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Prognostic Value of Coronary Artery Calcium Screening in Subjects With and Without Diabetes

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OBJECTIVES The study was done to determine the interaction of coronary artery calcium and diabetes mellitus for prediction of all-cause death.

BACKGROUND Diabetes is a strong risk factor for coronary artery disease (CAD) and is associated with an elevated overall mortality. Electron beam tomography (EBT) provides information on the presence of subclinical atherosclerosis and may be useful for risk stratification.

METHODS We followed 10,377 asymptomatic individuals (903 diabetic patients) referred for EBT imaging. Primary end point was all-cause mortality, and the average follow-up was 5.0 ± 3.5 years. Cox proportional hazard models, with and without adjustment for other risk factors, were developed to predict all-cause mortality.

RESULTS Patients with diabetes had a higher prevalence of hypertension and smoking ($p < 0.001$) and were older. The average coronary calcium score (CCS) for subjects with and for those without diabetes was 281 ± 567 and 119 ± 341, respectively ($p < 0.0001$). Overall, the death rate was 3.5% and 2.0% for subjects with and without diabetes ($p < 0.0001$). In a risk-factor–adjusted model, there was a significant interaction of CCS with diabetes ($p < 0.00001$), indicating that, for every increase in CCS, there was a greater increase in mortality for diabetic than for nondiabetic subjects. However, patients suffering from diabetes with no coronary artery calcium demonstrated a survival similar to that of individuals without diabetes and no detectable calcium (98.8% and 99.4%, respectively, $p = 0.5$).

CONCLUSIONS Mortality from all causes is increased in asymptomatic patients with diabetes in proportion to the screening CCS. Nonetheless, subjects without coronary artery calcium have a low short-term risk of death even in the presence of diabetes mellitus. (J Am Coll Cardiol 2004; 43:1663–9) © 2004 by the American College of Cardiology Foundation

As a marker of atherosclerotic burden, coronary artery calcium has been found to be more prevalent and more extensive in diabetic patients (1–3). The most recent guidelines of the National Cholesterol Education Program recommend that diabetes mellitus be considered a coronary artery disease (CAD) equivalent, owing to the high incidence of atherosclerosis-related events in patients suffering from this ailment (4–8). Despite the high prevalence of coronary artery calcium, it remains to be determined whether screening diabetic patients with electron beam tomography (EBT) to detect subclinical disease improves a physician's ability to predict events. Furthermore, it is unclear whether a patient with diabetes but without detectable coronary artery calcium carries a risk of cardiovascular events similar to that of a subject with no diabetes and no evidence of coronary atherosclerosis. For the purpose of this analysis we utilized the U.S. National Death Registry to verify all-cause mortality in a cohort of 10,377 asymptomatic individuals submitted to EBT screening for coronary calcification between 1996 and 2000 at one clinical center. Survival data were analyzed in subjects with and without diabetes, and survival curves were compared in the two groups according to their baseline coronary calcium score (CCS).

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MATERIALS AND METHODS

Patient selection. We followed 10,377 asymptomatic individuals referred by their primary care physician between 1996 and 2000 for coronary calcium screening with EBT. Individuals were referred for screening based upon the presence of established risk factors for atherosclerosis, and as such were not an unselected cohort representative of the general population. All subjects were initially screened by an internist and had at least one of the following CAD risk factors: diabetes mellitus, systemic hypertension, hypercholesterolemia, current smoking, and a family history of premature CAD. Patients with a prior history of CAD (including hospital admission for chest pain, acute coronary syndromes, or prior coronary revascularization) were excluded.

