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Vasc Endovascular Surg 2010; 44; 241

DOI: 10.1177/1538574410362922

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Statin Therapy—Part I: The Pleiotropic Effects of Statins in Cardiovascular Disease

Vascular and Endovascular Surgery
44(4) 241-251
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DOI: 10.1177/1538574410362922
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Abstract

3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA-reductase) inhibitors, otherwise known as statins, are currently the medical treatment of choice for hypercholesterolemia. Hypercholesterolemia is a known risk factor for cardiovascular disease, and statin therapy has led to a significant reduction in morbidity and mortality from adverse cardiac events, stroke, and peripheral arterial disease. In addition to achieving a therapeutic decrease in serum cholesterol levels, statin therapy appears to promote other effects that are independent of changes in serum cholesterol. These “pleiotropic” effects include attenuation of vascular inflammation, improved endothelial cell function, stabilization of atherosclerotic plaque, decreased vascular smooth muscle cell migration and proliferation, and inhibition of platelet aggregation. This article is part I of a 2-part review, and it focuses on the pleiotropic effects of statins at the cellular level.

Keywords

statins, pleiotropic, hypercholesterolemia, cardiovascular disease

Introduction

3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA-reductase) inhibitors, commonly known as statins, inhibit the rate-limiting step of the cholesterol biosynthesis pathway.¹ They have become the cornerstone of medical treatment for hypercholesterolemia and have led to a marked reduction in morbidity and mortality from adverse cardiac events, stroke, and peripheral arterial disease.²⁻⁶ Interestingly, a wealth of both experimental and clinical evidence reveals the beneficial effects of statins extend beyond those obtained by simply lowering serum cholesterol levels.⁷⁻⁹ Statins are believed to have “pleiotropic effects,” a term used to collectively refer to the beneficial effects of statins that are independent of cholesterol levels (see Table 1).⁹ Secondary to these pleiotropic effects of statins, favorable outcomes using statin therapy have been appreciated in cardiovascular disease (CVD) as well as other disease states including cancer, sepsis, dementia, autoimmune disease, macular degeneration, osteoporosis, and inflammatory bowel disease.^{8,35-39}

With regard to treating CVD it appears that statins are more important than originally appreciated. In particular, some of the added benefits of statin treatment in CVD include attenuation of vascular inflammation, improved endothelial cell function, decreased vascular smooth muscle cell (VSMC) proliferation and migration, stabilization of atherosclerotic plaque, and inhibition of platelet aggregation.³⁹⁻⁴¹ This article is the first part of a 2-part review—part I focuses on the pleiotropic effects of

statin therapy at the cellular level, and part II addresses what is clinically known regarding the effects of statins on CVD.

Statin Structure and Pleiotropy

The water solubility of statins may determine some of their pleiotropic effects and is directly attributable to their chemical structure.⁴² Statin structure can be divided into three basic parts: an analogue of HMG-CoA, a hydrophobic ring structure that aids in binding to HMG-CoA reductase, and side groups on the rings.⁴² These side groups determine statin solubility and, as a result, many of the pharmacokinetic properties of statins.⁴² Atorvastatin, fluvastatin, lovastatin, pitavastatin, cerivastatin, and simvastatin are considered lipophilic, whereas pravastatin and rosuvastatin are considered hydrophilic as a result of polar side groups (see Table 2).^{43,44}

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Table 1. Pleiotropic Effects of Statins in Cardiovascular Disease^a

Cell Type	Pleiotropic Effect	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Platelets	Decreased activation	10		11			
	Decreased aggregation			12,13			
Endothelial cells	Increased eNOS expression/activity				14,15		14,15
	Decreased ROS			16			
	Increased endothelial progenitor cell activity/production	17-19					17,20
Vascular smooth muscle cells	Decreased proliferation						21
	Decreased migration						21
	Increased apoptosis	22	23	24	24		24
Macrophages/monocytes	Decreased proliferation		26			27	25
	Decreased MMP expression						
	Decreased oxLDL uptake				28-30		
Vascular inflammation	Decreased MHC-II expression	31			31	31	
	Decreased hs-CRP levels		32		33	34	

NOTES: eNOS = endothelial nitric oxide synthase; MMP = matrix metalloproteinase; oxLDL = oxidized low-density lipoprotein; MHC-II = major histocompatibility complex class II; hs-CRP = high-sensitivity C-reactive protein.

