Available online on 15.02.2026 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

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Review Article

Review on Cholesterol Metabolism and Mechanism-Based Pharmacotherapy

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A B S T R A C T

Cholesterol is an indispensable lipid molecule that contributes to membrane structure, cellular signaling, and the synthesis of steroid hormones and bile acids. Nevertheless, chronic elevation of circulating cholesterol, particularly low-density lipoprotein cholesterol (LDL-C), is a well-established causal factor in atherosclerotic cardiovascular disease (ASCVD). Continuous progress in molecular pharmacology has clarified the regulatory networks governing cholesterol homeostasis and has enabled the development of therapeutics precisely targeting these pathways. This review systematically summarizes the physiological mechanisms of cholesterol absorption, biosynthesis, transport, and elimination, and critically examines mechanism-based pharmacotherapies currently used or under development. Emphasis is placed on molecular targets, pharmacological mechanisms, and clinical relevance, with a focus suitable for pharmaceutical sciences. The integration of mechanistic insight with therapeutic strategy underscores the evolving role of precision pharmacotherapy in cholesterol management.

Keywords: Cholesterol metabolism, LDL cholesterol, pharmacology, statins, PCSK9, lipid-lowering therapy

A R T I C L E I N F O: Received 05 Jan 2026; Review Complete 28 Jan 2026; Accepted 10 Feb 2026; Available online 15 Feb. 2026

Cite this article as:
Cheolin P, Department of Biomedical Laboratory Science, Daegu Health College, Daegu, KOREA, Asian Journal of Pharmaceutical Research and Development. 2026; 14(1):16-24, DOI: http://dx.doi.org/10.22270/ajprd.v14i1.1689

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INTRODUCTION

Cholesterol metabolism constitutes a fundamental biochemical network essential for human physiology. Cholesterol maintains membrane integrity, regulates membrane protein function, and serves as a precursor for steroid hormones, vitamin D, and bile acids. Despite these critical roles, excessive cholesterol accumulation—particularly within the arterial wall—drives the initiation and progression of atherosclerosis, the pathological basis of ASCVD[1].

From a pharmacological perspective, cholesterol metabolism has long represented an attractive therapeutic target. Landmark discoveries linking LDL-C to cardiovascular risk established the rationale for lipid-lowering therapy as a preventive strategy[2]. The introduction of statins marked a paradigm shift, demonstrating that selective enzyme inhibition within cholesterol biosynthesis could substantially reduce cardiovascular morbidity and mortality.

Subsequent elucidation of cholesterol regulatory mechanisms, including sterol-sensing pathways and receptor-mediated lipoprotein clearance, has expanded the spectrum of actionable targets [3]. For pharmacy professionals, understanding these molecular mechanisms is essential for rational drug selection, optimization of combination therapy, and evaluation of emerging treatments. This review aims to provide a comprehensive and mechanistically oriented overview of cholesterol metabolism and its pharmacotherapeutic modulation.

Physiological Pathways of Cholesterol Metabolism

Intestinal Cholesterol Absorption

Cholesterol entering the intestine originates from both dietary intake and biliary secretion. Within the intestinal lumen, cholesterol is incorporated into mixed micelles formed by bile acids and phospholipids. Uptake into enterocytes is mediated primarily by the Niemann–Pick C1-like 1 (NPC1L1) transporter located on the apical membrane[4,13].

Following absorption, free cholesterol may be esterified by acyl-CoA:cholesterol acyltransferase 2 (ACAT2) and packaged into chylomicrons along with triglycerides and apolipoprotein B-48. These particles are transported via the

lymphatic system into the systemic circulation, where triglycerides are hydrolyzed and chylomicron remnants deliver cholesterol to the liver[5,30].

Endogenous Cholesterol Biosynthesis

Endogenous synthesis accounts for the majority of total body cholesterol. The liver plays a dominant role, although most cells possess the enzymatic machinery for cholesterol production. The biosynthetic pathway initiates with acetyl-CoA and proceeds through the mevalonate pathway, encompassing over twenty enzymatic **steps.**

The conversion of HMG-CoA to mevalonate by HMG-CoA reductase represents the rate-limiting step. This enzyme is subject to multilayered regulation, including transcriptional control by sterol regulatory element-binding protein-2 (SREBP-2), feedback inhibition by sterols, and post-translational modification via phosphorylation and proteasomal degradation[6,33].

