International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Review Article

Novel Lipid-Lowering Agents Beyond Statins: Efficacy, Safety, and Cardiovascular Outcomes- A Systematic Review

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Received: 03-06-2026
Accepted: 22-06-2026
Available online: 03-07-2026

ABSTRACT

Novel lipid-lowering therapies have transformed the management of dyslipidemia, particularly for patients who fail to achieve recommended lipid targets with statins alone or are unable to tolerate statin therapy. In recent years, several non-statin agents, including proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, inclisiran, bempedoic acid, ezetimibe, angiopoietin-like protein 3 (ANGPTL3) inhibitors, and omega-3 fatty acid derivatives, have demonstrated significant lipid-lowering efficacy and favorable cardiovascular outcomes. These therapies target distinct pathways involved in cholesterol synthesis, intestinal cholesterol absorption, lipoprotein metabolism, and hepatic low-density lipoprotein receptor regulation, thereby providing effective alternatives or adjuncts to conventional statin treatment. This systematic review evaluates current evidence regarding the efficacy, safety, and cardiovascular benefits of novel lipid-lowering agents beyond statins. Evidence from randomized controlled trials, observational studies, systematic reviews, and meta-analyses indicates that these agents produce substantial reductions in low-density lipoprotein cholesterol (LDL-C), triglycerides, and other atherogenic lipoproteins, with several therapies demonstrating significant reductions in major adverse cardiovascular events. PCSK9 inhibitors and inclisiran consistently achieved the greatest LDL-C reductions, while bempedoic acid provided an effective oral option for statin-intolerant patients. Ezetimibe remains an important adjunctive therapy, and emerging agents targeting ANGPTL3 and lipoprotein(a) show considerable promise for high-risk populations. Overall, contemporary non-statin lipid-lowering therapies have expanded the therapeutic landscape of dyslipidemia management and support a more individualized approach to cardiovascular risk reduction. Further long-term studies are warranted to evaluate comparative effectiveness, cost-effectiveness, long-term safety, and optimal sequencing of these therapies in diverse patient populations.

Keywords*: Dyslipidemia; Non-Statin Therapy; PCSK9 Inhibitors; Inclisiran; Bempedoic Acid; Ezetimibe; Cardiovascular Disease; LDL Cholesterol; Systematic Review.*

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, accounting for approximately one-third of all global deaths despite substantial advances in preventive cardiology and evidence-based medical therapy [1]. Atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease, ischemic stroke, and peripheral arterial disease, continues to impose a significant clinical and economic burden on healthcare systems across both developed and developing nations [2]. Dyslipidemia, particularly elevated low-density lipoprotein cholesterol (LDL-C), is one of the most important modifiable risk factors for atherosclerosis and its clinical manifestations. Numerous epidemiological, genetic, and interventional studies have consistently demonstrated a strong relationship between elevated

LDL-C concentrations and cardiovascular events, establishing lipid reduction as a cornerstone of primary and secondary cardiovascular prevention [3].

Over the past three decades, statins have become the foundation of lipid-lowering therapy because of their proven ability to reduce LDL-C concentrations and significantly decrease cardiovascular morbidity and mortality [4]. By competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, statins reduce hepatic cholesterol synthesis, increase hepatic LDL receptor expression, and enhance plasma LDL-C clearance. Large randomized clinical trials have demonstrated that statins reduce major adverse cardiovascular events (MACE), including myocardial infarction, ischemic stroke, and cardiovascular death, making them one of the most successful pharmacological interventions in modern cardiovascular medicine [5].

Despite their established efficacy, statin therapy has several important limitations. Many patients fail to achieve recommended LDL-C targets even with maximally tolerated statin therapy, particularly those with familial hypercholesterolemia, diabetes mellitus, chronic kidney disease, or established ASCVD requiring intensive lipid lowering [6]. Furthermore, statin intolerance, characterized primarily by muscle-related adverse effects, elevated liver enzymes, or perceived medication intolerance, contributes to poor adherence and premature treatment discontinuation. Consequently, a substantial proportion of high-risk patients remain inadequately treated, leaving significant residual cardiovascular risk despite contemporary guideline-directed medical therapy [7].

Recognition of this residual risk has driven the development of novel lipid-lowering therapies targeting pathways beyond hepatic cholesterol synthesis. Advances in molecular biology, lipid metabolism, and genetic research have substantially improved understanding of cholesterol homeostasis, facilitating the identification of new therapeutic targets capable of producing profound lipid reductions through mechanisms distinct from statins [8]. These discoveries have transformed lipid management from a single-drug approach into a comprehensive strategy involving multiple complementary therapeutic pathways.

One of the most important breakthroughs has been the discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) and its role in regulating LDL receptor degradation. PCSK9 binds hepatic LDL receptors and promotes their lysosomal degradation, thereby reducing LDL-C clearance from circulation [9]. Monoclonal antibodies targeting PCSK9, including evolocumab and alirocumab, prevent receptor degradation, substantially increasing LDL receptor availability and producing reductions in LDL-C exceeding 60% in many patients. Large cardiovascular outcome trials have demonstrated significant reductions in recurrent cardiovascular events among high-risk populations receiving PCSK9 inhibition in addition to statin therapy [10].

