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# THE LATEST APPROACHES TO DYSLIPIDEMIA MANAGEMENT. A NARRATIVE REVIEW

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**ABSTRACT**

Dyslipidemia is a significant, modifiable contributor to cardiovascular disease (CVD), exhibiting significant global prevalence and imposing a particularly high burden in Europe and around the world. Although statins are widely prescribed, a considerable proportion of patients do not achieve lipid targets or experience intolerance, highlighting the need for novel therapeutic strategies. This narrative review examines emerging therapeutic approaches that extend beyond conventional lipid-lowering agents(Cannon, 2022). The paper was prepared based on a review of the literature, with primary emphasis on studies published within the past five years and focused on providing a more detailed presentation of the following therapeutic approaches.

Bempedoic acid, an oral ATP-citrate lyase inhibitor, achieves effective LDL-C reduction with a favourable safety profile, particularly among statin-intolerant patients, and is associated with improved cardiovascular outcomes. Inhibition of angiopoietin-like protein 3 (ANGPTL3) offers a receptor-independent mechanism that results in substantial reductions in LDL-C and triglycerides, particularly in refractory conditions such as homozygous familial hypercholesterolemia. RNA-based therapies, including small interfering RNA (siRNA), provide highly specific and durable gene silencing, as demonstrated by inclisiran and other emerging agents targeting APOC3, ANGPTL3, and lipoprotein(a); infrequent dosing regimens may further enhance adherence.

Gene therapy and genome editing technologies, including CRISPR-based methods, represent a transformative paradigm with the potential to achieve long-term or permanent correction of dyslipidemia. Collectively, these innovations expand therapeutic options, address residual cardiovascular risk, and advance lipid management toward precision and potentially curative strategies.

**KEYWORDS**

Dyslipidemia, Hypercholesterolemia, Familial Hypercholesterolemia, Statins, Cardiovascular Disease

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# Intruduction

Dyslipidemia is characterised by elevated plasma lipid levels. These include total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG) and reduced high-density lipoprotein cholesterol (HDL-c). It is a major global risk factor for cardiovascular disease (CVD). Its epidemiology varies across genders, populations, regions, and demographic groups, and is also shaped by socioeconomic, genetic, lifestyle, and environmental influences. According to the World Health Organisation, the global prevalence of dyslipidemia among adults aged ≥25 years was approximately 39% in 2008. In Poland, the situation is even more concerning: the 2011 NATPOL survey revealed that 61% of adults aged 18–79 are affected (Zdrojewski et al., 2013). Across Europe, nearly one-third of all deaths in 2019 were caused by CVDs, and data from 2020 indicate that these conditions account for about 4 million deaths annually, with approximately 23% attributed specifically to high LDL cholesterol (Pirillo et al., 2021; Ray et al., 2022).

Given the magnitude of this health problem, there is a clear need for novel therapeutic solutions that offer greater efficacy than the currently available treatment modalities.

Recent advances in molecular biology and pharmacotherapy have led to the development of innovative lipid-lowering agents targeting novel pathways involved in lipid metabolism. These include bempedoic acid, inhibitors of angiopoietin-like protein 3 (ANGPTL3), RNA-based therapies such as small interfering RNA (siRNA), and emerging gene therapy and genome editing techniques. These approaches not only provide alternative options for patients inadequately controlled with traditional therapies but also offer the potential for more personalised and durable treatment effects.

The aim of this narrative review is to present and critically discuss these novel therapeutic modalities, focusing on their mechanisms of action, clinical efficacy, safety profiles, and potential role in the future management of dyslipidemia and cardiovascular risk reduction.

## Methods

This work is a narrative, non–systematic review aimed at synthesising contemporary evidence on emerging lipid-lowering therapies beyond statins, with a focus on gene-based interventions, ANGPTL3-targeted strategies, bempedoic acid, and small interfering RNA (siRNA)–based agents.

