STATINS IN MODERN CARDIOLOGY: FROM DISCOVERY EVIDENCE-BASED CARDIOVSCULAR PREVENTION

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Abstract. Statins stand among the most consequential pharmacological advances of the twentieth century, reshaping the management of dyslipidaemia and the prevention of atherosclerotic cardiovascular disease. Discovered through systematic screening of fungal cultures by Akira Endo in the 1970s, these HMG-CoA reductase inhibitors have evolved across successive generations from naturally derived compounds such as lovastatin and pravastatin to highly potent synthetic agents including atorvastatin, rosuvastatin, and pitavastatin. Landmark trials-the 4S, WOSCOPS, HPS, and TNT studies among them established mortality benefit across the cardiovascular risk spectrum, while the Cholesterol Treatment Trialists' Collaboration meta-analyses confirmed that each 1 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C) lowers the risk of major vascular events by approximately 22%. Residual cardiovascular risk, statin intolerance, and the limitations of monotherapy in familial hypercholesterolaemia subsequently drove the development of ezetimibe, PCSK9 inhibitors, bempedoic acid, and RNA-based therapeutics. This review traces the historical trajectory of statin research, examines the mechanistic basis of their cardioprotective effects, and situates their role within contemporary evidence-based guidelines.

Keywords: statins, HMG-CoA reductase inhibitors, LDL cholesterol, cardiovascular risk, atherosclerosis, dyslipidaemia, primary prevention, secondary prevention, statin intolerance, lipid-lowering therapy

Introduction

Cardiovascular disease (CVD) remains the leading global cause of death, claiming an estimated 17.9 million lives annually according to the World Health Organization. Atherosclerosis and its clinical sequelae myocardial infarction, ischaemic stroke, and peripheral arterial disease share a common pathophysiological substrate involving disturbed lipid metabolism, endothelial dysfunction, and chronic low-grade inflammation. Among modifiable risk factors, elevated plasma LDL-C occupies a central position, supported by epidemiological, genetic, and interventional evidence accumulated over more than six decades [1].

The realisation that fungi produce natural inhibitors of cholesterol biosynthesis opened an entirely new therapeutic chapter. Over the subsequent four decades, statins became the backbone of lipid-lowering pharmacotherapy, substantially reducing cardiovascular morbidity and mortality across primary and secondary prevention settings alike. Their clinical success catalysed a broader wave of pharmacological innovation, yielding agents that now complement or replace statins in patients who cannot tolerate them or require deeper LDL-C lowering [2].

This review outlines the history of statin discovery and development, examines the mechanisms underlying their cardiovascular benefits, and appraises their position within contemporary evidence-based cardiovascular prevention.

Discovery and Early Development

The statin story begins in early 1970s Tokyo, where biochemist Akira Endo, inspired by Alexander Fleming's discovery of penicillin from mould, systematically screened more than 6,000 fungal cultures in search of natural inhibitors of cholesterol synthesis. In 1973, Endo and colleagues at Sankyo isolated compactin (mevastatin) from Penicillium citrinum, identifying it as a potent competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase-the rate-limiting enzyme in the hepatic mevalonate pathway. Though compactin was never commercialised owing to safety signals observed in animal studies, its discovery provided the conceptual and pharmacological framework upon which all subsequent statins were built [3].

Working independently, researchers at Merck & Co. isolated lovastatin from Aspergillus terreus in 1979. Lovastatin received FDA approval in 1987, becoming the first commercially available statin in clinical practice. Pravastatin and simvastatin followed in 1991, both derived or semi-synthesised from natural fungal precursors. These first-generation compounds shared a dihydroxyheptanoic acid pharmacophore that mimics the HMG-CoA substrate and achieved LDL-C reductions in the range of 20-35% [3, 4].

The transition to fully synthetic statins brought a qualitative leap in potency. Fluvastatin (1994) was the first entirely synthetic agent, followed by atorvastatin (1996) and rosuvastatin (2003) compounds capable of reducing LDL-C by 40-55% and up to 60%, respectively, at maximum doses. Pitavastatin, approved in Japan in 2003 and the United States in 2009, occupies a distinct pharmacological niche owing to minimal CYP3A4 metabolism and a neutral effect on glycaemia, properties that set it apart within the third generation [4].

Mechanism of Action and Pleiotropic Effects

All statins act by competitively inhibiting HMG-CoA reductase, which catalyses the conversion of HMG-CoA to mevalonic acid in hepatocytes-the first committed step in cholesterol biosynthesis. Intrahepatic cholesterol depletion upregulates LDL

receptor expression on hepatocyte surfaces through proteolytic activation of sterol regulatory element-binding protein 2 (SREBP-2), enhancing clearance of circulating LDL particles. The result is a dose-dependent reduction in plasma LDL-C, alongside decreases in VLDL cholesterol and triglycerides and modest increases in HDL cholesterol [1, 5].