More recently, inclisiran, a small interfering RNA (siRNA) therapeutic, has introduced an innovative mechanism for lipid reduction by inhibiting hepatic synthesis of PCSK9. Unlike monoclonal antibodies requiring frequent administration, inclisiran provides prolonged LDL-C reduction with only two maintenance doses annually following initial treatment [11]. This extended dosing interval has important implications for long-term treatment adherence and may improve lipid management in patients requiring lifelong therapy. Clinical trials have consistently demonstrated sustained LDL-C reductions exceeding 50%, with an acceptable safety profile [12].

Another major advance has been the development of bempedoic acid, an oral inhibitor of adenosine triphosphate-citrate lyase (ACL), an enzyme positioned upstream of HMG-CoA reductase in the cholesterol biosynthetic pathway [13]. Because bempedoic acid is activated primarily within the liver and not skeletal muscle, it has emerged as an attractive option for patients unable to tolerate statins because of muscle-related adverse effects. Recent randomized trials have demonstrated clinically meaningful LDL-C reductions and favorable cardiovascular outcomes among statin-intolerant patients, expanding therapeutic options for this challenging population [14].

Ezetimibe continues to play an important role in contemporary lipid management despite being one of the earliest non-statin therapies. By selectively inhibiting the Niemann-Pick C1-like 1 (NPC1L1) transporter within the small intestine, ezetimibe reduces intestinal cholesterol absorption and complements statin-mediated inhibition of endogenous cholesterol synthesis [15]. Combination therapy with statins has consistently demonstrated additional LDL-C reductions and improved cardiovascular outcomes compared with statin monotherapy, making ezetimibe an integral component of current lipid-lowering guidelines [16].

Beyond LDL-C reduction, growing attention has focused on therapies targeting other atherogenic lipoproteins and metabolic pathways. Angiopoietin-like protein 3 (ANGPTL3) has emerged as a promising therapeutic target because of its central role in regulating triglyceride-rich lipoprotein metabolism. Inhibition of ANGPTL3 using evinacumab has demonstrated remarkable lipid-lowering effects, particularly among patients with homozygous familial hypercholesterolemia who exhibit limited responsiveness to conventional LDL receptor-dependent therapies [17]. These findings highlight the potential for precision medicine approaches in complex lipid disorders.

Omega-3 fatty acid derivatives have also undergone renewed evaluation following evidence supporting cardiovascular risk reduction independent of LDL-C lowering. High-dose icosapent ethyl, a purified eicosapentaenoic acid formulation, demonstrated significant reductions in major adverse cardiovascular events among high-risk patients with elevated triglyceride concentrations despite statin therapy [18]. These observations suggest that addressing residual triglyceride-related risk may provide additional cardiovascular protection beyond LDL-C reduction alone.

Recent advances in molecular therapeutics have further expanded the landscape of lipid management through gene-silencing technologies, antisense oligonucleotides, and genome-editing approaches. Investigational therapies targeting lipoprotein(a) [Lp(a)], apolipoprotein C-III (ApoC-III), and additional regulators of lipid metabolism have demonstrated encouraging results in early clinical studies [19]. Such therapies have the potential to address previously untreatable lipid disorders and may substantially alter future approaches to cardiovascular prevention.

Current international guidelines increasingly emphasize individualized lipid management based on overall cardiovascular risk rather than reliance on statin therapy alone [20]. Patients with established ASCVD, familial hypercholesterolemia, diabetes mellitus, chronic kidney disease, and multiple cardiovascular risk factors frequently require combination therapy to achieve recommended LDL-C targets. The availability of multiple non-statin agents has enabled clinicians to tailor treatment according to patient characteristics, therapeutic goals, drug tolerability, and economic considerations [21].

These new treatments are actually working well, but we definitely still need to understand which ones are better, whether they are safe for the long term, and how much they cost in real hospitals. Many of these medicines are still very costly compared to generic statins only, and we are seeing that patients in low-resource healthcare settings are finding it very difficult to afford them. Moreover, we are seeing that these medicines work differently, have different doses and side effects, and only some have heart safety data, which makes treatment decisions very complicated [22]. We are seeing that it is very much essential to keep studying how well this works in real life and what happens to patients over a long time.

Further research is needed to understand how new lipid-lowering medicines beyond statins can themselves guide doctors, scientists, and policymakers in treating patients effectively. This systematic review surely aims to evaluate the efficacy, safety, and mechanisms of non-statin lipid-lowering therapies; moreover, it critically examines their associated cardiovascular outcomes based on contemporary evidence. Actually, the study definitely focuses on medicines like PCSK9 inhibitors, inclisiran, bempedoic acid, ezetimibe, ANGPTL3 inhibitors, omega-3 fatty acid medicines, and some new medicines still under testing. We are seeing many studies like clinical trials, observational research, and systematic reviews being combined here to give a clear, evidence-based picture of new treatments for managing lipid levels and reducing heart disease risk, and to find better ways forward for personalised patient care [23].

