Current advances in statin treatment: from molecular mechanisms to clinical practice

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Abstract

Statins inhibit cholesterol biosynthesis and are beneficial in the primary and secondary prevention of cardiovascular disease. In some studies, the benefits of statin therapy appear to be greater and to occur much earlier than what might be expected from changes in lipid levels alone. Indeed, statins inhibits the synthesis of isoprenoids, which are important lipid attachments for intracellular signaling molecules such as Rho, Rac, and Cdc42. Inhibition of these signaling molecules may contribute to some of the cholesterol-independent or "pleiotropic" effects of statins. These effects include improvement in endothelial function, stabilization of atherosclerotic plaques, reduction of inflammation and oxidative stress, and inhibition of thrombogenic response. Thus, the overall benefits of statin therapy in cardiovascular disease may be due to cholesterol-dependent and -independent mechanisms.

Key words: statins, cholesterol, vascular, inflammation, atherosclerosis.

Introduction

Cardiovascular disease is the principal cause of mortality in developed countries. Framingham Heart Study showed that elevated serum cholesterol is an important risk factor for cardiovascular disease [1]. Although there is a clear association between elevated cholesterol and cardiovascular risks, the development of atherosclerosis depends upon many other factors and processes such as inflammation, oxidative stress, thrombosis and dyslipidemia [2]. The beneficial effects of statins, therefore, may not be solely explained by cholesterol lowering. Indeed, statins have been shown to exert cholesterol-independent or pleiotropic effects [3]. For example, in some clinical trials the observed benefits of statins were independent of baseline LDL cholesterol [4] and analysis showed that observed benefit from statins is greater than the benefits expected from LDL lowering alone [5].

By inhibiting the conversion of HMG-CoA to L-mevalonic acid, statins block the synthesis of important isoprenoids, which are precursors of cholesterol biosynthesis, such as farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP) [6] (Figure 1). Because isoprenylated proteins constitute about 2% of total cellular proteins [7] and play multiple roles in cellular and physiological processes, it is possible that statins exert cholesterol-independent effects through inhibition of protein isoprenylation. A recent report, however, showed that statins can bind directly to

β_2-integrin leukocyte function-associated antigen-1 (LFA-1) and inhibit the LFA-1 [5] and intercellular adhesion molecule-1 interaction [5], indicating a non-HMG-CoA reductase effect of statin pleiotropy.

Statins and isoprenylated proteins

In the human genome, there are more than 100 known and hypothetical prenylated CaaX-containing proteins. Protein isoprenylation permits the covalent attachment, subcellular localization, and intracellular trafficking of membrane-associated proteins [8]. The isoprenylation enables proteins to anchor to cell membranes and exert their biological function. Members of the Ras and Rho GTPase family are the major substrates for post-translational modification by prenylation [9]. These small GTP-binding proteins are important regulators of actin cytoskeleton and intracellular signaling pathways. Indeed, statins have been report to cause alterations in the actin cytoskeleton and assembly of focal adhesion complexes by inhibiting RhoA and Rac1 isoprenylation [10].

The major target of geranylgeranylation is Rho. Thus, it is likely that some of the pleiotropic effects of statins is mediated via inhibition of the Rho pathway and its downstream target, Rho-kinase (ROCK). ROCK phosphorylates and inhibits the myosin binding subunit of MLC phosphatase. Inhibition of MLC phosphatase increases MLC phosphorylation and myosin contractility, which drive the formation of stress fibers and focal adhesions [11]. ROCK activity is often elevated in disorders of the cardiovascular system [12]. Through inhibition of the isoprenylation by statins, translocation of the Rho to the cell membrane is prevented and thereby ROCK activity is inhibited [13]. Indeed, ROCK inhibitors have been shown to prevent cerebral vasospasm after subarachnoid hemorrhage [14], decrease atherogenesis [15], and prevent arterial remodeling after vascular injury [16]. Other processes or conditions involving the RhoA/ROCK pathway include angiogenesis [17], hypertension [18], cardiac hypertrophy [19], glomerulosclerosis [20], perivasclar fibrosis [21] and pulmonary hypertension [17]. As a result, the development of ROCK inhibitors has gained considerable interest in the pharmaceutical industry as the next blockbuster drug for cardiovascular disease after statins.

