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Research Paper

Pharmacological management of atherosclerotic cardiovascular disease risk: a narrative of lipid-lowering pharmacotherapy and the LDL-cholesterol dose-response relationship

Dr. Makbul Hussain Choudhury*
*Assistant Professor, Rahman Institute of Pharmaceutical Sciences and Research, Guwahati, Assam, India.

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ABSTRACT

Background: Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of mortality worldwide, with low-density lipoprotein cholesterol (LDL-C) established as a causal and dose-dependent contributor to atherosclerosis. Despite the availability of several lipid-lowering therapies beyond statins, a substantial gap persists between guideline-recommended LDL-C targets and their achievement in clinical practice.
Objective: To summarize current evidence on the efficacy, safety, and clinical utility of established and emerging lipid-lowering therapies and examine the relationship between LDL-C reduction, cardiovascular risk reduction, and the persistent treatment-target gap.
Methods: A narrative literature review was conducted using PubMed/MEDLINE, Scopus, and ClinicalTrials.gov for publications from January 2020 to mid-2025. Major clinical trials, prospective registries, systematic reviews, and meta-analyses were evaluated, with particular emphasis on lipid-lowering pharmacotherapy and the 2021 European Society of Cardiology prevention guideline. The evidence was qualitatively synthesized.
Result: Combination therapy with statins and ezetimibe, PCSK9-targeted monoclonal antibodies, or inclisiran provides additional LDL-C reductions of approximately 15–60% compared with statin therapy alone. Bempedoic acid reduced major adverse cardiovascular events by 13% among statin-intolerant patients. Large multinational registries, including DA VINCI and SANTORINI, reported that only 20–33% of high-risk patients achieved risk-stratified LDL-C targets. A meta-analysis of 60 randomized trials demonstrated an approximately 22% reduction in major cardiovascular events per 1.0 mmol/L reduction in LDL-C.
Conclusions: Statins remain the cornerstone of ASCVD prevention. Intensification with ezetimibe, PCSK9 inhibitors, bempedoic acid, and emerging RNA- and lipoprotein(a)-targeted therapies can improve LDL-C control and reduce cardiovascular risk.

Corresponding Author:
Dr. Makbul Hussain Choudhury
Assistant Professor, Rahman Institute of Pharmaceutical Sciences and Research, Guwahati, Assam, India.
Email: makbulchy200@gmail.com

1. INTRODUCTION

The burden of atherosclerotic cardiovascular disease (ASCVD) (including coronary artery disease, ischaemic stroke and peripheral artery disease) is still the top killer and greatest cause of disability-adjusted life years lost globally. In fact, the latest Global Burden of Cardiovascular Diseases (GBDC) analysis has revealed that the proportion of all cardiovascular disease (CVD) deaths has increased over the last 30 years, and this share is disproportionately concentrated in low- and middle-income countries where access to preventive pharmacotherapy is not consistent [1]. Although age-standardized mortality and disability-adjusted life-year (DALY) rates have declined with better control of the risk factors and pharmacological prevention, the Global Burden of Disease Study (GBD) 2021 estimated about 612 million prevalent cardiovascular disease (CVD) cases worldwide in 2021, representing about one-quarter of all deaths globally (26.8%) [2].

The LDL-C is not only a correlate but a causal, cumulative and modifiable function of atherogenesis. The LDL particles enter the intima of the artery, become oxidized and are taken up by macrophages to form foam cells, which trigger the inflammatory pathway leading to the formation of an atherosclerotic plaque. This causal claim has been accepted in the cardiovascular literature, and Mendelian randomization studies have demonstrated that the same amount of risk reduction is gained from early versus late LDL-C reduction. The review of this " LDL cumulative exposure hypothesis" states that the quantity and duration of exposure to LDL-C are both factors in ASCVD risk, and serial measurements of LDL-C over time are better biomarkers for risk than any one measurement alone; and suggests the timing and intensity of interventions [3].

