

# Atherosclerotic disease regression with statins: studies using vascular markers

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## Abstract

Vascular imaging techniques enable identification of atherosclerosis in the subclinical phase and allow assessment of interventions to modify disease progression. Angiography has limited utility for tracking the progression of atherosclerosis because of its invasive nature, limited sensitivity for detecting early lesions and relatively low interscan reproducibility. Intravascular ultrasound (IVUS) and electron beam computed tomography (EBCT) are more sensitive and reproducible; however, available data on their ability for tracking disease progression are few. Measurement of carotid intima media thickness (CIMT) by B-mode ultrasound is a well-validated procedure for this application. In comparison with angiography, CIMT demonstrates greater sensitivity for detecting early atherosclerosis and lipid-rich plaques that are vulnerable to rupture. Continued validation and development of imaging techniques, such as magnetic resonance imaging (MRI), will facilitate the assessment of atherosclerosis progression in intervention studies.

Statins are effective low-density lipoprotein cholesterol (LDL-C) lowering agents, and imaging studies have demonstrated their ability to slow progression and promote regression of atherosclerosis. The benefits of therapy on atherosclerosis regression appear to extend to soft atherosclerotic plaques that are still developing and treatment effects are independent of baseline LDL-C level. Hence, imaging studies support early intervention with statins in coronary heart disease patients, irrespective of lipid level.

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## 1. Introduction

Atherosclerosis is a progressive disease that starts early in life and is manifested clinically as coronary heart disease (CHD), cerebrovascular disorders or peripheral arterial disease. Various risk factors, such as raised low-density lipoprotein cholesterol (LDL-C) levels, smoking and hypertension, place stress on the arterial wall resulting in endothelial dysfunction and the onset of atherosclerosis [1,2]. The first stage in atherosclerotic lesion formation is a thickening of the intima that results from proliferation of smooth muscle cells. This thickening often begins early in life; approximately 17% of a western population have been shown to exhibit these early lesions by the age of 20 years [3]. Atherosclerosis progresses with the accumulation of lipids, carbohydrates, blood products, fibrous tissue and calcium deposits within the lesions, resulting in hard, calcified plaques [2,4]. The disease

may remain asymptomatic for many years as a result of remodelling of the arterial wall; initially the atherosclerotic lesion grows into the vessel wall, maintaining the diameter of the vessel lumen and thereby having little effect on blood flow [5]. However, further lesion progression may result in plaques protruding into the lumen of the artery, narrowing the vessel and ultimately leading to occlusion [2]. Vessel stenoses may be manifest clinically as stable conditions such as angina pectoris, although some patients may still remain asymptomatic for many years.

Acute manifestations of atherosclerosis such as unstable angina, acute myocardial infarction (MI), stroke or sudden cardiac death result from thrombosis following rupture of unstable plaques. Plaque stability is determined by the composition of the lesion—fibrous, calcified plaques are relatively stable, while soft plaques with a large lipid core, reduced numbers of smooth muscle cells and a thin fibrous cap are more vulnerable to rupture [6]. An acute coronary event resulting from thrombosis following plaque rupture is often the first clinical sign of disease; indeed, up to 62% of adult sudden deaths in Europe are attributed to atherosclerosis

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[7,8]. Hence, early assessment of the disease in the subclinical phase is important to identify patients at risk, who may benefit from risk factor intervention to slow progression of atherosclerosis and prevent the onset of symptoms.

Epidemiological studies have established elevated LDL-C levels as a major risk factor for the development of CHD [9,10] and LDL-C lowering has been identified as the primary goal of therapy for disease prevention [11,12]. Statins (hydroxy-methylglutaryl coenzyme A reductase inhibitors) are recommended as first-line therapy for the treatment of dyslipidemia because of their effective LDL-C lowering and good tolerability [11,12]. Landmark clinical trials have demonstrated that statins reduce the risk of major coronary events by 20–40% [13–18], and statins have been shown to slow progression of atherosclerosis [19–21].

This paper examines the evidence from imaging studies for the efficacy of statins in slowing atherosclerosis progression and promoting regression of disease. The advantages and disadvantages of various imaging techniques will be compared in terms of their utility for tracking disease progression in intervention studies.

## 2. Vascular markers of atherosclerotic burden

The availability of several imaging techniques for use as surrogate markers of atherosclerotic burden has enabled the effects of statins to be examined at the vascular level. These imaging modalities, which include angiography, B-mode ultrasonography, intravascular ultrasonography (IVUS), magnetic resonance imaging (MRI) and electron beam computed tomography (EBCT), differ in terms of method of assessment, sensitivity and ease of use; these differences influence the applicability of the techniques to the assessment of atherosclerotic burden in clinical trial populations.

Quantitative coronary angiography (QCA) is an invasive technique that can be used to assess diffuse atherosclerotic changes on a per-patient basis by calculating a mean vessel diameter from serial measurements made along a coronary artery or segment. The modified Gensini score, an assessment of the degree of angiographically determined stenosis in various coronary segments, may be used to quantify the extent and severity of coronary atherosclerosis [22]. Alternatively, focal disease can be determined by measuring minimum lumen diameter (MLD), also known as minimum obstructive diameter (MOD), at the site of an atherosclerotic lesion. Variations over time can be visually evaluated from angiograms by an expert panel and the overall degree of change categorized as the global change score. A patient may be assessed as having progression or regression of atherosclerosis based upon measurement of change in percentage diameter, stenosis of existing plaques and on the appearance of new lesions. QCA findings predict future cardiovascular events [23,24] and QCA-determined coronary atherosclerosis is related to atherosclerotic abnormalities elsewhere

in the arterial system [25,26]. However, QCA is an invasive procedure, which also involves exposure to X-ray radiation and is associated with certain morbidity and mortality risks that limit its use for studying progression of atherosclerosis in asymptomatic subjects. Moreover, QCA assessment of atherosclerotic plaques is based on measurement of luminal stenosis, and, as such, it has limited sensitivity for detecting early atherosclerotic lesions that do not protrude into the lumen.

