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Pleiotropic actions of statins beyond lipid lowering: molecular mechanisms and clinical implications

Abstract

Statins are widely used for cardiovascular risk reduction through their lipid lowering properties. However, accumulating evidence indicates that their clinical benefits extend beyond cholesterol modification. This review provides a comprehensive overview of the pleiotropic effects of statins, focusing on their molecular, cellular, and clinical implications. By inhibiting the mevalonate pathway, statins influence key intracellular signaling mechanisms that regulate endothelial function, inflammation, oxidative stress, immune activation, and thrombotic balance. These effects contribute to improved vascular homeostasis, stabilization of atherosclerotic plaques, and modulation of microvascular function independent of lipid lowering. Statins also exert immunometabolic effects through regulation of innate immune responses and trained immunity, linking metabolic pathways to inflammatory processes in atherosclerosis. In addition, their impact on vascular remodeling, myocardial function, and renal microcirculation highlights a broader role in cardiovascular and systemic disease modulation. Emerging data suggest that these mechanisms may help explain early clinical benefits observed in acute coronary syndromes, as well as effects on coronary microvascular dysfunction, atrial remodeling, and contrast related renal injury. While translation of pleiotropic mechanisms into clinical outcomes varies across disease states, understanding these non lipid mediated actions provides insight into the broader biological impact of statin therapy. Collectively, statins should be viewed not only as lipid lowering agents but also as modulators of vascular and inflammatory pathways with potential implications across diverse cardiovascular conditions.

Keywords: pleiotropic effects, endothelial function, immunometabolism, vascular inflammation, coronary microvascular dysfunction

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Introduction

Statins are widely recognized as the cornerstone of lipid lowering therapy due to their ability to inhibit 3 hydroxy 3 methylglutaryl coenzyme A reductase, the rate limiting enzyme in hepatic cholesterol synthesis. This pharmacologic action reduces intracellular cholesterol availability and leads to upregulation of low density lipoprotein receptors, ultimately lowering circulating LDL cholesterol levels and reducing atherosclerotic cardiovascular risk.[1] However, accumulating evidence over the past three decades has shown that the clinical benefits of statins cannot be fully explained by lipid reduction alone.

Observations from major clinical trials first raised this possibility. In studies such as the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial and the Pravastatin or Atorvastatin Evaluation and Infection Therapy TIMI 22 trial, early divergence of cardiovascular event curves occurred within weeks of statin initiation, well before significant plaque regression or substantial lipid modification could reasonably take place.[2,3] These findings suggested that statins exert rapid biological effects that extend beyond cholesterol lowering.

Subsequent experimental and translational research introduced the concept of pleiotropic effects, referring to lipid independent actions of statins on vascular biology. These effects include improvement in endothelial function, attenuation of vascular inflammation, stabilization of atherosclerotic plaques, modulation of oxidative stress, and regulation of thrombotic pathways.[4] Mechanistically, these benefits appear to be mediated through inhibition of isoprenoid synthesis within the mevalonate pathway, affecting intracellular signaling proteins involved in vascular homeostasis.

Importantly, pleiotropic actions may contribute to clinical outcomes in settings where lipid levels are unlikely to be the primary driver of pathology. For instance, statins have been associated with improved outcomes in acute coronary syndromes, modulation of atrial fibrillation burden, attenuation of heart failure progression, and preservation of renal function in high risk populations.[5] Such observations have broadened the conceptual framework through which statins are understood, from purely lipid lowering agents to modulators of vascular and inflammatory processes.

Recognizing these non lipid effects is clinically relevant, as it may explain early benefit in acute settings and inform therapeutic strategies in conditions characterized by endothelial dysfunction, systemic inflammation, or heightened thrombotic risk. The following sections explore the molecular and cellular mechanisms underlying statin pleiotropy and their translation into clinical practice.

The literature included in this review was identified through a comprehensive search of major biomedical databases including PubMed, Scopus, Web of Science, and Embase. The search strategy incorporated combinations of keywords such as statins, pleiotropic effects, endothelial function, inflammation, immunometabolism, oxidative stress, vascular remodeling, thrombosis, coronary microvascular dysfunction, heart failure, atrial fibrillation, and contrast induced nephropathy. Emphasis was placed on experimental, translational, and clinical studies published after 2000 that explored mechanisms beyond lipid lowering. Reference lists of relevant articles were also screened to identify additional pertinent studies and ensure inclusion of key contemporary evidence.

The purpose of this review is to provide a comprehensive overview of the pleiotropic effects of statins beyond lipid lowering, with a

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particular focus on their molecular, cellular, and clinical implications. By integrating evidence from experimental studies and clinical investigations, this review aims to highlight how statins influence endothelial function, inflammatory pathways, immune modulation, thrombotic balance, and vascular remodeling. Understanding these non lipid mediated actions may offer insight into the early clinical benefits observed with statin therapy and clarify their potential role in conditions where endothelial dysfunction and inflammation are central drivers of disease progression.

