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

Darryl Wan MD1, A. Yashar Tashakkor MD1, Jonathon Leipsic MD2, Paolo Raggi MD3, G.B. John Mancini MD1

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 have advocated selective 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 ultrasonography (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 CCTA 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 of available literature documenting the effects of statin therapy on the progression of CACS and non-calcium-based indices.

METHODS

A systematic search was performed from January 1, 1980 to April 28, 2016 using these databases: Cochrane Database,ACP Journal Club, Health Technology Assessment, Embase, NHS Economic Evaluation Database, Ovid MEDLINE, Health and Psychosocial Instruments. English language publications that serially measured relationships between statin therapy and CACS or non-calcium-based indices were included. Case reports, reviews and meta-analyses were excluded. Data regarding progression of calcium and non-calcium-based indices were extracted and analyzed.

RESULTS

2159 articles were retrieved for screening. Of these, 22 met pre-defined inclusion criteria; 9 were randomized controlled trials and 13 observational studies. Observational studies did not consistently demonstrate a reduction in the progression of CACS with statin therapy. No randomized trial demonstrated convincing evidence that statin therapy reduces the progression of CACS. Limited randomized trials of CCTA suggest that statin therapy may reduce non-calcified plaque volume, but increase dense calcium volume.

CONCLUSION

Based on studies using statins, serial assessment of non-calcified plaque volume, but not CACS, may be useful for the assessment of medical interventions with postulated effects on progression or regression of atherosclerosis.

Key Words: Coronary artery calcium; CT angiography; Statins

Figure 1) Selection of relevant articles from literature search

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Received: September 14, 2016, Accepted: December 07, 2016, Published: December 09, 2016

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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 selected for full-text review after initial screening by title and abstract. Finally, 21 studies met the pre-defined criteria after full-text review. Upon updating the search (January 12, 2016), a further 246 papers were 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

Table 1:

<table>
<thead>
<tr>
<th>Study information</th>
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<tr>
<td><strong>Table 1</strong></td>
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<td><strong>Author and year</strong></td>
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<td>Auscher et al. (41)2015</td>
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<td>Lo et al. (37) 2015</td>
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<td>Lemos et al. (29)2013</td>
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<td>Zeb et al. (38) 2013</td>
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<td>Plazak et al. (28) 2011</td>
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<td>Tenenbaum et al. (30) 2011</td>
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<td>Goh et al. (31) 2010</td>
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**Effect of statin therapy on Coronary Atherosclerosis**

- **At least 4 of American College of Rheumatology criteria for SLE and in stable clinical condition**
- **Previous treatment for coronary artery disease or unstable chest symptoms**
- **Elevated risk of CAD (PROCAM score > 3rd quintile)**
- **Severely calcified lesions on CTA or lesion segments with >75% luminal stenosis**
- **Clinical symptoms of coronary artery disease or heart failure, renal failure, respiratory failure**
- **Unstable chest symptoms or patients found to be at high risk requiring revascularization**
- **Patients with known cancer**
- **Patients with type 2 diabetes > 1 year duration, age 30 – 65 years, no prior history of coronary heart disease**
- **Men with elevated risk of CAD (PROCAM score 3rd quintile)**
- **Female patients**
- **Patients with moderate-severe aortic stenosis**
- **Patients 21 – 75 years of age with triglyceride levels <500 mg/dl, HDL ≤ 50 mg/dl, LDL 100 – 130 mg/dl, or 2 other risk factors that modify LDL goal**
- **Patients aged > 18 years with calcific aortic stenosis (grade 1 – 3 calcification on echocardiography)**
- **Peak post-valve velocity of ≥ 2.5m/s**
- **Patients who were taking or would be taking statins**
- **Intolerance to statins**
- **Last presentation chest symptoms with no prior cardiac CT**
- **Cholesterol levels <600 mg/dl, LDL 100-130 mg/dl, HDL ≤ 50 mg/dl, or 2 other risk factors that modify LDL goal with triglyceride levels <600 mg/dl**
- **Patients with previous cardiac events**
- **Patients with known cancer**
- **Patients with type 2 diabetes > 1 year duration, age 30 – 65 years, no prior history of coronary heart disease**
- **Male patients**
- **Elevated risk of CAD (PROCAM score 3rd quintile)**
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**Statistical Analysis**

