

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

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OBJECTIVES: The effect of statin therapy on coronary artery calcification is unclear. Early studies suggested a slower rate of coronary artery calcium score (CACs) progression, but recent prospective trials have failed to show this benefit. Recent studies have explored the use of Cardiac Computed Tomography Angiography (CCTA) to characterize plaque features. We provide 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*

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.

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. 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.

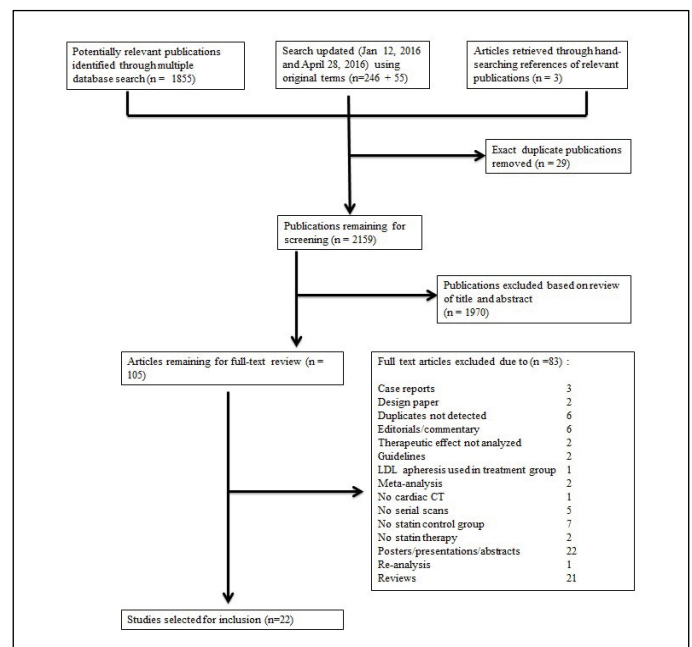


Figure 1) Selection of relevant articles from literature search

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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 55 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 1
Study information

Author and year	Study Design	Study Population	Inclusion	Exclusion	Imaging modality	Findings
Auscher et al. (41) 2015	Prospective randomized open-label	Documented STEMI or NSTEMI	<ul style="list-style-type: none"> Documented STEMI or NSTEMI according to current guidelines recruited <48h after admission 	<ul style="list-style-type: none"> Ongoing high-dose statin Contraindication to intensive statin therapy Prior or planned CABG Contrast allergy Impaired renal function Non-sinus rhythm 	MDCT	Statin therapy increases dense calcium volume but does not affect total plaque volume
Lo et al. (37) 2015	Randomized double blind placebo controlled	HIV-infected patients with subclinical atherosclerosis	<ul style="list-style-type: none"> Men and women 18-60 years of age with HIV disease Stable antiretroviral therapy LDL 1.81 – 3.37 mmol/L Evidence of subclinical atherosclerosis (plaques on coronary CTA without clinically significant stenosis) Evidence of arterial inflammation as assessed by FDG-PET 	<ul style="list-style-type: none"> Concurrent use of statin Contraindication to statin use AST or ALT greater than three times the upper limit of normal Treatment for active liver, renal or infectious disease B-blocker or nitroglycerin use Significant radiation exposure with 1 year of study Body weight greater than 136kg Allergy to iodine contrast Pregnancy or breastfeeding 	MDCT	Statins reduce non-calcified plaque volume and high risk plaque features
Lemos et al. (29) 2013	Open label randomized controlled	Nondialyzed CKD patients	<ul style="list-style-type: none"> Older than 18 years Followed by nephrologist by at least 3 months 	<ul style="list-style-type: none"> Presence of chronic inflammatory diseases Active malignancy HIV positive Viral hepatitis Chronic steroid use 	MDCT	Statin therapy does not delay progression of CAC
Zeb et al. (38) 2013	Retrospective observational	Patients being evaluated for CAD without known prior heart disease or revascularization	<ul style="list-style-type: none"> Patients undergoing coronary CTA between 2006-2009 2 consecutive scans at least 1 year apart, without prior known CAD Scans with good image quality 	<ul style="list-style-type: none"> Scans with significant artifact or poor image quality Interim coronary revascularization 	MDCT	Statin therapy results in reduced progression of low attenuation plaques and non-calcified plaques