Lipoprotein Assembly and Plasma Transport

Given its hydrophobic nature, cholesterol circulates in plasma within lipoprotein complexes. Very-low-density lipoproteins (VLDL), synthesized in the liver, transport endogenously produced triglycerides and cholesterol to peripheral tissues. Progressive lipolysis converts VLDL into intermediate-density lipoproteins and ultimately LDL.

LDL particles are the primary carriers of cholesterol in human plasma. Cellular uptake of LDL occurs mainly through LDL receptor (LDLR)-mediated endocytosis. Internalized LDL is degraded in lysosomes, releasing free cholesterol that modulates intracellular sterol homeostasis[7].

Reverse Cholesterol Transport

Reverse cholesterol transport (RCT) constitutes a critical anti-atherogenic mechanism by which excess cholesterol is removed from peripheral tissues and macrophages. High-density lipoprotein (HDL) particles accept cholesterol via ATP-binding cassette transporters, including ABCA1 and ABCG1.

Cholesterol carried by HDL is ultimately delivered to the liver, either directly through scavenger receptor class B type I (SR-BI) or indirectly via transfer to apoB-containing lipoproteins. Hepatic cholesterol is then converted into bile acids or excreted unchanged into bile[8,31].

Dysregulation of Cholesterol Homeostasis and Disease

Genetic and environmental factors can disrupt cholesterol metabolism, resulting in dyslipidemia. Familial hypercholesterolemia (FH), caused by mutations in LDLR, APOB, or PCSK9, exemplifies how impaired LDL clearance leads to markedly elevated LDL-C levels and premature ASCVD[9,32].

At the vascular level, excessive LDL infiltration into the arterial intima promotes oxidative modification. Modified LDL is taken up by macrophages through scavenger receptors, leading to foam cell formation and fatty streak development. These early lesions evolve into complex atherosclerotic plaques through sustained inflammation and cellular proliferation[10].

Mechanism-Based Pharmacotherapy

HMG-CoA Reductase Inhibitors (Statins)

Statins act as competitive inhibitors of HMG-CoA reductase, thereby suppressing hepatic cholesterol synthesis. Reduced intracellular cholesterol activates SREBP-2, resulting in upregulation of LDLR expression and enhanced plasma LDL clearance[11].

Statins lower LDL-C by approximately 20–60%, depending on potency and dosage. Extensive clinical evidence supports their efficacy in both primary and secondary prevention of ASCVD. Additional pleiotropic effects, including anti-inflammatory and endothelial-protective actions, may further contribute to clinical benefit.

Statins, such as atorvastatin, rosuvastatin, and simvastatin, are first-line agents for lowering LDL cholesterol by inhibiting HMG-CoA reductase. The most common adverse effects are muscle-related symptoms, including myalgia, muscle weakness, and elevations in creatine kinase. In rare but severe cases, statins may cause rhabdomyolysis. Mild and reversible elevations of liver transaminases may occur, and a small increase in blood glucose levels has been associated with statin therapy, potentially leading to new-onset diabetes mellitus. Gastrointestinal symptoms such as nausea and diarrhea can occur, and rare reports of cognitive impairment have been described[12].

Inhibition of Intestinal Cholesterol Absorption

Ezetimibe selectively inhibits NPC1L1, decreasing cholesterol uptake at the intestinal brush border. Reduced cholesterol delivery to the liver leads to compensatory upregulation of LDLR expression[13].

As monotherapy, ezetimibe provides modest LDL-C reduction, but when combined with statins, it produces additive lipid-lowering effects and improved cardiovascular outcomes, particularly in high-risk populations[14].

Ezetimibe lowers cholesterol by inhibiting intestinal absorption of dietary and biliary cholesterol. It is generally well tolerated, with common adverse effects including diarrhea, abdominal pain, and headache. When used in combination with statins, mild elevations in liver enzymes may occur. Muscle-related side effects are uncommon, making ezetimibe a useful option for patients with statin intolerance[15].

PCSK9 Modulation

PCSK9 binds to LDLR and directs it toward lysosomal degradation. Pharmacological inhibition of PCSK9 increases receptor recycling and enhances LDL clearance. Monoclonal antibodies targeting PCSK9 achieve profound LDL-C reductions of up to 60%[16,34].

Small interfering RNA (siRNA) therapies that suppress hepatic PCSK9 synthesis offer prolonged efficacy with infrequent dosing, representing an important advancement in lipid pharmacotherapy[17].

