Rates and Determinants of Coronary and Abdominal Aortic Artery Calcium Progression in the Veterans Affairs Diabetes Trial (VADT)

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OBJECTIVE — To determine the predictors of progression of calcified atherosclerosis and the effect of intensive glycemic control on this process in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — As part of the Risk Factors, Atherosclerosis, and Clinical Events in Diabetes (RACED) substudy of the Veterans Affairs Diabetes Trial (VADT), 197 and 189 individuals with type 2 diabetes received baseline and follow-up computed tomographic scans for measurement of coronary and abdominal artery calcium, respectively. Standard and novel risk factors were assessed at baseline, and progression of calcified atherosclerosis was determined by several methods. Progression was defined both as a categorical (square root increase of volumetric scores $\geq$2.5 mm^3) and continuous variable. In addition, annualized percent change of volume scores was determined.

RESULTS — After an average follow-up of 4.6 years, >75% of individuals demonstrated coronary (CAC) and abdominal artery calcification (AAC) progression. Progression increased with higher baseline calcium categories but was not influenced by standard risk factors. However, the albumin-to-creatinine ratio (ACR) ($P = 0.02$) and lipoprotein-associated phospholipase A_2 (Lp-PLA_2) ($P = 0.01$) predicted progression of CAC, and these results were not altered by adjustment for age and other traditional risk factors. Treatment assignment (intensive versus standard) within the VADT did not influence CAC or AAC progression, irrespective of baseline calcium category.

CONCLUSIONS — In patients with long-standing type 2 diabetes, baseline CAC, Lp-PLA_2, and ACR predicted progression of CAC. Intensive glycemic control during the VADT did not reduce progression of calcified atherosclerosis.

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Atherosclerosis is accelerated in patients with type 2 diabetes and underlies their higher incidence of cardiovascular disease (CVD) events. Noninvasive imaging of atherosclerosis, as measured by coronary (CAC) and abdominal aortic artery calcification (AAC), provides a useful tool to assess coronary and systemic atherosclerosis burden. Although both CAC and AAC scores have been shown to be strong predictors of subsequent cardiovascular morbidity and mortality (1,2), only a few studies have investigated the association of calcium progression with future events (3,4), and there is less certainty about the implications of progression of vascular calcification (5). In a study of asymptomatic subjects, CAC progression $\geq$15% was a strong predictor of future myocardial infarction (4). In addition, monitoring of CAC and AAC progression has been suggested as a possible method for assessing the treatment efficacy of medicines to reduce CVD risk (6,7). Therefore, an understanding of the determinants of progression of vascular calcium may provide insight into atherogenesis and development and treatment of CVD.

Although the relationship of risk factors with extent of vascular calcification is relatively well recognized, determinants of progression, particularly in type 2 diabetes, have been less well studied. The large Multi-Ethnic Study of Atherosclerosis (MESA) reported that most standard cardiovascular risk factors were modestly associated with progression of CAC (8) in individuals without known CVD, and diabetes and the baseline calcium score were strong predictors of CAC progression (8). In patients with diabetes, baseline CAC, blood pressure, central adiposity, urine albumin-to-creatinine ratio (ACR), and suboptimal glycemic control have been reported as predictors of CAC progression (9–11). However, AAC progression has been investigated only in patients with end-stage renal disease (12). In addition, although there are strong correlations between cross-sectional measures of CAC and AAC and they share associations with several standard risk factors, clear differences in association of risk factors with the extent of CAC and AAC exist (13). Whether determinants of CAC and AAC progression differ in those with or without type 2 diabetes is not known, as previous studies have not addressed this question within the same cohort. Moreover, although mounting evidence supports the role of inflammation in atherogenesis, the relationship of subclinical inflammatory markers with the burden and progression of calcified atherosclerosis is still unclear (14). Finally, although the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) showed that intensive glycemic treatment was associated with lower incidence of CVD over time (15),

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the effect of intensive glycemic control on progression of calcified atherosclerosis in type 2 diabetes has not been directly examined.

