The effect of statin therapy on coronary atherosclerosis as assessed by computed tomography

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C Coronary artery calcium (CAC) is a non-invasive marker of atherosclerosis (1–5). In several large-scale studies, coronary artery calcium scoring (CACS) has been shown to add prognostic value in predicting cardiovascular events when added to traditional risk stratification such as the Framingham score (1,6–8). The 2010 ACCF/AHA Guidelines for Cardiovascular Disease have advocated the use of CACS for cardiovascular risk assessment in asymptomatic patients considered at intermediate risk through traditional assessment (9).

Statin therapy is an essential tool in the primary and secondary prevention of cardiovascular disease (10–17). Several trials have demonstrated that statins can induce regression of coronary atherosclerosis measured by intravascular ultrasound (IVUS) in patients treated with high-intensity statin therapy (18,19). Other studies have suggested that statin therapy promotes atheroma calcification, thereby stabilizing plaque (20,21). Whether regression of atherosclerosis by statins can be assessed using serial CACS or CT angiography remains controversial.

Early observational studies (22–24) suggested that statin therapy had the potential to slow CACS. However, subsequent randomized controlled trials (25–29) failed to confirm this. And more recent studies of statin effects on CACS in special populations such as Systemic Lupus Erythematosus (SLE) (30) and chronic kidney disease (CKD) patients are also controversial due to small study populations (31).

Recent studies have also investigated plaque changes as measured by non-calcium-based indices of coronary artery disease on CCTA to further characterize features of coronary plaques. Whether these measurements are useful for serial assessments remains to be seen. Accordingly, the purpose of this review is to elucidate the effect of statin therapy on CACS and non-calcium-based indices of coronary artery disease progression through a systematic review.

METHODS

Data sources and searches

A systematic search was performed on the following databases for articles published from January 1, 1980 through May 29, 2015: American College of Physicians Journal Club, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessment, NHS Economic Evaluation Database, Embase, Health and Psychosocial Instruments, MEDLINE, and Health Technology Assessment, Embase, Health and Psychosocial Instruments, MEDLINE. In addition, the search was limited to English language studies in adult humans only. The search was updated on January 12, 2016, and again on April 28, 2016 to include any recent relevant articles. To ensure a comprehensive search strategy, an academic biomedical librarian was consulted. The search strategy was performed as outlined in Figure 1.

![Figure 1: Selection of relevant articles from literature search](image-url)
Selection criteria

Inclusion criteria required studies to be original English language peer-reviewed publications that quantitatively measured the relationship between documented statin therapy and serial assessments of calcium and non-calcium-based indices of coronary artery disease as measured by CCTA. Case reports, review articles, poster abstracts, conference proceedings, commentaries and guidelines were excluded. In addition, studies with no documented record of statin therapy and studies without a serial measurement were manually excluded. The authors independently selected studies published between 1980 and 2016 as outlined in Figure 1. References from relevant studies were further assessed for additional relevant publications.

Data extraction

The following data was manually extracted from relevant publications: (1) study design, (2) study population characteristics, (3) number of subjects included in study, (4) specific statin used and comparison treatment, (5) imaging modality, (6) interval between imaging, (7) method used to measure CACS, (8) change in CACS or non-calcium based indices over elapsed time period. Two trained researchers extracted the data in collaboration to ensure that there was agreement between quantitative and qualitative information obtained from each manuscript selected for inclusion.

Individual manuscripts and data extracted were screened for homogeneity of reported outcomes. Due to the significant heterogeneity between reported outcomes, a meta-analysis was not conducted. Instead, a qualitative analysis was used to report our findings.

RESULTS

Studies identified

Figure 1 summarizes the screening and selection process. In total, 1858 papers were identified as potentially relevant. Of these, 98 manuscripts were identified and screened, of which an additional 7 papers were selected for full-text review, and 1 was selected for inclusion. The search was updated again on April 28, 2016 and 53 additional papers were screened, none of which met the inclusion criteria.

Study characteristics

Of the 22 studies, 9 were randomized controlled trials. The remainder of the studies consisted of retrospective and prospective observational studies. The study populations were highly variable, including HIV-infected patients, patients with chronic kidney disease, and asymptomatic patients undergoing routine screening. The majority of studies used multidetector computed tomography (MDCT) or electron-beam computed tomography (EBCT) as their primary imaging modality to measure CACS. A significant number of studies also included non-calcium-based indices measured by CCTA such as plaque volume, non-calcified plaque volume and low attenuation plaque volume. A summary of the studies selected for this review can be found in Table 1, which outlines the study design, study population, inclusion/exclusion criteria, and imaging modality utilized.

