

EDUCATIONAL ARTICLE

The Rationale for Using HMG-CoA Reductase Inhibitors ('Statins') in Peripheral Arterial Disease[☆]

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Atherosclerosis is a systemic process, and the leading cause of morbidity and mortality in the developed world. HMG-CoA reductase inhibitors ('statins') are potent lipid lowering drugs, which have been shown to reduce morbidity and mortality in patients with coronary atherosclerosis. Objective: To present the up-to-date data concerning statin use in the prevention and treatment of extra-coronary atherosclerosis. Methods: Clinical trials with statins in patients with extra-coronary atherosclerosis were searched for via PUBMED. Findings and conclusions: The different forms of peripheral arterial disease (e.g. cerebrovascular disease, lower extremity peripheral arterial disease) are associated with significant cardiovascular morbidity and mortality, and hence constitute a coronary artery disease equivalent in terms of published practice guidelines. There is some evidence from small randomized controlled trials that statin therapy decreases cardiovascular morbidity and mortality in patients with peripheral arterial disease. The mechanism of action of statins may derive from their lipid lowering properties, or from other, pleiotropic effects. Further, larger randomized controlled studies with statins are needed to evaluate the efficacy of statin therapy in patients with stable peripheral arterial disease and in those undergoing vascular or endovascular surgery.

Keywords: Statins; Primary prevention; Peripheral arterial disease; Cerebrovascular disease.

Atherosclerosis is the leading cause of morbidity and mortality in the developed world. The most common presentation is coronary artery disease (CAD), but atherosclerosis is a systemic process, often involving other vascular sites, such as the carotid arteries, the aorta, the renal and mesenteric arteries and large peripheral arteries such as the iliac and femoral arteries. The benefit of HMG-CoA reductase inhibitors ('statins') in terms of reduction in cardiac morbidity and mortality in high-risk patients has been proved in numerous studies. However, the effect of statins on extra-cardiac manifestations of atherosclerosis has not been as extensively studied. The purpose of this review is to present the up-to-date data concerning statin use in the prevention and treatment of extra-coronary atherosclerosis. We will focus on two major

vascular beds: the cerebrovascular circulation and the arteries to the lower extremities.

Cerebrovascular Disease

In contrast with CAD, an association between the incidence of stroke and serum cholesterol levels has not been found, with the exception of adults younger than 45 years.^{1–3} However, stroke and transient ischemic attacks (TIAs) are presumed to be, at least in part, the outcome of atherosclerosis of the cerebrovascular bed. Therefore many statin studies have included stroke as a secondary outcome in the analysis, since stroke is an important cause of death and disability in developed countries.

A meta-analysis of 26 statin studies,⁴ including 90 000 participants, has shown that statin therapy results in a 21% relative risk reduction of fatal or non-fatal stroke, as compared with placebo. These studies have encompassed 7 different patient populations, including patients with hypercholesterolemia, coronary heart disease, hypertension, diabetes mellitus,

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normocholesterolemia, the elderly and patients with prior stroke or TIA. In a sub-group analysis, this meta-analysis failed to show any benefit in the minority of patients with prior stroke.

A randomized controlled trial⁵ was designed specifically to find out whether treatment with 80 mg atorvastatin in patients with a recent history of stroke or TIA, but with no history of coronary heart disease, and with low density lipoprotein cholesterol (LDL-C) levels between 100 and 190 mg/dL (2.6–4.9 mmol/L), resulted in less recurrent cerebrovascular events (fatal or non-fatal stroke). This study found a significant 16% relative risk reduction in the atorvastatin group, as compared with placebo. The absolute risk reduction was 2.2% (95% confidence interval (CI) 0.2–4.2%). The main benefit seemed to result from a reduction in the incidence of fatal stroke. This effect was believed to be an underestimation of the true benefit, since 7.5% of the placebo group had actually started non-study statin therapy during the study period, resulting in 78.1% net difference in statin use between the groups.

