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

Aramesh Saremi, MD ¹, Thomas E. Moritz, Ms², Robert J. Anderson, PhD²³, Carlos Abraira, MD⁴, William Duckworth, MD¹, Peter D. Reaven, MD¹ for the VADT

¹ Phoenix VA Health Care System, Phoenix, AZ
² Cooperative Studies Program Coordinating Center, Hines, IL
³ Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago, Chicago, IL
⁴ Miami VA Health Care Center, Miami, FL

Corresponding Author:
Peter Reaven, MD
Email: Peter.Reaven@va.gov

Submitted 19 July 2010 and accepted 24 August 2010.

Clinical trial reg. no. NCT00032487; www.clinicaltrials.gov

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

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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 “RACED” sub-study of the VADT, 197 individuals with type 2 diabetes received baseline and follow-up CT scans of coronary and 189 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 as a categorical (square root increase of volumetric scores $\geq 2.5 \text{ mm}^3$) and continuous variable. In addition, annualized percent change of volume scores was determined.

Results- After an average follow-up of 4.6 years, more than 75% of individuals demonstrated coronary and abdominal artery calcium (CAC and AAC) progression. Progression increased with higher baseline calcium categories, but was not influenced by standard risk factors. However, albumin-to-creatinine ratio (ACR, $P = 0.02$) and lipoprotein-associated phospholipase A2 (Lp-PLA2, $P = 0.01$) predicted progression of CAC and these results were not altered by adjustment for age and other traditional risk factors. Treatment assignment (intensive vs. standard) within the VADT did not influence CAC or AAC progression, irrespective of baseline calcium category.

Conclusions- In patients with longstanding type 2 diabetes, baseline CAC, Lp-PLA2 and ACR predicted progression of CAC. Intensive glycemic control during the VADT did not reduce progression of calcified atherosclerosis.

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 and abdominal aortic artery calcification (CAC and 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 futures events(3,4), and there is less certainty about the implications of progression of vascular calcification(5). In a study of asymptomatic subjects, a 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, understanding 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 appreciated, determinants of progression, particularly in type 2 diabetes is less well studied. The large Multi-Ethnic Study of Atherosclerosis (MESA) reported most standard cardiovascular risk factors were modestly associated with progression of CAC (8) in individuals without known
CVD, and diabetes and baseline calcium score were strong predictor 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 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 DCCT/EDIC showed that intensive glycemic treatment was associated with lower incidence of CVD over time (15), 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 longstanding type 2 diabetes. In addition, we determined the relationship of both standard and novel inflammatory risk markers (C-reactive protein, interleukin-6, adiponectin, lipoprotein-associated phospholipase A2) 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.

**METHODS**

**Subjects.** Data for this study utilize 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 previously described in detail (16), and further information is provided in the online appendix available at http://care.diabetesjournals.org. Of the 301 subjects participating in the RACED study with both CAC and AAC scans at baseline, 197 subjects completed follow-up CAC and 189 completed AAC scans. The main reasons for not obtaining following-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).

**Laboratory methods.** Lipoprotein-associated phospholipase A2 mass (Lp-PLA2) was measured by an enzyme immunoassay (PLAC® test, diaDexus) in plasma with intra-assay and inter-assay CVs ranging from 4 to 6% and 6 to 9 % respectively. Additional laboratory methods are provided in the online appendix.

**Assessment of coronary and abdominal artery calcium scores.** Coronary and abdominal aortic calcium were determined by using either electron-beam or multi-detector computed tomography cardiac scanning as previously described (1,17). 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 mm³, as this cutoff provides an estimate that is unbiased with respect to baseline calcium (20). Finally, for comparison to earlier studies of calcium progression, the annualized percent change in volumetric calcium scores was also calculated(3). Additional details are provided in the online appendix.

**Statistical Analysis.** Statistical analyses were performed with the SAS statistical package (The SAS Institute, Inc., Cary, NC, release 9.1). Means ± SD, medians (25%-75%), and proportions are reported. Between-group differences in normally distributed continuous variables were assessed with t-tests, while Mann-Whitney U tests were used for variables with skewed distributions, and X² 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. Gender was not included as one of covariates, since 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/m², and HbA1c of 9.2 ± 1.3 %. Sixty-eight percent (n=133) reported non-Hispanic White ethnicity/race (NHW), and other categories (Others) included Hispanic Whites (n=32), African Americans (n=24), 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 were 258 (18 - 872) and 922 (173 - 3841), respectively. Except for slightly lower urine albumin-to-creatinine ratio (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).

