Pleiotropic Effects of Statins on the Cardiovascular System

Adam Oesterle, Ulrich Laufs, James K. Liao

Abstract: The statins have been used for 30 years to prevent coronary artery disease and stroke. Their primary mechanism of action is the lowering of serum cholesterol through inhibiting hepatic cholesterol biosynthesis thereby upregulating the hepatic low-density lipoprotein (LDL) receptors and increasing the clearance of LDL-cholesterol. Statins may exert cardiovascular protective effects that are independent of LDL-cholesterol lowering called pleiotropic effects. Because statins inhibit the production of isoprenoid intermediates in the cholesterol biosynthetic pathway, the post-translational prenylation of small GTP-binding proteins such as Rho and Rac, and their downstream effectors such as Rho kinase and nicotinamide adenine dinucleotide phosphate oxidases are also inhibited. In cell culture and animal studies, these effects alter the expression of endothelial nitric oxide synthase, the stability of atherosclerotic plaques, the production of proinflammatory cytokines and reactive oxygen species, the reactivity of platelets, and the development of cardiac hypertrophy and fibrosis. The relative contributions of statin pleiotropy to clinical outcomes, however, remain a matter of debate and are hard to quantify because the degree of isoprenoid inhibition by statins correlates to some extent with the amount of LDL-cholesterol reduction. This review examines some of the currently proposed molecular mechanisms for statin pleiotropy and discusses whether they could have any clinical relevance in cardiovascular disease. (Circ Res. 2017;120:229-243. DOI: 10.1161/CIRCRESAHA.116.308537.)

Key Words: cardiovascular diseases ■ cholesterol, LDL ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ rho-associated kinases ■ vascular diseases

Cardiovascular diseases remain the leading cause of death worldwide. The development of coronary atherosclerosis involves a complex interplay between metabolic and inflammatory processes. Mechanistic and genetic evidence shows that ApoB-containing lipoprotein, specifically low-density lipoprotein cholesterol (LDL-C), is causal for atherogenesis. Statins decrease cholesterol biosynthesis and decrease serum LDL-C and triglyceride levels. Landmark clinical trials have demonstrated the efficacy of statins for both the primary and secondary preventions of coronary heart disease. It has been proposed that statins exert both LDL-C–dependent and LDL-C–independent (or pleiotropic) effects. Clinical studies show statin benefits in diseases that are not clearly related to LDL-C (Table 1), but some of the outcomes may be because of direct cholesterol lowering. Decreased gallstone formation could be because of decreased hepatic cholesterol formation; decreased cholesterol reduces platelet aggregation and could lead to less deep vein thrombosis and decreased cholesterol could affect the progression of renal disease by decreasing renal artery atherosclerosis. The clinical significance of the pleiotropic effects of statins in the cardiovascular system remains controversial, given the overwhelming benefits of cholesterol reduction in preventing cardiovascular events.

Pharmacokinetic Properties of Statins
HMG-CoA reductase produces mevalonate and is the rate-limiting enzyme for cholesterol biosynthesis in the liver, and it is competitively and reversibly inhibited by statins through their lactone ring and side chains that help them bind to the enzyme’s active site (Figure 1). Statins were initially identified as metabolites of fungi, have been on the market since 1987, and each vary in their lipophilicity, elimination half lives, and potency (Figure 2). Inhibition of cholesterol synthesis leads to decreased cholesterol production and upregulation of the LDL receptor.

The lipophilic statins cross cell membranes largely by passive diffusion, whereas pravastatin and rosuvastatin require activated carrier-mediated transport with organic anion transporting polypeptide 1B1 and are more selective for hepatic tissues. Similar transporters exist in other tissues, such as organic anion transporting polypeptide 1A4 and organic anion transporting polypeptide 2B1 although their efficacy in transporting hydrophilic statins is unknown. The concentrations of statins and mevalonate in different cell types are incompletely understood. It is unclear whether the pleiotropic effects of statins are because of the hepatic or nonhepatic effects of isoprenoid inhibition.

It is unclear whether statins exert effects independent of mevalonate synthesis inhibition. One article reported that statins
could bind to an allosteric site within the β2 integrin leukocyte function–associated antigen-1. Leukocyte function–associated antigen-1 is involved in leukocyte trafficking and T-cell activation and binds intercellular adhesion molecule-1. Intercellular adhesion molecule-1 is crucial for the adhesion of monocytes to the endothelium, and it is a biomarker for coronary events that is reduced by atorvastatin. However, to date, no consistent mevalonate-independent effects of any statin have been reported.

