Chapter 9

Pleiotropic Effects of Statins

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1. Introduction

Atherosclerosis is a multi-factorial condition involving dyslipidemia that can result in cardiovascular disease.

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or statins are potent inhibitors of cholesterol biosynthesis, and most of the benefits of statin therapy are owing to the lowering of serum cholesterol levels. Reduction of LDL-cholesterol leads to upregulation of the LDL receptor and increased LDL clearance. Statins are the principal drugs in the primary and secondary prevention of coronary heart disease. Recent evidence also shows that more intensive lowering of LDL-cholesterol by statins is associated with greater clinical benefits. The mechanisms attributed to lipid lowering with statin therapy include atheromatous plaque stabilization, modification of the atherosclerosis progression and improved endothelial functions.

Statins reduce cardiovascular events in not only hypercholesterolemic but also normocholesterolemic patients with coronary heart disease (CHD) or cardiovascular risks.

Moreover, clinical trials and clinical benefits have shown that statins' effects involved other pharmacological activities and not only changes in lipid levels. "Pleiotropic" effects of statins involve improving endothelial function, decreasing vascular inflammation and oxidative stress, and inhibiting the thrombogenic response. Moreover, some works shows statins' beneficial extrahepatic effects on the immune system, CNS, and bone. Many of these pleiotropic effects are mediated by inhibition of isoprenoids, which serve as lipid attachments for intracellular signaling molecules. In particular, inhibition of small GTP-binding proteins, Rho, Ras, and Rac, whose proper membrane localization and function are dependent on isoprenylation, may play an important role in mediating the pleiotropic effects of statins. By inhibiting the conversion of HMG-CoA to L-mevalonic acid, statins prevent the synthesis of the important isoprenoids mentioned above, and also farnesyl pyrophosphate (FPP) and geranylgeranyl

pyrophosphate (GGPP), which are precursors of cholesterol biosynthesis. Isoprenylated proteins can modify diverse cellular functions, therefore, statins have additional effects cholesterol-independent. Indeed, recent studies suggest that statins might be involved in immunomodulation, neuroprotection, and cellular senescence.

Therefore, statins might exert cholesterol-independent or "pleiotropic" effects through direct inhibition of these small GTP-binding proteins.

2. HMG-CoA reductase inhibition

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or Statins (Figure 1) are potent inhibitors of cholesterol biosynthesis, and most of the benefits of statin therapy are owing to the lowering of serum cholesterol levels. Because 60-70% of serum cholesterol is derived from hepatic synthesis and HMG-CoA reductase is the crucial rate-limiting enzyme in the cholesterol biosynthetic pathway, inhibition of this enzyme by statins results in a dramatic reduction in circulating low-density lipoprotein (LDL)-cholesterol. Reduction of LDL-cholesterol leads to up-regulation of the LDL receptor and increased LDL clearance. Moreover, statins increases HDL levels and decreases triglyceride levels. Statins are the principal drugs in the primary and secondary prevention of coronary heart disease for more than 25 million people at risk of cardiovascular disease worldwide. The Scandinavian Simvastatin Survival Study (4S) was the first randomized controlled trial to show significant risk reduction in cardiovascular mortality in patients with coronary-artery disease. Many studies,, such as 4S, Cholesterol and Recurrent Events (CARE), Long-term Intervention with Pravastatin in Ischemia Disease (LIPID), West of Scotland Coronary Prevention Study (WOSCOPS), Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), and the Heart Protection Study (HPS), have demonstrated the beneficial effects of statins in the prevention of cardiovascular disease. These works have shown significant risk reduction in cardiovascular mortality in patients with coronary artery disease, due to reduction in cholesterol levels and, therefore, reduction in atherosclerotic lesion development. The mechanisms attributed to lipid lowering with statin therapy include atheromatous plaque stabilization, modification of the atherosclerosis progression, and improved endothelial functions. The lowering of serum cholesterol levels is therefore thought to be the primary mechanism underlying the therapeutic benefits of statin therapy in cardiovascular disease. As 60-70% of serum cholesterol is obtained from hepatic synthesis mediated by HMG-CoA reductase, inhibition of this enzyme by statins is a principal way of reducing circulating low-density lipoprotein (LDL) cholesterol [1, 5, 7, 11, 10, 13, 16, , 24, 27, 30, 36, 39].