Alternative techniques that directly image the morphology of the arterial wall, such as ultrasonography, may provide greater sensitivity in assessing progression of atherosclerotic disease. B-mode (two-dimensional) ultrasonography is a non-invasive ultrasound technique that has been used frequently for tracking the progression of atherosclerosis. Most of the evidence on atherosclerosis, its determinants and sequelae obtained by B-mode ultrasound has been acquired by evaluating the carotid arteries. The boundaries between the arterial lumen and intima, and between the media and adventitia of an image of the carotid artery, can be accurately and precisely identified using this technique [27,28], enabling measurement of mean and maximum carotid intima media thickness (CIMT). The validity of CIMT as a marker of atherosclerotic burden has been demonstrated in numerous population- and hospital-based studies that have revealed a graded relationship between CHD risk factors and CIMT. In some studies, CIMT was related to absolute risk of cardiovascular disease as estimated by available risk functions [29–31]. Also, an increased CIMT has been associated with the presence of atherosclerosis in the abdominal aorta [32], in the arteries of the lower extremities [33–35] and with coronary calcium assessed by EBCT [36–38]. Studies of the relationship between CIMT and coronary atherosclerosis, as assessed by QCA, generally show modest positive associations [25,29,39–47]. Risk of CHD and stroke has been shown to rise with increasing CIMT in some [48–54], but not all studies [55]. A CIMT progression rate of  $\geq 0.03$  mm/year in subjects with previous CHD may be considered clinically relevant because it has been associated with a doubling in the incidence of coronary events [50].

In addition to assessing CIMT as a continuous variable, B-mode ultrasonography provides information on the presence of atherosclerotic plaques based either on arbitrarily chosen cut-off points of CIMT, typically  $>1.0$ – $1.2$  mm [56–58] or by an increase in CIMT of more than 50% compared with the adjacent CIMT. The plaque score, which is computed by summing the maximum thickness of all the CIMT complexes in the carotid artery [57] or as a sum of all plaques in all segments of the carotid artery, has been shown to relate to the QCA-determined Gensini score, and may be a more sensitive measure of the extent and severity of atherosclerosis than summation of CIMT [26]. However, few data are available on the use of plaque score as a marker of atherosclerosis progression.

IVUS is an invasive ultrasound procedure for imaging the arterial wall that enables tomographic assessment of

plaque size and composition. The external elastic membrane, located at the border between the media and adventitia, can be visualized using IVUS. Atherosclerotic burden is often assessed by measurement of the plaque index, which is the percentage of the external elastic membrane area occupied by atheroma (plaque area/external elastic membrane area  $\times 100$ ) [59]. Clinically, IVUS is used as an adjunct to angiography to improve diagnosis and aid intervention [59]; for example, unstable plaques that are not readily identified by angiography may be more easily detected by IVUS as areas of low echogenicity [60]. In patients with suspected coronary disease with no angiographically documented atherosclerosis, IVUS frequently detects occult disease [61–63], indicating the low sensitivity of QCA for assessment of early atherosclerosis. However, IVUS is an invasive procedure, and, given the availability of non-invasive ultrasound techniques, this may limit its use in intervention studies.

EBCT, a technique that detects coronary artery calcification [64,65], is a non-invasive method with potential for tracking progression in calcification of atherosclerotic plaques. As atherosclerosis develops, calcium is deposited within lesions in a process that resembles bone formation [65,66]. The traditional measure of coronary calcium derived from the EBCT scan is the Agatston calcium score, which is based on the area of calcium deposits and the maximum density within the lesion [67]. Evidence is accumulating for a relationship between the presence of coronary calcium and cardiovascular risk factors [68–70]. Also, coronary calcium correlates with atherosclerosis in the carotid arteries, the abdominal aorta and the arteries of the lower extremities [38]. Moreover, coronary calcium has been shown to predict cardiovascular events in patients and asymptomatic subjects [71,72]. However, the calcium score measurement is reported to have low interscan reproducibility, making it unsuitable for assessing changes in plaque size in serial recordings [71]. The calcium volume score (CVS), which is dependent upon plaque volume rather than density [73,74], demonstrates better interscan reproducibility. It is therefore likely to be a more appropriate marker for assessing changes in the rate of coronary atherosclerosis progression within a relatively short period [64]. However, few intervention studies using EBCT have been performed to date and investigators are cautioned that small changes in the volume of a calcified plaque observed over time ( $\leq 15\%$  after 1 year of follow-up) might not always be indicative of disease progression [74].

### 3. Statin therapy and vascular markers of atherosclerotic progression

The effects of statin therapy on the progression of atherosclerosis have been examined in several clinical trials using vascular imaging techniques (Table 1). The results of

these trials to quantify the effects of treatment on progression, stabilization or regression of atherosclerosis are significantly influenced by the assessment technique employed.

