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Statin Treatment and Progression of Atherosclerotic Plaque Burden

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Abstract

Atherosclerosis is a progressive systemic disorder that, in the initial stages, is often asymptomatic. The measurement of atherosclerotic burden using imaging techniques enables the clinical benefits of lipid-modifying therapies to be assessed in early atherosclerosis and facilitates more rapid evaluation of interventions in clinical trials compared with the measurement of clinical outcome.

The effect of HMG-CoA reductase inhibitors, commonly referred to as 'statins', on disease progression has been assessed in a number of imaging studies both in patients with established coronary heart disease (CHD) and in those with subclinical atherosclerosis. Statins slow plaque progression and, in early atherosclerosis, they have been demonstrated to promote regression of atherosclerotic lesions. The benefits of statin therapy on soft atherosclerotic plaques that are still developing support the use of vascular measures to detect subclinical atherosclerosis, and the subsequent early intervention with statin therapy. Moreover, given that the effects of statins on atherosclerosis progression are evident even in normocholesterolaemic patients at increased risk of developing CHD, early intervention with statin therapy may be effective in preventing CHD, irrespective of lipid level.

1. Introduction

Atherosclerosis is a major cause of morbidity and mortality worldwide.[1] Although a systemic condition, atherosclerosis may be clinically defined as coronary heart, cerebrovascular or peripheral arterial disease. Patients with one manifestation of the disease are at increased risk of developing plaques at another site within the vasculature with associated consequences for morbidity and mortality. Atherosclerosis is a progressive disease that starts early in life and may become symptomatic or may remain asymptomatic for a long time; indeed, in Europe atherosclerosis is associated with approximately 60% of adult sudden deaths.[2,3] Early assessment of atherosclerosis and subsequent intervention to prevent or postpone its progression or consequences are therefore important goals in reducing the burden of disease.

Statins (HMG-CoA reductase inhibitors) are effective low-density lipoprotein (LDL) cholesterol-lowering agents and produce improvements across the lipid profile.[4,5] The clinical benefits of statins are well established. Landmark clinical trials have demonstrated a 20–40% reduction in the risk of major coronary events with statin therapy as either primary or secondary prevention, and over a wide range of cholesterol levels.[6-10] Importantly, statins have been shown to slow the progression of atherosclerosis.[11-13]

This article provides an overview of the process of atherosclerotic plaque formation and lipid composition, and how disease progression/regression may be determined at a vascular level using several imaging modalities. The effects of statin therapy upon these vascular measures are discussed, together with the evidence supporting the value of early detection and intervention with statins in patients with atherosclerosis.

1.1 Atherosclerotic Plaque Development

The pathogenesis of plaque formation and rupture is determined by a complex interplay of mechanisms[14] and may be considered an inflammatory process.[15] Endothelial dysfunction is central to atherosclerotic plaque formation and progression.[16-18] Plaques develop as an accumulation of lipids, carbohydrates, blood products, fibrous tissue and calcium deposits, which reduces the visco-elastic properties of the artery wall, resulting in stiffening of the arterial tree.[19] In humans, soft lesions develop as a thickening of the vessel intima resulting from smooth muscle cell proliferation; these lesions are present in approximately 17% of the population by the end of the second decade of age.[20] Further development of the lesion in the intermediate phase is associated with lipid accumulation and increased connective tissue synthesis.[14] In later stages calcium is deposited within the lesions causing hardening in a process akin to bone formation;[21] the extent of calcification within a plaque is correlated with patient age and progression of atherosclerosis.[22,23] Initially, the coronary artery compensates for the effects of atherosclerotic plaque formation on blood flow by remodelling, whereby atherosclerotic material grows into the vessel wall thus preserving luminal diameter.[24] By this mechanism, patients can develop a large plaque burden that is clinically silent and remains undetected by imaging modalities that primarily focus on lumen diameter. Lesion development over time may progress to a stage where the plaque protrudes into the vessel lumen, resulting in vessel narrowing and ultimately occlusion.[14] Patients with stenoses may remain asymptomatic for decades or develop stable conditions such as angina pectoris. However, acute manifestations of atherosclerosis such as unstable angina, acute myocardial infarction, stroke or sudden cardiac death are not a consequence of luminal obstruction but rather of thrombosis following rupture of unstable plaques. Factors that trigger plaque rupture, including acute psychological stress,[25] play a critical role in this process.

Plaque stability is determined by the size and consistency of the atheromatous core. Vulnerable plaques that are most prone to rupture typically consist of a large lipid core, reduced numbers of smooth muscle cells and a thin fibrous cap.[26] The fibrous cap may be weakened by the action of proteolytic enzymes, such as metalloproteinases, secreted by activated macrophages.[27,28] Plaque rupture tends

to occur at the weakest point of the lesion, usually at the junction between the cap and the adjacent intima where cap thickness is thinnest.[29] Physical disruption of an atherosclerotic plaque permits direct contact between tissue factor contained within the atheromatous core and the blood supply, resulting in thrombosis. The amount of thrombus present and the extent of vessel stenosis is dependent upon several factors including the rheological characteristics of the vessel, i.e. flow and shear stress, and local thrombogenic and fibrinolytic conditions.[14] These considerations highlight the importance of studying lesion morphology when examining the atherosclerotic process, its risk factors and its consequences.

1.2 Therapeutic Effects of Statin Therapy Upon Atherosclerosis

Within the last decade, clinical trials have established the efficacy of the statins in modifying the lipid profile, and reducing cardiovascular morbidity and mortality in both primary[6,7] and secondary prevention.[8-10,30] These results provided the impetus for investigation of the effects of statin treatment at the vascular level.