**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 mm³ (3.3 - 11.2 mm³) and the median annualized percent change in CAC was 20% (9% - 41%). The median value for AAC progression was 11 mm³ (5-18 mm³) and the median annualized percent change in AAC was 17% (6%-35%). The cumulative incidence of progression (≥ 2.5 mm³) was 78% and 81% for CAC and AAC, respectively. Approximately 5% (9 subjects) and 12% (22 subjects) showed a decrease in CAC or AAC over time, respectively. A careful review of paired CAC scans showing a decrease indicated that, 8 of 9 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 3 categories; (0–10), (10–100), and (>100) for CAC, and (0–100), (100–1000) and (>1000) for AAC. The extent of CAC and AAC progression increased significantly (p <0.01) with higher baseline CAC or AAC categories (Supplementary Figure 1). 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, 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-PLA2 mass (P=0.01), and ACR (P=0.05). Pack-years smoking (P=0.04), prior CVD (P=0.03), Lp-PLA2 mass (P=0.04), and lower HbA1c (P=0.05) predicted progression of AAC (supplementary table 1). 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-PLA2 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-PLA2 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, HbA1c, total cholesterol-to-HDL ratio (TC/HDL), ACR, and on trial medications (statins, antihypertensives, 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-PLA2 were also measured approximately 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 level 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 Figure 2A), annual percent change (supplemental Figure 2B), or absolute progression (Figure 1). Moreover, no effects of treatment assignment were seen for progression of either CAC or AAC at any level of baseline calcium (Figure 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.

**DISCUSSION**

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 over 80% of individuals demonstrating true progression (20). These rates are in line with previously described progression rates in type 2 diabetes patients who sustained a myocardial infarction (4), and presumably help explain the high rate of CVD events reported in the VADT. As 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 was 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, 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 AAC, in univariable analysis. Higher HbA1c 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, comprised 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. While CRP, IL-6, and adiponectin were not found to be significantly related to CAC or AAC progression, Lp-PLA2 mass predicted progression of CAC after adjustment for other covariates. An association of Lp-PLA2 with AAC progression also existed, but was weaker in the multivariable model. Although this is the first study to assess the associations of Lp-PLA2 mass with CAC or AAC progression, one recent study reported an association between Lp-PLA2 mass and cross-sectional measures of calcified coronary plaque (22). The strong association of Lp-PLA2 with calcified atherosclerosis progression suggests a unique role for the postulated
pro-inflammatory Lp-PLA2 enzyme in ongoing plaque formation in type 2 diabetes. Numerous studies have reported an association between Lp-PLA2 mass and activity with CVD events (21), and have suggested that Lp-PLA2 may alter atherosclerotic plaque stability. Lp-PLA2 is produced by inflammatory cells, including macrophages within atherosclerotic plaques, and it binds primarily to apoB-containing lipoproteins such as LDL. Following LDL-oxidation, Lp-PLA2 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 pro-inflammatory activity, its local production by inflammatory cells and its close association with artery wall lipoproteins, LP-PLA2 is well positioned to exacerbate the ongoing inflammatory process within established plaques and thus promote further atherogenesis. As oxidative stress is commonly increased in the presence of hyperglycemia and dyslipidemia, Lp-PLA2 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, as 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 ACCORD and ADVANCE studies, where 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 those 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 1/3 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-PLA2. As our Lp-PLA2 measurement was limited to mass, future studies will be needed to determine whether Lp-PLA2 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 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 were relevant predictors of CAC or AAC progression. Finally, additional sensitivity testing using multivariable models which included average on-trial conventional risk factors and HbA1c, relevant medication use, or inclusion of subjects showing regression in calcium scores, did not appreciably change results.

In conclusion, 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. Importantly, 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 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. While baseline standard risk factors were not identified as being associated with progression of calcified atherosclerosis, Lp-PLA2 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-PLA2 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.

**Authors Contributions.** A.S and P.D.R participated in study design, data gathering, statistical analysis, interpretation and writing the report. T.E.M and R.J.A participated in study design, data gathering, statistical analysis, and critical review of the report. W.C.D and C.A participated in study design, data gathering, and critical review of the report.

Parts of this study were presented in abstract form at the 70th Scientific Sessions of the American Diabetes Association, Orlando Florida, 15-29 June 2010.

