Effect of Lipid Modification on Progression of Coronary Calcification

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Coronary artery calcification (CAC) reflects the anatomic presence of coronary atherosclerosis and the relative burden of coronary artery disease (CAD). Higher levels of CAC are seen in the presence of CAD risk factors, older age, and chronic kidney disease. The lipid profile (primarily low HDL cholesterol, elevated triglycerides, elevated LDL cholesterol, and elevated total cholesterol) are important factors in the calcification process. The annual progression of CAC can be reduced from 25 to 30% to 0 to 6% with LDL cholesterol reduction caused by statins and possibly sevelamer. At treated LDL cholesterol levels somewhere below 100 mg/dl, several sources of data suggest the anatomic burden of CAD, including CAC, regresses. Additional supportive studies indicate that carotid intimal medial thickness and the volume of coronary atheroma also can be reduced by LDL cholesterol reduction in concert with elevation of HDL cholesterol. This article reviews the data in support of altering the natural history of CAC with lipid modification.


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Atherosclerotic calcification begins as early as the second decade of life, just after fatty streak formation (1). Coronary artery lesions of young adults have revealed small aggregates of crystalline calcium within the lipid core of a plaque (1). Calcium phosphate (hydroxyapatite, Ca$_3$(PO$_4$)$_2$·Ca(OH)$_2$), which contains 40% calcium by weight, precipitates in diseased coronary arteries by a mechanism similar to that found in osteogenesis and remodeling (2). Hydroxyapatite, the predominant crystalline form in calcium deposits, is formed primarily in vesicles that pinch off from arterial wall cells, analogous to the way matrix vesicles pinch off from chondrocytes in developing bone (3,4). It has been postulated that vesicles, derived from apoptotic foam and smooth muscle cell debris and contained within extracellular matrix, may also serve as the sites of small calcium deposits. A very close spatial association between cholesterol deposits and hydroxyapatite also has been demonstrated (5). The exact mechanism and process of calcification within the arterial wall are not yet completely understood.

Coronary artery calcification (CAC) seems to occur exclusively in atherosclerotic arteries and is absent in normal vessel wall (6). Overall, recent findings lend credence to the idea that atherosclerotic calcification is not merely passive adsorption but instead is an organized, regulated process similar to bone formation. Thus, the finding of calcification on human imaging studies suggests the anatomic presence of atherosclerosis.

The presence of atherosclerosis is a necessary but not sufficient condition to result in a coronary artery disease (CAD) event. Plaque rupture, exposure of the lipid-rich core to the blood pool, thrombosis and vessel occlusion, and downstream embolization of the platelet-thrombin complexes are believed to be the sequence in which an acute coronary syndrome occurs. Hence, it makes sense that CAC (measured by noninvasive imaging methods) indicates that the substrate for an event is present; however, other risk factors for plaque rupture, including shear stress, conventional cardiovascular risk factors, and inflammatory cytokines, all still contribute to the risk for a future CAD event (7–10).

CAC as a Continuum

Considerable interest exists in identifying and quantifying CAC as a marker for CAD. In the general population, a high coronary calcium score (>100) on electron beam computed tomography (EBCT) carries a relative risk for future CAD events of approximately 10 compared with those with a score <100 (1,2) (Figure 1). Furthermore, it seems that a sufficiently high CAC score (>300) modifies the risk for future CAD events above that predicted by the conventional Framingham risk prediction (10). The absence of detectable CAC is associated with a low future event rate; however, this rate is not zero. Approximately 5% of patients with a CAC score of zero will incur a myocardial infarction or cardiac death in the next 5 to 7 yr after EBCT (8,9). This suggests that atherosclerotic plaque can exist without a sufficient amount of calcification to be detected by EBCT. This plaque, although uncommon, is thought to be lipid laden and potentially prone to plaque rupture and thrombosis.

In a study of 6093 patients for whom CAC by EBCT, lipids, personal health history, and body morphology were recorded, the correlation between HDL cholesterol and CAC was three times that of LDL cholesterol (11,12). Patients with an HDL cholesterol level <40 mg/dl had significantly higher CAC scores, whereas increases in HDL cholesterol were associated with a significant reduction in risk for the presence of any evidence.
calcified plaque. Multivariate logistic regression revealed that LDL cholesterol and HDL cholesterol were independent predictors of CAC with the relative risk (RR) being 1.05 times higher for each 10-mg/dl increase in LDL cholesterol ($P < 0.001$). An LDL cholesterol $\leq 160$ mg/dl had a 62% increase in odds for the presence of calcified plaque (12). CAC, once identified, seems to progress at a measurable, annual rate of approximately 30% in CAC volume on annual EBCT examinations (13). The progression of CAC has been linked to cigarette smoking, poor glycemic control in diabetes, and other conventional CAD risk factors (8,9,13) (Table 1). In patients with chronic kidney disease (CKD), the annual rate of progression is the same; however, the absolute magnitude of increase in CAC volume is large given the high CAC scores at baseline in this population (14).