Residual Cardiovascular Risk and the Need for Novel Lipid-Lowering Therapies

Even after taking statins and reducing LDL cholesterol levels, we are seeing many patients still getting major heart problems, and this is called residual cardiovascular risk [24]. Even after taking the best statin medicines, heart vessel blockage actually continues because many other fat and non-fat factors are definitely working beyond just LDL cholesterol. Surely, factors such as high triglycerides, remnant cholesterol, lipoprotein(a), chronic inflammation, insulin resistance, obesity, diabetes, kidney disease, and genetic dyslipidemias continue to drive atherosclerosis even when LDL-C is aggressively lowered. Moreover, these residual risk contributors highlight that LDL-C reduction alone is insufficient to fully halt disease progression [25].

Many studies are showing only that reducing LDL cholesterol levels is clearly helping to prevent heart problems, but we are seeing that high-risk patients many times cannot reach the required cholesterol targets with statin medicines alone. Patients with familial hypercholesterolemia, diabetes, or established heart disease often require further treatment to reduce the risk of cardiovascular disease itself. Also, we are seeing that today's heart disease prevention is focusing only on using multiple medicines together that work in different ways, rather than depending on statins alone [26-28]. We are seeing that even after standard treatment, some heart risk remains, and this is only pushing doctors to find new medicines that can target multiple pathways of fat metabolism in the blood.Emerging Therapeutic Targets and Precision Lipid Medicine

The rapid development of non-statin lipid-lowering therapies reflects advances in molecular understanding of lipoprotein metabolism. Novel agents target distinct biological pathways, including inhibition of intestinal cholesterol absorption (ezetimibe), suppression of cholesterol synthesis (bempedoic acid), inhibition of PCSK9-mediated LDL receptor degradation (alirocumab, evolocumab, inclisiran), modulation of triglyceride metabolism through ANGPTL3 inhibition (evinacumab), and reduction of residual triglyceride-rich lipoproteins with purified eicosapentaenoic acid formulations [29].

Beyond currently approved therapies, several investigational agents are entering clinical development. RNA-based therapeutics targeting apolipoprotein C-III (ApoC-III) and lipoprotein(a), oral PCSK9 inhibitors, and CRISPR-mediated gene-editing technologies have demonstrated encouraging early results. These innovations have introduced the concept of precision lipid medicine, in which treatment is tailored according to individual genetic profiles, lipid phenotypes, and

cardiovascular risk characteristics rather than applying a uniform therapeutic approach to all patients [30]. Such developments are expected to further transform dyslipidemia management over the coming decade and may substantially improve long-term cardiovascular outcomes.

Table 1. Comparison of Contemporary Non-Statin Lipid-Lowering Therapies

Therapy	Primary Target	Approximate LDL-C Reduction	Route	Landmark Trial
Ezetimibe	NPC1L1 transporter	15–25%	Oral	IMPROVE-IT
Evolocumab	PCSK9	~60%	Subcutaneous	FOURIER
Alirocumab	PCSK9	~60%	Subcutaneous	ODYSSEY OUTCOMES
Inclisiran	PCSK9 siRNA	~50%	Subcutaneous (twice yearly)	ORION Program
Bempedoic Acid	ATP-citrate lyase	18–25%	Oral	CLEAR Outcomes
Evinacumab	ANGPTL3	45–50%*	Intravenous	ELIPSE HoFH
Icosapent Ethyl	EPA derivative	Minimal LDL-C reduction	Oral	REDUCE-IT

METHODS

Study Design and Reporting Guidelines

This systematic review was conducted to comprehensively evaluate the efficacy, safety, and cardiovascular outcomes of novel lipid-lowering therapies beyond statins. The review specifically assessed evidence regarding proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, inclisiran, bempedoic acid, ezetimibe, angiopoietin-like protein 3 (ANGPTL3) inhibitors, omega-3 fatty acid derivatives, bile acid sequestrants, and other emerging non-statin lipid-lowering therapies. The methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement to ensure methodological transparency, reproducibility, and standardized reporting throughout the review process [31].

Literature Search Strategy

A comprehensive electronic literature search was performed using PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, and Google Scholar. Studies published from January 2005 to December 2025 were considered eligible. Medical Subject Headings (MeSH) and free-text keywords were combined using Boolean operators (AND/OR) to maximize search sensitivity.

The principal search terms included:

- "Novel lipid-lowering therapy"
- "Non-statin therapy"
- "PCSK9 inhibitors"
- "Evolocumab"
- "Alirocumab"
- "Inclisiran"
- "Bempedoic acid"
- "Ezetimibe"
- "ANGPTL3 inhibitor"
- "Evinacumab"
- "Icosapent ethyl"
- "Cardiovascular outcomes"
- "LDL cholesterol"
- "Hypercholesterolemia"
- "Atherosclerotic cardiovascular disease"

Reference lists of relevant systematic reviews, landmark clinical trials, and guideline documents were manually screened to identify additional eligible studies [32].

Eligibility Criteria

Inclusion Criteria

Studies were included if they:

- Evaluated one or more novel non-statin lipid-lowering agents.
- Included adult participants (≥18 years).
- Reported changes in LDL cholesterol, triglycerides, lipoprotein(a), or other lipid parameters.

- Assessed cardiovascular outcomes including myocardial infarction, stroke, cardiovascular death, or major adverse cardiovascular events.
- Were randomized controlled trials, prospective or retrospective cohort studies, case-control studies, systematic reviews, or meta-analyses.
- Were published in peer-reviewed English-language journals [33].