^a Numbers in the table correspond to references cited in this paper.

Table 2. Statin Brand Names and Basic Pharmacology

Statin	Brand Name	Lipophilicity	Daily Dosage (mg)	Half-Life (hours)
Atorvastatin	Lipitor, ^a Torvast ^a	Lipophilic	10-80	14
Cerivastatin	Lipobay, ^b Baycol ^b	Lipophilic	Withdrawn from market ^a	2-3
Fluvastatin	Lescol, ^c Lescol XL ^c	Lipophilic	20-80	2.5
Lovastatin	Mevacor, ^d Altocor, ^e Altoprev ^e	Lipophilic	20-80	1.1-1.7
Pitavastatin	Livalo, ^f Pitava ^f	Lipophilic	1-2	11
Pravastatin	Pravachol, ^g Selektine, ^g Lipostat ^g	Hydrophilic	10-40	77
Rosuvastatin	Crestor ^h	Hydrophilic	10-40	19
Simvastatin	Zocor, ^d Lipex ^d	Lipophilic	5-80	3

^a Pfizer Inc, New York, New York.

^b Bayer, Leverkusen, Germany.

^c Novartis, Basel, Switzerland.

^d Merck & Co. Inc, Whitehouse Station, New Jersey.

^e Andrx Pharmaceuticals Inc, Davie, Florida.

^f Kowa Pharmaceuticals, Tokyo, Japan.

^g Bristol-Myers Squibb, New York, New York.

^h AstraZeneca Pharmaceuticals, Wilmington, Delaware

Despite their differences in solubility, however, both lipophilic and hydrophilic statins are relatively hepatoselective.⁴² Lipophilic statins readily accumulate in hepatocytes due to facilitated passive diffusion, and the uptake of hydrophilic statins by the liver is quite extensive as well due to efficient carrier-mediated uptake.⁴⁵⁻⁴⁷ Interestingly, this carrier-mediated uptake is so efficient and specific to hepatocytes that hydrophilic statins actually have greater hepatoselectivity and less widespread tissue distribution than their lipophilic counterparts.⁴⁷⁻⁴⁹

When examining the pleiotropic effects of statins, widespread tissue distribution of the lipophilic statins may be beneficial. Corsini et al designed a series of in vitro experiments with VSMCs and demonstrated that the lipophilic statins fluvastatin, simvastatin, and lovastatin were able to decrease VSMC migration and proliferation in a dose-dependent manner; hydrophilic pravastatin, on the other hand, had no effect on VSMC migration or proliferation.⁵⁰ Further, van Vliet

et al showed in a series of in vitro experiments that simvastatin is a potent inhibitor of VSMC migration and proliferation, whereas pravastatin had little effect on either process.⁵¹

Atherosclerosis and Neointimal Hyperplasia

To better understand the pleiotropic effects of statins in CVD, it is important to understand the pathogenesis of atherosclerosis and neointimal hyperplasia. Both of these processes share common molecular and cellular pathways affected by statin administration.

Atherosclerotic Plaque Formation is a Response to Endothelial Injury

Atherosclerotic plaque formation involves a continual process of endothelial injury and dysfunction with subsequent remodeling and repair.⁵² After endothelial injury occurs, platelets are

among the first to respond by adhering to the injury site and recruiting macrophages to the area of injury.^{53,54} Macrophages phagocytize lipid-laden platelets and migrate into the intima where they take in more lipids.⁵⁴ These macrophages are commonly referred to as “foam cells,” as the large amount of lipid they ingest gives them a foamy appearance when viewed microscopically.⁵⁴ Additionally, VSMCs migrate from the media to the intima near the area of endothelial injury with many of them taking in large amounts of lipid to also become foam cells.⁵² Serum lipoproteins accumulate in the intima at these areas of injury and along with these three cell types, become part of what is termed the “fatty streak”—the earliest lesion in the formation of atherosclerotic plaque.⁵⁵

