjects

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OBJECTIVE — The South Bay Heart Watch is a cohort study designed to determine the significance of coronary calcium in high-risk asymptomatic patients. This is a report of the relative risk (RR) for outcomes of coronary artery calcium in diabetic and nondiabetic subjects.

RESEARCH DESIGN AND METHODS — A total of 1,312 diabetic and nondiabetic subjects underwent risk factor screening and computed tomography testing for coronary calcium at baseline and were followed clinically for 6.3 ± 1.4 years. End points were either 1) hard events of nonfatal myocardial infarction (MI) or coronary death or 2) any cardiovascular event (nonfatal MI, coronary death, coronary revascularization, or stroke).

RESULTS — The incidence rates of a hard event and any cardiovascular event for diabetic and nondiabetic subjects were 14.5 and 6.1% and 23.8 and 12.2%, respectively ($P < 0.001$). Cox regression analyses of the combined risk relationship of diabetes status and calcium score demonstrated that relative to nondiabetic subjects with low calcium scores (<2.8), diabetic subjects with calcium scores ≥ 2.8 exhibited at least a fourfold increase in the risk of either a hard or any cardiovascular event ($P < 0.001$). Cox regression analyses conducted separately for nondiabetic and diabetic subjects revealed that coronary calcium score risk groups were significantly associated with events in nondiabetic subjects ($RR \geq 2.6$, $P \leq 0.01$), but not in diabetic subjects ($RR \leq 1.7$, $P > 0.05$).

CONCLUSIONS — The risk of coronary heart disease increases with increasing calcium scores and diabetes status. Calcium scores have less prognostic value in diabetic subjects.

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D iabetic subjects experience a disproportionately large number of coronary heart disease events. Although microvascular complications adversely affect quality of life, macrovascular complications are responsible for

most cases of death and disability associated with diabetes. In particular, myocardial infarction, stroke, and sudden coronary death are of great importance (1–3). Standard coronary risk factors appear to carry greater significance in those

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Abbreviations: CABG, coronary artery bypass graft; CT, computed tomography; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; PTCA, percutaneous coronary intervention; RR, relative risk; SBHW, South Bay Heart Watch.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

with diabetes (4,5), but risk stratification using other risk factors does not explain their excess risk.

Pathologic studies have demonstrated a strong correlation between the presence of coronary calcium and the amount of atheromatous plaque (6,7). Furthermore, computed tomography (CT) calcium scanning has been shown to predict subsequent coronary events (7–10). However, few studies have examined the predictive accuracy of calcium measurement in diabetes.

The South Bay Heart Watch (SBHW) is a prospective cohort study designed to determine the relation between radiographically detectable coronary calcium and coronary outcomes in high-risk adults. This is a report of data obtained from the SBHW cohort to determine whether CT coronary calcium assessment is useful for prospectively discriminating diabetic subjects destined to suffer a coronary event.

RESEARCH DESIGN AND METHODS

Subjects and study design

The study design of the SBHW has been previously described (11–13). The cohort was comprised of respondents to a community-based campaign of letters mailed to residents inviting participation in a research project during the period between December 1990 and December 1992. At the time of enrollment, the cohort consisted of 1,461 asymptomatic subjects aged ≥ 45 years with cardiac risk factors. That number was reduced to 1,312 surviving subjects 30 months after enrollment, who then underwent a second medical and risk-factor evaluation, including phlebotomy concurrent with CT examinations for coronary calcium.

Subjects were classified as diabetic if they had a history of being on a diet or medication for diabetes, had been diagnosed with diabetes during a hospital ad-

mission and were discharged on insulin or oral hypoglycemic medications at the termination of that hospital stay, or had a random plasma glucose of ≥ 11.1 mmol/l (200 mg/dl) at the time of recruitment. All subjects gave informed consent at recruitment and again at the time of repeat risk factor assessment and CT scanning.

Procedures and laboratory methods

CT scans were performed within 2 ± 2 days after risk-factor evaluation according to a previously described protocol (11–13).