In this prospective VADT substudy, we characterized the pattern of both CAC and AAC progression in older patients with long-standing type 2 diabetes. In addition, we determined the relationship of both standard and novel inflammatory risk markers (C-reactive protein, interleukin-6 [IL-6], adiponectin, and lipoprotein-associated phospholipase A_2 [Lp-PLA_2]) with CAC and AAC progression. Finally, we provide the first report of the effect of intensive glycemic control on progression of CAC and AAC in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Data for this study use baseline examinations and follow-up imaging from participants in the Risk Factors, Atherosclerosis, and Clinical Events in Diabetes (RACED) study, which is a seven-site substudy (1) of the VADT. The VADT study design, exclusion/inclusion criteria, and study measures and activities have been described in detail previously (16), and further information is provided in the supplementary material (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc10-1388/DC1). Of the 301 subjects participating in the RACED study with both CAC and AAC scans at baseline, 197 subjects completed follow-up CAC scans and 189 subjects completed follow-up AAC scans. The main reasons for not obtaining follow-up scans in the other RACED participants included participant relocation, elective withdrawal from study, illness, or death. However, there were no significant differences in baseline characteristics between the subjects with no follow-up scans and those with repeat scans at follow-up (Table 1).

Table 1—*Baseline characteristics*

	With scans		
	Standard	Intensive	Without scans
n	104	93	104
Standard risk factors			
Age (years)	61 ± 9	61 ± 9	61 ± 9
NHW (%) vs. others	73	61	62
Smoker (%)	14	12	18
Hypertension (%)	77	84	80
Prior CVD (%)	37	37	39
BMI (kg/m^2)	31.2 ± 4.3	31.4 ± 4.2	31.4 ± 4.5
Duration (years)	12 ± 8	13 ± 8	12 ± 8
A1C (%)	9.2 ± 1.3	9.2 ± 1.4	9.5 ± 1.5
Total cholesterol (mg/dl)	178 ± 38	183 ± 42	179 ± 33
LDL cholesterol (mg/dl)	100 ± 31	108 ± 32	106 ± 29
HDL cholesterol (mg/dl)	36 ± 11	38 ± 11	36 ± 10
Triglycerides (mg/dl)	167 (126–266)	156 (117–208)	163 (113–233)
Total cholesterol-to-HDL ratio	5 ± 2	5 ± 1	5 ± 2
Novel risk factors			
ACR (mg/g)	21 (7- 83)	14 (4–36)*	18 (6–55)
C-reactive protein (mg/l)	3.1 (1.7–5.1)	2.5 (1.4–5.8)	3.3 (1.6–7.8)
IL-6 (pg/ml)	3.2 (2.1–5.1)	2.7 (1.8–5.7)†	3.3 (2.3–4.8)
Adiponectin (mg/l)	5.1 (3.1–7.9)	4.7(2.9–7.5)	5.7 (3.5–9.4)
Lp-PLA_2 (ng/ml)	294 (241–351)	284 (35–338)	289 (241–362)
Baseline CAC score	239 (17–808)	267 (27–981)	301 (23–849)
Baseline AAC score	917 (125–3,508)	848 (189–4,401)	1,674 (193–4,442)

Data are means ± SD, medians (25%–75%), or %. *$P < 0.05$; †$P < 0.01$ vs. standard group.

Laboratory methods

Lp-PLA_2 mass was measured by an enzyme immunoassay (PLAC test; diaDexus) in plasma with intra-assay and interassay coefficients of variation ranging from 4% to 6% and 6% to 9%, respectively. Additional laboratory methods are provided in supplementary material.

Assessment of coronary and abdominal artery calcium scores

Coronary and abdominal aortic calcium were determined by using either electron beam or multidetector computed tomographic cardiac scanning as described (1,17). The volumetric score as described by Callister et al. (18) was used to assess progression of vascular calcium.