Although the lipid-lowering efficacy of statins is considered to be primarily responsible for their effects on clinical outcomes, studies have demonstrated that statins have additional non-lipid, or pleiotropic effects, on atherosclerosis progression (figure 1). These benefits may result from their effects on endothelial function, inflammation, plaque stability and thrombus formation.[31-35] Statin therapy promotes improvements in endothelial function,[36,37] which have been shown to occur within 1 month of the start of treatment.[37] The mechanism by which statins exert their effect on endothelial function has yet to be fully elucidated, but is thought to be mediated by enhanced production of nitric oxide as a result of increased expression of endothelial nitric oxide synthase.[33-35] Nitric oxide helps to maintain the stability of the endothelium by various mechanisms, which include reducing leucocyte adhesion[35] and apoptosis of endothelial cells.[38] Statins reduce levels of inflammatory markers such as C-reactive protein[39,40] and inhibit the expression of adhesion molecules involved in leucocyte-endothelial interactions.[41,42] Further non-lipid effects of statins, including inhibition of smooth muscle cell proliferation[43,44] and promotion of phagocyte and smooth muscle cell apoptosis,[45-47] may contribute to their ability to slow the progression of atherosclerosis. In addition, statins promote plaque stability by a combination of their lipid-lowering properties and inhibitory effects on macrophage activation, inflammation and metalloproteinase activity, thereby reducing the risk of plaque rupture. Moreover, as a result of their antithrombotic properties, statins may prevent the occurrence of acute coronary events; they inhibit the deposition of platelets on damaged vessel walls and reduce platelet thrombus formation.[32,48,49]

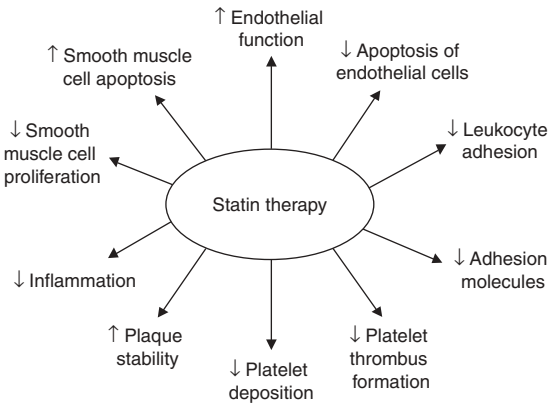

Fig. 1. Schematic diagram of the non-lipid effects of statins (HMG-CoA reductase inhibitors). ↑ indicates increase in; ↓ indicates decrease in.

These non-lipid effects support the use of direct measurements of atherosclerosis burden for assessing the clinical benefits of statins, rather than measuring changes in the lipid profile alone. Indeed, pleiotropic properties may explain the more rapid clinical benefit observed with statin monotherapy compared with other lipid-modifying drugs; the benefits of statins on clinical outcome begin to emerge after 1–2 years of treatment[10,13,50] compared with 2–5 years of treatment for non-statin lipid-modifying therapies, e.g. fibric acid derivatives (fibrates), nicotinic acid (niacin).[51]

2. The Relevance of Early Detection of Atherosclerotic Plaque Burden

Vascular measures of atherosclerotic burden allow the presence of subclinical atherosclerotic disease to be identified in asymptomatic individuals. Furthermore, these imaging techniques allow progression or regression of atherosclerosis to be examined over time in both asymptomatic patients and those with established coronary heart disease (CHD). Hence, the use of these measures enables the vascular benefits of a therapy to be established in a relatively short time and with fewer participants than clinical outcome trials. In imaging studies, the benefits of statin therapy begin to emerge after as little as 6 months of therapy,[50,52] although the extent to which these initial effects reflect changes in atherosclerosis progression or adaptive modifications in response to other factors [53] remains to be established.

The first clinical manifestation of atherosclerosis is often a major coronary event. Therapies that slow progression or promote regression of atherosclerosis in the subclinical stages of the disease are therefore important for reducing the mortality and morbidity associated with CHD. Moreover, it is often soft plaques that are most vulnerable to rupture, leading to acute coronary events.[54] Hence, intervention with therapies that are effective in controlling progression of these early lesions will have clinical benefits for the prevention of CHD. Given that atherosclerosis often remains asymptomatic for many years, the use of clinical outcome trials for examining the effects of early intervention therapy is problematic; these studies must be of sufficient duration to detect a difference in the incidence of coronary events between treatment groups. In contrast, imaging studies enable assessment of the effect of therapy on disease progression or regression prior to the appearance of symptoms, and are therefore particularly useful in determining the effect of therapy in the early stages of atherosclerotic disease. However, vascular imaging is not able to detect some of the non-lipid effects of statins, such as improved endothelial function, which may contribute to the potential of these agents for reducing CHD risk.

3. Methods for Determining Atherosclerotic Burden

Several imaging modalities are available for measuring atherosclerotic burden including angiography, B-mode ultrasonography, intravascular ultrasonography (IVUS), electron beam computed tomography (EBCT) and high-resolution magnetic resonance imaging (MRI). A number of factors influence the selection of the most suitable technique for investigating the effects of statins on atherosclerosis progression. The ideal vascular measure would have high sensitivity for detecting early and advanced atherosclerotic lesions and provide information on plaque composition. Non-invasive techniques can be repeated more frequently than invasive procedures, and have obvious advantages due to their greater acceptability to patients. High interscan reliability is essential to enable the progression or regression of atherosclerosis to be assessed from serial recordings.

3.1 Quantitative Coronary Angiography

Quantitative coronary angiography (QCA) is an invasive technique that can be used to identify the presence of atherosclerotic plaques in the coronary arteries based on the assessment of lumen diameter. The quantitative change in percent diameter stenosis may be used to define lesions as progressing or regressing and, together with the appearance of new lesions or stenoses, is used to determine whether the patient is considered to have progression or regression of atherosclerotic disease.

However, not all plaques project into the vessel lumen; in the early stages of atherosclerosis, plaques remodel the arterial wall and luminal narrowing only occurs late in the disease process.[55] Most acute coronary events originate at the site of smaller, unstable, lipid-rich lesions,[16,56] which may be angiographically 'silent'; 10–15% of patients undergoing catheterisation for suspected coronary disease have angiographically normal coronary arteries.[57] Histopathological studies have demonstrated that

the extent of positive remodelling of coronary arteries is related to plaque composition; arterial expansion, preserving or increasing lumen size, is more frequently associated with plaques that are vulnerable to rupture.[54,58,59]

Angiography has poor sensitivity for detecting the soft vulnerable plaques that do not cause stenosis. Importantly, progression and regression of unstable lesions in angiographically normal or minimally diseased coronary artery segments may have greater impact on clinical outcome than those that produce lumen narrowing.[60] Thus, although angiography is traditionally considered to be the 'gold standard' for the diagnosis of atherosclerosis, its use is limited to the assessment of disease progression in advanced plaques that protrude into the lumen; these lesions are relatively stable because of their fibrous matter and calcium content and, therefore, may be at low risk of rupture.