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Plazak et al. (28) 2011	Prospective randomized double blind controlled study	Systemic lupus erythematosus	<ul style="list-style-type: none"> At least 4 of American College of Rheumatology criteria for SLE and in stable clinical condition 	<ul style="list-style-type: none"> Patients with known cancer Clinical symptoms of coronary artery disease or heart failure, renal failure, respiratory failure 	MDCT	Statin therapy reduces progression of CACS
Tenenbaum et al. (30) 2011	Longitudinal	Patients with stable angina pectoris			MDCT	No change in CACS with statin therapy
Goh et al. (31) 2010	Prospective longitudinal	Westernized Hong Kong Chinese individuals with chest pain and coronary risk factors	<ul style="list-style-type: none"> Westernized ethnic Chinese urban inhabitants Positive cardiac risk factors and chest pain First presentation chest symptoms with no prior cardiac CT 	<ul style="list-style-type: none"> Previous treatment for coronary artery disease Unstable chest symptoms Patients found to be at high risk requiring revascularization 	EBCT	Statin therapy causes regression of CACS
Hoffmann et al. (39) 2010	Retrospective longitudinal	Patients who had repeat MDCT as follow-up to initial testing for suspected CAD	<ul style="list-style-type: none"> Consecutive patients undergoing MDCT as a follow-up to original CT study Referral by primary care physician 		MDCT	Statin therapy slows progression of non-calcified plaques
Inoue et al. (40) 2010	Prospective longitudinal	Patients undergoing coronary CTA for suspected CAD	<ul style="list-style-type: none"> Patients who underwent coronary CTA with suspected coronary artery disease 	<ul style="list-style-type: none"> Severely calcified lesions on CTA Lesion segments with >75% luminal stenosis Prior percutaneous coronary intervention 	MDCT	Statin therapy decreases plaque and necrotic core volumes
Anand et al. (32) 2007	Prospective longitudinal	Type 2 diabetics without prior history of coronary disease	<ul style="list-style-type: none"> Type 2 diabetes > 1 year duration Age 30 – 65 years No prior history of coronary heart disease 	<ul style="list-style-type: none"> Typical angina pectoris or angina equivalent symptoms History of positive stress test, myocardial infarction, heart failure, coronary revascularization Electrocardiographic evidence of Q-wave myocardial infarction, ischemic ST- or T-wave changes, complete left bundle branch block History of peripheral vascular disease, intermittent claudication, stroke or TIA Renal impairment or severe life threatening illness 	EBCT	Statin use is an independent predictor of CACS progression
Burgstahler et al. (33) 2007	Prospective longitudinal	Men with established cardiovascular risk, but no known CAD	<ul style="list-style-type: none"> Male patients Elevated risk of CAD (PROCAM score > 3rd quintile) Not receiving lipid lowering therapy 		MDCT	Statin therapy reduces non-calcified plaque burden but does not affect CACS
Mohler et al. (34) 2007	Single center prospective observational study	Patients with moderate-severe aortic stenosis	<ul style="list-style-type: none"> Aortic valve area 0.7 – 2.0cm² EBT and echocardiographic analysis at baseline and one year after enrollment 		EBCT	Statin therapy decreases progression of CACS
Terry et al. (25) 2007	Randomized controlled trial	21 to 75 years of age with triglyceride levels <600 mg/dl.	<ul style="list-style-type: none"> Patients 21 – 75 years of age Triglyceride levels <600 mg/dl 1 of the following: <ul style="list-style-type: none"> HDL ≤ 50 mg/dl LDL 100 – 130 mg/dl <2 other risk factors that modify LDL goal CAC ≥ 50U by Agatston method 	<ul style="list-style-type: none"> Documented history of vascular disease or diabetes Liver aminotransferase levels >20% upper limit of normal Creatinine kinase levels >50% upper limit of normal Creatinine >1.8mg/dl Untreated thyroid abnormalities Women capable of being pregnant and not on birth control >10 alcoholic drinks per week Untreated blood pressure >140/90mmHg Known history or intolerance of Simvastatin Significant incidental findings on baseline CT Patients taking other lipid-altering medications 	MDCT	Statin therapy does not reduce progression of CACS
Houslay et al. (24) 2006	Randomized controlled trial	Patients with calcific aortic stenosis and coronary artery calcification	<ul style="list-style-type: none"> Patients aged > 18 years with calcific aortic stenosis (grade 1 – 3 calcification on echocardiography) Peak post-valve velocity of ≥ 2.5m/s 	<ul style="list-style-type: none"> Women of childbearing potential without contraception Acute or chronic liver disease History of drug or alcohol misuse Severe mitral stenosis Severe mitral or aortic regurgitation Major left ventricular dysfunction Planned aortic valve replacement Intolerance to statins Patients who were taking or would be taking statins Baseline serum cholesterol < 4.0mmol/l Permanent pacemaker or cardio defibrillator No coronary artery calcification on CT 	MDCT	Statin therapy does not have an effect on the rate of CACS progression

