

Statins in Peripheral Arterial Disease

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Running Title: statins and peripheral arterial disease

Keywords: statins, outcomes, peripheral arterial disease, pleiotropic effects

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ABSTRACT

Peripheral arterial disease (PAD) is a common atherosclerotic condition affecting the lower extremities. PAD patients share similar cardiovascular risk factors to coronary artery disease patients and suffer from increased cardiovascular morbidity and mortality. Statins have been widely used in coronary artery disease patients but have been underused in patients with PAD. In the current review, we present data which support the beneficial role of statins in both reducing cardiovascular events and improving symptom-related outcomes in PAD patients. Alongside their lipid lowering effects, their pleiotropic actions are also discussed. Recent guidelines, which strongly recommend the administration of statins in PAD patients, are also presented.

ABBREVIATIONS

ABI – ankle-brachial index
ACC/AHA – American College of Cardiology/ American Heart Association
ADMA – asymmetric dimethylarginine
apoA1 – apolipoprotein A1
BH4 – tetrahydrobiopterin
CAD – coronary artery disease
CV-cardiovascular
CBVD – cerebrovascular disease
CLI – critical limb ischaemia
CRP – c-reactive protein
CVD – cardiovascular disease
eNOS – endothelial nitric oxide synthase
ESC – European Society of Cardiology
ET-1 – endothelin 1
FMD – flow mediated dilation
FPP – farnesylpyrophosphate
GGPP – geranylgeranylpyrophosphate
HDL-c – high density lipoprotein cholesterol
HMG-CoA – 3-hydroxy-3-methylglutaryl-coenzyme A
IC – intermittent claudication
ICAM-1 – intercellular adhesion molecule 1
IL-6 – interleukin 6
IMT – intima media thickness
LDL-c – low-density lipoprotein cholesterol
MACE – major adverse cardiac events
MPO – myeloperoxidase
NADPH-oxidase – nicotinamide adenine dinucleotide phosphate oxidase
NO – nitric oxide
ox-LDL-c – oxidised low density lipoprotein cholesterol
PAD – peripheral arterial disease
PI3K-Akt – phosphatidylinositol-3 kinase/a serine threonine kinase
PON-1 – paraoxonase 1
RCT – randomised controlled trial
ROS – reactive oxygen species
SMC – smooth muscle cells
SOD – superoxide dismutase
TNF- α – tumour necrosis factor α
VCAM-1 – vascular cellular adhesion molecule 1

INTRODUCTION

Peripheral arterial disease (PAD) is a term most commonly used to describe an atherosclerotic condition in the lower extremities and is thought to be the third most common cause of cardiovascular (CV) morbidity and mortality. Epidemiological data has suggested that up to 202 million people globally may currently be living with PAD, with this figure increasing with age from ~ 6% at the age of 50 years up to > 20% at the age of 90 years (1).

Although most PAD patients are asymptomatic, the predominant complication encountered in those who do report symptoms is that of intermittent claudication (IC) – a painful cramping of the leg typically brought on by exercise and occurring as a result of inadequate blood flow to the working muscle bed due to blocked or narrowed arteries. As the severity of the disease progresses, IC may develop into more serious complications such as leg ulcers, critical limb ischaemia (CLI), and the potential need for limb amputation. Even when asymptomatic, the presence of PAD (as most commonly identified by an ankle-brachial index (ABI) < 0.9) remains a strong risk marker for accompanying atherosclerotic disease, with up to 56% of individuals with PAD in major trials found to have accompanying CAD or cerebrovascular disease (CBVD) (2,3). While these concomitant diseases are most likely driven by the same risk factors, there are limited data available about the impact of risk factor modification on morbidity and mortality in PAD patients (4).

A range of different pharmacological therapies have been used for the treatment of PAD in order to both relieve symptoms and to slow atherosclerotic disease progression. HMG-CoA reductase inhibitors, more commonly known as statins, are among the most prescribed drugs in the world and are a cornerstone of CV disease management and treatment. Although the primary mechanism of statins is the lowering of cholesterol production through the competitive inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, it is now also clear that the inhibition of multiple other downstream pathways results in numerous pleiotropic effects which may act to further reduce atherosclerotic CV disease

risk over and above the lowering of LDL-c (5). While a wealth of research has provided evidence for the ability of statins to reduce CV risk in patients with established CAD and CBVD, much less attention has focused on their effectiveness in PAD patients.

In this review, we will present data supporting the clinical benefit of statins both in relieving symptoms and improving CV outcomes in patients with PAD, and will discuss mechanistic pathways relevant to the pathophysiology of PAD that can be affected by statin use.

