Published in final edited form as:

Trends Mol Med. 2008 January ; 14(1): 37–44. doi:10.1016/j.molmed.2007.11.004.

Pleiotropic effects of statin therapy:

molecular mechanisms and clinical results

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Abstract

Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is required for cholesterol biosynthesis, and are beneficial in the primary and secondary prevention of cardiovascular disease. Most of the benefits of statin therapy are owing to the lowering of serum cholesterol levels. However, by inhibiting HMG-CoA reductase, statins can also inhibit the synthesis of isoprenoids, which are important lipid attachments for intracellular signaling molecules, such as Rho, Rac and Cdc42. Therefore, it is possible that statins might exert cholesterol-independent or 'pleiotropic' effects through direct inhibition of these small GTP-binding proteins. Recent studies have shown that statins might have important roles in diseases that are not mediated by cholesterol. Here, we review data from recent clinical trials that support the concept of statin pleiotropy and provide a rationale for their clinical importance.

Pleiotropy of statins: beyond cholesterol lowering

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are principal therapeutic agents for the treatment of hypercholesterolemia. Several landmark clinical trials, such as Scandinavian Simvastatin Survival Study (4S) [1], Cholesterol and Recurrent Events (CARE) [2], Long-term Intervention with Pravastatin in Ischemia Disease (LIPID) [3], West of Scotland Coronary Prevention Study (WOSCOPS) [4], Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [5] and the Heart Protection Study (HPS) [6], have demonstrated the beneficial effects of statin therapy for primary and secondary prevention of cardiovascular disease. Because 60-70% of serum cholesterol is derived from hepatic synthesis and HMG-CoA reductase is the crucial, rate-limiting enzyme in the cholesterol biosynthetic pathway, inhibition of this enzyme by statins results in a dramatic reduction in circulating low-density lipoprotein (LDL)-cholesterol (Figure 1). In addition, reduction of LDL-cholesterol leads to upregulation of the LDL receptor and increased LDL clearance. The lowering of serum cholesterol levels is therefore thought to be the primary mechanism underlying the therapeutic benefits of statin therapy in cardiovascular disease [1].

Statins, however, might also exert cholesterol-independent or pleiotropic effects. By inhibiting the conversion of HMG-CoA to L-mevalonic acid, statins prevent the synthesis of important isoprenoids, such as farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP), which are precursors of cholesterol biosynthesis [7] (Figure 1). These intermediates serve as important lipid attachments for the post-translational modification of proteins, such as nuclear lamins, Ras, Rho, Rac and Rap [8]. These isoprenylated proteins constitute approximately 2% of total cellular proteins [9]. Protein isoprenylation (see Glossary) enables proper subcellular localization and trafficking of intracellular proteins. Given that isoprenylated proteins might

control diverse cellular functions, it is not surprising that statins might have additional effects beyond lipid lowering. Indeed, recent studies suggest that statins might be involved in immunomodulation [10], neuroprotection [11] and cellular senescence [12].

Cholesterol-lowering and statins

The Framingham Heart Study has demonstrated that elevated cholesterol is an important risk factor for cardiovascular diseases and lower cholesterol levels are associated with lower cardiovascular risks [13]. Recent evidence also shows that more intensive lowering of LDL-cholesterol by statins is associated with greater clinical benefits [14]. The mechanisms attributed to lipid lowering with statin therapy include atheromatous plaque stabilization, modification of the atherosclerosis progression and improved endothelial functions [15]. Hence, statins reduce cardiovascular events in not only hypercholesterolemic but also normocholesterolemic patients with coronary heart disease (CHD) or cardiovascular risks (Table 1).

