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LDL lowering in peripheral arterial disease: are there benefits beyond reducing cardiovascular morbidity and mortality?

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Abstract

Peripheral arterial disease affecting the lower extremities is associated with increased mortality due to cardiovascular events and reduced functional capacity due to claudication. There is abundant evidence to support the role of lipid lowering with statins in preventing cardiovascular events in patients with peripheral arterial disease. Over the last 10 years, multiple studies have been designed to test the theory that LDL C lowering with statins could result in improved exercise performance in patients with peripheral arterial disease. However, this remains an active area of investigation to better understand how the pleiotropic effects of statins could lead to enhanced functional capacity for patients with claudication. Furthermore, new insights into the complex pathophysiology of claudication may help us to understand the potential role of lipid lowering therapy in alleviating exercise induced symptoms.

Keywords

claudication; HMG CoA reductase inhibitors; LDL C; lipid lowering; peripheral arterial disease; statin

Importance of peripheral arterial disease

Peripheral arterial disease (PAD) affecting the lower extremities has an estimated prevalence of 27 million adults in Europe and North America [1]. The most important risk factors for development and progression of atherosclerotic PAD are age, smoking and diabetes; however, hyperlipidemia plays an important role (odds ratio [OR]: 1.68; 95% CI: 1.09–2.57) [2]. Individuals with PAD need to be identified and treated with appropriate risk factor modification as they have:

- Increased morbidity and mortality due to cardiovascular disease;
- Decreased exercise tolerance and impaired quality of life;
- Risk of limb ischemia and amputation.

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Increased morbidity & mortality due to cardiovascular disease

In a large study of almost 1500 patients with lower extremity PAD, there was a high mortality and major cardiovascular event rate (i.e., myocardial infarction, coronary revascularization, stroke or lower extremity ischemia) over 5 years [3]. More notably, in this study the risk of mortality was similar among asymptomatic patients found to have PAD by routine screening as compared with those with symptomatic PAD. Therefore, a primary focus in the medical treatment of patients with PAD will continue to be modifying the risk of future cardiovascular events.

Decreased exercise tolerance & quality of life

On an individual level, patients with symptomatic PAD struggle with their ability to complete their daily activities, limited by leg symptoms. One of the challenges in identifying patients with symptomatic PAD is that only approximately 20% will have typical intermittent claudication [4]. Although PAD was previously thought to be a stable disease, there is a decrease in 6-min walk distance over 2 years [5] demonstrating a clear decline of exercise tolerance over time. It is no surprise that patients with intermittent claudication have reduced health-related quality of life measures compared with those without symptomatic PAD [6]. As a result, there is keen interest in medical therapies aimed at improving exercise capacity in PAD.

Risk of limb ischemia & amputations

There is a relatively low incidence of critical limb ischemia in patients with PAD and a history of stable claudication [7]; however, this does occur more frequently in those patients with diabetes [8]. In a group of 2777 patients with PAD and claudication followed for 15 years, there was a mortality rate of 12% per year, driven mostly by cardiac disease. By contrast, the 10-year cumulative rate of amputations was less than 10% [9]. Although critical limb ischemia and amputation are feared complications, these outcomes occur in a minority of the PAD population with stable claudication.

Role of lowering LDL-C in PAD

We will address the evidence supporting lowering LDL-C in patients with PAD in order to impact overall cardiovascular mortality, reduce lower extremity ischemic complications, alter atherosclerotic plaque progression and, finally, to improve exercise tolerance.

Treating LDL to prevent cardiovascular mortality

The Heart Protection Study demonstrated a decrease in cardiovascular events (i.e., total mortality, vascular mortality, coronary heart disease events, strokes and noncoronary revascularizations) over 5 years with simvastatin 40 mg in over 20,000 patients with and without known PAD [10]. A notable aspect of the study is the association between statin therapy and improved outcomes regardless of the threshold level of hypercholesterolemia. A recent Cochrane review pooled data from clinical trials of lipid lowering in lower extremity PAD involving more than 10,000 individuals and found a significant reduction in total cardiovascular events (OR: 0.74; 95% CI: 0.55–0.98) primarily driven by decreased coronary events (OR: 0.76; 95% CI: 0.67–0.87) [11].

