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Research Paper

Pleiotropic mechanisms and clinical implications of statins in cardiovascular and neurodegenerative diseases

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ABSTRACT

Background: Statins are HMG-CoA reductase inhibitors widely prescribed for lowering low-density lipoprotein cholesterol and triglycerides while increasing high-density lipoproteins. Beyond lipid regulation, statins exhibit pleiotropic effects that may contribute to cardiovascular and neuroprotective benefits.
Objective: To summarize the pleiotropic mechanisms of statins and their therapeutic relevance in cardiovascular and neurodegenerative diseases, while highlighting current research gaps.
Methods: Relevant evidence from experimental and clinical studies investigating the molecular, anti-inflammatory, antioxidant, endothelial, and neuroprotective effects of statins was reviewed and synthesized.
Results: Statins exert pleiotropic effects partly through inhibition of the Rac/ROCK signalling pathway, increasing endothelial nitric oxide production, reducing inflammation and oxidative stress, and improving vascular smooth muscle function. In cardiovascular disease, statins enhance vascular relaxation, promote angiogenesis, inhibit platelet aggregation, and reduce vascular inflammation, lowering the risk of stroke, heart failure, atherosclerosis, and atrial fibrillation. In neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, and Multiple sclerosis, statins regulate cholesterol homeostasis, suppress neuroinflammation, reduce reactive oxygen species, and support neuronal survival. Improved endothelial function and cerebral blood flow further contribute to neuroprotection.
Conclusion: Statins possess pleiotropic properties beyond lipid lowering, offering therapeutic benefits in cardiovascular and neurodegenerative diseases. However, research gaps remain regarding dose-response relationships, underlying mechanisms, and translation of molecular effects into clinical outcomes.

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1. INTRODUCTION

One of the most widely used lipid-lowering agents are statins, which also called HMG-CoA reductase inhibitors, due to their ability to reduce cholesterol, low-density lipoprotein, triglycerides, and associated cardiovascular events [1]. HMG-CoA reductase inhibitors act by inhibiting the formation mevalonate (MA) from HMG-CoA, which is required for the formation of cholesterol and other isoprenoid compounds [2]. In humans' plasma cholesterol has two sources: dietary intake, where cholesterol is absorbed from food or de novo biosynthesis, were body synthesis cholesterol, mainly in the liver. Statins reduces the de novo cholesterol biosynthesis thus decreases levels cholesterol, where it inhibits the formation of mevalonate and increases the expression low-density lipoprotein (LDL) receptor, thus increasing the uptake of LDL from blood [1], [2]. Based on their lipophilicity, statins are divided into two groups that is lipophilic statins hydrophilic statins. Lipophilic statins include cerivastatin, atorvastatin, simvastatin, pitavastatin and hydrophilic statins includes rosuvastatin and pravastatin [3].

The word pleiotropy comes from the Greek roots "pleio (many) and tropic (affecting). Statin pleiotropy is defined as the ability of statins exhibit multiple pharmacological activities, although pleiotropic effects are described as a single gene affecting multiple biological system or phenotype [4]. In case of drug pleiotropic effects are additional effect of the drug which may not be directly related to original pharmacological effect and these effect maybe expected or unexpected effect [5]. Clinical studies have shown that statins may exert additional effects other than LDL-C reduction, thus indicating that statins can be repurposed for other diseases [3]. Over time, the number of clinical studies, like the landmark HPS and ASCOT-LLA trial, revealed the effect of statins that could not be explained alone by it's the lipid-lowering mechanism. The most likely pleiotropic effect of statins is due to the inhibition isoprenoids synthesis, thus reducing circulating isoprenoid levels in patients receiving treatment with statins [4].

The pleiotropic effect of statin improve cardiovascular function, has significant antioxidant and anti-inflammatory effects, neuroprotective effects, enhances bone formation and renal protective effects [2]. The pleiotropic effects of statins, includes anti-inflammatory, antioxidant, antiproliferative and immunomodulatory effects and also plaque stability, normalisation of sympathetic outflow, and prevention of platelet aggregation, are due to the reduction of isoprenoids compound and also by inactivating of signalling proteins such as Rho, Rac and Ras play vital role in various cellular processes [6]. Statins improve cardiac hypertrophy, endothelial dysfunction, vascular inflammation, and fibrosis independent of the ability of statins to lower LDL cholesterol by impairing Rac-1-mediated NADPH oxidase, thus reducing the production of reactive oxygen species and also inhibiting the Rho/ROCK kinase signalling, which modulates PPAR activity.

