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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.


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 be able 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 mor-

bidity 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 increasing 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 ischemia/reperfusion injury became elucidated and confirmed on evidence bases.

The pleiotropic 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-
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 influx 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 cytokins 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>
<thead>
<tr>
<th>Statin</th>
<th>Solubility</th>
<th>Protein binding</th>
<th>Active metabolites</th>
<th>Half-life</th>
<th>Metabolism by cytochrome isoform</th>
<th>Renal excretion</th>
<th>Metabolism by CYP</th>
<th>Protein binding</th>
<th>Cytochrome isoform</th>
<th>Renal excretion</th>
<th>Protein binding</th>
<th>Cytochrome isoform</th>
<th>Renal excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Lipophilic</td>
<td>&gt; 98 %</td>
<td>Yes</td>
<td>14 h</td>
<td>3A4</td>
<td>&lt; 5 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C8</td>
<td>6 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C8</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>Hydrophilic</td>
<td>&gt; 99 %</td>
<td>Yes</td>
<td>2–3 h</td>
<td>3A4</td>
<td>30 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C9</td>
<td>6 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C9</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Hydrophilic</td>
<td>&gt; 99 %</td>
<td>No</td>
<td>0.7 h</td>
<td>3A4</td>
<td>10 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C9</td>
<td>6 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C9</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Lipophilic</td>
<td>&gt; 95 %</td>
<td>Yes</td>
<td>3 h</td>
<td>3A4</td>
<td>10 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C9</td>
<td>6 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C9</td>
</tr>
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<td>Pravastatin</td>
<td>Hydrophilic</td>
<td>50 %</td>
<td>Yes</td>
<td>2.8 h</td>
<td>3A4</td>
<td>10 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C9</td>
<td>6 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C9</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Hydrophilic</td>
<td>90 %</td>
<td>Minor</td>
<td>19 h</td>
<td>Limited cyp450</td>
<td>13 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C9</td>
<td>6 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C9</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Lipophilic</td>
<td>98 %</td>
<td>Yes</td>
<td>2–3 h</td>
<td>3A4</td>
<td>10 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C9</td>
<td>6 %</td>
<td>3A4</td>
<td>Yes</td>
<td>2C9</td>
</tr>
</tbody>
</table>
sion of membrane bound adhesion molecules in the circulating peripheral mononuclear cells [38]. This reduction lowered the count of adhered mononuclear cells to 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 of 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 activity-limiting symptoms despite appropriate, non-invasive therapy.

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 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.

<table>
<thead>
<tr>
<th>Improvement</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase of six minute walk</td>
<td>0.045</td>
</tr>
<tr>
<td>Better faster walking velocity</td>
<td>0.006</td>
</tr>
<tr>
<td>Higher summary performance score</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Increase of pain-free walking time</td>
<td>0.025</td>
</tr>
<tr>
<td>Improvement in ambulatory ability</td>
<td>0.011</td>
</tr>
<tr>
<td>Increase of pain free walking distance</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Increase of total walking distance</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Increase of ABI at rest</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Increase of ABI after exercise</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

Table 3: Cornerstones for treatment of PAD with statins

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

Statins in PAVK
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 function [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].

Møller 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 PFWT. Unfortunately, this study was not designed to evaluate vascular events, however, most peripheral vascular events occurred in the placebo group. Nevertheless, Youssf 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 tamrop#vascular disease. Unfortunately, it was beyond the scope of these studies to measure endothelial function and thus the effect of statins on vascular tone or plaque stabilization.

Blam 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 if having any influ-

ence 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 angiographic revascularization 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 events including patients with PAD. These data also 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.

References

17. Sposito AC, Mansur AP, Coelho OR, Nicolau JC, Ramirez JA. Additional reduction in blood pressure 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 events including patients with PAD. These data also 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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