The fatty streak undergoes further remodeling to form a fibrous cap composed mainly of VSMCs and the extracellular matrix they secrete.⁵⁶ Underlying this cap is a core of necrotic cellular debris and foam cells packed with lipid.⁵⁶ Disruption of the fibrous cap initiates an inflammatory response that can lead to thrombus formation, with eventual incorporation into the complex atherosclerotic plaque itself.⁵² The end result of this process is narrowing or complete blockage of the vascular lumen with a resultant compromise in blood flow.⁵²

Neointimal Hyperplasia is a Response to Blood Vessel Wall Injury as Well

Neointimal hyperplasia is a significant cause of reconstructive failure in patients after angioplasty, stenting, and bypass procedures.⁵⁷ Both open and endovascular procedures produce blood vessel damage that triggers a physiologic response.⁵⁷ Platelets rapidly cause thrombus formation at the surface of vessel wall injury.^{57,58} An inflammatory cascade ensues, with monocytes, neutrophils, and lymphocytes migrating to the area of intimal injury.⁵⁶ Medial VSMCs migrate to this area of intimal injury as well, and over the next several months they proliferate and produce large amounts of extracellular matrix.⁵⁸⁻⁶⁰ The sum of these cellular and molecular responses leads to neointimal hyperplasia and restenosis of the instrumented blood vessel.⁶¹

Statins, THE Mevalonate Pathway, AND Small G Proteins

The pathologic processes of both atherosclerosis and neointimal hyperplasia are driven by a complex interplay of related factors, both molecular and cellular. Although statins were designed with the singular intent of decreasing serum cholesterol levels, their pleiotropic effects in CVD indicate they are able to do much more than originally intended.³⁹ A critical evaluation of the pathway where statins were originally designed to work—the mevalonate pathway—provides a starting point for understanding some of these pleiotropic effects.

HMG-CoA Reductase is Inhibited by Statins

Statins were originally designed to inhibit the rate-limiting step of the cholesterol biosynthesis pathway, otherwise known as

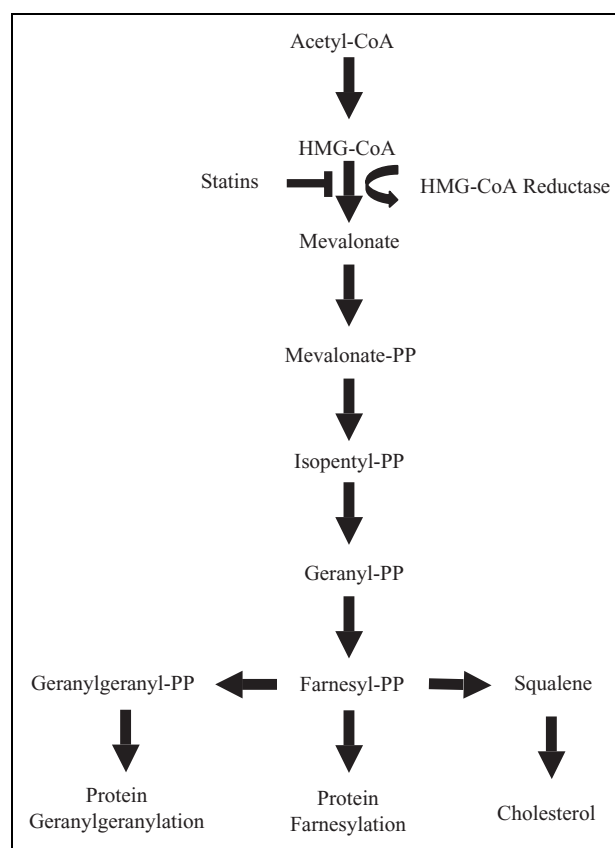


Figure 1. The mevalonate pathway. Statins are potent inhibitors of the rate-limiting step of the mevalonate pathway. They have a high affinity for HMG-CoA reductase and are able to significantly block the production of mevalonate, a necessary precursor for cholesterol synthesis. Mevalonate is the building block for a variety of other compounds as well including the isoprenoids farnesyl pyrophosphate and geranylgeranyl pyrophosphate, both of which exert important effects on vascular smooth muscle cells. PP indicates pyrophosphate. HMG-CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A.

