



Statins in Peripheral Arterial Disease

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75

INTRODUCTION

The term peripheral arterial disease generally refers to atherosclerosis when it obstructs the blood supply to the lower or upper extremities.¹ It is an important manifestation of systemic atherosclerosis, and is a strong marker for risk of major cardiovascular and cerebrovascular events. Among patients with peripheral artery disease, evidence of coronary heart disease is common (85% by coronary angiography) as is cerebrovascular disease (60% of patients with peripheral arterial disease have a carotid stenosis of > 30% by ultrasonography).² Moreover, it is associated with a substantial risk of illness and death and a marked reduction in ambulatory capacity and quality of life.³

Atherosclerosis in peripheral arterial disease involves several inter-related processes, including lipid disturbances, platelet activation, thrombosis, endothelial dysfunction, inflammation, oxidative stress and smooth muscle activation.⁴

HMG-CoA reductase inhibitors have beneficial effects on atherosclerosis beyond those related to cholesterol lowering.^{5,6} Statins stabilize atherosclerotic plaques, reduce oxidative stress and decrease vascular inflammation. In vascular endothelium, statins increase concentrations of nitric oxide, which has vasodilator, antithrombotic and antiproliferative properties.⁵ By virtue of these properties, statins retard the deleterious effects of atherosclerosis on leg arteries and improve lower extremity functioning in peripheral arterial disease.

PATHOPHYSIOLOGY OF PERIPHERAL ARTERIAL DISEASE

Pathophysiological considerations in patients with peripheral arterial disease takes into account the balance between circulatory supply of nutrients to the skeletal muscles and oxygen and nutrient demand of skeletal muscle.

Claudication occurs when blood flow to the extremity fails to meet the metabolic demand of the muscle during exercise. Critical limb ischemia is attributed to abnormalities in the microcirculation. The number of perfused skin capillaries is reduced in patients with severe limb ischemia.

RISK FACTORS

The risk factor most correlated with the onset and progression of peripheral arterial disease is cigarette smoking, followed by

diabetes mellitus. Abnormalities in lipid metabolism are also associated with an increased prevalence of peripheral arterial disease. Relative risk for peripheral arterial disease is about 1.1 for each 10 mg / dl increase in total cholesterol with similar increases for development of claudication.⁷ In the Framingham Heart Study, the odds ratio for claudication was 1.2 for each 40 mg / dl increase in the total cholesterol.⁸

PLATELET ACTIVATION AND THROMBOSIS

Thrombosis is most likely to occur at sites of plaque rupture or erosion and plays an important role in modulating the risk of acute ischemic events in peripheral arterial disease. It also plays an important role in progression of the disease and clinical symptoms in these patients.⁹

ENDOTHELIAL DYSFUNCTION

The vascular endothelium is an important centre of vascular control and participates importantly in regulation of vascular tone, nutrient delivery, waste removal, inflammation, thrombosis and coagulation. Endothelial regulation of these processes stems primarily from the production of autocrine and paracrine mediators including nitric oxide, prostaglandins, endothelium derived hyperpolarizing factors, endothelin and angiotensin II. The balance between these opposing substances ultimately determines the contractile and mitogenic state of underlying vascular smooth muscles. Any imbalance between these substances leads to endothelial dysfunction, which is defined as the decreased synthesis, release, and/or activity of endothelial derived nitric oxide. This contributes to impaired vascular relaxation, platelet aggregation, increased vascular smooth muscle proliferation, and enhanced leukocyte adhesion to the endothelium in patients with peripheral arterial disease.¹⁰ Endothelial dysfunction is one of the earliest manifestations of atherosclerosis, even in the absence of angiographic evidence of disease.¹¹

Endothelial inflammatory response

Atherosclerosis is a complex inflammatory process that is characterized by presence of monocytes or macrophages and T-lymphocytes in the atheroma.¹² Inflammatory cytokines secreted by these macrophages and T-lymphocytes can modify endothelial function, smooth muscle cell proliferation, collagen degradation, plaque disruption and thrombosis.¹³

Oxidant Stress

Excessive generation of reactive oxygen species (ROS) represents an important pathological process in atherogenesis. Each component of the atherosclerotic blood vessel has been demonstrated to increase production of ROS, primarily superoxide anion.