#### 3.1. The angiographic trials

Several trials to date have used QCA to investigate the effects of statin monotherapy upon atherosclerotic progression (Tables 1 and 2). Due to the invasive nature of QCA, statin trials using this imaging modality are confined to the assessment of atherosclerosis progression in patients with established CHD. Quantitative comparisons between studies are limited as a result of a lack of uniformity in study design and angiographic methods used. However, these QCA trials have consistently demonstrated significantly smaller changes in MLD in the treatment group compared with placebo (Table 2), indicating that statin therapy slows progression of atherosclerosis. In the Monitored Atherosclerosis Regression Study (MARS), the effect of treatment on the primary end point, change in mean percent stenosis (1.6% vs. 2.2% for placebo), and on change in MLD (Table 2) were not statistically significant; however, patients receiving lovastatin exhibited significantly less disease progression as indicated by the mean global change score (0.41 vs. 0.88 for placebo;  $P=0.002$ ) [75].

The effects of statin therapy have been analyzed according to baseline severity of disease in a number of QCA trials. In MARS and the Multicentre Anti-atheroma Study (MAAS), statin therapy slowed progression to a greater extent in large plaques that narrowed the lumen to  $< 50\%$  compared with smaller lesions [19,75]. In contrast, the effects of therapy were more pronounced on lesions causing  $< 50\%$  stenosis than larger plaques in the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) [76] and the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries Study (PLAC I) [21]. Together, these studies indicate that the benefits of statin therapy extend to smaller lesions. Moreover, statin therapy has been shown to approximately halve the appearance of new QCA-defined coronary lesions in CCAIT [76], PLAC I [21], the Lipoprotein and Coronary Atherosclerosis Study (LCAS) [77] and MAAS [19], and it has been suggested that this may be more important than the effect of statins on established plaques [76].

The benefits of statin therapy were shown to be independent of baseline LDL-C level in the REGression GRowth Evaluation Statin Study (REGRESS) [20] and LCAS [77]. Indeed, in LCAS, fluvastatin treatment was associated with significant benefits even in normocholesterolemic patients (LDL-C  $< 3.4$  mmol/l [130 mg/dl]) [77]. Similar results were found in the Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT), which examined the effect of LDL-C lowering with simvastatin in normocholesterolemic subjects; simvastatin significantly reduced

Table 1  
Summary of statin trials measuring atherosclerotic progression

Trial	Patient details	Baseline cholesterol level	N	Statin treatment regimen (mg/day)	Length of study (years)	Measurement of lipid levels	Measurement of CHD events/mortality
<i>Angiographic trials</i>							
MARS [75]	CHD patients (91% male)	TC: 4.9–7.6 mmol/l (190–295 mg/dl)	270	Lovastatin 80	2.2	Y	Y
CCAIT [76]	CHD patients (81% male)	TC: 5.7–7.8 mmol/l (220–300 mg/dl)	331	Lovastatin 20–80	2	Y	Y
PLAC I [21]	CHD patients (38% male)	LDL-C: 3.4–<4.9 mmol/l (130–<190 mg/dl)	408	Pravastatin 40	3	Y	Y
REGRESS [20]	Male CHD patients	TC: 4.0–<8.0 mmol/l (155–<310 mg/dl)	885	Pravastatin 40 <sup>a</sup>	2	Y	Y
LCAS [77]	CHD patients (81% male)	LDL-C: 3.0–4.9 mmol/l (115–190 mg/dl)	429	Fluvastatin 40 <sup>b</sup>	2.5	Y	Y
CIS (Coronary Intervention Study) [78]	Male CHD patients	TC: 5.3–9.0 mmol/l (207–350 mg/dl)	254	Simvastatin 20–40 <sup>c</sup>	2.3	Y	Y
MAAS [19]	CHD patients (88% male)	TC: 5.5–8.0 mmol/l (213–310 mg/dl)	381	Simvastatin 20	4	Y	Y
SCAT [79]	Patients (89% male) with angiographic documented coronary atherosclerosis	TC: 4.1–6.2 mmol/l (159–240 mg/dl)	460	Simvastatin 40	4	Y	Y
<i>B-mode ultrasound trials</i>							
REGRESS subgroup [80]	Male CHD patients	TC: 4.0–<8.0 mmol/l (155–<310 mg/dl)	255	Pravastatin 40	2	Y	Y
PLAC II [81]	CHD patients (85% men) [82]	LDL-C: 60–90th percentile for age and sex	151	Pravastatin 10–40	3	Y	Y
LIPID [83]	CHD patients (88% male)	TC: 4.0–7.0 mmol/l (155–271 mg/dl)	522	Pravastatin 40	4	Y	Y
MARS subgroup [84]	CHD patients (92% male)	TC: 4.9–7.6 mmol/l (190–295 mg/dl)	188	Lovastatin 80	2–4	Y	Y
ASAP [85]	Patients (39% male) with familial hypercholesterolemia. 31% with a history of CHD	LDL-C: >4.5 mmol/l (174 mg/dl)	325	Atorvastatin 80 vs. simvastatin 40	2	Y	N
ARBITER [86,87]	Male and female asymptomatic and CHD patients	TC: ≥4.1 mmol/l (160 mg/dl)	161	Atorvastatin 80 vs. pravastatin 40	1	Y	N
ACAPS [88]	Patients (52% male) with asymptomatic atherosclerosis	LDL-C: 3.4–4.9 mmol/l (130–189 mg/dl)	919	Lovastatin 20–40	3	Y	Y
CAIUS [27]	Patients (53% male) with asymptomatic atherosclerosis	LDL-C: 3.9–6.5 mmol/l (150–250 mg/dl)	305	Pravastatin 40	3	Y	Y
KAPS [89]	Male patients with asymptomatic atherosclerosis <sup>d</sup>	LDL-C: >4.0 mmol/l (155 mg/dl)	424	Pravastatin 40	3	Y	Y
BCAPS [58]	Subjects (46% male) with asymptomatic atherosclerosis	TC: ≤8.0 mmol/l (310 mg/dl)	793	Fluvastatin 40	3	Y	Y
METEOR [90]	Male and female subjects at low risk of CHD	LDL-C: 3.1–<4.1 mmol/l (120–<160 mg/dl) for patients with a 10-year CHD risk of <10%; 3.1–<4.9 mmol/l (120–<190 mg/dl) for patients with no additional CHD risk factor other than age	840	Rosuvastatin 40	2	Y	N
<i>IVUS trials</i>							
Takagi et al. [91]	Male patients with CHD who had undergone PTCA	TC: 5.2–6.8 mmol/l (200–260 mg/dl)	36	Pravastatin 10	3	Y	Y
Hagenaars et al. [92]	Patients (90% male) with CHD undergoing PTCA	NS	10	Statin monotherapy	1	N	N
REVERSAL [59]	Male and female CHD patients	LDL-C: 3.2–5.4 mmol/l (125–210 mg/dl) <sup>e</sup>	502 <sup>e</sup>	Atorvastatin 80 vs. pravastatin 40	1.5	Y	N