### Changing the Rate of Calcification with Modification of Lipids

#### LDL Cholesterol Reduction

Several nonrandomized studies using treatment with 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitors (statins) have demonstrated attenuation of progression in CAC associated with LDL cholesterol reduction (15,16). In a study of 66 patients who were followed during a period without statin treatment and then during treatment with cerivastatin 0.3 mg/d orally, the median annualized relative change was significantly higher in the untreated interval compared with the treated interval (25 versus 8.8%; $P < 0.0001$) (15). The annualized relative change of the CAC score in 32 patients who achieved an LDL cholesterol level of $<100$ mg/dl decreased from 27 to $-3.4\%$ ($P < 0.0001$; Figure 1). Callister et al. (16) reported on 149 patients with CAD, 105 of whom were taking statins, who underwent baseline and then follow-up EBCT studies at 12 to 15 mo. As shown in Figure 2, patients who had LDL cholesterol reductions $<120$ mg/dl on statins almost ex-
clusively populated the lower left quadrant, demonstrating regression of CAC. There was a correlation ($r = 0.50$) between the reduction in LDL cholesterol and the change in CAC by EBCT with regression in CAC beginning to occur on the line of best fit at an approximate LDL cholesterol level $<100$ mg/dl (Figure 3). Some patients in these studies had had arrest or reversal in the calcification process; however, the determinants beyond LDL cholesterol reduction of this reversal process are not completely understood (Figure 3) (16).

In an analogous study using the percentage change in coronary atheroma volume, 502 assessable patients with CAD and considerable overweight/obesity (body mass index 30.5 kg/m²) were randomly assigned to pravastatin 40 mg versus atorvastatin 80 mg/d (17). Intravascular ultrasound examinations of the coronary tree were performed at baseline and at 18 mo. The LDL cholesterol values were lowered from 150.2 to 110.4 (25.2% reduction) and 150.2 to 78.9 (46.3% reduction) mg/dl with 40 mg of pravastatin and 80 mg of atorvastatin, respectively. This resulted in a slight overall regression of coronary atheroma volume and, we infer, the overall burden of CAC if it had been measured (Figure 4). Thus, studies using EBCT and intravascular ultrasound suggest that somewhere at or below an LDL cholesterol of 100 mg/dl on treatment, CAD and CAC begin to regress.

**LDL Cholesterol Reduction in Patients with ESRD**

Patients with ESRD that requires dialysis are the highest risk states for incident and accelerated cardiovascular disease (18,19). Previous studies have shown that vascular calcification is enhanced in ESRD, and recent data using EBCT has shown a modest relationship between calcium scores and calcium-phosphorus ion product (20). In contrast, when it has been evaluated, vascular calcification has been related consistently to the dyslipidemia of ESRD, including a modestly elevated LDL cholesterol, depressed HDL cholesterol, and elevated triglycerides (TG) (14).

A variety of stimuli have been shown to induce or modulate phenotypic transformation of vascular smooth muscle cells to osteoblast-like cells with subsequent mineralization in vitro, including phosphorus, oxidized LDL cholesterol, calcitriol, parathyroid hormone (PTH), and parathyroid hormone–related peptide (21). As reviewed below, the clinical studies in ESRD suggest that the process is driven much more by the age, length of time on dialysis, and lipid status (22). A systematic review of the literature concerning CKD and ESRD (1982 to 2002, $n = 2919$) found 31 studies that were split on either finding or not finding significance of serum calcium (Ca), serum phosphorus (PO₄), calcium-phosphorus product (CPP), PTH, or treatments for calcium-phosphorus (Ca-PO₄) balance including phosphate binders, calcium, and vitamin D analogues, in relation to CAC (22). When taken into consideration, the lipid profiles (primarily HCL cholesterol, elevated TG, elevated LDL cholesterol, and elevated total cholesterol) were predictive factors in four analyses. Most studies were too small for valid multivariate analyses, but five studies did use various techniques in an attempt to identify the independent predictors. When this was done, measures of Ca-PO₄, in general, either dropped out of the model or markedly attenuated as predictive factors.