- **MDCT**: Statin therapy reduces progression of CACS
- **EBCT**: Statin therapy causes regression of CACS

**Conclusion**

- Statin therapy is effective in reducing CACS progression in various patient populations and clinical settings.

**References**

1. Goh et al. (31) 2010
2. Hoffmann et al. (39) 2010
3. Inoue et al. (40) 2010
4. Anand et al. (32) 2007
5. Burgstahler et al. (33) 2007
6. Mohler et al. (34) 2007
7. Terry et al. (25) 2007
8. Houslay et al. (24) 2006
### Schmermund et al. (26) 2006
Randomized controlled trial
Patients with no history of CAD and no evidence of high-grade coronary stenosis, and with ≥2 CV risk factors and CAC≥30
- Men and women aged 32 – 80 years
- Weight less than 115kg
- No history of myocardial infarction or coronary revascularization
- No hemodynamically significant stenosis demonstrated by angiogram or exercise stress test
- LDL 130-250 mg/dl without HMG-CoA reductase inhibitor therapy, or between 100-130 mg/dl with therapy
- Triglyceride < 400 mg/dl
- At least 2 cardiovascular risk factors
- History of ischemic heart disease
- Unstable angina pectoris
- Symptomatic chronic heart failure and/or left ventricular ejection fraction < 40%
- Atrial fibrillation or other arrhythmias that interfere with ECG-gated triggering of EBCT
- Type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus
- Treatment with bile acid sequestrants, fibrates, nicotinic acid derivatives, orlistat
- Lack of effective contraception or pregnancy and lactation in women of childbearing potential
- EBCT
- Statin therapy does not affect CACS progression

### Arad et al. (23) 2005
Randomized controlled trial
Asymptomatic apparently healthy men and women ages 50-70 with CAC scores at or above 90th percentile
- Men and women aged 50 – 70 years
- No history, symptoms or signs of atherosclerotic cardiovascular disease
- Insulin-dependent diabetes
- Triglycerides >500mg/dL
- LDL ≥175mg/dl in men
- Total cholesterol >300mg/dl in women
- Weight >136kg
- Disease likely to cause death within 5 years
- Current therapy with estrogens or glucocorticoids
- Refusal to discontinue lipid-lowering drugs, vitamin C or vitamin E
- Uncontrolled hypertension
- LDL <90mg/dl
- EBCT
- Statin therapy does not affect the progression of CACS

### Budoff et al. (35) 2005
Cross-sectional
Physician-referred asymptomatic patients with type 2 diabetes
- Type 2 diabetic patients without evidence of CAD
- Patient has contraindication to use of statins
- Treatment with lipid-lowering drugs other than HRT within 3 months of screening
- Evidence of secondary hyperlipidemia
- Renal dysfunction
- Uncontrolled Type 1 or 2 diabetes mellitus
- Myocardial infarction <6 months before screening
- Uncontrolled hyperthyroidism
- Plasma triglyceride >600mg/dL
- EBCT
- Statin therapy induces a reduction in the rate of CACS progression

### Raggi et al. (27) 2005
Randomized controlled trial
Hyperlipidemic postmenopausal women
- Postmenopausal women aged 55 – 75 years
- Menopause as defined by amenorrhea for at least 1 year or receipt of hormone replacement for at least 1 year
- LDL ≥130mg/dl for women with CHD, CHD risk equivalents or ≥ 2 risk factors and 10-year CHD risk of 10-20%
- LDL ≥160mg/dl for patients with ≥ 2 CHD risk factors and 10-year CHD risk of <10%
- Patients with 0 – 1 risk factors
- Total calcium volume score ≥30 at baseline
- EBCT
- Statin therapy does not affect CACS progression