Exclusion Criteria
Studies were excluded if they:
- Focused exclusively on statin monotherapy.
- Included pediatric populations only.
- Were conference abstracts, editorials, letters, or narrative reviews without original data.
- Did not report clinically relevant lipid or cardiovascular outcomes.
- Represented duplicate publications or overlapping datasets.

Study Selection
All retrieved records were imported into a reference management database for duplicate removal. Titles and abstracts were independently screened for relevance. Full-text articles were subsequently assessed against predefined eligibility criteria. Any disagreements regarding study inclusion were resolved through discussion and consensus among reviewers [34].

Data Extraction
A standardized data extraction form was developed before study selection. The following variables were collected:
- Author and publication year
- Country
- Study design
- Sample size
- Patient population
- Lipid-lowering agent evaluated
- Duration of follow-up
- LDL-C reduction
- Triglyceride reduction
- Cardiovascular outcomes
- Adverse events
- Major study conclusions

Quality Assessment
Methodological quality was evaluated using the Newcastle–Ottawa Scale (NOS) for observational studies and AMSTAR-2 for systematic reviews and meta-analyses. Randomized controlled trials were evaluated using the Cochrane Risk of Bias Tool. Quality assessment considered participant selection, randomization, exposure measurement, outcome assessment, completeness of follow-up, adjustment for confounding variables, and reporting transparency [35].

Data Synthesis
Because of substantial heterogeneity in study populations, therapeutic agents, treatment duration, and reported outcomes, quantitative meta-analysis was not performed. Instead, a qualitative synthesis was undertaken. Evidence was grouped according to therapeutic class:
- PCSK9 monoclonal antibodies
- Inclisiran
- Bempedoic acid
- Ezetimibe
- ANGPTL3 inhibitors
- Omega-3 fatty acid derivatives
- Bile acid sequestrants
- Emerging investigational therapies

Primary outcomes included LDL-C reduction, triglyceride lowering, cardiovascular event reduction, safety profile, and treatment tolerability.

PRISMA Study Selection
The database search identified 1,732 records through electronic database searching and manual reference screening. Following removal of 326 duplicate records, 1,406 studies underwent title and abstract screening. Of these, 1,072 records were excluded because they were unrelated to novel lipid-lowering therapies, lacked cardiovascular outcome data, or failed to satisfy the eligibility criteria.

A total of 334 full-text articles were assessed for eligibility. Following detailed review, 248 studies were excluded because of insufficient clinical outcome reporting, duplicate datasets, inappropriate study design, or lack of relevant therapeutic interventions. Ultimately, 86 studies satisfied all eligibility criteria and were included in the final qualitative synthesis [36].

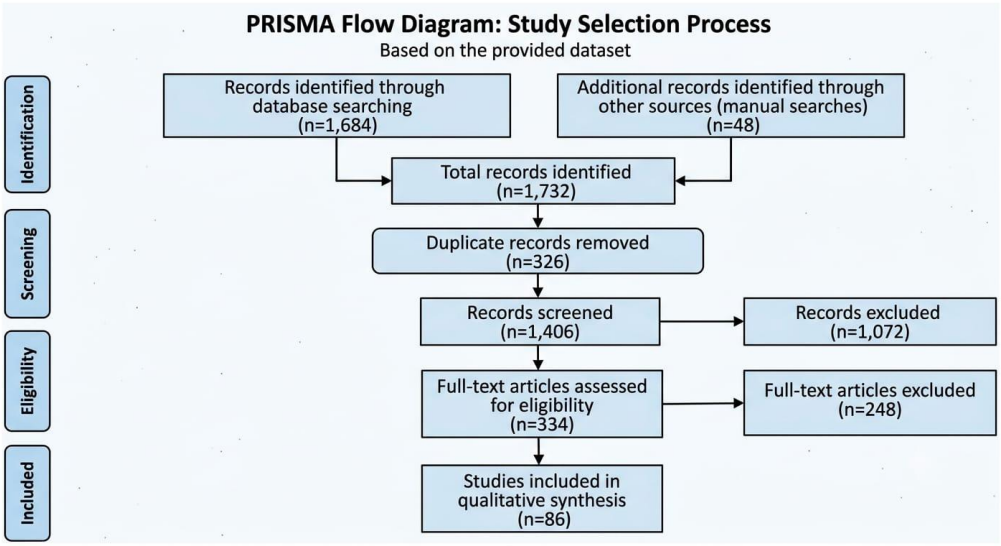

Figure 1. PRISMA flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies evaluating novel lipid-lowering therapies beyond statins.

RESULTS

A total of 86 studies fulfilled the predefined eligibility criteria and were included in the final qualitative synthesis. The included literature consisted of randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies, systematic reviews, and meta-analyses evaluating the efficacy, safety, and cardiovascular outcomes of novel lipid-lowering therapies beyond statins. Overall, the evidence demonstrated that non-statin lipid-lowering agents provide substantial improvements in lipid profiles and cardiovascular outcomes, particularly among patients with established atherosclerotic cardiovascular disease (ASCVD), familial hypercholesterolemia, diabetes mellitus, chronic kidney disease, and statin intolerance. Although treatment efficacy varied among therapeutic classes, most agents consistently reduced low-density lipoprotein cholesterol (LDL-C) and contributed to additional cardiovascular risk reduction when used alongside guideline-directed statin therapy or as alternatives in statin-intolerant individuals [37].