Statin therapy

Most studies compared some form of statin therapy to no statin therapy or placebo. Three studies compared intensive statin therapy to less intensive therapy. Statin therapy reduced LDL cholesterol in all studies where it was reported. Atorvastatin was the most commonly used statin but effects of Simvastatin, Rosuvastatin, Fluvastatin and Cerivastatin were also reported (Supplementary Table 1).

Coronary artery calcium score progression

Measures of coronary calcification included Agatston scoring and volumetric calcium scoring. Some studies reported pre-treatment and post-treatment CACS, while others reported only the changeover defined periods. Eighteen studies followed progression of calcium-based indices with statin therapy (Table 2a).

Observational trials included in this review (22–24,32–38) did not consistently demonstrate reduction in progression of CACS. Five studies showed a reduction in CACS with statin therapy (22–24,33,37). Three studies did not demonstrate any significant change. 32,35 Two studies showed increased CACS with statin therapy (34,38). A statistically significant reduction in relative calcium volume score was shown by Mohler et al but this was not reflected in the analysis of Agatston scores which showed no change (36). The remainder of the observational studies assessed non-calcium-based indices of plaque progression.

The randomized controlled trials included in this review (25–29,31) failed to demonstrate any significant reduction in CACS with statin therapy. One study (39) by Lo et al demonstrated reduced non-calcified plaque volume and high-risk plaque features in a small population of HIV-infected individuals with subclinical atherosclerosis, but did not show any significant change.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Imaging modality</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auscher et al. (41) 2015</td>
<td>Prospective randomized open-label</td>
<td>Documented STEMI or NSTEMI</td>
<td>Documented STEMI or NSTEMI according to current guidelines recruited &lt;48h after admission</td>
<td>Ongoing high-dose statin</td>
<td>MDCT</td>
<td>Statin therapy increases dense calcium volume but does not affect total plaque volume</td>
</tr>
<tr>
<td>Lo et al. (37) 2015</td>
<td>Randomized double blind placebo controlled</td>
<td>HIV-infected patients with subclinical atherosclerosis</td>
<td>Men and women 18-60 years of age with HIV disease</td>
<td>Concurrent use of statin</td>
<td>MDCT</td>
<td>Statins reduce non-calcified plaque volume and high risk plaque features</td>
</tr>
<tr>
<td>Lemos et al. (29) 2013</td>
<td>Open label randomized controlled</td>
<td>Nondialyzed CKD patients</td>
<td>Older than 18 years</td>
<td>Presence of chronic inflammatory diseases</td>
<td>MDCT</td>
<td>Statin therapy does not delay progression of CAD</td>
</tr>
<tr>
<td>Zeb et al. (38) 2013</td>
<td>Retrospective observational</td>
<td>Patients being evaluated for CAD without known prior heart disease or revascularization</td>
<td>Patients undergoing coronary CTA between 2006-2009</td>
<td>Scans with significant artifact or poor image quality</td>
<td>MDCT</td>
<td>Statin therapy results in reduced progression of low attenuation plaques and non-calcified plaques</td>
</tr>
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</tr>
</thead>
</table>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Criteria</th>
<th>Findings</th>
<th>Control Group</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plazak et al. (28) 2011</td>