Molecular basis of statin pleiotropy

The pleiotropic effects of statins originate primarily from their impact on the mevalonate pathway beyond cholesterol synthesis. While inhibition of HMG CoA reductase reduces hepatic cholesterol production, it simultaneously limits the formation of key nonsterol intermediates such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate. These intermediates are essential for post translational modification of small guanosine triphosphate binding proteins including Rho, Rac, and Ras. These signaling molecules regulate a wide range of cellular functions related to vascular tone, inflammation, oxidative stress, and cellular proliferation.[6]

Inhibition of isoprenoid synthesis leads to reduced prenylation and membrane localization of these small GTP binding proteins. Among them, the Rho family plays a central role in mediating endothelial dysfunction and vascular remodeling. Reduced Rho activity has been associated with upregulation of endothelial nitric oxide synthase expression and improved nitric oxide bioavailability through stabilization of endothelial signaling pathways.[7] This process enhances endothelial homeostasis and contributes to improved vascular function independently of lipid lowering.

Statins also modulate intracellular signaling through effects on the phosphoinositide 3 kinase and Akt pathway. Activation of this pathway promotes endothelial nitric oxide synthase phosphorylation and enhances nitric oxide production. At the same time, inhibition of Rac dependent pathways reduces activation of nicotinamide adenine dinucleotide phosphate oxidase, thereby decreasing reactive oxygen species generation and preserving nitric oxide signaling.[8] This dual effect improves endothelial redox balance and reduces oxidative stress.

Another important consequence of impaired isoprenoid availability is suppression of nuclear factor kappa B mediated transcription. Nuclear factor kappa B regulates expression of numerous pro inflammatory genes including cytokines, adhesion molecules, and chemokines. By attenuating this pathway, statins reduce vascular inflammation and leukocyte recruitment, contributing to a more stable vascular environment.[9]

Collectively, these molecular changes translate into improved endothelial function, reduced inflammatory signaling, and stabilization of vascular cellular interactions. Importantly, these effects occur through modulation of intracellular signaling rather than through changes in circulating lipid levels. Experimental and translational studies have consistently shown that these signaling alterations represent a central mechanistic foundation for the pleiotropic actions of statins in cardiovascular disease.[10,11] The principal molecular pathways involved in statin mediated pleiotropy are summarized in Table 1. The molecular mechanisms linking inhibition of the mevalonate pathway to the pleiotropic vascular effects of statins are schematically illustrated in Figure 1.

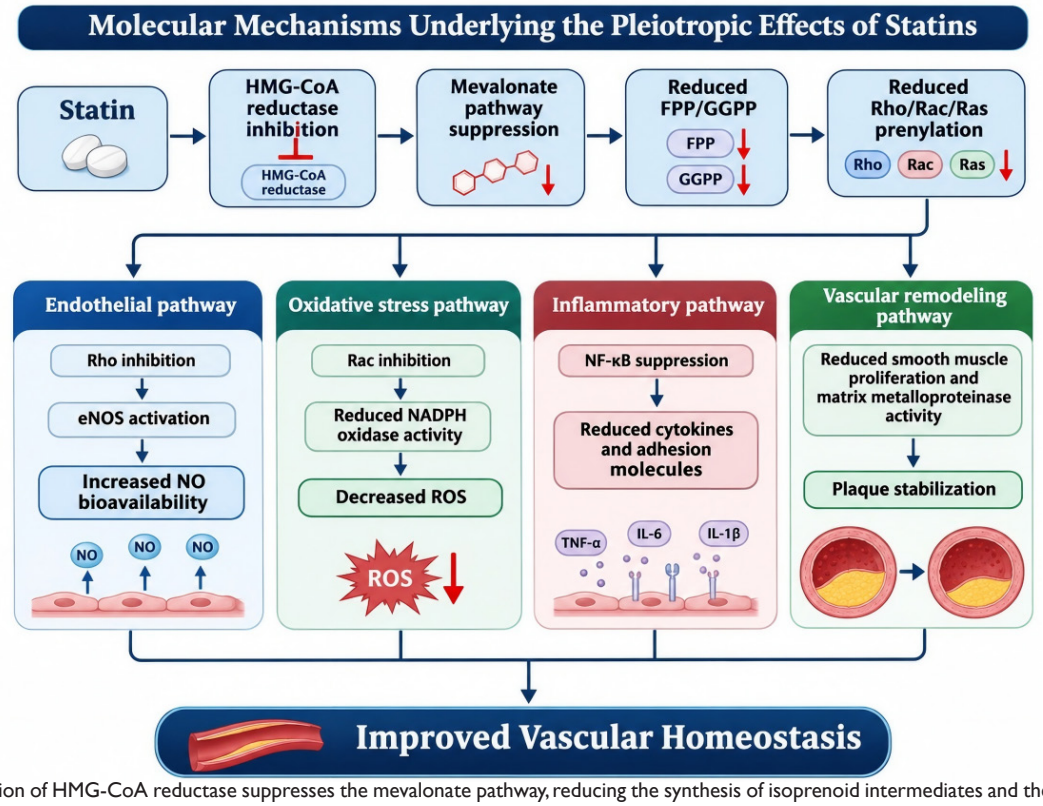


Figure 1 Inhibition of HMG-CoA reductase suppresses the mevalonate pathway, reducing the synthesis of isoprenoid intermediates and the prenylation of small GTP-binding proteins, including Rho, Rac, and Ras. These molecular changes modulate endothelial nitric oxide signaling, oxidative stress, inflammatory pathways, and vascular remodeling, collectively contributing to improved vascular homeostasis.