The mechanism by which statin therapy reduces cerebrovascular events is not known. The SPARCL study investigators had assigned most of this effect to a significant 53% reduction in LDL-C levels in the atorvastatin group, although this is not necessarily the case, and plasma LDL-C levels might serve as a marker for statin treatment, with the actual benefit resulting from pleiotropic effects (see below).⁶

Lower Extremity Peripheral Arterial Disease

Lower extremity peripheral arterial disease (LE-PAD) affects 3–4% of adults 40 years old, and over 20% of the elderly, 70 years and older.^{7,8} It is usually defined as an ankle-brachial index (ABI) of less than 0.9 on Doppler examination. In many cases, lower extremity PAD is asymptomatic, but in others it may present as intermittent claudication, leg pain at rest, or critical limb ischemia. Accordingly, it may have minor to life-threatening outcomes.

Three main issues are relevant for decision making about statin treatment for patients with lower extremity PAD: 1. Secondary prevention of coronary heart disease; 2. Treatment of lower extremity peripheral arterial disease; and 3. Perioperative treatment of patients with peripheral arterial disease.

1. Secondary prevention of coronary heart disease in LE-PAD patients

The AHA/ACC has acknowledged LE-PAD to be a CAD equivalent,⁹ and has instituted a class I

recommendation for statin treatment for all LE-PAD patients, with a target LDL-C level of less than 100 mg/dL (2.6 mmol/L).¹⁰ For patients with very high risk of ischemic events, a target LDL-C of less than 70 mg/dL is recommended (class IIa recommendation).

A few trials have studied the secondary prevention of CAD in patients with LE-PAD. Their results are summarized in Table 1.

Schillinger *et al.*¹¹ reported the results of a prospective non-randomized non-interventional trial, which was designed to study the association between statin treatment, inflammatory activity and cardiovascular outcome of patients with severe LE-PAD. Statin users tended to have more baseline risk factors, and lower inflammatory activity, as assessed by serum biomarkers. Statin users had a significantly reduced risk of death (RR = 0.52, 95% CI 0.30–0.91, $p = 0.022$) and of the cumulative end-point of death or myocardial infarction (RR = 0.48, 95% CI 0.29–0.79, $p = 0.004$). However, stratification for inflammatory activity (Hs-CRP below or above median of 0.42) resulted in no significant benefit for patients with low Hs-CRP, as opposed to a 42% significant reduction in risk of mortality in the high Hs-CRP group ($p = 0.046$). The authors conclude that statin therapy decreased the risk for adverse cardiovascular outcome in patients with severe LE-PAD, most probably by an anti-inflammatory mechanism.

An 8-year observational study, reported by Feringa *et al.*,⁷ showed similar results: statin use (as well as the use of aspirin, beta blockers or ACE inhibitors) was found to be independently associated with a reduced incidence of long-term mortality (HR = 0.46, 95% CI 0.58–0.80, $p < 0.001$).

REGRESS was a study primarily designed to assess the effect of two year treatment with 40 mg pravastatin on the coronary lumen. A sub-study within REGRESS used B-mode ultrasound to quantitate the intima-media thickness (IMT) of the carotid and femoral arteries, and aimed to compare changes in the coronary lumen with changes in peripheral IMT.¹² This sub-study showed a significant effect of pravastatin on clinical events: 79.8% of placebo allocated patients were free of clinical events (myocardial infarction, coronary death, revascularization, stroke or TIA or any death) after two years, as compared with 90.1% of the pravastatin group ($p = 0.02$). Pravastatin also positively influenced the combined femoral and carotid IMT. However, there was only a mild-moderate correlation between the change in coronary lumen measures and the change in peripheral IMT, and there was no correlation in treatment effects between the two vascular beds.

The Heart Protection Study¹³ was a randomized placebo-controlled double-blind study designed to