### Hecht et al. (22) 2002
Prospective cohort
Patients who underwent EBCT, CAC score ≥20, no known CAD, LDL >130mg/dL
- Coronary calcification in EBCT
- LDL >130mg/dL
- No lipid-lowering therapy
- Time interval of at least 12 months since EBCT scan with documented Agatston score ≥20
- No known CAD or symptoms suggestive of disease
- Sinus rhythm
- Normal renal function
- EBCT
- Statin therapy reduces progression of CACS

### Budoff et al. (21) 2000
Observational
Asymptomatic patients referred by primary physician to evaluate the presence and amount of coronary calcium
- Asymptomatic patients who underwent 2 consecutive EBCT scans at least 12 months apart
- Documented CAD before entry into the study
- Inadequate images for analysis on either EBCT scan
- EBCT
- Statin therapy induces a reduction in the rate of CACS progression

### Callister et al. (20) 1998
Retrospective observational
Patients with no history of CAD, referred by primary care physician for screening EBCT
- Asymptomatic patients with no history of CAD
- Referred by primary care physicians for serial EBCT at intervals of 12-15 months
- Inadequate image quality
- Initial calcium volume score <30
- EBCT
- Statin therapy reduces CACS progression

### Progression of non-calcium-based indices
Several observational studies have reported changes in plaque volume as derived from CCTA (Table 2b) (35,40–42).
### 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>Agatston Score 1.7</td>
<td>Agatston Score 0.9</td>
<td>p = 0.74</td>
</tr>
<tr>
<td>Lemos et al. 2013</td>
<td>24 months</td>
<td>Agatston score</td>
<td>Agatston Score 99.7 +/- 190.8 (absolute)</td>
<td>Agatston Score 99.3 +/- 283.7 (absolute)</td>
<td>p = 0.28 (absolute)</td>
</tr>
<tr>
<td>Plazak et al. 2011</td>
<td>1 year</td>
<td>Agatston score</td>
<td>Agatston Score 32.1 +/- 39.1 vs. 59.5 +/- 54.4</td>
<td>Agatston Score 48.8 +/- 50.6 vs. 54.9 +/- 62.5</td>
<td>p = 0.35 (relative)</td>
</tr>
<tr>
<td>Tenenbaum et al. 2011</td>
<td>Median 5.6 years</td>
<td>Coronarycalcification score</td>
<td>Total calcium score 1452 +/- 515</td>
<td>Total calcium score 495 +/- 588</td>
<td>p = 0.05 (untreated)</td>
</tr>
<tr>
<td>Goh et al. 2010</td>
<td>10 +/- 1.5 years</td>
<td>Agatston score</td>
<td>Agatston Score 33.2% /year</td>
<td>Agatston Score 24% /year</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>Anand et al. 2007</td>
<td>Mean follow-up 2.5 +/- 0.4 years</td>
<td>Agatston and volumetric calcium scores</td>
<td>CACS 6 mm^3 /year</td>
<td>Calcium volume score 25 mm^3 /year</td>
<td>Statin use as an independent predictor of CAC progression (OR 2.27, p = 0.001)</td>
</tr>
<tr>
<td>Burgstahler et al. 2007</td>
<td>488 +/- 138 days</td>
<td>Calcium score, noncalcified plaques and volumetric plaque burden</td>
<td>Agatston Score 873 +/- 1011 vs. 1017 +/- 1268</td>
<td>Calcium volume score 251 +/- 301 vs. 293 +/- 366</td>
<td>p &gt; 0.05 (untreated)</td>
</tr>
<tr>
<td>Mohler et al. 2007</td>
<td>1 year</td>
<td>Coronary artery calcium volume Agatston score</td>
<td>Calcium volume score 7.1 +/- 3.9 (absolute)</td>
<td>Calcium volume score 57.9 +/- 53.7 (absolute)</td>