A large population suffer from cardiovascular and neurodegenerative disease thus researchers need to introduce new therapies for the treatment as the available therapies fail meet the clinical demand. For many years statin have played an important role in coronary artery disease and stroke. Some clinical trials should evaluate the efficacy of statin prevention of primary and secondary coronary heart disease. Statins exert cardiovascular protective effects as they inhibit the production of isoprenoid compound such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GPP) in the cholesterol biosynthetic pathway due to their pleiotropic effect. Satin demonstrated its effect on the primary prevention of CVD in several clinical studies conducted and thus reduces mortality and morbidity rates modestly in patients suffering from cardiovascular diseases [7]. Several clinical investigations have demonstrated that statin

therapy provides cardioprotective benefits in patients undergoing cardiopulmonary bypass surgery, by reducing lipid peroxidation levels and enhancing cardioprotective markers [8].

Neurodegenerative disorders are characterised by progressive deterioration of neuronal cells and affecting both peripheral and central nervous systems. Due to their antioxidant, anti-inflammatory, anti-apoptotic, and anti-excitotoxicity activities, statin can be useful in various neurological condition or diseases, including Alzheimer's disease (AD), Parkinson's diseases (PD), multiple sclerosis diseases (MD), Huntington's diseases (HD), epilepsy, depression, and stroke, which has been demonstrated in several pre-clinical and clinical trials [9]. In AD and PD statin reduce amyloid plaques and protein aggregation, improve psychomotor symptoms in HD and in MD supports remyelination, thus acting as neuroprotective.

This article comprehensively reviews the pleiotropic effects of statins and their clinical significance in cardiovascular and neurodegenerative diseases.

2. RELATED WORK

2.1 Primary Mechanism of Action of Statins

Statins inhibit cholesterol biosynthesis competitively HMG-CoA reductase and thereby reduce cholesterol, triglycerides, LDL and VLDL and can moderately increase the HDL as explained in Figure 1.

The reduced intracellular cholesterol within hepatocytes activates the protease enzyme, which breakdown the membrane-bound sterol regulatory element-binding proteins (SREBP). The cleaved SREBP will translocate to the nucleus where they bind to sterol response elements (SRE) in DNA, leads to enhances expression of the LDL receptor gene, which finally increases the synthesis of the LDL receptor. This newly synthesised receptor will be translocated cell membrane of the liver. The LDL and VLDL particles in the blood will bind to these receptors present on the cell membrane of hepatocytes. Then subsequently endocytosed and are metabolised into bile acids or salts, and then excreted or recycled. This process will enhance the catabolism of LDL and VLDL cholesterol, which ultimately decreases plasma cholesterol level.

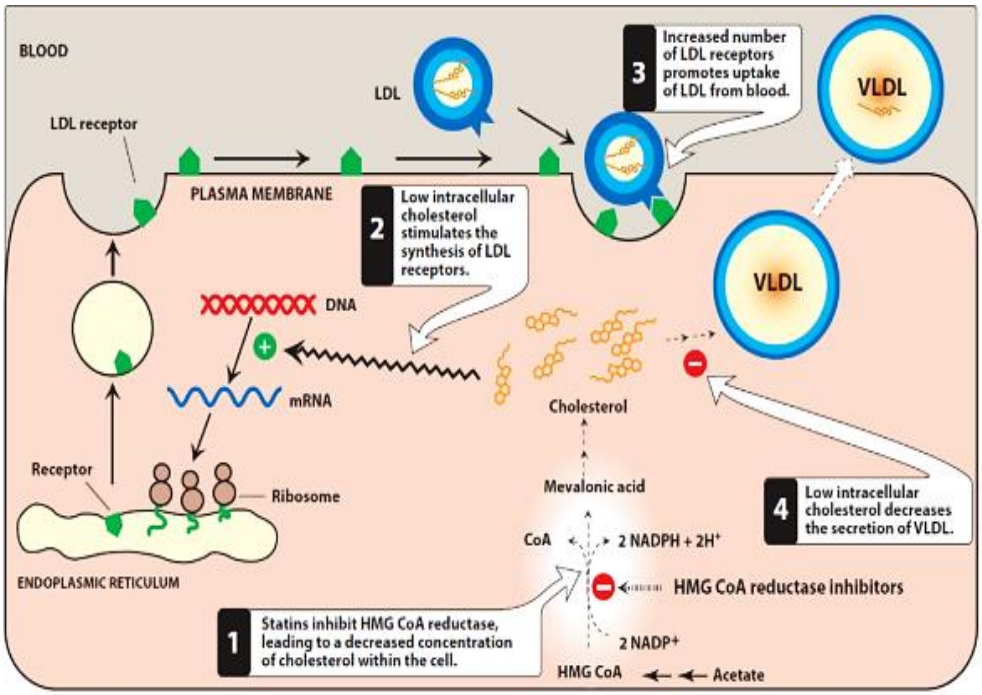


Figure 1. Primary Mechanism of Action of Statins as an Antihyperlipidemic Agent [7]

2.2 Mechanisms Underlying the Pleiotropic Effect of Statins

According to basic and clinical studies, statins may have other effects than reducing LDL cholesterol level, known as pleiotropic effects [9]. Few of the pleiotropic effects are depicted in Figure 2, [10].

