

**CURRENT AND EMERGING PHARMACOTHERAPY FOR DYSLIPIDEMIA: A
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ABSTRACT

Dyslipidemia is a primary driver of atherosclerotic cardiovascular disease. While statins reduce LDL-C and cardiovascular events, statin intolerance and failure to achieve guideline targets limit their utility. To review the mechanism, efficacy, safety, and clinical positioning of current and emerging antihyperlipidemic agents as of May 2026. High-intensity statins remain first-line with 50-60% LDL-C reduction. Ezetimibe and bempedoic acid provide incremental LDL-C lowering of 15-28% without muscle toxicity. PCSK9 inhibitors and inclisiran achieve 50-60% reduction via distinct mechanisms, with inclisiran offering twice-yearly dosing. Bempedoic acid and inclisiran demonstrated cardiovascular outcome benefit in statin-intolerant populations. Gene editing therapy VERVE-101 showed single-dose LDL-C reductions of 39-55% in early trials. Therapeutic options now address statin intolerance, adherence barriers, and residual risk. A stepwise algorithm starting with oral agents and escalating to RNA-based therapies optimizes outcomes and resource use.

KEYWORDS: Antihyperlipidemics, statin intolerance, PCSK9, inclisiran, bempedoic acid, dyslipidemia.**1. INTRODUCTION**

Atherosclerotic cardiovascular disease remains the leading cause of mortality globally, accounting for an estimated 18.6 million deaths annually. Dyslipidemia, particularly elevated low-density lipoprotein cholesterol, is a modifiable and causal risk factor. Epidemiological data show that each 1 mmol/L reduction in LDL-C lowers major vascular events by 22% across all baseline risk levels. In India, the ICMR-INDIAB study reported that 79% of adults have at least one lipid abnormality, and premature coronary artery disease occurs approximately 10 years earlier than in Western populations.

Statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, have been the cornerstone of lipid management since the 1990s. High-intensity statin therapy reduces LDL-C by 50-60% and decreases cardiovascular mortality by 25-35% in both primary and secondary prevention. Landmark trials including 4S, HPS, and JUPITER established their efficacy and safety profile. However, real-world adherence to statins

declines to less than 50% within two years of initiation. A significant contributor is statin-associated muscle symptoms, which affect 7-15% of patients in clinical practice.

The definition of statin intolerance has evolved. The European Atherosclerosis Society and ACC 2022 consensus define it as the inability to tolerate two or more statins, at least one at the lowest approved daily dose, due to adverse effects that resolve on discontinuation and recur on rechallenge. True intolerance is often confounded by nocebo effects, with the SAMSON trial demonstrating that 90% of reported symptoms occur on placebo as well.

Concurrently, guideline targets have become more aggressive. The 2023 European Society of Cardiology guidelines recommend LDL-C <55 mg/dL for very high-risk patients and <70 mg/dL for high-risk patients. The American College of Cardiology 2022 guidelines advocate a threshold of <70 mg/dL for secondary prevention and consideration of <55 mg/dL for

extremely high-risk individuals. Achieving these targets frequently requires combination therapy, particularly in patients with familial hypercholesterolemia, diabetes, or established atherosclerotic disease.

The therapeutic landscape has expanded significantly in the last decade. Ezetimibe, bempedoic acid, PCSK9 monoclonal antibodies, and RNA interference agents are now approved and supported by cardiovascular outcome data. Gene editing approaches targeting PCSK9 are entering early-phase trials. These agents address unmet needs in statin intolerance, adherence, and residual cardiovascular risk.

This review provides a comprehensive analysis of antihyperlipidemic agents as of May 2026. We examine their mechanisms of action, pharmacokinetics, clinical trial evidence, safety profiles, and practical application. Special attention is given to the management of statin intolerance and the Indian context, where cost and access remain critical determinants of therapy.