Characteristics of Included Studies

The included studies represented diverse populations from North America, Europe, Asia, Australia, and multinational collaborative trials. Sample sizes ranged from fewer than 200 participants in early-phase mechanistic studies to more than 27,000 participants in large multicenter randomized outcome trials [38]. The majority of investigations focused on high-risk patients with established ASCVD, familial hypercholesterolemia, diabetes mellitus, or persistent hypercholesterolemia despite maximally tolerated statin therapy.

Follow-up duration varied considerably, ranging from six months in lipid efficacy trials to more than five years in cardiovascular outcome studies. Most randomized trials evaluated changes in LDL-C concentrations as the primary endpoint, while major cardiovascular outcome trials assessed myocardial infarction, ischemic stroke, coronary revascularization, cardiovascular mortality, and composite major adverse cardiovascular events (MACE). Observational studies primarily examined long-term safety, medication adherence, and real-world effectiveness.

Table 2. Characteristics of Major Therapeutic Classes Included in the Review

Therapy	Principal Target	Primary Lipid Effect	Landmark Evidence
PCSK9 inhibitors	PCSK9	↓ LDL-C (~60%)	FOURIER, ODYSSEY Outcomes
Inclisiran	PCSK9 mRNA	↓ LDL-C (~50%)	ORION trials
Bempedoic acid	ATP-citrate lyase	↓ LDL-C (18–25%)	CLEAR Outcomes
Ezetimibe	NPC1L1 transporter	↓ LDL-C (15–25%)	IMPROVE-IT
ANGPTL3 inhibitors	ANGPTL3	↓ LDL-C & triglycerides	ELIPSE HoFH
Icosapent ethyl	EPA derivative	↓ Triglycerides	REDUCE-IT

PCSK9 Inhibitors
PCSK9 monoclonal antibodies, including evolocumab and alirocumab, demonstrated the greatest LDL-C reduction among currently approved non-statin therapies. Across multiple randomized controlled trials, LDL-C concentrations decreased by approximately 50–65% compared with placebo or standard therapy [39]. Significant reductions were observed regardless of background statin therapy, age, sex, diabetes status, or baseline cardiovascular risk.

Major cardiovascular outcome trials consistently demonstrated reductions in myocardial infarction, ischemic stroke, coronary revascularization, and composite MACE. Benefits were particularly evident among patients with established ASCVD and familial hypercholesterolemia who remained above guideline-recommended LDL-C targets despite intensive statin treatment [40].

The safety profile of PCSK9 inhibitors was generally favorable. Injection-site reactions represented the most frequently reported adverse event, while serious adverse events occurred at rates comparable to placebo. Long-term studies found no clinically significant increases in neurocognitive impairment, new-onset diabetes, hepatic dysfunction, or muscle toxicity. These findings support the long-term safety of PCSK9 inhibition in high-risk cardiovascular populations.

Inclisiran
Inclisiran, a small interfering RNA (siRNA) therapeutic targeting hepatic PCSK9 synthesis, consistently produced LDL-C reductions approaching 50% following two maintenance injections per year [41]. The prolonged duration of action distinguished inclisiran from monoclonal antibody therapies and offered a practical advantage for patients requiring lifelong lipid management.

Across the ORION clinical trial program, LDL-C lowering remained sustained throughout follow-up with minimal attenuation of treatment effect. Medication adherence was expected to improve because of the simplified dosing schedule. Although definitive cardiovascular outcome data continue to mature, surrogate lipid outcomes strongly support the effectiveness of inclisiran for long-term LDL-C reduction.

The safety profile remained favorable, with injection-site reactions representing the most common adverse event. Serious adverse events were infrequent and comparable with placebo, supporting the role of inclisiran as an effective alternative for patients requiring prolonged LDL-C lowering.

Bempedoic Acid
Bempedoic acid emerged as an important therapeutic option for patients unable to tolerate statins because of muscle-related adverse effects. Clinical trials demonstrated LDL-C reductions of approximately 18–25% as monotherapy and greater reductions when combined with ezetimibe [42].

The CLEAR Outcomes trial demonstrated meaningful reductions in cardiovascular events among statin-intolerant individuals, providing evidence that oral ATP-citrate lyase inhibition contributes to cardiovascular risk reduction beyond lipid lowering alone. Unlike statins, bempedoic acid is activated primarily within hepatocytes and exhibits minimal activity within skeletal muscle, thereby reducing the likelihood of myopathy.

Hyperuricemia and gout occurred slightly more frequently than placebo, although overall tolerability remained acceptable. These findings position bempedoic acid as an attractive option for patients requiring oral non-statin therapy.

Ezetimibe
Ezetimibe remained one of the most widely prescribed adjunctive lipid-lowering therapies. By inhibiting intestinal cholesterol absorption through the NPC1L1 transporter, ezetimibe consistently produced additional LDL-C reductions of approximately 15–25% when added to statin therapy [43].