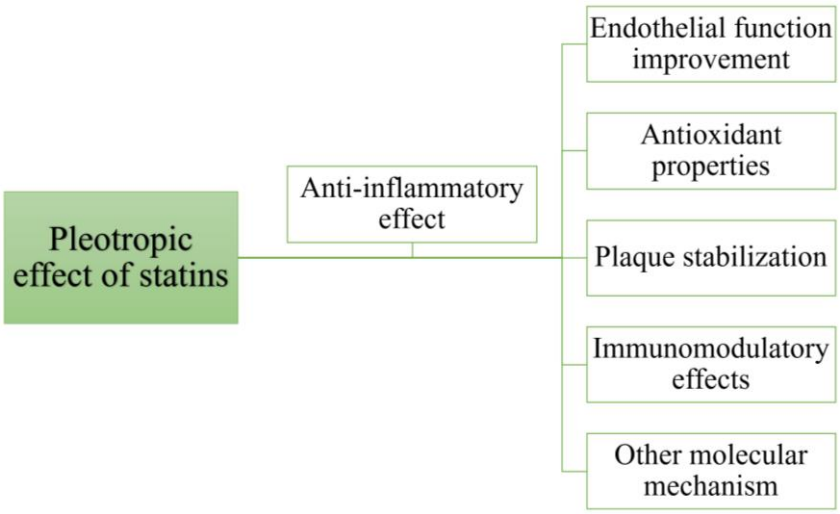


Figure 2. Pleiotropic Effect of Statins

2.2.1 The Rho GTPase Cycle Regulation

Rho proteins are small intracellular GTPases bound to GDP and remain inactive. Guanine nucleotide exchange factors (GEFs) promote GDP to GTP exchange, activating Rho. This activated Rho further activates the ROCK (Rho-associated coiled-coil containing kinase), which mediates the downstream effects of Rho and has an effect on endothelial cells, inflammatory cells, fibroblasts, cardiomyocytes, and vascular smooth muscle cells (SMC) that promote atherosclerosis, heart failure, inflammation and stroke.

Statins inhibit the synthesis of mevalonate, thus decreasing geranylgeranyl (GG) pyrophosphate, leading to the prevention of geranylgeranylation of Rho and the activation of ROCK, as explained in Figure 3, [11]. Pleiotropic effects of statins include enhancement in endothelial function improvement, stabilization the atherosclerotic plaques', reduction oxidative stress and inflammation, and thrombogenic response. Additionally, statins may have a protective effect on the immune system, CNS, and bone.

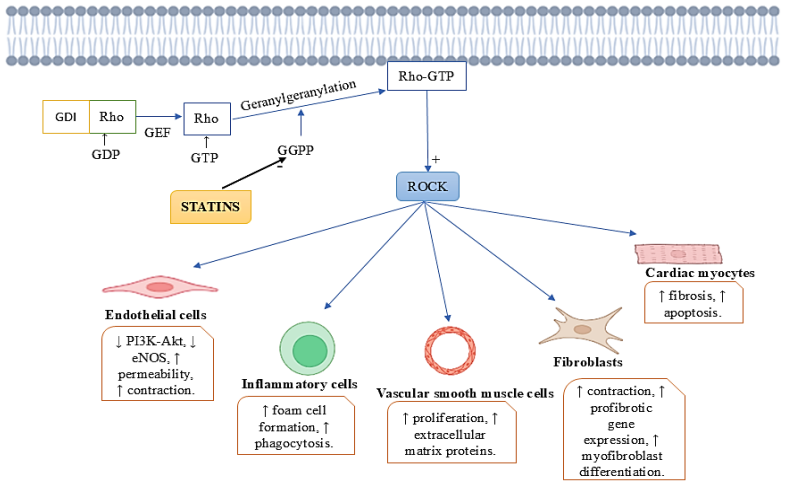


Figure 3. Mechanism of Statin Mediated Inhibition of Rho-GTP and Downstream Cellular Effects

2.3 Regulation of Rac1 Signalling and oxidative Stress Pathways

Rac member of the small GTPase subfamily with a 20-39 kDa monomeric G-protein. The major Rac1 signalling pathway involves activation of Rac1 by NADPH oxidase leading to oxidative stress causing myocardidal hypertrophy. Statins, by inhibition of isoprenonids component will inactive Rac1 induced by NADPH oxidase finally leading to cardiac remodelling, as explained in Figure 4, [12] One of the example for Rac1 signalling is a mouse model where in a mouse model, simvastatin prevented angiotensin II (ANGII) or

pressure overload-induced hypertrophy through inhibition of Rac1-mediated nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase activity in vascular smooth muscle and heart.