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	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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 80 th percentile	<ul style="list-style-type: none"> Men and women aged 50 – 70 years No history, symptoms or signs of atherosclerotic cardiovascular disease 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Type 2 diabetic patients without evidence of CAD 		EBCT	Statin therapy induces a reduction in the rate of CACS progression
Raggi et al. (27) 2005	Randomized controlled trial	Hyperlipidemic postmenopausal women	<ul style="list-style-type: none"> Postmenopausal women aged 55 – 75 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 	<ul style="list-style-type: none"> 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 does not affect CACS progression
Hecht et al. (36) 2003	Observational	Asymptomatic patients with EBCT evidence of subclinical atherosclerosis	<ul style="list-style-type: none"> Asymptomatic patients who underwent serial EBCT at intervals of >1 year 		EBCT	Statin therapy increases CACS
Achenbach et al. (22) 2002	Prospective cohort	Patients who underwent EBCT, CAC score ≥ 20 , no known CAD, LDL >130mg/dL	<ul style="list-style-type: none"> Coronary calcification in EBT LDL >130mg/dL No lipid-lowering therapy Time interval of at least 12 months since EBT 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	<ul style="list-style-type: none"> Asymptomatic patients who underwent 2 consecutive EBT scans at least 12 months apart 	<ul style="list-style-type: none"> Documented CAD before entry into the study Inadequate images for analysis on either EBT 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	<ul style="list-style-type: none"> Asymptomatic patients with no history of CAD Referred by primary care physicians for serial EBCT at intervals of 12-15 months 	<ul style="list-style-type: none"> Inadequate image quality Initial calcium volume score <30 	EBCT	Statin therapy reduces CACS progression

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).

