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HMG-CoA-Reductase Inhibitors/Statins: An Improval for Patients Suffering from Peripheral Vascular Disease

D. G. Haider, M. Baghestanian

Abstract: In the past, numerous studies have investigated the benefit of statin use in patients suffering from coronary arterial disease and the adjacent diseases for cardiac tissue. Up to now, more than 31,000 patients participated in these trials and we can say without any doubt that for all of those under statin therapy it became an enormous advance in reducing their cardiovascular morbidity. Nevertheless, atherosclerosis and cardiovascular morbidity is not only limited to specific areas and so peripheral vascular disease became a major clinical problem, especially for elder patients. Unfortunately, statin use in patients with peripheral vascular disease is not as well investigated as it is in patients with coronary arterial and associated heart diseases. Recent published data showed the possible power of statin therapy in patients with peripheral arterial disease. The results and possible benefits seem to warrant a more detailed view upon the published papers. Thus, this review strikes the current trials and studies concerning statins in their effect, use and benefit in patients suffering from peripheral vascular disease in order to elucidate specific functions and their associated results in a cohort of such patients.

Kurzfassung: HMG-CoA-Reduktase-Inhibitoren/Statine: Verbesserung des kardiovaskulären Krankheitsbildes bei Patienten mit peripherer arterieller Verschlußkrankheit. In der Vergangenheit haben verschiedene Studien den positiven Nutzen der Einnahme von Statinen, besonders bei Patienten mit koronarer Herzkrankheit und damit assoziierten Erkrankungen des kardialen Gewebes, gezeigt. Bisher nahmen mehr als 31.000 Patienten an diesen Studien teil, so daß wir heute ohne jeden Zweifel behaupten können, daß diejenigen, denen Statine verabreicht wurden, eine enorme Verbesserung ihres kardiovaskulären Krankheitsbildes erfuhren. Nichtsdestotrotz bleiben kardiovaskuläre Morbidität und Atherosklerose nicht auf bestimmte Gefäßregionen begrenzt, so daß die periphere arterielle Verschlußkrankheit (PAVK) besonders für ältere Patienten ein großes klinisches Problem darstellt. Leider ist der Nutzen der Statintherapie bei Patienten mit PAVK nicht so gut erforscht wie bei Patienten mit koronarer Herzkrankheit. Kürzlich veröffentlichte Daten zeigten dabei das mögliche positive Potential der Statintherapie bei Patienten mit PAVK. Diese Resultate und der mögliche positive Nutzen initiierten daher eine genauere Betrachtung des Sachverhalts der bisher publizierten Artikel. Daher soll sich dieser Review mit den aktuellen Studien und Versuchen, die den Effekt, Gebrauch und Nutzen der Statintherapie bei Patienten mit peripherer arterieller Verschlußkrankheit behandeln, auseinandersetzen, um den genauen Gebrauch und die daraus folgenden Resultate in einer Patientenkohorte ins genauere Betrachtungslicht zu rücken. **J Kardiol 2004; 11: 84–9.**

Introduction

Elevated blood cholesterol is a major risk factor for atherosclerosis. Recent studies show that lowering cholesterol reduces the risk of vascular disease, but the precise mechanisms for vascular improvement are not fully understood.

The first studies, using lipid-lowering drugs, such as the early fibrates, the acid sequestrant resins, provided, at best, equivocal results, which fuelled the arguments for inaction or procrastination among physicians. When the statins were introduced into clinical practice and, more importantly, when they were tested in randomised controlled clinical trials, these arguments disappeared. The statins were proven to provide clinical benefits in terms of reduction in all-cause mortality and coronary morbidity in a wide spectrum of patients.

With the discovery of the low-density lipoprotein (LDL) receptor by Brown and Goldstein [1], our understanding of the cholesterol economy of the cell took a major step forward. Further breakthroughs by that team and others have now given us the framework to understand in detail the effects of a drug that manipulates and changes that finely balanced economy [2].

The 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins are an important group of drugs that have such an effect. By manipulating intracellular cholesterol concentrations, we can achieve the regulation of several key proteins involved in lipid and lipoprotein metabolism [3]. All statins have structural similarities, and from these structures a mechanism of action is immediately apparent: that of competitive inhibition of HMG-CoA reductase through mimicry of this enzyme's substrate (Tab. 1).