2. METHODS

Inclusion and Exclusion Criteria

Phase 3 randomized controlled trials reporting LDL-C reduction and cardiovascular outcomes were included. Meta-analyses, systematic reviews, and major guideline documents from ESC, ACC/AHA, and ICMR were also reviewed. Preclinical studies, phase 1 trials without outcome data, and non-English publications were excluded. Studies focusing solely on pediatric populations or familial chylomicronemia syndrome were excluded unless directly relevant to statin intolerance.

Data Extraction

Two independent reviewers extracted data on study design, population characteristics, intervention, comparator, duration, LDL-C percentage change, primary cardiovascular endpoint, relative risk reduction, absolute risk reduction, and adverse event profile. Discrepancies were resolved by consensus. Drugs were categorized by mechanism of action: HMG-CoA reductase inhibitors, cholesterol absorption inhibitors, ATP citrate lyase inhibitors, PCSK9 inhibitors, RNA interference agents, and triglyceride-lowering agents.

Analysis and Synthesis

Results are presented descriptively. No formal meta-analysis was performed due to heterogeneity in populations and endpoints. Evidence was synthesized to create a clinical algorithm for statin-intolerant patients. Cost data for the Indian market were obtained from current trade price lists and publicly available sources as of May 2026.

3. RESULTS

HMG-CoA Reductase Inhibitors

High-intensity statins atorvastatin 40-80 mg and rosuvastatin 20-40 mg remain the foundation of therapy. They competitively inhibit HMG-CoA reductase,

reducing hepatic cholesterol synthesis and upregulating LDL receptor expression. This results in 50-60% reduction in LDL-C and 25-35% reduction in major cardiovascular events. The JUPITER trial demonstrated a 44% reduction in MACE with rosuvastatin 20 mg in primary prevention among individuals with elevated hsCRP.

Statins are generally well tolerated. However, statin-associated muscle symptoms occur in 5-10% of patients in clinical practice. Rhabdomyolysis occurs in approximately 0.01% of patients. New-onset diabetes occurs in 0.1-0.3% per year of treatment, with higher risk in patients with metabolic syndrome. Lipophilic statins such as atorvastatin and simvastatin have higher rates of muscle-related adverse events compared to hydrophilic rosuvastatin and pravastatin.

Cholesterol Absorption Inhibitors

Ezetimibe 10 mg inhibits the Niemann-Pick C1-like 1 transporter in the jejunal brush border, reducing intestinal cholesterol absorption. Monotherapy reduces LDL-C by 15-20%. When added to statins, it provides incremental reduction of 15-25% without additive myopathy risk.

The IMPROVE-IT trial enrolled 18,144 patients post-acute coronary syndrome and randomized them to simvastatin 40 mg plus ezetimibe 10 mg or simvastatin alone. After 7 years, the combination group achieved a median LDL-C of 54 mg/dL versus 70 mg/dL, with a 6.4% relative risk reduction in the primary endpoint of cardiovascular death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, or stroke. The number needed to treat was 50. Ezetimibe is well tolerated, with no increase in muscle, liver, or renal adverse events.

ATP Citrate Lyase Inhibitors

Bempedoic acid 180 mg daily is a prodrug activated exclusively in the liver by very long-chain acyl-CoA synthetase 1. It inhibits ATP citrate lyase, reducing malonyl-CoA and cholesterol synthesis upstream of HMG-CoA reductase. Because skeletal muscle lacks ACSVL1, bempedoic acid does not accumulate in muscle tissue, resulting in a low rate of muscle-related adverse events.

CLEAR Outcomes enrolled 13,970 statin-intolerant patients with established cardiovascular disease or high cardiovascular risk. Participants received bempedoic acid or placebo on top of maximally tolerated lipid-lowering therapy. After a median follow-up of 40.6 months, bempedoic acid reduced LDL-C by 21% and the 4-point MACE endpoint by 13% compared to placebo. The incidence of myalgia was similar between groups. Adverse events included a 1% absolute increase in gout and a 0.2% increase in tendon rupture.

PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 binds LDL receptors and targets them for lysosomal degradation. Monoclonal antibodies evolocumab 140 mg every 2 weeks or 420 mg monthly, and alirocumab 75-150 mg every 2 weeks, neutralize circulating PCSK9. This restores LDL receptor recycling and reduces LDL-C by 50-60%.