TABLE 2a
Calcium-based indices

Study	Length of Treatment	Calcium Measurement Method	CAC Progression in Untreated Group	CAC Progression in Treated Group	Significant difference
Lo et al. 2015	1 year	Agatston score, calcium mass, calcium volume, calcium density	Agatston Score Δ 1.7	Agatston Score Δ 0.9	Agatston Score p=0.74
Lemos et al. 2013	24 months	Agatston score	Agatston Score Δ 99.7 +/- 190.8 (absolute) Δ 56.5 +/- 70.8% (relative)	Agatston Score Δ 99.3 +/- 283.7 (absolute) Δ 69.6 +/- 74.3% (relative)	Agatston Score p=0.28 (absolute) p=0.35 (relative)
Plazak et al. 2011	1 year	Agatston score	Agatston Score 32.1 +/- 39.1 vs. 59.5 +/- 54.4	Agatston Score 44.8 +/- 50.6 vs. 54.9 +/- 62.5	Agatston Score p<0.05 (untreated) p=NS (treated)
Tenenbaum et al. 2011	Median 5.6 years	Coronary calcification score	Total calcium score Δ 452 +/- 515	Total calcium score Δ 495 +/- 588	Total calcium score p=0.512
Goh et al. 2010	10 +/- 1.5 years	Agatston score	Agatston Score Δ 33.2%/year	Agatston Score Δ 24%/year	Agatston Score p<0.001
Anand et al. 2007	Mean follow-up 2.5 +/- 0.4 years	Agatston and volumetric calcium scores	CACS Δ 6 mm ³ /year	CACS Δ 25 mm ³ /year	Statin use as an independent predictor of CAC progression (OR2.27, p=0.001)
Burgstahler et al. 2007	488 +/- 138 days	Agatston score, noncalcified plaques and volumetric plaque burden	Agatston Score 873 +/- 1011 vs. 1017 +/- 1268 Δ + 32%	Agatston Score 261 +/- 301 vs. 293 +/- 366 Δ + 17%	Agatston Score p > 0.05 (untreated) p=0.59 (treated)
Mohler et al. 2007	1 year	Coronary artery calcium volume Agatston score	Calcium volume score Δ 19.2 +/- 308.9 (absolute) Δ 58.2 +/- 76.3% (relative) Agatston Score Δ -45.2 +/- 416 (absolute) Δ 15.8 +/- 40.9% (relative)	Calcium volume score Δ 59.0 +/- 435.3 (absolute) Δ 16.9 +/- 52.7% (relative) Agatston Score Δ 38.6 +/- 524.7 (absolute) Δ 14.8 +/- 53.8% (relative)	Calcium volume score p=0.56 (absolute) p=0.02 (relative) Agatston Score p=0.92 (absolute) p=0.71 (relative)
Terry et al. 2007	6 months and 12 months	CAC Agatston core	Agatston Score 659 +/- 116 vs. 691 +/- 24 Δ + 5%	Agatston Score 593 +/- 132 vs. 645 +/- 24 Δ + 9%	Agatston Score p=0.12
Houslay et al. 2006	Median 2 years	Agatston Score	Agatston Score Δ 18%/year	Agatston Score Δ 26%/year	Agatston Score p=0.18
Schmermund et al. 2006	12 months	Agatston CAC score and calcium volume score	Atorvastatin 10mg Agatston Score Δ 26% CAC Volume Score Δ 25%	Atorvastatin 80mg Agatston Score Δ 28% CAC Volume Score Δ 27%	Agatston Score p=0.7 CAC Volume Score p=0.6
Arad et al. 2005	Mean follow-up 4.3 years	Agatston score	Agatston Score Δ 323 +/- 385 (absolute) Δ 73 +/- 93% (relative)	Agatston Score Δ 331 +/- 421 (absolute) Δ 81 +/- 89% (relative)	Agatston Score p=0.80 (absolute) p=0.76 (relative)
Budoff et al. 2005	27 +/- 15 months	Agatston score	CAC Progression 32%/year	CAC Progression 18%/year	CAC Progression p=0.02
Raggi et al. 2005	12 months	Calcium volume score	Pravastatin 40mg Calcium Volume Score Δ 30.9 (absolute) Δ 19.8 % (relative)	Atorvastatin 80mg Calcium Volume Score Δ 28.5 (absolute) Δ 20.1 % (relative)	Calcium Volume Score p=0.21 (absolute) p=0.64 (relative)
Hecht et al. 2003	1.2 +/- 0.7 years for treated 1.4 +/- 0.5 years for untreated	Coronary calcium and calcium volume scores	Calcium Score Δ 28 +/- 44 (absolute) Δ 10.4%/year (relative) Volume Score Δ 22 +/- 39 (absolute) Δ 10.7%/year (relative)	Calcium Score Δ 41 +/- 145 (absolute) Δ 8.9%/year (relative) Volume Score Δ 35 +/- 91 (absolute) Δ 9.6%/year (relative)	Calcium Score p<0.001 (absolute) Volume Score p<0.001 (absolute)
Achenbach et al. 2002	EBCT performed on patients with mean interval of 14 months without treatment, then again after 12 months of treatment	Volumetric calcium score, Agatston score	Agatston Score Δ 28 (absolute) Δ 25% (relative) Volume Score Δ 25 mm ³ (absolute) Δ 25% (relative)	Agatston Score Δ 20 (absolute) Δ 11% (relative) Volume Score Δ 11 mm ³ (absolute) Δ 8.8% (relative)	Agatston Score p=0.07 (absolute) p=0.002 (relative) Volume Score p=0.01 (absolute) p=0.0001 (relative)
Budoff et al. 2000	2.2 +/- 1.1 years	Agatston score	Agatston Score Δ 39 +/- 12%/year	Agatston Score Δ 15 +/- 8%/year	Agatston Score p<0.001
Callister et al. 1998	13.7 +/- 0.6 months	Volumetric calcium score	Calcium volume score Δ 52 +/- 36%	Calcium volume score Δ 5 +/- 28%	Calcium volume score p<0.001