This causal relationship has been key in the development of pharmacological agents for the past forty years. Statins, which were introduced in the late 1980s, continue to be the backbone of ASCVD prevention, and there is an extensive evidence base of hundreds of thousands of randomized participants. In the last ten years, this foundation has been expanded through three strategies with dedicated outcome/safety trial proof: the use of ezetimibe as add-on therapy to statins; large effect size LDL-C lowering therapies (monoclonal antibodies and the siRNA agent inclisiran) and oral ATP-citrate lyase inhibitors (statin-intolerant patients), which showed benefit in CLEAR Outcomes [4]. Meanwhile, agents that target residual triglyceride-rich lipoprotein (rLRP) risk and lipoprotein(a) – a largely LDL-independent genetic risk which is now in advanced development using RNA therapeutics [5], [6], [7] – have expanded risk reduction beyond LDL-C.

Despite this growing and growing arsenal, a significant, documented, and documented difference between the recommended LDL-C goals and real-world LDL-C levels has existed, and still exists. Therapeutic inertia, under-dosing of statins and poor use of non-statin combination therapy, even in those who would benefit from it, has been confirmed by large, multinational, observational studies since the 2019 ESC/EAS dyslipidaemia guidelines were published, resulting in most patients in high and very high-risk groups remaining above the target [8], [9]. This is a longstanding evidence to practice gap and is supported by the growing body of trial evidence for more and more effective, well-tolerated options.

1.1 Objectives

This review will: (i) provide a summary of the comparative pharmacology: mechanism of action, LDL-C-lowering efficacy, and adverse-effect profile, of the main classes of lipid-lowering and residual-risk-reducing drugs currently available; (ii) synthesize the latest (2020–2025) trial and pooled-analysis evidence for each class, with particular regard for the three new drug classes: bempedoic acid, inclisiran and the lipoprotein(a)-directed RNA therapeutics; (iii) quantify the relationship between achieved LDL-C reduction and cardiovascular risk reduction across the classes of drugs, using recent meta-analytic synthesis; and (iv) characterize the size of, and contributors to, the continuing gap between guideline LDL-C targets and their achievement, based on recent registry evidence.

2. RELATED WORK

There is a significant amount of recent literature on specific aspects of lipid-lowering pharmacotherapy, but only a few studies have integrated the pharmacology of individual drug classes, level of study efficacy, goal achievement in clinical trials, and new lipid residue risk therapies into a single context. This section places the current review in four relevant, interrelated contexts: (i) guideline and risk-stratification systems, (ii) the statin era pharmacology and intolerance-tackling, (iii) non-statin and combination trial evidence, and (iv) real-world LDL-C goal-attainment registries.

2.1 Guideline and Risk-Stratification Frameworks

The Guidelines from the ESC 2021 are the latest broad consensus update on how to stratify risk for ASCVD that includes the SCORE2 and SCORE2-Older Persons risk algorithms and a step-up, personalised LDL-C, BP and glycaemic management approach [10]. The guidelines keep the LDL-C targets for risk stratification outlined in the 2019 ESC/EAS guidelines and serve as the reference points for the assessment of the actual attainment in the real world below. The LDL cumulative exposure hypothesis suggests that LDL-C is no longer a target, but a time-integrated exposure variable and as such, increasing emphasis on lifetime risk rather than a single exposure is provided for in the guidelines [3].

2.2 Statin Pharmacology, Tolerability, and the Nocebo Phenomenon

Statins are being actively investigated to better understand the actual occurrence and mechanism of statin-associated muscle symptoms (SAMS) the most commonly suggested reason for stopping statins. An n-of-1 crossover study (the SAMSON trial) comparing statin, placebo and no-tablet months in patients who had stopped taking statins for perceived side effects showed a nocebo ratio of ~0.90, meaning that the majority of muscle symptoms reported are associated with taking tablets rather than with the statin molecule [11]. It has guided clinical advice: The National Lipid Association (NLA) has updated their statement to include at least two trials of statins at the lowest dose before categorizing statin intolerance, recommending dose reduction, alternate-day dose, statin switching and judicious use of non-statins [12]. In a related review non-statin monotherapy is advocated for only for proven intolerance and not for symptoms [13].