<td>p = 0.56 (absolute)</td>
</tr>
<tr>
<td>Terry et al. 2007</td>
<td>6 months and 12 months</td>
<td>CAC Agatston core</td>
<td>Agatston Score 659 +/- 116 vs. 691 +/- 24</td>
<td>Calcium volume score 593 +/- 132 vs. 645 +/- 24</td>
<td>p = 0.12</td>
</tr>
<tr>
<td>Houslay et al. 2006</td>
<td>Median 2 years</td>
<td>Agatston Score</td>
<td>Agatston Score 18% /year</td>
<td>Calcium volume score 26% /year</td>
<td>p = 0.18</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 Agatston Score 26%</td>
<td>Calcium Volume Score 27%</td>
<td>p = 0.7</td>
</tr>
<tr>
<td>Arad et al. 2005</td>
<td>Mean follow-up 4.3 years</td>
<td>Agatston score</td>
<td>Agatston Score 323 +/- 385 (absolute)</td>
<td>Calcium Volume Score 331 +/- 421 (absolute)</td>
<td>p = 0.80 (absolute)</td>
</tr>
<tr>
<td>Budoff et al. 2005</td>
<td>27 +/- 15 months</td>
<td>Agatston score</td>
<td>Agatston Score 32% /year</td>
<td>Calcium Volume Score 32% /year</td>
<td>p = 0.76 (relative)</td>
</tr>
<tr>
<td>Raggi et al. 2012</td>
<td>12 months</td>
<td>Calcium Volume Score</td>
<td>Pravastatin 40mg Calcium Volume Score 30.9 (absolute)</td>
<td>Calcium Volume Score 28.5 (absolute)</td>
<td>p = 0.21 (absolute)</td>
</tr>
<tr>
<td>Hecht et al. 2003</td>
<td>1.2 +/- 0.7 years for treated 1.4 +/- 0.5 years for untreated</td>
<td>Coronary calcium and calcium volume score</td>
<td>Calcium Score 28 +/- 44 (absolute)</td>
<td>Calcium Score 41 +/- 145 (absolute)</td>
<td>p = 0.001 (absolute)</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 28 (absolute)</td>
<td>Calcium Score 20 (absolute)</td>
<td>p = 0.07 (absolute)</td>
</tr>
<tr>
<td>Budoff et al. 2000</td>
<td>2.2 +/- 1.1 years</td>
<td>Agatston score</td>
<td>Agatston Score 39 +/- 12% /year</td>
<td>Calcium score 15 +/- 8% /year</td>
<td>p = 0.001</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 52 +/- 36%</td>
<td>Calcium volume score 5 +/- 28%</td>
<td>p = 0.001</td>
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### TABLE 2b
Non-calcium-based indices

<table>
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<tr>
<th>Study</th>
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<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auscher et al. 2005</td>
<td>12 months</td>
<td>Plaque volume, plaque composition, total dense calcium volume</td>
<td>Total plaque volume 2084.7 +/- 613.2 mm^3 /vs. 2103.7 +/- 628.8 mm^3</td>
<td>Total plaque volume 2134.5 +/- 569.6 mm^3 /vs. 2177.5 +/- 566.9 mm^3</td>
<td>p = 0.57</td>
</tr>
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</table>

Effect of statin therapy on Coronary Atherosclerosis
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). Auscher 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 volume and low attenuation plaque volume (Table 2b). 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**

We would like to acknowledge Dean Giustini, University of British Columbia Library, for his contributions and input regarding search strategies and optimization.

**DISCLOSURES**

Wan, Tashakkor and Mancini: None

Leipsic: Circle Cardiovascular Imaging, GE, Samsung, Phillips

Raggi: None

**REFERENCES**