This protocol uses electron beam scanning (Imatron C-100) with 100-msec exposures triggered at 80% of the relative risk (RR) interval and a 6-mm slice thickness (12,13). A subgroup of 319 participants underwent 6-mm and the alternate 3-mm protocols for purposes of validation. Protocols for scanning and reading were otherwise similar. Prevalence of calcium was 77% using thick and 80% using thin images ($P = 0.05$). The Spearman rank correlation coefficient from the two methods was 0.94, indicating that 88% of the variance in thin-scan calcium score was accounted for by the thick-scan calcium score. These 319 subjects, followed for cardiovascular events for a period of 7 ± 0.5 years, experienced 77 events. Receiver-operating characteristic curves were constructed, and the areas under these curves were calculated for thick and thin image slices. The mean areas (\pm SEM) were 0.672 ± 0.040 and 0.674 ± 0.040 for thick and thin images, respectively (NS).

All subjects were scanned over a bone mineral density phantom (Image Analysis, Columbia, KY). A single cardiologist blind to all clinical outcome and serological data quantitated the amount of coronary calcium in all scans. The scoring software used was the same as that used for the Multi-Ethnic Study of Atherosclerosis (MESA). All scans were rescored in 2001 specifically for this research. This rescoring included a pixel adjustment that used the following formula: new pixel value = (old pixel value – intercept)/slope, where slope and intercept refer to the results of a least-squares linear fit relating standard radiographic densities to the measured mean CT numbers in the calibration phantom scanned under the subjects. The coronary calcium score was calculated according to the formula of Agatston et al. (14), using National Insti-

tutes of Health MESA criteria for a minimum lesion size (4.1 mm^3).

Evaluation of study end points

Subjects were contacted every year for 7 years after CT examinations. Coronary heart disease was assessed using questions concerning intervening hospital admissions. We considered a follow-up attempt successful for surviving subjects when they returned to the clinic or completed a telephone interview and all relevant medical records were obtained for them, and successful for deceased subjects when relevant medical records, a transcribed conversation with the next of kin, a death certificate, or an autopsy report was obtained.

A committee of three board-certified cardiologists reviewed medical records and transcripts of conversations with next of kin, without knowledge of other data, and applied majority rule to determine the occurrence of the hard events of myocardial infarction or coronary death. The additional events of coronary revascularization with either coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PTCA) as well as stroke were likewise ascertained. The committee considered coronary heart disease–related death to have occurred if the death 1) was proven to be attributable to coronary atherosclerosis by autopsy, 2) occurred within 1 h after the onset of prolonged chest pain and occurred suddenly in subjects for whom there was no other known cause, or 3) occurred during hospital admission for acute myocardial infarction. The committee considered stroke to be present if there was a persistent neurological deficit (>48 h) with corroborative imaging evidence by CT or magnetic resonance imaging. Coronary revascularization with either CABG or PTCA was ascertained by review of operative and catheterization reports.

Statistical analysis

Two study end points were defined: the hard end point was the occurrence of nonfatal myocardial infarction (MI) or coronary death, and the any cardiovascular event end point was the occurrence of nonfatal MI, coronary death, revascularization, or stroke.

Baseline characteristics were compared between diabetic and nondiabetic groups using independent Student's *t* tests or Wilcoxon's rank-sum tests for

continuous variables (depending on the normality of the distributions) and χ^2 tests for discrete variables. Baseline factors found to be significantly different between the groups, as well as factors recognized as risk factors for cardiac events, were used as covariates in subsequent analyses.