Definitions of progression

Progression of vascular calcium was determined using three different approaches. First, progression was calculated as the difference between the square root (dSQRT) transformation of the follow-up and baseline volumetric calcium scores (19). Second, progression as a dichotomous variable was defined as present when the dSQRT of volume scores was ≥2.5 mm^3, as this cutoff provides an estimate that is unbiased with respect to baseline calcium (20). Finally, for comparison with earlier studies of calcium progression, the annualized percent change in volumetric calcium scores was also calculated (3). Additional details are provided in the supplementary material.

Statistical analysis

Statistical analyses were performed with the SAS statistical package (release 9.1; SAS Institute, Cary, NC). Means ± SD, medians (25–75%), and proportions are reported. Between-group differences in normally distributed continuous variables were assessed with *t* tests, Mann-Whitney *U* tests were used for variables with skewed distributions, and χ^2 tests were used for proportions. To determine predictors of progression, univariable and multivariable linear regression analyses were performed separately for the two dependent variables (dSQRT of CAC and AAC). Predictor variables with skewed distributions were log-transformed to approach a normal distribution. Sex was not included as one of covariates, because only 7% ($n = 14$) of the study population were women. With exclusion of women from the analyses, the results did not change appreciably. To assess the possibility of effect modification, pairwise interaction terms of predictor variables were evaluated. However, none of the interaction terms were significant and, therefore, were not included in the final models.

RESULTS

Baseline characteristics

The study population included 197 subjects with a mean age of 61 ± 9 years, diabetes duration of 12 ± 8 years, BMI of 31 ± 4 kg/m^2, and A1C of 9.2 ± 1.3%. Of the subjects, 68% ($n = 133$) reported

non-Hispanic white (NHW) ethnicity/race, and other categories (others) included Hispanic whites ($n = 32$), African Americans ($n = 24$), and Asians or those of mixed races ($n = 8$). The majority had a history of hypertension (81%) and 37% had prior CVD. Median (25–75%) baseline CAC and AAC scores were 258 (18–872) and 922 (173–3,841), respectively. Except for slightly lower urinary ACR ($P < 0.02$) and IL-6 ($P < 0.01$) levels in the intensive treatment group, there were no significant differences between the two treatment groups at baseline (Table 1).

Table 2—*Multivariable linear regression models for predictors of CAC progression*

	Regression coefficients				
	Model 1	Model 2	Model 3	Model 4	Model 5
Log(ACR)	0.72 ± 0.32*	0.62 ± 0.29*	0.61 ± 0.29*	1.02 ± 0.42†	0.86 ± 0.42*
Log(Lp-PLA$_2$)	4.57 ± 1.88*	3.77 ± 1.69*	3.77 ± 1.70*	4.55 ± 1.73†	4.51 ± 1.73*

Data are means ± SEM. All models include log(ACR) and log(Lp-PLA$_2$) at the same time. Model 1: adjusted for age, diabetes duration, BMI, ethnicity (NHW vs. others), pack-years smoking (number of packs of cigarettes per day × number of years smoked), hypertension, prior CVD, A1C, and total cholesterol-to-HDL ratio. Model 2: adjusted for model 1 + baseline CAC. Model 3: adjusted for model 2 + treatment assignment. Model 4: adjusted for model 3 + mean of on-trial variables (A1C, BMI, ACR, and total cholesterol-to-HDL ratio). Model 5: adjusted for model 4 + on-trial medication (statins, antihypertensive agents, ACE inhibitors, and angiotensin II receptor blockers). *$P < 00.05$; †$P \leq 0.01$.

Progression of vascular calcium

After a mean follow-up time of 4.6 ± 0.6 years in the whole cohort, the median (25–75%) CAC progression was 6.5 mm^3 (3.3–11.2 mm^3) and the median annualized percent change in CAC was 20% (9–41%). The AAC progression was 11 mm^3 (5–18 mm^3) and the annualized percent change in AAC was 17% (6–35%). The cumulative incidence of progression (≥2.5 mm^3) was 78 and 81% for CAC and AAC, respectively. Approximately 5% (9 subjects) and 12% (22 subjects) of subjects showed a decrease in CAC or AAC over time, respectively. A careful review of paired CAC scans showing a decrease indicated that eight of nine resulted from poor images, mislabeled scans, or scan artifacts (e.g., surgery clips). We therefore believe negative scans do not generally represent true regression and may interfere with identification of relationships of determinants with progression of calcified atherosclerosis. Subsequent data analyses are reported after exclusion of individuals with negative values.