the mevalonate pathway (Figure 1). The enzyme responsible for catalyzing this rate-limiting step is HMG Co-A reductase; it catalyzes the production of mevalonate from HMG-CoA.³⁹ As more than two thirds of the body's total cholesterol is manufactured by the body itself (mainly in the liver)⁴⁷ and not consumed, the necessity of blocking this pathway to achieve a therapeutic decrease in serum cholesterol is apparent.⁶²

Production of Isoprenoid Intermediates is Inhibited by Statins

The sole product of the mevalonate pathway is not cholesterol, however, and blocking HMG-CoA reductase has far-reaching consequences that extend beyond decreased cholesterol production.⁹ A diverse array of cellular and biologic processes are affected by the isoprenoid intermediates derived from mevalonate, and the end products formed from these intermediates carry out a variety of vital functions.^{63,64} Some of these end products and their functions include ubiquinone—involved

in electron transport, dolichol—involved in glycoprotein synthesis, and isopentenyl adenine—a component of transfer RNA.⁶³

Two isoprenoid intermediates of the mevalonate pathway that have indirect but important roles in vascular structure and function are farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). These two isoprenoids are both used to provide proteins with lipophilic attachments to the cell membrane.^{65,66} Two protein families that require these lipophilic attachments for appropriate localization within the membrane and proper functional activity are the Ras and Rho families of small G proteins.^{65,66} In particular, FPP is involved with membrane attachment and biologic activity for the Ras family of small G proteins, and GGPP performs the same function for Rho and its isoforms.^{65,66} Without modification of Ras by farnesylation and Rho by geranylgeranylation, neither protein will function properly or localize to its appropriate place within the cell membrane.^{67,68} Furthermore, both Ras and Rho are vital components of second messenger systems known to affect vascular inflammation, hypertrophy, and hyperplasia, and these second messenger systems are intimately involved in promoting vascular remodeling in disease states such as atherosclerosis and diabetes.⁶⁹

Ras

Ras has been shown to be relevant to both VSMC migration and proliferation.⁷⁰⁻⁷³ In vitro experimentation with manumycin A, an inhibitor of Ras farnesylation, demonstrated significant inhibition of migration and proliferation of rat VSMCs stimulated by platelet-derived growth factor (PDGF).⁷⁰ Further research performed with manumycin A in a murine model of atherosclerosis showed decreased activation of the Ras signaling pathway, along with a subsequent reduction in fatty streak lesion size and VSMC composition of the neointima.⁷¹ In vivo experimentation with dominant negative Ras mutants in a rat carotid injury model indicated that Ras inhibition significantly decreased VSMC proliferation at the site of injury.⁷²

Investigators working with a recombinant adenovirus expressing a Ras mutation (AdRasN17, a dominant negative mutant) have shown that VSMC proliferation and neointima formation are inhibited by this mutant in a rat carotid injury model.⁷³ This same group of investigators developed a porcine carotid injury model to test the efficacy of AdRasN17 in a circulatory system more comparable to that of humans.⁵⁹ Results showed a significant decrease in VSMC proliferation and neointima formation just as in their rat model.⁵⁹ Collectively, these studies provide evidence that inhibition of Ras activation may slow the progression of atherosclerosis and neointimal hyperplasia.

Rho

Rho GTPases affect a broad array of biologic processes including regulation of the actin cytoskeleton, cellular migration, neuronal development, morphogenesis, gene transcription

and mRNA stability, and cell division and adhesion.^{39,74,75} Rho also has a role in vascular structure and function.⁷⁵⁻⁷⁸ In particular, direct inhibition of Rho with *Clostridium botulinum* C3 transferase and inhibition of Rho geranylgeranylation by statins both inhibit VSMC proliferation and progression through the cell cycle.⁷⁶ In endothelial cells, Rho acts as a negative regulator of endothelial nitric oxide synthase (eNOS) expression and activity through a reduction in messenger RNA (mRNA) stability.^{77,78} Taken together, the effects of Rho on VSMCs and endothelial cells can be proatherogenic; blocking geranylgeranylation of Rho, therefore, should protect against the progression of both atherosclerosis and neointimal hyperplasia.