Cox regression analyses were used to estimate the risk factor–adjusted RRs of the calcium score risk groups for each of the study end points. The dependent variable was the time to the first event (MI or coronary death for the hard end point; MI, coronary death, PTCA, CABG, or stroke for the second end point). Calcium score risk groups were determined according to tertiles of the distribution of calcium scores using the subgroup of nondiabetic subjects without any coronary event. Cox regression analyses were initially conducted for six risk groups (bivariate risk group analyses) defined by diabetes status (nondiabetic, diabetic) and calcium score risk group (low, medium, or high). For the bivariate risk group analyses, the reference group was the subgroup of nondiabetic subjects in the calcium score first tertile. In addition, Cox regression analyses were also used to evaluate the interaction of diabetes status with the calcium score risk groups. If significant interactions were found, Cox regression analyses were then conducted separately for nondiabetic and diabetic subjects (stratified risk group analyses) to determine the prognostic utility of the three calcium score risk groups within each subgroup of study participants. The reference group for the analysis in nondiabetic subjects was the subgroup of nondiabetic subjects in the calcium score first tertile, and for the diabetic subjects was the subgroup of diabetic subjects in the calcium score first tertile.

Finally, we evaluated the robustness of our findings by evaluating the risk-group relations under different design conditions, including different criteria for defining diabetes and different cut points for defining calcium risk groups. All analyses were conducted at the 0.05 significance level.

RESULTS— Of the 1,312 subjects in the study cohort, 1,157 (88%) were males and 155 (12%) were females; 269 (20%) subjects had diabetes and 1,043 (80%) were diabetes-free. The average age was 66 years (range = 48–91 years).

Table 1—Baseline characteristics of diabetic and nondiabetic subjects

Characteristic	Nondiabetic subjects (n = 1043)	Diabetic subjects (n = 269)	All subjects (n = 1,312)	P
Male	939 (90)	218 (81)	1,157 (88)	<0.0001
Age (years)	65.7 ± 7.8	66.4 ± 7.4	65.9 ± 7.7	0.18
BMI	27.4 ± 4.5	28.8 ± 4.9	27.7 ± 4.6	<0.0001
Smoking history				
Current smoker	284 (27)	68 (25)	352 (27)	0.41
Former smoker	535 (51)	150 (56)	685 (52)	
Non smoker	224 (22)	51 (19)	275 (21)	
Alcohol usage	656 (64)	104 (39)	760 (59)	<0.0001
Exercise regularly	676 (69)	170 (64)	846 (68)	0.17
Systolic blood pressure (mmHg)	141.0 ± 19.8	145.1 ± 21.3	141.9 ± 20.2	0.003
Cholesterol (mmol/l)	6.00 ± 1.07	5.71 ± 1.30	5.94 ± 1.13	0.0009
HDL cholesterol (mmol/l)	1.20 ± 0.41	1.05 ± 0.36	1.17 ± 0.41	<0.0001
Triglycerides (mmol/l)	1.94 ± 1.41	2.42 ± 2.49	2.04 ± 1.70	0.002
Calcium score	47.7 (0.00, 254.2)	104.7 (9.4, 433.3)	57.8 (0.00, 285.1)	<0.0001

Data are n (%) or mean ± SD, unless otherwise indicated. Calcium score expressed as median (25th, 75th quartile). Statistical testing used two-sample *t* tests (for continuous variables), χ^2 tests (for discrete variables), and the Wilcoxon rank-sum test for the calcium score. The Welch *t* test was used for variables with unequal variance (cholesterol, HDL cholesterol, triglycerides). To convert cholesterol values to mg/dl, multiply by 38.6; for triglycerides, multiply by 88.5.

Table 1 contrasts baseline characteristics overall and between diabetic and nondiabetic subjects. No significant differences were found for age, smoking status, or exercise ($P > 0.05$). Proportionately more nondiabetic subjects were males and current alcohol drinkers ($P < 0.0001$). Diabetic subjects had significantly greater BMI, systolic blood pressure, and triglyceride levels ($P < 0.005$), whereas nondiabetic subjects had significantly higher levels of total cholesterol and HDL cholesterol ($P < 0.001$). The coronary calcium score for diabetic subjects was statistically significantly greater than that for nondiabetic subjects ($P < 0.0001$). Based on these results, all subsequent analyses controlled for the following risk factors: age, sex, BMI, smoking status, alcohol consumption, exercise, systolic blood pressure, and total cholesterol, HDL cholesterol, and triglyceride levels. A total of 103 subjects had hard events (64 in the nondiabetic group, 39 in the diabetic group), and 191 had any cardiovascular event (127 in the nondiabetic group, 64 in the diabetic group).