Statins in use today are: lovastatine, simvastatine, pravastatine, fluvastatine, athorvastatine and rosuvastatine. Lovastatine, simvastatine, and pravastatine are natural compounds, obtained from the fungi *Aspergillus terreus*, and the other statins are synthetic compounds [1, 22, 30].

Another statin used in the past was cerivastatine, but it produced some fatal adverse effect of rhabdomyolysis. Therefore, this drug was discontinued in 2000 [4].

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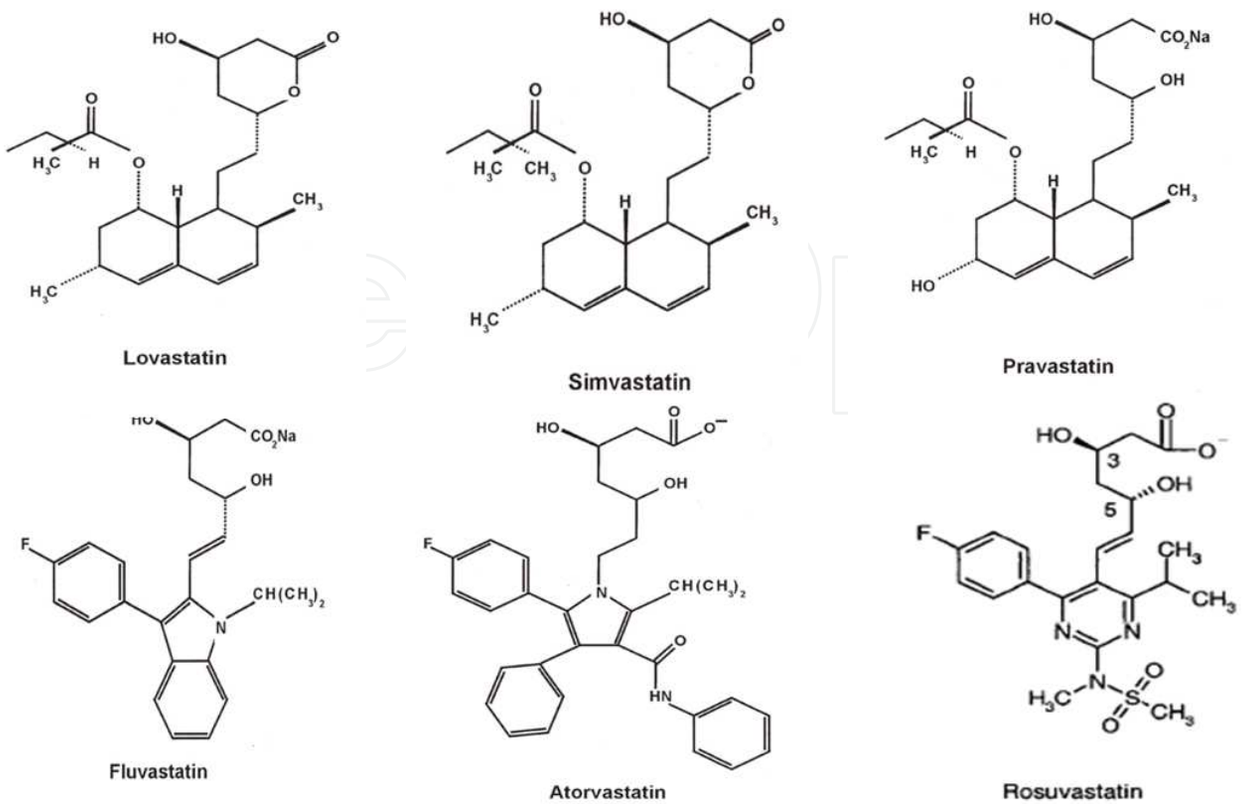

Figure 1. Chemical structure of statins [22, 30].