**ACKNOWLEDGMENTS**
We would like to thank the VADT study participants, study staff and the investigators at the Phoenix, San Diego, Long Beach, Hines, Pittsburgh, Tucson, and Miami Veteran Affairs Medical Centers for the participation in this study. We would also like to acknowledge the contributions of the Hines VA Cooperative Studies Program Coordinating Center, the Tufts Lipid Metabolism Laboratory and the Harbor UCLA CT Reading Center. This work was supported by the Office of Research and Development, Medical Research Service and Cooperative studies program, Department of Veteran Affairs, and by NIH grants RO1067690 (P.D.R), P01 HL076491, P01 HL77107, HL70621, Kronos Research Institute, and a clinical research award from the American Diabetes Association (P.D.R).

Duality of interest: None

REFERENCES
10. Elkeles RS, Godsland IF, Rubens MB, Feher MD, Nugara F, Flather MD. The progress of coronary heart disease in Type 2 diabetes as measured by coronary calcium score from


Table 1. Baseline characteristics

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<th>Without Scans</th>
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<tr>
<td></td>
<td>(197)</td>
<td>(104)</td>
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<td>Standard Risk factors</td>
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<tr>
<td>Age (years)</td>
<td>61 ± 9</td>
<td>61 ± 9</td>
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<td>NHW (%) vs. Others</td>
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<td>Prior CVD (%)</td>
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<tr>
<td>BMI (kg/m^2)</td>
<td>31.2 ± 4.3</td>
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<td>Duration (years)</td>
<td>12 ± 8</td>
<td>13 ± 8</td>
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<tr>
<td>HbA1c (%)</td>
<td>9.2 ± 1.3</td>
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<td>Novel Risk Factors</td>
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<td>ACR (mg/g)</td>
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<td>Interleukin-6 (pg/mL)</td>
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<td>2.7 (1.8 - 5.7)**</td>
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<td>Adiponectin (mg/L)</td>
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<td>4.7 (2.9 - 7.5)</td>
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<td>Lp-PLA2 (ng/mL)</td>
<td>294 (241 - 351)</td>
<td>284 (35 - 338)</td>
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<tr>
<td>Baseline CAC score</td>
<td>239 (17 - 808)</td>
<td>267 (27 - 981)</td>
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<tr>
<td>Baseline AAC score</td>
<td>917 (125 - 3508)</td>
<td>848 (189 - 4401)</td>
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Data are means ± SDs, medians (25%-75%), or percentages.
NHW: non-Hispanic Whites; Lp-PLA2: Lipoprotein-associated phospholipase A2; TC/HDL ratio: total cholesterol to HDL cholesterol ratio; ACR: albumin to creatinine ratio

*P < 0.05; ** P < 0.01 vs. standard group.
Table 2. Multivariable linear regression models for predictors of CAC progression

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
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<tr>
<td>Log (ACR)</td>
<td>0.72 ± 0.32*</td>
<td>0.62 ± 0.29*</td>
<td>0.61 ± 0.29*</td>
<td>1.02 ± 0.42**</td>
<td>0.86 ± 0.42*</td>
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<tr>
<td>Log (Lp-PLA2)</td>
<td>4.57 ± 1.88*</td>
<td>3.77 ± 1.69*</td>
<td>3.77 ± 1.70*</td>
<td>4.55 ± 1.73**</td>
<td>4.51 ± 1.73*</td>
</tr>
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*P < 0.05, **P ≤ 0.01

All models include Log (ACR) and Log (LP-PLA2) 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 x number of years smoked) hypertension, prior CVD, HbA1c, TC/HDL
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 (HbA1c, BMI, ACR,TC/HDL)
Model 5 -adjusted for model 4 + on trial medication (statins, antihypertensives, ACEs, angiotensin II receptor blockers)

Figure 1. Progression of CAC or AAC by treatment assignment

Panel A)
Median and 25th-75th percentiles of CAC progression by treatment group in all participants and by baseline CAC categories.
P-value for the comparison between the treatment groups was not significant in all participants or in any baseline CAC categories.

Panel B)
Median and 25th-75th percentiles of AAC progression by treatment group in all participants and by baseline AAC categories, and in all.
P-value for the comparison between the treatment groups was not significant in all participants or in any baseline AAC categories.

White bars represent the standard group.
Black bars represent the intensive treatment group.
Figure 1 A

Figure 1 B