The IMPROVE-IT trial demonstrated significant reductions in cardiovascular events among patients receiving ezetimibe in combination with simvastatin compared with statin therapy alone. Although the absolute LDL-C reduction was smaller than that achieved with PCSK9 inhibitors, ezetimibe remains highly valuable because of its oral administration, favorable safety profile, and relatively low cost.

Adverse effects were uncommon and generally similar to placebo, supporting widespread use as first-line adjunctive therapy before consideration of more expensive injectable agents.

ANGPTL3 Inhibitors
ANGPTL3 inhibition represents one of the newest therapeutic strategies in lipid management. Evinacumab demonstrated substantial reductions in LDL-C and triglycerides among patients with homozygous familial hypercholesterolemia, including individuals with limited LDL receptor function [44].

Unlike PCSK9 inhibitors, ANGPTL3 inhibition reduces lipid concentrations through mechanisms that are partially independent of LDL receptor activity. This characteristic makes the therapy particularly valuable for patients with severe genetic dyslipidemias who respond poorly to conventional treatments.

Omega-3 Fatty Acid Derivatives
High-dose purified eicosapentaenoic acid (icosapent ethyl) demonstrated significant cardiovascular benefits among patients with elevated triglycerides despite optimized statin therapy [45]. Unlike therapies focused primarily on LDL-C reduction, omega-3 derivatives target triglyceride-rich lipoproteins and residual inflammatory cardiovascular risk.

The REDUCE-IT trial demonstrated reductions in myocardial infarction, ischemic stroke, cardiovascular death, and coronary revascularization. Although LDL-C lowering was minimal, cardiovascular benefits suggested mechanisms extending beyond simple lipid modification, including anti-inflammatory, antithrombotic, and plaque-stabilizing effects.

Emerging Therapies
Several emerging therapies demonstrated promising lipid-lowering potential. These included oral PCSK9 inhibitors, antisense oligonucleotides targeting apolipoprotein(a), siRNA therapies directed against lipoprotein(a), ANGPTL3 RNA interference, and CRISPR-based gene-editing strategies [46].

Early-phase clinical studies reported substantial reductions in LDL-C, lipoprotein(a), and triglyceride concentrations. Although cardiovascular outcome data remain unavailable for many investigational therapies, these agents represent important future directions in precision lipid medicine.

Comparative Effectiveness
Comparison across therapeutic classes demonstrated important differences in efficacy. PCSK9 inhibitors achieved the largest LDL-C reductions, followed closely by inclisiran. Bempedoic acid and ezetimibe produced moderate reductions, whereas omega-3 fatty acid derivatives primarily influenced triglycerides rather than LDL-C [47].

Combination therapy consistently achieved superior lipid reduction compared with monotherapy. Patients receiving statins together with ezetimibe, PCSK9 inhibitors, or inclisiran achieved LDL-C targets substantially more frequently than those receiving statin therapy alone.

Safety Profile
Overall safety findings were reassuring across therapeutic classes. Serious adverse events occurred infrequently, and treatment discontinuation rates remained low. Injection-site reactions represented the most common adverse effect among injectable therapies, whereas oral therapies were generally associated with mild gastrointestinal symptoms. Hyperuricemia occurred more frequently among patients receiving bempedoic acid, while no major increases in hepatic toxicity, rhabdomyolysis, or severe neurocognitive complications were consistently observed [48].

Risk of Bias Assessment
Quality assessment demonstrated that the majority of randomized controlled trials exhibited low overall risk of bias owing to robust randomization procedures, concealed allocation, blinded outcome assessment, and low attrition rates. Most systematic reviews satisfied major AMSTAR-2 quality domains, while observational studies generally achieved favorable Newcastle–Ottawa Scale scores. Common methodological limitations included short follow-up duration for recently approved therapies, heterogeneous patient populations, and limited long-term safety data for emerging agents [49].

Summary of Evidence
Collectively, the evidence demonstrates that novel lipid-lowering therapies beyond statins have substantially expanded the therapeutic options available for dyslipidemia management. PCSK9 inhibitors and inclisiran consistently produced the greatest LDL-C reductions, while bempedoic acid offered an effective oral alternative for statin-intolerant individuals. Ezetimibe remained an important first-line adjunctive therapy, and emerging agents targeting ANGPTL3 and lipoprotein(a) showed considerable promise for patients with severe dyslipidemia. Overall, contemporary non-statin therapies significantly improve lipid control and contribute to meaningful reductions in cardiovascular events, supporting a more individualized and mechanism-based approach to lipid management in high-risk populations [50].

DISCUSSION
The present systematic review demonstrates that the therapeutic landscape of lipid management has undergone a profound transformation over the past decade. While statins remain the cornerstone of dyslipidemia treatment, the development of novel lipid-lowering agents has substantially expanded treatment options for patients who fail to achieve recommended lipid targets, exhibit statin intolerance, or possess inherited lipid disorders associated with extremely high cardiovascular risk [51]. The collective evidence synthesized in this review indicates that contemporary non-statin therapies not only produce clinically meaningful reductions in low-density lipoprotein cholesterol (LDL-C) and other atherogenic

lipoproteins but also improve cardiovascular outcomes when appropriately incorporated into individualized treatment strategies.