Data collection. Information regarding the presence of categorical cardiac risk factors was collected in every patient by written questionnaires. Systemic arterial hypertension was defined as a documented history of high blood pressure or treatment with antihypertensive medications. Current smoking or cessation of smoking within three months of testing was defined as positive smoking status. Hypercho-

Abbreviations and Acronyms

CAD = coronary artery disease
CCS = coronary calcium score
CI = confidence interval
EBT = electron beam tomography
ROC = receiver operating characteristic

lesterolemia was defined as known but untreated hypercholesterolemia or current treatment with lipid-lowering medications. Individuals were classified as affected by diabetes if they carried an established diagnosis of diabetes mellitus made by a physician and/or were receiving treatment with insulin or oral hypoglycemic agents. An estimated Framingham risk score was calculated on each patient, and the methodology has been previously reported from this data set (9).

Electron beam tomography. Patients signed an informed consent to undergo screening by EBT and to release their medical records for the purpose of conducting clinical research. The EBT imaging was performed on either an Imatron C-100 or a C-150 scanner (GE-Imatron, South San Francisco, California). Thirty-six to 40 contiguous 3-mm-thick tomographic sections were obtained starting at the level of the carina and extending to the diaphragm with 100-ms scan time per section. Tomographic imaging was electrocardiographically triggered at 60% to 80% of the RR interval. Coronary calcification was defined as a plaque of at least three contiguous pixels (voxel size = 1.03 mm^3) with an attenuation ≥130 HU. Quantitative CCSs were calculated according to the method described by Agatston et al. (10). All EBT scans were reviewed by either one of two experienced investigators (P.R. and T.Q.C.) in random order on a NetraMD workstation (ScImage, Los Altos, California). Because calcium scoring was performed for clinical purposes and not for research purposes it was calculated only once for each patient. Although both intra- and interobserver score variabilities are not available for this study, prior local verification and published evidence revealed a median interscan and interreader variability of 8% to 10% (11,12).

Follow-up procedures. The occurrence of all-cause death was verified by the National Death Index. All screened individuals provided informed consent for follow-up, and our human investigations committee approved procedures for follow-up, including review of medical records. The average follow-up interval between the time of EBT screening and the verification of death via the National Death Index was 5 ± 3.5 years (range 2 to 5 years).

Statistical analysis and estimation of risk. The primary end point for this analysis was time to all-cause mortality. Preliminary comparative analyses included statistical comparison of traditional cardiac risk factors and CCS in both diabetic and nondiabetic individuals. For comparisons of categorical variables, a chi-square statistic was employed. For comparisons of statistical differences in the average age of diabetic and nondiabetic subjects, a univariable analysis of variance test was applied. Both univariable and multivariable Cox proportional hazards survival models were employed to assess time to demise. Initially, cumulative differences in survival between subjects with and without diabetes were compared using an unadjusted (i.e., univariable) Cox proportional hazards model for time to five-year survival. A stratified (by diabetic status) Cox proportional hazards model was employed to compare all-cause survival by CCS for subjects with and without diabetes. In subset analyses of diabetic individuals, stratified Cox models were also employed to calculate all-cause survival by CCS for female, hypercholesterolemic, elderly (i.e., age ≥70 years), and hypertensive diabetic patients. A first-order test for interaction was employed to evaluate survival differences in patients with and without diabetes with a CCS of 0 versus >0.

A multivariable (or risk factor-adjusted) Cox proportional hazards survival model was calculated to evaluate the statistical significance of traditional risk factors (i.e., age, gender, hypertension, hyperlipidemia, smoking, and family history of premature coronary disease) and of CCS in diabetes and no-diabetes subsets. Candidate variables included those with an initial $p < 0.10$ based upon the univariable analysis. The final model included all variables with a $p \leq 0.20$.

Finally, a receiver operating characteristic (ROC) curve was utilized to evaluate the event classification ability for estimated Framingham risk score and CCS in the prediction of all-cause mortality (9).

Table 1. Clinical Characteristics of the 10,377 Asymptomatic Subjects Undergoing Coronary Calcium Screening With Electron Beam Tomography

	Diabetes (n = 903)	No Diabetes (n = 9,474)	p Value
Age	57 ± 10	53 ± 10	< 0.0001
Women	43.0%	40.1%	0.10
Hypertension	63.2%	41.7%	< 0.0001
Family history of premature coronary disease	64.5%	69.1%	0.005
Hyperlipidemia	64.0%	60.1%	0.112
Current smoker	44.1%	39.2%	0.005

Mean ± SD or percent.