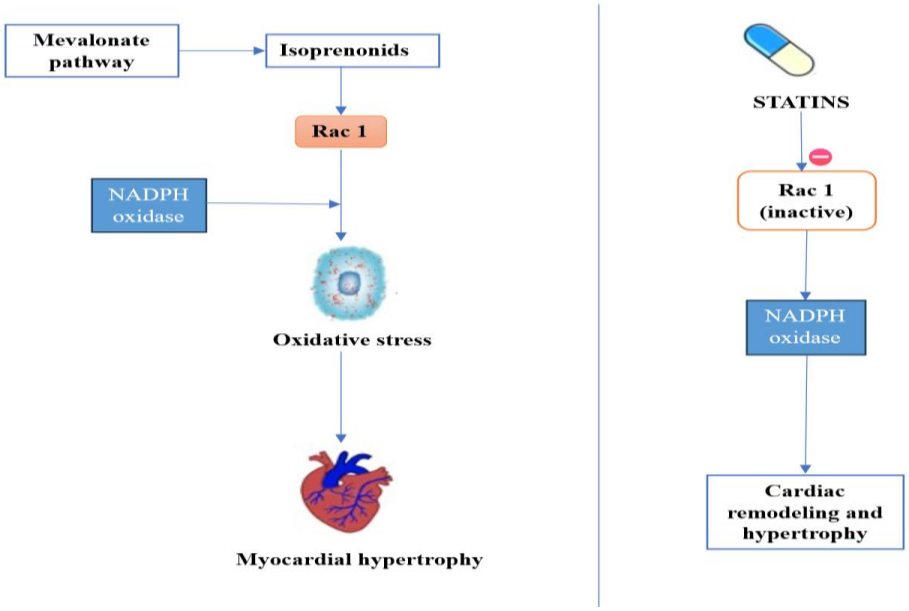


Figure 4. Inhibition of Rac1-Mediated Oxidative Stress and Cardiac Hypertrophy by Statins

2.4 Regulation of PPAR Signalling Pathways by Statins

Statins upregulate the transcription of peroxisome proliferator-activated receptors (PPARs) in immune cells. In THP-1 macrophages exposed to monosodium urate crystals, pretreatment with simvastatin, atorvastatin enhanced both PPAR-γ mRNA and protein levels, while concurrently reducing the expression of the pro-inflammatory NLRP3 inflammasome, caspase-1 and IL-1β [13]. This PPAR-γ induction is linked to the inhibition of lipopolysaccharide-driven inflammatory mediators like tumour necrosis factor-α (TNF-α) and monocyte-chemoattractant protein-1 (MCP-1) through PPAR-α/γ-dependent repression of nuclear factor-κB and activator protein-1 (AP-1) pathways [14].

Simvastatin restores PPAR-α and PPAR-γ receptor expression and lowers inflammatory signalling in adipocytes by reversing TNF-α-induced down-regulation of these receptors. Simvastatin and a PPAR-γ agonist together cause additive regression of atherosclerotic plaques, according to experimental models.

3. METHODOLOGY

The article comprehensively collects, analyses, and summarises existing information on the pleiotropic mechanisms and clinical implications of statins in cardiovascular and neurodegenerative diseases. Statins have a wide range cholesterol independent action beyond lipid lowering effect by inhibiting HMG-CoA, which contributes to their various therapeutic potential. This review article provides insight on wide therapeutic potential of statins, with clinical evidence supporting that statins have effects beyond reducing cholesterol levels. A comprehensive literature search was performed, which included articles published in the English language up to the year 2025 using electronic databases including PubMed, Google Scholar, and ScienceDirect. Due to their wide range of clinical, pharmaceutical and biological research literature, these databases have been selected. Both controlled vocabulary terms and free text keywords are utilised in studies to maximize collection of relevant studies.

Primary keyword includes statins, pleiotropic effects, and HMG-CoA reductase inhibitors. Along with these secondary keywords like Rho/ROCK signalling, oxidative stress, Rac1, isoprenoids, prenylation, oxidative stress, reactive oxygen species, inflammation, endothelial dysfunction, immune modulation, nitric oxide, and PPAR signalling. Disease related keywords such as cardiovascular diseases, stroke, heart failure, atherosclerosis, atrial fibrillation, neurodegenerative disease, Alzheimer's disease, Huntington's disease

Parkinson's disease, and multiple sclerosis. These keywords were used individually and also in combination to cover mechanistic and clinical studies of statins.

Before the initiative of narrative review, inclusion and exclusion criteria were selected. Original research articles, clinical trials, observational studies, meta-analyses, and review articles that addressed the molecular mechanisms, pleiotropic actions, and clinical outcomes of statin therapy were considered as criteria for inclusion in this narrative review. Studies addressing the statin-mediated modulation of inflammatory signalling, oxidative stress pathways, endothelial function, immune responses, and intracellular signalling cascades such as Rho/ROCK, and nitric oxide-related pathways where specially emphasized. Studies solely focused on the lipid-lowering mechanism of statin without addressing pleiotropic mechanisms, lacked sufficient methodological detail or scientific rigour, were duplicate publications, or were published in languages other than English were excluded.