Table 2 contrasts the between-group incidence rates for both hard and any cardiovascular events. After adjusting for risk-factor covariates, statistically significant differences between diabetic and nondiabetic subjects were found for both hard and any events ($P \leq 0.001$). The incidence rate for hard events for diabetic compared to nondiabetic subjects was 14.5 vs. 6.1% (RR = 2.32, 95% CI =

1.48–3.64). The incidence rate for any event for diabetic versus nondiabetic subjects was 23.8 vs. 12.2% (RR = 1.78, CI 1.26–2.50). Based on the group of nondiabetic subjects without any coronary event, risk groups for the calcium scores were defined by tertiles as low (<2.8), medium (2.8–117.8), and high (>117.8).

Bivariate risk-group analyses

Figure 1 presents the risk-factor adjusted RRs for the primary and secondary end points according to bivariate risk groups defined by calcium score risk groups and diabetes status. Relative to the reference group (low calcium score and nondiabetic), there was increasing risk of hard events (Fig. 1A) for nondiabetic subjects in the high calcium score group (RR = 2.5, $P = 0.01$). For diabetic subjects, this risk significantly increased for the medium (RR = 4.3, $P = 0.0009$) and high

(RR = 4.3, $P = 0.0003$) calcium score risk groups compared to the reference group. For any cardiovascular event (Fig. 1B), relative to the reference group, there was increasing risk of the secondary end point for nondiabetic subjects for the high calcium score risk group (RR = 3.3, $P < 0.0001$). For diabetic subjects, this risk was significantly increased for the medium (RR = 3.9, $P = 0.0001$) and high (RR = 4.9, $P < 0.0001$) calcium score risk groups compared to the reference group.

Stratified risk group analyses

Multivariate Cox regression analysis for the entire cohort (diabetic and nondiabetic groups) demonstrated a significant interaction between diabetes status and calcium score ($P = 0.0001$ for hard events, $P = 0.01$ for any event). These findings justified conducting stratified analyses separately for nondiabetic and

Table 2—Comparison of incidence rates for events between diabetic and nondiabetic subjects

End point	Incidence rate (%)	RR	95% CI	P
Hard events				
Nondiabetic subjects	64/1,043 (6.1)	1.00	—	—
Diabetic subjects	39/269 (14.5)	2.32	1.48–3.64	0.0002
Any event				
Nondiabetic subjects	127/1,043 (12.2)	1.00	—	—
Diabetic subjects	64/269 (23.8)	1.78	1.26–2.50	0.001

Data are number of subjects with event/total number of subjects. *P* values determined by Cox regression analyses, controlling for age, sex, BMI, smoking status, exercise, alcohol consumption, systolic blood pressure, cholesterol, HDL cholesterol, and triglycerides.