Despite the limitations of angiography in detecting vulnerable lesions, studies have demonstrated that QCA findings do predict CHD risk, with greater progression of QCA-assessed atherosclerosis related to a higher incidence of clinical events.[61-64] Consistent with their greater risk of rupture, mild-to-moderate QCA-defined lesions have been demonstrated to be more predictive of subsequent CHD events than more severe stenotic plaques.[61] However, for studying progression of atherosclerosis in asymptomatic individuals, QCA is limited by low interscan reliability, the invasive nature of the procedure, the exposure to X-ray radiation, and certain morbidity and mortality risks associated with the technique.

3.2 Ultrasonography

In contrast with QCA, ultrasonography enables direct imaging of the arterial wall rather than assessment of plaques based on luminal stenoses. It measures both the size and composition of atherosclerotic plaques, and has greater sensitivity for detecting soft, vulnerable plaques compared with QCA.

The most frequently used ultrasound technique for tracking the progression of atherosclerosis is B-mode (2-dimensional) ultrasonography, which uses high-frequency sound waves to non-invasively image the morphology of the carotid or femoral artery wall. The intima media thickness of the carotid artery wall (CIMT) has been demonstrated to be a valid measure of atherosclerotic burden,[65-68] and has been shown to predict risk of CHD and stroke[68-75] and to correlate with assessment of risk functions.[65,76,77] Given its greater sensitivity and non-invasive nature, B-mode ultrasonography may be a more appropriate method than QCA for tracking the early changes in atherosclerotic disease progression/regression associated with lipid-modifying therapy. As such, it is currently the best method for this purpose.

IVUS, an invasive ultrasound procedure currently mostly used for imaging coronary arteries, is mainly used clinically as an adjunct to angiography to aid diagnosis and intervention.[57] However, due to the invasive nature of the procedure, IVUS is used less frequently than B-mode ultrasonography in intervention studies.

The resolution of ultrasound imaging techniques depends upon the ultrasonic wavelength used; higher frequencies result in better resolution.[78] However, attenuation of the ultrasound signal as it passes through tissue is more pronounced at higher frequencies,[78] thus limiting the penetration that can be achieved. High ultrasound frequencies (20–50 mHz) and, consequently, excellent resolution can be achieved with IVUS,[57] whereas a lower frequency (5–10 mHz) is necessary with non-invasive imaging using B-mode ultrasound because of the greater depth of penetration required.[78] Despite the lower resolution of B-mode ultrasonography, this technique has been shown to be sufficiently sensitive to distinguish between fibrous, calcified plaques (echorich) and those with a high lipid content that are vulnerable to rupture (echolucent).[79]

3.3 Computed Tomography

EBCT is a promising imaging modality for assessing the effect of therapy on atherosclerosis, as determined by calcifications in the coronary arteries.[80] With EBCT imaging, the coronary artery tree

can be visualised non-invasively, and vascular calcification is easily detected and its extent quantified.

However, the degree to which the coronary calcium-volume score reflects unstable coronary disease has been the subject of some debate.[81] Rupture-vulnerable plaques are often present in the absence of EBCT-defined coronary artery calcification and it has been suggested that calcification is a characteristic of stable CHD.[81] Nevertheless, coronary calcium is a common component of unstable plaques,[82] and has been shown to predict cardiovascular events in patients and the general population[83,84] and to be related to CHD risk factors.[85-87]

Hence, although EBCT does not reliably identify individual plaques at risk of rupture, it provides an index of extent of coronary atherosclerosis, which is predictive of cardiovascular events.[81] However, guidelines only cautiously recommend the use of EBCT for screening specific populations of patients for coronary artery disease because of its low sensitivity.[80]

In contrast, the potential of EBCT for determining changes in calcium scores correlated with regression or progression of atherosclerosis has been recognised.[80] Few intervention studies using EBCT have been performed to date and thus the applicability of this technique needs to be assessed in more detail. Recent improvements in the measurement of coronary calcium deposits[88] have led to greater reproducibility, although it has been suggested that only changes in calcium-volume scores that exceed 15% after 1 year of follow-up should be considered indicative of a true change in atherosclerotic burden.[88]

The new generation of computed tomography techniques, such as multislice computed tomography (MSCT),[89-92] which are more widely available and appear to provide images of similar quality to EBCT, will further aid assessment of coronary calcification and progression in cardiovascular research and clinical practice. Moreover, recent results have shown that MSCT enables identification of non-calcified plaques and differentiates between soft, intermediate and calcified lesions,[92] thereby making it a more sensitive method for detecting rupture-vulnerable plaques compared with EBCT.

3.4 Magnetic Resonance Imaging

In recent years, the potential of MRI as one of the leading forms of non-invasive *in vivo* imaging techniques for the characterisation of atherosclerotic plaques has become recognised increasingly. It utilises biophysical and biochemical parameters such as chemical composition and water content to differentiate between the components of the plaque.[93]

A histopathological study of atherosclerotic lesions in the carotid artery demonstrated the high sensitivity and specificity of *ex vivo* MRI for characterising atherosclerotic plaques.[94] Studies in pigs have shown MRI can be used to effectively characterise coronary atherosclerotic lesions *in vivo*; however, cardiac and respiratory motion artefacts, the nonlinear course and relatively small size of the coronary arteries have been identified as potential problems when using this technique.[95,96] These problems are major challenges when characterising plaques or assessing atherosclerosis in humans and, as a result, the experience with *in vivo* coronary imaging using MRI is limited. However, several groups have produced encouraging results with MRI.[97-99] Furthermore, recent data indicate that MRI is a reproducible technique for assessing aortic anatomy and total atherosclerosis.[100] The utility of MRI may also extend to determining the impact of lipid-modifying therapy on atherosclerotic disease.[101]

4. Effects of Statins on Progression and Regression of Atherosclerotic Plaque Burden

Several imaging modalities have been used in clinical trials to assess the effects of statin therapy on the progression of atherosclerosis (table I and table II). The benefits of therapy have been assessed both in patients with CHD and in individuals with early, subclinical atherosclerosis.

