ONLINE APPENDIX

SUPPLEMENTARY METHODS

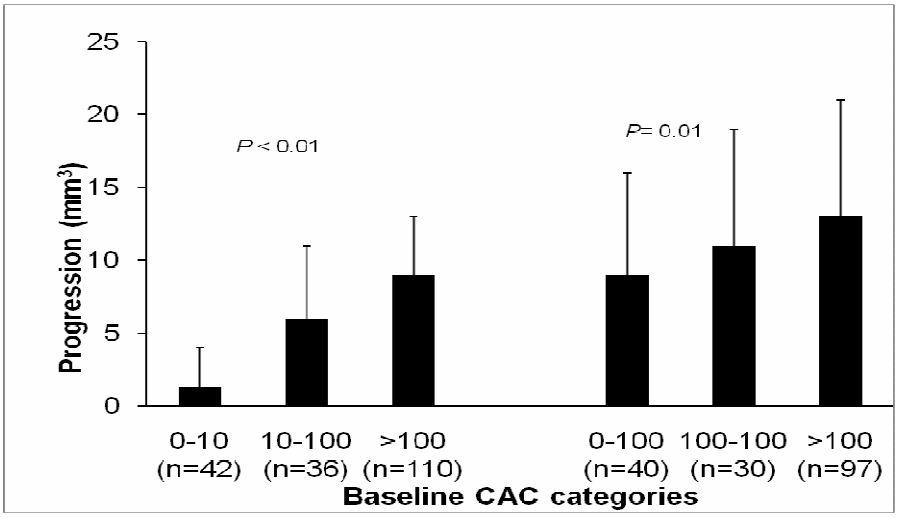
Subjects. The VADT randomized veterans 40 years of age or older, with longstanding type 2 diabetes and poor glycemic control to an intensive glycemic control arm with a goal of near normal HbA1c levels or to a standard arm with more usual glycemic control. An average HbA1c separation of >1.5% desired and was maintained between the two treatment groups throughout the study (24). The primary objective of the VADT was the assessment of the effect of intensive glycemic treatment on cardiovascular events. Approximately 95% of all subjects who were recruited into the VADT study at sites participating in the RACED sub-study also gave written informed consent and agreed 1) to undergo baseline and follow-up computed tomography scans of the coronary and abdominal aortic vascular beds, and 2) to provide blood samples for assessment of emerging risk factors.

Laboratory Methods. Plasma total cholesterol, triglycerides, and HDL cholesterol concentrations were measured using standard enzymatic methods on a Hitachi 911 analyzer, with reagents obtained from Roche Diagnostics (Indianapolis, IN). Serum high sensitivity CRP levels were measured by an enzyme-linked immunosorbant assay (ELISA kit, Alpha Diagnostic International, San Antonio, Texas), that yields an intra-assay CV% of 2.1, 3, and 4.5 for low, medium, and high serum CRP samples, and an inter-assay CV% of 2.7, 5, and 7. IL-6 was measured by an ELISA kit (R&D systems) with intra-assay and inter-assay CVs ranging from 4 to 6% and from 5 to 10% respectively. Adiponectin levels were assayed with an RIA kit (Linco Research, St. Charles, MO), with intra- and interassay CVs of 3.0 and 6.0%, respectively.

