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Role of statins: A review

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Abstract
Cardiovascular disease (CVD) remains the leading cause of death globally. Over decades of research, it is firmly established that elevated LDL-C levels significantly contribute to atherosclerosis and CVD. Statin therapy is very effective in lowering LDL-C, supported by robust evidence demonstrating reduced cardiovascular events and mortality. Statins inhibit the enzyme HMG-CoA reductase, which plays a key role in cholesterol synthesis. Beyond lowering cholesterol, they possess additional beneficial properties including anti-inflammatory effects and plaque stabilization. Statin therapy forms the foundation of lipid-lowering treatments for secondary CVD prevention and conditions like familial hypercholesterolemia or diabetes. Evidence also supports statin use in some moderate/low risk primary prevention settings. However, risk assessment tools have limitations in identifying individuals with substantial lifelong CVD risk. Statins reduce major vascular events by ~22% per 1 mmol/L LDL-C reduction. Benefits are demonstrated with various statins like rosuvastatin across differing baseline CRP levels. High-intensity statins regress coronary atherosclerosis. Statin therapy confers advantages in chronic kidney disease patients except end-stage disease requiring dialysis. It lowers CVD events in diabetes by 21% per 39 mg/dL LDL-C reduction. Side effects like new onset diabetes, neurocognitive dysfunction, and hepatotoxicity may occasionally occur with statins.

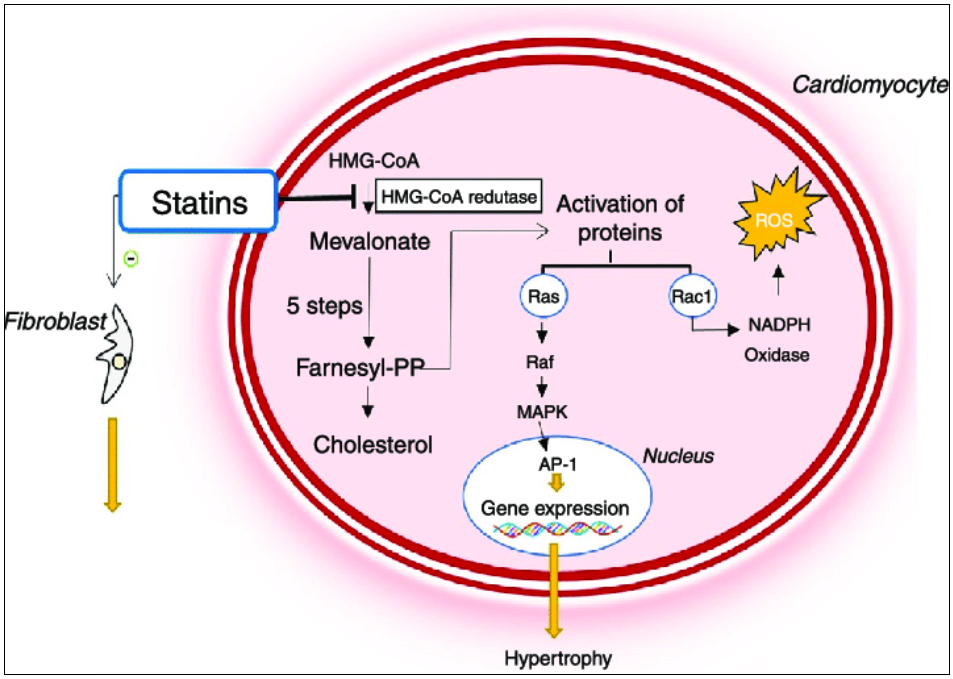
Keywords: Statins, cholesterol, cardiovascular diseases, atherosclerosis, LDL-C

Introduction

Cardiovascular disease (CVD) continues to be the leading global cause of mortality. Over decades of research, it has been firmly established that low-density lipoprotein cholesterol (LDL-C) plays a pivotal role in the development of atherosclerotic CVD. Statin therapy, supported by a substantial body of evidence, has proven its exceptional effectiveness in reducing LDL-C levels and subsequently lowering the risk of cardiovascular events. As a result, it is currently the cornerstone of lipid-lowering treatments, as recommended by international guidelines. Statin therapy is recommended for individuals in the secondary prevention of atherosclerotic CVD and for those with genetic predispositions like familial hypercholesterolemia. However, this strategy primarily targets individuals at the highest risk, overlooking the fact that a significant portion of cardiovascular events occurs in individuals at moderate to low risk. Moreover, there is emerging evidence supporting the use of statins in primary prevention, particularly in individuals with conditions like diabetes mellitus, chronic kidney disease, and a high predicted risk of future atherosclerotic CVD according to risk assessment tools. Nevertheless, these risk prediction tools have their limitations, particularly in identifying individuals with low short-term but substantial lifelong cardiovascular risk.