Table I. Summary of trials of statin (HMG-CoA reductase inhibitor) therapy that measured atherosclerotic progression/regression in patients with coronary heart disease (CHD)

Trial	No of patients; details [lipid levels]	Statin regimen (mg/day)	Imaging modality	LDL-C lowering		Length of study (y)	Effect of statin on atherosclerosis	p-Value
				% reduction from baseline with statin	p-Value			
Comparisons with placebo								
MARS[102,103]	270; CHD (91% male) [TC: 4.9–7.6 mmol/L (190–295 mg/dL)]	Lov 80	QCA (n = 270)	38	<0.001	2.2	Slowed progression[a]	0.002[a]
			B-mode ultrasound (n = 188)[b]	45	<0.001		Regression	<0.001
CCAIT[104]	331; CHD (81% male) [TC: 5.7–7.8 mmol/L (220–300 mg/dL)]	Lov 20–80	QCA	29	<0.001	2	Slowed progression	0.01
PLAC I[13]	408; CHD (38% male) [LDL-C: ≥3.4–<4.9 mmol/L (130–<190 mg/dL)]	Prav 40	QCA	28	<0.001	3	Slowed progression	0.04
PLAC II[105]	151; CHD [LDL-C: 60–90th percentile for age and sex]	Prav 10–40	B-mode ultrasound	28	<0.001	3	Slowed progression	0.03[c]
REGRESS[12,106]	885; male with CHD [TC: 4.0–<8.0 mmol/L (155–<310 mg/dL)]	Prav 40	QCA (n = 885)	29	<0.001	2	Slowed progression	0.001
			B-mode ultrasound (n = 255)[b]	28	<0.001		Regression	0.0085
LIPID[107]	522; CHD (88% male) [TC: 4.0–7.0 mmol/L (155–271 mg/dL)]	Prav 40	B-mode ultrasound	28[d]	<0.0001[d]	4	Regression	<0.0001
Takagi et al.[60]	36; male with CHD undergoing PTCA [TC: 5.2–6.8 mmol/L (200–260 mg/dL)]	Prav 10	IVUS	26	<0.0005	3	Regression	<0.0005
LCAS[108]	429; CHD (81% male) [LDL-C: 3.0–4.9 mmol/L (115–190 mg/dL)]	Fluv 40[e]	QCA	23	<0.0001	2.5	Slowed progression	0.0161
CIS[109]	254; male with documented CHD [TC: 5.3–9.0 mmol/L (207–350 mg/dL)]	Simv 20–40	QCA	35[f]	<0.0001	2.3	Slowed progression	0.002
MAAS[11]	381; CHD (88% male) [TC: 5.5–8.0 mmol/L (213–310 mg/dL)]	Simv 20	QCA	31	<0.001	4	Slowed progression	0.007

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Table I. Contd

Trial	No of patients; details [lipid levels]	Statin regimen (mg/day)	Imaging modality	LDL-C lowering		Length of study (y)	Effect of statin on atherosclerosis	p-Value
				% reduction from baseline with statin	p-Value			
SCAT[110]	460; angiographic documented coronary atherosclerosis (89% male) [TC: 4.1–6.2 mmol/L (159–240 mg/dL)]	Simv 40	QCA	31	<0.001	4	Slowed progression	0.0001
Comparison with usual care								
GAIN[111]	131; CHD who had undergone IC revascularisation (85% male) [LDL-C: >4.1 mmol/L (160 mg/dL) untreated; >3.4 mmol/L (130 mg/dL) treated[g]]	Ator 20–80	IVUS	42	<0.0001[h]	1	Slowed progression	NS[h]
Comparisons between statins								
SARIS[112]	50; CHD eligible for balloon angioplasty and/or stent placement [TC: 5.0–8.0 mmol/L (194–310 mg/dL)]	Ator 10 vs 80	IVUS			1	Ongoing	
REVERSAL[57][i]	600; CHD	Ator 80 vs prav 40	IVUS			1.5	Ongoing	
ARBITER[113]	200; with or without CHD [TC: ≥4.1 mmol/L (160 mg/dL)]	Ator 80 vs prav 40	B-mode ultrasound			1	Slowed progression	0.03

a As indicated by global change score.

b B-mode ultrasound subgroup.

c Effect limited to the common carotid artery.

d After 3 years of follow up.

e A subgroup of patients received cholestyramine in addition to fluvastatin. Data presented are for fluvastatin monotherapy.

f % Difference vs placebo.

g LDL-C: >4.1 mmol/L (160 mg/dL) if not treated with lipid-lowering therapy at screening, or >3.4 mmol/L (130 mg/dL) if treated with lipid-lowering therapy.

h p-Value for comparison with usual care (≥1 lipid-lowering therapies from statins other than atorvastatin, fibric acid derivatives and cholestyramine).

i Expected to be completed 2002.

ARBITER = ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol; **Ator** = atorvastatin; **CCAIT** = Canadian Coronary Atherosclerosis Intervention Trial; **CIS** = Coronary Intervention Study; **Fluv** = fluvastatin; **GAIN** = German Atorvastatin INtravascular ultrasound study; **IC** = intracoronary; **IVUS** = intravascular ultrasonography; **LCAS** = Lipoprotein and Coronary Atherosclerosis Study; **LDL-C** = low-density lipoprotein cholesterol; **LIPID** = Long-term Interventions with Pravastatin in Ischemic Disease; **Lov** = lovastatin; **MAAS** = Multicentre Anti-Atheroma Study; **MARS** = Monitored Atherosclerosis Regression Study; **NS** = not significant; **PLAC I** = Pravastatin Limitation of Atherosclerosis in the Coronary arteries; **PLAC II** = Pravastatin, Lipids, and Atherosclerosis in the Carotids; **Prav** = pravastatin; **PTCA** = percutaneous transluminal coronary angioplasty; **QCA** = quantitative coronary angiography; **REGRESS** = REgression GRowth Evaluation Statin Study; **REVERSAL** = REVERSal of Atherosclerosis with Lipitor; **SARIS** = Statin on Atherosclerosis and vascular Remodeling assessed with Intravascular Sonography; **SCAT** = Simvastatin/enalapril Coronary Atherosclerosis Trial; **Simv** = simvastatin; **TC** = total cholesterol.