The two best characterized effects of ROS include oxidation of low-density lipoproteins and scavenging of endothelium-derived nitric oxide, which ultimately leads to endothelial dysfunction.⁷

MICROCIRCULATORY DISTURBANCES

When a hemodynamically significant stenosis is present, distal pressure and flow are reduced. However in patients with lower extremity peripheral arterial disease there is a poor correlation between the pressure drop across the limb and ischemic symptoms and function. This is largely attributable to the microcirculatory disturbances seen in these patients. The number of perfused skin capillaries is reduced in patients with severe limb ischemia. The other potential causes of decreased capillary perfusion include reduced red cell deformability, increased leukocyte adhesivity, platelet aggregates, fibrinogen, microthrombosis, excessive vasoconstriction and interstitial edema.¹⁴

ROLE OF STATINS IN TREATMENT OF PERIPHERAL ARTERIAL DISEASE

The goals of treatment for patients with peripheral arterial disease are to relieve their exertional symptoms, improve walking capacity and quality of life with the additional goals of relieving ischemic pain at rest, healing ischemic ulceration, and preventing limb loss in those with critical limb ischemia.

Decision-making and management of patients with peripheral arterial disease must take into two cardinal aspects - the first is that peripheral arterial disease is a marker of systemic atherosclerosis and as a result patients are at increased risk of myocardial infarction, stroke and death. Second, patients with peripheral arterial disease frequently have a reduced functional capacity manifested by decreased walking speed or distance, intermittent claudication, or critical limb ischemia that limits their ability to perform daily activities.

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins are potent inhibitors of cholesterol biosynthesis.¹⁵ The beneficial effects of statins extend beyond their effects only on serum cholesterol levels. Recent experimental and clinical evidence indicates that some of the cholesterol-independent or "pleiotropic" effects of statins involve restoring or improving endothelial function, enhancing the stability of atherosclerotic plaques, and decreasing oxidative stress and vascular inflammation.¹⁵

STATINS AND LIPIDS

Lipid modification with statins has been advocated in the treatment of patients with peripheral arterial disease based mainly on their beneficial effects in coronary artery disease, demonstrating a reduction in cardiovascular events.¹⁶

The current National Cholesterol Education Program (NCEP) guideline recommendation for patients with peripheral arterial disease is to achieve a serum LDL cholesterol concentration of < 100 mg / dl (2.6 mmol per liter) and a serum triglyceride concentration of < 150 mg / dl (1.7 mmol per liter).^{2,17}

STATINS AND ENDOTHELIAL FUNCTION

In patients with peripheral arterial disease, therapy with a statin not only lowers serum cholesterol concentrations, but also improves endothelial function, as well as other markers of atherosclerotic risk, such as serum P-selectin concentrations.³

Statins increase nitric oxide bioavailability by stimulating and upregulating endothelial nitric oxide synthase (eNOS), or by decreasing oxidative stress.⁵ Furthermore, statins have been shown to restore eNOS activity in the presence of hypoxia and oxidized low-density lipoproteins, conditions that lead to endothelial dysfunction. Statins also increase the expression of tissue type plasminogen activator and inhibit the expression of endothelin-1, a potent vasoconstrictor and mitogen.⁵ Thus statins exert many favorable effects on the endothelium and attenuate endothelial dysfunction.

STATINS AND INFLAMMATORY RESPONSE

Statins possess anti-inflammatory properties and have been shown to reduce the number of inflammatory in atherosclerotic plaques.¹⁸ In addition a recent study has shown that statins can suppress the inflammatory response independent of HMG-CoA reductase inhibition by binding directly to a novel regulatory site of the β_2 integrin, leukocyte function antigen-1.¹⁸

ANTIOXIDANT EFFECTS OF STATINS

Statins improve endothelial function through their antioxidant effects. They have been shown to enhance endothelium-dependent relaxation by inhibiting the production of reactive oxygen species (ROS), such as superoxide and hydroxyl radicals.¹⁹ Statins also attenuate angiotensin II induced free radical production in vascular smooth muscle cells by downregulating angiotensin type I receptor expression.¹⁹

STATINS AND PLAQUE STABILITY

Plaque rupture leads to acute ischemic events in peripheral arterial disease.