3. Pleiotropic effects of statins

However, the overall clinical benefits observed with statin therapy appear to be greater than what might be expected from changes in lipid profile alone, suggesting that the beneficial effects of statins may extend beyond their effects on serum cholesterol levels.

Statins reduce cardiovascular events in not only hypercholesterolemic but also normocholesterolemic patients. Because of the effects of lipid lowering on atherosclerosis, statins reduce morbidity and mortality in patients with ischemic heart failure. Statins also improve heart function and survival in patients with non-ischemic heart failure. Indeed, statins improve neurohormonal imbalance and idiopathic dilated cardiomyopathy. Thus, the improvements in heart function by statins might be owing to cholesterol-independent mechanisms [2, 5, 7, 11, 13, 19, 22, 24, 29, 30, 32].

Moreover, clinical trials and clinical benefits had shown that statins' effects involved other pharmacological activities and not only changes in lipid levels. Cholesterol-independent or "pleiotropic" effects of statins involve improving or restoring endothelial function, decreasing oxidative stress and vascular inflammation, enhancing the stability of atherosclerotic plaques, inhibiting the thrombogenic response, and lowering oxidative stress. Moreover, some works shows statins beneficial extrahepatic effects on the immune system, CNS, and bone.

Statins might exert cholesterol-independent or pleiotropic effects by inhibiting the conversion of HMG-CoA to L-mevalonic acid and, in this manner, prevent the synthesis of important isoprenoids, such as farnesylpyrophosphate (FPP), geranylgeranyl pyrophosphate (GGPP) and ubiquinone, which are precursors of cholesterol biosynthesis and of lipid attachments for intracellular signaling molecules. In particular, inhibition of small GTP-binding proteins, Rho, Ras, and Rac, whose proper membrane localization and function are dependent on isoprenylation, may play an important role in mediating the direct cellular effects of statins on the vascular wall. These isoprenylated proteins constitute approximately 2% of total cellular proteins, and isoprenylated proteins might control diverse cellular functions, as signal transduction, growth of vascular smooth muscle, apoptosis and in the regulation of the vascular activity of NAD(P) H oxidase.

Ras and Rho isoprenylation by statins, lead to increase of the amount to both compounds in the cytoplasm cells. As Rho is the more important target in the geranylgeranylation way, inhibition of Rho y de Rho-kinasa is an very important mechanism for the pleiotropic effects of statins at the vascular wall [8, 19, 25] (Figures 2 and 3).

Hypocholesterolemic effects of statins can be explained by hepatic HMG-CoA reductase inhibition, whereas the independent cholesterol effects can be found in all kinds of cells.

As isoprenylated proteins might control diverse cellular functions, we can explain that statins might have additional effects beyond lipid lowering [3, 4, 8, 17, 20, 23, 25, 37] (Li et al., 2002].

Indeed, recent studies suggest that statins might be involved in immunomodulation, neuroprotection, and cellular senescence [2, 5, 7, 11, 13, 18, 22, 24, 29, 30, 31, 32, 35].

Finally, statin therapy can be used for patients with autoimmune diseases, such as multiple sclerosis [26, 34, 35]. Furthermore, in a 6 month, randomized, double-blind placebo-controlled clinical trial, patients with rheumatoid arthritis who received atorvastatin showed a reduction in disease activity [21]. However, it is too early to predict whether these promising data can translate into clinical benefit by statins in patients with autoimmune disease.

The potential clinical implications of statin pleiotropy suggests that perhaps other biomarkers, in addition to lipid levels, should be used to gauge the full efficacy of statin therapy in patients with cardiovascular risks or that statin therapy may be effective in disease states, such as inflammatory conditions, ischemic stroke, or cancer, where elevated cholesterol levels have not been shown to be a strong epidemiological risk for these diseases [2, 5, 7, 8, 11, 12, 13, 19, 20, 22, 24, 25, 29, 30] (Vaughan et al., 2003).