Peripheral arterial disease (PAD) or peripheral vascular disease (PVD) is a manifestation of systemic atherosclerosis and is associated with an increased risk of cardiovascular morbidity and mortality. PAD is a major clinical problem, affecting 8 % of people 60 to 69 years old and at least 18 % of people over the age of 70 [4] and is diagnosed by decreased ankle-brachial index (ABI). A minor part of these patients with PAD report intermittent claudication (IC) [5]. It appears that proportionally to the increase of population ages, IC is an increasingly common cause of disability, particularly in elderly women [6]. Patients with PAD have about a 30 % rate of coronary artery disease [7] and a 44 % to 52 % rate of cerebrovascular disease [8]. Thus, PAD is significant, not only because of disability, but also because patients with PAD have an excess risk of myocardial infarction, stroke, and death.

Pleiotropic Effects of Statins (Tab. 2)

Data from animal models and clinical studies indicate that statin treatment can influence a spectrum of molecular and cellular mechanisms, that are intimately related to the pathogenesis of atherosclerosis. These trials include the reduction of circulating levels of atherogenic lipoproteins (very low density lipoprotein, very low density lipoprotein remnants, intermediate density lipoprotein, and low density lipoprotein) and thus of arterial lipid deposition. Further the decrease of inflammation, modulation of thrombogenesis and thrombolysis, improvement of endothelial dysfunction, and reduction of ischaemia/reperfusion injury became elucidated and confirmed on evidence bases.

The atheroprotective effects of statins appear to be proportional to the reduction in LDL cholesterol, and the odds get even better with therapy that is more prolonged. On the other hand, vascular diseases are by definition multifactorial, and the beneficial effects of statins occur earlier than what would be expected from simple plaque regression.

Statin Action on Endothelial Dysfunction

Vascular endothelial cells play a key role in modulation of leukocyte and platelet adherence, thrombogenicity, anti-

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coagulation, vessel wall contraction and relaxation, so that endothelial dysfunction maintained the investigative field for vascular disease [9]. Indeed, there is now evidence that statins improve endothelial function in a number of ways, increasing production of nitric oxide, promoting blood flow, dampening inflammation, antagonizing thrombogenicity, and reducing endothelial vasoresponses [10].

In patients with hypercholesterolaemia, endothelium-dependent vasodilator function is impaired in coronary and systemic arteries [11, 12]. The proposed mechanism for such dysfunctional vasomotion involves an enhanced inactivation and decreased production of NO by endothelial cells [13, 14]. Vasomotor dysfunction is extended to conduit and small resistance vessels and can be ameliorated after some weeks of statin treatment or immediately after LDL apheresis [15–18].

In addition, statins might influence vascular tone by modulating the expression of endothelial vasoactive factors, such as endothelin-1, or by their direct effects on calcium inflow response in vascular myocytes [19, 20]. Reendothelialization is a limiting step in the improvement of arterial function and perfusion after plaque disruption. Llevadot et al. [21] and Dimmeler et al. [22] demonstrated that inhibitors of HMG-CoA reductase also promote vasculogenesis, which is also in ischaemic limbs of normo-cholesterolaemic rabbits possible [23]. Endothelial cell progenitors have been shown to leave the bone marrow in response to cytokines or ischaemic injury, and they are recruited to the periphery to promote compensatory new blood vessel formation. In male persons, statin therapy is associated with a significant increase in the number of circulating endothelial progenitor cells (EPCs) after 1 week of treatment [24]. Thus, given the established role of circulating EPCs in endothelial repair, the differentiation and mobilization of EPCs after short-term statin treatment may contribute potentially to the rapid amelioration of endothelial function. Secondly, Akt activation has emerged as an indispensable signalling gateway at the crossroads between angiogenesis and endothelial stem cell recruitment and differentiation. Walter et al. [25] observed that statin treatment accelerates the reendothelialization of balloon injured arterial segments in rats by mechanisms related to the phosphatidylinositol 3-kinase/Akt pathway. The Akt protein kinase is a multifunctional regulator involved in cell growth, survival, and glycogen synthesis [26]. Statins rapidly induce phosphorylation of Akt at serine residue 473, which increases its protein kinase activity. In consequence of this mechanism, statins increase EPC proliferation, survival, and mobilization to sites of endothelial denudation [22, 25].