Table 1. Secondary prevention of CAD in patients with LE-PAD

Study type	No. of participants	Characteristics of participants	Statin used	Follow-up time	End-points	Results	Reference
Observational	515	Admitted for PCI for lower extremity PAD	Any	Median, 21 months	1': all-cause mortality; 2': composite of death and MI	For statin users, RR = 0.52 ($p = 0.022$) for mortality; RR = 0.48 ($p = 0.004$) for death or MI; after stratification for inflammatory activity: benefit only for high hs-CRP group	Schillinger <i>et al.</i> , Eur Heart J 2004 ¹¹
Observational	2420	Patients with lower extremity PAD	Any	Median, 8 years	Overall mortality	For statin users, HR = 0.46 ($p < 0.001$)	Feringa <i>et al.</i> , J Am Coll Cardiol 2006 ⁷
Sub-study within double-blind, placebo controlled, angiographic study	124 placebo, 131 active treatment	Men under 70 years old with symptomatic CAD	Pravastatin	2 years	1': Mean change in IMT; 2': composite of MI, coronary death, stroke/TIA, any death	79.8% placebo users free of clinical events, vs. 90.1% of pravastatin users	DeGroot <i>et al.</i> , J Am Coll Cardiol 1998 ¹²
Randomized, double-blind, placebo-controlled trial	4047 with lower extremity PAD at baseline (20 536 total)	Men and women with total cholesterol above 135 mg/dL with substantial 5-year risk of coronary death	Simvastatin	Mean, 5 years	1': Total mortality; 2': Major vascular events (coronary event, stroke or re-vascularization)	In patients with PAD at baseline: 27.6% major vascular events in simvastatin allocated vs. 34.3% in placebo allocated	Heart Protection Study Group, Lancet 2002 ¹³

Abbreviations: RR = relative risk, HR = hazard ratio, CI = confidence interval, CAD = coronary artery disease, PAD = peripheral arterial disease, MI = myocardial infarction, hs-CRP = high sensitivity C reactive protein, IMT = intima-media thickness, TIA = transient ischemic attack.

assess the long-term effects of lipid lowering by simvastatin on vascular and non-vascular mortality and morbidity, in several pre-defined high-risk groups of patients. In patients with LE-PAD at baseline, there was a 25% statistically significant reduction in the rate of major vascular events (i.e. major coronary event, stroke or any revascularization) for the simvastatin group as compared with the placebo group. Of note, the proportional risk reduction was not restricted to patients with high baseline cholesterol or triglyceride levels, and was similar in patients with pre-treatment LDL-C levels below 116 mg/dL (3 mmol/L). This reduction was believed to be an under-estimation of the true benefit, since many of the placebo-allocated group had actually started receiving non-study statins during the study period.

Despite the above data, and although LE-PAD has long been acknowledged as a CAD equivalent, LE-PAD patients remain undertreated with respect to atherosclerosis risk factor control.¹⁴⁻¹⁸ However, this must not be the case. For example, Rehring *et al.*¹⁶ show that use of a pharmacist-managed, physician-monitored algorithm for the treatment of LE-PAD in an outpatient setting resulted in higher adherence to published guidelines, and a higher percentage of patients achieving target levels.

2. Treatment of lower extremity PAD

A beneficial effect of serum cholesterol reduction on femoral atherosclerosis was first described by Blankenhorn *et al.*,¹⁹ in the Cholesterol Lowering Atherosclerosis Study (CLAS). This was a randomized controlled angiographic trial of colestipol, niacin and low fat diet versus placebo and higher-fat diet. Computer estimated atherosclerosis was calculated following femoral angiography at baseline and after two years of follow-up. On average, the actively treated group showed less progression in estimated atherosclerosis as compared with the placebo treated group. However, since the prescribed diet also differed between groups, a clear-cut benefit for the pharmacological therapy could not be proved.

Several small trials have shown that statin therapy improves symptoms and function in patients with lower extremity PAD. Their results are summarized in Table 2.

A cross-sectional report of 641 patients, 392 with LE-PAD (ABI < 0.9) and 249 without LE-PAD (ABI between 0.9 and 1.5), described by McDermott *et al.*²⁰ showed that statin users had better 6-minute walk performance, faster walking velocity and a higher summary performance score than patients not receiving