Statins, Platelets, and Lipoproteins

The many cellular and molecular components involved in the evolution of atherogenesis and neointimal hyperplasia are important to consider because statin administration affects the role of these components in plaque formation. Two such components are platelets and low-density lipoproteins (LDL).^{54,79} Platelets adhere to areas of endothelial injury and exposed collagen.⁵⁴ Platelet activation then occurs and stimulates VSMC migration and proliferation at the site of injury via secretion of various growth factors and cytokines.⁵⁴ Further, platelets promote cholesterol accumulation in arterial wall cells directly and indirectly through their effect on LDL receptor activity.⁷⁹ LDL and very-low-density lipoproteins (VLDL) have been shown to enhance platelet activation, and this enhancement is even more pronounced when the lipoproteins are derived from patients with hyperlipidemia.⁵⁴ Additionally, platelets from patients with hyperlipidemia demonstrate hyperaggregability in vitro.⁵⁴ With these relationships between platelets and LDL in mind, their interaction likely contributes to the engine that drives atherogenic plaque formation.

Statins Decrease Platelet Activation and Platelet Aggregability

Statin administration attenuates both platelet activation and platelet aggregability.¹⁰⁻¹³ Two surface glycoproteins of platelets that serve as important markers of activation are CD62 (also known as PADGEM, GMP140, or P-selectin) and CD63 (also known as Gp53).⁸⁰ On the surface of activated platelets, both of these proteins are expressed 10-fold more than on the surface of quiescent platelets.⁸⁰ Huhle et al showed through a series of experiments with platelets obtained from patients with hypercholesterolemia that both platelet surface markers were significantly decreased after treatment with fluvastatin.¹¹ In a similar series of experiments, Labios et al demonstrated that atorvastatin decreased the expression of CD62 at the platelet surface as well.¹⁰

Platelet aggregation is enhanced in patients with hypercholesterolemia, but the way by which statins attenuate platelet aggregability remains an area of debate.^{12,13,79,81,82} Some believe statins decrease platelet aggregability by way of a

direct relationship with lowering serum cholesterol, whereas others believe it is a pleiotropic effect of statin therapy.^{12,13} One early theory posited that the increased cholesterol content of platelets in hypercholesterolemic patients was the main reason for platelet aggregation.⁸³ A series of *in vitro* experiments by Shattil et al with platelets obtained from patients with normocholesterolemia provided some evidence for this theory.⁸³ Their experiments involved incubating normocholesterolemic platelets with cholesterol-rich liposomes to increase the cholesterol content of the platelets.⁸³ These platelets showed a 39.2% increase in cholesterol content, with a resultant increase in aggregability when exposed to the aggregating agents epinephrine and adenosine diphosphate.⁸³

More recent studies have shown there are other factors involved in enhancing platelet aggregability. These factors include impaired release of platelet-derived nitric oxide,¹² oxidative stress,¹² increased platelet cholesterol/phospholipid molar ratio,¹³ and binding of cholesterol-rich LDL to the platelet surface.⁸⁴ Statins are able to attenuate these factors and, as a result, decrease platelet aggregability.^{12,13} Specifically, Haramaki et al demonstrated that fluvastatin improves the intracellular redox state of platelets (an index of oxidative stress) with a resultant decrease in platelet aggregability.¹² Hussein et al demonstrated that fluvastatin administration decreased the platelet cholesterol/phospholipid molar ratio and led to a subsequent decrease in platelet aggregation.¹³ Through this same series of experiments, however, Hussein's group also showed a direct relationship between decreased platelet aggregability and binding of fluvastatin to the platelet surface.¹³ These studies suggest that statins decrease platelet aggregability in both cholesterol-dependent and cholesterol-independent manners.