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Table 1 Molecular pathways underlying the pleiotropic effects of statins

Pathway affected	Mechanism of action	Downstream effect	Clinical relevance
Mevalonate pathway inhibition	Reduced synthesis of isoprenoids	Impaired prenylation of Rho, Rac, Ras proteins	Improved endothelial signaling
Rho pathway suppression	Increased eNOS stability	Enhanced nitric oxide bioavailability	Improved vascular tone
Rac inhibition	Reduced NADPH oxidase activation	Decreased oxidative stress	Protection against endothelial dysfunction
NF kappa B modulation	Reduced transcription of inflammatory genes	Lower cytokine production	Plaque stabilization
PI3K Akt activation	eNOS phosphorylation	Improved endothelial repair	Microvascular protection

Abbreviations: eNOS, endothelial nitric oxide synthase; Rho, Ras homolog gene family; Rac, Ras related C3 botulinum toxin substrate; Ras, rat sarcoma protein; NF kappa B, nuclear factor kappa B; PI3K, phosphoinositide 3 kinase; Akt, protein kinase B; NADPH, nicotinamide adenine dinucleotide phosphate

Endothelial effects

One of the most consistently demonstrated pleiotropic actions of statins involves improvement of endothelial function. Endothelial dysfunction is an early and central feature of atherosclerosis and contributes to impaired vasomotor regulation, inflammation, and thrombogenesis. Statins exert favorable effects on endothelial homeostasis through mechanisms that are independent of lipid lowering and primarily mediated through enhanced nitric oxide bioavailability.[12]

Upregulation of endothelial nitric oxide synthase plays a pivotal role in this process. By inhibiting Rho signaling, statins increase endothelial nitric oxide synthase mRNA stability and enzymatic activity, leading to greater nitric oxide production. This results in improved endothelium dependent vasodilation and restoration of vascular tone regulation.[13] In addition, statins reduce inhibitory interactions between endothelial nitric oxide synthase and caveolin, further enhancing nitric oxide availability and promoting vasoprotective signaling.

Statins also attenuate oxidative stress within the vascular wall. Reduced activation of Rac dependent nicotinamide adenine dinucleotide phosphate oxidase decreases superoxide generation, thereby limiting nitric oxide degradation and improving redox balance.[14] Preservation of nitric oxide signaling contributes not only to vasodilation but also to inhibition of leukocyte adhesion and smooth muscle proliferation.

Beyond these biochemical effects, statins promote endothelial repair mechanisms through mobilization of endothelial progenitor cells. Activation of phosphoinositide 3 kinase and Akt signaling enhances progenitor cell survival and recruitment to sites of vascular injury, facilitating endothelial regeneration and maintenance of vascular integrity.[15] This regenerative capacity has been linked to improved outcomes in vascular injury models and may contribute to plaque stabilization.

Clinical studies support these mechanistic observations. Improvement in flow mediated dilation has been documented following statin initiation, often occurring before significant changes in lipid levels are observed.[16] Such findings reinforce the concept that statins improve endothelial function through direct biological effects rather than solely through lipid reduction.

Statin mediated improvement in endothelial function may also have important implications for coronary microvascular physiology. Coronary microvascular dysfunction is increasingly recognized as a major contributor to ischemia in the absence of obstructive coronary artery disease. Impaired nitric oxide signaling and increased oxidative stress play a central role in this condition. By enhancing endothelial nitric oxide synthase activity and reducing reactive oxygen species generation, statins may improve microvascular vasomotor regulation and reduce functional ischemia at the microcirculatory level.[17] This mechanism may be particularly relevant in patients with ischemia and non obstructive coronary arteries, where endothelial dysfunction rather than epicardial stenosis predominates.[18] Improvements in coronary flow reserve and microvascular reactivity observed in statin treated populations support the concept that pleiotropic endothelial effects extend beyond large vessel atherosclerosis to include regulation of microvascular function.[19]

Taken together, enhanced nitric oxide bioavailability, reduced oxidative stress, and improved endothelial repair represent key pathways through which statins exert vascular protective actions. These endothelial effects form an essential component of their broader pleiotropic profile.

Anti inflammatory effects

Inflammation plays a central role in all stages of atherosclerosis, from initiation to plaque rupture. Beyond their lipid lowering capacity, statins exert significant anti inflammatory effects that influence both vascular and systemic inflammatory pathways. These effects are mediated through modulation of intracellular signaling and transcriptional activity rather than through changes in circulating lipid concentrations.

Statins have been shown to reduce levels of key pro inflammatory cytokines including interleukin 6 and tumor necrosis factor alpha. Importantly, reductions in C reactive protein occur independently of LDL cholesterol lowering, supporting the concept that statins directly influence inflammatory pathways.[20,21] This effect has been consistently demonstrated in clinical trials where decreases in inflammatory markers were observed even in patients with relatively normal baseline lipid levels.

At the cellular level, statins alter immune cell behavior within the vascular wall. Macrophage activation is attenuated through inhibition of prenylation dependent signaling pathways, resulting in reduced expression of inflammatory mediators and a shift toward a less pro inflammatory phenotype.[22] This modulation of macrophage function contributes to stabilization of atherosclerotic plaques by limiting local inflammatory activity.