Table II. Summary of trials of statin (HMG-CoA reductase inhibitor) therapy that measured atherosclerotic progression/regression in patients with subclinical athersclerosis

Trial	No of patients; details [lipid levels]	Statin regimen (mg/day)	Imaging modality	LDL-C lowering		Length of study (y)	Effect of statin on atherosclerosis	p-Value vs placebo
				% reduction from baseline with statin	p-Value vs placebo			
Comparisons with placebo								
ACAPS[50]	919; asymptomatic atherosclerosis (52% male) [LDL-Cholesterol: 3.4–4.9 mmol/L (130–189 mg/dL)]	Lov 20–40	B-mode ultrasound	28	<0.0001	3	Regression	0.001
CAIUS[52]	305; asymptomatic atherosclerosis (53% male) [LDL-C: 3.9–6.5 mmol/L (151–252 mg/dL)]	Prav 40	B-mode ultrasound	22	0.0001	3	Regression	0.0007
KAPS[114]	424; male with asymptomatic atherosclerosis[a] [LDL-C: >4.0 mmol/L (155 mg/dL) after dietary advice]	Prav 40	B-mode ultrasound	27	<0.001	3	Slowed progression	0.005
BCAPS[115]	793; asymptomatic atherosclerosis (46% male) [TC: ≤8.0 mmol/L (310 mg/dL)]	Fluv 40	B-mode ultrasound	23		3	Slowed progression	0.002[b]
METEOR[116]	840; subclinical atherosclerosis with low risk of CHD [LDL-cholesterol: 3.4–<4.1 mmol/L (130–<160 mg/dL)]	Ros 40	B-mode ultrasound			2	Ongoing	
Comparison with no statin								
Callister et al.[117]	149; asymptomatic athersclerosis (61% male) [Mean LDL-cholesterol[c]: 3.8 mmol/L (147 mg/dL) for untreated patients; 3.6 mmol/L (139 mg/dL) for patients treated to ≥3.1 mmol/L (120 mg/dL); 2.6 mmol/L (100 mg/dL) for patients treated to below 3.1 mmol/L (120 mg/dL)]	Statin monotherapy	EBCT			1–1.25	Regression in statin-treated patients achieving LDL-C <3.1 mmol/L (120 mg/dL)	0.01
							Slowed progression in statin-treated patients not achieving LDL-C ≤3.1 mmol/L (120 mg/dL)	<0.001
Comparison with baseline								
Achenbach et al.[118]	66; asymptomatic atherosclerosis (89% male) [LDL-C ≥3.4 mmol/L (130 mg/dL)]	Cer 0.3	EBCT	35		1[d]	Slowed progression	0.0001[e]

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Table II. Contd

Trial	No of patients; details [lipid levels]	Statin regimen (mg/day)	Imaging modality	LDL-C lowering		Length of study (y)	Effect of statin on atherosclerosis	p-Value vs placebo
				% reduction from baseline with statin	p-Value vs placebo			
Comparisons between statins								
ASAP[119]	325; familial hypercholesterolaemia (39% male). 31% with a history of CHD [LDL-C: >4.5 mmol/L (174 mg/dL)]	Ator 80	B-mode ultrasound	51	<0.0001[e]	2	Regression with atorvastatin[e]	0.0001[f]
		Simv 40		41	<0.0001[e]		Progression with simvastatin[e]	
BELLES[120]	600; postmenopausal women with asymptomatic CHD [LDL-C: above target level according to NCEP ATP II guidelines[121]]	Ator 80 vs prav 40	EBCT			1	Ongoing	

a A history of myocardial infarction was reported in a small proportion (<10%) of subjects.

b Effect in the common carotid artery.

c Average LDL-C levels throughout study.

d Length of treatment period.

e For comparison versus baseline.

f For comparison of atorvastatin with simvastatin.

ACAPS = Asymptomatic Carotid Artery Progression Study; **ASAP** = Atorvastatin versus Simvastatin on Atherosclerotic Progression; **Ator** = atorvastatin; **BCAPS** = Beta-blocker Cholesterol-lowering Asymptomatic Plaque Study; **BELLES** = Beyond Endorsed Lipid Lowering with EBCT Scanning; **CAIUS** = Carotid Atherosclerosis Italian Ultrasound Study; **Cer** = cerivastatin; **CHD** = coronary heart disease; **EBCT** = electron beam computed tomography; **Fluv** = fluvastatin; **KAPS** = Kuopio Atherosclerosis Prevention Study; **LDL-C** = low-density lipoprotein cholesterol; **METEOR** = Measuring Effects on intima media Thickness – an Evaluation Of Rosuvastatin; **NCEP ATP II** = National Cholesterol Education Program – Adult Treatment Panel II; **Prav** = pravastatin; **Ros** = rosuvastatin; **Simv** = simvastatin; **TC** = total cholesterol.

4.1 Patients with Coronary Heart Disease

The Monitored Atherosclerosis Regression Study (MARS) was the first trial to assess the effects of statin monotherapy upon coronary artery lesions at the vascular level[102] (table I). In comparison with placebo, lovastatin treatment had no significant effect on the primary endpoint, change in mean percent diameter stenosis assessed by QCA (1.6% vs 2.2%; $p > 0.20$). However, global change score, the degree of change assessed on a 4-point scale from 0 (no demonstrable change) to 3 (extreme change) by an expert panel who were temporally blinded, revealed that patients receiving lovastatin had significantly less disease progression compared with those treated with placebo (0.41 vs 0.88; $p = 0.002$). Moreover, B-mode ultrasonography was performed in a subgroup of patients and demonstrated significant regression of CIMT with lovastatin therapy compared with placebo (−0.038 mm/year vs +0.019 mm/year; $p < 0.001$),[103] reflecting a greater sensitivity of B-mode ultrasound for detecting regression of atherosclerosis. The effect of lovastatin on disease progression in the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)[104] was consistent with that reported for MARS. In CCAIT, lovastatin therapy significantly reduced progression of disease, measured by change in minimum lumen diameter (MLD), in comparison with placebo (−44%; $p = 0.01$). In addition, fewer lovastatin-treated patients exhibited QCA-determined disease progression compared with those receiving placebo (33% vs 50%; $p = 0.003$).