Table 1 (continued)

Trial	Patient details	Baseline cholesterol level	N	Statin treatment regimen (mg/day)	Length of study (years)	Measurement of lipid levels	Measurement of CHD events/mortality
<i>IVUS trials</i>							
SARIS [93]	Male and female patients with CHD eligible for balloon angioplasty and/or stent placement	LDL-C: $\leq 3.0$ mmol/l (116 mg/dl)	50	Atorvastatin 10 vs. 80	1	NA	NA
ASTEROID [94]	Male and female CHD patients	NS	450	Rosuvastatin 40	2	Y	N
<i>EBCT trials</i>							
Callister et al. [73]	Asymptomatic patients (61% male)	Mean LDL-C <sup>f</sup> : 3.8 mmol/l (147 mg/dl) for untreated patients; 3.6 mmol/l (139 mg/dl) for patients treated to $\geq 3.1$ mmol (120 mg/dl); 2.6 mmol/l (100 mg/dl) for patients treated to below 3.1 mmol (120 mg/dl)	149	Statin monotherapy	1–1.25	Y	N
Achenbach et al. [95]	Asymptomatic patients (89% male)	LDL-C: $\geq 3.4$ mmol/l (130 mg/dl)	66	Cerivastatin 0.3	1 <sup>g</sup>	Y	Y
BELLES [96]	Postmenopausal women	LDL-C: above NCEP ATP II target [97]	600	Atorvastatin 80 vs. pravastatin 40	1	Y	N

CHD=coronary heart disease, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, PTCA=percutaneous transluminal coronary angioplasty, NS=not stated, NA=not available.

<sup>a</sup> Patients whose TC level rose above 8.0 mmol/l (310 mg/dl) on repeated assessments and who did not respond to enhanced dietary therapy had open-label cholestyramine added to their treatment.

<sup>b</sup> A subgroup of patients received cholestyramine in addition to fluvastatin.

<sup>c</sup> A resin was added at 12 weeks of treatment if LDL-C was  $> 3.1$  mmol/l (120 mg/dl) in the simvastatin group or  $> 6.5$  mmol/l (250 mg/dl) in the placebo group.

<sup>d</sup> A history of MI was reported in  $< 10\%$  of subjects.

<sup>e</sup> Data presented at the American Heart Association Meeting 2003.

<sup>f</sup> Average LDL-C throughout the study.

<sup>g</sup> Length of treatment period.

the mean change in MLD (Table 2) and the percent change in maximum stenosis compared with placebo (1.67% vs. 3.83%, respectively;  $P=0.0003$ ) [79]. The findings of these QCA trials are consistent with those of

the recent Heart Protection Study (HPS), which demonstrated that simvastatin reduced the risk of CHD mortality and morbidity among patients with baseline LDL-C below recommended target levels [18].

Table 2  
Placebo-controlled angiography trials measuring mean change in MLD

Trial	Statin (mg/day)	% LDL-C lowering			Mean change in MLD (mm)		
		Treatment	Placebo	P	Treatment	Placebo	P
MARS [75]	Lovastatin 80	-38.0	-0.9	$< 0.001$	-0.03	-0.06	0.20
CCAIT [76]	Lovastatin 20–80	-29.0	-1.6	$< 0.001$	-0.05	-0.09	0.01
PLAC I [21]	Pravastatin 40	-28	+1	$< 0.001$	-0.03 <sup>a</sup>	-0.05 <sup>a</sup>	0.04
REGRESS <sup>b</sup> [20]	Pravastatin 40	-24.7	+2.1	$< 0.001$	-0.03 <sup>c</sup>	-0.09 <sup>c</sup>	0.001
LCAS <sup>d</sup> [77]	Fluvastatin 40	-22.5	-2.2	$< 0.0001$	-0.024	-0.094	0.0161
CIS <sup>e</sup> [78]	Simvastatin 20–40	-35.0 <sup>f</sup>	NA <sup>g</sup>	$< 0.0001$	-0.02	-0.10	0.002
MAAS <sup>b</sup> [19]	Simvastatin 20	-31.1	+0.7	$< 0.001$	-0.04	-0.13	0.007
SCAT [79]	Simvastatin 40	-30.5	+3.5	$< 0.001$	-0.09	-0.16	0.0001

LDL-C=low-density lipoprotein cholesterol.

<sup>a</sup> Value shown for mean change in MLD per year.

<sup>b</sup> Values for percentage change in LDL-C have been calculated from absolute values presented in source reference.

<sup>c</sup> Median, defined as MOD.