**Evidence of Statin Pleiotropy in Clinical Trials**

The concept of anti-inflammatory pleiotropic effects of statins has been tested for perioperative risk reduction. Several studies provide evidence for beneficial effects of statins on atrial fibrillation and outcomes after cardiac surgery. In contrast, in a study with 1922 patients in sinus rhythm who underwent elective cardiac surgery, there was no reduction of CRP in 1 study, and statin therapy did not prevent postoperative atrial fibrillation or myocardial damage. Similarly, in a large trial among patients undergoing cardiac surgery, atorvastatin treatment did not reduce the risk of acute kidney injury. Cardiac surgery is proinflammatory and rosuvastatin reduced C-reactive protein (CRP) in 1 study, but subgroup analyses are not available from either study by CRP level. Although these clinical studies do not show benefits of statin therapy, they do not exclude whether statin pleiotropy exists, but rather that statins are not beneficial in these diseases.

Additional considerations on the pleiotropic effects of statins come from their effects on CRP. JUPITER (Rosuvastatin to Prevent Vascular Events in Men and Women With Elevated C-Reactive Protein) was the primary prevention trial between rosuvastatin and placebo for 17,802 patients with a LDL-C of <130 mg/dL and a CRP of ≥2.0 mg/L. Rosuvastatin reduced LDL-C by 50%, CRP by 37%, and the primary end point by 44%. Plotting the expected benefit from JUPITER based on LDL-C lowering on the Cholesterol Treatment Trials’ Collaboration regression line suggests that the realized benefit may be greater than the expected benefit based on LDL-C reduction alone (Figure 3). In contrast, the recent HOPE-3 study (Cholesterol Lowering in Intermediate-Risk Persons Without Cardiovascular Disease) was a primary prevention trial with rosuvastatin 10 mg that did not have LDL-C or CRP as inclusion criteria and rosuvastatin reduced LDL-C by 26.5% and the coprimary outcomes by 24% and 25%. The benefit of rosuvastatin occurred in both high and normal CRP groups, and whereas rosuvastatin did lower CRP, the HOPE-3 study suggests that the benefit of statins may be primarily because of LDL-C lowering. In the A-Z trial (Early Intensive vs a Delayed Conservative Simvastatin Strategy in Patients With Acute Coronary Syndromes Phase Z of the A to Z Trial), patients with acute coronary syndrome received either simvastatin 40 mg for 1 month followed by titration to 80 mg versus placebo for 4 months and then simvastatin 20 mg. High-dose simvastatin lowered LDL-C more effectively, but there was no difference in CRP levels at 30 days and the trial did not achieve its prespecified end point. From month 4 onward, there was a reduction of CRP in the high-intensity simvastatin group, and the trend to benefit was stronger after 4 months than earlier. Both groups had relatively low CRP (2.5 versus 2.4 mg/L) at 1 month, which may explain the lack of effect. The MIRACL trial (Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering) was an acute coronary syndrome trial comparing atorvastatin 80 mg with placebo, and atorvastatin lowered the primary end point in patients with both high and normal LDL-C and lowered CRP by 83%. Although these data on CRP suggest that statins reduce inflammation, there are no data showing the change in CRP correlates with efficacy and it is unclear whether the benefit seen with CRP reduction on medication is because of statin therapy or a lower baseline CRP, indicating a lower risk cohort.

It is difficult to separate the LDL-C–lowering benefit of statins from their potential pleiotropic effects in clinical trials, given the strong association between elevated cholesterol and coronary heart disease. Lowering ApoB-containing lipoproteins, therefore, represents the most important mechanism of statins. Nevertheless, there is cumulative evidence for the existence of pleiotropic effects in humans, but the contribution in addition to LDL-C lowering remains unknown for 2 reasons:

1. Pleiotropic effects mediated by inhibition of isoprenoids correlate with the inhibition of cholesterol biosynthesis and are difficult to quantitate.

