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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METHODS

We performed a PubMed search using the following search terms: coronary calcification
(n=5726), calcium score (n=2970), coronary atherosclerosis (n=101 609), and chronic kidney disease (CKD) (n=95 187). Citations were dated from 1928 to 2009. The search was then refined to include randomized trials only (n=63); these articles were reviewed and 13 were found to be the primary reports of randomized controlled trials. Two trials consisting of 10 patients or fewer in each arm were considered pilot studies and excluded.4,5 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 = (CAC follow-up − CAC baseline)/CAC baseline (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-
ing 4 years with atorvastatin calcium, 20 mg, compared with placebo (6.9% vs 9.9%, \( P = .08 \)).\(^7\) The International Nifedipine Study: Intervention as Goal for Hypertension Therapy trial, comparing long-acting nifedipine with a combination of hydrochlorothiazide and amiloride hydrochloride, found a lower rate of CAC progression with nifedipine. However, the extracted annual rates could not be compared without additional information.\(^7\) 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).\(^6\) 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 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.\(^7\) 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.\(^\text{22}\) 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) (\( P = .05 \)).\(^{23}\)

**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**

- **Population**
  - HTN, ≥1 CVD RF
  - Asymptomatic, screened for CAC
  - Postmenopausal
  - Asymptomatic, screened for CAC, ≥2 CVD RFs
  - Aortic stenosis

- **Age, y**
  - 67
  - 69-368 men
  - 26
  - 20 mg
  - 64
  - 255
  - 26
  - 62
  - 277

- **Female sex, %**
  - 25
  - 60
  - 100
  - 26
  - 24

- **Drug and dosage**
  - Nifedipine, 30 mg/HCTZ, 25 mg + amiloride hydrochloride, 2.5 mg
  - Atorvastatin calcium, 20 mg + ascorbic acid, 1 g + alpha tocopherol, 1000 U/placebo
  - Atorvastatin calcium, 80 mg/pravastatin sodium, 40 mg
  - Atorvastatin calcium, 80 mg/atorvastatin calcium, 10 mg
  - Atorvastatin calcium, 80 mg/placebo

- **No. with evaluable data**
  - 101/100
  - 490/515
  - 218/257
  - 175/191
  - 39/49

- **CT**
  - DHCT
  - EBCT
  - EBCT
  - EBCT
  - DHCT

- **Qualifying score for entry**
  - Agatston
  - Volumetric
  - Volumetric
  - Agatston
  - None

- **Baseline CAC score, %**
  - 528/563
  - 205/268
  - 348/371
  - 195/235

- **Follow-up duration, mo**
  - 36
  - 48
  - 12
  - 12
  - 24

- **Follow-up CAC score, %**
  - 3
  - 859/886\(^a\)
  - 233/298
  - 396/434
  - 246/277\(^a\)

- **Annualized rate of CAC progression, %**
  - 2.5 mg
  - 10 mg
  - 100 U/placebo

- **Value for difference in CAC progression**
  - .76
  - .64
  - .60
  - NR

- **Author-reported or extracted**
  - Author-reported
  - Extracted
  - Author-reported
  - Author-reported

**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.

\(^{a}\) Calculated from article.

\(^{b}\) Annual rate of CAC progression = (CAC\(_\text{follow-up}\) – CAC\(_\text{baseline}\))/(CAC\(_\text{baseline}\)\times\text{interscan years}).
for the most part, were treated by mul-
not collected in the CVD trials and,
and parathyroid hormone levels were
CAC progression. Because baseline
P

United States.

Kidney Disease; CT, computed tomography; EBCT, electron-beam CT; MSCT, multislice CT; NR, not reported; RIND, Renagel in New Dialysis; TTG, Treat to Goal; US, United States.

Figure 3 demonstrates the in-
verse 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 be-
tween the change in LDL-C level and
the percentage LDL-C reduction was
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 mul-
tiple drugs as in the CKD trials, scatter-
plots for these changes were not
constructed.