TABLE 2b
Non-calcium-based indices

Study	Length of Treatment	Calcium Measurement Method	CAC Progression in Untreated Group	CAC Progression in Treated Group	Significant difference
Auscher et al. 2015	12 months	Plaque volume, plaque composition, total dense calcium volume	Total plaque volume 2084.7 +/- 613.2 mm ³ vs. 2103.7 +/- 628.8 mm ³ Δ 19.1 +/- 190.2 mm ³ Dense calcium volume (median) 24.1 [9; 81] mm ³ vs. 21.5 [12;79] mm ³ Δ 1.9 [-6; 8] mm ³	Total plaque volume 2134.5 +/- 569.6 mm ³ vs. 2177.5 +/- 566.9 mm ³ Δ 43.5 +/- 225.8 mm ³ Dense calcium volume (median) 37.0 [12; 71] mm ³ vs. 45.0 [17; 82] mm ³ Δ 10.6 [-0.13; 21.4] mm ³	Total plaque volume p=0.57 Dense calcium volume p<0.001

Lo et al. 2015	1 year	Agatston score, calcium mass, calcium volume, calcium density	Non-calcified plaque volume Δ 6.7 mm ³ Total plaque volume Δ 12.0 mm ³	Non-calcified plaque volume Δ -8.2 mm ³ Total plaque volume Δ -0.8 mm ³	Non-calcified plaque volume p=0.03 Total plaque volume p=0.02
Zeb et al. 2013	Mean follow-up 406 +/- 92 days	Volumetric assessment of low attenuation plaque, non-calcified and calcified plaque	Low attenuation plaque 38.1 +/- 55.8 mm ³ vs 45.3 +/- 60.4 mm ³ Δ 5.9 +/- 23.1 mm ³ Non-calcified 137.7 +/- 172.8 mm ³ vs. 150.1 +/- 184.9 mm ³ Δ 13.8 +/- 76.6 mm ³ Calcified 262.5 +/- 375.5 mm ³ vs. 274.1 +/- 375.9 mm ³ Δ 10.0 +/- 53.2 mm ³	Low attenuation plaque 44.9 +/- 50.2 mm ³ vs 28.6 +/- 35.6 mm ³ Δ -12.2 +/- 19.2 mm ³ Non-calcified 166.0 +/- 162.3 mm ³ vs. 114.4 +/- 135.3 mm ³ Δ -47.7 +/- 71.9 mm ³ Calcified 292.7 +/- 304 mm ³ vs. 326.4 +/- 339 mm ³ Δ 29.3 +/- 67.9 mm ³	Low attenuation plaque p<0.001 Non-calcified p<0.001 Calcified p=0.245
Hoffmann et al. 2010	25 +/- 3 months	Volumetric plaque assessment	Linear random intercept model showed growth rate of non-calcified plaques were significantly slowed by statin (P=0.01, B2=-0.0036)		p=0.01
Inoue et al. 2010	Median 12 months	Total plaque volume, low attenuation plaque volume, lumen volume, remodeling index	Total plaque volume 94.4 +/- 21.2 mm ³ vs. 98.4 +/- 28.6 mm ³ Low attenuation plaque 2.1 +/- 3.0 mm ³ vs. 2.3 +/- 3.6 mm ³	Total plaque volume 92.3 +/- 37.7 mm ³ vs. 76.4 +/- 26.5 mm ³ Low attenuation plaque 4.9 +/- 7.8 mm ³ vs. 1.3 +/- 2.3 mm ³	Total plaque volume p=0.48 (untreated) p<0.01 (treated) Low attenuation plaque p=0.91 (untreated) p=0.01 (treated)
Burgstahler et al. 2007	488 +/- 138 days	Agatston score, noncalcified plaques and volumetric plaque burden	Total plaque burden 0.647 +/- 0.607 mL vs. 0.628 +/- 0.523 mL Noncalcified plaques "Enlargement of plaque volume"	Total plaque burden 0.149 +/- 0.108 mL vs. 0.128 +/- 0.075 mL Noncalcified plaques 0.042 +/- 0.029 mL vs. 0.030 +/- 0.014 mL	Total plaque burden p=0.228 (treated) p=0.81 (untreated) Noncalcified plaques p<0.05 (treated)

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.