### Table 1. Effect of Statins on Low-Density Lipoprotein–Cholesterol–Independent Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Effect of Statins</th>
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<tbody>
<tr>
<td>Kidney disease</td>
<td>↓ Creatinine with normal and abnormal renal function19,20</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>↓ Incidence22</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>↓ Incidence21</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>↓ Whole brain atrophy23</td>
</tr>
<tr>
<td>Bone strength</td>
<td>↓ Hip fracture in postmenopausal women24</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>↓ Cholecystectomy for gallstones25</td>
</tr>
<tr>
<td></td>
<td>↓ Pancreatitis with normal triglycerides26</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>↑ Function in sildenafil nonresponders27</td>
</tr>
<tr>
<td>Periodontal disease</td>
<td>↓ Periodontal inflammation28</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>↓ Inflammatory markers and improved disease activity score29</td>
</tr>
</tbody>
</table>

### Nonstandard abbreviations and Acronyms

- **CRP**: C-reactive protein
- **EC**: endothelial cells
- **eNOS**: endothelial nitric oxide synthase
- **FPP**: farnesylpyrophosphate
- **GGPP**: geranylgeranylpyrophosphate
- **IL**: interleukins
- **LDL-C**: low-density lipoprotein cholesterol
- **LVH**: left ventricular hypertrophy
- **NADPH**: nicotinamide adenine dinucleotide phosphate
- **NO**: nitric oxide
- **PCSK9**: proprotein convertase subtilisin kexin 9 inhibitors
- **PPAR**: peroxisome proliferator–activated receptor
- **ROCK**: Rho kinase
- **ROS**: reactive oxygen species
- **SMC**: smooth muscle cells

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2. Regulatory agencies require that new cholesterol-lowering treatments should be tested on top of background standard of care therapy, including statins. This does not allow quantitating potential cholesterol-independent effects of statins because potential pleiotropic statin effects are present in both treatment arms.

Nonstatin LDL-C–lowering therapies could reduce the risk of coronary heart disease, thus confirming the cholesterol hypothesis. A recent meta-analysis suggests that nonstatin therapies that increase the LDL receptor have the same benefits as statins and fall on the Cholesterol Treatment Trialists regression line.55,56 Nonstatin trials often take longer to show a benefit than statin trials. In the LRC-CPPT (Lipid Research Clinic-Coronary Primary Prevention Trial) with cholestyramine, the Program on the Surgical Control of Hyperlipidemias with partial ileal loop bypass surgery, and the IMPROVE-IT trial (Ezetimibe Added to Statin Therapy After Acute Coronary Syndromes) with ezetimibe in addition to simvastatin, benefits occurred after 7.4, 9.7, and 7.0 years, respectively, whereas most of the statin trials showed benefits within 5 years (Table 2).56–58 Interpreting the time to benefit data are difficult because the low event rates early in the trials prevent the separation of survival curves, and both LRC-CPPT and Program on the Surgical Control of Hyperlipidemias were primary prevention trials with lower event rates but many of the statin trials are secondary prevention trials and the IMPROVE-IT trial was conducted until a prespecified total event number was reached. Guidelines have generally recommended lifestyle changes and statins as the first-line pharmacotherapy, with or
without LDL-C targets. At present, nonstatins are indicated only as adjunctive therapy for patients who are unable to reach their lipid goals despite optimal statin therapy.

Studies using clamped cholesterol designs, eg, comparing the effect of statin-mediated LDL-C lowering with equal LDL-C lowering mediated by another intervention (eg, diet) have reported pleiotropic effects of statins in animals including cynomolgus monkeys. Nonstatins such as the inhibitor of Niemann–Pick C1–like protein, ezetimibe, have been used in humans for this purpose. Ezetimibe lowers LDL-C by 15% to 20% and can only be compared with less potent statins, which makes vascular effects more difficult to observe. Ezetimibe reduces cholesterol absorption in the small intestine, and animal data suggest an increase in the LDL-C receptor, but human data are inconsistent. Nevertheless, multiple small studies have attempted to determine whether statins have pleiotropic effects compared with ezetimibe. These studies are characterized by surrogate end points. For example, a randomized study of patients with heart failure with simvastatin 10 mg or ezetimibe 10 mg found a 15% reduction in LDL-C for both groups, but only simvastatin improved radial artery flow-dependent vasodilation, increased functionally active endothelial progenitor cells, and increased superoxide dismutase. Several studies randomized healthy volunteers or patients with coronary heart disease to protocols comparing high-dose statins to a combination of lower dose statins and ezetimibe and reported greater improvement in endothelial function and vascular inflammation with high-dose statins, despite comparable lowering of LDL-C in both groups. Other studies did not find differences between groups, suggesting the absence of statin pleiotropy. Additional evidence for pleiotropy stems from studies that report effects of statins that were observed before serum LDL-C was lowered. All of these studies were relatively small, were performed in heterogeneous patient populations with different outcome measures and duration of therapy, and showed conflicting results. These studies provide interesting data, but do not provide definitive clinical evidence of statin pleiotropy.