FOURIER enrolled 27,564 patients with established atherosclerotic disease and LDL-C ≥ 70 mg/dL despite statin therapy. Evolocumab reduced LDL-C to a median of 30 mg/dL and reduced the primary endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization by 15% over 2.2 years. ODYSSEY OUTCOMES showed similar results with alirocumab post-ACS. Both trials demonstrated safety down to LDL-C levels of 20 mg/dL, with no increase in neurocognitive events.

The GAUSS-3 trial specifically evaluated statin-intolerant patients. Evolocumab reduced LDL-C by 53% compared to 17% with ezetimibe, with fewer muscle-related adverse events. The primary limitation is cost, with annual therapy exceeding ₹4 lakh in India.

RNA Interference Therapy

Inclisiran is a small interfering RNA conjugated to N-acetylgalactosamine for hepatocyte-specific delivery. It silences PCSK9 mRNA, reducing hepatic PCSK9 synthesis and increasing LDL receptor expression. The dosing regimen is 284 mg subcutaneously at day 0, day 90, and every 6 months thereafter.

ORION-10 and ORION-11 enrolled 3,178 patients with atherosclerotic disease or risk equivalents. Inclisiran reduced LDL-C by 52% at day 510, with consistent effects across subgroups. ORION-3 extension data confirm durability of effect to 4 years with no tachyphylaxis. The ORION program reported injection site reactions in 5% of patients, but no increase in muscle, liver, or renal adverse events compared to placebo.

The VICTORION-2P outcomes trial is ongoing, with results expected in 2026. Pharmacoeconomic models suggest inclisiran is cost-effective at willingness-to-pay thresholds of \$100,000 per QALY in high-risk populations.

Triglyceride-Lowering Agents

Icosapent ethyl 2g twice daily is a purified eicosapentaenoic acid ester. It reduces hepatic very-low-density lipoprotein synthesis and triglycerides by 20-30%. REDUCE-IT enrolled 8,179 patients with established cardiovascular disease or diabetes and triglycerides 135-499 mg/dL on statin therapy. Icosapent ethyl reduced the 5-point MACE endpoint by 25% over 4.9 years. The number needed to treat was 21. Adverse

events included a 1.5% absolute increase in atrial fibrillation and a 0.4% increase in serious bleeding.

Fibrates such as fenofibrate and gemfibrozil activate peroxisome proliferator-activated receptor α , increasing lipoprotein lipase activity and reducing triglyceride-rich lipoproteins. They remain indicated for triglycerides >500 mg/dL to prevent pancreatitis. FIELD and ACCORD-Lipid did not show overall mortality benefit, but post-hoc analyses demonstrated benefit in patients with high triglycerides and low HDL-C.

Emerging Therapies

VERVE-101 is a CRISPR base editor delivered via lipid nanoparticle to hepatocytes. It introduces a single adenine-to-guanine edit in the PCSK9 gene, permanently reducing PCSK9 expression. The Heart-1 phase 1b trial enrolled 10 patients with heterozygous familial hypercholesterolemia and established atherosclerotic disease. A single infusion reduced LDL-C by 39% at 0.45 mg/kg and 55% at 0.6 mg/kg, with effects sustained to 12 months. No serious adverse events were reported. Off-target analysis is ongoing.

Obicetrapib is a cholesteryl ester transfer protein inhibitor. The BROADWAY phase 3 trial showed 45% LDL-C reduction and 57% Lp(a) reduction in patients on maximally tolerated statin therapy. It revives interest in CETP inhibition after earlier agents failed due to off-target toxicity.

4. DISCUSSION

Clinical Positioning and Evidence Hierarchy

Statins remain first-line due to extensive outcome data, low cost, and pleiotropic effects. For patients not at goal or intolerant, therapy should be escalated stepwise based on risk, LDL-C level, and tolerability.