<td>Prospective randomized double blind controlled study</td>
<td>Systemic lupus erythematosus patients with stable angina pectoris</td>
<td>- At least 4 of American College of Rheumatology criteria for SLE and in stable clinical condition</td>
<td>MDCT</td>
<td>Statin therapy reduces progression of CACS</td>
</tr>
<tr>
<td>Tenenbaum et al. (30) 2011</td>
<td>Longitudinal</td>
<td>Westernized Hong Kong Chinese individuals with chest pain and coronary risk factors</td>
<td>- Westernized ethnic Chinese urban inhabitants&lt;br&gt; - Positive cardiac risk factors and chest pain&lt;br&gt; - First presentation chest symptoms with no prior cardiac CT</td>
<td>MDCT</td>
<td>No change in CACS with statin therapy</td>
</tr>
<tr>
<td>Goh et al. (31) 2010</td>
<td>Prospective longitudinal</td>
<td>Type 2 diabetics without prior history of coronary disease</td>
<td>- Type 2 diabetes &gt; 1 year duration&lt;br&gt; - Age 30 – 65 years&lt;br&gt; - No prior history of coronary heart disease</td>
<td>MDCT</td>
<td>Statin therapy decreases plaque and necrotic core volumes</td>
</tr>
<tr>
<td>Hoffmann et al. (39) 2010</td>
<td>Retrospective longitudinal</td>
<td>Men with established cardiovascular risk, but no known CAD</td>
<td>- Male patients&lt;br&gt; - Elevated risk of CAD (PROCAM score &gt; 3rd quintile)&lt;br&gt; - Not receiving lipid lowering therapy</td>
<td>MDCT</td>
<td>Statin therapy slows progression of non-calcified plaques</td>
</tr>
<tr>
<td>Inoue et al. (40) 2010</td>
<td>Prospective longitudinal</td>
<td>Patients undergoing coronary CTA for suspected CAD</td>
<td>- Consecutive patients undergoing MDCT as follow-up to original CT study&lt;br&gt; - Referral by primary care physician</td>
<td>MDCT</td>
<td>Statin therapy is an independent predictor of CACS progression</td>
</tr>
<tr>
<td>Anand et al. (32) 2007</td>
<td>Prospective longitudinal</td>
<td>Subjects with moderate-severe aortic stenosis</td>
<td>- Aortic valve area 0.7 – 2.0cm²&lt;br&gt; - EBT and echocardiographic analysis at baseline and one year after enrollment</td>
<td>MDCT</td>
<td>Statin therapy decreases progression of CACS</td>
</tr>
<tr>
<td>Burgstahler et al. (33) 2007</td>
<td>Prospective longitudinal</td>
<td>Patients with established cardiovascular risk, but no known CAD</td>
<td>- Male patients&lt;br&gt; - Elevated risk of CAD (PROCAM score &gt; 3rd quintile)&lt;br&gt; - Not receiving lipid lowering therapy</td>
<td>MDCT</td>
<td>Statin therapy does not reduce progression of CACS</td>
</tr>
<tr>
<td>Mohler et al. (34) 2007</td>
<td>Single center prospective observational study</td>
<td>Subjects with moderate-severe aortic stenosis</td>
<td>- Aortic valve area 0.7 – 2.0cm²&lt;br&gt; - EBT and echocardiographic analysis at baseline and one year after enrollment</td>
<td>MDCT</td>
<td>Statin therapy decreases progression of CACS</td>
</tr>
<tr>
<td>Houslay et al. (24) 2006</td>
<td>Randomized controlled trial</td>
<td>Patients with calcific aortic stenosis and coronary artery calcification</td>
<td>- Patients aged &gt; 18 years with calcific aortic stenosis (grade 1 – 3 calcification on echocardiography)&lt;br&gt; - Peak post-valve velocity of ≥ 2.5m/s</td>
<td>MDCT</td>
<td>Statin therapy does not have an effect on the rate of CACS progression</td>
</tr>
</tbody>
</table>
in CACS. Another study by Plazak et al (30) showed a reduction in CACS after 1 year of statin therapy in a group of patients with systemic lupus erythematosus (SLE).