Some clinical trials, such as MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering), TNT (Treating to New Targets), PROVE IT-TIMI 22, and SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), have shown that statins, when used in high doses, can reduce vascular risks better than when used in low doses. Although high doses, adverse effects are relatively low, except atorvastatin 80-mg, that is associated with higher rates of elevated hepatic transaminase, and simvastatin 80-mg with higher rates of myopathy and rhabdomyolysis. A challenge today is to discover if high-dose statin therapy provides greater benefits due to lower cholesterol levels or due to statin pleiotropic effects [2, 5, 7, 11, 13, 18, 19, 22, 24, 29, 30, 31, 35] (Vaughan et al., 2003).

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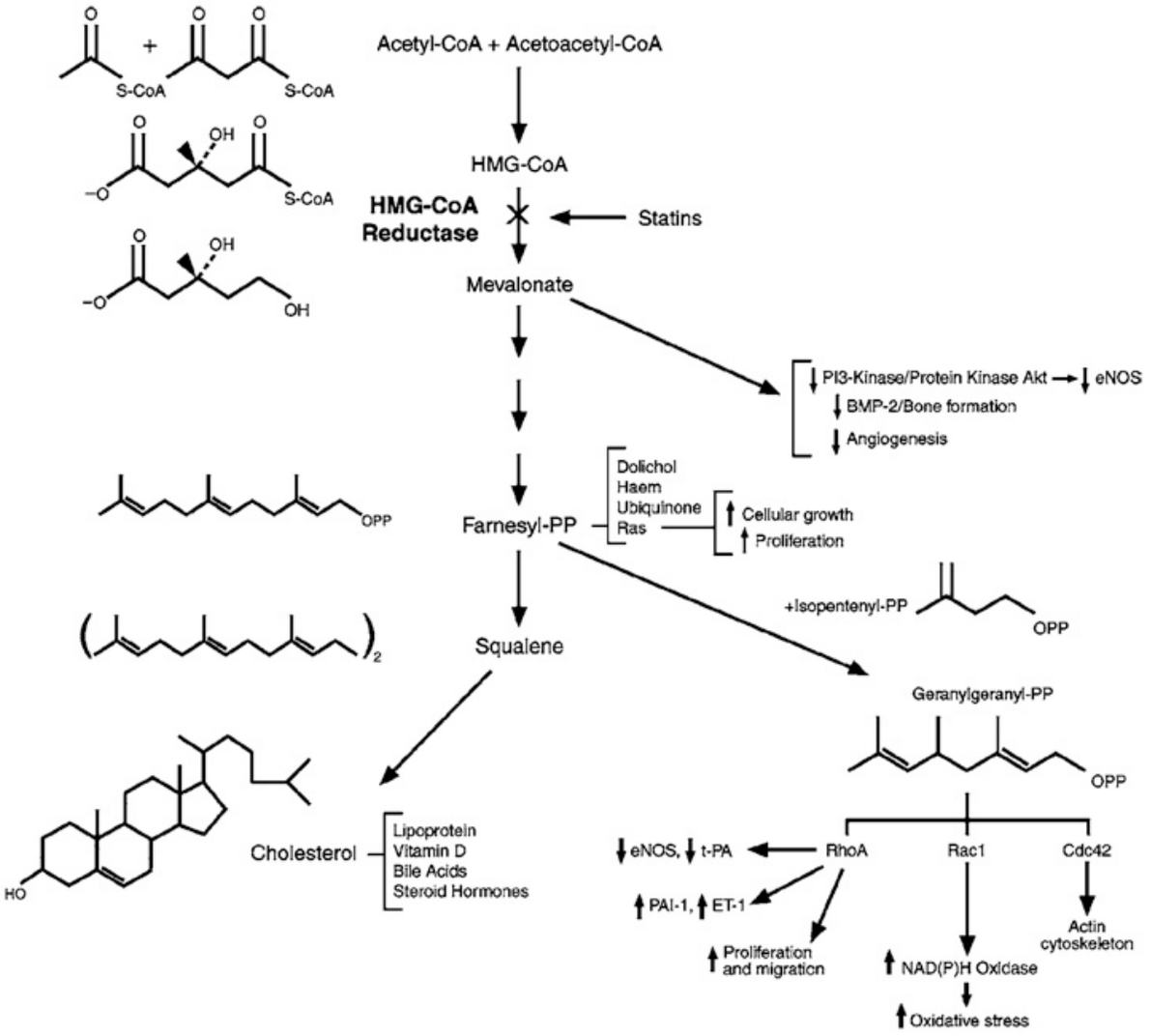