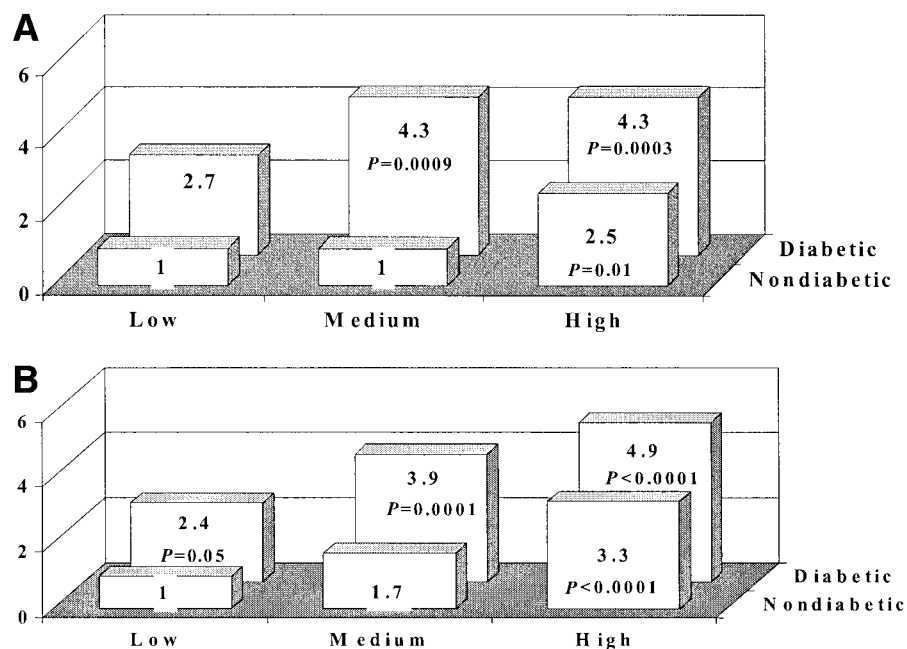


Figure 1—A: RRs of nonfatal MI or coronary death associated with diabetes status and calcium score risk groups (low, <2.8; medium, 2.8–117.8; high, >117.8). B: RRs of nonfatal MI, coronary death, PTCA, CABG, or stroke associated with diabetes status and calcium score risk groups (low, <2.8; medium, 2.8–117.8; high, >117.8).

diabetic subjects to evaluate the risk relation across calcium score risk groups.

Figure 2A presents the risk factor-adjusted RRs for hard events across calcium score risk groups for the nondiabetic and diabetic groups. For the nondiabetic group, after adjusting for risk factors, the high-calcium score risk group was significantly associated with hard events (RR = 2.6, P = 0.01). In contrast, the calcium score risk groups were not significantly related to hard events for the diabetic group (RR ≤ 1.4, all P > 0.52).

Figure 2B presents the risk factor-adjusted RRs for any event across calcium score risk groups for the nondiabetic and diabetic groups. After adjusting for risk factors, the high calcium score risk group was significantly associated with any event for the nondiabetic group (RR = 3.4, P < 0.0001). In contrast, the calcium score risk groups were not significantly related to any event for the diabetic group (RR ≤ 1.7, all P > 0.18).

Robustness of findings

To determine if the finding of decreased RR in diabetic subjects withstood changes in the definitions of calcium score tertiles and the definition of diabetes, we repeated the calculations with varying defi-

nitions. First, we redefined the tertile groups of calcium scores using the full cohort and also using only the diabetic

subjects in the cohort to evaluate if the finding of a relatively low predictive accuracy was robust under these conditions. When the full cohort was used, tertiles were defined as low (<3.7), medium (3.7–138.3), and high (>138.3). When only diabetic subjects were used, tertile groups were defined as low (<21.5), medium (21.5–278.8), and high (>278.8). We also reran the Cox regression analyses for nondiabetic and diabetic subjects using a more strict definition of diabetes (namely, participants were classified as having diabetes if the participant had a history of being on a diet or medication for diabetes or had been diagnosed with diabetes during a hospital admission). These results are shown in Table 3. Note that all of these analyses showed similar trends in both groups (i.e., significant adjusted RRs in higher risk groups for nondiabetic but not for diabetic subjects).

Finally, we also reran the Cox regression analyses for nondiabetic and diabetic subjects using “traditional” cut points for calcium scores (i.e., 0, >0–10, >10–100, >100–400, and >400). Under these conditions, results were similar.

