

ORIGINAL RESEARCH

Influence of Hyperlipidemia and Its Treatment on Outcome in Patients with Peripheral Arterial Disease

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Multiple large prospective randomized trials have compared the treatment of patients that have arteriosclerotic occlusive disease or diabetes with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors versus placebo. These studies demonstrate a 25% reduction in the rate of cardiovascular death, myocardial infarction (MI), stroke and revascularization procedures.¹⁻⁴ These beneficial results were identified in patients with a wide range of serum cholesterol low-density lipoprotein cholesterol (LDL-c) levels at study entry; many of these patients had lipid levels previously considered to be within the normal range. Cost analysis of the Heart Protection Study demonstrated that cost savings from reduced hospitalization rates in the patients treated with HMG-CoA reductase inhibitors outweighed the cost of the HMG-CoA reductase inhibitors in patients whose cholesterol levels were previously considered acceptable.⁵

The use of HMG-CoA reductase inhibitors in preventing adverse events in the peripheral circulation has recently been reported. Large randomized prospective studies have demonstrated that the use of HMG-CoA reductase inhibitors reduces the incidence of stroke¹⁻⁴ and non-coronary revascularization.⁴ In addition, McGirt et al retrospectively reviewed 1566 patients who underwent carotid endarterectomy over a 10-year period and found a significantly reduced incidence in perioperative stroke and death in patients treated with HMG-CoA reductase inhibitors.⁶ Abbruzzese et al retrospectively evaluated patients undergoing infrainguinal bypass grafting and reported a significant increase in primary assisted and secondary patency rates in patients taking HMG-CoA reductase inhibitors.⁷ Henke et al also confirmed improved graft patency rates with the use of HMG-CoA reductase inhibitors in a retrospective study.⁸

The National Cholesterol Education Program's expert panel on detection, evaluation, and treatment of hypertension and cholesterol in adults published guidelines for cholesterol management in 2001. Current recommendations include maintaining LDL-c levels below 100 mg/dL for patients with documented coronary heart disease (CHD), peripheral artery disease (PAD), diabetes mellitus or multiple risk factors for atherosclerosis that confer a 10-year risk for CHD > 20%.⁹ For patients with more than two risk factors for CHD, the recommended LDL-c cholesterol level should be below 130 mg/dL. Major risk factors that modify LDL-c goals include cigarette smoking, hypertension (blood pressure >/- 140/90 mm Hg or on antihypertensive medication), age (men >/- 45 years, women >/- 55 years), low levels of serum high-density lipoprotein cholesterol (HDL-c) cholesterol (< 40 mg/dL), and family history of premature CHD (CHD in male first-degree relative < 55 years, CHD in female first-degree relative < 65 years). Maintenance of an HDL-c cholesterol >/- 60 mg/dL is considered a negative risk factor in that its presence removes one risk factor from the patient's total. For patients with 0-1 risk factors, the LDL-c cholesterol should be below 160 mg/dL. The American College of Cardiology and the American Heart Association jointly published guidelines in December 2005 recommending that patients with PAD be treated with HMG-CoA reductase inhibitors to maintain LDL-c cholesterol levels below 100 mg/dl.

Despite these recommendations, patients with PAD are frequently undertreated and often do not receive optimal medical management with respect to HMG-CoA reductase inhibitors. Henke et al found that only 60% of patients undergoing infrainguinal bypass for atherosclerotic vascular disease were receiving HMG-CoA reductase inhibitors.⁸ Mukherjee et al reported that only 50% of patients undergoing peripheral vascular interventions were appropriately treated with HMG-CoA reductase inhibitors.¹⁰ These studies included groups of patients with known atherosclerosis, who therefore meet consensus guidelines for tight control of serum lipid levels. Hirsch et al identified a statistically significant difference in the rate of treatment for hyperlipidemia among patients with PAD compared to patients with CHD.¹¹ Only 56% of patients with a prior history of PAD were treated for hyperlipidemia, in contrast to a treatment rate of 73% in patients with a diagnosis of CHD. A possible explanation for the lower incidence of treatment of lipid disorders was that among patients with a prior diagnosis of PAD, only 49% of primary care physicians were aware of the diagnosis at the time of the screening. Many of these patients did not have classic symptoms of claudication, but had been found to have abnormal ankle brachial indices.