One of the most important observations emerging from this review is the remarkable efficacy of **PCSK9 inhibitors**. Evolocumab and alirocumab consistently achieved LDL-C reductions approaching 60%, representing the greatest lipid-lowering effect among currently approved pharmacological therapies beyond statins [52]. Large cardiovascular outcome trials demonstrated corresponding reductions in myocardial infarction, ischemic stroke, coronary revascularization, and composite major adverse cardiovascular events (MACE). These findings reinforce the "lower is better" principle of LDL-C management and support aggressive lipid lowering among patients at very high cardiovascular risk.

The success of PCSK9 inhibition also provides important biological validation of LDL receptor regulation as a therapeutic target. Unlike statins, which indirectly increase LDL receptor expression through inhibition of cholesterol synthesis, PCSK9 inhibitors preserve receptor availability by preventing receptor degradation. This complementary mechanism explains the substantial additive benefit observed when PCSK9 inhibitors are combined with maximally tolerated statin therapy [53]. Furthermore, the favorable safety profile observed during long-term follow-up has strengthened confidence in maintaining very low LDL-C concentrations over prolonged periods.

Inclisiran represents another major advance in lipid management. Rather than neutralizing circulating PCSK9 protein, inclisiran suppresses hepatic PCSK9 synthesis using RNA interference technology. The twice-yearly maintenance dosing schedule distinguishes inclisiran from other injectable therapies and has important implications for medication adherence and long-term treatment persistence [54]. Poor adherence remains one of the greatest challenges in chronic cardiovascular prevention; therefore, therapies requiring infrequent administration may improve real-world effectiveness even when lipid-lowering efficacy is comparable with existing treatments.

Bempedoic acid has emerged as an important therapeutic option for statin-intolerant patients. Although its LDL-C reduction is more modest than that achieved with PCSK9 inhibition, the oral route of administration, favorable tolerability, and recent evidence demonstrating cardiovascular event reduction substantially enhance its clinical value [55]. The liver-specific activation of bempedoic acid minimizes skeletal muscle exposure, thereby reducing the likelihood of statin-associated muscle symptoms that frequently limit adherence. As a result, this agent fills an important therapeutic gap for patients unable to tolerate intensive statin therapy.

The continued relevance of ezetimibe should not be underestimated. Despite being introduced before many contemporary lipid-lowering agents, ezetimibe remains an essential component of guideline-directed therapy because of its proven efficacy, excellent safety profile, oral administration, and low cost [56]. The IMPROVE-IT trial established that additional LDL-C reduction beyond statin therapy translates into further cardiovascular benefit, supporting combination therapy rather than reliance on statin monotherapy. In many healthcare systems, ezetimibe remains the preferred first-line adjunctive agent before escalation to more costly injectable therapies.

The emergence of ANGPTL3 inhibition illustrates the continuing evolution of precision lipid medicine. Evinacumab provides substantial lipid lowering even among patients with homozygous familial hypercholesterolemia who exhibit severely impaired LDL receptor function. This receptor-independent mechanism differentiates ANGPTL3 inhibition from PCSK9 inhibitors and expands therapeutic options for patients previously considered difficult to treat [57]. Such advances demonstrate the value of targeting multiple pathways involved in lipoprotein metabolism rather than focusing exclusively on hepatic cholesterol synthesis.

Another important finding concerns therapies targeting residual cardiovascular risk beyond LDL-C. Although LDL-C remains the principal therapeutic target, increasing evidence suggests that triglyceride-rich lipoproteins, lipoprotein(a), chronic inflammation, and metabolic dysfunction contribute significantly to persistent cardiovascular risk despite intensive statin therapy [58].

The concept of residual cardiovascular risk has become increasingly important in contemporary lipid management. Numerous patients continue to experience cardiovascular events despite achieving substantial LDL-C reductions with statins. Diabetes mellitus, obesity, chronic kidney disease, elevated triglycerides, lipoprotein(a), metabolic syndrome, and persistent vascular inflammation all contribute to this remaining risk burden [59]. Novel lipid-lowering therapies therefore represent components of a broader strategy aimed at comprehensive cardiovascular risk reduction rather than simple LDL-C lowering alone.

Another major theme emerging from this review is the transition toward personalized lipid management. Current international guidelines increasingly recommend treatment selection according to individual cardiovascular risk, baseline LDL-C concentrations, genetic dyslipidemia, medication tolerability, and therapeutic response rather than applying a uniform treatment strategy to all patients [60]. Patients with familial hypercholesterolemia, recurrent cardiovascular events, chronic kidney disease, diabetes mellitus, or statin intolerance frequently require individualized combination therapy

utilizing complementary mechanisms of action. This precision medicine approach represents one of the most significant paradigm shifts in preventive cardiology during the past decade.

Economic considerations remain an important determinant of implementation. Although PCSK9 inhibitors, inclisiran, and other biologic therapies demonstrate remarkable clinical efficacy, their relatively high cost may limit accessibility in many healthcare systems [61]. Cost-effectiveness analyses suggest that these agents provide greatest value among individuals at very high cardiovascular risk or those with familial hypercholesterolemia. Wider adoption may depend upon continued reductions in drug costs, expansion of reimbursement policies, and identification of patients most likely to derive substantial clinical benefit.