Statins also influence adaptive immune responses. Reduced activation of T lymphocytes and decreased expression of major histocompatibility complex class two molecules have been observed following statin exposure. These immunomodulatory effects are partly mediated through suppression of nuclear factor kappa B signaling and reduced antigen presentation, leading to diminished vascular inflammation.[23]

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In addition, emerging evidence suggests that statins may modulate inflammasome activity. Experimental studies indicate that inhibition of small GTP binding proteins can reduce activation of inflammatory complexes such as NLRP3, thereby limiting downstream cytokine production and vascular injury.[24] This pathway may be particularly relevant in acute coronary syndromes where inflammasome activation contributes to plaque instability.

Clinical observations further support these mechanisms. Reduction in systemic inflammatory burden has been associated with improved outcomes in patients with coronary artery disease, even after adjustment for lipid changes.[25] Such findings underscore the importance of anti inflammatory actions as a major component of statin mediated cardiovascular protection.

Together, suppression of cytokine production, modulation of immune cell function, and attenuation of inflammasome activity illustrate how statins exert broad anti inflammatory effects that extend beyond lipid lowering and contribute to stabilization of the vascular environment. The key vascular and immune targets influenced by statin therapy are outlined in Table 2.

Table 2 Pleiotropic effects of statins on vascular and ımmune function

Biological target	Statin effect	Functional outcome	Clinical ımplication
Endothelium	Increased nitric oxide availability	Improved vasodilation	Reduced ischemia
Macrophages	Altered activation state	Reduced foam cell formation	Plaque stability
Platelets	Decreased aggregation	Reduced thromboxane activity	Lower thrombotic risk
Smooth muscle cells	Reduced proliferation	Limited neointimal formation	Improved vascular remodeling
Innate immunity	Modulation of trained immunity	Reduced persistent inflammation	Residual risk reduction

Abbreviations: NO, nitric oxide

Antithrombotic and hemostatic effects

In addition to their vascular and anti inflammatory actions, statins exert important effects on thrombotic and hemostatic pathways. Thrombosis plays a critical role in the clinical manifestations of atherosclerosis, particularly in acute coronary syndromes where plaque disruption leads to platelet activation and coagulation cascade initiation. Statins influence these processes through multiple mechanisms that are independent of lipid lowering.

One of the primary effects involves modulation of platelet function. Statin therapy has been associated with reduced platelet aggregation and decreased thromboxane A2 production. These changes are partly mediated through improved endothelial nitric oxide availability and reduced oxidative stress, both of which inhibit platelet activation.[26] In addition, statins may directly affect platelet signaling pathways by altering membrane cholesterol composition and reducing prenylation dependent intracellular signaling.

Statins also influence the coagulation cascade. Experimental and clinical studies have shown that statin therapy reduces tissue factor expression in endothelial cells and circulating monocytes. Tissue factor is a key initiator of the extrinsic coagulation pathway and plays a central role in thrombus formation following plaque rupture.[27]

By downregulating tissue factor expression, statins reduce thrombogenic potential at sites of vascular injury.

Another important mechanism involves enhancement of endogenous anticoagulant pathways. Statins have been shown to increase thrombomodulin expression on endothelial surfaces, promoting activation of protein C and thereby exerting anticoagulant effects.[28] This shift toward a less prothrombotic state contributes to improved vascular stability.

Furthermore, statins appear to favorably influence fibrinolysis. Increased expression of tissue plasminogen activator and reduced levels of plasminogen activator inhibitor one have been observed in patients receiving statin therapy.[29] This enhances clot resolution and may reduce the persistence of occlusive thrombi following vascular injury.

Clinical studies support these biological observations. Reduced thrombotic complications and improved outcomes following acute coronary events have been linked to statin therapy even when lipid levels are comparable.[30] These findings suggest that modulation of platelet function, coagulation activity, and fibrinolytic balance represents an important component of the pleiotropic actions of statins.

Taken together, the combined effects on platelet activation, coagulation pathways, and fibrinolysis contribute to a more stable hemostatic environment and may help explain the early clinical benefits observed after statin initiation.

Effects on vascular remodeling and plaque stability

Vascular remodeling and plaque stability are critical determinants of clinical outcomes in atherosclerotic disease. Beyond lipid lowering, statins exert direct effects on the structural components of the vascular wall that contribute to stabilization of atherosclerotic plaques and modulation of disease progression.

One of the central mechanisms involves inhibition of vascular smooth muscle cell proliferation and migration. These processes are regulated in part by small GTP binding proteins such as Rho and Ras, whose activity depends on isoprenoid mediated prenylation. By reducing availability of these intermediates, statins limit smooth muscle cell activation and reduce neointimal formation, thereby influencing vascular remodeling.[31]

Statins also modulate extracellular matrix turnover through effects on matrix metalloproteinases. Increased metalloproteinase activity contributes to degradation of the fibrous cap and promotes plaque vulnerability. Experimental studies have demonstrated that statins reduce expression and activity of these enzymes, leading to enhanced fibrous cap integrity and decreased risk of plaque rupture.[32]

In addition to inhibiting matrix degradation, statins may promote a more stable plaque phenotype through effects on macrophage activity and collagen synthesis. Reduced inflammatory signaling within the plaque microenvironment favors extracellular matrix preservation and contributes to structural stability.[33]