PCSK9 inhibitors, such as evolocumab and alirocumab, are monoclonal antibodies administered by subcutaneous injection that markedly reduce LDL cholesterol levels. The most frequently reported adverse effects are injection-site

reactions, including pain, redness, and swelling. Patients may also experience flu-like symptoms, fatigue, or mild muscle pain. Serious allergic reactions are rare, and hepatotoxicity and myopathy are uncommon[17].

ATP-Citrate Lyase Inhibition

ATP-citrate lyase (ACL) generates cytosolic acetyl-CoA, linking carbohydrate metabolism to lipid synthesis. Bempedoic acid inhibits ACL upstream of HMG-CoA reductase, reducing hepatic cholesterol synthesis without significant skeletal muscle exposure.This pharmacokinetic characteristic makes bempedoic acid a valuable option for patients with statin intolerance[35].

Bempedoic acid is generally well tolerated; however, several major adverse effects have been reported in clinical trials and post-marketing data. The most clinically significant adverse effects include hyperuricemia and gout, due to increased serum uric acid levels, which may precipitate acute gout attacks, particularly in patients with a prior history of gout. Tendon rupture or tendon injury, especially involving the Achilles tendon, has also been observed, with a higher risk in elderly patients, those receiving corticosteroids or fluoroquinolones, and patients with renal impairment[18]. In addition, elevations in liver enzymes (alanine aminotransferase and aspartate aminotransferase) may occur, necessitating periodic monitoring of hepatic function. Musculoskeletal pain, including back pain and extremity pain, is another commonly reported adverse effect. Less frequently, anemia, upper respiratory tract infections, and abdominal pain have been described.

Molecular Regulation and Advanced Pharmacotherapy

Cholesterol homeostasis is tightly regulated through coordinated control of intestinal absorption, hepatic synthesis, intracellular trafficking, and receptor-mediated clearance of circulating lipoproteins. Dysregulation of these processes contributes directly to atherosclerotic cardiovascular disease, making molecular targets within cholesterol metabolism central to modern lipid-lowering pharmacotherapy.

At the molecular level, hepatic cholesterol synthesis is primarily regulated by 3-hydroxy-3-methylglutaryl–coenzyme A reductase (HMG-CoA reductase), the rate-limiting enzyme of the mevalonate pathway[6]. Its activity is controlled by sterol regulatory element–binding proteins (SREBPs), particularly SREBP-2, which upregulates genes involved in cholesterol synthesis and LDL receptor (LDLR) expression under conditions of intracellular cholesterol depletion. Conversely, increased intracellular cholesterol suppresses SREBP activation, reducing cholesterol synthesis and uptake[19,20].

Clearance of circulating low-density lipoprotein cholesterol (LDL-C) depends largely on LDL receptor–mediated endocytosis in hepatocytes. The availability of LDL receptors on the cell surface is negatively regulated by proprotein convertase subtilisin/kexin type 9 (PCSK9), which promotes lysosomal degradation of LDLRs. Inhibition of PCSK9 therefore enhances LDLR recycling and significantly lowers plasma LDL-C levels[20].

Advanced pharmacotherapy for cholesterol lowering exploits these regulatory pathways. Statins, the cornerstone of lipid-lowering therapy, competitively inhibit HMG-CoA reductase, reducing hepatic cholesterol synthesis and secondarily upregulating LDL receptor expression. Despite their proven efficacy, statins may be limited by intolerance or insufficient LDL-C reduction in high-risk patients[21].

To address these limitations, non-statin therapies targeting complementary mechanisms have been developed. Ezetimibe inhibits the Niemann–Pick C1-like 1 (NPC1L1) transporter in the intestinal brush border, reducing dietary and biliary cholesterol absorption. PCSK9 inhibitors, including monoclonal antibodies (evolocumab, alirocumab) and small interfering RNA (inclisiran), markedly enhance LDL-C clearance by preventing LDLR degradation[22].

More recently, bempedoic acid has emerged as a novel agent acting upstream of HMG-CoA reductase by inhibiting ATP citrate lyase (ACL), an enzyme linking mitochondrial citrate export to cytosolic cholesterol synthesis. Because bempedoic acid is activated primarily in the liver and not in skeletal muscle, it offers a therapeutic advantage for patients with statin-associated muscle symptoms[23].

In addition, therapies targeting triglyceride-rich lipoproteins and residual cardiovascular risk—such as angiopoietin-like protein 3 (ANGPTL3) inhibitors—highlight the expanding scope of lipid pharmacology beyond LDL-C alone. Together, these advances reflect a shift toward mechanism-based, individualized lipid-lowering strategies that integrate molecular regulation with clinical risk stratification[24].