Statins Attenuate LDL Promotion of Platelet Aggregation

Whatever be the mechanism of enhanced platelet aggregation in the atherogenic process, it is apparent that plasma LDL is important. Plasma LDL increases the tendency of platelets to aggregate through LDL receptors on the platelet surface,⁸⁵ thus providing some evidence that serum cholesterol levels have a direct relationship with platelet aggregability. To further test this theory, Schror et al demonstrated that platelets from patients with familial hypercholesterolemia were hyperreactive and displayed enhanced aggregation; however, treatment with simvastatin for 8 months resulted in a decrease in both the total cholesterol and serum LDL levels toward control.⁸⁶ In addition, platelet aggregation, thromboxane formation, and ATP secretion decreased to the levels of the normocholesterolemic controls.⁸⁶ Additionally, some studies have shown that statins may alter the structure of the LDL particle itself, which in turn may lead to decreased platelet aggregability.^{79,87,88}

Statins Decrease the Proatherogenic Effects of Oxidized LDL

One of the earliest events in the pathogenesis of atherosclerosis is oxidation of both the lipid and apolipoprotein B components

of LDL.⁸⁹ In its oxidized form, LDL exerts proatherogenic effects on certain cell types. For example, oxidized LDL (oxLDL) is able to promote macrophage proliferation.²⁵ Furthermore, oxLDL promotes cholesterol accumulation within macrophages, resulting in foam cell production.^{89,90} Oxidized LDL is also chemotactic for monocytes⁹¹ and T-cells,⁹² 2 of the major cellular components of the atherogenic plaque.⁹² Other research with oxLDL has shown it is cytotoxic to cultured endothelial cells,⁹³ and it also decreases eNOS activity and endothelial cell adhesion, which are vasoprotective.⁹⁴

Statins are able to combat the proatherogenic effects of oxLDL in several ways. Senokuchi et al were able to demonstrate in a series of experiments with mouse peritoneal macrophages that statins inhibit macrophage proliferation through inhibition of p38 mitogen activated protein kinase (MAPK) signaling cascades.²⁵ Statins are also able to decrease foam cell production by inhibiting the uptake of oxLDL by macrophages.²⁸⁻³⁰ Specifically, *in vitro* studies have shown that statins are able to downregulate the receptors on macrophages that permit the uptake of oxLDL.²⁸⁻³⁰ With regard to endothelial cells, statins are able to counteract the detrimental effects of oxLDL as well. Endothelial cells have a receptor known as LOX-1 that is responsible for the uptake of oxLDL.⁹⁴ Li et al were able to demonstrate that statins decreased LOX-1 expression and subsequent uptake of oxLDL in human coronary artery endothelial cells.⁹⁴

STATINS AND ENDOTHELIAL CELLS

Endothelial cells form a protective barrier between circulating blood and the rest of the blood vessel wall.^{95,96} Endothelial injury is one of the inciting events in the development of atherosclerosis and neointimal hyperplasia.^{95,97} Physiologically, endothelial cells are involved in mediating a variety of processes including vasoconstriction and vasodilation, thrombosis and fibrinolysis, angiogenesis, vascular inflammation, and production of extracellular matrix components.^{95,96}

Endothelial-Derived Nitric Oxide is Antiatherogenic

One important function of endothelial cells that helps prevent atherosclerosis is the production and release of nitric oxide (NO), a potent vasodilator, synthesized by eNOS.⁹⁸ Endothelial-derived NO inhibits the progression of atherogenesis by several different mechanisms. One such mechanism may be through inhibition of VSMC proliferation.⁹⁹ In a series of experiments with rat aortic VSMCs, Garg et al were able to show that three independent NO-generating vasodilators could inhibit VSMC proliferation.⁹⁹ Platelet aggregation, another important component in the pathogenesis of atherosclerosis, is also inhibited by NO.¹⁰⁰ Finally, monocyte adhesion to the endothelial surface is proatherogenic and is attenuated by eNOS as well.¹⁰¹