In a prospective, observational cohort study, 1374 patients with PAD were followed for an average of 6.4 ± 3.6 years to determine whether higher doses of statins and lower levels of LDL-C were associated with improved cardiovascular outcomes [12]. By multivariate analysis, higher doses of statins (per 10% increase) and lower 6-month LDL-C levels (per 10 mg/dl decrease) were independently associated with a reduction in all-cause mortality and

cardiac death. Given the independent association of statin dose and LDL-C reduction, this supports the presence of a beneficial effect of statin therapy beyond lipid reduction.

Treating LDL to prevent lower extremity ischemic complications

The primary role of lipid-lowering therapy in PAD has been to reduce cardiovascular mortality, with limited data supporting any benefit on the incidence of lower extremity ischemic complications over time. However, the Heart Protection Study found a 16% relative reduction in the incidence of first peripheral vascular event, independent of the baseline LDL, which was driven by a 20% relative reduction in noncoronary revascularization procedures [10].

Treating LDL to prevent atherosclerotic plaque progression

Studies have demonstrated a consistent relationship between statin therapy and either stabilization or regression of atherosclerotic plaque using a variety of imaging modalities [13]. Low doses of atorvastatin (20 mg) improved femoral and carotid intima–media thickness (CIMT) in PAD patients after 8 weeks of treatment [14]. The authors' group used MRI techniques to quantify atherosclerotic plaque volume in approximately 15–20 cm of the superficial femoral artery of 67 patients with symptomatic PAD treated with lipid-lowering therapy for 2 years [15]. The study found that initiation of a simvastatin with or without ezetimibe resulted in a halting of atherosclerotic plaque progression. Over 2 years, the plaque volume in the statin-naive group randomized to simvastatin was unchanged (11.0 ± 1.5 to 10.5 ± 1.4 cm^3; p = not significant), with similar findings in the group randomized to simvastatin plus ezetimibe (11.5 ± 1.4 to 10.5 ± 1.3 cm^3; p = not significant). However, for patients who were already on a statin, with LDL levels >80 mg/dl, who had ezetimibe added, there was plaque progression (10.0 ± 0.8 to 10.8 ± 0.9 cm^3; $p < 0.01$) despite a 22% reduction in LDL-C. This study suggests that the benefit of statins on atherosclerotic plaque volume may depend on the relative timing of drug therapy as well as the mechanism of LDL lowering.

Other clinical trials of ezetimibe, a nonstatin lipid-lowering drug, have also failed to show a positive effect on atherosclerotic plaque despite effective LDL lowering [16]. A recent study, ARBITER-6 HALTS [17], had niacin added to background statin therapy and was associated with regression of CIMT, which was not seen in the group randomized to ezetimibe plus statin therapy despite a further lowering of LDL. Paradoxically, there was actually an increase in CIMT and cardiovascular events in the ezetimibe group. Therefore, the mechanism of LDL lowering with statins appears critical for altering atherosclerotic plaque burden.

Treating LDL to improve claudication symptoms & exercise tolerance

In addition to the mortality benefit and decreased myocardial revascularization procedures seen with simvastatin therapy given to patients with coronary heart disease in the Scandinavian Simvastatin Survival Study (4S) [18], there was also a 38% reduction seen in the incidence of new or worsened intermittent claudication among patients randomized to simvastatin over a median follow-up of 5.4 years (relative risk reduction: 0.62; 95% CI: 0.44–0.88) [19]. The claudication end point was part of a *post-hoc* analysis of the 4S trial. However, the Kaplan–Meier curve for new or worsened intermittent claudication had a progressive divergence over the 72 months of follow-up supporting the long-term benefit of statin therapy in these patients [19].