The effect of pravastatin monotherapy on plaque progression was evaluated using QCA in the Pravas-

tatin Limitation of Atherosclerosis in the Coronary arteries (PLAC I) study[13] (table I). Disease progression was correlated with level of LDL cholesterol such that every 0.6 mmol/L (22 mg/dL) increment in LDL cholesterol level resulted in an additional decrease in MLD of 0.01 mm/year. Pravastatin treatment was associated with significant reductions in LDL cholesterol level, and progression of atherosclerosis, as assessed by change in MLD, was reduced by 40% compared with placebo ($p = 0.04$).

In the Pravastatin, Lipids, and Atherosclerosis in the Carotids (PLAC-II) trial the efficacy of pravastatin in slowing the progression of atherosclerosis in CHD patients was assessed using B-mode ultrasound[105] (table I). Although pravastatin reduced the progression rate of mean maximum CIMT by 12% compared with placebo (0.0593 vs 0.0675 mm/year), this change was not statistically significant. The effect of pravastatin on slowing CIMT progression appeared to be limited to the common carotid artery (35% reduction vs placebo; $p = 0.03$).

The REgression GRowth Evaluation Statin Study (REGRESS) examined the effect of pravastatin in patients with coronary atherosclerosis and normal to moderately elevated serum cholesterol levels (table I).[12] Significant changes in LDL cholesterol levels were apparent within two months for patients receiving pravastatin compared with placebo ($p < 0.001$) and were sustained over the 2-year study period ($p < 0.001$). Change in luminal diameter as assessed by QCA was reduced by 67% in pravastatin-treated patients compared with placebo ($p = 0.001$). These results were similar to those reported in CCAIT and indicate that net progression of atherosclerosis was decreased. In REGRESS, there was no significant effect of baseline LDL cholesterol level upon the QCA endpoints, suggesting that statins slow progression of atherosclerosis independent of baseline LDL cholesterol. In this study, more patients remained free of clinical events in the pravastatin treatment group compared with placebo (89% vs 81%; $p = 0.002$). Patients were categorically classified as regressors, stable or progressors as defined by QCA outcome (MLD) and clinical events;[12] more patients in the placebo group were classified as progressors compared with patients receiving pravastatin ($p = 0.0035$).

Carotid and femoral intima media thickness (IMT) was assessed by B-mode ultrasound in a subset of patients in the REGRESS study[106] enabling the effect of pravastatin on the primary endpoint, IMT across both coronary and peripheral arteries, to be assessed. In contrast with the QCA findings, which showed that pravastatin slowed progression of disease, mean IMT was significantly reduced by pravastatin (–0.05mm) compared with no change in the placebo group ($p = 0.0085$). The difference in the effect of statin therapy on QCA-defined atherosclerosis and IMT was similar to that observed in MARS and may be a reflection of a greater sensitivity of B-mode ultrasound for detecting disease regression.

Consistent with the results of the REGRESS ultrasound substudy, regression of CIMT in patients with CHD was also observed with pravastatin in the Long-term Interventions with Pravastatin in Ischemic Disease (LIPID) trial (–0.014 vs +0.048mm for placebo; $p < 0.0001$).[107] Similarly, plaque regression was observed with pravastatin in a study that used IVUS to assess the effect of therapy on atherosclerotic lesions[60] (table I); pravastatin reduced plaque index by 7% compared with an increase of 27% with placebo in coronary artery segments with <25% stenosis at baseline ($p < 0.0005$). A second IVUS study, the German Atorvastatin INtravascular ultrasound study (GAIN) examined the effect of atorvastatin compared with usual care with one or more lipid-lowering therapies (either statins other than atorvastatin, fibrates or cholestyramine) on plaque volume and plaque echogenicity[111] (table I). Over the 1-year follow-up period, a greater increase in plaque volume was observed in the usual-care group compared with atorvastatin-treated patients (11.8 vs 2.5%); however, the difference between treatment groups failed to achieve statistical significance ($p = 0.138$).

Slowing of progression of atherosclerosis assessed by QCA was observed with fluvastatin therapy in the Lipoprotein and Coronary Atherosclerosis Study (LCAS)[108] (table I). Analysis of the

primary endpoint of change in MLD showed significantly less progression in fluvastatin patients than in the placebo group (–74%; p = 0.0161). In agreement with REGRESS, the treatment effect of the statin did not vary with baseline LDL cholesterol; in a post-hoc analysis, fluvastatin treatment was associated with regression of atherosclerotic plaque even in patients with normal LDL cholesterol levels (<3.4 mmol/L [130 mg/dL]). Patients in the LCAS study were classified as exhibiting atherosclerotic regression, no change or progression based upon change in MLD; there were fewer patients with progression (28.7%) and more with regression (14.0%), in the fluvastatin group compared with placebo (35.6% and 7.6%, respectively).

The Coronary Intervention Study (CIS) and the Multicentre Anti-Atheroma Study (MAAS) investigated the effects of simvastatin versus placebo on coronary progression in CHD patients using QCA (table I). In CIS, simvastatin reduced mean change in MLD by 80% compared with placebo (p = 0.002) and slowed progression of disease as determined by mean global change score (+0.20 vs +0.58; p = 0.02).[109] Similar results for MLD were reported in MAAS (table I); simvastatin reduced change in MLD by 69% in this study (p = 0.007).[11]

The Simvastatin/enalapril Coronary Atherosclerosis Trial (SCAT) extended the evidence for the effect of simvastatin on atherosclerotic progression by evaluating the effect of LDL cholesterol-lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis in normocholesterolaemic individuals[110] (table I). The mean decrease in MLD was significantly reduced in patients receiving simvastatin compared with placebo recipients (–44%; p = 0.0001), and the percent change in maximum stenosis also differed significantly between treatments (1.67 and 3.83% for simvastatin and placebo, respectively; p = 0.0003). These results indicate that statin therapy reduced progression of coronary atherosclerosis even in individuals with normal cholesterol levels.