To determine whether progression varied according to severity of baseline calcification, baseline CAC and AAC Agatston scores were divided into three categories: 0–10, 10–100, and >100 for CAC and 0–100, 100–1,000, and >1,000 for AAC. The extent of CAC and AAC progression increased significantly ($P < 0.01$) with higher baseline CAC or AAC categories (supplementary Fig. 1, available in an online appendix). Interestingly, the majority (59%) of subjects with a CAC Agatston score of 0 at baseline maintained a CAC score of 0 at follow-up, and the median (25–75%) Agatston score at follow-up in the remaining 41% was only 15 (8–34). Of the 23 subjects with an AAC Agatston score of 0 at baseline, the score in 35% did not increase further at follow-up, and the median AAC Agatston score in the remaining 65% was 44 (9–172).

Predictors of progression

Univariable predictors of CAC progression were NHW ethnicity ($P = 0.01$), Lp-PLA$_2$ mass ($P = 0.01$), and ACR ($P = 0.05$). Pack-years smoking ($P = 0.04$), prior CVD ($P = 0.03$), Lp-PLA$_2$ mass ($P = 0.04$), and lower A1C ($P = 0.05$) predicted progression of AAC (supplementary Table 1, available in an online appendix). No other standard or novel risk factor was associated with progression of CAC and/or AAC in univariable models. As shown in Table 2, after adjustment for standard risk factors (model 1), Lp-PLA$_2$ mass ($P = 0.01$) and ACR ($P = 0.02$) remained significant predictors of CAC progression. After adjustment for standard risk factors, the association between Lp-PLA$_2$ mass and AAC progression did not remain significant ($P = 0.22$) (data not shown). Adjustment for baseline calcium, treatment assignment, mean on-trial variables BMI, A1C, total cholesterol-to-HDL ratio, and ACR, and on trial-medications (statins, antihypertensive agents, ACE inhibitors, and angiotensin II receptor blockers) that might conceivably influence outcomes did not appreciably change these conclusions (models 2–5). Plasma levels of Lp-PLA$_2$ were also measured ~9 months into the study, but they did not change significantly from baseline. Furthermore, adjustment for the 9-month levels or the mean of baseline and 9-month levels did not change the results (data not shown).

Effect of intensive glycemic treatment on progression

Treatment assignment did not significantly influence either CAC or AAC progression, whether determined by cumulative incidence (supplemental Fig. 2*A*, available in an online appendix), annual percent change (supplemental Fig. 2*B*), or absolute progression (Fig. 1). Moreover, no effects of treatment assignment were seen for progression of either CAC or AAC at any level of baseline calcium (Fig. 1). Similarly, even though there was evidence for different rates of CAC progression between NHW and other ethnic/racial groups (supplementary Table 1) treatment assignment did not influence CAC or AAC progression in either of these groups.

CONCLUSIONS — The present study, which characterized the nature of progression of both CAC and AAC in older patients with a relatively long duration of type 2 diabetes, revealed several important findings. The incidence and yearly relative rates of both CAC and AAC progression were quite high in our study, with >80% of individuals demonstrating true progression (20). These rates are in line with previously described progression rates in type 2 diabetic patients who had a myocardial infarction (4) and presumably help explain the high rate of CVD events reported in the VADT. Because this is the first description of AAC progression in type 2 diabetes, we cannot compare the results with previous studies. However, these high AAC progression rates are certainly consistent with the relatively high prevalence of peripheral vascular disease in individuals with many years of diabetes. One strength of this study is the long interval between scans and the extensive absolute change in calcium that occurred, providing additional confidence in the estimates of the rates of vascular calcium progression.