STATINS AND CARDIOVASCULAR EVENTS IN PVD (Table 1)

The largest study to date on the efficacy of statin therapy in peripheral vascular disease is that of the Heart Protection Study (HPS), a multi-centre randomised clinical trial of over 20,000 patients in which 6748 patients were identified as having PAD. In this study, 40mg of simvastatin daily over a median of 5 years was found to significantly reduce the occurrence of major CV events in patients with PAD by approximately one-quarter. The magnitude of this effect was similar to that seen in the trial population as a whole, was unaffected by whether patients had any record of prior myocardial infarction or CAD, and was evident even in those presenting with low levels of LDL-c prior to treatment (6). Another prospective observational study in a cohort of 660 elderly patients with symptomatic PAD and serum LDL-c levels > 3.23mmol/L confirmed these findings. With a mean follow-up of 39 months, those treated with statins had a relative risk ratio for new coronary events of 0.48 if they had suffered a previous myocardial infarction or 0.41 if they had not (7). Similar findings were also reported in a longer-term observational study looking at statin use in 2,420 patients with an ABI < 0.9 who were followed for 8 years. This study showed a 54% reduction in mortality in patients treated with statins after adjustment for all baseline variables and propensity scores (8).

Expanding upon these findings, a number of studies have assessed the effect of more intense lipid-lowering therapy on both PAD incidence and long-term

mortality outcomes. Stoekenbroek and colleagues investigated the effect of high-dose atorvastatin therapy vs. usual-dose simvastatin therapy in 8888 randomly-allocated post-MI patients enrolled in the IDEAL trial, reporting a significantly lower hazard ratio for developing PAD (HR = 0.70) in the high-intensity group over a median 4.8 year follow-up. In addition, in those already suffering from PAD, the authors noted a significant reduction in overall CV and coronary events in the high-intensity group alongside significantly fewer coronary revascularisations (9). A separate study, investigated the effect of intensified lipid-lowering therapy on long-term mortality outcomes in relation to LDL-c levels and reported that further lowering of LDL-c was associated with reduced all-cause mortality and higher statin doses were also associated with improved outcomes overall (10). These results have been supported by the data of a Cochrane meta-analysis on 17 lipid lowering trials, revealing a 26% reduction of CV events in patients treated with statins – mostly due to reduction in the incidence of coronary events (11). Although a number of lipid lowering drugs were assessed, the most consistent benefits on CV mortality and morbidity were shown with statins, particularly simvastatin when used in patients with high cholesterol levels (>3.5mmol/L).

STATINS AND SYMPTOM-RELATED OUTCOMES IN PAD (Table 2)

Irrespective of their effect on CV mortality, the use of statins in PAD patients has been associated with improvement in clinical symptoms – i.e. symptoms of IC, improvement in walking distance, and outcomes following vascular interventions/surgery. This was first evidenced in a sub-analysis of the aforementioned 4S study, where a 38% reduction in the risk of new or worsening intermittent claudication and a 48% reduction in new or worsening carotid bruits was reported in patients assigned to simvastatin treatment and who were followed up for a median of 5.4 years (12).

A number of additional studies from the early 2000s further supported this positive effect of different statins on IC and walking distance. Mohler and colleagues randomised 354 patients with PAD and IC to receive either placebo, 10mg or 80mg atorvastatin daily for 12 months and noted a significant increase

in community based physical activity (as assessed by questionnaire) in both groups as well as increased pain-free walking time in the 80mg statin group (63% vs. 38% increase) when compared to placebo at 12 months (13). Similar results were subsequently reported in patients taking 40mg simvastatin daily, with a 24% and 42% increase in exercise-induced time to onset of claudication at 6 and 12 months respectively (14). Likewise, in 86 hypercholesterolaemic patients randomised to 40mg simvastatin daily or placebo for 6 months, those in the statin group had improvements in pain-free walking distance, total walking distance, ankle-brachial index, and symptoms of claudication (15). These beneficial actions of statins in reducing morbidity in PAD patients are thought to occur due to mechanisms over and above their primary lipid-lowering actions. For instance, in a study where lower-extremity function was investigated in 392 patients both with and without PAD, individuals on statins had superior leg functioning compared to those who did not receive statin and this effect was independent of cholesterol levels. These findings suggest that other mechanisms such as decreased inflammation and improved endothelial function may account for the improvement in performance noted in PAD patients (16).

In patients with more advanced forms of lower-extremity PAD requiring surgical intervention or limb amputation, there is also good evidence for the ability of statins to reduce post-operative mortality risk (17–21). Results on local events such as restenosis, graft patency and limb salvage, however, come predominantly from retrospective reviews, and are therefore less clear. In those undergoing arterial reconstructions, statins have been shown to improve patency of autogenous infrainguinal bypass grafts in some (22,23) but not all studies (19). Data involving the effects of statins on restenosis following surgical interventions is limited, although a retrospective review of 218 patients undergoing either endovascular interventions or bypass grafts has suggested a beneficial effect of statin use in these individuals (24). Beneficial findings have also been reported in a number of studies involving patients presenting with CLI, with those on statins found not only to have lower rates of overall mortality and major adverse cardiovascular events, but also to have improved limb salvage and amputation-free survival outcomes (18,20,23,25). Similar to findings

surrounding graft patency, however, these outcomes have not been consistently reproduced in all studies, and warrant further investigation (17,19).