Table 2. Treatment of lower extremity PAD with statins

Study type	No. of participants	Characteristics of participants	Statin used	Follow-up time	End-points	Results	Reference
Observational, longitudinal	544	332 PAD, 212 non-PAD	Any statin, any dose	3 years	Walking distance, walking velocity, summary performance score	Slower functional decline in statin treated PAD patients	Giri <i>et al.</i> , J Am Coll Cardiol 2006 ²¹
Cross-sectional	641	392 PAD, 249 no-PAD	Any statin, any dose	N/A	Walking distance, walking velocity, summary performance score	Better scores in statin treated patients; benefit attenuated after adjustment for CRP levels	McDermott <i>et al.</i> , Circulation 2003 ²⁰
Randomized, double-blind, placebo-controlled trial	LE-PAD at baseline: 123/2223 placebo, 130/2221 simvastatin	Men and women with hypercholesterolemia	Simvastatin	Median, 5.4 years	2: new or worsening intermittent claudication (per Hx)	For simvastatin users, RR = 0.62 ($p = 0.008$)	Pedersen <i>et al.</i> , Am J Cardiol 1998 ²²
Randomized, placebo-controlled	69	PAD, intermittent claudication	Simvastatin 40 mg	12 months	Pain free treadmill exercise time	Improvement in statin treated group	Aronow <i>et al.</i> , Am J Cardiol 2003 ²⁴
Randomized, double-blind, placebo-controlled	86	PAD, intermittent claudication, hypercholesterolemia	Simvastatin 40 mg	6 months	Pain free walking distance, total walking distance, ABI, claudication self-assessment	Improvement in all of the above measures in the statin treated group	Mondillo <i>et al.</i> , Am J Med 2003 ²⁵
Randomized, double-blind, placebo-controlled, parallel group	354	PAD, intermittent claudication	Atorvastatin 10 or 80 mg	12 months	1 st : maximal walking time (MWT) ^{2nd} : pain-free walking time (PFWT), quality of life	PFWT but not MWT improved by statin treatment; on measure of quality of life also improved	Mohler <i>et al.</i> , Circulation 2003 ²⁶

Abbreviations: ABI = ankle-brachial index.

statins, despite the fact that statin users had, in general, more risk factors for atherosclerosis. Adjustment for CRP levels attenuated the associations, which remained significant only for the summary performance score, and borderline significant for walking velocity. However, these differences were significant for LE-PAD as well as non-LE-PAD patients.

A further report by the same group after 3 years of follow-up in the same cohort²¹ suggests that yearly functional decline is slower in LE-PAD patients who receive statins, as compared with LE-PAD patients with no statin treatment. This effect was not seen in non-LE-PAD patients.

The first randomized controlled study to show that statin treatment improves PAD outcomes was the 4S.²² This study randomized 4444 men and women between 35 and 70 years of age, with plasma total cholesterol levels of 5.5–8.0 mmol/L (213–310 mg/dL) to placebo or 20–40 mg simvastatin daily, for a median follow up period of 5.4 years. The patients were asked about symptoms of intermittent claudication and were examined for carotid and femoral bruits at the beginning of the study and on yearly follow-up. No objective tests were undertaken for the diagnosis of LE-PAD. At baseline, 123 of the 2223 placebo-allocated patients and 130/2221 of simvastatin-allocated patients had intermittent claudication.²³ The risk of new or worsening intermittent claudication was reduced by 38% in the active treatment group (RR = 0.62, 95% CI 0.44–0.88, $p = 0.008$).

A short report by Aronow *et al.*²⁴ describes randomization of 69 patients with LE-PAD and intermittent claudication to 40 mg simvastatin or placebo. The simvastatin treated patients had improved treadmill exercise time until onset of intermittent claudication in 6 months and in 12 months after initiation of treatment.

Mondillo *et al.*²⁵ have shown that 6-months' treatment with 40 mg simvastatin in patients with intermittent claudication resulted in a significant increase in pain free walking distance, in total walking distance, in rest and post-exercise ABI and in claudication self-assessment, as compared with patients who received placebo. The functional improvement was greater than the increase in ABI, which suggested that statin effect was not solely mediated by regression of the atheroma.

Mohler *et al.*²⁶ conducted a multi-center, double-blind, placebo-controlled, parallel group study to evaluate the effect of 12-months treatment with atorvastatin (10 or 80 mg/d) on walking distance in 354 patients with lower extremity PAD and intermittent claudication. The primary end-point of improvement in maximal walking time was not reached, but a

secondary end-point of improvement in pain free walking time was increased by 63% in the 80 mg atorvastatin group, as compared with 38% in the placebo group ($p = 0.025$). One (of several) measure of subjective improvement in the quality of life (LOPAR questionnaire) was also found to be improved by atorvastatin treatment. There was no improvement in the ABI.