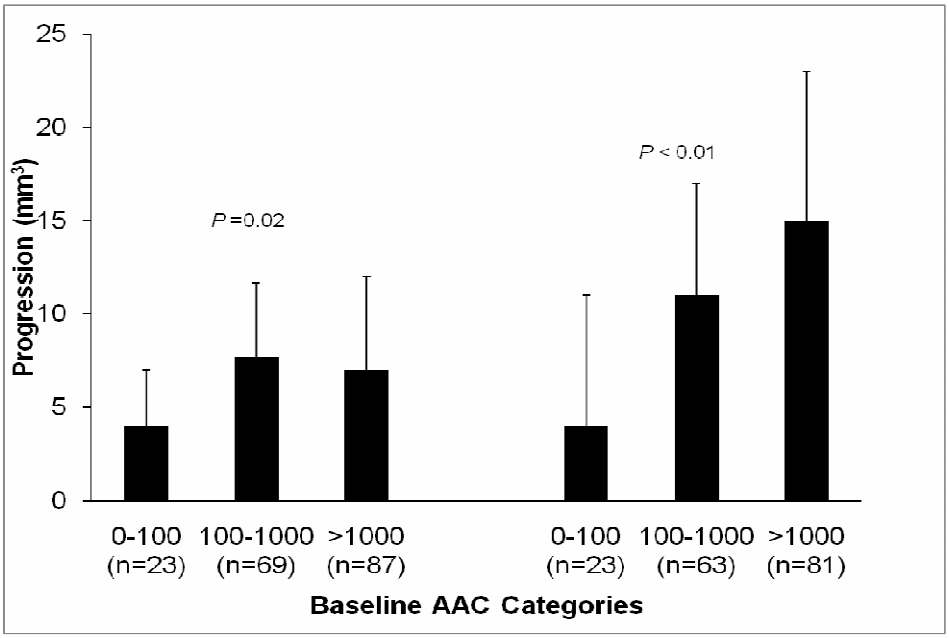
Assessment of coronary and abdominal artery calcium scores. The volumetric score has been shown to have better reproducibility than the standard score, and is a useful method for assessing the progression of calcification. The total volume scores (mm^3) were derived by summing all lesion volumes. In our study, the correlation between Agatston and volume scores was more than 0.99 for both CAC and AAC. Annualized percent change in calcium was calculated by dividing the annualized absolute change in Agaston scores by the baseline scan score multiplied by 100. For this calculation, a minimum baseline calcium of 20 was required, as a relative change could not be calculated in patients with no calcium at baseline, and very small calcium scores have been reported to show low reproducibility.

Supplementary Figure 1. Progression of CAC and AAC by baseline CAC and AAC
Median and 25th-75th percentiles of CAC and AAC progression (dSQRT of volume scores) are shown.

Panel A: *P* < 0.01 for the differences in CAC progression across baseline CAC categories, and *P* = 0.01 for the differences in AAC progression across baseline CAC categories.

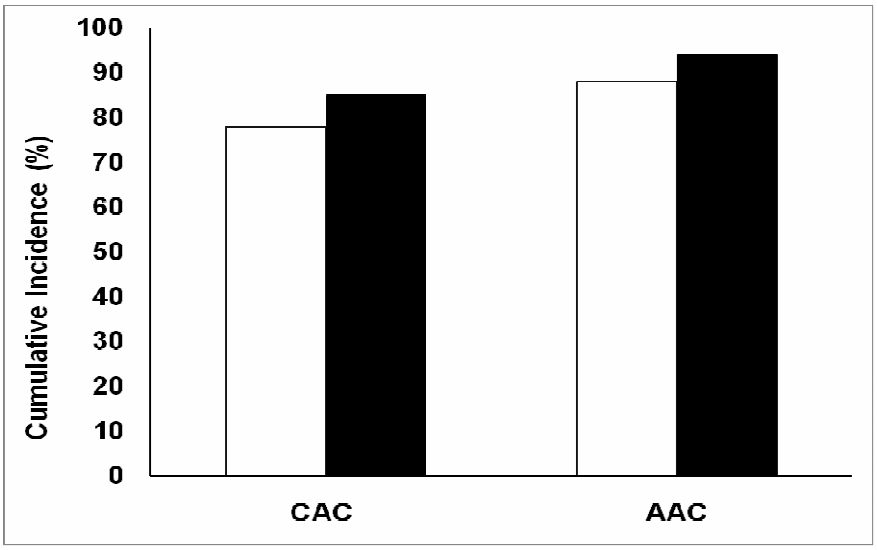


Panel B: *P* =0.10 for the differences in CAC progression across baseline AAC categories, and *P* < 0.01 for the differences in AAC progression across baseline AAC categories.