ANTI-ATHEROSCLEROTIC EFFECTS OF STATINS IN PAD

- **Pathophysiology of atherosclerosis (Figure 1)**

The prevailing theory of atherogenesis involves lipid retention and oxidation within the vessel wall in response to a compromised endothelium, and therefore the primary beneficial effect of statins is commonly attributed to their ability to lower LDL cholesterol levels, slowing atherosclerotic progression and leading to regression of established atheroma. Alongside lipid retention, however, multiple other inflammatory, oxidative, and proliferative pathways contribute to the complex atherosclerotic process. The accumulation of modified lipid particles within the sub-intimal space triggers an innate inflammatory response, further activating endothelial cells and stimulating the secretion of adhesion molecules (e.g. ICAM-1, VCAM-1), reactive oxygen species (e.g. superoxide) and numerous pro-inflammatory cytokines and chemokines (e.g. CRP, TNF- α , IL-6) which act to draw monocytes and lymphocytes into the vessel wall. Upon entry, monocytes differentiate first into macrophages and then, after the uptake of oxidised lipids, into foam cells. Over time, smooth muscle cells (SMCs) proliferate in the lesion due to both migration from the tunica media and also division of existing muscle cells within the intima itself. The production of interstitial collagen and elastin by these cells results in the formation of a fibrous cap overlying a lipid-rich necrotic core, the latter of which is formed from the apoptosis of SMCs and lipid-laden macrophages and subsequent release of their contents. Once established, these atherosclerotic plaques are common causes of major CV events such as myocardial infarction or stroke, and may contribute to the symptoms experienced in PAD.

- **Statins and lipid profiles in PAD**

While the lipid profile of patients with PAD is commonly that of the metabolic syndrome, comprising of high triglyceride levels and low HDL cholesterol, alteration in these lipid fractions has been studied less than the effect of lowering the LDL cholesterol. Statins lower LDL primarily through the inhibition of the HMG-CoA-reductase enzyme, which catalyses the first step of cholesterol synthesis in the mevalonate pathway. This inhibition results in up-regulation of LDL receptor on the hepatocyte membrane, thereby increasing uptake of LDL particles from the plasma. While the ability of newer statins to lower LDL by up to 50% is well known (26), they have also been shown to decrease triglyceride levels to a lesser degree (up to 20%), presumably through the inhibition of its synthesis in the liver and enhancement of lipoprotein lipase enzyme activity in the adipocytes (27).

Statins have also been shown to increase levels of high density lipoprotein (HDL) by up to 10%, but the precise mechanism of this effect is unclear. HDL inhibits the progression of the atherosclerotic process by facilitating the reverse transport of cholesterol from lipid laden monocytes in the vascular wall and also by modulating the inflammatory response (28). The HDL-raising properties of statins may result from the induction of the apolipoprotein-A1 (apoA1) gene through the activation of peroxisome proliferator-activated receptors (29). However other pathways, affected by statins, might contribute to improvement not only in the levels but also in the function of HDL. HDL can become dysfunctional and pro-atherogenic in the presence of increased oxidative stress which is commonly seen in patients with PAD (30). Increased levels of myeloperoxidase (MPO), a key generator of oxidative stress, has been associated with increased CV risk in PAD patients(31) and statins can reduce oxidative stress by reducing both MPO activity (32) but also increases in PON-1 activity(33).

- **Statins and plaque stabilisation/regression in PAD**

Clinical studies have shown that the improvement in lipid profile observed following statin therapy is associated with a halt in the progression or even regression of atherosclerosis in PAD. Numerous studies have reported a slowing

or regression of intimal-medial thickening (IMT) – a commonly used surrogate marker for atherosclerotic disease progression – in various vascular beds following statin treatment. In the carotid artery, multiple studies have reported beneficial changes in IMT in patients with established CV risk factors such as hypercholesterolemia (34–36) or hypertension (37). In the Kuopio Atherosclerosis Prevention Study (KAPS), this effect was found to occur even in individuals at low overall risk of atherosclerotic disease and was observed to be greater in smokers than non-smokers (36). Similar results have been reported in the superficial femoral artery, a site particularly prone to the development of lower-extremity PAD (38,39), and have been shown to be visible in as early as 4–8 weeks following statin treatment, which suggests the contribution of non-lipid-lowering mechanisms to the observed response (38). These changes appear to follow a dose-response pattern, with more aggressive therapy promoting IMT regression. For example, in type 2 diabetic patients – a population at increased risk of PAD – two years of cerivastatin or simvastatin treatment showed no effect on cIMT progression (40). In a later study assessing a similar population, however, although standard lipid lowering treatment had no effect on cIMT progression (0.039mm increase over 3 years), more aggressive lipid lowering (LDL lowered by ~ 30 mg/dl) therapy was found not only to slow progression, but to result in a significant regression of cIMT of 0.012mm when used alone, or 0.025mm when combined with ezetimibe (41).