Clinical trials with statins

Statins are the principal therapy for more than 25 million people at risk of cardiovascular disease worldwide. The 4S study was the first randomized controlled trial to show significant risk reduction in cardiovascular mortality in patients with coronary-artery disease. The evidence supporting the role for cholesterol in atherosclerosis is irrefutable because cholesterol contributes to the atherosclerotic lesion development [16]. For example, modified or oxidized LDL (oxLDL) can promote inflammatory processes in the arterial wall, activate monocytes or macrophages, increase free radical generation and lead to endothelial dysfunction [17]. Therefore, lowering of oxLDL levels by statins might contribute to some of the cholesterol-dependent effects of statins. Furthermore, data from meta-analysis of lipid-lowering trials suggest that lipid modification alone accounts for the clinical benefits associated with statin therapy [18]. However, both the level of efficacy and early treatment benefits as a result of statin therapy have so far been greater than the beneficial effects of non-statin lipid-lowering therapies. For example, in the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction 22) study, the benefits of statin therapy in patients with acute coronary syndrome were observed within 30 days of treatment [14]. Furthermore, statins appear to have therapeutic benefits in diseases that are unrelated to elevated serum cholesterol levels, such as rheumatologic diseases [19] and ischemic stroke [1]. These findings suggest that statins might exert beneficial effects beyond cholesterol reduction.

Because of the effects of lipid lowering on atherosclerosis, it is not surprising that statins reduce morbidity and mortality in patients with ischemic heart failure [20] because the major etiology of ischemic heart failure is due to atherosclerosis, whereas non-ischemic heart failure is usually unrelated to atherosclerosis. What is surprising is that statins also improve heart function and survival in patients with non-ischemic heart failure [21-24]. Patients with severe heart failure without evidence of ischemic etiology have reduced all-cause mortality and are free from urgent transplantation on statin therapy [25]. Indeed, short-term statin therapy improves cardiac function, neurohormonal imbalance and symptoms associated with idiopathic dilated cardiomyopathy [21]. Thus, the improvements in heart function by statins might be owing to cholesterol-independent mechanisms. Currently, there are two large ongoing prospective trials, CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure) and GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico - Insufficienza Cardiaca), which will help to determine whether statin therapy is effective in patients with ischemic and non-ischemic heart failure [26,27].

When comparing statin and non-statin lipid-lowering trials, statin-treatment trials demonstrate benefits within 5 years compared with greater than 7 years for non-statin trials [28,29]. Furthermore, subgroup analysis of WOSCOPS and CARE studies indicate that, despite comparable serum cholesterol levels among patients in the statin and placebo groups, patients who are treated with statin have 47% lower risk of developing subsequent events [2,4]. Recently, two clinical trials with ezetimibe support the notion of statin pleiotropy in humans. Ezetimibe is a lipid-lowering agent, which acts by decreasing cholesterol absorption in the intestine [30]. It is used alone or in combination with statin therapy to enhance lipid lowering [31]. In patients with heart failure, 4 weeks of simvastatin but not ezetimibe treatment improved endothelial function and reduced oxidative stress, despite comparable reduction in serum cholesterol levels [32]. Furthermore, compared with 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 [33] and lower platelet activation and chemokine levels [34]. Thus, the LDL-lowering benefits of ezetimibe remain to be determined.

Finally, evidence is emerging that patients with autoimmune diseases might also benefit from statin therapy. Clinical trials have demonstrated that statins can reduce morbidity in patients with multiple sclerosis [35,36]. Furthermore, in a 6 month, randomized, double-blind placebo-controlled clinical trial, patients with rheumatoid arthritis who received atorvastatin showed a reduction in disease activity [19]. However, it is too early to predict whether these promising data can translate into clinical benefit by statins in patients with autoimmune disease.

High-dose statin therapy

Recent clinical trials, such as MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering), TNT (Treating to New Targets), PROVE IT-TIMI 22 and SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), have shown that high-dose statins, especially atorvastatin 80-mg, can further reduce vascular risks compared with low- or moderate-dose statin therapy [14,20]. Consequently, in 2004, the National Cholesterol Education Program Adult Treatment Panel (NCEP) recommended an optional LDL goal of less than 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 [37]. It should be noted that the pleiotropic effects of statins are often greater with higher doses of statin. However, despite high statin dose, serious hepatic or musculoskeletal adverse effects are relatively low (0.6% and 1.3%, respectively) [14,20], although atorvastatin 80-mg is associated with higher rates of elevated hepatic transaminase and simvastatin 80-mg is associated with higher rates of myopathy and rhabdomyolysis. Therefore, although high-dose statin therapy appears to provide greater benefits, it is difficult to tease out whether the benefits are really due to lower cholesterol levels or to statin pleiotropy.