The notion of whether statin pleiotropy has clinical relevance in terms of cardiovascular risk reduction may benefit from ongoing trials with the proprotein convertase subtilisin kexin 9 inhibitors (PCSK9) that lower LDL-C levels by ≈60% alone and could be compared with a high-dose statin in terms of equivalency in LDL-C reduction. High-dose...
statin therapy has demonstrated impressive benefits on plaque reduction that has been postulated to be because of their anti-inflammatory effects in addition to their intensive LDL-C–lowering effects.73,74 The GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound; NCT01813422) results have been recently announced and will be published later this year and demonstrate that the PCSK9i reduce plaque size on top of optimal statin therapy, demonstrating that plaque regression may not be primarily because of pleiotropic effects of statins. The large FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Antibody as Measured by Intravascular Ultrasound; NCT01813422) results have been recently announced and will be published later this year and demonstrate that the PCSK9i reduce plaque size on top of optimal statin therapy, demonstrating that plaque regression may not be primarily because of pleiotropic effects of statins. The large FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Antibody as Measured by Intravascular Ultrasound; NCT01813422) results have been recently announced and will be published later this year and demonstrate that the PCSK9i reduce plaque size on top of optimal statin therapy, demonstrating that plaque regression may not be primarily because of pleiotropic effects of statins. The large FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Antibody as Measured by Intravascular Ultrasound; NCT01813422) results have been recently announced and will be published later this year and demonstrate that the PCSK9i reduce plaque size on top of optimal statin therapy, demonstrating that plaque regression may not be primarily because of pleiotropic effects of statins. The large FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Antibody as Measured by Intravascular Ultrasound; NCT01813422) results have been recently announced and will be published later this year and demonstrate that the PCSK9i reduce plaque size on top of optimal statin therapy, demonstrating that plaque regression may not be primarily because of pleiotropic effects of statins. The large FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Antibody as Measured by Intravascular Ultrasound; NCT01813422) results have been recently announced and will be published later this year and demonstrate that the PCSK9i reduce plaque size on top of optimal statin therapy, demonstrating that plaque regression may not be primarily because of pleiotropic effects of statins. The large FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Antibody as Measured by Intravascular Ultrasound; NCT01813422) results have been recently announced and will be published later this year and demonstrate that the PCSK9i reduce plaque size on top of optimal statin therapy, demonstrating that plaque regression may not be primarily because of pleiotropic effects of statins.
modification of heterotrimeric G proteins, including Ras and Rho.77 Ras and Rho regulate cell proliferation, differentiation, apoptosis, and the cytoskeleton.78 In endothelial cells (ECs), Ras translocation is dependent on farnesylation, whereas Rho translocation is dependent on geranylgeranylation.79,80 Although the inhibition of isoprenoid intermediate synthesis is central to the possible pleiotropic effects of statins, it is unclear whether the primary LDL-C–lowering benefit of statins is because of reduced cholesterol production and reduced mevalonic acid production or upregulation of the LDL receptor.81 There is a relative paucity of human studies on the levels of FPP and GGPP with chronic statin therapy.

**Statins and Rho/Rho Kinase**

Rho kinases (ROCKs) are protein serine/threonine kinases of 160 kDa that contribute to the downstream effects of Rho GTPases.82 ROCK shifts to an active open conformation when RhoA binds to ROCK (Figure 4).82 ROCKs regulate actin cytoskeletal changes through effects on myosin light chain phosphorylation. This affects focal adhesion complex formation, smooth muscle contraction, cell migration, and gene expression.83

In human aortic ECs, simvastatin prevented tissue factor induction by thrombin in a Rho/ROCK-dependent manner.84 In animal models, inhibition of ROCK has cardiovascular effects similar to statins, the ROCK inhibitors (fasudil and Y27632), limit cardiac fibrosis, hypertrophy, and pathological remodeling in response to angiotensin II and Nω-nitro-arginine methyl ester, transfuse aortic constriction, and myocardial infarction.85–88 Increased leukocyte ROCK activity is observed in patients with hypertension, pulmonary hypertension, metabolic syndrome, dyslipidemia, coronary artery disease, coronary vasospasm, left ventricular hypertrophy (LVH), and in heart failure with decreased systolic function.89–99 Statins reduce ROCK activity (Table 3).100–107 Statins have demonstrated the inhibition of leukocyte ROCK activity in humans independent of LDL reduction.108 ROCK inhibition is a candidate for
mediating statin pleiotropy because of ROCK’s effects on the cardiovascular system, ROCK activity is a biomarker of cardiovascular disease, and ROCK inhibition by statins occurs through cholesterol-independent mechanisms.