Similar results have been reported for established atherosclerotic plaques. Statin treatment has been shown to reduce plaque volume and prevent acute, unstable coronary events through stabilisation of the “vulnerable plaque”. Statins have the ability to improve the stability of these vulnerable plaques through the depletion of lipid levels; inhibition of LDL oxidation, inflammation, smooth muscle cell proliferation and apoptosis; and increase in collagen content within the plaque itself (42). In support of this, previous imaging studies have shown the slowing of PAD progression, when statin was administered over a 2 year period, in men < 70 years old with established CAD, serum cholesterol levels of 155 – 310 mg/dl, and triglycerides < 354 mg/dl (39). Similar results have also been observed following low dose atorvastatin treatment (20mg/day), with reduction in

femoral artery IMT being observed within as little as 4 weeks from initiation of treatment (38).

- **Pleiotropic effects of statins in PAD**

Although the primary mechanism of statins is the lowering of cholesterol production, it is now also clear that the inhibition of multiple other downstream pathways results in numerous pleiotropic effects which may act to further reduce atherosclerotic CVD risk over and above the lowering of LDL-c (5). This is especially pertinent in PAD, given that the association between plaque size/stability and symptoms is less clear than that encountered in CAD. With evidence suggesting that the predominant PAD symptom of IC may be more closely linked to factors such as inflammation, endothelial dysfunction, skeletal muscle adaptations, and mitochondrial dysfunction rather than simply the presence of a flow-limiting lesion within the vessel lumen (15), the pleiotropic effects of statins in this population may offer benefits over and above that caused by lipid lowering alone.

Statins and endothelial function in PAD

Endothelial dysfunction underlies every stage of atherosclerotic disease and numerous studies have demonstrated disturbed endothelial physiology in patients suffering from peripheral vascular disease, measured both invasively via vasodilator infusion (43,44) and non-invasively via flow-mediated dilation (FMD) of the brachial artery (45). Furthermore, inverse relationships between PAD severity and endothelial function have been observed when comparing PAD patients with age- and sex-matched controls, with FMD in symptomatic PAD being less than half that of healthy equivalents (5.1% vs. 11.7%) (45). Similar findings have been reported in a study of 199 patients presenting for elective vascular surgery and subsequently followed for 1.2 years, with significantly lower FMD reported in patients who experienced a major cardiovascular event than those who did not (4.4% vs. 7%) (46). Although the mechanisms by which statins can affect the endothelium in the setting of PAD have not been explored,

it is reasonable to believe that statins can affect similar pathways to those reported in CAD patients or in individuals who share the same risk factors as PAD patients.

The effect of statins on endothelial function was initially thought to be simply related to its lipid lowering actions (47). For instance, a study in patients with known CAD has previously reported a sustained improvement in FMD over 10 months which occurred in combination with a lowering of LDL-c levels by ~ 25% following statin therapy(48). Similar improvements have also been observed in hypercholesterolaemic men following eight weeks of simvastatin treatment (49), while cessation of the same statin for 6 weeks had the opposite effect (50). Furthermore, a single session of LDL apheresis has previously been shown to acutely improve endothelial function (51), and *in vitro* studies have demonstrated the ability of oxidised LDL to reduce endothelial nitric oxide (NO) release (52). However, numerous studies have demonstrated that statins may exert additional beneficial endothelial effects through alternative pathways (53). Seminal work by Laufs and colleagues supported this hypothesis by showing the ability of statins to exert direct effects on endothelial NO synthesis and bioavailability through the upregulation of endothelial nitric oxide synthase (eNOS)(54). These effects are likely to be mediated through the ability of statins to block the synthesis of isoprenoid intermediates such as farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP), molecules which lie on the same metabolic pathway as that responsible for cholesterol synthesis and are therefore simultaneously affected by HMG-CoA reductase inhibition (55). Furthermore, activation of a separate phosphatidylinositol-3 kinase/Akt (PI3K-Akt) mediated pathway has also been reported following statin treatment (56), providing yet another alternative pathway for eNOS activation. Statins can also increase NO synthesis by lowering plasma levels of asymmetric dimethylarginine (ADMA)-an endogenous inhibitor of nitric oxide synthesis- which is upregulated in PAD patients and has been shown to predict risk of major adverse cardiovascular events (MACE)(57)(58).