Based on their mechanical and clinical significance, relevant data were selected from the studies. By keeping in mind that the objective of narrative data is obtained narratively rather than statistically. Here, clinical data and mechanistic findings obtained from studies were combined to provide a narrative and particle perspective. Here, the role of mevalonate pathways and isoprenoid intermediates was analysed in detail. Clinical studies included in this review were classified based on disease category and evaluated outcome parameters. This review is mainly focused on intracellular signalling pathways linked with the pleiotropic effects of statins. As this review is based on a previously published article, ethical approval is not required. The selected literature was critically reviewed and narratively summarised to provide a comprehensive overview of the pleiotropic effects of statins and their translational significance in cardiovascular and neurodegenerative disorders.

4. RESULTS AND DISCUSSION

4.1 Pleiotropic Actions

4.1.1 Anti-inflammatory Effects

Evidence supports the anti-inflammatory effects of statins, in subjects taking a statin irrespective of extent of decrease LDL cholesterol, there was the reduction of the levels of C-reactive protein (CRP). Furthermore, statins inhibit molecules involved in the inflammatory response such as IL-1β, TNF-α, and NF-kB in vitro models. The anti-inflammatory actions exerted by the statins are summarised in Table 1, [14].

4.1.2 Endothelial Function improvement

The development of atherosclerosis is influenced by various cardiovascular risk factors, such as high blood sugar levels, smoking and hypertension, frequently through endothelial dysfunction.

Statins play an important role in enhancing synthesis of endothelium-derived nitric oxide synthetase (eNOS) by preventing the prenylation of Rac and Rho proteins. Increases the production of nitric oxide, leading to vasodilation. Nitric oxide also hinders the leukocyte adhesion, prevents platelet aggregation, and reduces smooth muscle proliferation. Due to this, nitric oxide plays a protective role in cardiovascular events Table 1, [15].

4.1.3 Antioxidant Properties

As the primary regulator, Nrf2 along with other proteins involved in the Nrf2/HO-1 signalling pathway, are vital for cellular responses to oxidative stress and statins shown to significantly increase the DNA- Nrf2 binding activity, thus inducing the expression of its target genes, including HO-1 and GPX. By stimulating Nrf2 through the PI3K/Akt pathway, statins also decrease the synthesis of reactive oxygen species (ROS).

4.1.4 Plaque Stabilisation

Current research shows that anti-atherosclerotic medications, especially statins, would suppress the plaque progression. These effects collectively decrease the likelihood of plaque rupture and subsequent

thrombotic events. Recently, the combination of statins with PCSK9 inhibitors has resulted in a significant reduction in LDL-C level by more than 50% along with plaque stabilisation in high-risk patients [16].

4.1.5 Antithrombotic Action

Statins not only reduce the cholesterol level but also reduce the thrombus formation and cardiovascular events, forming the basis of the management of atherosclerotic vascular disease as summarised in Table 1. They also reduce the risk of venous thromboembolism (VTE), although VTE prophylaxis is not yet approved in clinical guidelines [17].

Table 1. Pleiotropic Actions of Statins

Action	Key Mechanism	Effect
Anti-inflammatory	Decrease of Chemokines, Adhesion molecules, MHC Class II, Activity of T cells, Monocyte activation levels and Increase in NO levels, PLA2-COX pathway	Reduced vascular inflammation and plaque formation
Endothelial function	Inhibit prenylation of Rac/Rho, increase eNOS and NO	Vasodilation prevents platelet aggregation and reduces smooth muscle proliferation
Antioxidant	Activation of Nrf2/HO-1 pathway, Reduced ROS	promote antioxidation and restore redox balance
Plaque stabilisation	Suppression of plaque progression, LDL-C reduction	Reduced plaque rupture and thrombosis events
Antithrombotic	Reduced thrombus formation, thrombin, Increase in thrombomodulin and protein C activation	Reduced arterial and venous thrombosis

4.2 Clinical Implications in Cardiovascular Diseases

All studies conducted on the effects of statins for the primary prevention of CVD demonstrated that lowering the LDL cholesterol level is associated with a modest reduction in overall mortality, at least in the short term, and that significant decreases in CVD morbidity. [7], [18]. Statins may be useful in treating patients with CVD, by increasing eNOS expression and NO bioavailability, lowering proinflammatory cytokine and production oxidative stress and preventing ROS production and apoptosis, as shown in Table 2, [13].

