

# Progression of Coronary Artery Calcium and Occurrence of Myocardial Infarction in Patients With and Without Diabetes Mellitus

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**Abstract**—Progression of coronary artery calcium, a marker of atherosclerosis, can be slowed with statins, and continued progression of calcium is associated with an increased risk of myocardial infarction. However, it is not known whether statins are effective in slowing calcium progression in diabetes mellitus. In a retrospective study, we examined 1153 nondiabetic and 157 diabetic subjects who underwent sequential electron beam tomography scans at a minimum 1-year interval to assess progression of coronary calcium. A yearly score increase >15% was considered evidence of true progression. The use of statins and occurrence of myocardial infarction were recorded. There was no difference in baseline calcium score between diabetic and nondiabetic patients. Diabetic patients with no coronary calcium on the baseline scans developed it more often than nondiabetic subjects (42% versus 25%;  $P=0.046$ ) during follow-up. Calcium progression was 33% greater in diabetic patients than nondiabetic subjects ( $P<0.001$ ) if no statin therapy was provided and 17.7% greater when statins were used ( $P<0.001$ ). Among the 49 subjects who experienced a myocardial infarction, the calcium score increased on average 20% more in diabetic than nondiabetic patients ( $P<0.001$ ). In logistic models, diabetes mellitus and systemic hypertension were the best predictors of calcium progression (odds ratio, 3.1 and 1.9, respectively), whereas baseline calcium score percentile and statin therapy were the best predictors of infarction. These findings support the notion that diabetes mellitus causes accelerated atherosclerosis, even in the presence of statin therapy, and provide evidence that coronary calcium monitoring is an effective method to assess treatment efficacy. (*Hypertension*. 2005;46:238-243.)

**Key Words:** calcium ■ atherosclerosis ■ diabetes mellitus

Diabetes mellitus is currently considered a cardiovascular disease equivalent because of the high rate of events experienced by patients with this ailment.<sup>1</sup> Indeed, patients with type 2 diabetes mellitus have been reported to have a risk of death from cardiovascular causes 2- to 4-fold higher than individuals without diabetes,<sup>2</sup> and the cardiovascular mortality rate among patients with type 2 diabetes without a previous history of coronary artery disease (CAD) is as high as that of nondiabetic subjects with previous CAD.<sup>3</sup> Therefore, the current recommendations of the National Cholesterol Education Panel III include treatment of dyslipidemia in diabetes to levels as low as those of patients with preexisting coronary heart disease.<sup>1</sup> Noninvasive imaging of the atherosclerotic plaque may offer a means to assess the effectiveness of medical therapy on plaque burden reduction and composition. In the past, disease stabilization and regression were assessed by invasive angiography, and stenosis regression was associated with a substantial reduction in event rates.<sup>4-7</sup> During the past several years, coronary artery calcium (CAC) measured by electron beam tomography (EBT) has evolved into a useful tool for risk prediction,<sup>8-12</sup> and

monitoring of CAC progression over time has been proposed as a tool to follow the evolution of the atherosclerotic plaque burden.<sup>13,14</sup> To further support the utility of this tool, initial evidence indicates that progression of CAC is linked to an unfavorable prognosis.<sup>15,16</sup>

In this retrospective study, we reviewed the data collected in 1310 individuals submitted to sequential EBT scanning, 157 of whom were affected by diabetes, to assess the difference in plaque burden growth in patients with and without diabetes mellitus. We considered 4 different groups: subjects without CAC at baseline; subjects with CAC at baseline who did not receive statin therapy after the initial EBT scan; subjects with CAC at baseline who received statin therapy after the initial scan; and patients with CAC at baseline who experienced a myocardial infarction (MI) after having undergone at least 2 sequential EBT scans a minimum of 12 months apart.