Conclusion and Future Directions

This review briefly explains the prescription medications currently used in hospitals to lower

cholesterol, their mechanisms of action, and their side effects (Table 1). While the medications prescribed by doctors may vary depending on the patient's condition, selecting the most effective medication based on accurate diagnosis and test results is crucial for more effective treatment.

Cholesterol-lowering medicines have long played a central role in the prevention and management of cardiovascular diseases (CVDs), which remain a leading cause of morbidity and mortality worldwide. Over several decades, substantial clinical and epidemiological evidence has established elevated low-density lipoprotein cholesterol (LDL-C) as a major modifiable risk factor for atherosclerotic ccardiovascular disease (ASCVD)[25]. Consequently, pharmacological interventions aimed at reducing LDL-C levels have become a cornerstone of modern cardiovascular medicine. Among these, statins have demonstrated unparalleled efficacy in reducing cardiovascular events and mortality, therebysetting the foundation for current lipid-lowering strategies[26].

Despite the proven benefits of statin therapy, clinical limitations such as residual cardiovascular risk, statin intolerance, and interindividual variability in treatment response have highlighted the need for alternative and complementary therapeutic options. In response, the past decade has witnessed significant advances in the development of novel cholesterol-lowering agents with

distinct mechanisms of action[27]. Drugs such as ezetimibe, PCSK9 inhibitors, inclisiran, and bempedoic acid have expanded the therapeutic landscape, enabling more effective LDL-C reduction in high-risk patients who fail to achieve target lipid levels with statin monotherapy. These innovations underscore a paradigm shift from a "one-size-fits-all" approach toward more individualized lipid management mstrategies[28]. The emergence of PCSK9-targeting therapies represents a particularly transformative milestone in cholesterol management. Monoclonal antibodies and small interfering RNA (siRNA)-based agents have demonstrated profound LDL-C lowering effects and favorable cardiovascular outcomes in large- scale clinical trials. Moreover, long-acting formulations such as inclisiran offer the potential to improve patient adherence through infrequent dosing schedules, addressing one of the major challenges in chronic lipid-lowering therapy[29]. These developments not only enhance therapeutic efficacy but also suggest that future cholesterol management may increasingly prioritize convenience and long-term adherence alongside biochemical outcomes. Looking ahead, the future of cholesterol-lowering medicines is likely to be shaped by advances in precision medicine, genomics, and digital health technologies. Genetic profiling and biomarker-based risk stratification may allow clinicians to tailor treatment choices more effectively, optimizing both efficacy and safety for individual patients. Furthermore, ongoing research into novel lipid pathways, such as lipoprotein(a) and triglyceride-rich lipoproteins, may broaden the scope of lipid management beyond LDL-C alone, offering more comprehensive cardiovascular risk reduction[30].

Nevertheless, several challenges remain to be addressed. Long-term safety data for newer agents are still being accumulated, and their high cost continues to raise concerns regarding accessibility and healthcare sustainability, particularly in low- and middle-income countries[31,34]. Real-world evidence will be essential to confirm whether the impressive results observed in clinical trials translate into routine clinical practice. In addition, integrating pharmacological therapy with lifestyle modification, patient education, and public health interventions remains critical for maximizing overall cardiovascular benefit [32,33].

In conclusion, cholesterol-lowering medicines have evolved significantly from the early era of statin monotherapy to a diverse and rapidly expanding therapeutic arsenal. Continued innovation, supported by robust clinical research and health policy initiatives, will be essential to ensure that these therapies are both effective and accessible. As our understanding of lipid biology and cardiovascular risk deepens, cholesterol-lowering treatment is poised to become increasingly personalized, ultimately contributing to a sustained reduction in the global burden of cardiovascular disease[34].

Table 1: Comparative Pharmacokinetics of Major Lipid-Lowering Drugs

(Summary of the differentiating factors of various agents)

Drug class	Drug	Primary Target	Metabolism	Major side effects
Statin	Rosurastatin	HMG-CoA reductase	Minimal CYP450(2C9)	Myalgia, New-onset diabetes
Cholesterol Absorption Inhibitor	Ezetimibe	NPC1L1	Glucuronidation (Intestitine)	Diarrhea, URT infection
PCSK9mAb	Evolocumab	Circulating PCSK9	Proteolysis	Injection site reaction
siRNA	Inclisiran	PCSK9 mRNA	Nucleases(Hepatic)	Injection Site reaction
ACL Inhibitor	Bempedoic acid	ATP Citrate Lyase	Glucuronidation(Liver)	Hyperuricemia, Gout

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