<sup>d</sup> A subgroup of patients received cholestyramine in addition to fluvastatin. Data presented are for fluvastatin monotherapy.

<sup>e</sup> Lipid levels measured over 30 months, angiographic end points over a mean of 2.3 years.

<sup>f</sup> % difference vs. placebo.

<sup>g</sup> NA = not available.

A number of QCA trials have examined the effect of statin therapy on the risk of coronary events, although these studies were not specifically designed to detect differences in the incidence of clinical end points between treatment groups. In REGRESS, 89% of pravastatin-treated patients remained free of clinical events compared with 81% in the placebo group ( $P=0.002$ ). Similarly, the incidence of MI (fatal and nonfatal) was significantly reduced in patients receiving pravastatin therapy in comparison with placebo (8 events vs. 17; risk reduction 53%;  $P\leq 0.05$ ) in PLAC I [21]. In agreement with these findings, the incidence of cardiac morbidity was lower in the fluvastatin treatment group compared with placebo (14.5% vs. 19.1%) in LCAS, although this difference did not achieve statistical significance [77]. In these studies, the effects of therapy on clinical end points is consistent with the benefits of statin therapy on QCA measures, thereby demonstrating further the validity of QCA as a surrogate marker for assessing atherosclerosis progression.

### 3.2. B-mode ultrasound trials

Several studies have examined the effect of statin therapy on the rate of progression of CIMT measured by B-mode ultrasonography (Tables 1 and 3). The REGRESS subgroup [80], Pravastatin, Lipids and Atherosclerosis in the Carotids (PLAC II) [81], the Long-term Intervention with Pravastatin in Ischemic Disease Trial subgroup (LIPID) [83] and MARS subgroup [84] studies examined the effect of statin therapy, in comparison with placebo, on B-mode ultrasound in patients with CHD (Table 1). Statin therapy caused regression of CIMT compared with baseline in REGRESS, LIPID and MARS, while progression of CIMT or no change was observed in the placebo groups (Table 3). In the PLAC II

Study, progression of mean maximum CIMT was reduced by 12% with pravastatin therapy compared with placebo (0.0593 vs. 0.0675 mm/year); however, this treatment effect was not statistically significant and the effect of pravastatin on CIMT appeared to be limited to the common carotid artery ( $P=0.03$ ; Table 3) [81].

The benefit of statin therapy on CIMT has been shown to be associated with improved clinical outcome. For example, in the REGRESS CIMT substudy, 90.1% of patients treated with pravastatin remained event free during the 2-year treatment period compared with 79.8% of placebo patients ( $P=0.02$ ) [80]. Similarly, in PLAC II a 60% reduction in the incidence of coronary events was observed in the pravastatin-treated patients compared with those receiving placebo [81].

The Atorvastatin vs. Simvastatin on Atherosclerotic Progression (ASAP) Study [85] and the ARterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) Trial [87] highlighted differences in the efficacy of statins in slowing or reversing atherosclerotic progression. In ASAP, atorvastatin reduced CIMT in patients with familial hypercholesterolemia by 0.031 mm over the 2-year treatment period [85]. In contrast, CIMT increased by 0.036 mm with simvastatin therapy ( $P=0.0001$  for the difference between treatments). Regression of CIMT was observed in 66% of patients in the atorvastatin group compared with 42% of patients treated with simvastatin. Patients with high baseline CIMT values responded better to treatment with atorvastatin than those with low baseline values. Both statins are effective LDL-C lowering agents, although atorvastatin demonstrated a significantly greater reduction in LDL-C level compared with simvastatin ( $-50.5\%$  vs.  $-41.2\%$ ;  $P=0.0001$ ). ARBITER compared change in CIMT following 12 months of treatment with atorvastatin or pravastatin [87]. Consistent with the results of ASAP, a larger

Table 3

Placebo-controlled B-mode ultrasound statin trials measuring mean change from baseline in LDL-C level and CIMT

Trial	Statin (mg/day)	% LDL-C lowering			Mean change in CIMT (mm/year)		
		Treatment	Placebo	<i>P</i>	Treatment	Placebo	<i>P</i>
REGRESS <sup>a</sup> [80]	Pravastatin 40	-29	-1	<0.001	-0.05 <sup>b,c</sup>	0 <sup>b,c</sup>	0.0085
PLAC II <sup>a</sup> [81]	Pravastatin 10–40	-28	+1	<0.001	+0.0295 <sup>d</sup>	+0.0456 <sup>d</sup>	0.03
LIPID <sup>a</sup> [83]	Pravastatin 40	-28 <sup>e</sup>	-5 <sup>e</sup>	<0.0001	-0.014 <sup>f,g</sup>	+0.048 <sup>f,g</sup>	<0.0001
MARS [84]	Lovastatin 80	-45	-2	<0.001	-0.038 <sup>e,f</sup>	+0.019 <sup>e,f</sup>	<0.001
ACAPS [88]	Lovastatin 20–40	-28	0	<0.0001	-0.009 <sup>h</sup>	+0.006 <sup>h</sup>	0.001
CAIUS <sup>a</sup> [27]	Pravastatin 40	-22	+2	0.0001	-0.0043 <sup>h</sup>	+0.0089 <sup>h</sup>	0.0007
KAPS [89]	Pravastatin 40	-27	+2	<0.001	+0.017 <sup>h</sup>	+0.031 <sup>h</sup>	0.005
BCAPS [58]	Fluvastatin 40	-23	0	-	+0.011 <sup>e,f</sup>	+0.0036 <sup>e,f</sup>	0.002
					+0.170 <sup>e,i</sup>	+0.211 <sup>e,i</sup>	>0.05

LDL-C = low-density lipoprotein cholesterol.