4.2.1 Stroke

Many clinical trials have demonstrated the role of statins in stroke prevention. Statins reduce the risk of stroke by 25% and 48% as per the Heart Protection Study and the Treating to New Targets study and JUPITER trial respectively [6], [19].

Effectiveness of atorvastatin for secondary stroke prevention and ability of simvastatin reduces the risk of transient ischemic attack (TIA) were demonstrated in The SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) and Scandinavian Simvastatin Survival Study (4S) respectively [5], [20].

The pleiotropic effect of statin in stroke may be due eNOS, as mice lacking eNOS have an increased infarct size. Also, ROCK inhibitors enhance eNOS and cerebral blood flow, which indicates that the effect of statins in stroke may be mediated through Rho/ROCK [21].

4.2.2 Heart Failure

Statins reduce ROCK activity, hence may be helpful for heart failure patients. A small randomised controlled trial showed statins decrease the QTc interval in heart failure patients [22]. A study was conducted in individuals with severe ischemic and non-ischemic failure; the use of statins reportedly reduces the mortality rate [23]. Similarly, a randomised study was conducted to compare ezetimibe 10 mg

and simvastatin 10 mg in heart failure, LDL-C reduction upto 15% in both groups, but there is improved radial artery flow-dependent vasodilation, increased functionally active endothelial progenitor cells and superoxide dismutase only in simvastatin.

4.2.3 Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the vascular wall initiated by elevated levels of LDL-C and is mediated by activated T lymphocytes, B lymphocytes, macrophages, and smooth muscle cells. Statins reduce Rac1-mediated ROS species production and oxidation-sensitive inflammatory signalling pathways. In vitro studies showed statins inhibited monocyte chemoattractant protein-1 expression, IL-6–induced monocyte chemotaxis, block Janus kinase/ signal transducers and activator of transcription (JAK/STAT) pathway, an effect that was reversed by GGPP.

4.2.4 Atrial Fibrillation

AF is a complex disorder with a variety of predisposing cardiac and non-cardiac factors, such as atherosclerosis, obesity, diabetes, and other pro-inflammatory diseases. AF is linked with elevated atrial fibrosis and abnormal autonomic nervous system activity, and while it is association with cardiac risk factors, it is not linked with raised LDL-C level. Animal models indicates that statins may lower AF incidence by prolonging the atrial refractory period, reducing pro-inflammatory markers like CRP, and desensitizing beta-adrenergic stimuli, and the effect was blocked by GGPP and mevalonate. JUPITER trial demonstrated statins due the anti-inflammatory effects of may reduce AF up to 27% [24].

Table 2. Pleiotropic Benefits of Statins in Cardiovascular Disorders

Disease	Primary Mechanisms	Clinical Outcome
Stroke	Increase in eNOS activity, Rho/ROCK pathway inhibition and anti-inflammatory effects	Reduced stroke incidence and infarct size, improved cerebral blood flow
Heart Failure	reduced ROCK activity, improved endothelial function and antioxidant effects	Reduced QTc interval and mortality, improved vascular function
Atherosclerosis	reduced Rac1-mediated ROS, inhibition of MCP-1 and JAK/STAT signalling	Attenuation of vascular inflammation and plaque progression.
Atrial Fibrillation	Anti-inflammatory effects, reduced CRP, and autonomic modulation	Reduced AF risk and atrial remodelling

4.3 Neuroprotective Effects in Neurodegenerative Diseases

Neurodegenerative disorders are characterised by the gradual degeneration of neuronal cells, which impacts both the central and peripheral nervous systems. Statins due to their antioxidant effect and anti-inflammatory, may be useful for neurodegenerative diseases, as shown in Table 3.

4.3.1 Alzheimer's Disease

The development of AD has been found to significantly influenced by cholesterol metabolism [25]. Amyloid beta (Aβ) plaques or lesions, and neurofibrillary tangles clinical characteristics of AD are. Several studies showed that the use of statins may help in the management of AD and may exhibit neuroprotective actions. Besides reducing Aβ plaques, statins, which simvastatin, showed clinical evidence that they inhibit several inflammatory mediators, inhibit microglial activation, enhances stimulation of Brain Derived Neurotropic Factor (BDNF), suppress iNOS mediated inflammatory responses, and inhibit apoptosis, as explained in Figure 5, [26]. Statin therapy is associated with significant reduction in the risk of all-cause dementia and AD up to 21% and 29% respectively according to meta-analysis [13], [27].