## Methods

### Patient Selection

The medical records of patients who had undergone sequential EBT scans at 2 centers in the United States (Torrance, Calif and Nashville,

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**TABLE 1. Baseline Patients' Clinical Characteristics**

Group	CS=0		No Statins (CS >0)		Statins (CS >0)		MI (CS >0)	
	No DM (381)	DM (36)	No DM (312)	DM (51)	No DM (421)	DM (60)	No DM (39)	DM (10)
Age ±SD	49±9.2	46±8.0	61±8.0	65±7.2	59±8.9	59±7.3	57±7.5	60±4.4
<i>P</i> value	0.040		0.001		NS		NS	
Men (%)	49	33	76	59	72	53	79	70
<i>P</i> value	NS		0.017		0.005		NS	
Hypertension (%)	40	83	48	65	50	68	51	60
<i>P</i> value	0.000		0.025		0.006		NS	
Hypercholesterolemia (%)	66	56	52	63	88	85	74	80
<i>P</i> value	NS		NS		NS		NS	
Smoking (%)	31	36	32	33	34	48	41	50
<i>P</i> value	NS		NS		0.033		NS	
Statin therapy (%)	12	36	0	0	100	100	87	90
<i>P</i> value	0.003		NS		NS		NS	

*P* values compare the prevalence of categorical risk categories among subjects identified according to diabetic status and baseline calcium score. CS indicates calcium score; DM, diabetes mellitus.

Tenn) were reviewed. Patients with previous history of cardiovascular disease and renal failure were excluded because of the high prevalence of CAC and rapid rate of CAC accumulation in these patients. Those whose charts were reviewed were mostly ( $\approx 95\%$ ) physician-referred subjects with a minimum of 1 risk factor for CAD (Table 1). We identified 157 diabetic patients and 1153 nondiabetic subjects with the above characteristics; of the 1310 total patients, 64% were men. The mean age for the entire cohort was  $56 \pm 10$ . The average follow-up period was 2.2 and 2.7 years for diabetic and nondiabetic subjects, respectively. Information on risk factors for CAD and medical treatment provided for such factors was collected by means of detailed questionnaires distributed at the time of the baseline EBT scan. Hence, no continuous variables were available for analysis because risk categories and dichotomous information regarding medication use were collected. At the time of scanning, patients gave consent to use their imaging data for research purposes, and the research protocol was approved by the local internal review boards.

### EBT Protocol

Patients underwent EBT scanning at 2 centers in the United States that used identical equipment (C-150 GE/Imatron) and imaging protocols. Prospective electrocardiographic triggering of the EBT gun was used and set at 60% to 80% of the R-R interval. Single slice volume mode was used and imaging occurred at a speed of 100 ms per slice during a single end-expiratory effort for a total imaging time of 30 to 35 s. The tomographic slice thickness and table increments were kept at 3 mm, and 30 to 40 slices were obtained from the bronchial carina to the diaphragm to cover the entire heart span. A total radiation dose of 1.0 mSv was administered with each scanning session. A calcium volume score (CVS) was calculated to quantify the extent of CAC as described previously.<sup>17</sup> This method was used because of its superior reproducibility for sequential computed tomography (CT) scanning.<sup>17</sup> The CVS unit corresponds to 1/1000 mL, and for simplicity in this article, we present the numerical value alone without the attached unit symbol. A minimum baseline CVS of 20 was required to calculate the relative score change over time. Obviously, a relative change could not be calculated in patients with no CAC at baseline, and very small calcium scores have been reported to show low reproducibility.<sup>18</sup>

### Statistical Methods

The index MI should have occurred after the performance of a minimum of 2 EBT scans at least 1 year apart. This allowed us to relate the CVS change measured on sequential scanning to the hard

event rather than having to consider it a consequence of the event. A positive or negative yearly score change of  $>15\%$  was considered evidence of true change and not a measurement error. This threshold is based on a previous analysis of interscan variability of the CVS<sup>17</sup> and has been used in previous studies on progression of CAC.<sup>15,16</sup>

For each patient between 30 and 80 years of age, a sex- and age ( $\pm 2$  years)-specific percentile was calculated by comparison with patients from a database of 7761 asymptomatic patients who had CAC on EBT scanning (percentile=0, when score=0).

In each case, the effect of diabetes mellitus was tested by using Welch's *t* test to compare absolute and relative change in score and change in percentile after adjusting for risk factors from the best scientific models derived without diabetes mellitus as a risk factor. These models were chosen by minimizing the Bayesian Information Criterion (BIC) among the best models from each best subset regression analysis.<sup>19–20</sup> We accommodated intergroup heteroscedasticity by using Welch's *t* test; *P* values for these pairwise comparisons are referred to as "marginal" whenever they correspond to Bonferroni family error rates  $>0.05$  (2-sided).