3. Perioperative treatment of patients with LE-PAD

The hypothesis that statin therapy has a beneficial effect on outcomes after vascular surgery is relatively new. A single, small randomized trial has shown that peri-operative atorvastatin treatment reduced by 3-fold the number of cardiovascular events occurring within 6 months of surgery.²⁷ This finding has received support from a few retrospective studies reporting some benefit for pre-operative statin treatment, and their results are summarized in Table 3. The peri-operative management of patients with peripheral arterial disease will be the subject of a later review in this series.

Abdominal Aortic Aneurysm

Although an association between abdominal aortic aneurysm (AAA) and atherosclerosis has been described in many epidemiological studies, the causal relationship between these two entities remains unclear. On the contrary, the emerging concept regarding formation of AAA focuses primarily on changes in the vascular smooth muscle cell (including over expression of matrix metalloproteinases) and inflammation, rather than on atherosclerosis being the primary causal initiating factor.³² The medical management of AAA will be the topic of the last in these series of vascular medicine reviews, but there is accumulating evidence that statin therapy reduces cardiovascular risk in AAA patients as well as potentially having direct effects to slow AAA expansion rates.^{33,34}

Clinical Recommendations

The evidence for the use of statins in patients with carotid and lower limb atherosclerosis as well as for patients with abdominal aortic aneurysms leads to the clinical recommendations shown in Fig. 1.

Arterial Stiffness

Increased arterial stiffness, the clinical correlate of which is increased pulse pressure, is an independent predictor of cardiovascular events.³⁵ Increased arterial

Table 3. Peri-operative statin treatment for patients with PAD

Study type	No. of participants	Type of surgery	Statin used	Follow-up time	End-points	Results	Reference
Case-control	160 cases, 320 controls	86% AAA, 11% lower extremity, 4% carotid	Any	N/A	30-day post-operative survival	8% statin use in cases vs. 25% in controls, $p < 0.001$.	Poldermans <i>et al.</i> ²⁸ <i>Circulation</i> 2003
Retrospective	1163 hospitalizations, 997 patients	53.5% lower extremity, 31.3% carotid, 15.2% AAA	Any	N/A	Fatal and non-fatal vascular complications	In statin users, OR = 0.56 (95% CI 0.39–0.79) for death, MI or myocardial ischemia.	O'Neill-Callahan <i>et al.</i> , <i>J. Am. Coll. Cardiol</i> 2005 ²⁹
Retrospective	446 patients	Lower extremity	Any	N/A	30-day post-operative cardiovascular complications	6.9% combined CV complications in statin users vs. 20.1% in non-users ($p < 0.008$)	Parker <i>et al.</i> , <i>Int J Cardiol</i> 2005 ³⁰
Retrospective	172 patients	Lower extremity bypass using greater saphenous vein	Any	N/A	2-year primary revised and secondary graft patency	Higher patency in statin users: 94% and 92% vs. 83% and 87%, respectively	Abbruzzese <i>et al.</i> , <i>J Vasc Surg</i> 2004 ³¹

Abbreviations: AAA = abdominal aortic aneurysm, MI = myocardial infarction, CV = cardiovascular.

1. All patients presenting with peripheral arterial disease (cerebrovascular, lower extremity, abdominal aortic aneurysm) should be considered at high risk for coronary artery disease (CAD equivalent).
2. A fasting plasma lipid profile (including total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides) should be obtained for all patients.
3. Statin therapy should be initiated for all patients with PAD, if no contra-indication exists.
4. The target level for fasting plasma LDL-cholesterol should be less than 100mg/dl (2.58mmol/L). A secondary target of non-HDL cholesterol below 130mg/dl (3.35mmol/L) applies to patients with elevated triglycerides.

Fig. 1. Clinical recommendations.

stiffness is seen with advancing age, supposedly due to degeneration of elastic fibers in the vascular wall, with a relative increase in the collagen, non-elastic component.³⁶

Hypercholesterolemia, alone or when combined with hypertension, results in an increase in arterial stiffness.^{37,38} The effects of statins on arterial stiffness have been studied in several small non-randomized trials, using different vascular beds and different measures for the assessment of arterial stiffness. Their findings are somewhat conflicting, and are summarized in Table 4.