CONCLUSIONS— The pathobiological substrate for coronary events is

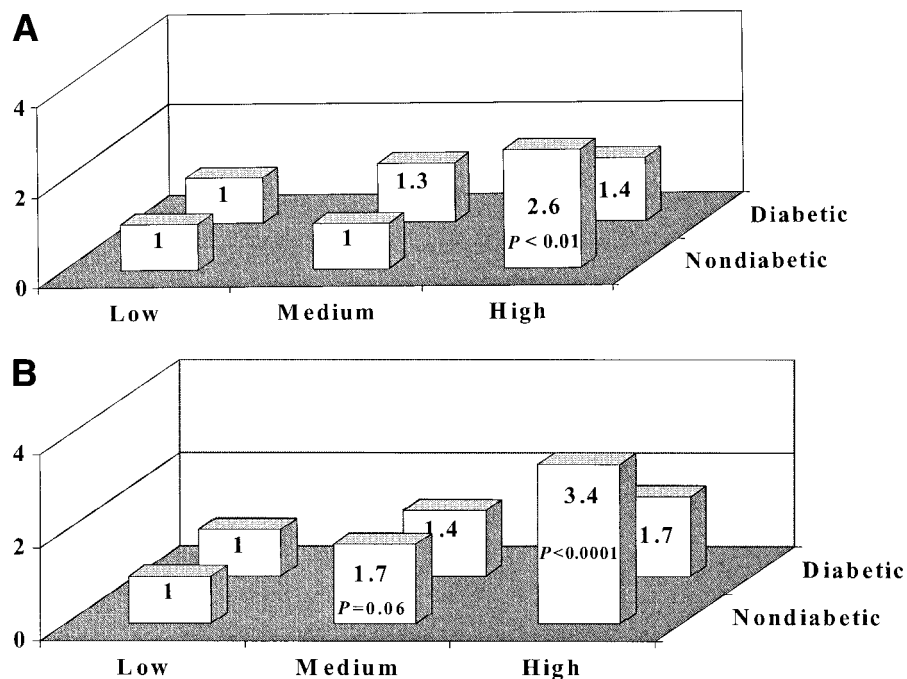


Figure 2—A: RRs, stratified by diabetes status, of nonfatal MI or coronary death associated with calcium score risk groups (low, <2.8; medium, 2.8–117.8; high, >117.8). B: RRs, stratified by diabetes status, of nonfatal MI, coronary death, PTCA, CABG, or stroke associated with calcium score risk groups (low, <2.8; medium, 2.8–117.8; high, >117.8).

Table 3—Robustness of findings: RRs of medium and high tertiles compared to low tertile with different definitions of tertiles and diabetes

Calcium score tertile	Nondiabetic subjects (hard events/any event)			Diabetic subjects (hard events/any event)			
	Tertiles based on nondiabetic subjects	Based on full cohort	Strict definition of diabetes, based on nondiabetic subjects	Tertiles based on nondiabetic subjects	Based on full cohort	Based on diabetic subjects	Strict definition of diabetes, based on nondiabetic subjects
Medium	1.0/1.7	1.2/2.1	1.1/1.9*	1.3/1.4	1.5/1.5	1.8/2.1	1.2/1.1
High	2.6*/3.4*	2.8*/3.6*	2.7*/3.5*	1.4/1.7	1.5/1.8	1.4/1.4	1.4/1.7

* $P < 0.05$ compared to low tertile.

coronary atherosclerosis, which can be identified by radiographic detection of coronary calcium (7–11). Our investigation sought to determine whether coronary calcium assessment might be useful in prospectively identifying diabetic subjects destined to have a coronary event. If so, these individuals could be targeted for aggressive preventive measures.

We found that calcium scores were significantly greater in diabetic than in nondiabetic subjects ($P < 0.0001$), with diabetic subjects experiencing twice as many clinical events. After adjusting for the effects of coronary risk factors, the coronary calcium score was significantly associated with the occurrence of coronary events in nondiabetic subjects. However, in diabetic subjects, there was no significant relation observed between baseline CT calcium scores and the subsequent occurrence of coronary events. In our analyses by tertiles, there were 89–90 diabetic subjects per tertile. Power analyses demonstrated that with this sample size, we were adequately powered to detect “clinically relevant” RRs of 1.8 or greater, with 80% power at the 0.05 significance level. Our analysis of the interaction term demonstrated that the prognostic power of CT calcium scores was less in those with diabetes. Determination of RRs after readjusting the tertile cut points using the entire cohort yielded similar results, indicating the robustness of our findings.