**Statins and Rac**

Rac is a 20- to 39-kDa monomeric G protein and a member of the Rho GTPase subfamily. Rac modulates phosphorylation of intercellular proteins occludin, vascular endothelial cadherin, and β-catenin, which are critical for tight junction and adherence junction integrity. Rac1 activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and produces reactive oxygen species (ROS) leading to LVH. ROS could also modify LDL to oxidized LDL, which is atherogenic and mediates foam cell formation. Elevated Rac1 and NADPH oxidase activity is seen in rats undergoing transverse aortic constriction, vascular smooth muscle cells (SMC) stimulated by angiotensin II, in saphenous vein grafts and internal mammary artery after coronary artery bypass, in ischemic and nonischemic cardiomyopathy, and atrial fibrillation and is attenuated by statins. The inhibition of Rac1 links statins to reduced ROS and NADPH oxidase activity and may explain some of the pleiotropic actions of statins.

**Statins and the Peroxisome Proliferator–Activated Receptor**

Statins have been shown to activate peroxisome proliferator–activated receptors (PPARs). Statins acutely decrease lipopolysaccharide-related inflammation in wild-type mice but not in PPARα-null mice, independent of cholesterol-lowering mechanisms. Statins increase PPAR-γ activity and inhibit lipopolysaccharide-induced tumor necrosis factor-α and monocytic chemotactic protein-1 activity. The administration of simvastatin in combination with PPAR-γ agonists elicits additive beneficial vascular effects. Atorvastatin reduces advanced glycation end products in rats and attenuates fibroblast proliferation and cardiac fibrosis, which was reversed with the PPAR-γ antagonist GW9662. Statins reduced ROS production by augmenting the mRNA expression of the PPAR-γ coactivator, which is an important regulator of mitochondrial biogenesis. However, statins, especially the high-intensity statins, increase the risk of diabetes mellitus. Thus, the ability of the PPAR-γ agonists, thiazolidinediones, to lower blood sugar is in contrast to the effects of statins on PPAR-γ and demonstrates the complex nature of statin interactions with other pathways, including glucose metabolism.

**Cellular Effects of Statins**

**Statins and the Endothelium**

Endothelial dysfunction is caused by hypercholesterolemia and is characterized by impaired bioavailability of endothelial-derived nitric oxide (NO). Endothelial NO is important for vasodilation, platelet aggregation, vascular smooth muscle proliferation, and endothelial–leukocyte interactions. Statins increase endothelial NO production, in part, by up-regulating endothelial NO synthase (eNOS), which may be a pleiotropic effect of statins (Table 4). Although the increase in eNOS is important, it should be noted that much of the animal studies examining eNOS and other cellular targets...
Table 4. Pleiotropic Effects of Statins by Cell Type

<table>
<thead>
<tr>
<th>Endothelial cells</th>
<th>↑ eNOS expression and activity&lt;sup&gt;79,80&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Plasminogen activator inhibitor-1 expression, and ↑ Tissue-type plasminogen activator expression&lt;sup&gt;104&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ Endothelin-1 synthesis and expression&lt;sup&gt;102&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ ROS&lt;sup&gt;117&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↑ Peroxisome proliferator–activated receptor-α and γ expression&lt;sup&gt;118–121&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ Proinflammatory cytokines (IL-1β, IL-6, and cyclooxygenase-2) expression&lt;sup&gt;37,167&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ CD40 expression&lt;sup&gt;103&lt;/sup&gt;</td>
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</tbody>
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<thead>
<tr>
<th>Vascular smooth muscle cells</th>
<th>↓ Migration and proliferation&lt;sup&gt;142,144&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ ROS&lt;sup&gt;115,174,178&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ NADPH oxidase activity&lt;sup&gt;111,115,116&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ AT&lt;sub&gt;1&lt;/sub&gt; receptor expression&lt;sup&gt;113&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ Platelet-derived growth factor&lt;sup&gt;141&lt;/sup&gt;</td>
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<tr>
<th>Myocardium</th>
<th>↓ NADPH oxidase activity&lt;sup&gt;114,151&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>↓ ROS&lt;sup&gt;112&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ Left ventricular fibrosis and hypertrophy&lt;sup&gt;141,149&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↑ Nitric oxide&lt;sup&gt;103,116&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>↑ Apoptosis&lt;sup&gt;102&lt;/sup&gt;</td>
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<table>
<thead>
<tr>
<th>Platelets</th>
<th>↓ Platelet reactivity&lt;sup&gt;83,106&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>↓ Thromboxane A&lt;sub&gt;2&lt;/sub&gt; biosynthesis&lt;sup&gt;107&lt;/sup&gt;</td>
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<table>
<thead>
<tr>
<th>Monocyte/macrophages</th>
<th>↓ Macrophage growth&lt;sup&gt;111&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>↓ MMP expression and secretion&lt;sup&gt;113,172&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ Tissue factor expression and activity&lt;sup&gt;114&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ Proinflammatory cytokines (IL-1β, IL-6, IL-8, and TNF–α) expression&lt;sup&gt;36,110&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ Monocyte chemotactant protein–1 secretion&lt;sup&gt;103,111,114&lt;/sup&gt;</td>
<td></td>
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<table>
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<tr>
<th>Vascular inflammation</th>
<th>↓ CRP level&lt;sup&gt;12,32&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Leukocyte-endothelial cell adhesion&lt;sup&gt;41,42,164,178,179&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ T-cell activation&lt;sup&gt;144,168,173,174&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>↓ Nuclear factor–κB activation&lt;sup&gt;141,169&lt;/sup&gt;</td>
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| Endothelial progenitor cells                            | ↑ Mobilization of stem cells<sup>126</sup>    |