There are three prospective trials in patients with PAD that found an improvement in walking performance for patients randomized to statin therapy; two involved simvastatin and one study used atorvastatin [20–22]. In the placebo-controlled study by Aronow *et al.* of

69 patients with moderate PAD (mean 75 years of age and ankle–brachial index [ABI] 0.63 ± 0.12), those randomized to receive simvastatin for 1 year had a significantly improved treadmill time to onset of claudication at 6 months (24% increase; 54 s; $p < 0.0001$) and at 1 year (42% increase; 95 s; $p < 0.0001$) [20]. In this study, LDL-C improved in the simvastatin arm (156 ± 23 to 100 ± 17 mg/dl) without a change in HDL or triglycerides. A similar study was performed by Mondillo *et al.*, wherein 86 patients with PAD and intermittent claudication were randomized to simvastatin 40 mg or placebo and followed for 6 months [21]. The simvastatin group had an improved mean pain-free walking distance by 90 m (95% CI: 64–116 m; $p < 0.005$) and increased total walking distance by 126 m (95% CI: 101–151 m; $p < 0.001$) compared with placebo. The average LDL in both groups was quite high at study entry (189 ± 32 mg/dl for simvastatin and 188 ± 32 mg/dl for placebo). After 6 months, as expected, the LDL-C improved to 124 ± 29 mg/dl in the simvastatin group without a change in the placebo arm.

The study by Mohler *et al.* was a multicenter, double-blind, placebo-controlled trial to determine the efficacy of atorvastatin on treadmill walking distance after 1 year in patients with PAD and intermittent claudication [22]. There were two atorvastatin dosing arms, 10 mg and 80 mg, in addition to the placebo group. There was a significant decrease in total cholesterol, LDL-C and triglycerides for both atorvastatin groups, with the largest change in the 80-mg group. Although there was no difference in the primary end point of mean walking time, there was an improvement in the pain-free walking time by 63% (81 ± 15 s) in the atorvastatin 80 mg group compared with 38% (39 ± 8 s; $p = 0.025$) in the placebo group. There was a trend towards a greater improvement in those study participants whose LDL-C fell to below a median of 123 mg/dl. There was no change in ABI across groups.

A retrospective study by McDermott *et al.* found that in nearly 400 patients with intermittent claudication, the use of statins was independently associated with a modestly superior 6-min walk performance compared with non-use of statins, even after adjusting for potential confounders [23]. The relationship between statin use versus nonuse and improved functional capacity was present regardless of serum cholesterol levels, providing additional evidence to support the benefits of statins beyond their lipid-lowering properties. Further work by the same group demonstrated a decreased decline in annual walking performance for PAD patients on statins compared with patients not receiving statin therapy [24].

In a 2-year clinical trial of patients with symptomatic lower extremity PAD, the authors evaluated the impact of lipid lowering (using either simvastatin or simvastatin in combination with ezetimibe in statin-naive patients or adding ezetimibe to those previously on statins) on 6-min walk and exercise treadmill parameters as well as MRI techniques to quantify calf muscle microvascular perfusion and mitochondrial function [25]. Despite effective LDL lowering over 2 years, there was no improvement in any exercise parameter, calf muscle perfusion or energetics. However, resting ABI did improve although exercise ABI did not. The study was limited by statistical power for the exercise end points and absence of an untreated control group. However, given the known decline in walking performance over time in PAD patients, the absence of a functional decline with statin therapy may in fact be a positive finding in light of the inexorable decline noted in many PAD patients.

A recent multicenter trial of lovastatin plus niacin in patients with PAD and claudication found no improvement in either peak treadmill-walking time or claudication onset time in the groups randomized to either high- or low-dose niacin plus lovastatin compared with dietary intervention [26]. The limitations to this study are the relatively short duration of follow-up at 28 weeks and low average LDL-C at study entry of 123 ± 26 mg/dl. The prior studies that showed an improvement in exercise performance with statin therapy had a

higher baseline LDL-C level and primarily saw changes in pain-free walking time and the claudication onset time. No study has shown consistent improvement in treadmill peak exercise performance.

In the Cochrane review of lipid lowering in PAD, pooling of the results from several small trials of statin therapy showed an improvement in total 6-min walking distance (mean distance 152 m; 95% CI: 32.11–271.88) and pain-free walking distance (89.76 m; 95% CI: 30.05–149.47); however, there was no change in the ABI [11]. In the studies of statin therapy to improve exercise symptoms in PAD there has not been a corresponding increase in resting ABI, suggesting that the mechanism of benefit is not simply related to aggregate lower extremity blood flow.