A comprehensive literature search was conducted in PubMed/MEDLINE, Embase, and the Cochrane Library. The literature search was conducted between December 2025 and April 2026 and was last updated in April 2026. We searched electronic databases including PubMed, cochrane and Google Scholar using combinations of keywords such as "dyslipidemia," "hypercholesterolemia," "familial hypercholesterolemia," "PCSK9," "LDLR," "ANGPTL3," "APOC3," "lipoprotein(a)," "gene therapy," "gene editing," "CRISPR," "base editing," "bempedoic acid," "adenosine triphosphate-citrate lyase," "antisense oligonucleotide," and "small interfering RNA" (inclisiran, olpasiran, etc.). Databases and clinical trials were manually searched for additional studies.

We included peer-reviewed articles written in English that reported mechanistic, translational, or clinical data on: gene addition or genome-editing approaches for lipid disorders; ANGPTL3- and APOC3-targeted therapies (monoclonal antibodies, antisense oligonucleotides, siRNA);bempedoic acid and related ACLY inhibitors; and siRNA therapies directed at lipid-related targets (e.g., PCSK9, LPA). Both human and relevant preclinical studies were considered. Editorials, commentaries without original data, single-patient case reports, and non-peer-reviewed sources were excluded, except when used for mechanistic clarification or regulatory context.

Given the heterogeneity of study designs and outcomes, a qualitative, narrative synthesis was performed. No formal risk-of-bias tool was applied; instead, greater interpretive weight was given to large randomised controlled trials and phase 2/3 data over early-phase or preclinical studies. Evidence is organised by therapeutic modality and primary molecular target (gene therapy/editing, ANGPTL3 inhibition, bempedoic acid, siRNA-based therapies).

In each section, we first outline the underlying mechanism of action, then review the most relevant clinical trial data and safety profiles. Particular attention is given to the durability of lipid-lowering effects, available evidence on major adverse cardiovascular outcomes, and the potential of these therapies to address residual cardiovascular risk.

No formal risk-of-bias tool was applied; instead, greater interpretive weight was given to large randomised controlled trials and phase 2/3 data over early-phase or preclinical studies.

## Bempedoic acid

Bempedoic acid is a non-statin, orally administered prodrug, active lipid-lowering agent indicated for adults with primary hypercholesterolemia or mixed dyslipidemia (4–6). It functions as an inhibitor of adenosine triphosphate-citrate lyase (ACLY), an enzyme upstream of the HMG-CoA reductase pathway which statins target (7). Because it is a prodrug activated exclusively in the liver by very long-chain acyl-CoA synthetase-1, it avoids systemic exposure to muscle tissue, which minimises the muscle-related adverse effects often associated with statin therapy(4).

As monotherapy, bempedoic acid reduces LDL cholesterol (LDL-C) by approximately 20% to 24% (5,6). Its clinical utility is particularly strong in combination therapies, especially for patients unable to reach LDL-C goals despite maximally tolerated statin doses. When used in a fixed-dose combination with ezetimibe, LDL-C reduction can reach almost 40% (6). The drug is also used effectively in combination with high-intensity statins and PCSK9 inhibitors to achieve more aggressive lipid-lowering targets.

The CLEAR Outcomes trial, a large-scale study involving statin-intolerant patients, established the cardiovascular benefits of bempedoic acid. Treatment was associated with a 13% reduction in the risk of major adverse cardiovascular events (4,8). Further analysis of this study confirmed significant reductions in specific outcomes, including a 23% reduction in myocardial infarction and a 19% reduction in coronary revascularisation. Beyond lipid parameters, the drug has demonstrated consistent anti-inflammatory effects, evidenced by a reduction in high-sensitivity C-reactive protein (hsCRP) by 18% to 35% (Banach et al., 2023; Nissen et al., 2023; Ruscica et al., 2022).