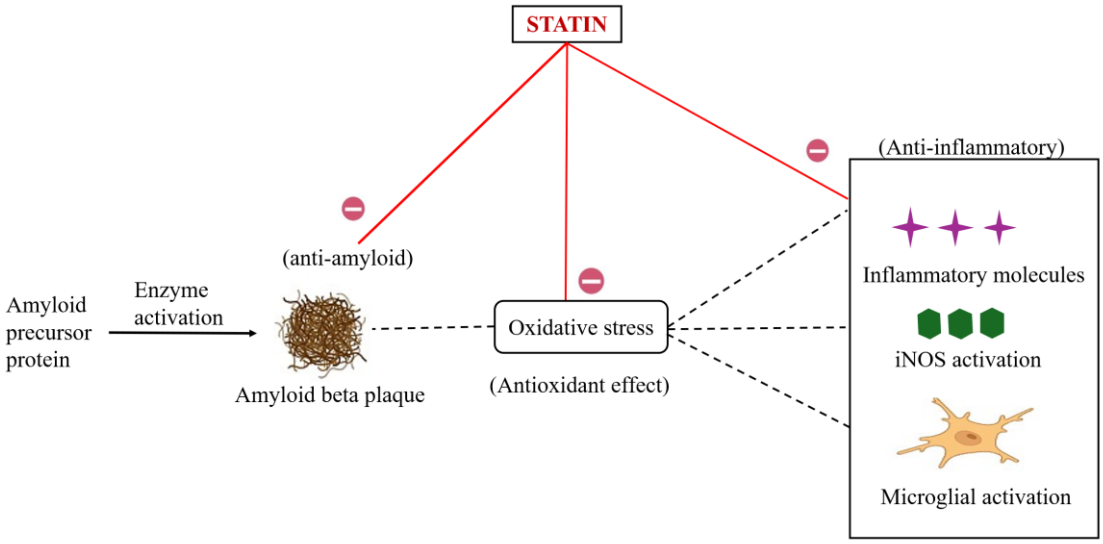


Figure 5. Pleiotropic Effect of Statin in Alzheimer's Disease

4.3.2 Parkinson's Disease

The histopathological markers indicates that PD characterized by aggregation of α-synuclein protein, known as Lewy bodies, malfunction of the mitochondrial Electron Transport Chain (ETC), build-up of oxidative stress and elevation of the proinflammatory mediators. Use statins showed a reduction in aggregation α-synuclein by decrease in the cholesterol level. Statin not only prevents protein aggregation but also as a powerful antioxidant and anti-inflammatory effect explained in Figure 6.

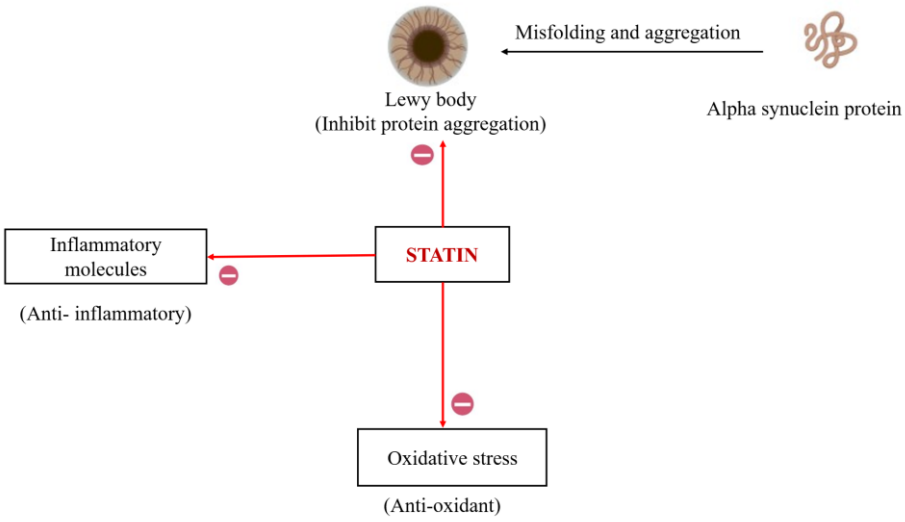


Figure 6. Pleiotropic Effect of Statins in Parkinson's Disease

4.3.3 Huntington's Disease

HD caused by abnormal expansion of the C-A-G (cytosine, adenine, guanine) trinucleotide repeat sequences in the huntingtin gene [HTT], result in the production of a mutant huntingtin protein. Treatment with statins will activate the SREBP-2 signalling, leading to an increase in cholesterol synthesis and transport of cholesterol from astrocytes into neurons, lowering TNF-alpha, IL-1 and reducing neuroinflammation, upregulating NO synthase, maintaining and protecting the membrane against NMDA-mediated cellular excitotoxicity, and producing neurogenesis by stimulating and enhancing the vascular endothelial growth factor and BDNF, as explained in Figure 7.