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Imaging studies have provided clinical support for these biological effects. Intravascular ultrasound and optical coherence tomography investigations have shown that statin therapy is associated with reductions in lipid rich plaque components and increases in fibrous tissue content. These structural changes occur even in the absence of marked plaque regression, suggesting that stabilization rather than simple size reduction is a key therapeutic effect.[34]

Furthermore, statins have been linked to modulation of vascular calcification processes. Although the relationship between statins and calcification is complex, some evidence suggests that they may promote transition toward more stable calcified plaque forms, potentially reducing rupture risk.[35]

While statin therapy has been associated with increased coronary calcification in some imaging studies, this finding does not necessarily indicate adverse vascular remodeling. Rather, emerging evidence suggests that statins may promote a transition from lipid rich vulnerable plaques toward more stable calcified phenotypes. This shift reflects reduced inflammatory activity and enhanced structural integrity within the plaque rather than accelerated disease progression.[36] In this context, increased calcification may represent a marker of plaque stabilization rather than heightened rupture risk, supporting the concept that statins influence plaque composition beyond size reduction alone.[37]

Taken together, the ability of statins to inhibit smooth muscle proliferation, regulate extracellular matrix turnover, and promote structural plaque stability represents an important aspect of their pleiotropic actions and may contribute to reduction in acute coronary events.

Myocardial and electrophysiologic effects

Beyond their vascular actions, statins exert important effects on myocardial structure and electrophysiologic stability. These effects are largely mediated through anti inflammatory, antioxidative, and antifibrotic mechanisms that influence cardiac remodeling and electrical conduction.

Atrial fibrillation provides one of the most extensively studied clinical contexts in which these non lipid effects are observed. Inflammation and oxidative stress contribute to atrial structural remodeling and electrical instability. Statin therapy has been associated with reduced incidence of atrial fibrillation, particularly in postoperative settings, suggesting a role in modulation of atrial substrate vulnerability.[38] These effects appear to be linked to attenuation of inflammatory signaling and improved endothelial function within the atrial myocardium.

Statins also influence myocardial fibrosis. Experimental data indicate that inhibition of isoprenoid dependent signaling reduces fibroblast activation and collagen deposition. This may limit adverse structural remodeling and contribute to improved ventricular compliance.[39] Such antifibrotic effects have been proposed as a potential mechanism underlying the observed benefits of statins in selected heart failure populations.

However, large randomized clinical trials have not consistently demonstrated mortality benefit of statin therapy in established heart failure populations. Studies such as CORONA and GISSI HF showed neutral effects on major clinical outcomes despite strong mechanistic rationale for benefit.[40] This apparent dissociation between biological effects and clinical outcomes suggests that while statins may favorably influence myocardial remodeling and inflammatory pathways, these pleiotropic mechanisms do not necessarily translate into improved survival once advanced heart failure is established.[41]

In the context of ischemia and reperfusion injury, statins have demonstrated protective effects at the myocardial level. Enhancement of nitric oxide signaling and reduction of oxidative stress improve microvascular function and may reduce infarct size in experimental models.[42] These mechanisms are consistent with observations of improved myocardial perfusion following statin pretreatment in acute coronary settings.

Statins may also influence ion channel function indirectly through modulation of cellular signaling pathways. Reduced inflammatory activation and improved redox balance contribute to stabilization of myocardial electrophysiology, potentially lowering susceptibility to arrhythmogenesis.[43]

Clinical studies support these mechanistic findings. Reduced occurrence of postoperative atrial fibrillation and improved myocardial recovery following ischemic events have been associated with statin use, even after adjustment for lipid levels.[44] These observations reinforce the concept that statins exert direct myocardial and electrophysiologic effects that extend beyond their lipid lowering properties.

Taken together, modulation of atrial remodeling, attenuation of myocardial fibrosis, and protection against ischemia related injury represent key pathways through which statins contribute to cardiac stability and functional preservation.

Renal and systemic effects

Statins also exert important effects on renal function and systemic vascular homeostasis that extend beyond lipid lowering. The kidney is particularly sensitive to endothelial dysfunction and inflammatory activation, both of which contribute to progression of chronic kidney disease and susceptibility to acute injury. Through improvement of endothelial function and reduction of oxidative stress, statins may enhance renal microvascular integrity and perfusion.[45]

One of the key mechanisms involves attenuation of glomerular endothelial dysfunction. Enhanced nitric oxide availability and reduced oxidative stress promote preservation of glomerular filtration barrier function. Clinical studies have demonstrated modest reductions in proteinuria among patients receiving statin therapy, suggesting a protective effect on renal microvascular structure.[46]

Statins may also influence renal inflammatory pathways. Reduced expression of pro inflammatory cytokines and adhesion molecules limits leukocyte recruitment and vascular injury within the renal circulation. These effects are particularly relevant in conditions characterized by heightened systemic inflammation, where renal dysfunction often reflects microvascular damage rather than structural nephron loss.[47]

In addition to chronic renal protection, statins have been investigated for their potential role in mitigating acute kidney injury related to contrast exposure. Anti inflammatory and endothelial stabilizing effects may reduce susceptibility to contrast induced nephropathy, particularly in high risk cardiovascular populations. Although results across studies are variable, some clinical trials have suggested a reduction in acute kidney injury incidence with short term statin therapy prior to contrast administration.[48]