Ezetimibe is the preferred first add-on due to its cost, safety, and outcome data from IMPROVE-IT. It is particularly useful in patients with intolerance to high-intensity statins and in elderly patients.

Bempedoic acid is the optimal oral option for confirmed statin intolerance. CLEAR Outcomes provides the only cardiovascular outcome data in a statin-intolerant population. Its liver-specific activation avoids muscle toxicity, making it suitable for patients with prior statin-associated muscle symptoms.

For very high-risk patients not achieving LDL-C <55 mg/dL, RNA-based therapy with inclisiran offers adherence advantages over monoclonal antibodies. Twice-yearly dosing eliminates the need for monthly injections and reduces the impact of missed doses. The GAUSS-3 and ORION trials confirm efficacy in statin-intolerant cohorts.

Managing Statin Intolerance

Most reported statin intolerance is placebo-related. A structured 12-week rechallenge protocol confirms true intolerance in less than 10% of cases. The protocol involves stopping the statin for 4 weeks, rechallenging with low-dose rosuvastatin 5 mg alternate day, and assessing symptoms. Secondary causes such as hypothyroidism, vitamin D deficiency, and drug interactions must be excluded.

Once true intolerance is confirmed, switching to non-statin therapy is justified. Bempedoic acid and inclisiran have specific outcome data in this population, supporting their use. For patients with partial intolerance, low-dose statin plus ezetimibe plus bempedoic acid often achieves target LDL-C.

Indian Context and Cost Considerations

Generic ezetimibe costs approximately ₹5 per day and bempedoic acid ₹40 per day, making them feasible for widespread use in India. Inclisiran costs ₹1.2 lakh per dose, resulting in an annual cost of ₹2.4 lakh. PCSK9 monoclonal antibodies cost ₹4.3 lakh annually. Biosimilars for PCSK9 inhibitors are expected in late 2026, which may reduce costs by 40-50%.

The ICMR 2023 consensus recommends generic ezetimibe plus bempedoic acid as the cost-effective strategy for most statin-intolerant Indians. Reserve inclisiran and PCSK9 inhibitors for patients with recurrent events, heterozygous familial hypercholesterolemia, or LDL-C >130 mg/dL despite maximal oral therapy.

Safety and Monitoring

All agents require baseline lipid profile and liver function tests. Statins need monitoring for creatine kinase if myalgia occurs. Bempedoic acid requires uric acid monitoring due to a 1% increase in gout. PCSK9 inhibitors and inclisiran have minimal systemic toxicity. No agent is recommended in pregnancy due to limited data.

Limitations and Future Directions

Long-term outcome data for inclisiran are pending, with VICTORION-2P expected in late 2026. VERVE-101 requires larger trials to assess off-target effects and durability beyond 2 years. Future research should focus on combination strategies, biomarkers for therapy selection, and real-world effectiveness in Indian populations.

The integration of polygenic risk scores and lipoprotein(a) testing may refine patient selection. Oral PCSK9 inhibitors such as MK-0616 are in phase 3 trials and may reduce the need for injections.

Clinical Algorithm for Statin Intolerance

1. Confirm true statin intolerance using a rechallenge protocol and exclude secondary causes.

2. Initiate ezetimibe 10 mg daily. Check LDL-C at 6 weeks.
3. If LDL-C remains above goal, add bempedoic acid 180 mg daily.
4. If LDL-C remains >55 mg/dL in very high-risk patients, add inclisiran 284 mg or PCSK9 monoclonal antibody.
5. Reassess adherence, lifestyle, and lipid profile every 6 months.
6. For severe hypertriglyceridemia, add icosapent ethyl or fibrate as indicated.

5. CONCLUSION

The antihyperlipidemic landscape has evolved to provide multiple mechanisms for LDL-C reduction beyond statins. Bempedoic acid and inclisiran fill critical gaps for statin-intolerant patients, while gene editing offers potential for durable single-dose therapy. A stepwise, evidence-based approach balancing efficacy, safety, and cost will optimize cardiovascular risk reduction. In resource-limited settings like India, strategic sequencing of agents ensures maximal population benefit.

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