Bempedoic acid generally maintains a favourable safety and tolerability profile, with adverse event rates comparable to placebo (Nissen et al., 2023; Ray et al., 2019). Notably, the drug does not negatively impact glucose metabolism and is associated with a lower risk of new-onset or worsening diabetes. However, some specific adverse events have been identified, including a small increase in the incidence of gout and elevated

uric acid levels—likely due to competition for renal transporters—as well as infrequent reports of cholelithiasis and reversible elevations in liver enzymes or creatinine (Banach et al., 2023; Drexel & Mader, 2024; Ray et al., 2019). Overall, bempedoic acid provides a crucial therapeutic option for managing dyslipidemia in patients with statin intolerance or in those requiring additional lipid-lowering support to reach cardiovascular risk reduction targets.

## ANGPTL3

ANGPTL3 inhibitors represent a novel and promising therapeutic class for the management of dyslipidemia, particularly for patients with severe hypertriglyceridemia, homozygous familial hypercholesterolemia (HoFH), or refractory LDL-C levels (Katzmann et al., 2020; Rosenson et al., 2021). Angiopoietin-like 3 (ANGPTL3) is a liver-secreted protein that regulates lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (Katzmann et al., 2020; Rosenson et al., 2021)

Pharmacologic inhibition of ANGPTL3 enhances LPL and endothelial lipase activity, accelerating the clearance of triglyceride-rich lipoproteins (TRLs) and reducing LDL-C, apolipoprotein B (apoB), and triglycerides(Geladari et al., 2019; Rosenson et al., 2020, 2021) . Crucially, this lipid-lowering mechanism is independent of the LDL receptor (LDLR) pathway, providing an effective treatment option for patients who do not achieve adequate control with conventional therapies or those with limited LDLR function, such as individuals with HoFH (Geladari et al., 2019; Rosenson et al., 2021). Genetic evidence strongly supports this therapeutic approach; individuals with loss-of-function variants in the *ANGPTL3* gene consistently exhibit lower plasma lipid levels and a reduced risk of atherosclerotic cardiovascular disease (Dewey et al., 2017).

**Several therapeutic modalities have been developed to target ANGPTL3:**

**Monoclonal Antibodies:** Evinacumab has demonstrated significant efficacy, achieving up to 49% reductions in LDL-C in HoFH patients and substantial decreases in triglycerides(Katzmann et al., 2020; Ray et al., 2025).

**ASOs and siRNA:** RNA-targeting therapies, including antisense oligonucleotides (e.g., AKCEA-ANGPTL3-LRx, vupanorsen) and small interfering RNAs (e.g., Solbinsiran), offer potent, dose-dependent lipid reductions(Katzmann et al., 2020; Ray et al., 2025). Solbinsiran, in particular, has shown durable efficacy; repeat dosing maintains significant reductions in ANGPTL3, triglycerides, and atherogenic lipoproteins for several months (Ray et al., 2025; Rosenson et al., 2020). Additionally, Solbinsiran has demonstrated a reduction in hepatic fat fraction, suggesting potential benefits for patients with metabolic dysfunction-associated liver conditions (Ray et al., 2025).

**Safety Profile:** ANGPTL3 inhibitors generally exhibit a favourable safety and tolerability profile. Reported adverse events are typically mild and include headache, injection-site reactions, and transient, asymptomatic elevations in liver transaminases (Ray et al., 2025). While some early antisense therapies raised concerns regarding hepatic fat accumulation and liver enzyme elevations, newer siRNA approaches like Solbinsiran have demonstrated more favourable hepatic safety profiles (Gurevitz et al., 2025).

By targeting ANGPTL3, these agents provide a powerful tool for lowering atherogenic lipids and addressing residual cardiovascular risk. While current clinical data are highly encouraging, ongoing and future long-term cardiovascular outcome trials are necessary to fully establish the clinical utility and long-term safety of these therapies in comprehensive cardiovascular disease prevention strategies.