Statins Promote eNOS Production and Function

Statins are able to promote eNOS production and function in endothelial cells in several ways. In a series of experiments with vascular endothelial cells, Laufs et al demonstrated that statin treatment upregulated eNOS expression and activity through stabilization of eNOS mRNA.¹⁴ Their study also demonstrated that statins can prevent the downregulation of eNOS expression and activity by oxLDL.¹⁴ Furthermore, statins also promoted eNOS activity by attenuating hypoxia-mediated downregulation of eNOS expression.¹⁵ Statins also display an antioxidant effect that may improve endothelium-mediated relaxation, as reactive oxygen species are known to limit the bioavailability of NO.^{16,102,103}

Statins and Endothelial Progenitor Cells

In addition to augmenting mature endothelial cell function, statin administration also affects endothelial progenitor cell activity. Investigators have shown that statins promote endothelial progenitor cell proliferation, migration, and cell survival in vitro via the Akt signaling pathway, an important signaling pathway involved in cell growth and survival.^{17,20} Statins also appear to prevent endothelial progenitor cell senescence while promoting endothelial progenitor cell proliferation ex vivo;¹⁸ this alteration in endothelial progenitor cells may be due to the stabilization of telomeres by a telomere repeat-binding factor, TRF2, whose expression is upregulated by statin administration.¹⁹

Statins and VSMCs

Statins Decrease VSMC Migration and Proliferation

Vascular smooth muscle cell migration and proliferation are 2 other major components of both atherogenesis and neointimal hyperplasia, and both of these components are affected by statin administration.^{21,104} As mentioned previously, the small G proteins Ras and Rho play a large role in VSMC migration and proliferation, and statin administration is able to attenuate the effects of both small G protein families. Through a series of experiments with human saphenous vein grafts, Porter et al demonstrated that simvastatin inhibits both VSMC proliferation and migration.²¹ Jaschke et al were able to show significant inhibition of neointima formation using a cerivastatin-eluting stent in a rat carotid injury model.¹⁰⁴

Statins Promote VSMC Apoptosis

Vascular smooth muscle cell apoptosis appears to be important in the pathogenesis of both atherosclerotic disease and neointimal hyperplasia.^{24,105} Multiple studies have shown that statins promote VSMC apoptosis. Guijarro et al demonstrated that atorvastatin showed cellular changes consistent with apoptosis including cell rounding, detachment from adjacent cells, reduction in cellular DNA content, and chromatin condensation and fragmentation in cultured rat VSMCs.²² Kaneider et al reported similar findings in their studies with rat aortic VSMCs treated

with cerivastatin; specifically, they noted an increase in caspase-3 activity indicative of an increase in VSMC apoptosis.²³ Consistent with these studies, Erl et al demonstrated that cultured rat neointimal aortic VSMCs underwent increased apoptosis when exposed to simvastatin, lovastatin, or fluvastatin.²⁴

Although most investigators feel that VSMC apoptosis would be beneficial for preventing neointimal hyperplasia after revascularization,²⁴ the benefits derived from increased VSMC apoptosis are less clear-cut for atherosclerotic disease. Vascular smooth muscle cell apoptosis may halt the progression of neointimal thickening seen in early atherosclerotic lesions, or it may contribute to plaque instability by thinning out the fibrous cap.²² More studies are needed, therefore, to determine the effects of statin-induced VSMC apoptosis on the progression of atherosclerotic disease.

Statins and Vascular Inflammation

Inflammatory cells are a large part of atherosclerotic plaque. In particular, macrophages and T-cells are present in abundance, and they secrete a wide variety of cytokines and inflammatory mediators that promote endothelial dysfunction, VSMC proliferation and migration, and thrombosis.¹⁰⁶ Furthermore, some patients with atherosclerosis mount a systemic immune response to oxLDL, heat shock proteins, and *Chlamydia pneumoniae*.¹⁰⁷ These observations provide evidence that adaptive immunity may be important in the pathogenesis of atherosclerosis.¹⁰⁷

