Annual Progression of Coronary Calcification in Trials of Preventive Therapies

A Systematic Review

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Background: Coronary artery calcification (CAC) measured by computed tomography is radiographic confirmation of atherosclerosis, predicts cardiovascular events, and has been evaluated as a surrogate measure in randomized trials.

Methods: We performed a literature search for prospective randomized trials in which CAC was measured at baseline and at 1 year or more of follow-up. We computed the weighted mean annualized rate of CAC progression for a variety of therapies tested in these trials.

Results: Ten trials (n=2612) met our criteria and were included. Electron-beam, double-helix, and multislice computed tomography were used in 6, 2, and 2 trials, respectively. Agatston (8 trials) and volumetric (2 trials) methods were used for CAC evaluation. In 5 trials in subjects with cardiovascular disease (CVD) (n=2135; age, ~64 years; ~39% women; follow-up, ~26 months), therapies included statins (n=1370), placebo (n=564), and antihypertensives (n=201). In 5 trials in subjects with chronic kidney disease (n=477; age, ~55 years; ~34% women; follow-up, ~14 months), interventions included low-phosphorus diet (n=29), sevelamer hydrochloride (n=229), and calcium-based phosphate binders (n=219). The mean (SD) weighted annualized CAC increase overall and in patients with CVD and chronic kidney disease was 17.2% (6.7%), 16.9% (5.2%), and 18.4 (11.1%), respectively ($P < .001$). The rate among those assigned blinded placebo was 14.6% (1.0%) (2 trials). There was no consistent or reproducible treatment effect of any therapy on this outcome measured at 1 year.

Conclusion: The 1-year change in CAC does not appear to be a suitable surrogate end point for treatment trials in patients with CVD or chronic kidney disease.

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CORONARY ARTERY CALCIFICATION (CAC) measured by computed tomography (CT) is an accepted measure of coronary atherosclerosis and identifies patients at higher risk of cardiovascular events in a graded fashion according to the coronary calcium score.1 Two early nonrandomized studies using statins observed attenuation of progression in CAC measured by electron-beam CT (EBCT) associated with low-density lipoprotein cholesterol (LDL-C) reduction.2,3 The annualized relative change of the CAC score in 32 of 66 patients who achieved an LDL-C level of less than 100 mg/dL (to convert to millimoles per liter, multiply by 0.0259) with cerivastatin sodium at a daily oral dose of 0.3 mg decreased from 27% to ~3.4% ($P < .001$) on serial EBCT examinations.2 Callister and colleagues3 demonstrated in 149 patients with coronary artery disease that, among patients with an achieved target LDL-C of less than 120 mg/dL, regression of CAC was noted by EBCT at 12 to 15 months. There was a correlation ($r = 0.50$) between the reduction in LDL-C level and the change in CAC by EBCT, with CAC regression beginning to occur on the line of best fit at an approximate LDL-C level of less than 100 mg/dL. Some patients in these studies had an arrest or reversal in the calcification process, suggesting the potential promise of this imaging variable as a response measure of atherosclerotic disease activity. Multiple investigative groups have measured the annual rate of CAC increase as a surrogate for the advancement of atherosclerosis in clinical trials. We sought to evaluate published, prospective randomized trial data concerning CAC progression as an outcome variable specifically in response to a variety of treatment strategies.

METHODS

We performed a PubMed search using the following search terms: coronary calcification...
Chronic kidney disease (CKD) and coronary artery disease (CAD) are prevalent conditions that have increased in prevalence and incidence in recent decades. The prevalence of chronic kidney disease (CKD) was estimated to be 10.8% in the United States, affecting over 30 million adults. Similarly, the prevalence of cardiovascular disease (CVD) is high, with an estimated 86.6 million adults in the United States having some form of CVD. These conditions are often interrelated, with CKD being a risk factor for CAD and CAD a risk factor for CKD.