Beyond lipid lowering, statins exert pleiotropic effects that may independently contribute to cardiovascular benefit. These include improved endothelial function through enhanced nitric oxide bioavailability, plaque stabilisation via attenuation of macrophage infiltration and metalloproteinase activity, suppression of systemic and vascular inflammation through NF-κB inhibition, antioxidant activity, and modulation of platelet aggregation and coagulation pathways. While the clinical weight of these effects relative to LDL-C reduction has long been debated, their importance in acute cardiovascular settings-particularly in the peri-infarction period-is increasingly accepted [5, 6].

The classification of statins into generations, although somewhat arbitrary, reflects important pharmacological differences. First-generation statins (lovastatin, pravastatin, and simvastatin) are fungal-derived compounds characterized by moderate lipophilicity and an ability to reduce low-density lipoprotein cholesterol (LDL-C) levels by approximately 20-35%. Second-generation statins (fluvastatin and cerivastatin) were synthetic compounds; however, their clinical use remained limited. Third-generation statins, including atorvastatin, rosuvastatin, and pitavastatin, comprise highly effective, long-acting agents that currently dominate clinical practice.

The concept of “fourth-generation” lipid-lowering therapy requires careful definition. In a narrow sense, it refers to agents that extend the traditional statin paradigm through improved pharmacokinetic properties and additional metabolic benefits, with pitavastatin often considered a representative example. More broadly, the term encompasses novel lipid-lowering drug classes that are used either in combination with statins or as alternatives in patients who are unable to tolerate statin therapy. These agents include PCSK9 inhibitors, bempedoic acid, inclisiran, and emerging oral therapies targeting PCSK9 degradation.

Contemporary lipid management has shifted from achieving specific LDL-C targets toward reducing cumulative lifelong exposure to atherogenic lipoproteins. Within this evolving therapeutic landscape, pitavastatin occupies a distinctive position due to its favorable balance of efficacy and safety. The drug was approved in Japan in 2003, followed by the United States in 2009 and Europe in 2010. Clinical studies have demonstrated LDL-C reductions of approximately 38-44% with a daily dose of 4 mg, while maintaining a metabolic profile that differs from that of atorvastatin and rosuvastatin [3,4].

A notable pharmacological advantage of pitavastatin is its limited metabolism via

cytochrome P450 enzymes. The drug undergoes minimal metabolism through CYP2C9 and is largely independent of CYP3A4, the principal enzyme responsible for many statin-related drug interactions. Its glucuronide-derived metabolite, pitavastatin lactone, undergoes enterohepatic recirculation, contributing to an effective elimination half-life of approximately 12 hours.

Pitavastatin has been shown to increase high-density lipoprotein cholesterol (HDL-C) levels more effectively than atorvastatin and rosuvastatin, while achieving comparable reductions in low-density lipoprotein cholesterol (LDL-C). These effects are thought to be mediated, at least in part, through activation of the ABCA1 transporter and stimulation of apolipoprotein A-I (ApoA-I) synthesis. Although HDL-C elevation does not always directly correlate with a reduction in cardiovascular risk, these mechanisms may contribute to enhanced reverse cholesterol transport [9].

In patients with prediabetes, insulin resistance, or HIV infection receiving antiretroviral therapy, pitavastatin is often considered a preferred statin due to its minimal interaction with the CYP3A4 enzyme system and its favorable metabolic profile.

Bempedoic acid (ETC-1002; Nexletol) represents the first novel oral LDL-C-lowering agent with a distinct mechanism of action introduced since the development of ezetimibe. It inhibits adenosine triphosphate-citrate lyase (ACL), an enzyme located upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway. As bempedoic acid is a prodrug activated by the hepatic enzyme ACSVL1, which is absent in skeletal muscle, it is not associated with the myopathy typically observed with conventional statin therapy.

Lipoprotein(a) [Lp(a)] has emerged as one of the most important contributors to residual cardiovascular risk that remains insufficiently addressed by current lipid-lowering therapies. Elevated Lp(a) concentrations, largely determined by genetic variants of the LPA gene, are present in approximately 20% of the population and are recognized as an independent risk factor for atherosclerotic cardiovascular disease, aortic valve disease, and heart failure. Unlike LDL-C, Lp(a) levels are minimally affected by conventional statin therapy, and some studies have reported modest increases of 10-20% during statin treatment. These observations highlight the need for targeted therapeutic strategies aimed specifically at reducing Lp(a)-associated cardiovascular risk. [7]

Several RNA-based therapies targeting lipoprotein(a) [Lp(a)] are currently in advanced clinical development. Lepodisiran (Eli Lilly) and zerlasiran (Silence Therapeutics), both designed to suppress apolipoprotein(a) mRNA expression, are undergoing Phase III clinical evaluation. In Phase I and II studies, these agents achieved sustained reductions in Lp(a) levels of approximately 90-96% with dosing frequencies as low as once or twice annually. Another investigational therapy,

pelacarsen, an antisense oligonucleotide targeting apolipoprotein(a), has completed patient enrollment in the Phase III Lp(a)HORIZON trial. The results of this study are expected to provide important evidence regarding whether selective Lp(a) reduction translates into a lower incidence of cardiovascular events [7,8]

Lp(a) remains one of the least adequately addressed determinants of residual cardiovascular risk. Among patients who experience myocardial infarction despite achieving LDL-C levels below 70 mg/dL with intensive lipid-lowering therapy, elevated Lp(a) concentrations are disproportionately common, affecting approximately 25-30% of cases. Evidence from Mendelian randomization studies supports a causal relationship between elevated Lp(a) and cardiovascular disease. Furthermore, analyses from contemporary clinical studies have demonstrated that patients with baseline Lp(a) concentrations exceeding 100 nmol/L remain at substantially higher risk of recurrent cardiovascular events, even when optimal LDL-C targets are achieved, underscoring the importance of Lp(a) as an independent therapeutic target.