RESULTS

Comparison of traditional risk factors. The clinical characteristics of the 10,377 subjects are shown in Table 1 About 10% of the subjects were affected by diabetes mellitus, and men and women were equally represented in either patient cohort. Hypertension and smoking were more prevalent in subjects with diabetes, whereas family history of CAD was less prevalent in this group (Table 1).

All-cause mortality rates in patients with and without diabetes. The Cox survival curves showed that overall mortality was significantly greater (chi-square = 43, $p < 0.0001$) in patients with diabetes than in those without diabetes (Fig. 1). Furthermore, when comparing risk-factor

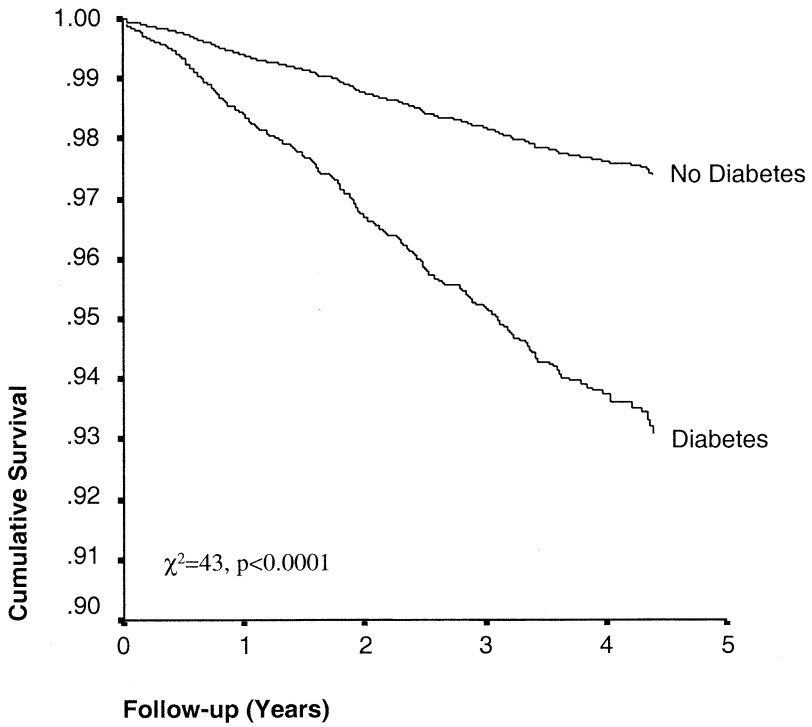

Figure 1. Cox proportional hazards survival model cumulative risk-adjusted mortality by diabetes status.

subsets, all-cause mortality was greater in patients with diabetes (Table 2). Statistically significant differences in all-cause mortality were noted for several patient subsets, including the elderly (i.e., age ≥70 years), hypertensive subjects, and current smokers. As an example, five-year mortality was 15.8% and 7.8% for individuals with diabetes and without diabetes, respectively, 70 years of age and older ($p < 0.05$ for all comparisons of diabetic vs. nondiabetic individuals).

All-cause survival by CCS. Figure 2 shows the survival curves for subjects with and without diabetes mellitus according to the amount of coronary calcium found at the time of EBT screening. As shown, mortality increased with increasing baseline CCS levels for both diabetic and nondiabetic individuals and was highest in subjects with a CCS >400. In a risk-adjusted model, there was a significant interaction of CCS with diabetes ($p < 0.00001$), indicating that for every increase in CCS there was a greater increase in mortality for diabetic compared to nondiabetic subjects.