Stepwise logistic regression was used to find the best model for the occurrence of score progression ( $>15\%$  annualized change) among patients with CAC at baseline and for the conversion to positive scores among patients without CAC at baseline. The final model was selected by minimizing BIC subject to appropriate goodness-of-fit criteria (Hosmer–Lemeshow  $\chi^2 P > 0.15$ ; percent concordant  $>65\%$ ). A similar procedure was used to select the best logistic model for MIs; the follow-up time was not a significant predictor in this logistic regression.

## Results

### CVS Progression Within Diabetic and Nondiabetic Patient Groups

The baseline clinical characteristics are shown in Table 1. The baseline CVS and the unadjusted yearly CVS change for diabetic and nondiabetic subjects in each subgroup are shown in Table 2 and represented in Figure 1. In diabetic and nondiabetic subjects, the baseline CVS of those who did not receive statins tended to be smaller than that of patients who received statins and those who experienced an MI during follow-up but did not generally reach statistical significance.

Statin therapy significantly slowed the progression of absolute, relative, and percentile CVS compared with no treatment among diabetic patients and nondiabetic subjects

**TABLE 2. Baseline and Annualized Change in Calcium Score**

Variables	Patients Without Diabetes Mellitus				Patients With Diabetes Mellitus			
	CS=0	CS>0	CS>0	MI	CS=0	CS>0	CS>0	MI
Calcium score								
Treatment	—	No statins	Statins		—	No statins	Statins	
No. of patients	(381)	(312)	(421)	(39)	(36)	(51)	(60)	(10)
Baseline score	0	285±426	350±541	445±566	0	275±402	398±724	411±352
% Score change	—	17±26*	8.3±23.4*†	21±9.4†	—	51±38*	24±36*	42±20
Absolute score change	1.1±2.9	72±153‡	45±86 ‡§	136±160§	3.8±5.9	93±112‡	38±83‡	139±108
Baseline percentile	0	61±22	70±21†	74±24	0	57±25*	73±19*	73±18
Percentile change	2.2±5.2	3.0±4.9*	0.8±4.4*§	2.7±3.0§	5.4±7.4	4.4±4.0*	1.1±4.2*	3.6±3.5

The annualized change in absolute, relative calcium score, and calcium score percentile shown in this table are not risk adjusted. Subjects are identified according to diabetic status and baseline calcium score.

Values are expressed as mean ±SD. *P* values represent within-group comparisons.

CS indicates calcium score.

\*†*P*<0.001; ‡*P*=0.005; §*P*=0.001; ||*P*=0.004.

(Table 2). Furthermore, among patients receiving statins, the progression of CVS was greater in patients who experienced an MI than among all others who received statins (27±15% versus 10±26%; 95% confidence interval [CI] for difference, 11%, 22%; *P*=0.000). On the contrary, statin-untreated subjects and MI patients showed a similar CVS progression (Table 2). Of interest, 87% of the nondiabetic subjects and 90% of the diabetic patients who experienced an MI were receiving statins during the months leading to the acute coronary event. Hence, it would appear that some patients may escape the beneficial effects of statins on the atherosclerotic plaque, with continued accumulation of disease in the vessel wall and an attendant increased risk of events.

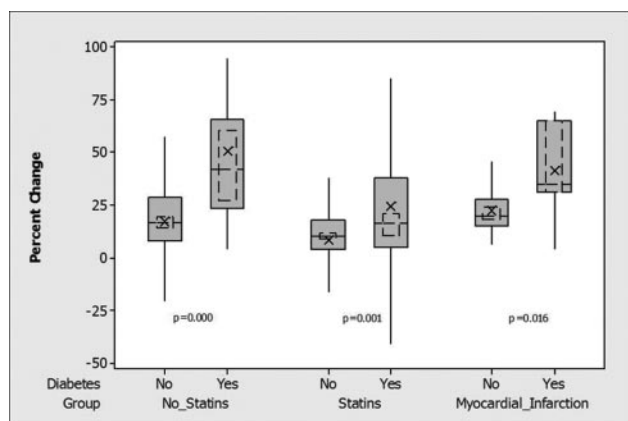
### Comparison of Calcium Score Progression Between Diabetic and Nondiabetic Patients