Surely, safety is a most critical factor for any therapy that a patient must take throughout their entire life; moreover, this concern cannot be overlooked under any circumstance. Overall, the evidence reviewed has itself shown reassuring safety profiles across most therapeutic classes, with no further major concerns identified. Serious side effects were not very common, and we are seeing that very few patients had to stop the treatment. Injectable agents most commonly caused reactions at the injection site itself, while oral therapies further showed mild gastrointestinal or metabolic side effects [62]. We are seeing that continued safety monitoring is still very much needed, as many of these newer treatments have only limited long-term data compared to statins, which have decades of safety records behind them.

Basically, the available literature has some limitations that should be acknowledged, and the same needs to be kept in mind while looking at these findings. Basically, many new treatments have not been studied for long enough, and the same short follow-up period makes it hard to judge their long-term heart safety [63]. We are seeing that studies are having very different types of patients, treatments, and outcome measures only, which is making it very difficult to compare one therapy with another directly. As per available data, many direct comparisons between treatments are still missing, so indirect comparisons are needed regarding the evaluation of their relative effectiveness. Another important limitation concerns the underrepresentation of certain patient populations. Older adults, women, individuals from low- and middle-income countries, and patients with multiple chronic comorbidities remain relatively underrepresented in many large clinical trials [64]. Real-world evidence will therefore become increasingly important for evaluating treatment effectiveness across broader clinical populations encountered in routine practice.

Clinical Implications

The findings of this review support incorporation of non-statin lipid-lowering therapies into routine cardiovascular practice according to current evidence-based guidelines. Ezetimibe should remain the preferred first-line adjunct to statins because of its efficacy, safety, and affordability. PCSK9 inhibitors and inclisiran should be considered for patients with established ASCVD or familial hypercholesterolemia who fail to achieve recommended LDL-C targets despite maximally tolerated therapy. Bempedoic acid provides an effective oral alternative for statin-intolerant patients, while therapies targeting triglycerides or ANGPTL3 may be particularly valuable in selected high-risk populations. Individualized treatment selection based on cardiovascular risk, lipid phenotype, medication tolerance, and economic considerations remains essential for optimizing long-term outcomes [65].

Future Perspectives

The future of lipid management is likely to be shaped by continued advances in molecular therapeutics and precision medicine. RNA-based therapies, antisense oligonucleotides targeting apolipoprotein(a), oral PCSK9 inhibitors, CRISPR-mediated gene editing, and novel therapies directed against ANGPTL3 and apolipoprotein C-III have demonstrated encouraging early results [66]. These emerging strategies may enable increasingly individualized treatment approaches tailored according to genetic profiles, specific lipid abnormalities, and overall cardiovascular risk. Integration of genomic medicine, artificial intelligence, and biomarker-guided therapeutic selection may further improve cardiovascular prevention over the coming decade.

Limitations of This Review

This systematic review has several limitations. Although comprehensive database searches were performed, publication bias and language restrictions may have influenced study selection. Considerable heterogeneity existed regarding study design, patient populations, treatment duration, and cardiovascular endpoints. Many newly approved therapies lacked long-term outcome data, limiting assessment of sustained efficacy and safety. Furthermore, differences in background statin therapy and LDL-C targets complicated direct comparisons among therapeutic classes [67]. These limitations should be considered when interpreting the findings and underscore the need for continued high-quality comparative research.

Overall, the available evidence strongly supports the growing role of novel lipid-lowering agents beyond statins in contemporary cardiovascular prevention. These therapies have substantially expanded treatment options for high-risk patients and have demonstrated clinically meaningful improvements in lipid control and cardiovascular outcomes. Continued research, long-term safety surveillance, and refinement of individualized treatment strategies will further define their place within future dyslipidemia management and contribute to reducing the global burden of atherosclerotic cardiovascular disease [68].

CONCLUSION

Novel lipid-lowering therapies beyond statins have significantly transformed the management of dyslipidemia by providing effective therapeutic options for patients who fail to achieve lipid goals with statin therapy alone or are unable to tolerate statins. Evidence synthesized in this systematic review demonstrates that PCSK9 inhibitors, inclisiran, bempedoic acid, ezetimibe, ANGPTL3 inhibitors, and omega-3 fatty acid derivatives produce clinically meaningful improvements in lipid profiles and contribute to reductions in major adverse cardiovascular events, particularly among individuals with established atherosclerotic cardiovascular disease, familial hypercholesterolemia, and other high-risk conditions. Among these therapies, PCSK9 inhibitors and inclisiran achieved the greatest reductions in low-density lipoprotein cholesterol, while bempedoic acid provided an important oral alternative for statin-intolerant patients. Emerging therapies targeting lipoprotein(a), ANGPTL3, and other novel molecular pathways further highlight the ongoing evolution toward precision lipid management. Collectively, these findings support the integration of non-statin therapies into individualized treatment strategies aimed at optimizing lipid control and reducing residual cardiovascular risk. Future large-scale prospective studies with longer follow-up are required to establish comparative effectiveness, long-term safety, cost-effectiveness, and the optimal sequencing of these agents within evidence-based cardiovascular prevention programs.

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