Guidelines for lipid management in PAD

Taking into account the weight of the evidence discussed for reduction in cardiovascular events, the guidelines for the management of patients with PAD highlight the importance of lipid-lowering therapy (Table 1). The Inter-Society Consensus for the Management of PAD (TASC II) published revised guidelines in 2007 that recommend goal LDL-C levels <100 mg/dl for all patients with PAD (level of evidence A) and a more aggressive LDL lowering to <70 mg/dl for patients with atherosclerosis involving other vascular beds (level of evidence B) [27]. If patients do not reach LDL goals with diet and exercise, statins are the preferred drug therapy. For PAD patients with low HDL and high triglycerides, treatment with niacin or fibrates should be considered (level of evidence B).

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of PAD have similar recommendations for lipid-lowering therapy including a class 1 indication for statins in all patients with PAD to achieve a LDL-C level <100 mg/dl (level of evidence B) [28]. There is a class 2a recommendation for treating to LDL-C <70 mg/dl (level of evidence B) for those patients at very high risk of ischemic events, such as those with atherosclerosis involving multiple vascular territories, diabetes, continued smoking or poorly controlled risk factors. The use of fibric acid derivatives has a class 2a recommendation (level of evidence C) for patients with PAD and low HDL and elevated triglycerides.

The recent European Society of Cardiology (ESC) guidelines [29] on the diagnosis and treatment of PADs have similar recommendations as the TASC II and ACC/AHA guidelines. An LDL-C level <100 mg/dl in all patients with PAD is a class 1 recommendation. The guidelines further recommend that a LDL-C level <70 mg/dl is considered optimal. In patients where it is not possible to achieve this goal, the LDL-C should be lowered to <50% of baseline.

Pleiotropic effects of statins

In addition to upregulating the hepatic LDL receptors, resulting in lower serum LDL levels, statins have important pleiotropic effects including improved endothelial function, stabilization of atherosclerotic plaque and decreased vascular inflammation [30]. These pleiotropic effects have the potential to result in improved exercise capacity in PAD.

Statins have endothelium-dependent effects [31] resulting in vasodilation in systemic arteries mediated through increased levels of nitric oxide [32,33]. Changes in local microcirculation by statin effect or altered levels of LDL-C may impact lower extremity blood flow [34]. For patients with known coronary artery disease treated with statin therapy there is a measurable beneficial effect on endothelial vasomotor function and nitric oxide

levels [35]. Future studies are needed in PAD to determine whether statin therapy impacts the lower extremity endothelial function.

Brachial artery flow-mediated dilation (FMD) allows for a noninvasive assessment of endothelial dysfunction and is abnormal in patients with PAD [36]. Abnormal FMD reflects the systemic nature of the atherosclerosis; however, it may not correlate with the degree of PAD severity [37]. Despite this, degree of FMD is independently associated with higher levels of physical activity among patients with PAD even after adjusting for potential confounders [38]. In multiple, randomized, placebo-controlled clinical trials, statin use was associated with an improvement in FMD [39]; however, these studies were not specifically addressing lower extremity PAD. Measurement of endothelial dysfunction with FMD may be a useful clinical end point in drug therapy aimed at improving functional performance in patients with PAD [40].

The role of statins in atherosclerotic plaque stabilization and regression has been previously discussed [13]. Reducing inflammation is another benefit of statin therapy. Inflammation as measured by elevated serum C-reactive protein (CRP) is known to be independently associated with the severity of lower extremity PAD measured by ABI [41]. In a study of over 500 patients with severe PAD, those treated with statins had a lower level of high-sensitivity CRP and improved survival compared with those not on statins [42]. Furthermore, those patients with elevated high-sensitivity CRP had a mortality and cardiovascular event reduction, which was not seen in patients with low CRP.

Another potential mechanism of benefit for statin therapy is improved angiogenesis, which may be related to pleiotropic effects [43] or potentially to lowering of serum cholesterol [44]. Lastly, statins have specific antiatherothrombic effects [45].