Beyond systemic anti inflammatory effects, statins may directly influence susceptibility to contrast induced renal injury through

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modulation of endothelial activation and oxidative stress within the renal microcirculation. Improved nitric oxide bioavailability and reduced reactive oxygen species generation may preserve medullary perfusion and limit ischemic tubular injury following contrast exposure.[49] In addition, attenuation of inflammatory cell activation and endothelial dysfunction may reduce microvascular damage, providing a mechanistic link between statin therapy and lower incidence of contrast induced nephropathy observed in high risk cardiovascular populations.[50]

Systemically, statins contribute to improved vascular homeostasis through modulation of endothelial activation and oxidative balance. These effects may extend to multiple organ systems, including cerebral and peripheral circulations, where endothelial dysfunction plays a central pathogenic role.[51]

Taken together, preservation of endothelial integrity, reduction of inflammatory injury, and improvement in microvascular function represent key mechanisms through which statins exert renal and systemic protective effects.

Immunometabolic and innate immune modulation

Beyond their established anti inflammatory effects, statins influence immune cell behavior through modulation of intracellular metabolic pathways. Inhibition of the mevalonate cascade alters not only cholesterol synthesis but also immune cell function by limiting the availability of isoprenoid intermediates that regulate cellular signaling and metabolism. This connection between lipid metabolism and immune regulation forms the basis of the immunometabolic effects of statins.[52]

Macrophages represent a key cellular target in this context. Statin mediated reduction of isoprenoid synthesis affects small GTP binding proteins involved in macrophage activation, migration, and cytokine production. These changes promote a shift toward a less pro inflammatory phenotype and influence intracellular cholesterol trafficking, reducing foam cell formation within the atherosclerotic plaque environment.[53] This mechanism links metabolic modulation directly to plaque stability.

In addition, statins appear to influence innate immune signaling pathways. Experimental data suggest that interference with mevalonate dependent pathways can attenuate toll like receptor mediated responses, thereby reducing downstream inflammatory activation.[54] Such effects may limit excessive immune activation in vascular tissues and contribute to a more controlled inflammatory milieu.

Emerging evidence also indicates that statins may modulate trained immunity, a process through which innate immune cells develop sustained pro inflammatory responsiveness following metabolic or inflammatory stimuli. By interfering with the metabolic programming required for this adaptive response, statins may reduce persistent inflammatory activation associated with atherosclerosis progression.[55]

Collectively, these immunometabolic effects extend the concept of pleiotropy beyond endothelial and vascular signaling to include direct regulation of innate immune function. This broader framework provides a mechanistic link between metabolic pathways and inflammatory processes and may help explain the residual cardiovascular risk reduction observed in statin treated populations independent of lipid lowering.[56]

Clinical translation: where pleiotropy matters most

The pleiotropic effects of statins gain clinical significance when considered across disease states in which lipid levels alone do not fully explain therapeutic benefit. In acute coronary syndromes, statin therapy has been associated with rapid risk reduction that precedes meaningful changes in plaque burden. This early benefit is thought to reflect improvement in endothelial function, reduction in inflammatory activity, and attenuation of thrombogenicity within vulnerable plaques.[57]

In the setting of percutaneous coronary intervention, statins may improve microvascular function and reduce periprocedural myocardial injury. Enhanced nitric oxide bioavailability and reduced oxidative stress contribute to preservation of microcirculatory integrity, which may limit distal embolization related injury and improve myocardial perfusion.[58]

Heart failure represents another clinical context where pleiotropic mechanisms may be relevant. Although large outcome trials have yielded mixed results, experimental and observational studies suggest that statins may influence ventricular remodeling through antifibrotic and anti inflammatory effects. These mechanisms may contribute to improved endothelial myocardial interaction and modulation of adverse structural changes.[59]

In atrial fibrillation, statins appear to reduce arrhythmia burden particularly in postoperative or inflammatory states. This effect is likely mediated through suppression of inflammatory signaling and stabilization of atrial electrophysiologic properties.[60]

Chronic kidney disease also illustrates the clinical importance of non lipid effects. Improvement in endothelial function and reduction in inflammatory activation may contribute to slowing of renal injury and reduction in cardiovascular complications in this high risk population.[61]

In cerebrovascular disease, statins have demonstrated benefits beyond lipid reduction, including stabilization of atherosclerotic plaques and reduction of thrombotic risk. These effects may help explain improved outcomes following ischemic stroke independent of cholesterol lowering magnitude.[62]

Taken together, these observations indicate that the clinical impact of statins extends beyond modification of lipid profiles. The pleiotropic actions discussed in previous sections appear to play a meaningful role in diverse cardiovascular and systemic conditions characterized by endothelial dysfunction, inflammation, and heightened thrombotic risk.[63] The major clinical conditions in which statin pleiotropy may contribute to therapeutic benefit are summarized in Table 3. The potential clinical implications of these pleiotropic mechanisms across cardiovascular and systemic conditions are schematically illustrated in Figure 2.