**COMMENT**

We found that the annualized per-
centage increase in CAC is a mea-
surable variable in humans ame-
nable to randomized trials. The rates of
annualized increases in CAC are
higher for CKD and dialysis popu-
lations than for general CVD popu-
lations in which renal function is not
specified. Despite the reported find-

ings in 4 of these trials (International
Nifedipine Study: Intervention as Goal for Hypertension Therapy, Russo et al,12 Treat to Goal [TTG],13 and Renagel in New Dialy-
sis14) that there was a differential
treatment effect on the change in
CAC, we found that there was no
clear and consistent impact of a spe-
cific 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 Kid-
ney Foundation Kidney Disease Out-
comes Quality Initiative Clinical
Practice Guidelines for Bone Me-
tabolism and Disease in Chronic
Kidney Disease stated that non–
calcium-containing phosphate bind-
ers (ie, sevelamer) were preferred in
patients undergoing dialysis who
had severe vascular calcification.24

Our analysis suggests that the find-

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**Table 2. Clinical Trials Measuring CAC as an Outcome in the Population With CKD**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Drug and dosage</th>
<th>Population</th>
<th>Age, y</th>
<th>Female sex, %</th>
<th>No. with evaluable data</th>
<th>CT Modality</th>
<th>Baseline CAC score</th>
<th>Follow-up duration, mo</th>
<th>Follow-up CAC score</th>
<th>Annualized rate of CAC progression</th>
<th>P value for difference in CAC progression</th>
<th>Author-reported or extracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer hydrochloride, 1.6 g/calcium carbonate, 2 g/low-phosphorus diet alone</td>
<td>Sevelamer hydrochloride, 6.5 g/calcium-based phosphate binder (calcium acetate, 4.6 g, in US; calcium carbonate, 3.9 g, in Europe)</td>
<td>Stage 3-5 CKD, not receiving dialysis</td>
<td>54</td>
<td>15</td>
<td>27/28/29</td>
<td>MSCT</td>
<td>415/340/369</td>
<td>24</td>
<td>453/473/547</td>
<td>−3.0/13.4</td>
<td>.09</td>
<td>Extracted</td>
</tr>
<tr>
<td></td>
<td>Sevelamer hydrochloride, 8 g/calcium-based phosphate binder, 2.3 g of elemental calcium (3 patients received calcium acetate; 38, calcium carbonate; 14, both)</td>
<td>Stage 5 CKD, receiving hemodialysis</td>
<td>57</td>
<td>35</td>
<td>62/70</td>
<td>EBCT</td>
<td>1125</td>
<td>12</td>
<td>1666</td>
<td>13.4/25.3</td>
<td>.09</td>
<td>Extracted</td>
</tr>
<tr>
<td></td>
<td>Sevelamer hydrochloride, 7.3 g + atorvastatin, 28 mg/calcium carbonate, 5.5 g + atorvastatin, 33 mg</td>
<td>Stage 5 CKD, new to hemodialysis</td>
<td>58</td>
<td>37</td>
<td>45/47</td>
<td>EBCT</td>
<td>889</td>
<td>6</td>
<td>735/836</td>
<td>29/30</td>
<td>.09</td>
<td>Extracted</td>
</tr>
<tr>
<td></td>
<td>Sevelamer hydrochloride, ≥12 g/calcium carbonate, ≥2.63 g of elemental calcium</td>
<td>Stage 5 CKD, receiving hemodialysis</td>
<td>59</td>
<td>49</td>
<td>49/58</td>
<td>EBCT</td>
<td>1069b</td>
<td>12</td>
<td>1116/1297</td>
<td>27.1/26.8</td>
<td>.13</td>
<td>Extracted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage 5 CKD, receiving hemodialysis</td>
<td>47</td>
<td>767/1263</td>
<td>27/16</td>
<td>MSCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** BRiC, Bone Remodeling and Coronary Calcification; CAC, coronary artery calcification; CARE-2, Calcium Acetate Renagel Evaluation-2; CKD, chronic kidney disease; CT, computed tomography; EBCT, electron-beam CT; MSCT, multislice CT; NR, not reported; RIND, Renagel in New Dialysis; TTG, Treat to Goal; US, United States.

- Numbers represent the patients who started therapy.
- *Calculated from article.
- Annual rate of CAC progression = (CACfollow-up − CACbaseline)/(CACbaseline)(interscan years).
ings of the TTG place the sevelamer-treated group as an outlier with reversal of CAC. This may have been due to α 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 Renalag 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 by approximately 25%. In 1 trial (Renagel in New Dialysis), treatment with sevelamer or the restriction of oral calcium with this strategy did 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.26,27 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.28 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.29 Schoenhagen and Tuzcu10 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, phytanidine, 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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REFERENCES