Statins Decrease the Inflammatory Response

T-cell activation is mediated by major histocompatibility complex class II (MHC-II) molecules.³¹ Some cell types, including endothelial cells and monocyte-macrophages, express MHC-II molecules after induction by interferon γ .³¹ Kwak et al were able to demonstrate that statins block the induction of MHC-II by interferon γ in both endothelial cells and monocyte-macrophages in a dose-dependent manner.³¹ This same effect was seen in human VSMCs and fibroblasts as well.³¹

Another important component of the vascular inflammatory response is the CD40-CD40L pathway.¹⁰⁸ CD40 and its ligand CD40L are members of the tumor necrosis factor family of proteins.¹⁰⁸ The interactions between CD40 and CD40L are important in a wide variety of inflammatory processes, which include leukocyte adhesion and migration, chemokine and cytokine induction, and fibroblast activation.¹⁰⁸ The importance of the CD40-CD40L pathway in atherogenesis was demonstrated by Mach et al in a series of experiments with hyperlipidemic mice.¹⁰⁹ Their protocol involved using an anti-CD40L blocking antibody, and their results showed a decrease in the size of atherosclerotic lesions as well as a decrease in the number of T-cells and macrophages within the plaques themselves.¹⁰⁹ Statins are able to attenuate the effects of this pathway, as experimentation with both human endothelial cells and monocyte-macrophages has shown that statin treatment decreases CD40 expression on both cell types.¹¹⁰

C-Reactive Protein Levels Are Decreased by Statin Administration

High-sensitivity C-reactive protein (hs-CRP) is an acute phase reactant produced by the liver that serves as a marker of inflammation.¹¹¹ It displays several proatherogenic properties including induction of plasminogen activator inhibitor expression, complement activation, increased expression of cellular adhesion molecules, and decreased eNOS expression.³⁹ Multiple studies have shown that statins are able to decrease hs-CRP levels.³²⁻³⁴ Whether a decrease in hs-CRP levels by statins confers clinical benefits separate from that of the lipid-lowering effects of statins remains unclear.

Statins and Plaque Stabilization

Atherosclerotic plaque rupture is a major cause of acute ischemic episodes in both the cardiac and peripheral vascular systems.¹¹² Rupture of the fibrous cap exposes thrombogenic components of the atheroma to the blood.¹¹² Activation of both platelets and the coagulation cascade ensues, with subsequent thrombus formation that may lead to partial or complete blood vessel occlusion.¹¹²

Statins potentially stabilize atherosclerotic plaque in a couple ways. First, accumulation of lipids in the atherosclerotic plaque causes both mechanical and biologic instability of the plaque itself.¹¹³ Lipid lowering through statin therapy should, therefore, promote mechanical stability while attenuating the oxidative stress and inflammatory response caused by biologically active lipids.¹¹³

Second, and perhaps more importantly, plaques prone to rupture contain an abundance of macrophages that express matrix metalloproteinases (MMPs) and tissue factor (TF).^{26,114} Matrix metalloproteinases are proteolytic enzymes that weaken the fibrous cap through collagen degradation,¹¹⁴ and TF is a prothrombotic molecule that causes plaque instability as well.^{26,115,116} Aikawa et al demonstrated that cerivastatin treatment decreased macrophage growth and subsequent expression of MMPs and TF both in vitro and in vivo in a hypercholesterolemic rabbit model.²⁶ Crisby et al studied the effects of pravastatin on human carotid plaque composition and reported a significant reduction in MMP-2 immunoreactivity.²⁷ Even the reduction of plasma lipid through simple dietary changes was shown to decrease MMP proteolytic activity and increase the collagen content of atherosclerotic plaque in a rabbit model of atherosclerosis.¹¹⁷

Conclusion

The pleiotropic effects of statins in CVD are secondary to a variety of processes at both the molecular and cellular levels. Some of these beneficial effects of statins include improvement in endothelial cell function, inhibition of platelet activation/aggregation, inhibition of VSMC migration and proliferation, decreased vascular inflammation, and increased stability of atherosclerotic plaques. With these pleiotropic effects in mind,

the indications for statin use may continue to expand, as the mechanisms for these effects are fully elucidated.

Acknowledgment

This work was supported by a Merit Award from the Veterans Administration.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

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