Five-year all-cause survival was similar for diabetic and nondiabetic individuals with no coronary calcium at the time of EBT screening (Fig. 3) (survival, 98.8% vs. 99.4%, respectively, $p = 0.49$). These similarities were noted despite the greater prevalence of hypertension (59% vs. 35% in nondiabetic subjects, $p < 0.0001$), women (57% vs. 49% in nondiabetic subjects, $p < 0.0001$), and older age (mean, 52 ± 9 vs. 49 ± 9 years in nondiabetic subjects, $p < 0.0001$) in the diabetic patient cohort with a calcium score of 0. Using a first-order test for interaction, no significant differences existed in survival between diabetic subjects and nondiabetic individuals with a calcium score of 0 ($p = 0.19$). The statistical power of this test was: beta = 0.47 for alpha = 0.05.

Mortality with diabetes and other co-morbidities. Table 3 shows a pattern of increasing mortality with higher baseline calcium scores in diabetic subjects affected by other co-morbidities. The trend was evident in diabetic women, hypercholesterolemic subjects, hypertensive subjects, and the elderly (≥70 years of age).

Multivariable models estimating mortality. In a multivariable model, predictors of all-cause mortality in subjects affected by diabetes mellitus were age, systemic hypertension, smoking, and CCS (Table 4). There was a 44% (95% confidence interval [CI] 20% to 80%) increased risk of death for every increase in CCS grouping from 11 to 100 to 101 to 400, 401 to 1,000, and >1,000 ($p = 0.0001$). Individuals without diabetes mellitus demonstrated similar predictors of mortality as did the diabetic subjects. Although hypercho-

Table 2. All-Cause Mortality Rates by Clinical Characteristics in the Study Population

	Diabetes (n = 903)		No Diabetes (n = 9,474)	
	Survivors	Deceased	Survivors	Deceased
Age ≥70 yrs	84.2%	15.8%	92.2%	7.8%
Women	94.8%	5.2%	97.8%	2.2%
Hypertension	92.3%	7.7%	97.2%	2.8%
Family history of premature coronary disease	95.0%	5.0%	98.1%	1.9%
Hyperlipidemia	95.3%	4.7%	98.2%	1.8%
Current smoker	93.0%	7.0%	96.8%	3.2%

$p < 0.05$ for all comparisons of diabetic vs. nondiabetic individuals.

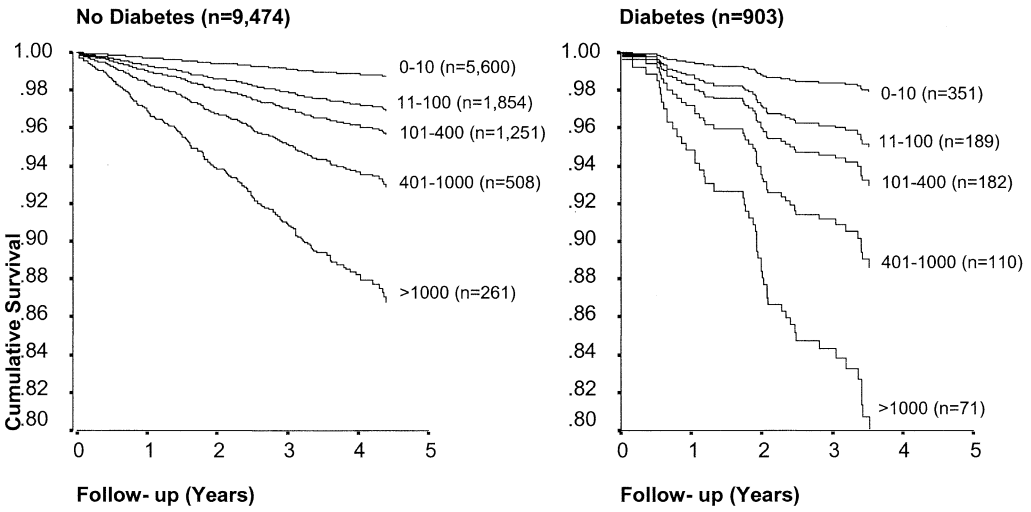

Figure 2. Cox proportional hazards survival (n = 10,377) by electron beam tomography coronary calcium measurements in subjects with and without diabetes mellitus (chi-square = 204, $p < 0.0001$). The number of subjects in each calcium score category is in parentheses.

lesterolemia was not an independent predictor of all-cause death in diabetic patients (Table 4), it was associated with decreased all-cause mortality in nondiabetic subjects (Table 5).