Statin-Mediated Effects on Inflammation

Statins reduce the residence time of LDL particles in the circulation and so the substrate available for generation of oxidized LDL, the prerequisite for reducing the inflammatory stimulus. A large number of trials observed that statin treatment can result in local inflammatory modification. In a rabbit model of diet-induced atherosclerosis, lipid lowering by diet or statin treatment reduced the content and activation of macrophages in atherosclerotic plaques [27–29]. In the same model, lipid lowering equally promoted the accumulation of mature smooth muscle cells and collagen in the atherosclerotic intima, thereby increasing tensile strength within the plaque [30, 31].

The inflammatory activity measured by systemic inflammatory markers decreased after statin treatment. Clinical trials involving pravastatin, cerivastatin, lovastatin, simvastatin, and atorvastatin treatments in dyslipidaemic patients have consistently demonstrated a decrement in plasma CRP levels, which is a marker of overall systemic inflammation unrelated to their effects on LDL- or HDL-cholesterol levels [32–35]. In the Cholesterol and Recurrent Events (CARE) trial, patients showed progressive reduction of CRP levels (up to 37.8 %) during the 5-year follow-up period under pravastatin treatment. This might have been an indication that the anti-inflammatory effect is progressive and maintained over a prolonged period [35]. The effect of statins on systemic inflammatory markers may result from lipid-lowering-dependent and -independent actions [36]. Arterial wall macrophages, stimulated by oxidized LDL, secrete proinflammatory cytokines, such as interleukin-6, which, in turn stimulate hepatic production of CRP and other acute-phase reactants [36].

According to this, Rezaie-Majd et al. investigated the potential effects of simvastatin decreasing proinflammatory cytokines [37]. They demonstrated in a cohort of 107 hypercholesterolaemic patients, who have been treated with either 20 or 40 mg simvastatin daily, caused a significant reduction in serum level of IL-6, IL-8 and monocyte chemoattractant protein-1. They discussed that this reduction might contribute to attenuation of the systemic inflammatory marker, CRP in patients with hypercholesterolaemia. The authors showed in the same patients cohort, that simvastatin reduced the expres-

Table 2: Effects of statins potentially contributing to protection and treatment in PAD

- Cholesterol lowering
- Amelioration of endothelial cell dysfunction by increase of endothelial NO
- Anti-inflammatory effects
  - Decrease of serum level of CRP
  - Decrease of serum level of proinflammatory cytokines
  - Decrease of membran bound and soluble adhesion molecules
- Inhibition of platelet activation and enhancement of fibrinolysis
  - Decrease of thromboxane A2, vWf, PAI-1
  - Increase of tPa
- Increase of circulating endothelial progenitor cells
  - Akt activation inducing angiogenesis

Table 1: Comparison of statins

	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Solubility	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Protein binding	> 98 %	> 99 %	> 99 %	> 95 %	50 %	90 %	98 %
Active metabolites	Yes	Yes	No	Yes	Yes	Minor	Yes
Half-life	14 h	2–3 h	0.7 h	3 h	2.8 h	19 h	2–3 h
Metabolism by cytochrome isoform	3A4	3A4 2C8	2C9	3A4	None	Limited cyp450	3A4
Renal excretion	< 5 %	30 %	6 %	10 %	60 %	10 %	13 %

sion of membrane bound adhesion molecules in the circulating peripheral mononuclear cells [38]. This reduction lowered the count of adhered mononuclear cells at the endothelial cells. Additionally, statins can reduce the inflammatory response with mechanisms related to the inhibition of mevalonate synthesis but also with mechanisms independent of HMG-CoA reductase inhibition [39–43].These mechanisms, involving lipid-lowering-dependent and -independent actions, are operating concomitantly. It is not clear whether there may be a preponderance of one these mechanisms in the statin-induced reduction in plasma CRP levels.