<sup>a</sup> Values for percentage change in LDL-C have been calculated from absolute values presented in source reference.

<sup>b</sup> Combined mean intima media thickness of femoral and carotid arteries.

<sup>c</sup> Mean change from baseline after 2 years.

<sup>d</sup> Mean maximal CIMT of the common carotid artery.

<sup>e</sup> Change from baseline after 3 years.

<sup>f</sup> Mean CIMT of the common carotid artery.

<sup>g</sup> Mean change from baseline after 4 years.

<sup>h</sup> Mean maximal CIMT.

<sup>i</sup> Mean CIMT of the carotid bifurcation.

reduction in LDL-C was associated with greater atherosclerosis regression; pravastatin reduced LDL-C by 27.2% and CIMT increased by 0.025 mm over the study period, while a LDL-C reduction of 48.5% with atorvastatin ( $P < 0.001$  vs. pravastatin) was associated with a reduction in CIMT of 0.034 mm ( $P = 0.03$  vs. pravastatin). However, the observed differences between the statins in their effect on disease progression cannot be entirely accounted for by differences in their LDL-C lowering efficacy and may be influenced by their non-lipid or pleiotropic effects [98].

The non-invasive nature of B-mode ultrasound has facilitated its use in clinical trials examining the effects of statin therapy on atherosclerosis progression in asymptomatic subjects with early atherosclerotic disease (Table 1). Consistent with the results of B-mode ultrasound trials in CHD patients, these studies have demonstrated significant regression (Asymptomatic Carotid Artery Progression Study [ACAPS] [88] and Carotid Atherosclerosis Italian Ultrasound Study [CAIUS] [27]) or slowing of progression (Kuopio Atherosclerosis Prevention Study [KAPS] [89] and Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study [BCAPS] [58]) of CIMT with statin therapy (Table 3), and benefits of therapy were evident after as little as 6–12 months [27,88].

The Measuring Effects on intima media Thickness—an Evaluation Of Rosuvastatin (METEOR) Study, which will examine the effect of rosuvastatin therapy on atherosclerosis using B-mode ultrasound, is currently ongoing [90]. Rosuvastatin has demonstrated greater efficacy in reducing LDL-C levels compared with atorvastatin, pravastatin and simvastatin [99–103]. METEOR is a placebo-controlled study assessing the effect of rosuvastatin on progression and regression of CIMT in asymptomatic patients with low risk of CHD who have evidence of atherosclerotic disease [90].

### 3.3. IVUS trials

Few intervention studies performed to date have used IVUS to examine the effects of statin therapy on the progression of atherosclerosis. In one IVUS Study conducted in 36 male CHD patients, pravastatin was observed to reduce plaque index by 7% compared with an increase of 27% with placebo ( $P < 0.0005$ ) [91] (Table 1). In a recent, small retrospective study ( $N = 10$ ), IVUS was performed immediately after percutaneous transluminal angioplasty and at 1-year follow up, and revealed that plaque volume in non-dilated segments of artery increased over the study period in both statin-treated and non-statin-treated patients (+4 and +2%, respectively) [92]. Increases in plaque volume were accompanied by increases in vessel and lumen size for statin-treated patients (+2 and +1%, respectively) and decreases for patients not receiving statins (–2 and –4%, respectively). Although these results did not achieve statistical significance, they support the hypothesis that statin therapy may induce positive remodelling of vascular segments containing atherosclerotic plaques.

The REVERSal of Atherosclerosis with Lipitor (REVERSAL) Trial compared the effects of atorvastatin and pravastatin therapy over 18 months on progression of atherosclerosis measured by IVUS in patients with CHD [59]. Initial data presented at the American Heart Association meeting in 2003 demonstrated significant progression of atherosclerosis with pravastatin 40 mg (mean change in atheroma volume = 2.7%,  $P = 0.02$ ), while no change in atherosclerosis progression was observed with atorvastatin 80 mg (mean change in atheroma volume = –0.4%,  $P = 0.98$ ). Atorvastatin produced a greater reduction in LDL-C compared with pravastatin (46.3% vs. 25.2%;  $P < 0.0001$ ). In addition, C-reactive protein, a marker of inflammation, was also reduced more by atorvastatin than pravastatin (–36.4% vs. –5.2%;  $P < 0.0001$ ) and this was thought to contribute to the difference between treatments on the progression of atherosclerosis.

Other IVUS studies are ongoing, including the Statin on Atherosclerosis and vascular Remodeling assessed with Intravascular Sonography (SARIS) Trial [93]. This is a prospective study designed to assess the morphological and functional cardiovascular effects of atorvastatin in CHD patients with normal to mildly elevated cholesterol levels. The effect of atorvastatin on plaque volume and vascular remodelling will be assessed after 1 year of statin therapy using IVUS. A further IVUS Study, A Study To evaluate the Effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden (ASTEROID), will examine the effect of rosuvastatin over 2 years on progression of atherosclerosis in approximately 450 patients with CHD [94].

### 3.4. EBCT (coronary calcification) studies

Callister et al. [73] assessed changes in coronary plaque volume with lipid-lowering therapy using EBCT-derived CVS in asymptomatic, hyperlipidemic patients (Table 1). In this study, CVS of statin-treated patients was compared with that of patients not prescribed statin therapy. Patients treated with a statin were divided into two groups according to whether or not they had achieved a LDL-C level  $< 3.1$  mmol/l (120 mg/dl). CVS was reduced by 7% ( $P = 0.01$ ) in patients achieving this LDL-C level, which indicates regression of atherosclerosis in this group. In statin-treated patients who failed to reach this target, an increase in CVS of 25% was observed. Although this indicates progression of atherosclerosis, the magnitude of the increase was lower than that observed in untreated patients (25% vs. 52%;  $P < 0.001$ ).