Tomochika *et al.*³⁸ aimed to assess the morphological and functional characteristics of the thoracic aorta in familial hypercholesterolaemia (FH) patients and in normal controls. However, they also report the results of 13-month treatment with diet, pravastatin (20 mg/d) and probucol (1000 mg/d) in a non-randomized uncontrolled fashion, in 12 of 22 FH patients. They found a significant correlation between reduction of serum total cholesterol and LDL-cholesterol levels and reduction in the calculated stiffness parameter.

Smilde *et al.*³⁹ studied 45 patients with familial hypercholesterolemia (FH), who were treated with 40–80 mg/d of simvastatin or atorvastatin. They report a significant increase in the distensibility coefficient and in the compliance coefficient, both measures of arterial stiffness, in the common femoral but not in the common carotid artery, after 1 year of statin therapy.

Leibovitz *et al.*⁴⁰ studied 17 patients with severe hypercholesterolemia (LDL-C above 170 mg/dL), and measured arterial compliance. After 4 months of treatment with atorvastatin (mean dose 16 mg/d), the large artery elasticity index showed a tendency to increase, but this was not clinically significant. The small artery elasticity index increased by

21% ($p < 0.01$) after treatment, as compared with pre-treatment values. Systolic and diastolic blood pressures also decreased slightly but significantly.

Shige *et al.*⁴¹ designed a small prospective double-blind cross-over study with 20/40 mg simvastatin, in order to explore the relationship between lowering cholesterol levels and arterial compliance. They examined systemic arterial compliance (SAC), as well as regional pulse-wave velocity (PWV) over the trunk (aorto-femoral circulation) and the leg (femoral-distal tibial). They found that despite a significant LDL-C lowering effect achieved by treatment with simvastatin, SAC and central PWV did not change. However, peripheral PWV was higher, indicating better compliance, after treatment with simvastatin. These findings indicate that lipid lowering by simvastatin improves compliance of smaller peripheral arteries, but not the compliance of large central arteries. This study did not include any clinical end-points.

Giannattasio *et al.*⁴² studied the functional properties of the radial artery before and after induced ischemia in 13 normotensive FH patients and 10 normotensive non-FH controls. In 7 FH patients, they have repeated those studies after 6 and 24 months of treatment with simvastatin 40 mg/d. In those patients, maximal forearm blood flow was significantly increased and minimal forearm vascular resistance was significantly reduced after 6 months of therapy. These changes became more pronounced after 24 months. Pre-ischemic radial artery distensibility and compliance did not change after 6 months, but significantly increased after 24 months of statin therapy. Post-ischemic values were slightly increased, but these results did not reach statistical significance.

Ferrier *et al.*⁴³ studied 22 patients with isolated systolic hypertension and normocholesterolemia, in a double-blind, placebo-controlled, cross-over study

Table 4. The effect of statin therapy on arterial stiffness

Study type	No. of participants	Patient characteristics	Type of intervention	Follow-up time	Measure for arterial stiffness	Results	Reference
Non-randomized, uncontrolled	12	Familial hypercholesterolemia	Diet, pravastatin and probucol	13 months	β , derived from dimensional changes in descending aorta, visualized by TEE, and brachial artery cuff-measured pressure	Significant association between reduction in TC and LDL-C and a decrease in β	Tomochika <i>et al.</i> , ATVB 1996 ³⁸
Prospective, non-randomized	7	Normotensive familial hypercholesterolemia	40 mg simvastatin	24 months	Pre- and post-ischemic radial artery compliance and distensibility; maximal forearm bloodflow and minimal forearm vascular resistance	Improvement in pre-ischemic compliance and distensibility after 24 but not after 6 months of therapy; no significant change in post-ischemic values; increased maximal forearm bloodflow and decreased minimal vascular resistance after 6 and 24 months of therapy	Giannattasio <i>et al.</i> , Atherosclerosis 1996 ⁴²
Prospective, non-randomized	45	Familial hypercholesterolemia	40–80 mg/d simvastatin or atorvastatin	One year	Distensibility coefficient (DC) and compliance coefficient (CC) of CCA and CFA	Significant increase in DC and CC in CFA but not in CCA	Smilde <i>et al.</i> , Eur J Clin Invest 2000 ³⁹
Prospective, non-randomized	17	LDL-C > 170 mg/dL	Atorvastatin, mean dose 16 mg/d	4 months	Large and small artery elasticity indices	Significant 21% increase in small artery elasticity index ($p < 0.01$)	Leibovitz <i>et al.</i> , Am J Hyperten 2001 ⁴⁰
Prospective, double-blind, cross-over	20	Hypercholesterolemia	20–40 mg simvastatin	8 weeks	Systemic arterial compliance (SAC); regional pulse wave velocity (PWV): aorto-femoral and femoral-distal tibial	No change in SAC or central PWV; increased peripheral PWV after treatment	Shige <i>et al.</i> , Atherosclerosis 2001 ⁴¹
Double-blind, placebo-controlled, cross-over	22	Isolated systolic hypertension, normocholesterolemia	80 mg atorvastatin	6 months	Systemic arterial compliance	24% significant increase in compliance after 3 months of therapy	Ferrier <i>et al.</i> , JACC 2002 ⁴³