## siRNA

Small interfering RNA (siRNA) therapies represent a precise class of drugs that leverage the body's natural RNA interference (RNAi) pathway to selectively silence the expression of specific genes (Carugo et al., 2023a; Gao et al., 2026). By targeting messenger RNA (mRNA) for degradation in a sequence-specific manner, these therapies prevent the synthesis of proteins involved in disease processes, such as those regulating lipid metabolism

These agents utilise the RNA interference (RNAi) pathway and are typically conjugated with N-acetylgalactosamine (GalNAc) for targeted hepatic delivery. Once inside hepatocytes, the siRNA guide strand loads into the RNA-induced silencing complex (RISC), where it cleaves specific messenger RNA (mRNA) transcripts, preventing the synthesis of target proteins (Soffer et al., 2022).

**Clinical Efficacy by Target:**|

PCSK9 (Inclisiran): Inclisiran inhibits PCSK9 synthesis, enhancing LDL receptor recycling and clearance of circulating LDL-C . Phase 3 trials (ORION-9, -10, -11) demonstrated sustained LDL-C reductions averaging ~50%. A pooled analysis suggests a 26% composite reduction in major adverse cardiovascular events (MACE) 1 9. The regimen—an initial dose, a second at 3 months, and maintenance every 6 months—significantly improves medication adherence compared to daily therapies (Soffer et al., 2022).

(APOC3 and ANGPTL3): Systematic reviews confirm that siRNA therapies are significantly beneficial in improving lipid profiles in hypertriglyceridemia and mixed dyslipidemia. The research observed significant reductions in triglycerides (pooled mean difference -52%), non-HDL-C (-21.9%), apoB (-12.6%), and remnant cholesterol (-64.8%). Clinical outcomes vary by target, supporting a phenotype-guided approach(Gao et al., 2026).

APOC3-targeted agents: Significantly increase HDL-C (40.9%) while showing neutral effects on LDL-C.

ANGPTL3-targeted agents: Reduce triglycerides and remnant cholesterol, as well as LDL-C (-13.2%), but cause a concurrent reduction in HDL-C (-20.2%) (Gao et al., 2026).

Lipoprotein(a): Targeting the LPA gene with agents like olpasiran and SLN360 has shown dose-dependent reductions in lipoprotein(a), with some trials achieving decreases ranging from 70% to over 100% (Carugo et al., 2023a; Soffer et al., 2022).

Because siRNA therapies act upstream of protein synthesis to prevent production at the genetic level, they offer a highly potent and specific therapeutic approach. Their durability allows for infrequent dosing—often only twice per year—which significantly improves patient adherence.

## Gene editing and gene therapy

Gene therapy and genome editing represent a transformative frontier in the management of dyslipidemia, offering the potential for durable, long-term solutions that overcome the burden of lifelong, daily lipid-lowering medications (Gurevitz et al., 2025).

**The field utilises two primary strategies:**

Gene Addition (Transfer): This involves introducing a functional copy of a gene into cells to supplement or replace defective ones, typically using adeno-associated virus (AAV) vectors . While this has historical precedence, such as the (now withdrawn) alipogene tiparvovec, it remains an active area of research for homozygous familial hypercholesterolemia (HoFH) (Brandts & Ray, 2021; Gurevitz et al., 2025; Stankov & Cuchel, 2023a).

Gene Editing: This approach directly modifies endogenous DNA. Techniques include CRISPR-Cas9 (nuclease editing), which creates targeted double-strand breaks, and more precise, newer methods like base editing and prime editing**.** These advanced tools allow for single-nucleotide modifications without requiring double-strand breaks, significantly reducing the risk of unintended off-target effects. Additionally, epigenome editing is being explored to modulate gene expression without altering the DNA sequence itself(Brandts & Ray, 2021; Gurevitz et al., 2025; Stankov & Cuchel, 2023b).