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REFERENCES

- Greenland P, Labree L, Azen SP, et al. Coronary artery calcium score combined with framingham score for risk prediction in asymptomatic Individuals. *JAMA* 2004;291:210-15.
- Kondos GT, Hoff JA, Sevrukov A, et al. Electron-beam tomography coronary artery calcium and cardiac events: A 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. *Circulation* 2003;107:2571-76.
- O'Malley PG, Taylor AJ, Jackson JL, et al. Prognostic Value of coronary electron- beam computed tomography for coronary heart disease events in asymptomatic populations. *Am J Cardiol* 2000;85:945-948.
- Pletcher MJ, Tice JA, Pignone M, et al. Using the coronary artery calcium score to predict coronary heart disease events. *Arch Intern Med* 2004;164:1285-92.

5. Shaw LJ, Raggi P, Schisterman E, et al. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology* 2003;228:826-33.
6. Elias-Smale SE, Proença RV, Koller MT, et al. Coronary calcium score improves classification of coronary heart disease risk in the elderly: The Rotterdam study. *J Am Coll Cardiol* 2010;56:1407-14.
7. Erbel R, Möhlenkamp S, Moebus S, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: The Heinz Nixdorf Recall study. *J Am Coll Cardiol* 2010;56:1397-1406.
8. Polonsky TS, McClelland RL, Jorgensen NW, et al. Coronary Artery calcium score and risk classification for coronary heart disease prediction. *JAMA* 2010;303:1610-16.
9. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2010;56:e50-e103.
10. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
11. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *NEJM* 2005;352:1425-35.
12. The long-term intervention with pravastatin in ischaemic disease study group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *NEJM* 1998;339:1349-57.
13. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *NEJM* 1996;335:1001-09.
14. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-89.
15. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *NEJM* 1995;333:1301-07.
16. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. *JAMA* 1998;279:1615-22.
17. Pedersen TR, Faergeman O, Kastelein JJP, et al. High-Dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction. *JAMA* 2005;294:2437-46.
18. Nissen SE, Nicholls SJ, Siphani I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis. *JAMA* 2006;295:1556-65.
19. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. *NEJM* 2011;365:2078-87.
20. Puri R, Nicholls SJ, Shao M, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. *J Am Coll Cardiol* 2015;65:1273-82.
21. Yla-Herttuala S, Bentzon JF, Daemen M, et al. Stabilization of atherosclerotic plaques: an update. *Eur Heart J* 2013;34:3251-58.
22. Callister TQ, Raggi P, Cooil B, et al. Effect of HMG-CoA reductase inhibitors on coronary artery disease as assessed by electron-beam computed tomography. *NEJM* 1998;339:1972-78.
23. Budoff MJ, Lane KL, Bakhsheshi H, et al. Rates of progression of coronary calcium by electron beam tomography. *Am J Cardiol* 2000;86:8-11.
24. Achenbach S, Ropers D, Pohle K, et al. Influence of lipid-lowering therapy on the progression of coronary artery calcification: a prospective evaluation. *Circulation* 2002;106:1077-82.
25. Arad Y, Spadaro LA, Roth M, et al. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin c, and vitamin E. *J Am Coll Cardiol* 2005;46:166-72.
26. Houslay ES, Cowell SJ, Prescott RJ, et al. Progressive coronary calcification despite intensive lipid-lowering treatment: a randomised controlled trial. *Heart* 2006;92:1207-12.
27. Terry JG, Carr JJ, Kouba EO, et al. Effect of simvastatin (80 mg) on coronary and abdominal aortic arterial calcium (from the coronary artery calcification treatment with zocor [CATZ] study). *Am J Cardiol* 2007;99:1714-17.