Mechanism of action

There is a suggestion that the remarkable and substantial benefits observed with statin therapy may be attributed not only to the reduction in cholesterol levels but also to additional properties or mechanisms of action that extend beyond cholesterol-lowering [1]. The positive impacts of statins in cardiovascular disease primarily stem from their ability to improve the lipid profile, hinder LDL oxidation, possess anti-inflammatory properties, block the migration of immune cells, and restrain the proliferation of smooth muscle cells. Furthermore, statins exhibit anti-atherosclerotic characteristics by preventing the formation of new atherosclerotic lesions and bolstering the stability of existing plaques through the reduction in tissue factor (TF) expression. Additionally, statins indirectly promote the production of nitric oxide by the endothelium and reduce platelet aggregation. These effects contribute to a decreased risk of acute coronary events [2, 3]. Among these risk factors, none has garnered more attention than cholesterol. We now have a deeper understanding that cholesterol synthesis occurs through a series of reactions in the mevalonate pathway, starting from acetyl-coenzyme A (acetyl-CoA). This synthesis primarily takes place in the liver, and the conversion of acetyl-CoA to mevalonate is facilitated by the rate-limiting enzyme known as 3-hydroxy-3-methylglutaryl-CoA reductase. In a significant breakthrough in 1973, the Japanese scientist Akira Endo successfully isolated the first-known inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase, which was initially referred to as compactin. This discovery laid the foundation for the development of statins, a class of medications that have revolutionized the management of cholesterol and cardiovascular health [4, 5]. Statin therapy stands out for its exceptional effectiveness in lowering LDL-C levels and reducing the risk of cardiovascular events. This superior efficacy is supported by a more extensive body of evidence compared to other lipid-modifying therapies like fibrates, nicotinic acid, bile acid sequestrants, and ezetimibe. It is for this reason that statin therapy is currently considered the primary approach in lipid-lowering therapy [6, 7].



Statins on cardiovascular system

Blocking the synthesis of cholesterol results in reduced cholesterol generation and an increase in the expression of LDL receptors [8]. Lipophilic statins primarily traverse cell membranes through passive diffusion, whereas pravastatin and rosuvastatin rely on activated carrier-mediated transport involving organic anion transporting polypeptide 1B1. These two statins exhibit greater selectivity for hepatic tissues [9, 10]. Similar transporters can be found in other tissues, including organic anion transporting polypeptide 1A4 and organic anion transporting polypeptide 2B1. However, it's uncertain how effective these transporters are in carrying hydrophilic statins [12, 13]. Leukocyte function–associated antigen-1 plays a role in leukocyte movement and the activation of T-cells, and it binds to intercellular adhesion molecule-1 [14]. Intercellular adhesion molecule-1 (ICAM-1) is essential for monocyte adhesion to the endothelium, and it serves as a biomarker for coronary events. The levels of ICAM-1 can be lowered by atorvastatin [15].

Benefits of statins on cholesterol

Statins hold the distinction of being the most commonly prescribed and well-supported lipid-lowering medications globally. They are highly effective in lowering LDL-C levels and have a robust body of evidence supporting their role in reducing cardiovascular morbidity and mortality, both in primary prevention (preventing the first occurrence of cardiovascular events) and secondary prevention (preventing recurrent cardiovascular events in individuals with a history of such events) [16].

The positive effects of rosuvastatin were observed in both high and normal CRP (C-reactive protein) groups. Although rosuvastatin did reduce CRP levels, findings from the HOPE-3 study indicate that the advantages of statins may primarily stem from their ability to lower LDL-C (low-density lipoprotein cholesterol) [17] Intensive high-dose statin therapy has shown remarkable advantages in reducing plaque buildup, which is believed to result not only from their potent LDL-C (low-density lipoprotein cholesterol) lowering effects but also from their anti-inflammatory properties [18, 19]. mA meta-analysis underscores the advantages of lowering LDL-C (low-density lipoprotein cholesterol), revealing that for every 1 mmol/L (38.7 mg/dL) reduction in LDL-C, there is a substantial 22% relative risk reduction in major vascular and coronary events [20]. To explore the potential benefits of statin therapy in patients with heart failure (HF), two randomized controlled trials were initiated with a specific focus on statin treatment in HF populations. The GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca) trial established the GISSI-HF trial for this purpose [21].