In a recent study in coronary artery disease subjects, the ROCK inhibitor, fasudil, inhibited leukocyte ROCK activity and improved endothelial function [22]. These findings support the hypothesis that inhibition of ROCK may contribute to some of the vascular protective effects of statins. However, statins also inhibit other small GTPases such as Rac1 [23]. The inhibition of Rac1 by statins could also contribute to some of the pleiotropic effects of statins. Indeed, the activation of Rac1 in the vascular wall leads to increase NADPH oxidase activity and is observed in atherosclerosis, neointimal proliferation, cardiac hypertrophy and endothelial dysfunction [24].

Statins and the cardiovascular system

Statins differ in their tissue permeability and metabolism. Different statins differ in their potencies for extrahepatic HMG-CoA reductase inhibition [25]. These differences in tissue permeability and pharmacokinetics might account for the observed differences in their systemic effects and also possibly their side effects. For example, the lipophilic statins, including simvastatin and atorvastatin, would be expected to penetrate cell membranes more effectively and rapidly than the hydrophilic statins, like pravastatin and rosuvastatin. Thus, it is possible that lipophilic statin could cause more side effects as well as pleiotropic effects. However, both lipophilic and hydrophilic statins have been shown to exert pleiotropic effects [25]. Whether lipophilic statins have more pleiotropic effects than hydrophilic statins remains to be determined. Regardless, statins exert may effects on the cardiovascular system, including effects on endothelial cells, smooth muscle cells, leukocytes, and platelet (Figure 1).

Endothelial cells

In some clinical studies with statins, restoration of endothelium-dependent vasomotion occurs before significant reduction in serum cholesterol. Indeed, statins can upregulate endothelial NO synthase and restore endothelial NO synthase activity under hypoxic and hypercholesterolemic conditions [26]. Statins improve endothelial function through several mechanisms. These include cholesterol lowering, inhibition of caveolin, activation of phosphatidylinositol 3-kinase/protein kinase Akt pathway, increasing NO production, induction of tissue-type plasminogen activator expression, inhibition of endothelin-1 expression, and promoting antioxidant effects [25]. Many of these mechanisms appear to be cholesterol-independent. Indeed, a recent clinical study in patients with heart failure and endothelial dysfunction showed that four weeks of simvastatin treatment, but not ezetimide, a cholesterol absorption inhibitor, improves endothelial-dependent vasodilation and endothelial progenitor cell (EPC) numbers despite a similar reduction in LDL cholesterol [3].

Several studies have shown that statins can increase the number of endothelial progenitor cells [27, 28]. EPCs play important role in myocardial infarction, re-endothelialization, angiogenesis and atherosclerosis [29]. The mechanism underlying EPC mobilization and migration may be linked to the ability of statins to activate phosphatidylinositol 3-kinase (PI3K)/protein kinase Akt and eNOS [30, 31]. These studies are in agreement with clinical

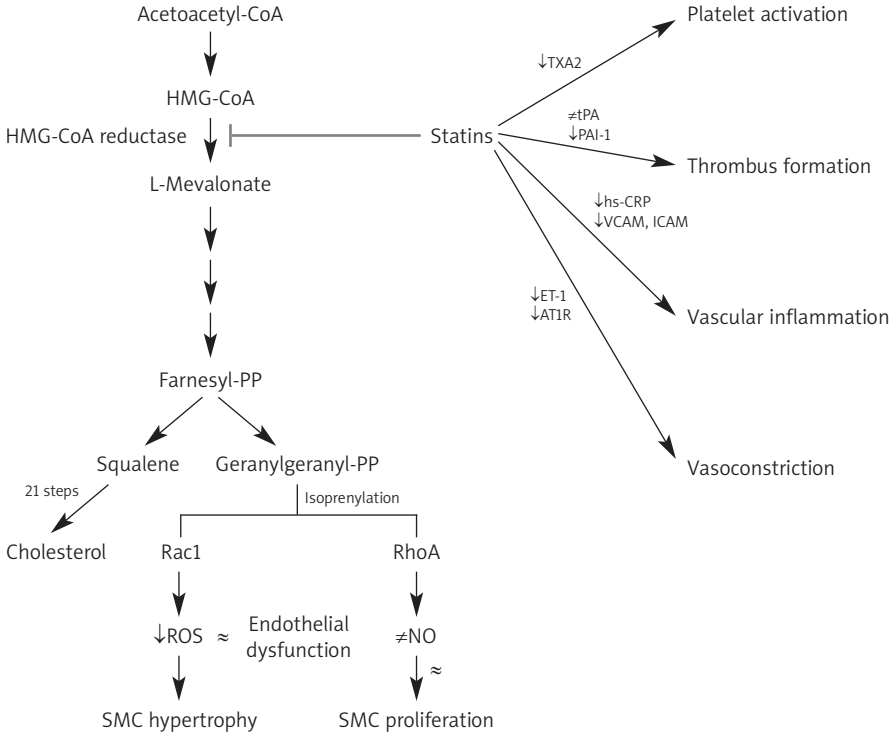

Figure 1. Pleiotropic effects of statins and mevalonate pathway: TXA2 – thromboxane A_2, tPA – tissue-type plasminogen activator, PAI-1 – plasminogen activator inhibitor-1, hs-CRP – high-sensitivity C-reactive protein, VCAM – vascular cell adhesion molecule-1, ICAM – intercellular cell adhesion molecule-1, ET1 – endothelin 1, AT1R – angiotensin 1 receptor, ROS – reactive oxygen species