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Table 3. Clinical conditions ınfluenced by statin pleiotropy

Clinical setting	Key mechanism	Observed ımpact
Acute coronary syndromes	Anti inflammatory and endothelial effects	Early risk reduction
Coronary microvascular dysfunction	Improved nitric oxide signaling	Enhanced microvascular perfusion
Atrial fibrillation	Reduced inflammatory remodeling	Lower arrhythmia burden
Chronic kidney disease	Endothelial stabilization	Reduced proteinuria
Contrast induced nephropathy	Reduced oxidative stress	Lower renal injury risk
Atherosclerotic plaque instability	Matrix stabilization	Reduced rupture tendency

Abbreviations: ACS, acute coronary syndrome; CKD, chronic kidney disease; CIN, contrast induced nephropathy

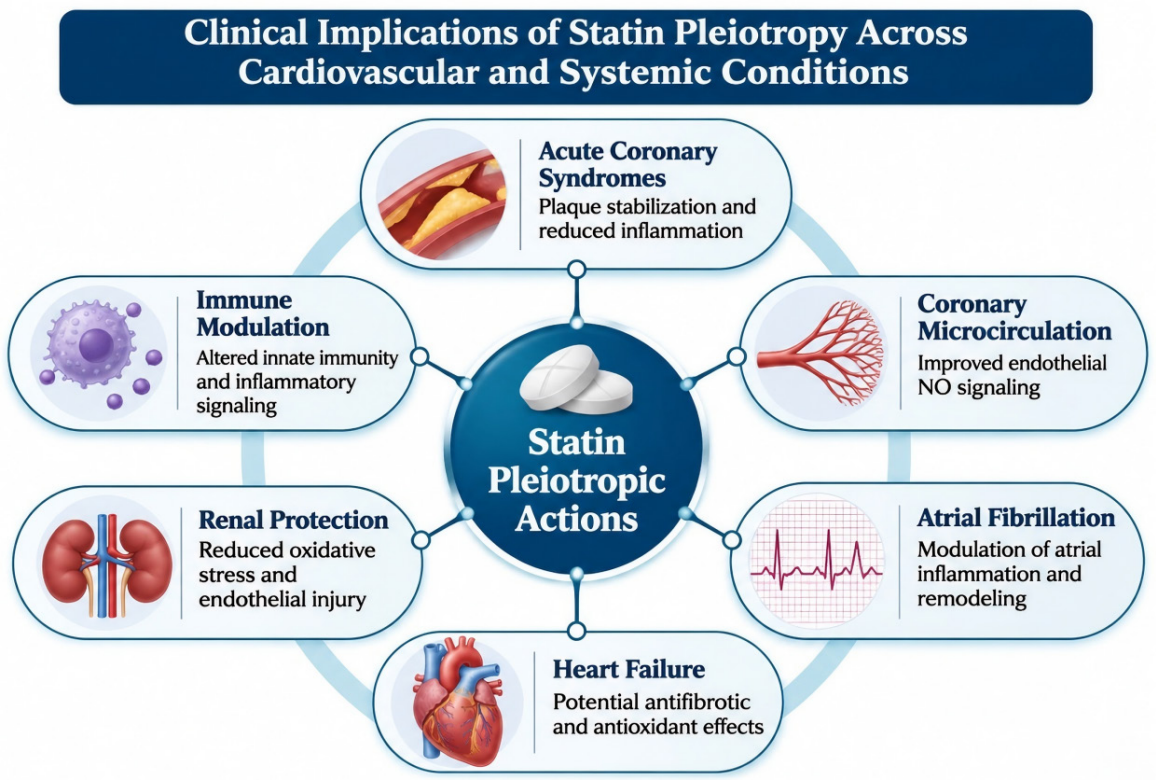


Figure 2 Schematic overview of the potential clinical implications of statin pleiotropy in acute coronary syndromes, coronary microvascular dysfunction, atrial fibrillation, heart failure, renal injury, and immune modulation. The illustrated pathways represent mechanistic and potential clinical associations, with varying levels of evidence supporting their translation into clinical outcomes.

Controversies and Limitations

Despite substantial experimental evidence supporting pleiotropic effects, several controversies remain regarding their clinical relevance and consistency.[64] One of the main areas of debate concerns whether these effects represent a true class property or vary among individual statins. Lipophilic statins such as atorvastatin and simvastatin may more readily penetrate extrahepatic tissues, potentially exerting stronger intracellular signaling effects compared with hydrophilic agents such as pravastatin or rosuvastatin.[65,66] However, clinical data comparing pleiotropic impact across different statins remain inconclusive.

Another unresolved issue relates to dose dependency. Some studies suggest that higher statin doses are required to achieve meaningful anti inflammatory or endothelial effects, whereas others indicate that pleiotropic actions may occur even at moderate doses.[67] This raises questions regarding whether observed benefits reflect pharmacologic thresholds or patient specific responses.

Timing of therapy also appears to be important. Early initiation of statins in acute settings has been associated with improved outcomes, yet it remains uncertain whether this benefit is entirely attributable to pleiotropic mechanisms or to more rapid lipid lowering.[68] Similarly, short term statin use in non atherosclerotic inflammatory conditions has yielded variable results.

In heart failure populations, large randomized trials such as CORONA and GISSI HF did not demonstrate significant mortality benefit despite strong mechanistic rationale. These findings highlight the potential gap between experimental evidence and clinical translation.[40]

In systemic inflammatory conditions such as sepsis, initial observational studies suggested improved outcomes with statin therapy, yet subsequent randomized investigations failed to confirm consistent benefit. This inconsistency underscores the complexity of translating molecular effects into clinical efficacy.[69]

Taken together, these limitations suggest that while pleiotropic mechanisms are biologically plausible and experimentally supported,

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their clinical impact may vary according to patient population, disease context, statin type, and treatment timing.