As has been reported in cross-sectional studies of calcium accumulation (13,21), there were differences between CAC and AAC in relationships between risk factors and progression of calcium. Although age, BMI, duration of diabetes,

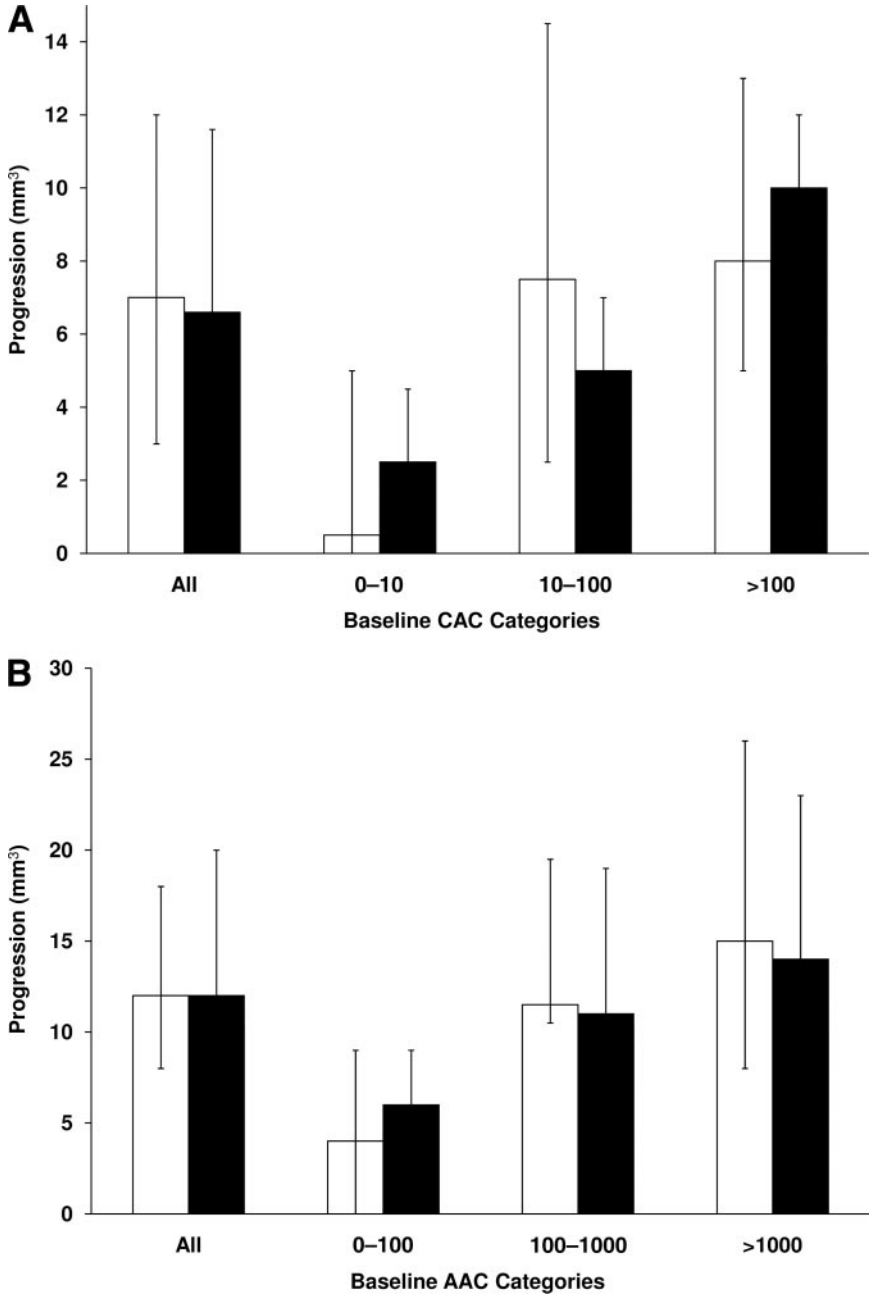

Figure 1—*Progression of CAC or AAC by treatment assignment.* A*: Median and 25th–75th percentiles of CAC progression by treatment group in all participants and by baseline CAC categories. The* P *value for the comparison between the treatment groups was not significant in all participants or in any baseline CAC categories.* B*: Median and 25th–75th percentiles of AAC progression by treatment group in all participants and by baseline AAC categories. The* P *value for the comparison between the treatment groups was not significant in all participants or in any baseline AAC categories.* □*, standard group;* ■*, intensive treatment group.*

pack-years smoking, and history of hypertension and/or prior CVD were associated with the extent of CAC and AAC (data not shown), they did not predict the progression of CAC in univariable models. In contrast, age, pack-years smoking, and history of prior CVD predicted AAC progression in univariable models. Interestingly in a cross-sectional study, NHW ethnicity, which we had previously reported was associated with increased CAC and AAC (17), was related to progression of CAC, but not of AAC, in univariable analysis. Higher A1C values were associated with reduced progression of both CAC and AAC. However, after multivariable adjustment, none of the above baseline standard risk factors remained significant predictors of either CAC or AAC progression. One may speculate that vascular calcification is in part a response to vascular injury, inflammation, and atherogenesis initiated by standard risk factors. Once a more advanced atherosclerotic plaque, composed of modified lipoproteins, cellular debris, and activated and proinflammatory vascular cells, has developed, the atherogenesis and ectopic calcification process in vessels becomes self-propagating, and the role for standard risk factors diminishes. This possibility is consistent with the fact that preexisting calcium in each vascular bed was a strong predictor of CAC or AAC progression in this and other studies (9–11). In fact, individuals with a CAC or AAC score of 0 demonstrated either no or modest levels of calcified atherosclerosis progression.