observations that statins promote vascular repair after balloon injury, augment ischemia-reduced neovascularization and improve postischemic cardiac function through the effects via EPCs [32-34].

Smooth muscle cells

Statins could affect the vascular smooth muscle proliferation through inhibition of the isoprenylation of small GTP binding proteins Rho or Rac. Rho can destablize $p27^{Kip1}$ protein [35] which can increase smooth muscle cell proliferation and Rac is important in cellular oxidative stress regulation [11]. Through modification of Rho and Rac isoprenylation, statins have been shown to inhibit vascular smooth muscle proliferation by arresting the cell cycle between the G1/S phase transition. Recent studies showed that statins attenuate vascular proliferative disease, such as transplant-associated arteriosclerosis, postangioplasty restenosis and venous graft occlusion [36]. Statins can also decrease platelet-derived growth factor (PDGF)-induced DNA synthesis in vascular smooth muscle cells and PDGF-induced Rb phosphorylation and cycline-dependent kinase activity [37]. Since proliferation of vascular smooth muscle cells play important role in the pathogenesis of various vascular lesions, it is likely that inhibition of smooth muscle proliferation by statins mediates important mechanisms of its pleiotropic effects.

Platelet

Statins influence platelet function through several potential mechanisms, including upregulation of endothelial NO synthase, downregulation of thromboxane A_2 and modification of cholesterol content in platelet membranes [38]. Animal studies suggest that statins decrease CD40 ligands, inhibit platelet accumulation and reduces thrombus formation in damaged vessels [39]. In addition, platelet activation is associated with mural thrombus formation and cytokine releasing at the site of vascular injury and plaque rupture [40]. Since the role of platelets in acute coronary syndrome is critical, inhibition of platelet activation by statins could play important roles in acute coronary syndrome and thrombus formation.

Vascular inflammation

Atherosclerosis is a progressive disease and the association between atherosclerosis and lipids is irrefutable. The proliferation of smooth muscle cells and the prominent role of inflammation and immune response both contribute the pathogenesis of atherosclerosis and the development of atheroma [2]. Several lines of evidence suggest that the statins exert beneficial effects through inhibition of vascular inflammation [39, 41-43]. Statins modulate inflammatory response through multiple mechanisms, such

as regulation of inflammatory gene expression, alteration of chemokines and chemokine receptors, inhibition of adhesion molecules and leukocyte recruitement and regulation of MHC class II.

Statins exert their immunomodulatory effects through multiple proinflammatory transcription factors, such as NF-κB, signal transducer of transcription 1 (STAT-1), hypoxia-infucible factor (HIF) [43], peroxisome proliferators-activated receptors alpha (PPAR-α) [44] and kruppel-like factor 2 (KLF2) [45]. Various statins stabilize IκBα and decrease basal NF-κB DNA-binding activity [43]. Statins also increase activity of PPAR-α and suppresses NF-κB and AP-1 mediated gene activation through activation of PPAR-α [44].

Chemokines and their receptor are important in regulating leukocyte traffic. Statins can decrease monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α) and multiple chemokine receptors [46]. In addition to leukocyte traffic, statins also regulates leukocyte adhesion through inhibition of ICAM and VCAM pathway [47]. Cell adhesion molecules contribute the proinflammatory activation of endothelial cells, leukocyte migration, and vascular permeability [48].

Stroke

From the meta-analysis of non-statin trials, stroke has not been statistically associated with serum cholesterol levels [49]. However, in the CARE, LIPID and 4S trials with statins, stroke were unquestionably reduced [13]. Because LDL cholesterol is not a strong risk factor for stroke, these results support the notion that statins exert pleiotropic effects beyond LDL lowering. Statins can increase cerebral blood flow via upregulation of endothelial NO synthase. Statins attenuate P-selectin expression and leukocyte adhesion. Others also showed that statins upregulate tissue-type plasminogen activator (t-PA) and downregulate plasminogen activator inhibitor (PAI)-1 expression [50]. In humans, atherosclerosis of precerebral arteries, thromboembolism and plaque rupture contribute to cerebral infarction. The statins may also exert additional protective effects through anti-atherosclerotic and plaque stabilization effects. Second, stroke has many different causes and it is important to separate the hemorrhagic events from ischemic events. Although statins are protective in the primary and secondary prevention of ischemic stroke, some studies suggest that LDL levels <70 mg/dl is associated with higher risk for hemorrhagic stroke [51].