In addition to their beneficial effects on NO bioavailability, statins have also been shown to affect circulating levels of numerous other vasoactive peptides produced by the endothelium. Endothelin-1 (ET-1) is a potent vasoconstrictor implicated in the pathophysiology of PAD (59,60) and has been shown in a recent meta-analysis of 15 RCTs to be significantly lowered following statin use (weighted mean difference of - 0.30 pg/ml) when compared to placebo (61). This decrease is thought to be related to the down-regulation of prepro-endothelin-1 mRNA via Rho protein-associated pathways (62,63), and is maintained even in the presence of ox-LDL (62). In addition to reducing ET-1 synthesis, statins may also exert additional beneficial effects through the attenuation of vascular smooth muscle responsiveness to ET-1 vasoconstriction, as shown by the ability of simvastatin to exert a concentration-dependent relaxation of isolated aortic rings pre-contracted with ET-1 (64).

Anti-inflammatory effects of statins in PAD

Increased inflammatory markers are associated with both intermittent claudication and increased CV mortality in patients with PAD. A nested case-control study carried out in 1998 as part of the Physicians Health Study was one of the first major studies to specifically investigate the association between C-reactive protein (CRP) and future risk of developing symptomatic PAD (65), and found that median CRP levels were not only significantly higher in participants who developed PAD, but that the relative risk of future complications increased in line with baseline CRP concentration. These findings were replicated in a cohort of 475 women in the RATIO study (66), and in the Edinburgh Artery Study, in which CRP was found to be related to PAD severity in a cohort of over 1500 individuals (67). After 12 years of follow-up in the latter study; the inflammatory markers CRP, interleukin-6 and intercellular adhesion molecule -1 were all shown to be associated with the progression of atherosclerotic disease, even after adjustment for other CV risk factors. Although these effects may occur due to a lowering of inflammatory ox-LDL within the vascular wall, a wealth of evidence also exists to suggest additional anti-inflammatory effects of statins that occur over and above their LDL-lowering properties and that these are

mediated through mechanistic pathways lying downstream of HMG-CoA inhibition. The PRavastatin Inflammation/CRP Evaluation (PRINCE) trial, conducted in 2001, was the first major trial to investigate whether the pleiotropic properties of statins could reduce inflammation independent of their cholesterol-lowering properties in a normolipidaemic population (68). In this randomised, placebo-controlled, double-blind clinical trial, 1702 individuals with no prior history of CVD were assigned to receive 40 mg/d pravastatin or placebo for 24 weeks, with the changes in CRP and cholesterol assessed at both baseline and end of study. At the half-way point of the study, a decrease in CRP levels was already evident in the statin group (14.7% reduction), and this was maintained until the end of the study (16.9% reduction). These changes were independent of the statins effect on LDL-c, and were subsequently replicated in a second open-label trial carried out by the same investigators (68). Similarly, in the JUPITER trial, 20 mg/daily rosuvastatin for 1.9 years was shown to reduce CRP by 37% in patients who presented with normolipidaemia (< 130 mg/dl) but elevated CRP levels (> 2.0 mg/l) (69). Likewise, in a secondary prevention trial involving PAD patients, patients receiving statin therapy had significantly lower levels of numerous inflammatory markers when compared to controls (70).

Statins and oxidative stress in PAD

Patients with established PAD exhibit higher levels of oxidative stress when compared to healthy controls (71), with this increase occurring due to a combination of both increased reactive oxygen (ROS) production and decreased antioxidant enzyme activity. ROS can be produced at multiple sites within the vascular wall via pathways such as NAD(P)H oxidase, xanthine oxidase, myeloperoxidase, eNOS uncoupling, a dysfunctional electron transport chain, and the activation of macrophages and T-cells (72,73). Under normal physiological conditions, the production of these free radicals is balanced by endogenous antioxidant activity such as superoxidase dismutase (SOD) and glutathione reductase, preventing their accumulation and subsequent generation of oxidative stress. This balance is disrupted in PAD leading to an excess of reactive oxygen species and chronic oxidative stress.