To explore the possibility that less traditional CVD risk factors may contribute to progression of calcified atherosclerosis, we evaluated several of the more common novel markers. Whereas C-reactive protein, IL-6, and adiponectin were not found to be significantly related to CAC or AAC progression, Lp-PLA_2 mass predicted progression of CAC after adjustment for other covariates. An association of Lp-PLA_2 with AAC progression also existed but was weaker in the multivariable model. Although this is the first study to assess the associations of Lp-PLA_2 mass with CAC or AAC progression, one recent study reported an association between Lp-PLA_2 mass and cross-sectional measures of calcified coronary plaque (22). The strong association of Lp-PLA_2 with calcified atherosclerosis progression suggests a unique role for the postulated proinflammatory Lp-PLA_2 enzyme in ongoing plaque formation in type 2 diabetes. Numerous studies have reported an association between Lp-PLA_2 mass and activity with CVD events (21) and have suggested that Lp-PLA_2 may alter atherosclerotic plaque stability. Lp-PLA_2 is produced by inflammatory cells, including macrophages within atherosclerotic plaques, and it binds primarily to apolipoprotein B-containing lipoproteins such as LDL. After LDL oxidation, Lp-PLA_2 rapidly hydrolyzes oxidized phospholipids, leading to the generation of two inflammatory products, lysophosphatidylcholine and the released oxidized fatty acid (23), within the vessel wall. By virtue of this proinflammatory activity, its local production by inflammatory cells, and its close association with artery wall lipoproteins, LP-PLA_2 is well posi-

tioned to exacerbate the ongoing inflammatory process within established plaques and thus promote further atherogenesis. Because oxidative stress is commonly increased in the presence of hyperglycemia and dyslipidemia, Lp-PLA_2 may have a particularly important role in atherosclerosis progression in type 2 diabetes.

The present study suggests that ACR is a predictor of CAC progression, even after adjustment for other baseline risk factors. Consistent with these data, an association between ACR and CAC progression has been reported in patients with type 2 diabetes (10). We note that ACR levels were below microalbuminuric ranges in the majority (66%) of participants in the present study, suggesting that ACR may be a sensitive indicator or mediator of vascular processes that promote calcified atherosclerosis.

