Annual Progression of Coronary Calcification in Trials of Preventive Therapies

A Systematic Review

Peter A. McCullough, MD, MPH; Kavitha M. Chinnaiyan, MD

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.

Arch Intern Med. 2009;169(22):2064-2070

©2009 American Medical Association. All rights reserved.

For editorial comment see page 2051

METHODS

We performed a PubMed search using the following search terms: coronary calcification...
chronic kidney disease (CKD) (n=101,609), and coronary atherosclerosis.

The Women's Health Initiative Coronary Artery Calcium Study was excluded because it had no baseline CAC score and a single measurement was obtained at the midpoint of the trial period.6 This approach yielded 10 trials that met our search criteria (Figure 1).

Each trial was evaluated and had data extracted only on those subjects who had a baseline scan and at least 1 follow-up scan. Only 1 repeated measure, taken at the point in time closest to 12 months, was used in the analysis. In trials in which there was more than 1 follow-up scan, the scan nearest to 1 year was used for the analysis. For quantitative synthesis, the technique of obtaining and computing the CAC as well as baseline and follow-up scores was recorded. In the event that either the baseline or the follow-up mean calcium score was not given, it was calculated from the mean absolute change reported in the article. The mean annualized progression of CAC was computed by means of the following formula: CAC progression = (CACfollow-up − CACbaseline)/(CACbaseline) (interscan years). All extracted data were entered into a database, and statistical analysis was performed with SPSS version 10 (SPSS Inc, Chicago, Illinois). Descriptive statistics are reported as means (SDs) or counts with proportions as appropriate. The annualized rates of progression were weighted according to the number of subjects in the randomized groups (sample size). Because trials recruited very different populations and therapies affected different biological measures (blood pressure, lipids, calcium, or phosphate), quantitative comparisons were not attempted with respect to differential efficacy or harm of treatment between studies (ie, no meta-analytic techniques were used).

RESULTS

A total of 10 trials were identified, reporting data on 2612 patients with evaluable data.7–16 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 = 777; 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.17–20 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.8–11 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 dur-

**Figure 1.** Derivation of clinical trials included for systematic review. CAC indicates coronary artery calcium; WHI, Women’s Health Initiative.
Figure 2

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></th>
<th>INSIGHT,7 2001</th>
<th>St Francis Heart Study,8 2005</th>
<th>BELLES Trial,9 2005</th>
<th>Schermmund et al.,10 2006</th>
<th>SALTIRE,11 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>HTN, ≥1 CVD RF</td>
<td>Asymptomatic, screened positive for CAC</td>
<td>Postmenopausal</td>
<td>Asymptomatic, screened positive for CAC, ≥2 CVD RFs</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>Age, y</td>
<td>67</td>
<td>59</td>
<td>64</td>
<td>-62</td>
<td>-70</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>38</td>
<td>26</td>
<td>100</td>
<td>26</td>
<td>24</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, 80 mg/atorvastatin calcium, 10 mg</td>
<td>Atorvastatin calcium, 80 mg/placebo</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>
<td>39/49</td>
</tr>
<tr>
<td>Blinding CT</td>
<td>Yes</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>
<td>DHCT</td>
</tr>
<tr>
<td>Blinding</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hounsfield threshold for calcification, U</td>
<td>&gt;90</td>
<td>&gt;130</td>
<td>&gt;130</td>
<td>&gt;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>
<td>2.7</td>
</tr>
<tr>
<td>Method</td>
<td>Agatston</td>
<td>Agatston</td>
<td>Volumetric</td>
<td>Volumetric</td>
<td>Agatston</td>
</tr>
<tr>
<td>Qualifying score for entry</td>
<td>≥10</td>
<td>≥80th Percentile CAC for age and sex score (26-128 women, 69-368 men)</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Baseline CAC score</td>
<td>108/118</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>
<td>24</td>
</tr>
<tr>
<td>Follow-up CAC score</td>
<td>151/208</td>
<td>859/886</td>
<td>233/298</td>
<td>396/434</td>
<td>246/277</td>
</tr>
<tr>
<td>Annualized rate of CAC progression b</td>
<td>13.3/25.4</td>
<td>15.7/14.3</td>
<td>13.7/11.1</td>
<td>27/25</td>
<td>26/18</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>
<td>NR</td>
</tr>
<tr>
<td>Author-reported or extracted</td>
<td>Author-reported</td>
<td>Extracted</td>
<td>Author-reported</td>
<td>Author-reported</td>
<td>Author-reported</td>
</tr>
</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.

aCalculated from article.

bAnnual rate of CAC progression = (CAC_{follow-up} − CAC_{baseline})/CAC_{baseline}\times\text{(interscan years)}.

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. 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. In addition, in this trial, the interset variance 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. 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).
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 scatterplot 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 percentage 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, \(^{7}\) Russo et al., \(^{12}\) Treat to Goal [TTG], \(^{13}\) and Renagel in New Dialysis), \(^{14}\) 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. \(^{24}\)

Our analysis suggests that the find-
effect occurred with sevelamer in the cause the largest single treatment needed to evaluate evolving patterns in the rate of calcification. Be-

ting that greater durations may be 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 due to 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

Figure 2. Annualized weighted mean increase in coronary artery calcification (CAC) progression per year expressed as a percentage increase from baseline in cardiovascular disease (CVD) trials (n=5) and chronic kidney disease (CKD) trials (n=5). Mean (SD) baseline CAC scores are given below the graph.

Figure 3. Annualized weighted mean increase in coronary artery calcification (CAC) progression per year according to baseline CAC score for all 10 trials, showing 21 treatment groups. ATV indicates atorvastatin calcium; BLS, Beyond Endorsed Lipid Lowering With EBT (electron-beam tomography) Scanning; BRiC, Beyond Renagel in Dialysis, treatment with sevelamer plus a mild reduction in LDL-C level appeared to translate into an attenuation of CAC change due to 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.

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 planned include statins, sevelamer, calcitriol and its analogues, 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.

Accepted for Publication: August 18, 2009.

Correspondence: Peter A. McCullough, MD, MPH, Divisions of Cardiology and Nutrition and Preventive Medicine, William Beaumont Hospital, Beaumont Health Center, 4949 Coolidge, Royal Oak, MI 48073 (peteramccullough@gmail.com).

Author Contributions: Study concept and design: McCullough. Acquisition of data: McCullough. Analysis and interpretation of data: McCullough and Chinnaiyan. Drafting of the manuscript: McCullough and Chinnaiyan. Critical revision of