Our results of increased risk and increased calcium in diabetic subjects are consistent with the current understanding of the pathobiology of atherosclerosis, which is accelerated in the metabolic milieu of diabetes. Our findings of increased prevalence of coronary calcium in diabetic subjects are in accordance with the recently reported findings of smaller retrospective cross-sectional studies (15,16). It is probable that atherosclerosis progressed more rapidly in diabetic

subjects; furthermore, the amount of coronary calcium would be expected to change accordingly. However, although this may in part have accounted for the high event rate we observed in diabetic subjects, it did not explain why the relation between CT calcium score and events was not significant in these subjects.

It is conceivable that there were differences in the relative proportions of specific plaque components other than calcium in our diabetic and nondiabetic subjects, and that this might in part explain our finding. In recent years, it has been revealed that plaque disruption is the proximate cause of the greater proportion of coronary events (17–19). The propensity of plaques to rupture is not related to the extent of luminal narrowing, but instead appears to be related more to the specific features of plaque composition (20). In diabetes, coronary arterial compensatory remodeling (21) and distensibility (22) are impaired. Furthermore, a study of coronary atherectomy specimens found that diabetic patients' plaques had more lipid, greater macrophage infiltration, and more frequent overlying thrombus (23). We suggest that our results might be most consistent with the notion that diabetes somehow alters plaque composition in such a way that it is rendered less stable. Calcium is one plaque component that has been hypothesized to render plaques more stable (9,24); it could be that the relative proportion of calcium compared to total plaque was similar, but that the relative proportion of other features (e.g., lipid pools) that could tend to destabilize plaques might have been increased in diabetic subjects. However, our study did not evaluate plaque composition or stability directly, and thus this notion remains speculative.

Limitations

The screening strategy used in this study led to a higher proportion of diabetic sub-

jects in the entire sample than in the population from which they were taken. Because risk in the population was calculated using the Framingham equation and only those over a certain threshold were selected, nondiabetic subjects would have tended to have more other risk factors (e.g., hyperlipidemia, hypertension) than would have occurred in a random sample of nondiabetic subjects in the population. However, although this might have resulted in sampling nondiabetic subjects with higher levels of risk factors when compared to diabetic subjects, this was not generally seen according to the data presented in Table 1. Only total cholesterol was significantly higher in the nondiabetic subjects. Other risk factors such as blood pressure, HDL cholesterol, and triglycerides had a more adverse profile than that found in the diabetic subjects or what one would expect from independent random samples.

Our use of random plasma glucose levels in the definition of diabetes was slightly different from that recommended by the American Diabetes Association (25), as we did not obtain histories of diabetic symptoms. Neither did we have data regarding HbA_{1c}, fasting glucose levels, nor duration of diabetes. However, we do not think that these limitations would have greatly affected our results, as repeating our analyses with a more conservative definition of diabetes had little effect.

In a prior report regarding our entire cohort (13), we found a relatively weaker relation between coronary calcium scores and future events than that reported by others (12). A partial explanation lies in our inclusion of large numbers of diabetic subjects in whom coronary calcium may not accurately predict events. Because diabetes incurs “disease equivalent” risk, which deserves the highest degree of preventive therapy for atherosclerosis, these individuals would not benefit from fur-

ther screening in any case. Thus our finding does not detract from the potential clinical value of coronary calcium screening in general, but rather partially explains our prior, rather disappointing findings.

The CT scanning protocol used for this study involved the use of 6-mm thick slices. This protocol differs from that used in other research and therefore requires validation (see 12,13 and RESEARCH DESIGN AND METHODS for validation). It should be noted that in a study involving only 46 subjects who underwent 6-mm scanning, Callister et al. (26) found lower calcium scores than expected. This may have been because of decreased sensitivity of the 6-mm protocol or an increased false positive rate of the 3-mm protocol. Our current results suggest that, at least regarding incident disease, the two protocols are equivalent.

The subjects were informed via letter of their calcium and risk factor results. This letter stated the calcium score and the fact that the investigators and medical community were unaware of the clinical significance of the score and invited the participants to call the principal investigator with questions. It is possible that such information may have biased the results either toward more invasive interventions or toward fewer hard events (because of risk factor modification).

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