In the VADT, intensive glycemic control did not reduce the development of CVD events (24), and it remains unknown whether one explanation for this treatment strategy failure was an inability to slow atherosclerosis. The current results support this possibility, because intensive glycemic control did not reduce progression of calcified atherosclerosis over the time frame of this study. These novel results may also have implications for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) studies, in which intensive glucose-lowering therapy also failed to reduce CVD events. These results do not address whether improved glucose control may have succeeded in favorably altering lesion composition or specifically slowing soft plaque progression. However, these favorable outcomes seem unlikely, given the rapid rate of calcified atherosclerosis progression in both groups. Neither CAC nor AAC progression was slowed in intensively treated groups at any beginning level of calcium, suggesting that the benefit of intensive glycemic control, originally found in the subset of individuals with less advanced disease (25), may be the effect of improved glucose values on thrombogenesis or plaque rupture. Some support for this notion may be drawn from the relatively rapid divergence in survival curves between individuals receiving intensive or standard glucose-lowering treatment (24). However, this hypothesis needs confirmation in future studies.

Several study limitations deserve mention. The RACED cohort consisted mainly of older men, limiting the ability to generalize our findings to a broader diabetes population. Approximately one-third of the initial cohort was not available for repeat scans, raising the possibility that they were less healthy and their exclusion could have affected the results. However, the baseline characteristics of these individuals did not differ from those with follow-up scans (Table 1) and their incidence of CVD events during the study was similar (32 vs. 28%; $P = 0.53$). A larger sample size may also have permitted detection of additional predictors of progression that were less robust than ACR and Lp-PLA_2. Because our Lp-PLA_2 measurement was limited to mass, further studies will be needed to determine whether Lp-PLA_2 activity would also predict CAC progression. This study of baseline predictors of progression of calcified atherosclerosis was conducted within a trial of glucose control, which has the potential to induce greater variation during the trial in certain risk factors in the intensively treated groups, thereby possibly lessening the association with CAC or AAC progression. However, standard CVD risk factors were equally well controlled in both treatment groups during the study (24). Although glucose levels differed between groups, neither glycemic control nor treatment assignment was a relevant predictor of CAC or AAC progression. Finally, additional sensitivity testing using multivariable models, which included average on-trial conventional risk factors and A1C, relevant medication use, or inclusion of subjects showing regression in calcium scores, did not appreciably change the results.

In summary, in this older group of individuals with a relatively long duration of type 2 diabetes and a high prevalence of CVD, the progression of CAC and AAC proceeded at a remarkably high rate. Of importance, intensive glycemic treatment did not appear to slow the rate of progression, and this was true even in those with very low baseline CAC. This result provides further support for the limited role that improved glycemic control may have on slowing atherosclerosis and may contribute to our understanding of why the VADT and other large trials of intensive glycemic control did not succeed in reducing CVD events. Although baseline standard risk factors were not identified as being associated with progression of calcified atherosclerosis, Lp-PLA_2 mass significantly predicted CAC progression even after adjustment for standard risk factors and predicted AAC progression in the univariable model. These data suggest that in the setting of excellent control of lipids and blood pressure, Lp-PLA_2 provides additional prediction of progression of calcified atherosclerosis beyond standard risk factors. These overall study findings provide novel information about the nature of progression of calcified atherosclerosis and relevant determinants of progression in type 2 diabetes and demonstrate that within the time frame of this study, intensive glucose lowering was relatively ineffective in reducing progression of calcified atherosclerosis in this subset of the VADT.

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A.S. and P.D.R. participated in study design, data gathering, statistical analysis, and interpretation and wrote the manuscript. T.E.M. and R.J.A. participated in study design, data gathering, and statistical analysis and reviewed/edited the manuscript. C.A. and W.C.D. participated in study design and data gathering and reviewed/edited the manuscript.

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