Several baseline clinical characteristics were significantly different between diabetic and nondiabetic patients (Table 1). Therefore, risk adjustment was necessary when comparing CVS progression between groups. Whereas Figure 1 presents the unadjusted CVS change in various categories of diabetic

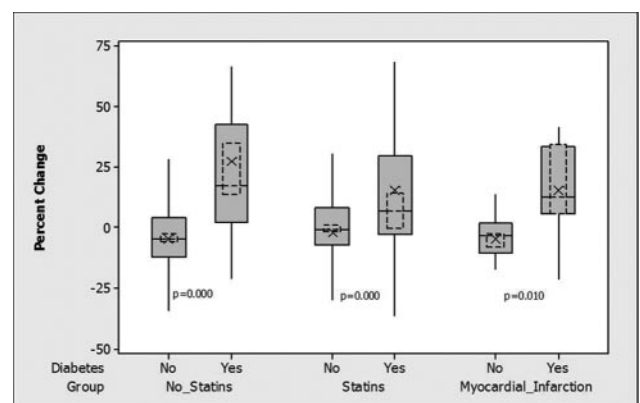
and nondiabetic subjects, Figure 2 shows the theoretical expected difference between diabetic and nondiabetic patients once all other risk factors have been adjusted for.

### Event-Free Subjects Without Coronary Calcium on Baseline Exams

In this category, we included 36 diabetic patients and 381 nondiabetic subjects. Diabetic patients developed CAC more frequently than nondiabetic subjects (42% versus 25%; *P*=0.046; 2-sided 95% CI for difference in proportions, 3% to 34%). After correcting for other risk factors, the odds ratio for converting to a positive score for diabetic relative to nondiabetic subjects was 3 (95% CI, 1.4 to 6.4). Furthermore, the absolute score progression was significantly greater in diabetic patients than in nondiabetic subjects, with an average difference 2.8 points higher per year for diabetic subjects (*P*=0.008; 2-sided; 95% CI, 0.8 to 4.8). Similarly, the CVS percentile change per year was ≈3.2 percentile points higher for diabetic patients relative to nondiabetic subjects (*P*=0.014; 95% CI, 0.7 to 5.7) after adjusting for other risk factors. The best predictors of absolute CVS progression were age and diabetes mellitus (*P*<0.001 for both).



**Figure 1.** Yearly risk-unadjusted relative coronary calcium score change in groups identified by diabetic status and treatment with statins. Boxplots include the mean (X) and the 95% CI for the median (—). All comparisons between diabetic and nondiabetic patients were statistically significant (*P*=0.000, 0.001, and 0.016, respectively).



**Figure 2.** Yearly risk-adjusted relative coronary artery calcium score change in groups identified by diabetic status and treatment with statins. Boxplots include the mean (X) and the 95% CI for the median (—). All comparisons between diabetic and nondiabetic subjects were statistically significant (*P*=0.000, 0.000, and 0.010, respectively).

### Event-Free Subjects With Coronary Calcium on Baseline Exams and No Subsequent Statin Therapy

In this group, 54% of the 312 nondiabetic subjects and 90% of the 51 diabetic patients showed a CVS progression defined as a >15% per year increase (Fisher's exact test;  $P=0.000$ ).

After adjusting for other risk factors, the relative change in calcium score was 32% greater in diabetic than nondiabetic patients (Figure 2;  $P=0.000$ ; 95% CI, 22% to 43%). However, there was no significant difference in progression of absolute and percentile scores per year ( $P=0.26$  and  $P=0.20$ , respectively) between patients with and without diabetes. Age, diabetes mellitus, hypertension, and baseline percentile rank of CVS were associated with relative CVS progression ( $P<0.05$ ).