Figure 2. Biological actions of isoprenoids [19].

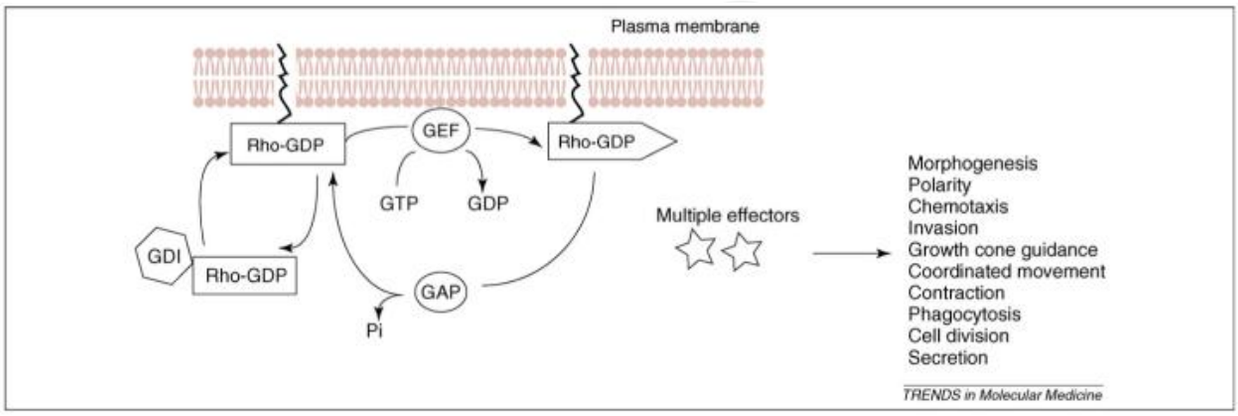

Figure 3. Regulation of the Rho GTPase cycle. Rho proteins cycle between a cytosolic, inactive GDP-bound state and a, membrane, active, GTP-bound state [35].

3.1. Improve or restore endothelial function

Hypercholesterolemia impairs endothelial function, and endothelial dysfunction is one of the earliest manifestations of atherosclerosis. When endothelial dysfunction appears, its principal sign is the impaired synthesis, release, and activity of endothelial-derived nitric oxide (NO). Endothelial NO inhibits several components of the atherogenic process, such as vascular relaxation and platelet aggregation, vascular smooth muscle proliferation, and endothelial-leukocyte interactions. [9, 15, 17, 19, 28, 38].

Statins could restore endothelial function, in part, by lowering serum cholesterol levels. Indeed, statins increase endothelial NO production by action over NO synthase (eNOS). Also, statins restore eNOS activity in hypoxia condition. Statins also inhibit the expression of endothelin-1, a potent vasoconstrictor and mitogen [6, 14].

3.2. Oxidative stress

Oxidative stress is defined as tissue injury resulting from a disturbance in theequilibrium between the production of reactive oxygen species (ROS) also known as free radicals and antioxidant defense mechanisms [3].

ROS have been implicated in many disease states, including neurodegenerative disease like Alzheimer and Parkinson disease, atherosclerosis, inflammatory conditions, certain cancers, diabetes mellitus (DM), cataract in the eye, pulmonary, renal, heart diseases, and the process of aging.