Methods

A total of 10 trials were identified, reporting data on 2612 patients with evaluable data. In 5 trials of patients at risk for or having cardiovascular disease (CVD) (n = 2135; age, 64 years; 39% women; follow-up, 26 months), therapies included statins (n = 1370), placebo (n = 564, of whom 515 were from the St Francis Heart Study), and antihypertensives (n = 201) (Table 1). In 5 trials performed in subjects with CKD (n = 77; age, 55 years; 34% women; follow-up, 14 months), treatment consisted of low-phosphorus diet alone (n = 29), sevelamer hydrochloride (n = 229), calcium-based phosphate binders (n = 219) (Table 2). Placebo arms were used in 2 and 0 of the CVD and CKD trials, respectively. Electron-beam CT, double-helix CT, and multislice CT were used in 6, 2, and 2 trials, respectively. Multiple previous studies have shown that CAC obtained by double-helix CT and multislice CT is comparable to that from EBCT with respect to accuracy and reproducibility. The methods of measuring and reporting CAC score were similar and used either the Agatston (8 trials) or volumetric (2 trials) methods of assessment. The baseline CAC score varied according to how the populations were screened and whether there was a minimum threshold of CAC to be eligible for the trial. The overall mean weighted annualized progression of CAC was 17.2% (6.7%), and among those with CVD and CKD the rates were 16.9% (5.2%) (range, 14.6% [1.0%] to 19.3% [6.1%]) and 18.4% (11.1%) (range, 14.2% [13.3%] to 24.1% [1.0%]), respectively (P < .001). The rate among those assigned blinded placebo was 14.6% (1.0%).

All 5 of the CVD trials were prospective, double-blind, randomized controlled trials. At baseline, the mean weighted CAC score was 391.5 (159.8) (range, 108.0-563.0). All 4 of the statin trials achieved a significant difference in LDL-C level between groups, but none of them found a statistically significant difference in the rates of progression of CAC. Of note, the St Francis Heart Study is the largest trial included in Table 1. In this study, despite a lack of difference in the rate of CAC increase, a significant reduction in cardiovascular events was observed during the trial.

Results

A total of 10 trials were identified, reporting data on 2612 patients with evaluable data. In 5 trials of patients at risk for or having cardiovascular disease (CVD) (n = 2135; age, 64 years; 39% women; follow-up, 26 months), therapies included statins (n = 1370), placebo (n = 564, of whom 515 were from the St Francis Heart Study), and antihypertensives (n = 201) (Table 1). In 5 trials performed in subjects with CKD (n = 77; age, 55 years; 34% women; follow-up, 14 months), treatment consisted of low-phosphorus diet alone (n = 29), sevelamer hydrochloride (n = 229), and calcium-based phosphate binders (n = 219) (Table 2). Placebo arms were used in 2 and 0 of the CVD and CKD trials, respectively. Electron-beam CT, double-helix CT, and multislice CT were used in 6, 2, and 2 trials, respectively. Multiple previous studies have shown that CAC obtained by double-helix CT and multislice CT is comparable to that from EBCT with respect to accuracy and reproducibility. The methods of measuring and reporting CAC score were similar and used either the Agatston (8 trials) or volumetric (2 trials) methods of assessment. The baseline CAC score varied according to how the populations were screened and whether there was a minimum threshold of CAC to be eligible for the trial. The overall mean weighted annualized progression of CAC was 17.2% (6.7%), and among those with CVD and CKD the rates were 16.9% (5.2%) (range, 14.6% [1.0%] to 19.3% [6.1%]) and 18.4% (11.1%) (range, 14.2% [13.3%] to 24.1% [1.0%]), respectively (P < .001). The rate among those assigned blinded placebo was 14.6% (1.0%).

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Table 1. Clinical Trials Measuring CAC as an Outcome in Populations at Risk for or With Coronary Artery Disease Not Specifying Level of Kidney Function