Based upon the Framingham risk equation, all of the 903 diabetic subjects were considered high risk, whereas 62% and 24% of the nondiabetic subjects were intermediate and high risk, respectively ($p < 0.0001$). We then compared the added value of the CCS in estimating all-cause mortality over and above an estimated Framingham risk score by means of an ROC curve. For nondiabetic patients, the C-index for the Framingham risk score was 0.61 (95% CI 0.57 to 0.65, $p < 0.0001$) but increased to 0.70 when CCS was used (95% CI 0.66 to 0.74, $p < 0.0001$). For diabetic patients, the C-index was substantially higher for the CCS (C-index, 0.72, 95% CI 0.64 to 0.79, $p < 0.0001$) when compared with the estimation of mortality based upon the Framingham risk score alone (C-index, 0.50, 95% CI 0.42 to 0.58, $p = 1.0$).

DISCUSSION

Patients affected by diabetes mellitus have been shown to have extensive coronary artery calcium deposits on EBT imaging (1–3). In this large observational study, we showed that the presence of any degree of coronary artery calcium in patients with diabetes mellitus portends a higher risk for all-cause mortality than in nondiabetic patients. Additionally, the absence of coronary artery calcium indicated a low

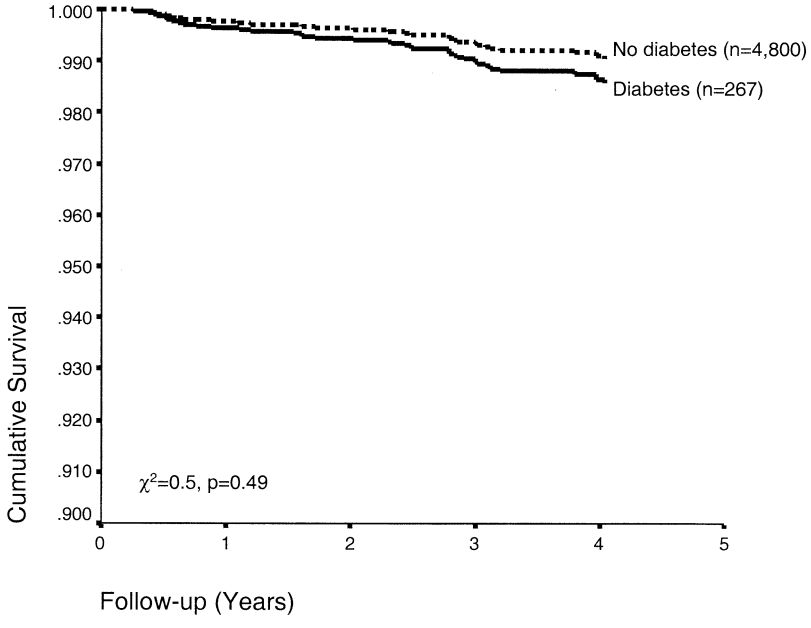

Figure 3. Cox proportional hazards cumulative survival for subjects with and without diabetes mellitus with a calcium score of 0. The number of subjects in each calcium score category is in parentheses.