Abbreviations: TEE = trans esophageal echocardiography, TC = total cholesterol, LDL-C = low density lipoprotein cholesterol, CCA = common carotid artery, CFA = common femoral artery.

with 80 mg atorvastatin. They have found that 3 months of atorvastatin treatment resulted in a significant 24% increase in systemic arterial compliance. Systolic, diastolic and mean blood pressures have all significantly decreased by 2–6 mmHg.

Taken together, these studies imply that statin therapy may have a beneficial effect on arterial stiffness in hypercholesterolemic, and maybe also in normocholesterolemic patients. However, the nature of this effect, its extent and location should all be further assessed by larger, randomized controlled studies.

Mechanism of Action of Statins

As implied by their name, HMG-CoA reductase inhibitors ('statins') have been primarily designed to lower serum cholesterol levels by inhibiting the rate limiting step in cholesterol biosynthesis. This inhibition results in up-regulation of the LDL receptor on the hepatocyte membrane, and hence in increased uptake of LDL particles from the plasma. This cholesterol lowering effect is expected to result in some clinical benefit only after months of treatment.

The finding that statins have an immediate beneficial effect on cardiovascular outcome implies that at least some of their effect is otherwise mediated. There is now much evidence that statins exert additional, pleiotropic and beneficial effects on atherosclerotic events by generating improvement in endothelial function, stabilization of atherosclerotic plaques, inhibition of platelet aggregation, inhibition of inflammation, inhibition of smooth muscle cell proliferation, antioxidant effects and accelerated angiogenesis.⁴⁴

Summary and Recommendations

Peripheral arterial disease is a definite marker for diffuse atherosclerosis and is associated with significant morbidity and mortality. It has long been acknowledged as a coronary artery disease equivalent in terms of the risk it carries and therefore the recommendations for treatment. Nevertheless, patients suffering from PAD remain undertreated as compared with their CAD counterparts and significantly undertreated with respect to published guidelines. The reasons for this may include (among others) patient and physician underestimation of the actual risk, treating physicians (e.g. vascular surgeons and interventionists) being less familiar with these drugs, or lack of awareness to published guidelines.

Although only a small number of studies, most of which were small and retrospective, have specifically addressed the question of statin therapy in different aspects of PAD treatment, the vast majority have proved at least some benefit for statin use.

Taking all this information together, it is clear that PAD patients should receive statin therapy as an integral part of their treatment plan, and should be fully advised as to the known benefits and risks associated with these drugs. The best regimen for statin treatment, in terms of specific drug or dose, remains to be evaluated by prospective randomized trials.

Furthermore, several other lipid-modifying drugs are currently undergoing clinical trials, including squalene-synthase inhibitors and cholesteryl-ester transfer protein (CETP) inhibitors. If any of these are proven beneficial for prevention of coronary outcomes, clinical trials in PAD patients should not be neglected.

Box 1.

In brief:

1. The different forms of peripheral arterial disease are associated with significant cardiovascular morbidity and mortality, and hence constitute a coronary artery disease equivalent in terms of published practice guidelines.
2. There is some evidence from small randomized controlled trials that statin therapy decreases cardiovascular morbidity and mortality in patients with peripheral arterial disease.
3. The mechanism of action of statins may derive from their lipid lowering properties, or from other, pleiotropic effects.
4. Further, larger randomized controlled studies with statins are needed to evaluate the efficacy of statin therapy in patients with stable peripheral arterial disease, and in those undergoing vascular or endovascular surgery.

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