Non Lipid Related Effects of Statins

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In both, primary and secondary prevention trials, statin therapy resulted in a significant reduction of cardiovascular morbidity and mortality. Statin therapy is associated with a rapid improvement of clinical outcomes, even without angiographic evidence of a substantial regression of atherosclerotic lesions. Clinical and experimental data suggest that the benefits of statins on vascular biology might extend beyond their lipid lowering effects. These so-called pleiotropic effects of statins include modulation of endothelial function, inflammation, coagulation and plaque stability. The contribution of the pleiotropic effects to the clinical outcome under statin therapy is intensively investigated, especially with respect to the role of statins in cardiovascular acute syndromes. J Clin Basic Cardiol 2002; 5: 205–8.

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Large landmark studies could clearly demonstrate that statin therapy results in a significant risk reduction of cardiovascular morbidity and mortality [1–5]. Because serum cholesterol levels are strongly associated with coronary artery disease it has been generally assumed that the significant cholesterol reduction by statins is the predominant mechanism underlying their beneficial effects. Statin therapy is associated with a rapid improvement in the clinical outcome [1, 3, 6], and meta-analyses of cholesterol-lowering trials could demonstrate that the risk of myocardial infarction in individuals treated with statins – despite a comparable reduction in cholesterol levels – is significantly lower than that in individuals treated by other cholesterol lowering agents [6, 7]. These data suggest advantages of statin therapy beyond the well-documented lipid lowering effects and thus offer an explanation for the very early benefit of statin therapy in acute cardiovascular syndromes [8]. The modulation of various biological mechanisms involved in atherogenesis have been summarised as so-called pleiotropic effects of statins.

The Mechanism of Pleiotropy

Statins serve as inhibitors of the key enzyme of cholesterol biosynthesis, the HMG-CoA reductase, resulting in a reduction of mevalonate (Fig. 1). In this way statins do not only inhibit the synthesis of cholesterol but also of isoprenoid intermediates, such as farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP). Isoprenoids serve as important lipid attachments for the posttranslational modification of a variety of proteins, including the GTP-binding protein Ras and Ras-like proteins [9]. These metabolites of the HMG-CoA reductase play an important role in the composition of transfer RNA, in glycoprotein synthesis, cell membrane function, electron transport, cellular signalling and differentiation, and thus provide the potential for many of the pleiotropic effects of statins. Statin pleiotropy can be inhibited by adding mevalonate to the experimental system, demonstrating that downstream metabolites in the cholesterol cascade regulate cellular events through isoprenylated proteins [9]. The pleiotropic effects in vascular biology include alterations of endothelial function, inflammation, smooth muscle cell proliferation, coagulation and plaque stabilization.

Endothelial Function

Endothelial dysfunction is one of the earliest manifestations of atherosclerosis. A central characteristic of endothelial dysfunction is the impaired synthesis, release and activity of endothelial-derived nitric oxide (NO) [10]. Endothelial NO plays a major role in vascular relaxation [11], endothelium-monocyte interaction [12], platelet aggregation [13] and smooth muscle cell (SMC) proliferation [14] (Fig. 2).

Statins increase NO bioavailability by the overall reduction of cholesterol, by stimulation and upregulation of endothelial NO synthase [15] and by antioxidative effects including a reduction of oxidized LDL [16, 17] (Fig. 3). The expression of the vasoconstrictor and mitogen endothelin-1 is inhibited by statins [18]. Hypercholesterolaemia is also associated with an increase in platelet reactivity arising from an increase in the cholesterol/phospholipid ratio. Further mechanisms involved in platelet hyper-reactivity are an increase in thromboxane A2 biosynthesis, platelet alpha-adrenergic receptor density, and...
platelet cytosolic calcium. Statin therapy also interacts with these regulators of platelet function and results in a reduced platelet aggregation [19, 20].

**Inflammation**

The secretion of inflammatory cytokines by macrophages and T-lymphocytes modify endothelial function, smooth muscle cell proliferation, collagen degradation and thrombosis.

Inflammatory processes are involved in endothelial dysfunction as an early sign of atherosclerosis and in the stability of the atherosclerotic plaque at an advanced stage of the disease [21]. By an inhibition of intercellular adhesion molecule-1 (ICAM-1) statins can reduce the number of inflammatory cells in the atherosclerotic plaques. ICAM-1 belongs to the immunoglobulin gene superfamily and mediates together with vascular cells adhesion molecule (VCAM-1), selectins and integrins, the adhesion of mononuclear leukocytes to the vascular endothelium.