NADPH oxidase is an important signaling mediator in the signaling pathway mediated alpha-1-AR, stimulating hypertrophy in adult rat cardiac myocytes. Moreover, recently had been identified calmodulin, Ras and Raf-1 as the upstream signaling molecules in this pathway. In addition, the role of NAD (P) H oxidase in the development of cardiac hypertrophy has been demonstrated. This indicated an interesting new direction in the research of alpha-1-AR signaling mechanisms.

Polyunsaturated lipid acids (PUFAS) in plasma are susceptible to the oxidation process mediated by EROs. This leads to the transformation of the native LDL (LDLn) to oxidative LDL (oxLDL). The oxLDLs does not bind to the LDLn hosts; however oxLDLs bind to the scavenger hosts in monocytes / macrophagues, endothelium and vascular smooth muscle cells, with the consequence of the increase of these compounds and the intracellular generation of the foam cells, an important sign of early atherosclerotic damage [2, 4, 6, 8, 9, 14, 15, 17, 18, 28, 29, 33, 38].

The proliferation of vascular smooth muscle cells is a central event in the pathogenesis of vascular lesions, including post-angioplasty restenosis, transplant arteriosclerosis and veinous graft occlusion.

Statins possesses antioxidant properties by reducing lipid generation and its peroxidation and ROS production by the vascular NAD (P) H oxidase pathway, the susceptibility of lipoproteins to oxidation both in vitro and in vivo, i.e. they decrease the LDL oxidation, especially simvastatine, pravastatine, and lovastatine [4, 6, 9, 14, 15, 17, 24, 27, 28, 33, 36, 38, 39], decrease the

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pro-oxidant effects of Angiotensin II and of Endothelin-1 (peptides that stimulate vasoconstriction and increase of vascular smooth muscle cells), decreasing the NAD(P)H oxidase activity and the generation of superoxide anion as in vascular cells as in phagocytes, and increase the vascular synthesis of nitric oxide. Moreover statins inhibit vascular SMC proliferation by arresting cell cycle between the G1/S phase transition, decrease inflammatory cytokines, C-reactive protein C, and adhesion molecules, stimulate NO release, and stimulate activated hosts by PPAR, therefore decrease plasma lipid peroxidation products [4, 9, 14, 15, 17, 24, 27, 28, 33, 36, 38].

4. Statins and dementia

Recent epidemiological reports suggest that statins might be protective for Alzheimer's disease and for other types of dementia, as cerebrovascular disease. Alzheimer's disease is related to the effects of β-amyloid, and some experimental and clinical trials have shown that there is a pathophysiologic relation between β-amyloid and cholesterol levels. Statins, regardless of their brain availability, have been suggested to induce alterations in cellular cholesterol distribution in the brain. However, major studies are necessary to establish a relationship between statin therapy and Alzheimer disease [19].

5. Clinical trials relationed to pleiotropic effects of statins

HPS and ASCOT showed that the relative risk reduction by statin was independent of the treatment for lipid levels. Also, other studies suggest that the risk of myocardial infarctions in patients treated with statins is significantly lower compared to individuals with other cholesterol-lowering agents [18].

6. Conclusions

Statins reduce cardiovascular events in not only hypercholesterolemic but also normocholesterolemic patients. Moreover, clinical trials and clinical benefits have shown that statins' effects involved other pharmacological activities and not only changes in lipid levels. Cholesterol-independent or "pleiotropic" effects of statins involve improving or restoring endothelial function, decreasing oxidative stress and vascular inflammation, enhancing the stability of atherosclerotic plaques, inhibiting the thrombogenic response, and lowering oxidative stress. Moreover, some works show that statins have a beneficial extrahepatic effects on the immune system, CNS, and bone.

Statins might exert cholesterol-independent or pleiotropic effects by inhibiting the conversion of HMG-CoA to L-mevalonic acid and, in this manner, prevent the synthesis of important isoprenoids, which are precursors of cholesterol biosynthesis and of lipid attachments for

intracellular signaling molecules. Inhibition of Rho GTPases in vascular cellwalls by statins improves expression of atheroprotective genes and inhibition of vascular SMC proliferation.

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