28. Schmermund A, Achenbach S, Budde T, et al. Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: A Multicenter, Randomized, Double-Blind Trial. *Circulation* 2006;113:427-37.
29. Raggi P, Davidson M, Callister TQ, et al. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: beyond endorsed lipid lowering with EBT scanning (BELLES). *Circulation* 2005;112:563-71.
30. Plazak W, Gryga K, Dziedzic H, et al. Influence of atorvastatin on coronary calcifications and myocardial perfusion defects in systemic lupus erythematosus patients: a prospective, randomized, double-masked, placebo-controlled study. *Arthritis Res Ther* 2011;13:R117.
31. Lemos MM, Watanabe R, Carvalho AB, et al. Effect of rosuvastatin and sevelamer on the progression of coronary artery calcification in chronic kidney disease: a pilot study. *Clin Nephrol* 2013;80:1-8.
32. Tenenbaum A, Shemesh J, Koren-Morag N, et al. Long-term changes in serum cholesterol level does not influence the progression of coronary calcification. *Int J Cardiol* 2011;150:130-34.
33. Goh VK, Lau C-P, Mohlenkamp S, et al. Outcome of coronary plaque burden: A 10-year follow-up of aggressive medical management. *Cardiovasc Ultrasound* 2010;8:5.
34. Anand DV, Lim E, Darko D, et al. Determinants of progression of coronary artery calcification in type 2 diabetes. Role of glycemic control and inflammatory/vascular calcification markers. *J Am Coll Cardiol* 2007;50:2218-25.
35. Burgstahler C, Reimann A, Beck T, et al. Influence of a lipid-lowering therapy on calcified and noncalcified coronary plaques monitored by multislice detector computed tomography: results of the New Age II Pilot Study. *Invest Radiol* 2007;42:189-95.
36. Mohler ER, Wang H, Medenilla E, et al. Effect of Statin treatment on aortic valve and coronary artery calcification. *J Heart Valve Dis* 2007;16:378-86.
37. Budoff MJ, Yu D, Nasir K, et al. Diabetes and progression of coronary calcium under the influence of statin therapy. *Am Heart J* 2005;149:695-700.
38. Hecht HS, Harman SM. Evaluation by electron beam tomography of changes in calcified coronary plaque in treated and untreated asymptomatic patients and relation to serum lipid levels. *Am J Cardiol* 2003;91:1131-34.
39. Lo J, Lu MT, Ithenachor EJ, et al. Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet HIV* 2015;2:e52-e63.
40. Zeb I, Li D, Nasir K, et al. Effect of statin treatment on coronary plaque progression - a serial coronary CT angiography study. *Atherosclerosis* 2013;231:198-204.
41. Hoffmann H, Frieler K, Schlattmann P, et al. Influence of statin treatment on coronary atherosclerosis visualised using multidetector computed tomography. *Eur Radiol* 2010;20:2824-33.
42. Inoue K, Motoyama S, Sarai M, et al. Serial coronary CT angiography-verified changes in plaque characteristics as an end point: evaluation of effect of statin intervention. *JACC Cardiovasc imaging* 2010;3:691-98.
43. Auscher S, Heinsen L, Nieman K, et al. Effects of intensive lipid-lowering therapy on coronary plaques composition in patients with acute myocardial infarction: Assessment with serial coronary CT angiography. *Atherosclerosis* 2015;241:579-87.
44. Henein M, Granåsen G, Wiklund U, et al. High dose and long-term statin therapy accelerate coronary artery calcification. *Int J Cardiol* 2015;184:581-86.
45. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression. *JAMA* 2004;291:1071-80.
46. Puri R, Libby P, Nissen SE, et al. Long-term effects of maximally intensive statin therapy on changes in coronary atheroma composition: Insights from SATURN. *Eur Heart J Cardiovasc Imaging* 2014;15:380-88.
47. Eshthardi PP, McDaniel MC, Dhawan SS, et al. Effect of intensive atorvastatin therapy on coronary atherosclerosis progression, composition, arterial remodeling, and microvascular function. *J Invasive Cardiol* 2012;24:522.