A slowing in the rate of progression of coronary calcification has also been demonstrated with cerivastatin [95] (Table 1) in a study initiated prior to the withdrawal of this drug because of an increased incidence of rhabdomyolysis [104]. The annualized progression rate of coronary calcification over a 1-year treatment period was found to be lower than that during the 14 months prior to initiation of cerivastatin therapy (8.8% vs. 25.0%;  $P = 0.0001$ ). Another

EBCT Study, the Beyond Endorsed Lipid Lowering with EBCT Scanning (BELLES) Trial is currently ongoing and will examine the benefits of statin therapy in asymptomatic postmenopausal women [96]. This study will compare the effects of atorvastatin and pravastatin on atherosclerosis progression over 1 year by assessment of the percent change from baseline in each patient's total coronary CVS.

The use of computer tomography techniques to detect coronary calcifications and study progression of atherosclerosis has great potential in cardiovascular research. New developments in computed tomography techniques, such as the multi-slice computed tomography (MSCT) [105–107] provide images of similar quality to EBCT. Their greater availability will facilitate wider use of these techniques both in cardiovascular research and clinical practice.

Despite differences in methodology, the majority of studies have demonstrated that statins, administered at doses used to lower LDL-C levels, are effective in controlling the progression of atherosclerosis in symptomatic and asymptomatic subjects. The effect of statin therapy on atherosclerosis progression appears to be independent of baseline LDL-C and beneficial in patients with subclinical disease.

#### 4. Future directions in the measurement of atherosclerotic burden

Studies have demonstrated that statins have effects on atherosclerosis progression in addition to LDL-C lowering; these benefits may result from their effects on endothelial dysfunction, platelet deposition, propensity for plaque rupture and thrombosis [21]. Imaging techniques enable direct assessment of statin therapy at the vascular level, at the site of action of these non-lipid effects.

Measurement of the change in atherosclerosis burden, assessed by imaging techniques, allows the clinical benefits of a therapy to be established in a relatively short time and with fewer subjects compared with clinical outcome trials. Significant clinical benefits of statins on markers of atherosclerosis burden have been demonstrated in studies of patients followed up for as little as 12–15 months using EBCT [73]. Furthermore, the effect of statins on atherosclerotic progression begin to emerge as early as 6 months after

the start of therapy in studies assessing CIMT by B-mode ultrasonography [27,88], although this initial change in CIMT may reflect adaptive modifications in response to other factors [48] rather than changes in atherosclerosis progression.

The choice of the most suitable technique for investigating the effects of statins on atherosclerosis progression is determined by a number of factors, including sensitivity and reliability of the imaging method, and whether the procedure is invasive or non-invasive (Table 4). Angiography is well established for the diagnosis of atherosclerosis. Although considered the 'gold standard', a major limitation for the use of angiography in tracking the progression of disease is that it is an invasive procedure requiring specialist personnel to obtain and assess the images. Furthermore, quantitative analysis is time consuming and the visual interpretation of angiograms exhibits significant observer variability and correlates poorly with the extent of atherosclerosis in post-mortem examination [59]. In addition to interscan variability and reproducibility, it has also been suggested that differences may exist between image analysis systems used for quantification [20].

QCA is used to indicate atherosclerotic progression/regression based upon the visualization of vessel stenoses. However, the smaller, unstable, lipid-rich lesions that are most prone to rupture [114,115] are often angiographically 'silent' as a result of remodelling of the arterial wall [116]. Indeed, 10–15% of patients undergoing catheterization for suspected coronary disease have normal coronary arteries on angiography [59], although diseased arteries are often detected in these patients using IVUS [61–63]. Furthermore, unstable lesions are more commonly characterized by positive remodelling (expansion) of the arterial wall, whilst negative remodelling (arterial shrinkage) is more often associated with stable plaques [117]. Hence, measurement of stenosis by QCA restricts the assessment of disease progression to plaques at low risk of rupturing. In addition, methodological considerations may limit the use of QCA for tracking plaque progression. The angiographic assessment of a lesion requires comparison of the luminal diameter within the lesion with a 'normal' reference section of artery. However, atherosclerotic disease is usually diffuse and angiographically normal reference sections may contain

Table 4  
Comparison of currently available imaging techniques for assessing plaque progression

Technique	Invasive/ non-invasive	Directly images arterial wall?	Provides information on plaque composition?	Well validated	Sensitivity	Interscan reliability
QCA	Invasive	N	N	Y	Low—only detects plaques that result in stenosis	69–93% [108,109]
B-mode ultrasound	Non-invasive	Y	Y	Y	High	>80% [110,111]
IVUS	Invasive	Y	Y	N	High	>80% [112]
EBCT	Non-invasive	N	Y	Y	Moderate—detects plaques >5 mm <sup>2</sup> [113]	85% [74]



atherosclerotic plaques within the arterial wall [59]. As a consequence of these limitations, QCA may not be the optimal method for assessing the effect of lipid-modifying drugs on atherosclerotic progression/regression, particularly in populations at low risk of CHD or with subclinical atherosclerosis.