Future directions

Growing understanding of the pleiotropic effects of statins has generated interest in their potential role beyond traditional lipid driven cardiovascular prevention. Future research may focus on identifying patient populations most likely to benefit from these non lipid effects through biomarker guided strategies. Inflammatory markers, endothelial dysfunction indices, and measures of oxidative stress may help refine therapeutic targeting and optimize individualized treatment approaches.[70]

Emerging evidence suggests that sirtuin 1 (SIRT1), a nicotinamide adenine dinucleotide-dependent deacetylase involved in endothelial homeostasis, oxidative stress regulation, and cellular senescence, may contribute to the pleiotropic effects of statins. Experimental studies have demonstrated that statins can modulate SIRT1 expression through Akt-dependent signaling, potentially enhancing endothelial nitric oxide synthase activity and attenuating endothelial senescence.[71] Furthermore, clinical investigations have suggested that the effects of statins on SIRT1 expression may vary among individual agents.[72] Although SIRT1 activation represents a potential therapeutic target, the influence of SIRT1 activators or inhibitors on statin efficacy remains insufficiently established.[73] Similarly, the clinical utility of circulating SIRT1 measurements for monitoring or optimizing statin therapy has not been established. Further studies are warranted to clarify whether modulation of SIRT1 signaling or assessment of circulating SIRT1 levels could contribute to individualized cardiovascular treatment strategies.

Another area of interest involves combination therapies that leverage complementary mechanisms. Integration of statins with emerging anti inflammatory agents may enhance vascular stabilization and reduce residual risk that persists despite optimal lipid control. This concept is supported by evidence demonstrating that inflammation remains an independent determinant of cardiovascular outcomes even in patients achieving low LDL levels.[74]

Advances in molecular imaging may also improve understanding of how statins influence plaque biology and microvascular function in vivo. Techniques capable of assessing vascular inflammation and endothelial activity may allow more precise evaluation of treatment effects beyond traditional lipid measurements.[75]

In addition, exploration of statin effects in structural heart disease and microvascular dysfunction may expand their therapeutic scope. Conditions characterized by endothelial impairment and inflammatory activation may represent potential targets for pleiotropic modulation.

Persistent residual inflammatory risk despite optimal lipid lowering has emerged as an important therapeutic challenge. In this context, the pleiotropic effects of statins may complement targeted anti inflammatory strategies aimed at reducing vascular inflammation independent of cholesterol levels.[76] Future approaches may involve integration of statin therapy with selective anti inflammatory agents to address both lipid driven and inflammation driven components of cardiovascular risk.[77] In addition, advances in biomarker profiling may enable more precise identification of patients in whom pleiotropic mechanisms contribute substantially to disease modulation, supporting the concept of precision statin therapy based on vascular and inflammatory phenotypes.[78]

As mechanistic insights continue to evolve, integration of pleiotropic concepts into clinical decision making may shift the perception of statins from purely lipid lowering agents toward broader modulators of vascular health.

Conclusion

Statins have long been established as fundamental agents in cardiovascular prevention through their capacity to reduce LDL cholesterol levels. However, a substantial body of mechanistic and clinical evidence indicates that their benefits extend beyond lipid modification. By influencing intracellular signaling pathways within the mevalonate cascade, statins affect endothelial function, inflammatory activity, oxidative balance, thrombotic processes, and vascular remodeling.

These effects contribute to stabilization of the vascular environment and modulation of disease progression across a range of cardiovascular and systemic conditions. Improvement in endothelial nitric oxide bioavailability, suppression of inflammatory signaling, reduction of platelet activation, and attenuation of fibrotic remodeling collectively support the concept that statins act as regulators of vascular biology rather than solely as lipid lowering agents.

The clinical relevance of these actions is particularly evident in settings where early therapeutic benefit is observed, such as acute coronary syndromes and periprocedural interventions, where changes in lipid levels alone cannot fully explain outcome improvement. Similarly, effects on arrhythmogenesis, myocardial remodeling, renal microvascular integrity, and plaque stability suggest a broader role for statins in modulating pathophysiologic processes driven by inflammation and endothelial dysfunction.

At the same time, variability in clinical trial outcomes highlights the need for careful interpretation. The magnitude of pleiotropic effects appears to depend on factors such as statin type, dosage, timing of initiation, and underlying disease context. Future investigations aimed at identifying patient populations most likely to benefit from these mechanisms may further refine therapeutic strategies.

Taken together, the pleiotropic actions of statins represent an important dimension of their pharmacologic profile and provide a mechanistic framework for understanding their impact across diverse cardiovascular conditions beyond lipid lowering alone.

Contributorship

All of the authors contributed planning, conduct, and reporting of the work. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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All of the authors have no conflict of interest.

Artificial intelligence disclosure

The authors confirm that no artificial intelligence or AI-assisted tools were used for interpreting the referenced article or for generating scientific content. Limited assistance was obtained solely for language editing and grammatical refinement, without any involvement in data interpretation, analysis, or conceptual input.

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