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>BELLES Trial, 2005</th>
<th>St Francis Heart Study, 2005</th>
<th>Schermur et al, 2006</th>
<th>SALTIRE, 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>HTN, CVD RF</td>
<td>Asymptomatic, screened positive for CAC</td>
<td>Postmenopausal</td>
<td>Asymptomatic, screened positive for CAC, CVD RFs</td>
</tr>
<tr>
<td>Age, y</td>
<td>–67</td>
<td>–59</td>
<td>–64</td>
<td>–62</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>38</td>
<td>26</td>
<td>100</td>
<td>26</td>
</tr>
<tr>
<td>Therapy</td>
<td>Nifedipine, 30 mg HCTZ, 25 mg + amiloride hydrochloride, 2.5 mg</td>
<td>Atorvastatin calcium, 20 mg + ascorbic acid, 1 g + alpha tocopherol, 1000 U/placebo</td>
<td>Atorvastatin calcium, 80 mg/pravastatin sodium, 40 mg</td>
<td>Atorvastatin calcium, 20 mg/atorvastatin calcium, 10 mg</td>
</tr>
<tr>
<td>Drug and dosage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with evaluable data</td>
<td>101/100</td>
<td>490/515</td>
<td>218/257</td>
<td>175/191</td>
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<tr>
<td>Blinding CT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Modality</td>
<td>DHCT</td>
<td>EBCT</td>
<td>EBCT</td>
<td>EBCT</td>
</tr>
<tr>
<td>Hounsfield threshold for calcification, IU</td>
<td>&gt;90</td>
<td>&gt;130</td>
<td>≥130</td>
<td>&gt;130</td>
</tr>
<tr>
<td>Section thickness, mm</td>
<td>NR</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Method</td>
<td>Agatston</td>
<td>Volumetric</td>
<td>Volumetric</td>
<td>Volumetric</td>
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<tr>
<td>Qualifying score for entry</td>
<td>≥10</td>
<td>&gt;80th Percentile CAC for age and sex score (26-128 women, 69-368 men)</td>
<td>None</td>
<td>Agatston</td>
</tr>
<tr>
<td>Baseline CAC score</td>
<td>528/563</td>
<td>205/268</td>
<td>348/371</td>
<td>195/235</td>
</tr>
<tr>
<td>Follow-up duration, mo</td>
<td>36</td>
<td>48</td>
<td>12</td>
<td>12</td>
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<tr>
<td>Follow-up CAC score</td>
<td>859/886</td>
<td>233/298</td>
<td>396/434</td>
<td>246/277</td>
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<tr>
<td>Annualized rate of CAC progression</td>
<td>13.3/25.4</td>
<td>15.7/14.3</td>
<td>13.7/11.1</td>
<td>27/25</td>
</tr>
<tr>
<td>P-value for difference in CAC progression rates</td>
<td>NR</td>
<td>.76</td>
<td>.64</td>
<td>.60</td>
</tr>
<tr>
<td>Author-reported or extracted</td>
<td>Author-reported</td>
<td>Extracted</td>
<td>Author-reported</td>
<td>Author-reported</td>
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</tbody>
</table>

Abbreviations: BELLES, Beyond Endorsed Lipid Lowering With EBT Scanning; CAC, coronary artery calcification; CT, computed tomography; CVD, cardiovascular disease; DHCT, double-helix CT; EBCT, electron-beam CT; HCTZ, hydrochlorothiazide; HTN, hypertension; INSIGHT, International Nifedipine Study; Intervention as Goal for Hypertension Therapy; NR, not reported; RF, risk factor; SALTIRE, Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression.

Follow-up CAC score 151/208 859/886 233/298 396/434 246/277
Follow-up duration, mo 36 48 12 27/25 26/18
Baseline CAC score 528/563 205/268 348/371 195/235
Annualized rate of CAC progression 13.3/25.4 15.7/14.3 13.7/11.1 27/25 26/18
P-value for difference in CAC progression rates .76 .64 .60 NR
Author-reported or extracted Author-reported Extracted Author-reported Author-reported

The weighted mean annualized rates of CAC increase for the CVD and CKD trials are shown in **Figure 2** along with the baseline CAC score for each group.