Statins have been shown to reduce oxidative stress by decreasing the expression and activation of key enzymes such as NADH/NADPH oxidase and xanthine oxidase. Atorvastatin therapy in normocholesterolaemic hypertensive rats resulted in improved endothelial function in line with a decrease in ROS (62% of control), a decrease in expression of the NAD(P)H oxidase subunit p22phox (63% of control), and an upregulation of eNOS mRNA expression and activity (74). In human studies, the assessment of gp91phox mRNA expression (a substrate-binding unit of endothelial NADPH oxidase) in internal mammary artery biopsies of patients both on and off statins has indicated the presence of a decreased level of vascular NAD(P)H-oxidase expression and superoxide formation only in the arteries extracted from statin patients (75). Although lipid-lowering *per se* can contribute to a reduction in oxidative stress (76), statins also appear to be able to further reduce ROS production through a separate NADPH-oxidase inhibitory pathway. Long-term rosuvastatin treatment in mice has been shown to decrease superoxide production through an NADPH-oxidase pathway (77), while atorvastatin treatment in hypercholesterolaemic patients displays a dose-dependent reduction in isoprostanes from as early as 3 days administration (78). Statins have also been shown to reduce superoxide formation from human monocyte-derived macrophages (79).

In vitro work has demonstrated the ability of cerivastatin to not only upregulate eNOS expression, but also to increase tetrahydrobiopterin (BH4) synthesis in endothelial cells through an upregulation of GTP-cyclohydrolase I gene expression (80). Similarly, in clinical studies, in patients undergoing coronary artery bypass surgery, pre-treatment with atorvastatin 3 days prior to surgery resulted in an increase in vascular BH4 and a corresponding decrease in superoxide production prior to any changes in lipid levels (81). As well as reducing oxidative stress through inhibition of ROS generating pathways, statins have also been shown to exert further reductions in oxidative stress by promoting antioxidant pathways, as evidenced by the ability of simvastatin to up-regulate superoxide dismutase activity in hypertensive rats (82).

GUIDELINES FOR THE USE OF STATINS IN PAD

A number of studies have provided strong evidence about the beneficial role of statins in patients with PAD. The European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of PAD recommend a target LDL-C below 100mg/dl and optimally below 70mg/dl (Class I recommendation) in all patients with PAD regardless of baseline LDL-C levels. When the target level cannot be reached, a reduction of >50% in LDL-C should be attempted (83). These recommendations are similar to those of the American College of Cardiology/ American Heart Association (ACC/AHA), who suggest a target for LDL-C level <100mg/dl (Class I recommendation) in all patients with PAD and LDL level <70mg/dl for patients at very high risk of ischaemic events (Class IIa recommendation). For patients with PAD and high triglycerides/low HDL but normal LDL, ACC has an additional Class IIa recommendation for the use of fibric acid derivatives (84). According to 2013 ACC/AHA guidelines moderate or high dose statin therapy is advocated in all symptomatic PAD patients to reduce the risk of CV events (85). For the management of PAD patients who are undergoing non-cardiac vascular surgery, the 2014 ACC/AHA guidelines also recommend the initiation of statin therapy, irrespective of their underlying risk factor profile, for reduction in the incidence of CV events (Class IIa recommendation) (86).

Although a threshold for LDL-C is recommended by the guidelines, there are still questions as to how intensive statin therapy should be, as side effects such as myopathy, liver damage, and an increased risk of type 2 diabetes are all well-recognised risks with this medication. In support of intensive statin therapy in PAD, higher statin doses have been shown not only to reduce CV events in patients with pre-existing PAD (10), but also to reduce the incidence of PAD in primary prevention (9). Two large scale meta-analyses have attempted to clarify the threshold at which the possible benefits of statins are outweighed by their adverse effects. Although high-dose statin therapy was found to provide substantial clinical benefit when compared to low-dose therapy and placebo, both studies reported an accompanying increase in the risk of adverse events in the intensively treated group (87,88). These events, however, were found to

consist predominantly of non-urgent conditions such as myalgia or liver enzyme elevations, with serious events remaining rare and not differing significantly between the high-dose and placebo groups (88). This increase in risk appeared to be significantly outweighed by its clinical benefits, however, with data suggesting a reduction in CV events of 37 per 1000 patients, as opposed to the appearance of only 5 adverse events in the same number of subjects. Similar findings have also been reported from the JUPITER trial, in which a reduction in all-cause mortality was observed in 20% of patients receiving rosuvastatin and in 46% of patients that attained target levels of LDL-C < 50mg/dl over a median period of 2 years (89). Notably in this trial, the rate of adverse effects was again similar in the placebo and statin groups (except for muscle symptoms). These findings strongly suggest that the benefits of intensive statin treatment outweigh the possible adverse effects, particularly in high-risk patients.

While there is limited evidence regarding the monitoring of lipid lowering treatment, the ESC recommends a first assessment of the response to therapy at 8+/-4 weeks following initiation of statin treatment and thereafter annual follow up monitoring once the patient has reached the lipid lowering targets (83). Furthermore, while there is no clear evidence of a high risk of adverse effects of low LDL-C levels, the ACC guidelines recommend decreasing statin dosage if two consecutive values of LDL-C are below 40mg/dl (84).