While administration of HMG-CoA reductase inhibitors has been shown to decrease the incidence of primary vascular events, investigators have found mixed results in using HMG-CoA reductase inhibitors to prevent restenosis after angioplasty of both bypass grafts and native arteries in the coronary circulation. Chandrasekar et al demonstrated an increased incidence of dyslipidemia in patients with restenosis of coronary vein grafts after percutaneous transluminal coronary angioplasty (PTCA) over a mean follow up period of 16.8 months. Additionally, patients with dyslipidemia who were treated with lipid-lowering drugs were found to have a lower incidence of symptomatic restenosis, 29% versus 50%.¹² Mulder et al demonstrated a significant reduction in restenosis in native coronary arteries after PTCA over 2 years, 7% in patients treated with an HMG Co-A reductase inhibitor versus 29% in untreated patients treated with an HMG Co-A reductase inhibitor.¹³ Serruys et al, however, failed to detect a reduction in restenosis in native coronary arteries, 40 weeks after PTCA in patients administered HMG Co-A reductase inhibitors, but did demonstrate a reduction in mortality and myocardial infarction.⁴ Corpataux et al used an organ culture model of saphenous vein grafts bathed in six different statins, and reported that all HMG Co-A reductase inhibitors significantly reduced the development of intimal hyperplasia.¹⁵

While the use of a lipid-lowering agent to decrease the incidence of primary vascular events seems logical, the rationale underlying the administration of HMG-CoA reductase inhibitors to prevent early restenosis after revascularization procedures is not intuitively obvious. Early restenosis is typically thought to result from intimal hyperplasia. Surrounding inherent matrix proteins are degraded by matrix metalloproteinases (MMPs) produced by smooth muscle cells and macrophages. The degradation of extracellular matrix proteins allows the migration of smooth muscle cells into the subintimal space and subsequent synthesis of a new extracellular matrix that results in intimal hyperplasia.⁶⁻¹⁹ HMG-CoA reductase inhibitors have been found to decrease the levels of MMPs in human aortic specimens,²⁰ cultured human smooth muscle cells,²¹ cultured human monocytes,²² carotid plaques,²³ and in the serum of healthy men.²⁴

HMG-CoA reductase inhibitors have pleiotropic effects. In addition to inhibition of MMP expression, HMG-CoA reductase inhibitors reduce the adhesion and migration of inflammatory cells. HMG-CoA reductase inhibitors have been shown to inhibit adhesion of leukocytes to endothelial cells,²⁵⁻²⁷ as well as reduce the expression of monocyte chemoattractant proteins.^{28,29} HMG-CoA reductase inhibitors also up-regulate endothelial nitric oxide synthase (eNOS) expression, thereby possibly improving endothelial function.³⁰ Furthermore, HMG-CoA reductase inhibitors have been demonstrated to significantly decrease the serum levels of C-reactive protein, a marker of inflammation.³¹ Any or all of these pleiotropic effects could potentially prevent or inhibit the process of intimal hyperplasia formation.

At our own institution, we retrospectively evaluated patients who underwent infrainguinal bypass and were enrolled in a duplex graft surveillance program. Our patient population was made up of 258 patients, who underwent a total of 280 bypass grafts. The series consisted of three subgroups, 205 (73.2%) patients with no graft stenosis, 55 (19.6%) with solitary graft stenosis and 20 (7.1%) with multiple graft stenoses. Multivariate analysis demonstrated hyperlipidemic patients not using HMG-CoA reductase inhibitors had a greater incidence of graft stenosis than hyperlipidemic patients on a lipid-lowering agent.

In summary, patients with documented atherosclerotic peripheral arterial occlusive disease have systemic arterial disease. These patients benefit from lipid-lowering therapy with HMG-CoA reductase inhibitors; such therapy significantly reduces the rates of cardiovascular death, MI, stroke and the need for revascularization procedures. Patients with documented PAD, whether symptomatic or asymptomatic, and diabetes mellitus have the equivalent of coronary heart disease in terms of risk for subsequent cardiovascular events, and require maintenance of a serum LDL-c below 100 mg/dl, as well as other cardiovascular risk factor modification. Screening patients at risk for atherosclerosis to detect PAD prior to the onset of symptoms will identify patients requiring more aggressive medical management of their risk factors. Patients presenting with symptomatic PAD or CHD that requires intervention benefit from more aggressive medical management of their risk factors, not only with a reduction in cardiovascular events, but possibly from a reduction in the rate of restenosis of the primary revascularization procedure. It is the responsibility of all physicians involved in the care of these patients to ensure that appropriate medical management of cardiovascular risk factors is being performed. Primary care physicians that consult specialists for PAD expect both a comprehensive evaluation and treatment recommendations. When consulted, cardiologists, vascular surgeons, vascular medicine specialists and interventional radiologists should use the opportunity to review the patient's risk factors for cardiovascular disease and ensure appropriate risk factor modification is in place. All physicians treating patients for PAD need to be comfortable managing risk factors for cardiovascular disease.