In the Treat to Goal trial by Chertow et al. (23), 200 patients were randomly assigned to sevelamer versus calcium carbonate (in Europe) or calcium acetate (in the United States) and had EBCT scans done at baseline and at 52 wk. Investigators were not blinded to the measures of Ca-PO₄ balance and were allowed to adjust phosphate binders and dialysate calcium or use vitamin D analogues. The baseline and final CPP values were 71 and 48 (difference 23) and 69 and 49 (difference 20) for the sevelamer and calcium groups, respectively. However, there was a large difference in the final LDL cholesterol levels between the sevelamer and the calcium groups, 65 versus 103 mg/dl, respectively ($P < 0.0001$). This is consistent with the known bile-acid sequestrant properties of sevelamer. Accordingly, there was attenuation of progression of CAC with sevel-

Figure 3. Correlation between LDL cholesterol level (treated in 105 of 149 with statins) and rate of progression of coronary artery calcification (CAC) over 12 to 15 mo in patients with established CAD. Adapted from reference 16, with permission.

Figure 4. Percentage of atheroma volume reduction over 18 mo when LDL cholesterol values were lowered from 150.2 to 110.4 (25.2% reduction) and 150.2 to 78.9 (46.3% reduction) mg/dl with 40 mg of pravastatin and 80 mg of atorvastatin, respectively. Data are from reference 17.
HDL Cholesterol Elevation

Two recent studies have evaluated measures of atherosclerotic plaque burden in patients with CAD with a specific attempt to raise HDL cholesterol. The Randomized Trial of a Strategy for Increasing High-Density Lipoprotein Cholesterol Levels: Effects on Progression of Coronary Heart Disease and Clinical Events (AFREGS) was performed in 143 military retirees with low HDL cholesterol levels (<40 mg/dl) and known stable CAD (24). None had diabetes or kidney disease. All had LDL cholesterol levels <160 mg/dl. Patients were randomly assigned to aggressive HDL cholesterol–increasing therapy with gemfibrozil, niacin, and cholestyramine or matching placebos for 30 mo. Drug doses were adjusted regularly, and niacin and cholestyramine were added at month 3 and month 6, respectively. Compared with those who were taking placebos, patients who were treated with lipid-modifying agents had a 26% decrease in LDL cholesterol level, 50% decrease in TG, and 36% increase in HDL cholesterol level. Coronary lesions regressed slightly (1.35 \text{ versus} -0.81\% stenosis; \text{P} = 0.04) by quantitative coronary angiography with drug therapy and progressed without drug therapy. As expected, patients who were randomly assigned to drug therapy had fewer total cardiovascular events.

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER-2) trial randomly assigned 149 patients with known CAD on a statin with LDL cholesterol < 130 mg/dl and HDL cholesterol < 45 mg/dl to extended-release niacin 1000 mg/d \textit{versus} placebo (25). Niacin elevated the HDL cholesterol from 39 to 47 mg/dl (21% increase). This resulted in a significant attenuation in the rate of progression of carotid intimal medial thickness over 12 mo (Figure 5). There was no regression reported in this surrogate measure of coronary atherosclerosis.

There are no trials of targeted HDL cholesterol elevation in patients with CKD or ESRD. However, given that low HDL cholesterol (<45 mg/dl) is a very common finding in these patients, it is conceivable that like reduction in LDL cholesterol, elevation in HDL cholesterol may be related to attenuation of the progression of atherosclerosis and CAD.

Conclusion

In conclusion, CAC is a common observation in CKD and ESRD and is mainly related to age, duration on dialysis, and possibly dyslipidemia. Whereas high levels of CAC almost certainly represent significant CAD in patients with ESRD, the attenuation of progression of CAC and its relation, if any, to CAD event reduction are unknown. The annual progression of CAC can be reduced from 25 to 30% to 0 to 6% with LDL cholesterol reduction caused by statins and possibly sevelamer. At treated LDL cholesterol levels somewhere below 100 mg/dl, several sources of data suggest that the anatomic burden of CAD, including CAC, regresses. Additional supportive studies indicate that carotid intimal medial thickness and the volume of coronary atheroma can also be reduced by LDL cholesterol reduction in concert with elevation of HDL cholesterol.

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