### Event-Free Subjects With Coronary Calcium on Baseline Exams and Subsequent Statin Therapy

The event-free subjects with coronary calcium on baseline exams and subsequent statin therapy group comprised 60 diabetic and 421 nondiabetic patients. Among the diabetic patients, 50% demonstrated a CVS progression of >15% per year, whereas this level of CVS growth was recorded in 35% of the nondiabetic subjects ( $P=0.028$ ). After adjusting for other risk factors, the relative CVS progression was significantly different between the diabetic and nondiabetic patients (Figure 2), whereas the absolute and percentile change were not. The adjusted difference in progression between diabetic and nondiabetic patients was 17.7% per year (95% CI, 8.5% to 26.9%;  $P=0.001$ ). Diabetes mellitus was the only variable to be significantly associated with relative CVS progression ( $P<0.001$ ).

### MI Patients

All MI patients had CAC on the baseline scan, highlighting the importance of CAC, or the absence thereof, as a marker of coronary risk. Ten of 157 diabetic patients (6.4%) and 39 of 1153 nondiabetic subjects (3.4%) experienced an MI during follow-up ( $P<0.001$ ). Of the 10 diabetic patients, 9 (90%) were receiving statins, and all of them showed a CVS increase of >15% per year. Among the 39 nondiabetic subjects, 34 (87%) received statins, and of these, 24 (71%) showed a CVS progression of >15% per year. The relative change in CVS was 20% greater in diabetic than nondiabetic patients (95% CI, 6.2% to 33.8%;  $P=0.000$ ), after correcting for other risk factors (Figure 2). The progression of absolute and percentile CVS was not significantly different. The best predictor of relative change in CVS was again diabetes mellitus.

### Logistic Regression for Predictors of Yearly Calcium Score Change >15%

Among patients with CAC at baseline, the best logistic model showed that diabetes (odds ratio, 3.1; 95% CI, 2.0 to 4.8;  $P<0.001$ ) and hypertension (odds ratio, 1.9; 95% CI, 1.4 to 2.5;  $P<0.001$ ) were significantly associated with true progression (relative annual score CVS change >15%; Table 3). Baseline age, statin therapy, and baseline CVS percentile were all associated with lower odds of progression. The

**TABLE 3. Best Logistic Model for Prediction of Calcium Score Progression**

Variable	Coefficient	Odds Ratio	Odds 95% CI
Intercept	4.07		
Diabetes mellitus	1.13	3.1	2.0–4.8
Hypertension	0.65	1.9	1.4–2.6
Baseline age	−0.050	0.95	0.93–0.97
Statin therapy	−0.83	0.44	0.32–0.59
Baseline CAC percentile	−1.76	0.17	0.09–0.34

Progression is defined as >15% yearly increase among patients with coronary artery calcium at baseline. All coefficients are significant and  $P<0.001$ .

receiver operator characteristic curve (ROCC) area for this model was 0.70.

### Logistic Regression for Predictors of MI

The best predictors for MI were the baseline CV percentile (odds ratio, 1.02 [ie, risk increase of 2% per percentile point increase]; 95% CI, 1.01 to 1.03;  $P=0.001$ ) and treatment with statins (odds ratio, 5.6; 95% CI, 2.3 to 13.7;  $P<0.001$ ). This model had an ROCC area of 0.79. None of the traditional risk factors had significant incremental value when added to the model (including diabetes;  $P=0.15$ ).

### Discussion

In this retrospective study, we showed that diabetic patients accumulate CAC faster and to a larger extent than nondiabetic subjects. Indeed, our data indicate that diabetes is the single most important predictor of CAC increase for patients receiving and not receiving statins and for those experiencing an MI. Because CAC is an accurate marker of atherosclerotic disease, our findings suggest that atherosclerosis progression is accelerated in diabetes mellitus. Interestingly, treatment with statins was a predictor of slower progression of CAC but also a marker of increased risk of MI. Hence, statins may reduce CAC progression, but in this observational analysis, they were a proxy of risk, likely because they were administered to patients at higher cardiovascular risk.

Our study highlights a few interesting points. The main findings support the notion that progression of atherosclerosis and effectiveness of therapy can be assessed by noninvasive imaging modalities that measure changes in CAC over time. Additionally, they provide further evidence that treatment with statins may slow progressive CAC accumulation. Finally, our data confirm previous published evidence<sup>21</sup> that high baseline CVS percentiles predict the occurrence of MI, likely because they reflect the presence of an accelerated atherosclerosis process.