Table 3. Cox Proportional Hazards 5-Year Survival in Key Diabetic Patient Subsets Undergoing Electron Beam Tomography Coronary Calcium Measurements Including Female, Hyperlipidemic, Hypertensive, and Elderly (≥70 Years of Age) Diabetic Patients

Coronary Calcium Score	0–10	11–100	101–400	401–1,000	>1,000
Female diabetic patients	97.8%	95.6%	93.8%	88.2%	71.4%
	$\chi^2 = 55$, $p < 0.0001$				
Hyperlipidemic diabetic patients	98.2%	96.4%	95.3%	90.7%	79.8%
	$\chi^2 = 54$, $p < 0.0001$				
Hypertensive diabetic patients	97.3%	94.4%	92.0%	86.2%	70.0%
	$\chi^2 = 47$, $p < 0.0001$				
Elderly (≥70 yrs) diabetic patients	94.6%	91.2%	86.1%	79.6%	59.8%
	$\chi^2 = 34$, $p < 0.0001$				

short-term risk of death for diabetic patients as well as subjects without diabetes. Hence, the absence of measurable atherosclerosis appears to be an important modifier of outcome even in the presence of established severe risk factors for atherosclerosis such as diabetes mellitus.

Our clinical experience closely resembles the observations recently made by Kang et al. (13) and Giri et al. (14). In those studies, patients affected by diabetes mellitus who underwent a stress myocardial perfusion single-photon emission computed tomography had a much greater risk of acute coronary events and death than did nondiabetic individuals for any degree of demonstrable perfusion abnormality. Similar data were published by Marwick and colleagues (15) using stress echocardiographic techniques. Taken together, these findings suggest that any extent of disease burden is more dangerous in diabetic patients than in nondiabetic individuals.

Because the risk of CAD-related events in patients with diabetes mellitus is as high as that of individuals with known CAD, diabetes is currently considered a CAD equivalent. In general, the findings on EBT imaging studies corroborate this clinical observation. In fact, the amount of coronary artery calcium detected by EBT in diabetic patients without established CAD is similar to that of nondiabetic subjects with known CAD (16,17). Furthermore, diabetes mellitus abolishes the well-known advantage of women over men in prevalence and extent of coronary artery calcium and atherosclerosis burden (18,19). However, the notion of diabetes as a CAD equivalent may not apply to diabetic subjects without evidence of coronary atherosclerosis by EBT. In this subset, which represented 30% of the diabetic patients in our cohort, the short-term mortality risk was equivalent to that of nondiabetic subjects. These findings imply that coronary calcium screening may identify a subgroup of diabetic patients who are at low risk of death, although nonfatal CAD events are of additional concern and could still occur.

The mechanisms causing the extensive accumulation of calcium in the arterial system of patients affected by diabetes mellitus are largely unknown but are likely multifactorial. Although pathological studies have demonstrated that the amount of calcium per plaque area is similar among diabetic and nondiabetic patients (20), diabetics tend to have a larger atherosclerotic plaque burden (18), likely explaining the observed larger amount of coronary calcium. Recent evidence indicates that advanced glycation end-products induce the expression of genes and enzymes involved in the active calcification processes taking place in the atherosclerotic plaque (21,22). In fact, hyperglycemia induces the expression of the bone morphogenic enzyme osteopontin in vascular smooth muscle cells (22). Osteopontin is in turn capable of inducing the expression of platelet-derived growth factor (22). Hence, hyperglycemia may initiate a pro-atherogenic and pro-thrombotic effect that ultimately results in calcification of the plaque. Vascular calcification in diabetic subjects is not limited to calcification in the subintimal space, but extends to the medial layer of the vessel wall (23,24). Though not associated with typical atherosclerotic processes, this form of calcification also poses a very substantial risk of cardiovascular events in diabetic patients (24) and can contribute to the larger degree of calcification seen in diabetes mellitus.

Diabetes mellitus carries a very high risk for cardiovascular complications; unfortunately, the incidence rates of this ailment and that of obesity and the metabolic syndrome—a precursor of diabetes—are rapidly increasing in

Table 4. Multivariable Model Predicting All-Cause Mortality in Asymptomatic Diabetic Patients Undergoing Coronary Calcium Screening

	Relative Risk Ratio	95% Confidence Intervals	Chi-Square	p Value
Age	1.06	1.03–1.09	15	< 0.0001
Hypertension	3.76	1.59–8.77	9	0.003
Hyperlipidemia	0.72	0.41–1.26	1	0.24
Current smoker	1.76	0.99–3.11	4	0.05
Coronary calcium	1.44	1.16–1.80	10	0.001

Model chi-square = 67, $p < 0.0001$. Calcium categories = 0–10, 11–100, 101–400, 401–1000, >1000.