Statin and isoprenoids

Protein isoprenylation occurs on proteins containing a C-terminal CaaX motif, where C is cysteine, a is an aliphatic amino acid and X is any amino acid. 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 lipophilic isoprenyl group enables these proteins to anchor to cell membranes, which, in most situations, is an essential requirement for biological function. Members of the Ras and Rho GTPase family are the major substrates for post-translational modification by prenylation [38]. These small GTP-binding proteins that

cycle between the inactive GDP-bound state and active GTP-bound state are important regulators of actin cytoskeleton and intracellular signaling pathways (Box 1 and Figure 2).

Box 1. Small GTPase family of proteins

The family of small GTPases is monomeric guanine nucleotide-binding proteins of approximately 20-25 kDa. There are now approximately eight subfamilies that have been identified in mammals. The small GTPases cycle between GDP-bound (inactive) and GTP-bound (active) states. Through these interchanging states, they serve as molecular signaling switches that regulate growth, morphogenesis, cell migration, cytokinesis and molecular trafficking. Currently, the Ras and Rho GTPase families are of special interest because they transduce extracellular stimuli to multiple intracellular signaling pathways [43].

Ras

Mutations in the Ras family of proto-oncogenes are found in 20-30% of human tumors. Inappropriate activation of the Ras has a key role in signal transduction, proliferation and malignant transformation.

Rho

Rho, Rac and Cdc42 are the best characterized subfamilies and regulate actin cytoskeletal change, microtubule dynamics, vesicle trafficking, cell polarity and cell-cycle progression.

Other small GTPases

Other small GTPases include Rab, Rap, Ran, Rheb, Rad, Rit and Arf. They are important for many cellular processes, such as membrane trafficking, nucleocytoplasmic transport and the regulation of cell proliferation.

Each member of the Rho GTPase family, which consists of RhoA, Rac and Cdc42, serves specific functions in terms of cell shape, motility, secretion and proliferation. For example, the activation of Cdc42 induces actin-rich surface protrusions, whereas activation of Rac1 leads to the formation of lamellipodia and membrane ruffles. By contrast, the activation of Rho and its downstream target, Rho-associated protein kinase (ROCK), regulates calcium-insensitive vascular smooth-muscle contraction in hypertension [39] and coronary spasm [40]. Because three-dimensional colocalization of intracellular proteins is regulated by cytoskeletal rearrangements, changes in statin-induced actin cytoskeleton could affect intracellular transport, membrane trafficking, mRNA stability and gene transcription. Indeed, statins have been reported to cause alterations in the actin cytoskeleton and the assembly of focal adhesion complexes by inhibiting RhoA and Rac1 isoprenylation [41].

Thus, statins might affect vascular function through the modulation of signaling proteins that depend on post-translational modification with isoprenoid.

Statins and Rho

The biological effects of Rho are mediated by its downstream effectors, including ROCK, protein kinase N-related kinases, citron kinase, rhotekin, mDia and the myosin-binding subunit of myosin light-chain (MLC) phosphatase [42]. Although the precise roles of these many effectors remain to be determined, the best characterized is the effect of ROCK on the actin cytoskeleton. 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 [43]. ROCK activity is often elevated in disorders of the cardiovascular system [14]. Thus, statins could affect vascular smooth-muscle contraction at least partially through effects on Rho/ROCK [39,43]. Through inhibition of isoprenylation of Rho, translocation of Rho to the cell membrane is

inhibited and the downstream activation of ROCK is reduced [44]. Indeed, ROCK inhibitors prevent cerebral vasospasm after subarachnoid hemorrhage [45], inhibit the development of atherosclerosis [46] and prevent arterial remodeling after vascular injury [47].