These studies have established the efficacy of statins in slowing the progression of atherosclerosis in patients with CHD. Furthermore, mean baseline LDL cholesterol levels in these trials ranged between 3.4 mmol/L (130 mg/dL) [SCAT] to approximately 4.7 mmol/L (181 mg/dL) [CCAIT] suggesting that statins have beneficial effects on plaque progression across a range of LDL cholesterol levels. Most imaging studies conducted in CHD patients to date have assessed the effects of statin therapy on QCA findings. The Statin on Atherosclerosis and vascular Remodeling assessed with Intravascular Sonography (SARIS) trial will extend these findings in CHD patients with normal to mildly elevated cholesterol levels by assessing the effects of statin therapy using IVUS,[112] which has greater sensitivity for detecting early plaques that are more vulnerable to rupture. In this prospective study, the effect of atorvastatin on plaque volume and vascular remodelling will be determined after 1 year of statin therapy.

Other imaging studies currently in progress include the REVERSal of Atherosclerosis with Lipitor (REVERSAL) trial and the ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol (ARBITER) study (table I). In REVERSAL, the effects of atorvastatin and pravastatin therapy over 18 months on progression of atherosclerosis will be compared using IVUS imaging of the coronary arteries in CHD patients.[57] This study is due to be completed in 2002 and will provide data on the comparative efficacy of these two statins on atherosclerosis progression in approximately 600 patients. In ARBITER, the effects of atorvastatin and pravastatin on CIMT have been examined in patients with total cholesterol level ≥4.1 mmol/L (160 mg/dL) who have not previously been treated with lipid-lowering drugs.[113] Atorvastatin and pravastatin differ in their LDL cholesterol lowering efficacy and non-lipid effects, and this study aimed to examine the effects of the statins on CIMT progression in relation to these differences over a 12-month period. Atorvastatin induced progressive CIMT regression over 12 months with a change in CIMT of −0.034 ± 0.021mm, whereas CIMT was stable in the pravastatin group (change 0.025 ± 0.017mm; p = 0.03).[122]

4.2 Patients with Asymptomatic Atherosclerosis

Clinical trials using B-mode ultrasonography and EBCT have examined the beneficial effects of statin therapy on progression in asymptomatic individuals with early atherosclerotic disease (table II).

In the Asymptomatic Carotid Artery Progression Study (ACAPS), lovastatin significantly reduced LDL cholesterol levels compared with baseline following a 6-month treatment period (–28%; $p < 0.0001$)[50] (table II). Significant regression of mean maximum CIMT was observed with lovastatin therapy (–0.009 mm/year) compared with CIMT progression with placebo (+0.006 mm/year; $p = 0.001$), and this benefit was evident after 6–12 months of therapy.

Similar results were demonstrated with pravastatin therapy in the Carotid Atherosclerosis Italian Ultrasound Study (CAIUS).[52] Pravastatin reduced LDL cholesterol levels by 22% and caused regression of mean maximum CIMT at a rate of –0.0043 mm/year compared with progression in the placebo group (+0.0089 mm/year; $p = 0.0007$), and these effects were noted after 6 months. Benefits of statin therapy on CIMT in asymptomatic individuals were also observed in the Kuopio Atherosclerosis Prevention Study (KAPS) [table II], in which pravastatin treatment reduced CIMT progression rate by 45% compared with placebo ($p = 0.005$).[114]

Similarly, the Beta-blocker Cholesterol-lowering Asymptomatic Plaque Study (BCAPS) [table II] recently demonstrated that fluvastatin significantly reduced progression of CIMT of the common carotid artery compared with placebo (–69%; $p = 0.002$), although no effect of fluvastatin was found for progression of CIMT in the bifurcation.[115]

One EBCT study has assessed changes in coronary plaque volume with lipid-lowering therapy using calcium-volume score (CVS) in asymptomatic, hyperlipidaemic patients[117] (table II). Of patients treated with a statin, those who achieved an LDL cholesterol level <3.1 mmol/L (120 mg/dL) demonstrated a mean reduction in the CVS of 7%, indicating plaque regression. In patients who failed to reach this target LDL cholesterol level despite statin therapy, CVS increased by 25%; however the magnitude of the increase was lower than that observed in untreated patients (25 vs 52%; $p < 0.001$).

A second EBCT study, initiated prior to the withdrawal of cerivastatin because of an increased incidence of rhabdomyolysis,[123] examined the change in the rate of progression of coronary calcification during treatment with this statin.[118] This study demonstrated that progression of coronary calcification was slower over a 1-year period during which patients received cerivastatin compared with the 14 months prior to drug initiation (8.8 vs 25.0%; $p = 0.0001$).

There are few comparative studies to date that have compared the effects of different statins on plaque progression. However, dissimilarities in the efficacy of statins in slowing or reversing CIMT progression were highlighted in the effects of Atorvastatin versus Simvastatin on Atherosclerotic Progression (ASAP) study in patients with familial hypercholesterolaemia[119] (table II), of which 69% were asymptomatic. The effect of therapy differed significantly between the two statins; overall, CIMT reduced over the 2-year treatment period with atorvastatin but increased following treatment with simvastatin (–0.031 vs +0.036mm; $p = 0.0001$). Although less beneficial than atorvastatin, no conclusion can be drawn regarding any positive effects of simvastatin in slowing progression of CIMT because of the lack of placebo group in this study. Regression of CIMT was observed in 66% of patients in the atorvastatin group compared with 42% of patients treated with simvastatin. Although both statins were effective in lowering LDL cholesterol levels, reductions were greater with atorvastatin than with simvastatin (–50.5% vs –41.2%; $p = 0.0001$). However, these observed differences in LDL cholesterol-lowering effects of the statins cannot entirely explain the differences in progression of CIMT between atorvastatin and simvastatin, which may be partially due to their pleiotropic effects.