As a result of the limitations of QCA, more sensitive imaging techniques that allow direct imaging of the arterial wall, such as ultrasonography, have been sought. B-mode ultrasonography can be used in asymptomatic patients because of its non-invasive nature. A further advantage of this technique over QCA is that it measures composition of atherosclerotic plaques in addition to size (Table 4). The findings of statin trials have clearly shown that B-mode ultrasonography is a suitable technique for assessing the effects of drug therapies on atherosclerosis progression. The REGRESS Study supports B-mode ultrasonography as a more reliable measure of atherosclerosis burden than QCA; pravastatin therapy was found to significantly reduce progression as indicated by B-mode ultrasound measurement of intima media thickness in the carotid and femoral arteries although no significant effect was observed on angiographically determined luminal diameter [80]. In addition, angiographically ‘silent’, early atherosclerotic lesions, which derive considerable benefit from statin therapy, can be assessed by measurement of intima media thickness [80]. One limitation of CIMT is that it measures atherosclerosis in the carotid arteries rather than the coronary arteries. Determination of plaque characteristics is only of value in assessing atherosclerotic burden if the plaque measured reflects the type of lesion present elsewhere in the arterial system. For example, it is unlikely that an unstable plaque in the carotid artery will cause a coronary event, however, plaques in the carotid artery may be used as a marker of the type and extent of lesions at other sites in the vasculature that are likely to present a risk to the patient. There is ample evidence that CIMT relates to coronary atherosclerosis, although the relation is not on a one-to-one basis. B-mode ultrasonography is currently the most well-validated method for assessing early changes in disease progression/regression with lipid-modifying therapy because of its sensitivity and non-invasive nature. However, quantitative quality control of sonographers and readers was found to be critical to the success of this technique in intervention studies [118]. The American Heart Association Writing Group III on Non-invasive Tests of Atherosclerotic Burden concluded that with the use of standardized protocols for scanning and monitoring of CIMT, this technique would be useful in the follow up of patients treated for plaque progression or regression [118]. This is reflected in the use of B-mode ultrasonography in the ARBITER and METEOR Studies, which aim to assess the effects of statins on progression of atherosclerosis burden.

IVUS, which exhibits greater sensitivity in detecting plaques compared with QCA, has the additional advantage of assessing plaque composition (Table 4). However, IVUS is invasive and this has limited its use for assessing atheroscle-

rotic progression in large population groups that are free from symptomatic CHD. Hence, there are few available data on its use for this application and non-invasive ultrasonographic techniques have been more widely used in intervention studies. Data from the REVERSAL Study and from a recent intervention study with a high-density lipoprotein mimetic (ETC-216) [119] support the use of IVUS in intervention studies. Indeed, treatment-related changes in the rate of atherosclerosis progression measured by IVUS were observed after as little as 5 weeks in the study with ETC-216 [119]. However, further studies are required to validate IVUS fully, and the SARIS and ASTEROID Trials, currently in progress, will provide additional data on the use of this technique for assessing disease progression.

EBCT and MSCT are promising, non-invasive imaging modalities for assessing the effect of therapy on coronary atherosclerosis, as measured by calcifications (Table 4). However, results from intervention studies using EBCT are limited at present and thus its applicability in these settings needs to be assessed in more detail. The increased availability of MSCT scanners, compared with EBCT scanners, may further boost the use of this imaging modality in cardiovascular research.

New non-invasive imaging methods are currently being investigated as suitable techniques for tracking plaque progression. Magnetic resonance imaging (MRI) has excellent soft tissue contrast, permitting visualization and analysis of the components of the atherosclerotic plaque and has the potential to distinguish between stable and unstable lesions [120,121]. Improvements in temporal, spatial and contrast resolution are necessary before the technique can be used clinically for assessing plaque burden [120]. However, MRI is a promising non-invasive method of evaluating both the extent of atherosclerotic lesions and their composition as exemplified by a number of recent studies [122–124].

Recent developments in, and continued validation of, imaging techniques for the measurement of atherosclerosis burden will facilitate the assessment of lipid-modifying therapies on the progression/regression of atherosclerotic disease. This will allow the clinical benefits of these drugs to be more rapidly identified and enable assessment of clinical effect on early and ‘silent’ atherosclerotic lesions, which may be unlikely to lead to cardiovascular events during the course of a clinical outcomes trial. Statin trials support the use of imaging studies in the assessment of lipid-modifying therapies on disease progression and demonstrate the benefits of early treatment of subclinical atherosclerosis in patients with lipid levels below recommended targets.

## 5. Conclusions

The efficacy of statins in reducing the risk of coronary events has been well established in clinical trials, and imaging techniques have enabled the benefits of statin

therapy to be demonstrated at the vascular level. Non-invasive techniques for assessing atherosclerotic progression/regression have been developed and have obvious advantages in terms of acceptability to patients and reduced risk of adverse events compared with invasive procedures such as angiography and IVUS. EBCT-assessed coronary calcium is a promising surrogate marker for atherosclerosis progression, and ongoing studies will provide further data on its utility for this application. MRI also has potential for non-invasively measuring the extent of atherosclerosis and for identifying vulnerable plaques based on the analysis of their components.

CIMT, measured by B-mode ultrasonography, is currently the most well-validated, non-invasive technique for tracking plaque progression. CIMT determines plaque size directly rather than estimating plaque burden on the basis of luminal stenosis. Hence, it may be a more sensitive technique for detecting subclinical atherosclerosis and lipid-rich plaques that are vulnerable to rupture.

The use of imaging techniques to quantify the change in atherosclerotic burden with lipid-modifying therapies enables assessment of atherosclerotic progression at the vascular level and allows the clinical benefits of treatment to be identified more rapidly than in clinical outcome trials. Furthermore, these studies support early intervention with statin therapy in patients with subclinical atherosclerotic disease, even in the absence of raised LDL-C levels.

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