Aggressive lipid management

In 1998, the report of the National Cholesterol Education Program Adult Treatment Panel (NCEP) set the LDL goal for high risk patients (those with clinical cardiovascular disease, diabetes, or 10-year coronary heart risk >20%) at <100 mg/dl. In 2004, NCEP suggested an optional LDL goal <70 mg/dl for those with highest risk, including patients with cardiovascular diseases with additional high-risk factors: diabetes mellitus, multiple cardiovascular risk factors, multiple risk factors of the metabolic syndrome, or severe or poorly controlled risk factors, especially smoking [52]. To achieve aggressive LDL lowering, high doses of statins or the use of more efficacious statins need to be employed. Although higher doses of statins were reasonably well tolerated in clinical trials, they still correlate with higher rate of adverse effects leading to discontinuation. For example, the drug related adverse events in high dose statin arms were 7~10% compared to that of moderate dose arms, 4~5% [53-55]. The adverse effects mostly are due to hepatic and musculoskeletal effects. However, the rates of hepatic enzyme elevation were quite low (<1.3%) and elevations were usually reversible. In clinical practice, baseline elevation of hepatic transaminases less than 3 times of upper limits of normal values are considered not a contraindication to statin therapy. However, niacin should be avoided and liver function should be closely monitored. For the musculoskeletal adverse effects, rates of myopathy and rhabdomyolysis are quite low. In the A to Z trial with simvastatin 80 mg, rhabdomyolysis occurred at a rate of 0.13%, highest among the current trials [56].

Clinical studies, especially in high risk patients, indicate that achieving an LDL level <70 mg/dl is beneficial. It is still controversial regarding how to achieve this goal and the long-term safety issues regarding the concomitant use of other classes of lipid lowering agents remains to be determined. For example, ezetimibe appears unlikely to increase the risk of myopathy of high dose statins, although rates of abnormal hepatic enzymes are increased. Future studies are needed to clarify the optimal strategy to achieve the current aggressive LDL goals in high risk patients.

Ezetimibe

Ezetimibe is a potent and selective inhibitor of cholesterol and phytosterol absorption. It reduces the overall delivery of cholesterol from the intestine to the liver and promotes the synthesis of ApoB48 LDL receptors, with a subsequent reduction of serum LDL [57]. Specifically, ezetimibe binds to the Niemann-Pick C1-Like 1 (NPC1L1) protein on the gastrointestinal track epithelial cells [58]. Therapy with ezetimibe results in modest LDL reduction of 15-20% [59]. Its greatest value is likely being as a combination agent with statins. On average, combination therapy leads to an incremental decrease in LDL-C by 15%, and add-on therapy provides an additional 20% decrease on top of statins [60, 61]. Ezetimibe, therefore, is an

adjunctive therapy for aggressively lowering serum LDL levels. However, ezetimibe may lack some of the pleiotropic effects of statins. In heart failure patients, four weeks of simvastatin treatment but not ezetimibe improved endothelial function and reduced oxidative stress, despite comparable reduction in serum cholesterol levels [3]. Furthermore, compared to patients receiving combination therapy of ezetimibe and statin, patients receiving a higher dose of statin to achieve equal levels of cholesterol lowering, have greater improvement in endothelial function [62], and lower platelet activation and chemokine levels [63]. Thus, despite the robust LDL lowering effects with statins and ezetimibe, it is unclear whether outcome benefits would be comparable to a higher dose of statins alone. Future studies on the long-term clinical benefits of ezetimibe are needed.

In conclusions statins have many pleiotropic effects beyond cholesterol lowering. These pleiotropic effects have extensive roles in endothelial function, vascular inflammation, smooth muscle proliferation, platelet activation and atherosclerosis. These pleiotropic effects mainly work through alteration of the isoprenylation of small GTP proteins, Rac and Rho. Recent development of new cholesterol lowering agents further imply that the importance of the statins pleiotropy. It remains to be determine what is the optimal strategy to achieve the aggressive cholesterol lowering goal in the highest risk patients.

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