Statin-Mediated Modulation of Thrombogenesis

The magnitude of increased tissue or blood thrombogenicity might result from interaction between inflammatory, lipid, and genetic factors.

Statin treatment reduces platelet aggregation, possibly by reducing thromboxane A2 production and the cholesterol content of platelet membranes [44, 45]. The antithrombotic effect of statins is attenuated by concomitant treatment with aspirin, consistent with the demonstrated effect of statin treatment on thromboxane-A2 production [46, 47]. High plasma levels or activities of factor VII, factor VIII, von-Willebrand factor (vWF), soluble thrombomodulin, tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) are thought to be associated with increased morbidity and mortality related to cardiovascular disease. Experimental studies and many clinical studies have recently shown that statins produce favourable effects on haemostatic parameters, including those that are risk factors for cardiovascular disease. Statins diminish procoagulant activity, which is observed at different stages of the coagulation cascade, including tissue factor (TF) activity, conversion of prothrombin to thrombin and thrombin activity [48].

■ Common Therapeutic Strategies in PAD

Hirsch et al. [5] demonstrated that atherosclerotic risk factors are very prevalent in patients with PAD, but these patients are treated less intensively with lipid-lowering agents, antiplatelet therapy, or antihypertensives. Pharmacotherapy should be considered once risk-factor modification, platelet inhibition, and exercise therapy have been implemented. Medication plays an important role in this patient who is unable to participate in exercise rehabilitation, who has not benefited from basic therapy, and who continues to be functionally limited. Endovascular or surgical intervention is generally considered only for the patient who experiences severe, disabling, and activity-limiting symptoms despite appropriate, non-invasive therapy.

Therapy begins with risk-factor modification concentrating on those areas that promise the highest rate of return, such as smoking cessation. Patients with PAD and diabetes should be managed with aggressive blood sugar control. Current recommendations include a fasting glucose range between 80 and 120 mg/dl, a postprandial target of 180 mg/dl, and haemoglobin A1c values < 7 % [49]. The treatment of hypertension follows well-established guidelines [50]. A low-density lipoprotein cholesterol level, 100 mg/dl may be achieved through dietary control or lipid-lowering agents [51]. Mukherjee et al. [52] assessed the intensity of risk factor modification and the use of evidence-based medical therapy in consecutive patients undergoing peripheral vascular intervention and examined predictors of clinical outcomes in these patients. In this study, the authors showed significant beneficial effects of the evidence-based use of statins, antiplatelet therapy, ACE inhibitors, and β-blockers in patients undergoing peripheral vascular interventions with an improvement in clinical out-comes at 6-month follow-up. The important limitation of that study is the small sample size of 66 patients. Thus, the authors considered it as hypothesis-generating. Unfortunately, the study did not point out clearly how many of the participants received statins in their lipid lowering therapy. However, minimal data exist on the effectiveness of statins in patients undergoing vascular interventions. One meta-analysis of randomised trials described 698 patients with PAD and demonstrated a trend for reduction in mortality [53].

Nevertheless, cardiovascular risk remains prominent without aggressive treatment of hyperlipidaemia. As mentioned above, the progress of systemic atherosclerosis not only concerns patients with CAD, but also patients with PAD. So they should be supposed to share the same benefits statins might have in therapeutic use, as follows.

■ Statins and their Therapeutic Use in Patients with PAD

Three recent studies investigated the effect of statins in patients suffering from PAD and have shown that among persons with and without PAD, statin users have better performance on objective measures of leg functioning than statin nonusers (Tab. 3). McDermott et al. [54] performed a clinical study including 392 participants (men and women) with an ankle brachial index (ABI) < 0.90 and 249 with an ABI of 0.90–1.50. Functional outcomes included 6-minute walk distance and 4-meter walking velocity. A summary performance score combined performance in walking speed, standing balance,