Clinical studies could demonstrate that the levels of soluble adhesion molecules, resulting from cleavage from endothelial cells, are increased in subjects with cardiovascular risk factors, such as dyslipidaemia [22], hypertension [23] and diabetes mellitus [24]. Increased levels of sICAM seem to be associated with cardiovascular events in women [25], and are positively related to the intima-media thickness of carotid arteries [26]. Fluvastatin therapy resulted in a decrease in plasma levels of sICAM and sP-selectin in hypercholesterolaemic patients [27]. In vitro studies could demonstrate that statins inhibit monocyte chemoattractant protein-1 (MCP-1) production in peripheral blood leukocytes [28], and thus monocyte recruitment in the vessel wall. An inhibition of leukocyte function antigen-1 by statins further suppresses the overall inflammatory response [29]. Statins also bind to the beta 2 integrin function antigen-1 (LFA-1) and inhibit the stimulation of lymphocytes. These effects could explain the benefits of statin therapy on survival and rejection after heart and kidney transplantation [30].

Elevated levels of high sensitive (hs) C-reactive protein (CRP) have been shown to be predictive of an increased risk of coronary artery disease in apparently healthy men and women [25, 31]. Measuring hsCRP was therefore suggested to belong to risk factor determination. In a re-evaluation of the CARE trial patients with elevated levels of hsCRP on placebo had the highest event rates [32]. Pravastatin therapy resulted in reduced CRP levels in all subgroups of patients, but no relation between changes in CRP and LDL cholesterol could be demonstrated [32]. The Pravastatin Inflammation/CRP Evaluation (PRINCE) trial studied prospectively the effects of pravastatin on CRP levels in primary and secondary prevention [33]. Also in this study, pravastatin therapy was associated with a significant decrease in CRP levels, but the study was not aimed at a reduction of cardiovascular end points and thus offers no information about clinical benefits associated with CRP reduction.

Pravastatin, simvastatin and atorvastatin were shown to reduce plasma CRP levels to a similar extent within weeks and without correlation to the reduction in LDL-cholesterol [34].

**Smooth Muscle Cell Proliferation**

All statins, with the exception of the hydrophilic pravastatin, decrease the replication of smooth muscle cells (SMC) [35]. SMC proliferation is of clinical importance in the development of the vascular lesions in postangioplasty restenosis, in transplant atherosclerosis and venous graft occlusion. The plaque derived growth factor (PDGF)-induced DNA synthesis in vascular SMC is decreased by statins [36], and SMC proliferation is inhibited by arresting the cell cycle between the G1 phase-t-S phase transition [35]. In vitro studies suggest that SMC apoptosis may be involved in the modulation of cellularity of the arterial wall in proliferative atherosclerotic lesions, and statins were also shown to induce apoptosis in cultured vascular SMC [37].

**Plateau Stability**

Rupture of an unstable plaque is the major cause of myocardial infarction (Fig. 4), while statin therapy was shown to result in a stabilization of the atherosclerotic lesion [9, 35]. The unstable atherosclerotic plaque is characterised by a large lipid-rich core and an intensive inflammatory response in the thin fibrous cap, including macrophages and their capacity to degrade the collagen-containing fibrous cap by proteolytic enzymes. Statins reduce the size of the lipid core by their highly effective lipid lowering capacity, as well as by a reduction of intracellular lipid accumulation by inhibition of cholesterol esterification [38]. The inhibitory effects on inflammation [27–29], coagulation [39] and thrombogenicity [19, 20] contribute to a decreased risk for plaque rupture under statin therapy.

This complex influence on plaque stability and coagulation offers an explanation for the favourable early effects of statin therapy. In the MIRACL study, atorvastatin was tested in patients with unstable angina or non-Q-wave infarction and resulted within weeks in a significant reduction of non-fatal acute myocardial infarction, cardiac arrest or worsening symptomatic ischaemia with objective evidence and hospitalization [8]. Acute withdrawal of chronic statin therapy in acute cardiovascular syndromes seems to be followed by a worse outcome, which could recently be demonstrated by a re-evaluation of the PRISM study [40].
Additional Statin Effects

A reduction in the incidence of type 2 diabetes of about 30% in pravastatin treated patients compared to the placebo group was shown in a re-evaluation of the West of Scotland Study [41]. Anti-inflammatory effects of statins are discussed as one possible mechanism involved in the reduction of type 2 diabetes, also because CRP levels were predictive for the development of diabetes.

Furthermore, statins seem to increase bone density by promoting osteoblast calcification [42].

The prevalence of Alzheimer’s disease was found to be 60% lower in patients taking statins compared to other medication [43].

Despite increasing clinical data and biological mechanisms modulated by pleiotropic effects of statins it still remains controversial whether pleiotropic effects consequently result in the reduction of cardiovascular events. Pleiotropic effects are furthermore inconsistent within the statin class, especially the effects on SMC proliferation by hydrophilic and lipo-philic substances, despite an overall feasible clinical outcome in all statin trials. Therefore, until further data are available, the lipid levels define the primary target of statin therapy.

References


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