Effect of statins on renal dysfunction

Another topic of discussion revolves around individuals with chronic kidney disease (CKD), which is characterized by either an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m² or those with maintained eGFR but an elevated urinary albumin-to-creatinine ratio of 3 mg/mmol or higher for a minimum of three months. It's important to note that CKD is linked to an elevated risk of cardiovascular disease (CVD) [22]. Patients with high serum creatinine levels (above 150 µmol/L for men and 130 µmol/L for women) were randomly given either simvastatin and ezetimibe or a placebo. The treatment group showed a significant 17% reduction (P=0.0021) in the primary outcome, which included events like heart attacks, coronary death, strokes, or revascularization. Notably, 37% of the treatment group had an eGFR of 30-60 mL/min per 1.73 m², and 41% had an eGFR of 15-30 mL/min per 1.73 m². However, there were no significant benefits in the primary outcome for patients already on hemodialysis, which aligns with findings from the 4D trial (Die Deutsche Diabetes Dialyse) [23]. Because predicting clinical outcomes in individuals with chronic kidney disease (CKD) plays a crucial role in providing patient guidance and treatment strategies, the International CKD Prognosis Consortium has created a calibrated risk assessment tool. This tool can forecast when and under what circumstances clinical events are likely to occur in patients with significantly reduced estimated glomerular filtration rate (eGFR), using readily available clinical data [24].

Effects of statins on diabetes

Diabetes elevates the risk of CVD and CKD. Effective glycemic control helps slow diabetic nephropathy, regardless of the medication used. Current guidelines suggest personalized HbA1c targets, typically aiming for an HbA1c below 7%, while prioritizing the prevention of hypoglycemia [25]. In 2008, a meta-analysis of 14 trials involving diabetic patients found that statin therapy significantly reduced major vascular events by 21% per 39 mg/dL reduction in LDL-C levels, with similar benefits for those with and without diabetes [26]. This effect remained consistent regardless of prior vascular disease or initial LDL-C levels. It also reduced all-cause mortality by 9% and mortality due to coronary heart disease [27]. While the incidence and prevalence of diabetes mellitus have been on the rise in the population, advancements in treatment have effectively lowered the risk of negative cardiovascular outcomes [28].

Effects of diabetes on stroke

Connecting diabetes to stroke risk is complex due to different stroke types. In a study of 116,316 women followed for 26 years, type 1 diabetes increased the risk of both ischemic and hemorrhagic strokes, while type 2 diabetes raised the risk of ischemic but not hemorrhagic strokes [29]. Diabetes mellitus worsens stroke outcomes, similar to its impact on coronary artery disease. A study of nearly 12,000 men in Western Australia revealed that diabetes significantly heightened the risk of death in stroke patients [30]

Side effects

Other side effects of statin therapy, which can be more serious, include new-onset type 2 diabetes mellitus, neurological and neurocognitive effects, hepatotoxicity, renal toxicity, and other conditions [31] In a research study involving 1,922 patients in sinus rhythm who underwent elective cardiac surgery and were administered perioperative rosuvastatin at a dosage of 20 mg or a placebo, it was found that statin therapy did not have a preventive effect on postoperative atrial fibrillation or myocardial damage [32]. Likewise, in a substantial clinical trial involving patients undergoing cardiac surgery, the use of atorvastatin did not lead to a decrease in the risk of acute kidney injury [33].

Conclusion

This review has highlighted the crucial role of statins in the management of cardiovascular disease (CVD) and the reduction of associated risks. Statins, through their inhibition of the HMG-CoA reductase enzyme, effectively lower LDL cholesterol levels, which is a well-established risk factor for atherosclerosis and CVD. However, the benefits of statins extend beyond their cholesterol-lowering effects, as they possess additional properties such as anti-inflammatory effects, plaque stabilization, and improvement of endothelial function. Extensive evidence from clinical trials and meta-analyses has demonstrated the remarkable efficacy of statins in reducing major cardiovascular events, including myocardial infarction and stroke, both in primary and secondary prevention settings. The benefits of statins have been observed across various patient populations, including those with diabetes, chronic kidney disease, and high cardiovascular risk profiles. Furthermore, high-intensity statin therapy has shown promising results in promoting the regression of coronary atherosclerosis, likely due to its potent LDL-C lowering capabilities and anti-inflammatory properties. While statins are generally well-tolerated, it is important to be aware of potential side effects, such as new-onset diabetes, neurocognitive dysfunction, and hepatotoxicity, which may occasionally occur. Overall, the findings presented in this review reinforce the importance of statin therapy as the cornerstone of lipid-lowering treatments for the effective management of cardiovascular disease risk and the prevention of cardiovascular events. Continued research and clinical practice guidelines will further refine the optimal utilization of statins in various patient populations.

Acknowledgments

Author contributions

All authors contributed equally

Conflict of interest

Non to declare

Ethics approval

Non to declare

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