The safety profiles of next-generation lipid-lowering therapies compare favorably with those of traditional high-intensity statins. Pitavastatin has not been associated with an increased risk of myopathy or hepatotoxicity beyond that observed for the statin class as a whole. Similarly, the muscle safety of bempedoic acid is attributable to its liver-specific activation and has been consistently demonstrated in clinical trials. PCSK9 inhibitors have also exhibited excellent safety profiles across studies encompassing more than 65,000 patient-years of exposure, with no significant increases in the incidence of myopathy, hepatotoxicity, or neurocognitive adverse events. Injection-site reactions occur in approximately 2-4% of patients receiving subcutaneous PCSK9-targeted therapies but are generally mild and rarely lead to treatment discontinuation. Inclisiran has demonstrated a tolerability profile comparable to that of monoclonal antibody PCSK9 inhibitors such as evolocumab and alirocumab. Treatment with bempedoic acid has been associated with a modest increase in the incidence of gout and cholelithiasis; however, the absolute risk remains low and is generally manageable with appropriate clinical monitoring [6].

Statin Intolerance and Residual Cardiovascular Risk

Two persistent clinical challenges have constrained the full realisation of statin benefits: statin intolerance and residual cardiovascular risk. Statin-associated muscle symptoms (SAMS) represent the most common cause of treatment discontinuation, with prevalence ranging from approximately 5% in clinical trials to 29% in observational cohorts a discrepancy reflecting differences in patient selection, monitoring intensity, and symptom ascertainment. The pathophysiology of SAMS is multifactorial, encompassing mitochondrial dysfunction, coenzyme Q10 depletion, and alterations in sarcolemmal cholesterol composition [10].

Residual cardiovascular risk persisting even at guideline-recommended LDL-C

targets—has become a central focus of contemporary pharmacological innovation. Patients with well-controlled LDL-C may still carry elevated lipoprotein(a), atherogenic remnant particles, chronic systemic inflammation, or insulin resistance, each contributing independently to atherosclerotic progression. The observation that statins do not meaningfully lower lipoprotein(a) and may modestly raise it has stimulated intensive investigation of targeted RNA-based therapies currently in Phase III clinical evaluation [2, 6].

Statins in Contemporary Guidelines

Current guidelines from the European Society of Cardiology / European Atherosclerosis Society (ESC/EAS, 2019) and the American College of Cardiology / American Heart Association (ACC/AHA, 2019) recommend high-intensity statin therapy as first-line treatment for patients at high and very high cardiovascular risk. For very high-risk individuals, the target LDL-C reduction is ≥50% with an absolute goal below 1.4 mmol/L (55 mg/dL). For those failing to achieve targets on maximally tolerated statin therapy, sequential addition of ezetimibe followed by PCSK9 inhibitors is endorsed, while bempedoic acid serves as an evidence-based option in statin-intolerant patients [1, 2].

A large systematic review and meta-analysis published in Cureus (2025), encompassing 506,813 patients across seven studies, confirmed significant reductions in all-cause mortality (RR 0.60; 95% CI 0.43-0.83) and major adverse cardiovascular events (RR 0.75; 95% CI 0.70-0.82) with statin therapy, further cementing its foundational role in cardiovascular prevention. The analysis reinforced that absolute benefits are greatest in patients with established CVD or multiple risk factors, underscoring the importance of structured risk stratification [11].

Conclusion

The central lesson of the statin era is that lowering LDL-C causally and proportionally reduces cardiovascular events, and that earlier, more sustained, and more intensive intervention yields greater cumulative benefit. As therapeutic options expand to include PCSK9 inhibitors, inclisiran, bempedoic acid, and lipoprotein(a)-targeting RNA therapies, the conceptual and evidentiary foundations built through decades of statin research remain indispensable guides for the pursuit of optimized cardiovascular prevention.

Emerging lipid-lowering agents offer the opportunity to address residual cardiovascular risk that persists despite optimal LDL-C control, particularly in patients with elevated lipoprotein(a) levels or statin intolerance. Collectively, these advances are driving a transition toward precision-based lipid management, in which treatment strategies are tailored according to individual risk profiles, genetic determinants, and therapeutic responsiveness. As ongoing clinical trials continue to evaluate long-term cardiovascular outcomes, next-generation therapies are expected to further redefine the

standards of preventive cardiology and improve patient outcomes across diverse high-risk populations.

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