The Rho/ROCK pathway could also regulate cellular functions other than the actin cytoskeleton. For example, ROCK can phosphorylate insulin receptor substrate-1 (IRS-1) and modulate the insulin/PI3K/Akt pathway [48]. The Rho/ROCK pathway is involved in oxidative stress, aortic stiffness and changes in blood pressure [49]. Furthermore, ROCK regulates cell survival through phosphorylation of the protein kinase B/Akt and FOXO (see Glossary) [50]. ROCK can also regulate adipogenesis and myogenesis. In p190-B Rho GAP-deficient mice, the Rho/ROCK pathway is activated chronically and there is a defect in adipogenesis with a predilection towards myogenesis [51]. Other processes or conditions involving the RhoA/ROCK pathway include angiogenesis [52], hypertension [39], cardiac hypertrophy [53], perivascular fibrosis [54] and pulmonary hypertension [52]. Fasudil, a selective ROCK inhibitor, improves endothelial function in patients with coronary artery disease [55]. These findings suggest that ROCK inhibition might contribute to some of the pleiotropic effects of statin therapy.

Statins and Rac

Two important effector-response pathways lie downstream of Rac: cytoskeletal remodeling and reactive oxygen species (ROS) generation. Rac1 influences multiple cytoskeletal remodeling proteins, such as Wiskott-Aldrich syndrome protein, calmodulin-binding GTPase-activating proteins and p21-activated kinase. Rac1 also binds to p67^{phox} and leads to activation of the NADPH oxidase system and subsequent generation of ROS. Indeed, Rac activity is closely related to ROS production and ROS generated by NADPH oxidase in response to growth factors and inflammatory cytokines is mediated by Rac [56]. Importantly, statins inhibit Rac1-mediated NADPH oxidase activity and thereby reduce angiotensin II-induced ROS production and hypertrophy in smooth muscle and heart [57,58]. The activation of Rac1 in the vascular wall has been associated with atherosclerosis, neointimal proliferation, cardiac hypertrophy and endothelial dysfunction [59]. Rac1 has multiple roles in diverse cellular processes and cardiovascular physiology [60]. Thus, Rac1 inhibition might also contribute to some of the pleiotropic effects of statins.

Statins and vascular dysfunction

The endothelium produces vasoactive substances in response to environmental factors and serves as an important autocrine and paracrine organ that regulates the vascular-wall contractile state and cellular composition. Endothelium-derived nitric oxide (NO) mediates vasodilation, inhibits platelet aggregation and leukocyte adhesion and decreases vascular smooth-muscle proliferation [61]. Endothelium-derived NO, therefore, is protective for the vasculature and decreased NO bioavailability is often associated with increased risk of cardiovascular disease [62]. As mentioned, endothelial dysfunction is one of the earliest manifestations of atherosclerosis [63].

Elevated serum cholesterol levels lead to endothelial dysfunction [64]. The mechanism by which LDL-cholesterol causes endothelial dysfunction and decreases NO bioactivity involves downregulation of endothelial NOS expression, decreased receptor-mediated NO release [65] and decreased NO bioavailability owing to increase in ROS production [66]. Furthermore, oxLDL can also recruit leukocytes to the arterial wall and activates NF- κ B, a major proinflammatory transcription factor that is crucial for the induction of vascular cell adhesion molecule (VCAM)-1 and monocyte chemotactic protein (MCP)-1 [67].

Statins improve endothelial function by cholesterol-dependent and -independent mechanisms. Clinical trials have shown that LDL apheresis, which removes plasma LDL particles physically, can improve endothelium-dependent vasomotion through acute reduction in serum cholesterol levels [68]. Cholesterol lowering modifies atherosclerotic-plaque biology, thereby decreasing vascular inflammation and leukocyte activation [69]. Thus, statins can improve endothelial function through reduction in serum cholesterol levels. However, in some studies, statins improve endothelial function before significant reduction in serum cholesterol levels occurs [70,71]. This, in part, is mediated by the upregulation of endothelial nitric oxide synthase (eNOS) in the presence of hypoxia [72] and oxLDL [73].