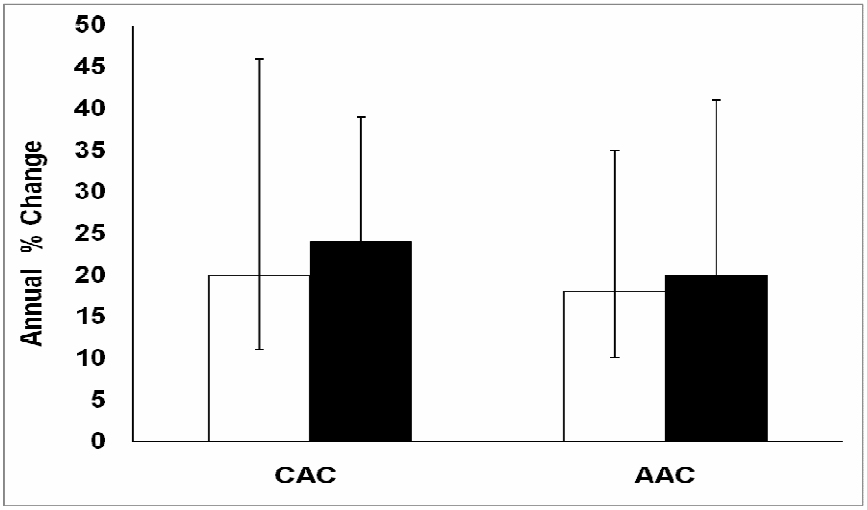
Supplementary Figure 2. Progression of CAC or AAC by treatment assignment

Panel A) Cumulative incidence (%) of CAC and AAC progression, as defined by having a dSQRT of volume score ≥ 2.5 mm^3, by treatment group.



P -value was not significant for CAC or AAC.

Panel B) Median and 25^{th}-75^{th} percentiles of CAC and AAC annual percent change (annualized absolute change in Agatston score by baseline score x 100) by treatment group.



P -value was not significant for CAC or AAC.
White bars represent the standard group and black bars represent the intensive treatment group.

Table 1. Univariable linear regression models for predictors of calcium progression

	Progression			
	CAC		AAC	
	β ± SD	p-value	β ± SD	p-value
Standard risk factors				
Age (per 5 years)	-0.03 ± 0.27	0.91	0.80 ± 0.44	0.07
Non-Hispanic Whites vs. Others (%)	2.41 ± 0.99	0.01	2.28 ± 1.69	0.17
Ever smoker (yes/no)	-0.09 ± 1.41	0.85	0.71 ± 2.29	0.75
Pack-years smoking	0.01 ± 0.01	0.26	0.06 ± 0.02	0.04
Hypertension (yes/no)	0.86 ± 1.18	0.46	2.25 ± 1.94	0.25
Prior CVD (yes/no)	1.49 ± 0.98	0.13	3.41 ± 1.61	0.03
BMI (kg/m^2)	0.17 ± 0.11	0.12	-2.23 ± 0.19	0.23
Duration (per 5 years)	0.09 ± 0.30	0.74	0.63 ± 0.51	0.22
HbA1C (%)	-0.24 ± 0.35	0.48	-1.11 ± 0.57	0.05
Total cholesterol (per 10 mg/dl)	-0.41 ± 0.58	0.49	-0.92 ± 0.97	0.34
LDL cholesterol (per 10 mg/dl)	-0.06 ± 0.16	0.70	0.02 ± 0.26	0.92
HDL cholesterol (per 10 mg/dl)	-0.06 ± 0.44	0.89	-0.75 ± 0.72	0.29
Triglycerides (per 50 mg/dl)	-0.16 ± 0.18	0.37	-0.19 ± 0.31	0.53
TC / HDL ratio	-0.15 ± 0.29	0.59	-0.06 ± 0.46	0.88
Novel risk factors				
Albumin / creatinine ratio (mg/g)*	0.59 ± 0.30	0.05	0.61 ± 0.50	0.22
C-reactive protein (mg/L)*	- 0.36 ± 0.41	0.45	-1.01 ± 0.71	0.16
Interleukin-6 (pg/mL)*	- 0.65 ± 0.82	0.96	-0.58 ± 1.41	0.68
Adiponectin (µg/mL)*	- 0.26 ± 0.69	0.70	-0.73 ± 1.18	0.53
Lp-PLA2 (ng/mL) *	4.08± 1.69	0.01	6.05± 2.99	0.04
CAC baseline categories	3.41 ± 0.52	< 0.01	2.66 ± 0.92	< 0.01
AAC baseline categories	0.76 ± 0.62	0.22	4.89 ± 0.95	< 0.01

* Log transformed; TC / HDL ratio: total to HDL cholesterol ratio. Baseline categories as defined in the text and supplementary Figure 1.