AT<sub>1</sub>, indicates angiotensin type 1; CD, cluster of differentiation; CRP, C-reactive protein; eNOS, endothelial nitric oxide; LDL, interleukin; MMP, matrix metalloproteinase; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; and TNF, tumor necrosis factor.

used significantly higher doses of statins than are used in clinical practice.

Statins upregulate eNOS through multiple mechanisms. One pathway involves Rho/ROCK signaling. In vitro studies show that Rho inhibition increases eNOS expression. Increased ROCK activity downregulates eNOS, and ROCK inhibitors (Y-27632 and fasudil) increase eNOS expression. The effects of statins on eNOS expression are not reversed by FPP or LDL-C, indicating that the effect is likely mediated through the geranylgeranylation of RhoA and ROCK signaling.

Statins also increase eNOS activity by post-translational activation of the phosphatidylinositol 3-kinase/protein kinase Akt pathway as eNOS is phosphorylated by Akt. Inhibition of the Rho/ROCK pathway activates the PI3k/Akt pathway and cardioprotection. ROCK is a negative regulator of the Akt pathway, possibly through the activation of phosphatase and tensin homologue.

Statins also act on caveolin 1, which is an integral membrane protein that binds to eNOS in caveolae and directly inhibits NO production. Statins decrease caveolin-1 expression in vitro and in mice, thereby promoting eNOS activity.

Statins could also exert pleiotropic effects through the transcription factor kruppel-like factor-2. Statins induce kruppel-like factor-2 mRNA in ECs, which may be required for eNOS expression. Statins reduce T proliferation through kruppel-like factor-2, which may explain some of their immunomodulatory effects.

Statins may exert pleiotropic effects by enhancing the mobilization of endothelial progenitor cells. Impaired endothelial progenitor cells are associated with impaired endothelial function and decreased NO levels. Atorvastatin increases endothelial progenitor cells in patients with coronary artery disease within 1 week. This effect is apparently observed only at low statin concentrations; higher concentrations of statins tend to have angiostatic effects, which may explain why high-intensity statins are able to reduce intraplaque angiogenesis in patients with atherosclerosis.

Statins and Vascular Smooth Muscle

The proliferation of vascular SMCs is important in vascular lesion pathogenesis. Transplant arteriosclerosis is an immune response directed against donor ECs and vascular SMCs independent of hypercholesteremia that is still attenuated by statins. Inhibition of isoprenoid synthesis by statins decreases platelet-derived growth factor–induced DNA synthesis in vascular SMCs by increasing the cyclin-dependent kinase, p27<sup>Kip1</sup>, which was possibly mediated by Rho GTPase. Simvastatin decreases intimal thickening and reduces cellular proliferation, leukocyte accumulation, and platelet-derived growth factor receptor phosphorylation in LDL receptor–deficient mice. In vitro, atorvastatin reduces the effects of the proinflammatory cytokine IL-18, which inhibits SMC migration, nuclear factor–κB activation, and matrix metalloproteinase-9 expression. In bovine pulmonary artery SMCs, atorvastatin inhibits the migration of pulmonary artery SMC, which was reversed by GGPP and mevalonate, again implicating the potential for the Rho/ROCK pathway in SMC proliferation.