Two studies, the Beyond Endorsed Lipid Lowering with EBCT Scanning (BELLES) trial and the Measuring Effects on intima media Thickness – an Evaluation Of Rosuvastatin (METEOR) trial, are

currently ongoing in asymptomatic patients (table II). BELLES has been designed to evaluate the benefits of lipid-lowering therapy in postmenopausal women.[120] Patients will be treated with either atorvastatin or pravastatin, and EBCT scanning will be conducted at baseline and after 1 year. The primary efficacy parameter will be the percent change from baseline in each patient's total coronary calcium-volume score. The effects of rosuvastatin, a new statin that has demonstrated greater efficacy in reducing LDL cholesterol levels compared with atorvastatin, pravastatin and simvastatin,[124-126] will be assessed in METEOR. This trial is a placebo-controlled study assessing the effect of rosuvastatin on progression and regression of CIMT, measured by B-mode ultrasonography, in patients with low risk of CHD who have evidence of subclinical atherosclerosis.[116] These studies will provide an insight into the potential benefits of statin therapy in groups of patients not currently eligible for statin therapy under current treatment guidelines.[127,128]

4.3 Highly Stenotic Versus Mildly Stenotic Lesions

Studies in asymptomatic patients and those with established CHD have clearly demonstrated the benefits of statin therapy on atherosclerosis progression. QCA studies have consistently demonstrated a slowing of progression of disease with statin therapy, while mean regression has been observed in trials using ultrasonography and EBCT. Given that QCA studies examine the effects of statins only on advanced lesions that result in vessel stenosis, the lack of regression in these trials may indicate that statins have greater benefits in smaller plaques that are more easily detected by other imaging techniques. Indeed, subgroup analyses according to baseline vessel stenosis performed in CCAIT and PLAC I appear to support this.[13,104]

In CCAIT, the benefit of treatment was most pronounced in the less severe plaques; for lesions with stenosis <50%, lovastatin slowed progression of MLD by 45% compared with placebo ($p = 0.014$).[104] However, there were no significant effects of treatment upon vessels with ≥50% stenosis, although comparatively few lesions fulfilled this criterion. In PLAC I, subset analysis was in agreement with that of CCAIT and revealed that the major effect of statin treatment was on lesions causing <50% stenosis at baseline.[13]

However, these findings are not consistent across all QCA trials. In MARS, lovastatin had significant beneficial effects on large lesions that narrowed the lumen by >50% but not on smaller lesions.[102] Similarly in MAAS, the effect of simvastatin therapy was greater on lesions causing >50% stenosis at baseline compared with smaller plaques.[11]

In CCAIT, the authors suggested that the ability of lovastatin to prevent the formation of new coronary lesions might be more important than its effect on established plaques; new QCA-defined coronary lesions developed in 16% of patients treated with lovastatin and 32% of placebo recipients ($p = 0.001$)[104] (figure 2). Similar results were found in PLAC I, LCAS and MAAS; in these trials the number of patients developing new stenotic lesions was approximately halved by statin therapy[11,13,108] (figure 2).

Given that QCA only detects plaques that cause stenosis, it may not be the most appropriate method for examining the effect of therapy on early lesions. Evidence for the benefits of statins on soft plaques,

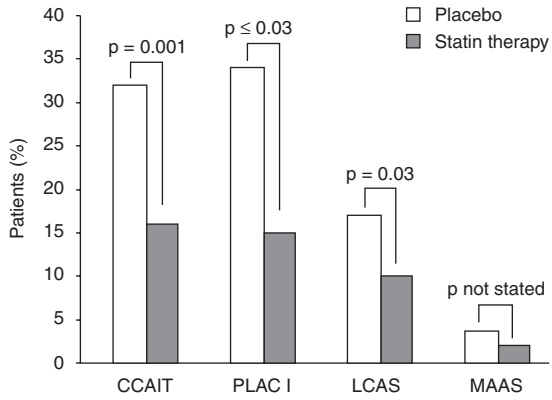

Fig. 2. Occurrence of new quantitative coronary angiography (QCA)-defined atherosclerotic plaques in trials of statin (HMG-CoA reductase inhibitor) treatment in patients with coronary heart disease patients.[11,13,104,108] **CCAIT** = Canadian Coronary Atherosclerosis Intervention Trial; **LCAS** = Lipoprotein and Coronary Atherosclerosis Study; **MAAS** = Multicentre Anti-Atheroma Study; **PLAC I** = Pravastatin Limitation of Atherosclerosis in the Coronary arteries.

which may be more vulnerable to rupture, comes from studies using more sensitive imaging techniques. Using IVUS, Takagi et al.[60] demonstrated plaque regression in mild lesions in coronary artery segments with minimal or no angiographically defined disease (<25% stenosis). Furthermore, analysis of the effect of treatment according to baseline CIMT in LIPID and ACAPS suggested that the benefits of statins extended to smaller lesions; degree of regression with statin therapy was independent of baseline CIMT.[50,107] In MARS, however, CIMT regression following lovastatin therapy was greater in patients with baseline CIMT ≥0.717mm compared with patients with CIMT <0.717mm ($p < 0.001$).[103] Consistent results were observed in KAPS for treatment with pravastatin.[114]

These studies suggest that, although the degree to which statins slow progression or promote regression of atherosclerosis may vary according to the stage of disease, these drugs effectively reduce progression in early lesions that cause minimal stenosis. These findings, together with the results of landmark primary prevention trials,[6,7] support the use of early intervention with statin therapy in patients with subclinical atherosclerosis. Studies such as METEOR, which will examine the effects of statin therapy on atherosclerosis progression in low risk individuals not currently eligible for lipid-lowering therapy,[116] will investigate further the benefits of early intervention with these agents.

5. Conclusions

A number of validated, vascular measures of atherosclerotic burden have been used to examine the effects of statins on disease progression. Although QCA has demonstrated that statins slow atherosclerosis progression in advanced plaques that protrude into the vessel lumen, this technique has limited use for assessing the benefits of treatment in early lesions that are more vulnerable to rupture. Imaging modalities with greater sensitivity for detecting small, soft plaques provide more information about the effect of statins on these early lesions, and due to its non-invasive nature, B-mode ultrasonography has been most widely used in studies of patients with asymptomatic atherosclerosis.

The benefits of statins on progression of atherosclerosis have been clearly demonstrated in imaging studies in patients with CHD, and their effects are evident even in normocholesterolaemic patients. Fewer data are available on the effects of statins in individuals with subclinical atherosclerosis, although these have also shown that statin therapy is beneficial. Data from ongoing studies and a number of studies in asymptomatic patients should provide further evidence in support of statin use for the treatment of subclinical atherosclerosis.

Analysis of the efficacy of statins in slowing progression and promoting regression of atherosclerotic plaques, at different stages of development, suggest the benefits of these agents extend to smaller lesions. The benefits of statin therapy on these early lesions support the early detection of atherosclerosis using vascular measures, and subsequent intervention with statin therapy while in the subclinical stage of the disease, irrespective of lipid levels. Such early intervention may have significant impact upon the considerable morbidity and mortality associated with CHD.

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