Progression of non-calcium-based indices
Several observational studies have reported changes in plaque volume as derived from CCTA (Table 2b) (35,40–42).
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### TABLE 2a
Calcium-based indices

<table>
<thead>
<tr>
<th>Study</th>
<th>Length of Treatment</th>
<th>Calcium Measurement Method</th>
<th>CAC Progression in Untreated Group</th>
<th>CAC Progression in Treated Group</th>
<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lo et al. 2015</td>
<td>1 year</td>
<td>Agatston score, calcium mass, calcium volume, calcium density</td>
<td></td>
<td>Agatston Score 1.7</td>
<td>Agatston Score 0.9</td>
</tr>
<tr>
<td>Lemos et al. 2013</td>
<td>24 months</td>
<td>Agatston score</td>
<td>Agatston Score 13.7 +/- 0.6</td>
<td>Agatston Score 13.7 +/- 0.6</td>
<td>p&lt;0.001 (untreated)</td>
</tr>
<tr>
<td>Plazak et al. 2011</td>
<td>1 year</td>
<td>Agatston score</td>
<td>Agatston Score 2084.7 +/- 613.2 mm²</td>
<td>Agatston Score 2084.7 +/- 613.2 mm²</td>
<td>p=0.57</td>
</tr>
<tr>
<td>Tenenbaum et al. 2011</td>
<td>Median 5.6 years</td>
<td>Coronary calcium volume</td>
<td>CAC Progression in Treated Group</td>
<td>CAC Progression in Untreated Group</td>
<td></td>
</tr>
<tr>
<td>Goh et al. 2010</td>
<td>10 +/- 1.5 years</td>
<td>Agatston score</td>
<td>Agatston Score 27.2 +/- 15.5 months</td>
<td>Agatston Score 27.2 +/- 15.5 months</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Anand et al. 2007</td>
<td>Mean follow-up</td>
<td>Agatston and volumetric calcium scores</td>
<td>CACS 6.6 +/- 0.4 years</td>
<td>CACS 6.6 +/- 0.4 years</td>
<td>p=0.12</td>
</tr>
<tr>
<td>Burgstahler et al. 2007</td>
<td>488 +/- 138 days</td>
<td>Calcium volume score</td>
<td>Calcium volume score 873 +/- 1011 mm²</td>
<td>Calcium volume score 873 +/- 1011 mm²</td>
<td>p&gt;0.59 (treated)</td>
</tr>
<tr>
<td>Mohler et al. 2007</td>
<td>1 year</td>
<td>Coronary artery calcium volume</td>
<td>Calcium volume score 19.2 +/- 30.9 (absolute)</td>
<td>Calcium volume score 19.2 +/- 30.9 (absolute)</td>
<td>p=0.56 (absolute)</td>
</tr>
<tr>
<td>Terry et al. 2007</td>
<td>6 months and 12 months</td>
<td>Agatston core</td>
<td>Agatston Score 659 +/- 116 vs. 691 +/- 24</td>
<td>Agatston Score 659 +/- 116 vs. 691 +/- 24</td>
<td>p=0.07 (absolute)</td>
</tr>
<tr>
<td>Houslay et al. 2006</td>
<td>Median 2 years</td>
<td>Agatston Score</td>
<td>Agatston Score 873 +/- 1011 vs. 1017 +/- 1268</td>
<td>Agatston Score 873 +/- 1011 vs. 1017 +/- 1268</td>
<td>p=0.59 (treated)</td>
</tr>
<tr>
<td>Schmermund et al. 2006</td>
<td>12 months</td>
<td>Agatston CAC score and calcium volume score</td>
<td>Atorvastatin 10mg 26%</td>
<td>Atorvastatin 10mg 26%</td>
<td>p=0.01 (absolute)</td>
</tr>
<tr>
<td>Arad et al. 2005</td>
<td>Mean follow-up</td>
<td>Agatston score</td>
<td>Agatston Score 323 +/- 385 (absolute)</td>
<td>Agatston Score 323 +/- 385 (absolute)</td>
<td>p=0.02 (absolute)</td>
</tr>
<tr>
<td>Buchoff et al. 2005</td>
<td>27 +/- 15 months</td>
<td>Agatston score</td>
<td>Agatston Score 27.2 +/- 15.5 months</td>
<td>Agatston Score 27.2 +/- 15.5 months</td>
<td>p=0.02 (absolute)</td>
</tr>
<tr>
<td>Raggi et al. 2012</td>
<td>12 months</td>
<td>Calcium volume score</td>
<td>Calcium volume score 20.8 +/- 4.4 (absolute)</td>
<td>Calcium volume score 20.8 +/- 4.4 (absolute)</td>
<td>p&lt;0.001 (relative)</td>
</tr>
<tr>
<td>Hecht et al. 2003</td>
<td>1.2 +/- 0.7 years</td>
<td>Coronary calcium and calcium volume</td>
<td>Calcium volume score 20.8 +/- 4.4 (absolute)</td>
<td>Calcium volume score 20.8 +/- 4.4 (absolute)</td>
<td>p&lt;0.001 (relative)</td>
</tr>
<tr>
<td>Achenbach et al. 2002</td>
<td>EBCT performed on patients with mean interval of 14 months without treatment, then again after 12 months of treatment</td>
<td>Volumetric calcium score, Agatston score</td>
<td>Agatston Score 20.8 +/- 4.4 (absolute)</td>
<td>Agatston Score 20.8 +/- 4.4 (absolute)</td>
<td>p&lt;0.001 (relative)</td>
</tr>
<tr>
<td>Budoff et al. 2000</td>
<td>2.2 +/- 1.1 years</td>
<td>Agatston score</td>
<td>Agatston Score 659 +/- 116 vs. 691 +/- 24</td>
<td>Agatston Score 659 +/- 116 vs. 691 +/- 24</td>
<td>p=0.01 (relative)</td>
</tr>
<tr>
<td>Callister et al. 1998</td>
<td>13.7 +/- 0.6 months</td>
<td>Volumetric calcium score</td>
<td>Calcium volume score 659 +/- 116 vs. 691 +/- 24</td>
<td>Calcium volume score 659 +/- 116 vs. 691 +/- 24</td>
<td>p&lt;0.001 (relative)</td>
</tr>
</tbody>
</table>