Table 5. Multivariable Model Predicting All-Cause Mortality in Asymptomatic Nondiabetic Subjects Undergoing Coronary Calcium Screening

	Relative Risk Ratio	95% Confidence Interval	Chi-Square	p Value
Age	1.06	1.04–1.08	52	< 0.0001
Gender	1.25	0.92–1.69	2	0.16
Hypertension	1.41	1.06–1.88	6	0.019
Hyperlipidemia	0.64	0.49–0.85	9	0.002
Current smoker	2.37	1.77–3.17	33	< 0.0001
Family history of premature coronary disease	0.83	0.62–1.11	2	0.20
Coronary calcium	1.36	1.21–1.54	25	< 0.0001

Model chi-square = 252, $p < 0.0001$. Calcium categories = 0–10, 11–100, 101–400, 401–1000, >1000.

both developed and developing countries (25–27). Several facts render an early and accurate diagnosis of coronary artery atherosclerosis desirable in diabetes mellitus: the decrease in cardiovascular mortality in diabetic patients has not matched the decrease seen in the general population (28); diabetic patients are often asymptomatic even with advanced stages of CAD (6,7); and both the complication and mortality rates of diabetic patients with acute coronary events far outweigh that of nondiabetic subjects (29–31). At the same time, recent evidence shows that aggressive medical management of lipids and systemic hypertension in diabetic patients led to a significant reduction in micro- as well as macrovascular disease along with a remarkable reduction in risk of cardiovascular events (32–36). Thus, screening for coronary artery calcium could prove to be a useful tool to risk-stratify asymptomatic diabetic subjects with the ultimate goal to conduct a more or less aggressive therapy tailored to the individual rather than the disease state.

Our findings differ in part from those of Qu et al. (37). Similar to our report, the investigators noted an increased risk of events in diabetic patients compared to nondiabetic subjects in the presence of coronary calcification (37). However, the investigators were unable to prove an interaction between diabetic status and coronary calcium score as we did in our study. Several important differences between our analyses should be noted. Qu et al. (37) studied a smaller cohort (1,312 individuals, 19% diabetic subjects) of high-risk subjects, mostly males and on average 10 years older than our patients. Furthermore, they used an EBT imaging protocol with reduced sensitivity for detection of coronary calcium (38) and chose a combination of cardiovascular outcomes as their end point rather than all-cause mortality. All of the above reasons may have contributed to the substantial differences noted between our studies.

There were a few limitations to our report. First, we utilized self-reported risk-factor categories without continuous variables. We did not collect information that would allow the clear distinction of insulin-dependent and insulin-independent individuals. Nonetheless, coronary calcification is equally increased in the two types of diabetes mellitus compared to the general population (1–3,16,17,19) and risk-factor categories appear to be as robust as continuous variables for appraisal of risk (39). Our patients were referred by primary care physicians and may not have been representative of the general population. We used all-cause mortality as an end point for our study rather than a cardiovascular end point. The use of all-cause mortality may actually reduce the amount of bias in classification of events noted in previous reports (40); it is receiving ever-growing approval as an end point for cardiovascular outcome research (41). Furthermore, the majority of fatal events are cardiovascular in nature in most developed and several developing countries. Of note, studies from three different continents showed that the risk of cardiovascular mortality and all-cause mortality associated with diabetes mellitus is very similar (42–44).

In summary, coronary artery calcification by EBT appears to be a useful tool for risk stratification of subjects suffering from diabetes mellitus. Aggressive medical therapy should be provided in the presence of calcification and potentially intensified according to the degree of coronary calcification. Patients suffering from diabetes mellitus and free of coronary artery calcification are at low risk of death in the short to intermediate time period.

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