Pathophysiology of intermittent claudication

The pathophysiology of intermittent claudication is complex as it involves both a reduction in blood flow to peripheral tissues as well as changes in the metabolic function of skeletal muscle, caused by repetitive episodes of ischemia [46]. There are clear mitochondrial changes and a shift in muscle fiber type that occur in lower extremity PAD [47]. Several imaging modalities, such as contrast ultrasound [48] and MRI [49], have noninvasively demonstrated abnormal lower extremity blood flow in patients with PAD.

Previous work from the authors' group [50] used MRI techniques to demonstrate the multiple determinants of functional capacity in patients with lower extremity PAD including calf muscle microvascular perfusion, skeletal muscle mitochondrial function and burden of atherosclerotic disease. Both the calf muscle microvascular perfusion and mitochondrial function correlated with impaired exercise capacity in patients with PAD and symptomatic claudication; however, these parameters had independent relationships with functional performance suggesting they are uncoupled.

In order to impact exercise capacity and symptoms of claudication, future studies will need to investigate therapies aimed at improving microvascular blood flow and skeletal muscle metabolism, both of which are impaired in PAD.

Role of treating HDLs & triglycerides in PAD

With regard to addressing non-LDL cholesterol in patients with PAD, the atherogenic lipid pro-file with low HDL-C, elevated triglycerides and increased levels of small dense LDL has been studied in patients with symptomatic lower extremity PAD. The presence of small dense LDL was strongly associated with the presence of PAD with an OR of 6.7 (95% CI:

1.1–45.1) [51]. In a multicenter, placebo-controlled trial of a fibrate (bezafibrate) in patients with known lower extremity PAD there was a rise in HDL concentration and lowering of triglycerides in the treatment group with fewer nonfatal coronary events and reduced severity of claudication symptoms after 3 years of therapy [52].

Nonstatin lipid-lowering therapy has also been shown to be effective in stabilization of femoral artery atherosclerosis measured by angiography in the Cholesterol Lowering Atherosclerosis (CLAS) study in which men with PAD were randomized to placebo or colestipol plus niacin [53]. The CLAS study demonstrated significant lowering of LDL-C, total cholesterol and triglycerides as well as an improvement in HDL-C in the treatment arm compared with the control. The Program on the Surgical Control of the Hyperlipidemias (POSCH) trial demonstrated a lower total cholesterol and LDL-C in the partial ileal bypass surgery group as well as a lower incidence of claudication or limb-threatening ischemia [54].

Clinical trials aimed primarily at improving the level of HDL-C in patients who have achieved goal LDL-C have not been performed in lower extremity PAD. However, the ARBITER trial evaluated the addition of niacin to statin therapy in patients with known coronary heart disease and low HDL-C and found a slowed progression of atherosclerosis measured by CIMT in the niacin group as compared with placebo [55].

In addition to traditional lipoproteins, LDL and HDL-C, there are specific lipoprotein particles that are associated with increased cardiovascular risk. Lipoprotein(a) is a lipid subtype that is prone to oxidative modification, facilitating deposition in atherogenic foam cells [56]. A recent study shows an independent correlation between elevated lipoprotein(a) levels and incidence of lower extremity PAD [57]. However, future investigation will be needed to understand this relationship with regard to any potential benefit of lipid-modification therapy.

Conclusion

There is a clear reduction in cardiovascular events with statin therapy and LDL lowering in patients with PAD. Given the symptoms of leg discomfort and reduction in exercise capacity in patients with PAD, there remains strong interest in medical therapy aimed at improving these symptoms. Although no individual trial has shown an increase in peak treadmill-walking time with statin therapy, several trials demonstrate a reduction in claudication symptoms. The Cochrane meta-analysis found an improvement in 6-min walk distance with statins, which may be more reflective of activities of daily living than an exercise treadmill test [11]. Clinical trials of statin therapy and exercise performance are influenced by the baseline LDL level, pre-existing treatment with statin drugs and study duration. Insight into the pleiotropic effects of statins and the complex pathophysiology of claudication has provided new avenues to understand how exercise capacity can be improved in PAD.