In the 5 CKD trials, the approach was to compare different strategies for controlling hyperphosphatemia, primarily with gastrointestinal phosphate binders (Table 2).12-16 All of the CKD trials were open label with blinded CT evaluation. In these trials, treating physicians adjusted doses of multiple medications, including the phosphate binder, calcitriol and its analogues, and other drugs, to control levels of phosphorus, calcium, and parathyroid hormone at acceptable levels. In all of these trials, the primary comparison involved sevelamer hydrochloride (a non–calcium-containing phosphate binder with bile acid sequestrant properties and lipid-lowering effects) vs calcium-based binders in the form of over-the-counter calcium carbonate, prescription calcium acetate, or both. Sevelamer has been demonstrated to reduce the LDL-C level by 31%, non–high-density lipoprotein cholesterol level by 20%, and high-sensitivity C-reactive protein level by 63% in patients undergoing dialysis.13,21 In the Calcium Acetate Renagel Evaluation-2 trial, atorvastatin was given to both groups to lower the LDL-C level with an attempt to control for this confounding effect of sevelamer.13 In addition, in this trial, the interscan variability was 11.8% by means of the Agatston score and 10.3% with the volumetric score. The correlation coefficient for the baseline and follow-up scans increased significantly with higher baseline CAC scores and reached 0.99 for scores greater than 400 at baseline.22 The mean weighted baseline CAC score in the CKD trials was 923.0 (402.4) (range, 340.0-1712.0). Only the Renagel in New Dialysis trial reported data on clinical outcomes, including 11 deaths with sevelamer therapy (5.3 per 100 patient-years) compared with 23 deaths with calcium-containing binders (10.6 per 100 patient-years) (P = .05).23
Figure 3 demonstrates the inverse relationship between baseline CAC score and the annualized mean weighted progression. There was a modest inverse relationship ($r = -0.19$, $P < .001$) between baseline CAC scores and the annualized change. Figure 4 displays the scatterplots between the change in LDL-C level and the annualized mean weighted change in CAC. The correlation between baseline coronary artery disease and the percentage LDL-C reduction was $r = 0.07$, $P < .001$. Likewise, there was a minimal correlation ($r = 0.10$, $P < .001$) between LDL-C change and CAC progression. Because baseline and follow-up calcium, phosphorus, and parathyroid hormone levels were not collected in the CVD trials and, for the most part, were treated by multiple drugs as in the CKD trials, scatterplots for these changes were not constructed.

**COMMENT**

We found that the annualized percent increase in CAC is a measurable variable in humans amenable to randomized trials. The rates of annualized increases in CAC are higher for CKD and dialysis populations than for general CVD populations in which renal function is not specified. Despite the reported findings in 4 of these trials (International Nifedipine Study: Intervention as Goal for Hypertension Therapy, Russo et al., Treat to Goal [TTG], and Renagel in New Dialysis) that there was a differential treatment effect on the change in CAC, we found that there was no clear and consistent impact of a specific treatment on the calculated mean annualized percentage CAC progression when only subjects with baseline and follow-up scans were analyzed. Importantly, partly on the basis of the positive findings of the TTG at the time, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease stated that non–calcium-containing phosphate binders (ie, sevelamer) were preferred in patients undergoing dialysis who had severe vascular calcification. Our analysis suggests that the find-
ings of the TTG place the sevelamer-treated group as an outlier with reversal of CAC. This may have been due to error or sources of bias within the trial. We found that subjects with very high baseline CAC scores appeared to have lower rates of annualized increases in CAC. However, within the TTG, there appeared to be a greater differential in the relative rates of CAC advancement from 26 to 52 weeks, suggesting that greater durations may be needed to evaluate evolving patterns in the rate of calcification. Because the largest single treatment effect occurred with sevelamer in the TTG, it is possible that the failure of the Calcium Acetate Renagel Evaluation-2 and Bone Remodeling and Coronary Calcification trials to confirm the TTG finding represents a lack of power in these small trials.

There was a very weak relationship between LDL-C reduction and the change in CAC. In trials with a 40% to 55% reduction in LDL-C level, there appeared to be unabated increases in CAC by approximately 25%. In 1 trial (Renagel in New Dialysis), treatment with sevelamer plus a mild reduction in LDL-C level appeared to translate into an attenuation of CAC change.

and lower mortality during follow-up. This trial was followed by the larger Dialysis Clinical Outcomes Revisited trial that failed to confirm mortality reduction in patients undergoing dialysis who were treated with sevelamer compared with calcium-based phosphate binders. Thus, either LDL-C reduction with sevelamer or the restriction of oral calcium with this strategy does not appear to affect CAC or cardiovascular outcomes. This statement is further supported by 2 large and well-conducted randomized trials of statins vs placebo in patients undergoing dialysis who show no difference in cardiovascular outcomes despite large reductions in LDL-C level. Conversely, in the St Francis Heart Trial, a large LDL-C reduction with atorvastatin had no effect on the advancement in CAC but did show a nonsignificant trend (33% risk reduction, \( P = .07 \)) for lower cardiovascular events during follow-up. A partial explanation for the null effect found in this study is that most of these trials were not placebo controlled; hence, there were minimal biological differences created by the 2 treatment allocations.