Lipid lowering by statins may contribute to plaque stability by reducing plaque size or by modifying the physicochemical properties of lipid core.²⁰ They also cause a decrease in macrophage accumulation in atherosclerotic lesions and inhibit matrix metalloproteinases production by activated macrophages. Thus statins lessens the propensity for plaque rupture.

STATINS AND MICROCIRCULATION

Statins induce improvement of vasomotor regulation of blood flow, particularly in the microcirculation in patients with peripheral arterial disease, by virtue of their beneficial effects on endothelium. Statins have also been shown to promote vasculogenesis independent of cholesterol reduction.²¹

STATINS AND AORTIC STENOSIS

Calcific aortic stenosis which was earlier thought to be a degenerative age-related condition is now thought to be an active inflammatory process with similarities to atherosclerosis. The aortic valve lesion simulates atheroma, and its progression is related to known atherosclerotic risk factors, such as hyperlipidemia. Once the condition is established, no known medical therapy exists that reduces the progression of stenosis and helps delay the need for aortic valve replacement.

The use of HMG-CoA reductase inhibitor has been shown to be associated with a significant reduction in the progression of calcific aortic stenosis as assessed by both valve area and pressure gradient.²²

RECENT TRIALS DEMONSTRATING THE BENEFITS OF STATINS IN PERIPHERAL ARTERIAL DISEASE

McDermott MM et al,⁶ in their study of statin use and leg functioning in patients with and without lower extremity peripheral arterial disease found that statin use is associated with superior leg functioning as compared to no statin use, independent of cholesterol levels and other potential confounders. The study included 392 men and women with an ankle-brachial index (ABI) < 0.90 and 249 with ABI between 0.9 – 1.50. Functional outcomes included 6 minutes walk distance and 4 meters walking velocity. A summary performance score combined performance in walking speed, standing balance, and time for five repeated chair rises into an ordinal score ranging from 0 – 12 (12 = best).

Adjusting for age, sex, ABI, comorbidities, cholesterol and other confounders, participants taking statins had better 6 minutes walk performance (1276 vs. 1218 feet), faster walking velocity (0.93 vs. 0.89 m/sec) and a higher, summary performance score (10.2 vs. 9.4) than participants not taking statins.

Mohler ER et al in their study “Cholesterol Reduction With Atorvastatin Improves Walking Distance in Patients with Peripheral Arterial Disease”,²³ have shown that atorvastatin improves pain-free walking distance and community based physical activity in patients with peripheral arterial disease. This randomized, double blind, parallel – design study included 354 persons with claudication attributable to peripheral arterial disease. Patients were treated with placebo, atorvastatin (10 mg per day), or atorvastatin (80 mg per day). The outcome measures included change in treadmill exercise time and patient reported measures of physical activity and quality of life based on questionnaires.

Although the maximum walking time after 12 months of treatment with atorvastatin did not change significantly, there was an improvement in pain-free walking time after 12 months of treatment for the 80 mg group compared with placebo.

Impact of Cholesterol Reduction on Peripheral Vascular Disease in The Program on The Surgical Control of Hyperlipidemias (POSCH)²⁴ was a randomized trial of ileal bypass surgery for the treatment of hyperlipidemia in 838 patients. After 5 years of treatment the relative risk of an abnormal ankle-brachial index value in the treatment group was 0.6 and the relative risk of claudication or limb threatening ischemia was 0.7 as compared to the control group.

Scandinavian Simvastatin Survival Study (4S)²⁵ - In this trial a subgroup of patients treated with simvastatin had reduced relative risk of new claudication or worsening of pre-existing claudication as compared to patients randomly assigned to placebo.

Recently The Heart Protection Study (HPS)²⁶ confirmed that statin treatment reduces the risk of death and adverse cardiovascular events in patients with coronary and non-coronary

atherosclerosis, including patients with peripheral artery disease who had not had a prior cardiovascular event.

CONCLUSION

Both direct and indirect endothelium dependent effects of statins play important roles in limiting the development of atherosclerosis and vascular inflammation in patients with peripheral arterial disease. This role seems to extend beyond the lipid lowering effect of statins. Also the benefits extend beyond improvement in mortality / morbidity benefits of treating peripheral artery disease alone. Statins should therefore form part of every prescription for a patient with peripheral artery disease.

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