Table 3: Cornerstones for treatment of PAD with statins

Authors	Substance	Dosage	Patients (n)	Improvement	P-value
McDermott et al. [54, 55]	All statins	Not notified	392	– Increase of six minute walk	0.045
				– Better faster walking velocity	0.006
				– Higher summary performance score	< 0.001
Mohler et al. [56]	Atorvastatin vs placebo	10 or 80 mg/d	354	– Increase of pain-free walking time	0.025
				– Improvement in ambulatory ability	0.011
Mondillo et al. [57]	Simvastatin vs placebo	40 mg/d	86	– Increase of pain free walking distance	< 0.005
				– Increase of total walking distance	< 0.001
				– Increase of ABI at rest	< 0.01
				– Increase of ABI after exercise	< 0.005

and time for 5 repeated chair rises into an ordinal score ranging from 0 to 12 (12 = best). Adjusting for age, sex, ABI, co-morbidities, education level, medical insurance status, cholesterol, and other confounders, participants taking statins had a better 6-minute walk performance (1276 vs 1218 feet; $p = 0.045$), faster walking velocity (0.93 vs 0.89 m/s; $p = 0.006$), and a higher summary performance score (10.2 vs 9.4; $p < 0.001$) than participants not taking statins. Positive associations were attenuated slightly after additional adjustment for C-reactive protein level but remained statistically significant for walking velocity and the summary performance score [54]. McDermott et al. further demonstrated that statin users have several characteristics associated with greater impairment in functioning compared with nonusers, including a higher prevalence of heart disease and stroke and a higher proportion of participants with ABI < 0.90 compared with nonusers [54]. The favourable association between statin use and functioning was also observed in participants with an ABI of 0.90–1.49. This beneficial association may relate to a favourable influence of statins on subclinical lower-extremity atherosclerosis. Previous work showed that non-PAD patients with ABI values of 0.90–1.10 have more poor functioning than patients with ABI values of 1.1–1.50, suggesting that subclinical lower extremity atherosclerosis impairs leg functioning [55]. Better functioning in the non-PAD group taking statins may additionally relate to beneficial effects of statins on inflammatory-mediated impairments in skeletal muscle function [58].

Mohler et al. [56] evaluated whether atorvastatin improves claudication symptoms in patients with PAD. Patients were treated with placebo, or atorvastatin (10 mg or 80 mg per day) for 12 months. Although maximal walking time (MWT) did not change significantly, the pain-free walking time (PFWT) improved after 12 months of treatment with atorvastatin. The change in PFWT is comparable to that achieved with other approved pharmacotherapies. The improvement in the LOPAR (LOw level Physical Activity Recall) questionnaire was consistent with the improvement in PWFT. Unfortunately, this study was not designed to evaluate vascular events, however, most peripheral vascular events occurred in the placebo group. Nevertheless, Youssef et al. [59] who investigated the early effect of atorvastatin on common femoral artery (CFA) intima media thickness (IMT) have confirmed these results. The measurements were performed using an automated radio frequency IMT technique pre-treatment and at 4 and 8 weeks post-treatment with 20 mg/day atorvastatin. Treatment with atorvastatin 20 mg/day leads to a decrease of common femoral artery (CFA)-IMT. This difference achieved significance after 8 weeks of treatment, but a trend was visible at 4 weeks.

Additionally, Mondillo et al. [57] analysed the effects of short-term therap#vascular disease. Unfortunately, it was beyond the scope of these studies to measure endothelial function and thus the effects of statins on vascular tone or plaque stabilization.

Blann et al. [60] analyzed this special part. Patients with peripheral artery disease were randomized in two parallel groups, each to receive a fixed dose of pravastatin (40 mg/day) or placebo for 4 months. This study demonstrated that pravastatin reduces von-Willebrand factor and sICAM-1. However, the greatest reduction was in levels of CRP, which decreased by an average of 45 %. This may indicate that the anti-inflammatory effects of pravastatin are more important in delaying the progression of atherosclerosis than in having any influence on the endothelium and platelets. In addition to the above mentioned trials, subgroup analyses of multinational clinical study investigated the effect of simvastatin vs placebo in patients with claudication. The risk of new or worsening intermittent claudication, bruits, and angina pectoris was reduced by simvastatin [61] and similar results have been shown by the heart protection study [62]. Both trials also showed their potential in reducing major vascular event including patients with PAD. These data suggest that non-cholesterol-lowering properties of statins may favourably influence functioning in persons with and without peripheral arterial disease. All this data together would indicate treatment of patients with peripheral arterial disease regardless their cholesterol level.

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