**Primary Targets:**

PCSK9: A central target for reducing LDL-cholesterol. Inactivation via gene editing (e.g., VERVE-101) has demonstrated substantial, durable efficacy in preclinical models and early human clinical trials (Gurevitz et al., 2025; Hoekstra & Van Eck, 2024).

LDLR: Strategies aim to correct mutations or restore LDLR expression, which is vital for patients with familial hypercholesterolemia (FH) (Brandts & Ray, 2021; Stankov & Cuchel, 2023a).

Other Targets: Genes such as ANGPTL3 and APOC3 are being edited to manage triglycerides and lipoprotein(a) concentrations, providing broader options for dyslipidemia management(Stankov & Cuchel, 2023a).

## Results

The literature search found data from lab studies and clinical trials across four main treatment areas: gene therapy/editing, ANGPTL3-targeted therapies, bempedoic acid, and siRNA-based drugs.

**Bempedoic acid**: a liver-targeted ACLY inhibitor lowered LDL-C by about 20–24% on its own and by up to 40% when combined with ezetimibe(Drexel & Mader, 2024). In the CLEAR outcomes trial in patients who could not tolerate statins, bempedoic acid was linked to a 13% drop in major cardiovascular events, a 23% drop in heart attacks, and a 19% drop in coronary revascularisation. It also reduced hsCRP by 18–35%, suggesting a consistent anti-inflammatory effect (Banach et al., 2023).

**ANGPTL3-targeted therapies**: genetic studies show that ANGPTL3 loss-of-function variants are associated with lower LDL-C, triglycerides, and apoB, as well as reduced ASCVD risk, establishing a strong causal target. Pharmacologic inhibition enhances LPL and endothelial lipase activity, lowering triglyceride-rich lipoproteins, LDL-C, and triglycerides via an LDLR-independent mechanism, which is particularly advantageous in HoFH.

Evinacumab, a monoclonal antibody to ANGPTL3, achieved up to 49 % LDL-C reduction in patients with refractory hypercholesterolemia, including HoFH, and significantly reduced triglycerides. GalNAc-conjugated siRNA agents such as solbinsiran produced potent, dose-dependent reductions in circulating ANGPTL3, triglycerides, apoB-containing lipoproteins, and remnant cholesterol, with effects sustained for several months and associated decreases in hepatic fat fraction(Geladari et al., 2019; Rosenson et al., 2021).

**siRNA-based therapies**: delivered predominantly via GalNAc conjugation to hepatocytes, showed robust, target-specific protein knockdown through the RNAi pathway.

Inclisiran, targeting PCSK9, produced sustained LDL-C reductions of about 50 % in phase 3 ORION trials, with a dosing schedule of baseline, 3 months, then every 6 months; pooled analyses suggest a 26 % reduction in composite MACE(Carugo et al., 2023b).

In hypertriglyceridemia and mixed dyslipidemia, siRNAs directed at APOC3 or ANGPTL3 reduced triglycerides by 52 %, non-HDL-C by 21.9 %, apoB by 12.6 %, and remnant cholesterol by 64.8 %. APOC3-targeted siRNAs markedly increased HDL-C (40.9 %) with neutral LDL-C effects, whereas ANGPTL3-targeted siRNAs reduced LDL-C (13.2 %) but lowered HDL-C (20.2 %)(Gao et al., 2026).
LPA-targeted siRNAs such as olpasiran and SLN360 achieved dose-dependent Lp(a) reductions ranging from 70 % to over 100 %, highlighting strong potential for patients with genetically elevated Lp(a)(Carugo et al., 2023b).

**Gene therapy and genome editing**: current gene-based approaches include AAV gene delivery and CRISPR editing (such as base, prime, and epigenome editing). Turning off PCSK9 (e.g., VERVE-101) and fixing LDLR defects have led to strong and lasting LDL-C reductions in animal studies and early human trials, especially in familial hypercholesterolemia. These methods can make very precise changes to DNA without cutting both strands, which may help reduce unwanted side effects(Gurevitz et al., 2025; Hoekstra & Van Eck, 2024).