There is considerable interest in noninvasive measures of coronary atherosclerosis that can be used to test therapies and act as surrogates for clinically meaningful end points such as quality of life, myocardial infarction, cardiovascular death, and all-cause mortality. Our analysis of the progression of CAC suggests that this variable is not a reliable surrogate. In addition, because calcification occurs early in the course of atherosclerosis (beginning with small amounts on cholesterol crystals within the lipid pool and later with transformation of vascular smooth muscle cells into osteoblastic cells), the process of calcification itself may not be directly related to an individual’s risk of plaque rupture. Schoenhagen and Tuzcu proposed that densely calcified plaques might represent later-stage lesions that may be less prone to rupture. In support of this concept, 3 studies using different forms of imaging to assess lesion calcification have suggested that more calcified plaques may be more stable over time than less calcified or noncalcified
Nicholls and coworkers have demonstrated that calcified plaques have smaller increases in atheroma volume, which also suggests that calcification may represent lesions less prone to rupture. Multiple studies have confirmed that the degree of CAC at baseline or the change in CAC over time is not related to changes in inflammatory factors, including high-sensitivity C-reactive protein or phospholipase A2.

How can our findings relate to the large body of work demonstrating that baseline and progressive CAC are risk predictors for cardiac events? It appears that CAC identified by CT scanning is a proxy for the burden of atherosclerosis summed over all 3 coronary arteries. Thus, coexistent more lipid-laden and less calcified lesions may be future culprit lesions in those identified with higher CAC scores at baseline. However, therapies aiming to reduce the overall CAC score have not been successful in the short term, and there appears to be no meaningful translation into hard clinical events. This is an important observation because several clinical trials are planned and under way that use the change in CAC score as an end point. On http://clinicaltrials.gov on February 27, 2009, we found 61 registered CAC trials, 19 of which were interventional studies with coronary calcification listed as a clinical outcome. Treatments included statins, sevelamer, calcium, its analogs, cinacalcet hydrochloride, bisphosphonates, parathyroidectomy, phytonadione, sodium thiosulfate, angiotensin receptor blockers, thiazolidinediones, stem cells, and lifestyle changes. Although our study does not offer hope that the annualized change in CAC can be a clinically useful end point, these ongoing trials will shed additional light on the impact, if any, of a variety of interventions on this component of atherosclerosis.

Our study has all the limitations of systematic reviews that use tabular information abstracted from published articles. In many studies, appropriate intent-to-treat principles were used. This means that all subjects with baseline scans contributed CAC data and only those with follow-up scans contributed the second data point. In addition, several studies reported only the numerical change in CAC without giving either the baseline or follow-up values. The reporting of mean changes, as the only reportable measures of central tendency for all studies, was problematic because it could not reflect varying rates of individual calcification according to disease severity. Thus, we used extraction to derive the best estimate of the change in calcification in those who had evaluable data and contributed both baseline and follow-up scans. It was impossible to derive measures of variance from the extracted CAC values; therefore, we did not report measures of 95% confidence limits around the mean annualized rates because this would not be an accurate reflection of confidence. All of the studies had dropout rates and some degree of crossover or drop-in of treatments for either CVD or CKD with bone and mineral disorders. It was not feasible by tabular methods to control for these factors. However, we did evaluate a range of baseline CAC scores and a large range in changes in LDL-C level and failed to demonstrate clinically meaningful relationships. We recognize that 1 year may have not been a long enough time to observe attenuation in the advancement of atherosclerosis; conversely, it was evident that, despite the intervention attempts, there appeared to be no treatment effect overall at a 12-month interval.

In conclusion, the annual rate of CAC increase was measured in 10 trials and had an observed rate of 17.2%, which was moderately higher for patients with CKD and those receiving dialysis. We observed no consistent or reproducible treatment effect of any therapy on this outcome. These data suggest that CAC may not be a suitable surrogate target for treatment trials in patients with cardiovascular or renal disease when measured after 12 months or reported on an annualized basis.

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the manuscript for important intellectual content: McCullough. Statistical analysis: McCullough. Financial Disclosure: None reported.

REFERENCES