Statins and the Myocardium

The GTP-binding proteins, Ras, Rho, and Rac play a critical role in cardiac hypertrophy. Mice without Rac1 showed decreased NADPH oxidase activity and myocardial oxidative stress, confirming that Rac1 is essential for myocardial hypertrophy. Rac1 also increases the activity of the mineralocorticoid receptor. In vitro, statins increase small GTP-binding
protein GDP dissociation stimulator and decrease Rac1 in a
lipid-independent fashion.145 Statins decrease Rac1 levels, car-
diomyocyte hypertrophy, and fibrosis in wild-type mice, but
not in mice that lack small GTP-binding protein GDP disso-
ciation stimulator.149 Rac1 contributes to doxorubicin-related
cardiotoxicity through both an ROS-dependent and ROS-
independent mechanism.150 Finally, preoperative atorvastatin
induced Rac1-mediated inhibition of NADPH in human atrial
myocardium.151

The effect of statins on the myocardium is also mediated
through RhoA and ROCK because both lead to increased apo-
tosis and increased fibrosis, which could lead to the develop-
ment of LVH and heart failure. Overexpression of RhoA in rat
ventricular myocytes induces increased caspase-9 activation,
DNA fragmentation, and apoptosis, which are blocked by
ROCK inhibitors.152 Mice with a genetic deletion of ROCK1
had less ischemic reperfusion-related fibrosis compared with
wild-type mice.153 Mice without ROCK2 demonstrated less
LVH, fibrosis, and apoptosis when exposed to angiotensin
II or transverse aortic constriction compared with wild-type
mice.154 In humans, leukocyte ROCK levels are 4.5x higher
in patients with LVH and hypertension than in those with
hypertension without LVH and ROCK activity also is increased
with LVH in chronic kidney disease.95,96 Statins increase NO
bioavailability, which increases myocardial blood flow under
hypoxic conditions and inhibits IL-6, IL-8, and vascular cell
adhesion molecule-1.155,157 In vitro studies show that statins
reduce mitochondrial dysfunction and cardiomyocyte death.158

There is, however, conflicting data about whether statins
improve outcomes in nonischemic cardiomyopathy. A co-
hort study demonstrated decreased mortality and a small
randomized controlled trial showed improvement in ejection
fraction, symptoms, and lower levels of proinflammatory
cytokines.159,160 However, both the large randomized GISSI-
HF (Effect of Rosuvastatin in Patients With Chronic Heart
Failure) and CORONA (Rosuvastatin in Older Patients With
Systolic Heart Failure) trials did not show any benefit for ei-
ther death or the composite end point.161,162 Although there are
questions about the efficacy of statins for heart failure, it is
possible that statin therapy is beneficial if started earlier in the
disease course.

**Statins and Platelets**

Platelets are essential in the pathogenesis of acute coronary
syndrome. Hypercholesterolemia is associated with increased
platelet reactivity and thrombin generation, which is de-
creased with pravastatin and is likely both cholesterol associ-
ated and LDL-C independent.163 Mice treated with atorvastatin
showed increased eNOS and downregulated platelet factor 4
and β-thromboglobulin in platelets, effects that are absent in
eNOS knockout mice.164 Fluvastatin acts through PPARα and
PPAR-γ to reduce platelet aggregation in response to arachi-
donic acid and decreased platelet aggregation compared with
colestimide.165,166 Atorvastatin acutely inhibited platelet re-
cruitment, decreased Nox2, Rac1, protein kinase C, platelet
phospholipase A2, and thromboxane A2 while increasing NO
levels.167 Finally, the antithrombotic effect was also shown in
the JUPITER trial because treatment with rosuvastatin was
associated with decreased thromboembolism, an effect that
is likely to be unrelated to cholesterol reduction because hy-
percholesterolemia is not a particularly strong risk factor for
venous thromboembolism.31

**Direct Non-LDL Effects on Statins in
Cardiovascular Disease**

**Statins and Atherosclerosis**

Atherosclerosis is a chronic inflammatory process of the vas-
cular wall that is initiated by excessive LDL-C and is mediat-
ed by activated macrophages, T lymphocytes, B lymphocytes,
and SMCs.2 Statins are anti-inflammatory and reduce inflam-
matory cytokines and adhesion molecules and acting on both
the innate and adaptive immune responses.168 Statins reduce
Rac1-mediated ROS species production and reduce the ox-
idation-sensitive inflammatory pathways.169 Statins decrease
inflammatory cytokines such as IL-6, IL-8, and monocyte che-
matotactic protein-1.170 In vitro statins inhibited IL-6–induced
monocyte chemotaxis and monocyte chemotactic protein-1
expression and inhibited Janus kinase and the signal transduc-
ers and activators of transmission pathway, an effect that was
reversed by GGPP.171 Statins reduce matrix metalloproteinase-
ase-1, matrix metalloproteinase-3, and matrix metalloprotein-
ase-9 from both SMCs and macrophages in a rabbit model,
which was reduced by both GGPP and mevalonate.172