## Discussion

This narrative review highlights how new non-statin therapies are changing dyslipidemia treatment by targeting different pathways, allowing long-lasting reductions in LDL cholesterol, triglycerides, and lipoprotein(a), and filling important gaps left by standard treatments. Bempedoic acid, siRNA-based drugs, ANGPTL3 inhibitors, and gene therapy/editing each offer specific benefits in clinical practice.

Bempedoic acid fills an important gap for patients who are statin-intolerant or remain above LDL-C targets, although maximally tolerated statins. Its safety profile is generally comparable to placebo, with no adverse impact on glycemia. It is impossible not to mention that modest increases in gout, hyperuricemia, and cholelithiasis. Therefore, it is wise to monitor the patient during this therapy.

ANGPTL3 inhibition represents a particularly attractive strategy because its lipid-lowering effects are largely independent of LDL receptors, making it valuable for patients with HoFH or markedly impaired LDLR function. Overall safety appears favourable, with mostly mild adverse events and improved hepatic tolerability in newer siRNA platforms compared with earlier antisense agents.

siRNA therapies enable highly specific gene silencing. Inclisiran, which is included in this group, consistently lowers LDL-C and reduces composite MACE in pooled analyses, supporting its role as a long-acting PCSK9-directed therapy that can improve adherence. siRNA agents targeting APOC3 and ANGPTL3

yield triglyceride reductions, large falls in remnant cholesterol, and meaningful changes in apoB and HDL C, enabling phenotype-guided treatment of hypertriglyceridemia and mixed dyslipidemia. LPA-directed siRNAs achieve lipoprotein(a) lowering. Therefore, the above therapies seem to be promising tools for individuals with genetic lipid disorders.

The most groundbreaking part of dyslipidemia treatment includes gene addition and genome editing. It offers the most profound conceptual shift, aiming for a one-time, long-lasting modification of lipid metabolism. Inactivation of PCSK9 with approaches such as base editing constructs, for example, VERVE 101 and correction of LDLR defects in familial hypercholesterolemia have shown sustained LDL-C lowering in preclinical and early clinical studies. But long term safety, off target risks, and ethical aspects remain incompletely defined. Future studies are necessary to expand the current evidence base.

Based on the collected data, the main unmet needs are robust long-term outcomes and safety data, as well as cost-effectiveness analyses of the therapies described above. Most hard endpoint evidence currently comes from bempedoic acid and, to a lesser extent, inclisiran, whereas gene editing, therapies targeting ANGPTL3 and APOC3, and Lp(a)-targeting siRNA still require large-scale clinical trials assessing their impact on the cardiovascular system.

Finally, the evidence clearly shows that long-lasting lipid-lowering strategies targeted to the disease mechanism can significantly reduce risk in dyslipidemia, especially in high-risk groups (e.g., patients with familial hypercholesterolemia) and those who do not respond well to treatment.

## Conclusions

The way we treat dyslipidemia is changing, moving away from daily pills toward longer-lasting treatments that target specific disease mechanisms and are easier for patients to follow. New options - such as bempedoic acid, ANGPTL3-targeted therapies, siRNA drugs, and gene-editing approaches can lower LDL cholesterol, triglycerides, and lipoprotein(a) through different pathways.

Results from major trials, including CLEAR and the ORION studies, show that these treatments not only improve lab results but also reduce serious cardiovascular events (MACE), which is especially important for high-risk patients and those who cannot tolerate standard therapies.

Early results on safety and effectiveness are encouraging, but the exact role of newer gene-editing methods and some siRNA drugs in everyday practice remains unclear until longer-term data are available. Overall, these advances point toward more personalised care and offer new tools to better reduce cardiovascular risk and manage even complex lipid disorders.

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