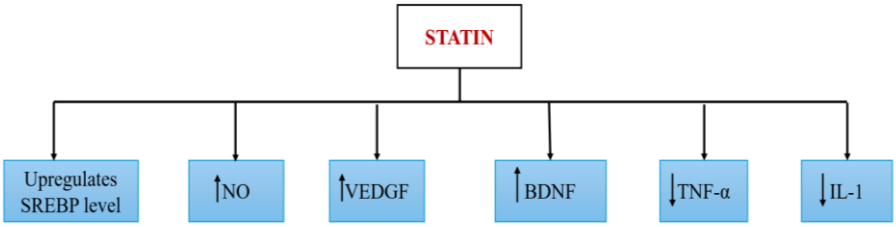


Figure 7. Pleiotropic Effect of Statins in Huntington Disease

4.3.4 Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disorder marked by persistent inflammation and demyelination [28]. Statins inhibit the precursor for the production of cholesterol, mevalonate, thereby inhibiting FPP and GGPP which are responsible for isoprenylation and activation of Roh, Rac and Ras proteins. Statins efficiently block activation and proliferation of macrophages, T cells and B cells, reduce the expression of adhesion molecules and promote remyelination explained in Figure 8.



Figure 8. Pleiotropic Effect of Statins in Multiple Sclerosis

Table 3. Pleiotropic Effects of Statins in Neurodegenerative Diseases

Disease	Key Pathology	Major Effects of Statins
Alzheimer's disease	Aβ plaques, neurofibrillary tangles, and neuroinflammation	Inhibit Aβ plaque formation and microglial activation, antioxidant and anti-inflammatory effects
Parkinson's disease	Dopaminergic neuron loss, α-synuclein aggregation	Inhibit α-synuclein aggregation, antioxidant and anti-inflammatory effects
Huntington's disease	Mutant huntingtin, excitotoxicity, and inflammation	Decrease in TNF-α and IL-1, increase in neuronal cholesterol transport, NO, BDNF
Multiple sclerosis	Autoimmune demyelination, T-cell activation	Inhibition of T/B cells and macrophages enhanced remyelination

4.4 Safety and Adverse Effects

Satin therapy significantly reduced morbidity and mortality in primary and secondary prevention of CVD. Patients with hypothyroidism, alcohol abuse, multiple medical co-morbidities and polypharmacy have an increased risk of developing statin-related myopathy.

Statin decreases risk of atherothrombotic stroke and total stroke but may be associated with slight increase in the risk of hemorrhagic stroke in cerebrovascular disease patients [28].

Some statins at higher doses, cause an increases the risk of developing diabetes. Overall, statins appear to be safe in most patients, and benefits of statin therapy outweigh the potential risks.

4.5 Future Prospectives

Future research should focus on the development of nanoparticle formulation, BBB penetrant analogues, and precision-based statin therapy to optimise safety and efficacy. Development of precision medicine by using pharmacogenomics can optimise the efficacy and reduce the risk [29]. Patients most likely to benefit from pleiotropic effects can be identified with the help of biomarker-based monitoring, such as endothelial function indices. However, there also exist several important research gaps, including an incomplete understanding of dose-response relationships for pleiotropy and how the molecular effect of statins actually leads to the clinical benefits.

5. CONCLUSION

Statins were first discovered as lipid-lowering drugs; later, they have demonstrated pleiotropic effects that extend beyond lowering cholesterol levels. They enhance endothelial nitric oxide production, lower inflammation, decrease oxidative stress, and improve vascular smooth muscle function by blocking the Rho/Rac signalling pathway. These mechanisms contribute to CVS and CNS protection benefits. In cardiovascular disease, the pleiotropic effect of statins increases vascular relaxation, improves plaque stability, and protects against major cardiovascular conditions like stroke, atherosclerosis, heart failure, atrial fibrillation etc, leading to significant cardio protection independent of LDL cholesterol lowering. Similarly, in neurodegenerative diseases, statins exhibit neuroprotection by decrease neuroinflammation and oxidative stress, and attenuating pathological mechanisms in Alzheimer's, Parkinson's, Huntington's, and multiple sclerosis. Future research should focus on the development of nanoparticle formulation, BBB penetrant analogues, and precision-based statin therapy to optimise safety and efficacy.

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Dr. Karunakar Hegde		✓				✓		✓	✓	✓	✓	✓	✓	

C: **C**onceptualisation
M: **M**ethodology
So: **So**ftware
Va : **Va**lidation
Fo: **Fo**rmal analysis
I: **I**nvestigation
R: **R**esources
D: **D**ata Curation
O: Writing-**O**riginal Draft
E: Writing-Review & **E**diting
Vi: **Vi**sualisation
Su: **Su**pervision
P: **P**roject administration
Fu: **F**unding acquisition

Conflict of Interest Statement

The authors declare no conflict of interest regarding the publication of this article.

Informed Consent

Not applicable. This article is a narrative review based on previously published studies and does not involve any experiments on human participants.

Ethical Approval

Not applicable. Ethical approval was not required for this study as it is a narrative review of existing literature and does not involve human or animal subjects.

Data Availability

Data sharing does not apply to this article as no new data were generated or analysed during the current study.

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