In the adaptive immune system, statins have effects on
T-cell differentiation. Simvastatin reduced the differentiation
of the proinflammatory IL-17 helper T cells and enhanced the
production of forhead box P3+ Cd4+ regulatory T cells
in a geranylgeranylation-dependent manner.173 Transforming
growth factor-β induces forhead box P3+ Cd4+ regulatory T
cells, and simvastatin acts through geranylgeranylation to in-
hibit the transforming growth factor-β inhibitors Smad6 and
Smad7 and therefore increase transforming growth factor-β
and forhead box P3+ Cd4+ regulatory T cell expression.174
Cd4+ T lymphocytes from patients with acute coronary syn-
drome induced EC apoptosis through an upregulated tumor
necrosis factor–related apoptosis-inducing ligand receptor
DR5 on ECs and increased tumor necrosis factor–related
apoptosis–inducing ligand expression on T lymphocytes, an
effect that was blocked by statins and may provide a pathway
for improved plaque stability by statins.175

Statins decrease the leukocyte and EC interaction that oc-
curs in atherogenesis. Intercellular adhesion molecule-1 and
vascular cell adhesion molecule-1 regulate the migration of
leukocytes to ECs and platelet and EC adhesion molecule-1
is involved in leukocytes crossing ECs.176,177 Statins inhibit vas-
cular cell adhesion molecule-1 through PPARα and increased
NO production.157,178 RhoA inhibition inhibits the clustering
of vascular cell adhesion molecule-1 and intercellular adhe-
sion molecule-1 and decreases monocyte adhesion to ECs.179
Lovastatin regulates platelet and EC adhesion molecule-1 ex-
pression, which was reversed by GGPP and mevalonate, sug-
cesting a role of Rho in regulating leukocyte migration.180

**Statins and Stroke**

Although elevated cholesterol and LDL-C are risk factors for
ischemic strokes in many epidemiological studies, it has not
been established in every study and the link remains more
controversial than the link for coronary artery disease.181 Nonetheless, statins reduce the risk of stroke by 25% in both the Heart Protection Study and the Treating to New Targets study and 48% in the JUPITER trial.10,182,183 The SPARC trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) demonstrated that atorvastatin is effective for stroke secondary prevention.184 Although there has been debate whether nonstatin cholesterol medications affect stroke incidence, the IMPROVE-IT trial showed the ezetimibe in addition to simvastatin had a 21% reduction in ischemic stroke.185 A potential pleiotropic target for statins in stroke is the effect of statins on eNOS, given that mice without eNOS demonstrate larger infarcts.186 The effects of statins are likely mediated by Rho/ROCK because ROCK inhibitors upregulate eNOS and improve cerebral blood flow in mice.128

Conclusion
Given the cell culture and the animal studies as well as indirect evidence from clinical trials, it remains important to assess whether the non-LDL-C–lowering effects of statins could be replicated by other cholesterol-lowering therapies or by agents that act downstream of isoprenoid synthesis, eg, squalene synthase inhibitors. Unfortunately, all of the current novel hyperlipidemia treatments are tested in patients receiving statins, which will only provide information on how much further to lower serum LDL-C, but does not exclude or include the potential pleiotropic effects of statins. The concept of statin pleiotropy has provided a window of opportunity to test and target other nonlipid-lowering signaling pathways that may affect cardiovascular disease. Agents that target inflammation alone, such as anti-IL-1β therapy (canakinumab) and methotrexate, are currently being tested in secondary prevention trials as adjunctive therapy to lipid lowering.185,186 Furthermore, the ROCK inhibitors, fasudil and ripasudil, which are currently approved in Japan for the treatment of cerebral vasospasm after subarachnoid hemorrhage and to treat glaucoma, respectively, may be of interest as novel therapies for reducing cardiovascular diseases. Finally, the PCSK9i may help provide evidence for statin pleiotropy, especially when low-dose PCSK9i is compared with high-potency statins that are matched for equivalent LDL-C lowering. This design would provide the opportunity to definitively test the clinical relevance of statin pleiotropy on cardiovascular outcomes.

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None.

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Pleiotropic Effects of Statins on the Cardiovascular System
Adam Oesterle, Ulrich Laufs and James K. Liao

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