Progression of Vascular Calcification Is Increased With Statin Use in the Veterans Affairs Diabetes Trial (VADT)

OBJECTIVE—To determine the effect of statin use on progression of vascular calcification in type 2 diabetes (T2DM).

RESEARCH DESIGN AND METHODS—Progression of coronary artery calcification (CAC) and abdominal aortic artery calcification (AAC) was assessed according to the frequency of statin use in 197 participants with T2DM.

RESULTS—After adjustment for baseline CAC and other confounders, progression of CAC was significantly higher in more frequent statin users than in less frequent users (mean ± SE, 8.2 ± 0.5 mm³ vs. 4.2 ± 1.1 mm³; P < 0.01). AAC progression was in general not significantly increased with more frequent statin use; in a subgroup of participants initially not receiving statins, however, progression of both CAC and AAC was significantly increased in frequent statin users.

CONCLUSIONS—More frequent statin use is associated with accelerated CAC in T2DM patients with advanced atherosclerosis.

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Because people with previous or incident CVD events may have accelerated progression of vascular calcification, we evaluated the effect of statins in the cohort after excluding these individuals. In these remaining participants (n = 105), those with frequent statin use had significantly greater CAC progression (7.1 ± 5.9 vs. 4.3 ± 5.4 mm³; P = 0.03). Progression of AAC was not significantly different in the whole group (Fig. 1); however, in those not receiving statins at the baseline examination (n = 76 with CAC and n = 73 with AAC scans, respectively), after adjustment for age and baseline calcium, progressions of both CAC and AAC were significantly higher in those who subsequently reported frequent statin use compared with less frequent users (CAC progression, 7.9 ± 0.8 vs. 3.5 ± 1.0 mm³; P < 0.01; AAC progression, 11.9 ± 1.3 vs. 7.6 ± 1.6 mm³; P = 0.04).

**CONCLUSIONS**—In this cohort of T2DM patients with advanced atherosclerosis, we found that more frequent statin use was associated with accelerated progression of CAC. These findings are consistent with those reported in a previous study of T2DM participants without previous coronary artery disease (7). Results of this earlier study were believed to result from higher baseline CAC scores and insufficient lowering of LDL at follow-up in the statin users (7). In our study, however, there were no significant differences in baseline CAC or AAC according to statin use (Supplementary Table 1). In addition, at the end of the study more frequent statin users had significantly lower and nearly optimal LDL-cholesterol levels. Moreover, adjustment for baseline and on-trial risk factors, including LDL cholesterol and baseline CAC, did not explain the greater CAC progression in frequent statin users.

Randomized controlled trials in largely nondiabetic populations with no previous coronary artery disease disease demonstrated that, despite potent lipid-lowering effects, statin agents do not reduce the progression of CAC (8) or AAC (9). In fact, there was a trend toward progression of CAC with statin treatment in several studies (9–11). We now demonstrate that even in a setting of optimal lipid lowering and similar baseline CAC and AAC, statin agents promote calcification in T2DM subjects with advanced atherosclerosis. Because the variation in progression of AAC scores is greater, it is possible that the lack of significantly greater AAC progression with statin use is a sample size issue. Among those not initially on statins at baseline, however, the magnitude of AAC progression in those with subsequent frequent statin use was large enough to achieve statistical significance.

Statins have been implicated in calcification of vascular smooth muscle cells and mesenchymal cells (12,13). Statins also lower the lipid-rich core of atherosclerotic plaques and may enhance the density of calcification (14) as part of a healing process, potentially contributing to plaque stabilization and decreased CVD events. Alternatively, accelerated progression of calcified atherosclerosis in T2DM by statins may have the effect of lessening these medications’ overall benefit. Long-term follow-up in this cohort will help determine whether accelerated CAC and AAC progression in statin users is associated with more or fewer CVD events compared with statin users with less progression.

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A.S. designed the study, researched the data, and wrote the manuscript. G.B. contributed to analysis and interpretation of the data and edited the manuscript. P.D.R. participated in critical review of the data and edited the manuscript. A.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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