As previously mentioned, moderate doses of statin therapy have been associated with myopathy, liver disease, increased incidence of diabetes development and cognitive impairment. In randomized clinical trials, however, myalgia - the most common adverse effect following statin use - has shown similar presentation in both statin and placebo groups (90). The European Atherosclerosis Society consensus panel recommends that, in the presence of muscle pain or weakness, creatine kinase levels should be obtained and, in case that the levels are elevated, statins should be discontinued and subsequently restarted at a lower dose. The American Academy of Family Physicians on the other hand offers a Class C recommendation and only in patients at high risk of muscle toxicity baseline creatine kinase levels should be obtained (91). Overall, the side effects reported

with statin use in PAD patients are rare and, for most patients, the risk-to-benefit calculation involving these adverse effects favours statin use.

CONCLUSIONS

Peripheral vascular disease is under-diagnosed and is a major risk factor for CVD morbidity and mortality. Despite the high prevalence of atherosclerotic risk factors in those suffering from the disease, PAD patients receive less intensive treatment than those diagnosed with CAD (2) and have a long-term prognosis that is significantly worse (92). A wealth of evidence exists for the ability of statins to exert beneficial effects on numerous pathophysiological pathways that underlie every stage of the disease, and clinical evidence from large-scale observational studies and randomised control trials provide strong evidence for their ability to significantly diminish morbidity and mortality. Better screening for PAD and improved pharmacological interventions with drugs such as statins are likely to improve outcomes and help to reduce the significant health and financial burdens associated with this prevalent disease.

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TABLE LEGENDS

Table 1: Statin use in PAD and CV outcomes

Abbreviations: RCT, randomised controlled study; CLI, chronic limb ischaemia; OR, odds ratio; HR, hazard ratio; PAD, peripheral arterial disease; LDL, low density lipoprotein; ACE, angiotensin converting enzyme; MI, myocardial infarction; MACE, major adverse cardiac events; RCT, randomized controlled trial; Rx, treatment; CV, cardiovascular

Table 2: Statin use in PAD and symptom-related outcomes

Abbreviations: RCT, randomised controlled trial; PAD, peripheral arterial disease; MI, myocardial infarction

FIGURE LEGEND

Figure 1: Pathways in the atherosclerotic process that may be affected by statin use

Alongside its primary lipid-lowering action, the blocking of multiple pathways downstream of HMG-CoA reductase pathway with statin use results in a number of pleiotropic effects that may additionally contribute to a reduction in atherosclerotic risk in PAD patients. These pathways have been shown to affect every stage of the disease process from the initial development of endothelial dysfunction to the stabilisation of vulnerable established plaques. The arrows demonstrate pathways that can be affected by statin use.

Table 1: Statin use in PAD and CV outcomes

Author/ Year	Study type	Study group	Statin / follow up	CV Outcome
HPS 2002 (6)	RCT	20536 adults 40-80 years with CAD, occlusive arterial disease or diabetes	Simvastatin 40mg/d vs placebo 5 year follow up	Reduced all-cause mortality in simvastatin group
HPS 2007 (93)	RCT	6748 patients with PAD and 13788 other high risk patients	Simvastatin 40mg/d vs placebo for mean of 5 years	Reduction in first major vascular event by 25% and that of peripheral vascular events by 1/6 in simvastatin group
Aronow & Ahn 2002 (7)	Prospective follow up study	264 men and 396 women mean age 80+/-9 years with PAD and LDL>125mg/dl . Among those 318 were on statin and the remaining on no lipid lowering treatment	90% of 318 patients who were treated with statins were on simvastatin 20-40mg/d, 9% with pravastatin 40mg/d and 1% with lovastatin 40mg	Significant reduction in incidence of coronary event in those treated with statins.
Schillinger et al 2004 (70)	Prospective observational study	515 patients with severe PAD (median age 70 years). 52% were on statin	No statin type or dose specified/ median follow up 21 months	Statin Rx was associated with improved intermediate-term survival only in PAD patients with high inflammatory activity
Feringa et al 2006 (8)	Prospective observational study	2420 PAD patients (64+/_11 yrs)	No statin dose or type specified/ median follow up 8 years	Statins, beta blockers, aspirin and ACE inhibitors are associated with reduction in long term mortality in PAD patients
Feringa et al 2007 (10)	Prospective observational study	1374 PAD patients (61+/-10 years)	Simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin/ mean follow up 6.4+/-3.6 yrs	Higher doses of statins and lower LDL cholesterol are independently associated with improved outcome in PAD patients
Stoekenbroek et al 2015 (9)	RCT	8888 post myocardial infarction patients	Atorvastatin 80mg/d vs simvastatin 20-40mg/d/ median follow up 4.8 years	High dose atorvastatin reduced the incidence of PAD and incidence of coronary events compared to simvastatin
Antoniou et al 2014 (94)	Systematic review-meta-analysis	12 observational cohort studies and 2 RCT in 19368 patients		Decreased all-cause mortality (HR:0.77[0.68-0.86] and incidence of stroke (OR:0.77[0.67-0.89] and trend towards improved CV mortality in statin users
De Martino et al 2016 (95)	Retrospective review from Vascular	3039 patients who underwent elective suprainguinal repair 8323 had infrainguinal bypass	Antiplatelet and statins	Preoperative statin and antiplatelet Rx were not associated with improved rated of in-hospital MI/death after major open vascular