There are few published reports on progression of CAC and none specifically addressing progression of CAC and outcome in diabetes mellitus. Preliminary evidence indicates that faster and greater CAC accumulation is associated with a higher risk of MI in the general population.<sup>15,16</sup> In the current study, the progression of CAC was similar in patients experiencing an MI, most of whom received statins, and subjects not receiving statins in diabetic and nondiabetic subjects. Hence, the beneficial effect of statins in curbing



atherosclerosis development and progression may be reduced in patients bound to experience a coronary event and in diabetic patients, as we have shown previously in a cohort of patients treated with statins and followed for 3 years after a screening EBT.<sup>16</sup>

Several mechanisms may explain the association of diabetes mellitus with accelerated CAC deposition in the arterial wall. Diabetic patients tend to have a larger atherosclerotic plaque burden than nondiabetic subjects matched for other risk factors,<sup>22</sup> and this may partly explain the large amount of CAC noted in diabetic subjects in previous reports.<sup>23–25</sup> Advanced glycation end-products induce the expression by vascular smooth muscle cells of genes and enzymes actively involved in the calcification process of the atherosclerotic plaque such as osteopontin.<sup>26,27</sup> In turn, osteopontin is capable of inducing the expression of platelet-derived growth factor.<sup>27</sup> Hence, hyperglycemia can initiate a proatherogenic and prothrombotic cascade that ultimately results in calcification of the vessel wall. Furthermore, diabetes mellitus is associated not only with atherosclerotic calcification in the subintimal space, but also with calcification of the tunica media of the vessel wall,<sup>28,29</sup> which also poses a substantial risk of cardiovascular events in these patients.<sup>29</sup>

Our results are partly discordant with those published by Beishuizen et al.<sup>30</sup> These investigators used sequential carotid artery intima-media thickness (IMT) measurements to assess the effect of statin therapy compared with placebo in 250 type 2 diabetes patients. At the end of 2 years of follow-up, there was no difference in the progression of carotid artery IMT, although the number of cardiovascular events was significantly smaller ( $P=0.006$ ) in patients treated with statins. The findings by Beishuizen et al.<sup>30</sup> were therefore consonant with those of the Heart Protection Study<sup>31</sup> and the Collaborative Atorvastatin Diabetes Study (CARDS),<sup>32</sup> in which statins significantly reduced events in diabetes. The reason there was a difference in imaging end points between the above-mentioned IMT study and our CT-based study is unclear. However, 2 main characteristics distinguished the studies: ours was retrospective and Beishuizen et al.'s<sup>30</sup> was prospective, and the changes in plaque burden at the level of the carotid and coronary arteries may follow different temporal patterns and not reflect the same pathobiological events.

There were several limitations to this study. The patients were physician referred, and the risk factors were self-reported and categorical. Of note, a modification of the Framingham risk scoring method uses risk categories<sup>33</sup> with results similar to those obtained with continuous variables. Furthermore, educated individuals have been shown to be reliable when self-reporting risk factors.<sup>34,35</sup> We had no information on body mass index and the presence of the metabolic syndrome. We did not conduct a prospective study with carefully controlled doses of statins, and the LDL level of patients taking statins and those experiencing an MI were not available. Nonetheless, the same proportion of diabetic and nondiabetic individuals were receiving statins when experiencing an MI. Finally, although the difference in CVS progression was significant in various subgroups, the CIs were large, especially in the diabetic patients. This was likely because of the small number of patients in the diabetic

subgroups as well as the inherent biological and test variability.

## Perspectives

Diabetic patients demonstrate a greater CAC accumulation than nondiabetic subjects, and although statins slow progression of CAC, they appear less effective in diabetes mellitus. Furthermore, disease progression is significantly greater in patients who experience an MI during follow-up compared with event-free survivors. Ultimately, atherosclerosis imaging may become very useful to assess effectiveness of medical therapy and motivate diabetic patients to adhere to risk-modifying therapies more strictly with the goal to improve overall outcome. A large prospective study with accurate collection of continuous variables in a similar population of patients will be important to confirm our preliminary observations.

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