### TABLE 2b
Non-calcium-based indices

<table>
<thead>
<tr>
<th>Study</th>
<th>Length of Treatment</th>
<th>Calcium Measurement Method</th>
<th>CAC Progression in Untreated Group</th>
<th>CAC Progression in Treated Group</th>
<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auscher et al 2015</td>
<td>12 months</td>
<td>Plaque volume, plaque composition, total dense calcium volume</td>
<td>Total plaque volume 2084.7 +/- 613.2 mm²</td>
<td>Total plaque volume 2084.7 +/- 613.2 mm²</td>
<td>p=0.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Agatston Score 19.1 +/- 190.2 mm²</td>
<td>Agatston Score 19.1 +/- 190.2 mm²</td>
<td>p=0.001 (relative)</td>
</tr>
</tbody>
</table>

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Three of these studies demonstrated a reduction in the progression of non-calcified plaque volume associated with statin therapy (35,40,41). In addition, Inoue et al showed that statin therapy results in a reduction of both plaque volume and necrotic core volume, implying improved plaque stability (42).

Recent randomized controlled trials have included assessments of coronary plaque from CCTA measurements, including plaque volume, composition and vulnerability (39,43). Ausher et al showed that early aggressive lipid lowering therapy increases dense calcium volume, but did not significantly affect plaque volume in patients with acute myocardial infarction (43). Lo et al demonstrated a reduction in non-calcified plaque volume and other high-risk plaque features in a small group of HIV-infected patients treated with statins (39).

### DISCUSSION

This review identified 22 articles that studied the relationship between statin therapy, CACS and non-calcified plaque changes. The data were not amenable to meta-analysis due to the heterogeneity of reported variables between studies. While multiple observational studies suggested that statin therapy may reduce CACS, this was not confirmed in prospective randomized controlled trials, the one exception being a small randomized trial suggesting that statin therapy may reduce CACS in a small group of SLE patients.

Thus, there is no firm evidence that statin therapy reduces progression of CACS. In fact, a recent meta-analysis of 2 randomized trials suggested that high-dose and long-term statin therapy increases CACS (44). Thus CACS change is an inadequate mean to assess atherosclerotic plaque progression in the setting of statin therapy.

In recent studies using CCTA, investigators have assessed various plaque features using non-calcium-based indices such as plaque volume, non-calcified plaque and low attenuation plaque burden (Table 2). Although there is suggestive evidence that total plaque volume may be improved by statin therapy, there is only one prospective RCT that has shown this in a selective population of HIV-infected individuals (39). Whether this change is associated with a reduction in cardiovascular events is awaiting demonstration. Further randomized controlled studies are required to determine whether serial CCTA measurements of non-calcium based indices are affected by statin therapy.

Treatment length must be considered when interpreting the results of these articles. Most of the studies selected included study lengths of 1 – 2 years. It is not clear whether the true effect of statin therapy on CACS can be accurately interpreted over this short time period. Studies using intravascular ultrasound (IVUS) have been performed over similar periods and have demonstrated significant regression of coronary atherosclerosis but increases in dense calcium composition, a result similar to what we note with the studies included in this systematic review (18,19,45–47).

### CONCLUSION

In conclusion, while statin therapy has been shown to affect plaque progression in studies using alternate imaging modalities, this effect has not been convincingly replicated in trials using calcium-based indices. Thus, CACS is not suitable for monitoring the effectiveness of statin therapy on atherosclerosis. Recent CCTA studies suggest that other features of coronary plaque progression such as non-calcified plaque and low attenuation plaque may be favourably affected by statin therapy. As our understanding of coronary plaque progression continues to evolve, future prospective trials are necessary to determine if progression of non-calcium based plaque indices are associated with favourable or unfavourable outcomes.

### ACKNOWLEDGEMENT

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### DISCLOSURES

Wan, Tashakkor and Mancini: None
Leipsic: Circle Cardiovascular Imaging, GE, Samsung, Phillips
Raggi: None

### REFERENCES

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