

# Coronary Artery Calcium: A Clue to the Enigma of Tight Glycemic Control and Cardiovascular Disease?

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**A**mong individuals with diabetes, dyslipidemia, hypertension, and other processes contribute to the development of atherosclerosis, which underlies most cardiovascular disease (CVD), the leading cause of mortality in diabetes (1). However, people with both type 1 and type 2 diabetes are likely more susceptible to CVD due to hyperglycemia, abnormal fatty acid metabolism, and insulin resistance, which have adverse effects on the vascular endothelium (2). The impaired endothelium promotes vasoconstriction, inflammation, and thrombosis, which in turn promote the formation of atherosclerotic plaques (2). Occlusion of coronary arteries by plaque rupture and thrombosis underlies coronary heart disease (CHD) (3). Calcium is deposited in early atherosclerosis lesions; in advanced plaques, the calcification is extensive and can be detected by chest computed tomography (CT) (4). The amount of coronary artery calcium (CAC) present is correlated strongly with the overall burden of atherosclerosis in the coronary arteries (4). There is increasing consensus that CAC score is predictive of future CHD and CVD events and may improve prediction beyond that of the Framingham Risk Score (5).

How to best prevent CVD among individuals with diabetes remains the focus of much research. Since the publication of the National Cholesterol Education Program's most recent guideline, it has been common to classify all adults with diabetes as CHD risk equivalents (i.e., Framingham Risk Score >2% per year) eligible for aggressive risk factor modification (6). There is evidence of benefit for lipid-lowering, antihypertensive, and antiplatelet therapies (7). Despite data supporting a direct relationship between glucose control and CVD (8), early randomized controlled trials (RCTs) did not demonstrate that glucose control prevented CVD (9). Three large, recently completed RCTs (ACCORD, ADVANCE, and VADT) also failed to demonstrate that tighter glycemic control reduces CVD in type 2 diabetic patients (10,11). ACCORD was particularly concerning, as it terminated early due to an increase in all-cause mortality in the intensive treatment group (12). These findings are in contrast to the long-term follow-up of the Diabetes Control and Complications Trial (DCCT) participants (type 1 diabetes), which demonstrated that over 17 years of follow-up, lower-

ing A1C reduced the risk of nonfatal myocardial infarction, stroke, or death from CVD by 57% (95% CI 12–79;  $P = 0.02$ ) (13).

In the current issue, Reaven et al. (14) report data from the Risk Factors, Atherosclerosis, and Clinical Events in Diabetes (RACED) study performed on a subsample of the VADT (15). The VADT enrolled 1,791 participants; for RACED, 301 participants had CAC assessed at baseline, and the relationship between CAC score, treatment arm, and incident CVD events was subsequently examined. The characteristics of the substudy sample were quite similar to those of the parent study, including the lack of a reduction in CVD events associated with intensive glucose control. There are several important findings. First, these participants had a substantial burden of coronary atherosclerosis (CAC scores >0 were observed in 84%). Second, CAC was predictive of incident CVD events. These results are not surprising. Among adults aged 45–85 years with diabetes but free of clinical CVD in the Multi-Ethnic Study of Atherosclerosis (MESA), 62% had detectable CAC (16). CAC has been demonstrated to be predictive of incident CVD, although there have been relatively few studies examining CAC exclusively in diabetic patients (5). In an observational study of 716 subjects with type 2 diabetes (mean age 55 years) but without CHD, only 15% had no CAC. CAC score related in a graded fashion to events; notably, only 3% of those with CAC 0–10 had incident CHD, compared with >30% for those with CAC >100, over an 8-year follow-up (17).

This study's novel finding lies in the assessment of interaction between CAC and the treatment arm. Another name for interaction is effect modification. Put simply, Reaven et al. present results supporting the hypothesis that the effectiveness of tight glycemic control in reducing CVD events is modified by CAC (i.e., it differs by level of advanced atherosclerosis). The data suggest that tight glycemic control was effective in reducing incident CVD among RACED participants with no or minimal CAC (CAC ≤100). In contrast, there was no apparent difference by arm in those with higher CAC scores. There are several limitations to this study, noted by the authors, including the relatively small sample, which limits the statistical power—for the stratified analyses in particular. Nevertheless, these results suggest several important hypotheses regarding the results of the VADT and, by extension, ACCORD and ADVANCE.

If the distribution of CAC was similar in the entire VADT subset, as is likely, it is reasonable to hypothesize that a similar result would have been observed in the parent study. The authors suggest that the results of ACCORD and ADVANCE may also be due to heterogeneity in effectiveness conditional on baseline atherosclerosis. It is also intriguing to consider the results from the DCCT alongside these results, despite the fact that they represent only type 1 diabetic patients (13). The prevalence of CAC in the DCCT population (age 13–40 years at baseline) (13) is not knowable; however, in one study CAC >0 in type 1 patients aged <30 years was

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prevalent in only 11% (18). Perhaps the discrepant results between DCCT and most glycemic control trials is less related to differences between type 1 and type 2 diabetes and instead due to age and the burden of advanced atherosclerosis.

The finding of an impressive benefit of tighter glycemic control in diabetic adults with limited CAC suggests the potential to retard the progression of atherosclerosis (or at least calcification). Indeed, MESA demonstrated that diabetes is independently associated with incident CAC (among those free of CAC at baseline) over a relatively short follow-up of 2.4 years and strongly associated with progression of CAC among those scores initially  $>0$  (19). Thus, an RCT would have the potential to test this hypothesis.

It remains unknown why there may, paradoxically, be no benefit of tight glycemic control among individuals with significant atherosclerosis. This observation is contrary to the usual pattern of greatest benefit of an intervention in patients who are at greatest baseline risk. While perplexing, this phenomenon is consistent with a number of other recent reports, including that of Aguilar et al. (20). Understanding the mechanism(s) of this phenomenon is critical. Are there genetic or environmental/behavioral factors that differentiate those with diabetes and minimal CAC? In addition to the other possible explanations offered by the authors, we suggest another, potentially controversial one. Is it possible that patients with baseline atherosclerosis do receive benefit but that this is counterbalanced by detriment via a different mechanism, such as more frequent hypoglycemic episodes leading to subclinical ischemia? The "U-shaped" relationship between A1C and cardiovascular outcomes in diabetic heart failure patients suggested in the report of Aguilar et al. (20) should give us pause. Importantly, despite some variation in the types of cardiovascular events, no sign of overall worsening of cardiovascular risk from intensive glycemic control was observed in the high-CAC group in the study by Reaven et al.

The notion that all with type 2 diabetes are CHD risk equivalents may also be questionable because this study and observational data suggest that those with minimal CAC burden have absolute rates of CHD substantially  $<2\%$  per year. This has important implications for power analyses in the design of trials to assess glycemic control and CHD in "low-risk" type 2 diabetes. Finally, the results of this study should prompt new questions about the potential utility of screening diabetic adults for CAC. While promising, it is premature, in our opinion, to suggest that clinical management of risk factors in diabetic patients should differ based on CAC screening results.

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