Statins affect eNOS expression and activity mainly through three mechanisms [74]. First, statins increase eNOS expression by prolonging eNOS mRNA half-life rather than by inducing *eNOS* gene transcription. The mechanism is owing to inhibition of RhoA geranylgeranylation, alteration of the cytoskeleton and localization of the eNOS mRNA [75]. Second, statins reduce caveolin-1 abundance. Caveolin-1 is an integral membrane protein and binds to eNOS in caveolae, thereby inhibiting NO production directly [76]. Third, statins can activate the phosphatidylinositol 3-kinase (PI3K)/protein kinase Akt pathway [77]. Akt is a serine/threonine kinase that regulates various cellular functions, such as survival, growth and proliferation. Because Akt, in turn, phosphorylates and activates eNOS, statins can also increase eNOS activity through the PI3K/Akt pathway [78].

Several vasoconstricting agents, such as endothelin-1 (ET-1) or angiotensin II, counteract the vasodilating effect of NO and might contribute to the development of atherosclerosis. ET-1 acts as a potent mitogenic agent, which promotes neointima formation and proliferation of smooth muscle cells [79]. ET-1 is found to be elevated in patients with severe atherosclerosis [80]. Statins inhibit the expression of preproET-1 [81] and downregulate endothelin and angiotensin subtype 1 receptors [82,83] in a RhoA-dependent manner.

Statins also affect the fibrinolytic system of vascular smooth muscle and endothelial cells [84]. Plasminogen activator inhibitor type-1 (PAI-1) is the major endogenous inhibitor of tissue plasminogen activator. Elevated PAI-1 level is an independent cardiovascular risk factor and is associated with atherothrombotic disease [85,86]. Statins increase the expression of tissue-type plasminogen activator and inhibit the expression of PAI-1 [73]. The inhibitory effect of statins on PAI-1 expression is mediated, in part, through the PI3K/Akt pathway [87].

Statins also induce the expression of heme oxygenase-1 (HO-1) [88]. HO-1 is a stress-response protein, which is induced in response to UV radiation, cytokines and free radicals. Induction of HO-1 leads to the degradation of heme to carbon monoxide and biliverdin. Biliverdin is then converted to the antioxidant bilirubin [89]. Interestingly, HO-1 prevents the development of atherosclerosis in mice [90]. Further studies are needed to determine whether some of the anti-atherosclerotic effects of statins are mediated by HO-1 induction.

Statins and immunomodulation

Inflammatory cells have an important role in the pathogenesis of atherosclerosis [91]. Immunomodulation by statins, therefore, might contribute to some of the cholesterol-independent effects of statins. For example, simvastatin inhibits MHC II expression, which is upregulated in myocarditis, multiple sclerosis and rheumatoid arthritis. Antigen presentation requires endocytosis of antigen, internal processing and presentation of MHC II

Box 2. Outstanding issues

Combination therapies

It is important to address the clinical importance of statin therapy in combination with other lipid-lowering strategies in lowering cardiovascular risks.

Statin and cancer

Large, prospective and randomized trials are needed to determine the effect of statins in relation to cancer prevention and treatment.

Differential effects of statins

It is not known whether different statins have different efficacy in inhibiting isoprenylation and therefore different potency for pleiotropic effects.

Statins and aging

Recent studies suggest that statins might be useful as an anti-aging therapy [99]. However, further studies are required to address and elucidate the role of statins in this area.

molecules at the cell surface. These processes all involve changes in the actin cytoskeleton, which are controlled by small GTPases. Indeed, the inhibitory effect of statins on MHC II expression is reversed by mevalonate and GGPP but not squalene (Figure 1), suggesting the involvement of small GTPases as the underlying mechanism [92]. Similarly, Cdc42 and Rac regulate the ability of dendritic cells to present antigen to T cells [93].

Statins decrease macrophage expression of tumor necrosis factor and interleukin (IL)-1 β and also inhibit the proliferation of peripheral blood mononuclear cells [94]. Statins also regulate T-cell phenotype. Statins prevent experimental T helper 1 (Th1)-mediated autoimmune diseases [95] and induce IL-4-dependent Th2-cell differentiation [96] and the secretion of anti-inflammatory Th2-type cytokines [97]. Finally, statins can also bind to a novel allosteric site within the β_2 -integrin function-associated antigen-1 protein, independent of mevalonate production [98]. Inhibition of β_2 -integrin function-associated antigen-1 can decrease lymphocyte adhesion to ICAM-1 and impair T-cell co-stimulation [98]. This is one of the few reported pleiotropic effects of statins that does not involve the inhibition of small GTPases.