	Quality Initiative database	3007 had open infrarenal abdominal aortic aneurysm repair		operations.
Schanzer et al 2008 (19)	Observational study	1404 patients with CLI who were randomized to test the efficacy of edifoligide for the prevention of graft failure	45% were on statins 59% were on beta-blockers and 80% were on antiplatelet drugs	Perioperative MACE and early mortality were not affected by the use of any drugs. Statin use was associated with improved survival in CLI patients 1 year after surgical revascularization
Suckow et al 2015 (17)	Observational study	2067 patients man age 67+/-11 years with CLI who underwent infringuinal bypass from 2003-2011 (Vascular Study group of New England registry)	74% were on statins perioperatively and at 1 year follow up	Statin therapy is associated with 5 year survival benefit. However, 1 year limb related outcomes were not influenced by statins.

Table 2: Statin use in PAD & symptom-related outcomes

Author	Study type	Patients	Medication/ Follow up	Symptom-related outcomes
Pedersen et al 1998 (12)	RCT	4,444 patients with prior MI and serum cholesterol 5.5 – 8 mmol/L	Simvastatin 20 or 40 mg/d vs. placebo for median 5.4 years	Statin treatment associated with 38% reduced risk of new or worsening IC and 48% reduced risk of new or worsening carotid bruits compared to placebo.
Mohler et al 2003 (13)	RCT	354 patients with claudications	Atorvastatin 10mg/d or 80mg/d vs. placebo for 12 months	The 80mg atorvastatin group improved pain free walking distance by 63% vs 38 % in the placebo. There was no difference between 10mg atorvastatin and placebo
Aronow et al 2003 (14)	RCT	69 patients with PAD	Simvastatin 40mg/d vs placebo	Increase in treadmill exercise time of 24% at 6 months and 42% at 12 months in simvastatin group compared to placebo
Mondillo et al 2003 (15)	RCT	86 patients with PAD	Simvastatin 40mg/d vs placebo	Simvastatin group was associated with significant increase in 90meters pain free walking distance compared to placebo
McDermott et al 2003 (16)	Prospective observational study	392 PAD patients	Statins, aspirin, beta blocker, ACE inhibitors and vasodilators	Statins were associated with superior leg functioning independent of cholesterol levels compared to no statin use
Khumbani et al 2014 (18)	Retrospective review	5,861 patients with symptomatic PAD	62.2% on statins at baseline (74.5% in patients with concomitant CAD and 64.0% in patients with concomitant CBVD) with 4 year follow-up	Statins were associated with 18% lower rate of adverse limb outcomes (worsening symptoms, peripheral revascularisations, ischaemic amputations) at 4 years
Westin et al 2014 (20)	Retrospective review	380 CLI patients following diagnostic angiography or endovascular intervention	65% on statins perioperatively with median 1 year follow-up	Statins were associated with increased amputation-free survival and lower rates of mortality and MACE

Abbruzzese et al 2004 (22)	Retrospective review	172 PAD patients undergoing autogenous infrainguinal reconstructions	49.7% of patients on statins at time of procedure with 2 year follow-up	Statin therapy associated with improved graft patency. Risk of graft failure 3.2x higher in control group.
Aiello et al 2012 (23)	Retrospective review	646 patients with PAD undergoing endovascular intervention for CLI	49.4% of patients on statins at time of procedure with 2 year follow-up	Statins associated with improved primary and secondary patency, limb salvage rates, and overall survival
Siracuse et al 2012 (24)	Retrospective review	218 patients undergoing their first intervention for claudication due to superficial femoral artery disease	Statin use at baseline in 62% of patients undergoing lower extremity bypass and 69% of patients undergoing percutaneous transluminal angioplasty ± stent	Statin therapy improved overall freedom from stenosis and symptom recurrence. No differences observed in 3 year mortality.
Henke et al 2004 (25)	Retrospective review	293 patients undergoing infrainguinal bypass, predominantly for limb salvage	Statins, ACE inhibitors, and antiplatelet agents or warfarin	Statin therapy associated with improved graft patency and limb salvage

Figure 1: Pathways in the atherosclerotic process that may be affected by statin use