Future perspective

In order to improve claudication symptoms and exercise performance in patients with PAD, future studies will need to focus on understanding the inter-related mechanisms of abnormal skeletal muscle microcirculation and metabolic function. Given the strong relationship between diabetes and lower extremity PAD [58], continued investigation is needed to better understand the relationship between dyslipidemia, endothelial dysfunction, inflammation and hyperglycemia as they relate to an individual’s exercise capacity and symptoms. Lastly, large clinical trials are needed to better understand the impact of statin therapy and resulting LDL reduction on exercise performance in patients with PAD.

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Executive summary

Importance of peripheral arterial disease

- Patients with peripheral arterial disease (PAD) suffer from increased risk of cardiovascular morbidity and mortality.
- There is a tremendous individual impact of having PAD, with evidence of decreased functional capacity over time and a reduced quality of life.
- Although critical limb ischemia and amputations are feared complications of PAD, these occur in a minority of the entire population of patients with claudication.

Role of lowering LDL-C in PAD

- There are multiple benefits linked to the reduction of LDL-C in patients with PAD, including reduction in overall cardiovascular mortality, decreased rates of lower extremity ischemic complications, evidence of reduction in atherosclerotic plaque progression and improved exercise tolerance.

Guidelines for lipid management in PAD

- The American College of Cardiology/American Heart Association guidelines and the Inter-Society Consensus for the Management of Peripheral Arterial Disease consensus statement recommend achieving a goal LDL level of <100 mg/dl in patients with PAD with preferential use of statins. In higher-risk patients, treatment of LDL to <70 mg/dl is appropriate.

Pleiotropic effects of statins

- Statins exert positive effects on endothelial function, microcirculation, plaque stabilization, inflammation and thrombosis. These pleiotropic effects lend insight into how the downstream benefit of statins extend far beyond simple lipid lowering.

Pathophysiology of intermittent claudication

- Ultimately the pathophysiology of claudication involves a reduction in lower extremity blood flow, microvascular dysfunction and repetitive cycles of ischemia and reperfusion, which mediate a skeletal muscle myopathy. Successful treatment of claudication and improvement in functional capacity must have a beneficial effect on one or more of these contributing factors.

Role of treating HDLs & triglycerides in PAD

- The bulk of clinical studies have investigated the role of LDL-C lowering in PAD. However, for patients with goal LDL and evidence of elevated triglycerides or low HDL-C, there is a role for addressing these specific components of dyslipidemia.

Conclusion & future perspective

- Exciting advances have been made in the treatment of lower extremity PAD to reduce morbidity and mortality as well as to improve functional capacity. Future studies will need to address the multifactorial pathophysiology of intermittent claudication in order to better understand the benefit of potential therapeutic agents.

Table 1

Guidelines for lipid management in peripheral arterial disease.

Guideline source	Year	LDL-C	HDL-C	Triglycerides	Ref.
ACCF/AHA	2011	Class 1: LDL <100 mg/dl, for all patients with PAD using HMG-CoA reductase inhibitor (statin) Class 2a: LDL <70 mg/dl, for those at high risk of ischemic events	Class 2a: low HDL, consider treatment with fibric acid derivative	Class 2a: elevated triglycerides, consider treatment with fibric acid derivative	[28]
TASC II	2007	LOE A: LDL <100 mg/dl, for all patients with PAD LOE B: LDL <70 mg/dl, for patients with atherosclerosis in other territories LOE A: statin drugs should be the primary agent used	LOE B: low HDL, consider treatment with niacin or fibrates	LOE B: elevated triglycerides, consider treatment with fibrates	[27]
ESC	2011	Class 1: LDL <2.5 mmol/l (100 mg/dl), for all patients with PAD Class 1: Optimal LDL <1.8 mmol/l (<70 mg/dl) Class 1: Goal >50% LDL reduction, if target level cannot be reached	Not addressed in guidelines	Not addressed in guidelines	[29]

ACCF: American College of Cardiology Foundation; AHA: American Heart Association; ESC: European Society of Cardiology; LOE: Level of evidence; PAD: Peripheral arterial disease; TASC II: Inter-Society Consensus for the Management of Peripheral Arterial Disease.