Concluding remarks

Statins exert many effects beyond cholesterol lowering. These effects include improving endothelial function, decreasing vascular inflammation, inhibiting smooth-muscle proliferation and immunomodulation. Recent studies suggest that most of these effects are mediated through inhibition of isoprenoid synthesis, with subsequent effects on multiple downstream signaling pathways (Box 2). However, further studies are needed to determine to what extent these pleiotropic effects contribute to the clinical benefits of statin therapy.

Glossary

AKT/PKB and FOXO, This term refers to serine-threonine protein kinase Akt (protein kinase B) and its downstream target forkhead transcription factors. It is an important regulator of cellular growth, survival and senescence.; **Caveolae**, Caveolae refers to approximately 50-100 nm invaginations of the plasma membrane in terminal differentiated cells. Caveolin is the principle protein of caveolae. Caveolae have important roles in endocytosis, oncogenesis, uptake of pathogenic bacteria and signal transduction.; **Isoprenylation**, This term refers to post-translational modification of proteins with isoprenoids. Isoprenylation of proteins is important for protein trafficking and compartmentalization.; **Neointima**, This term refers to vascular remodeling within the internal elastic lamina formed by a thickened layer of vascular smooth muscle and inflammatory cells. Formation of neointima occurs in response to vascular injury.; **Reactive oxygen species**, NADPH oxidase and p67^{phox}, Reactive oxygen species refers to

oxygen-derived free radicals. They are formed mainly through three processes: (i) they are a byproduct of cellular respiration, (ii) they are synthesized by dedicated enzymes such as NADPH oxidase or myeloperoxidase and (iii) they can be formed by ionizing radiation injury. The cytosolic protein p67^{phox} is a component of NADPH oxidase..

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Figure 1.

Isoprenoids and statins. Diagram of the cholesterol biosynthesis pathway and the effects of HMG-CoA-reductase inhibition by statins. Inhibition of small GTPase isoprenylation by statins leads to modulation of various cellular functions. Abbreviations: eNOS: endothelial nitric oxide synthase; Map3K: mitogen-activated protein kinase kinase; Pak: p21-activated kinase.

Figure 2.

Regulation of the Rho GTPase cycle. Rho proteins cycle between a cytosolic, inactive GDP-bound state and an active, membrane, GTP-bound state. This cycle is controlled by guanine nucleotide-exchange factors (GEF), GTPase-activating proteins (GAP) and guanine nucleotide-dissociation inhibitors (GDI). After isoprenylation and translocation to the cell membrane, they interact with effectors and affect various cellular functions.

Table 1
Characteristics and cardiovascular protection effects of statin clinical trials

Type and name of study	Year	Intervention	Population	Total, n	Mean follow-up, years	Baseline LDL-C, mean, mg/dl	LDL-C, % reduction	Non-fatal MI or death from CAD, % reduction (95% CI)
Stable CAD								
4S [1]	1994	Simvastatin	CAD	4444	5.4	188	35	31 (21 to 39)
CARE [2]	1996	Pravastatin	CAD	4159	5	139	28	24 (9 to 36)
LIPID [3]	1998	Pravastatin	CAD	9014	6.1	150	25	24 (15 to 32)
WOSCOPS [4]	1998	Pravastatin 40	High-risk men	6595	4.9	192	26	31 (17 to 43)
AFCAPS/TEPCAPS [5]	1995	Lovastatin 20-40	Moderate risk	6605	5.2	150	26.5	37 (20 to 50)
HPS [6]	2002	Simvastatin 40	CAD, DM	20536	5	131	30	26 (19 to 32)
ACS								
PROVE IT-TIMI 22 [14]	2004	Atorvastatin 80 versus Pravastatin 40	ACS	4162	2	106	42	16 (5 to 26)
CHF								
CORONA [27]	2007	Rosuvastatin	CHF	5011	2.3	137	45	8 (-2 to 17)
GISSI-HF [26]	2008	Rosuvastatin	CHF	7000	1.5	?	?	?

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.