2.3 Non-Statin and Combination Pharmacotherapy Trial Evidence

There has been a significant body of evidence since 2020 supporting non-statin therapy. In CLEAR Outcomes (placebo-controlled, n=13,970 statin-intolerant patients) bempedoic acid demonstrated an advantage for the composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke and revascularisation (-13%, HR 0.87, 95% CI 0.79–0.96, over 40.6 months) [4] and this was also the case in the diabetes subgroup [14], [15]. In ORION-10/ORION-11, OR placebo-subtracted LDL-C reductions of around 50% with every 6 months of dosed treatment were seen, and the results from pooled analyses were also seen with prior MI [16], polyvascular disease [17] and diabetes or obesity [18], with overall good tolerability in the programme [19]. These trials were not powered to look at events, so there are dedicated outcome trials (ORION-4, VICTORION-2-PREVENT) ongoing, and cardiovascular benefit can only be assumed and not proven.

Therapy for lipoprotein(a) [Lp(a)] has focused on this largely genetic, LDL-independent risk factor for ASCVD and calcific aortic valve disease, for which no current therapy has a more pronounced effect. The phase 2 OCEAN(a)-DOSE trial showed that the highest dose of olpasiran led to more than 95% of Lp(a) reduction with a favourable short-term safety profile [5]. Recent reviews list a growing pipeline of Lp(a) directed agents that are currently in phase 3 evaluation [6], [7] and report that Lp(a) should be measured routinely once in all adults, as this will help identify those approximately 20% of adults who will benefit after they are approved [20].

2.4 Real-World LDL-C Goal-Attainment Registries

A separate strand of literature reporting the gap between guideline and implementation exists. Only 54% of very-high-risk secondary-prevention patients (N=5,888) met the LDL-C goal set for 2016 in the DA VINCI study across the 18 European countries, and only 33% met the more stringent LDL-C goal set in 2019 in the DA VINCI study across the 18 European countries [8]. This has been confirmed by SANTORINI, which reported that only between one-fifth and one-third of patients met 2019 targets, and by national analyses including one Spanish analysis which reported 26.5% of those who did met 2019 targets, and under-titration and under-use of combination therapy were cited as major factors [9], [21]. Inertia has also been observed across the Spanish healthcare system as research on PCSK9-inhibitor eligibility in Spain also identified only a minority of eligible patients identified and treated [22].

Taken together, this literature provides a clear picture: There are more and more powerful and better-tolerated drugs available to lower LDL-C which have mostly not been fully exploited in clinical practice, based on registry data from the modern era. The present review is aimed at bringing together all of the above into an integrated, quantitative account of the efficacy of drugs by class, the relationship between the amount of LDL-C that can be reduced and the amount of risk reduced, and the evidence-to-practice gap that remains.

3. METHODOLOGY

This is a narrative review and no original patient level data was collected; nor were the present authors conducting a formal meta-analytic pooling. A structured search was performed on PubMed/MEDLINE, Scopus, and ClinicalTrials.gov using various combinations of the following keywords: LDL cholesterol, statin, ezetimibe, PCSK9 inhibitor, inclisiran, bempedoic acid, lipoprotein(a), atherosclerotic cardiovascular disease, randomize controlled trial, and goal attainment, limited to articles published from January 2020 through July 2025 and written in English.

3.1 Eligibility Criteria

Pre-specified, randomized, placebo-controlled cardiovascular outcome or safety trials (item (i) above); large-scale, meta-analysis or pooled, post hoc analyses of multiple randomized trials (item (ii) above); prospective, multinational registries of patients reporting LDL-C goal attainment versus a defined guideline standard (item (iii) above); and current ESC/EAS or National Lipid Association guidelines and consensus statements (item (iv) above). Editorials, single centre case series and preprints (not peer reviewed) were not included. If a landmark trial had been conducted before the window for the review of the studies (2020–2025), it was referred to indirectly as part of a contemporary meta-analysis or a pooled re-analysis of the data from that trial. This review focused on the most recent and synthesized evidence, and so a landmark trial prior to that window was used indirectly.

3.2 Data Extraction and Synthesis

The data extracted for each retained source included: mechanism of action, typical or observed (if available) percent LDL-C reduction, hazard ratio and 95% CI for the main composite endpoint, absolute and relative risk reduction, major adverse effects (and, in registries, percent of patients achieving risk-stratified LDL-C targets according to a specific guideline version). The HRs, CIs, ERs, and LDL-C levels listed in Section 4 are from cited primary or pooled-analysis publications and have not been re-calculated, re-

pooled or simulated. If a Figure 2 value is a model-based projection (and not a directly observed outcome), this is made clear in the text, in the figure legend, and in the corresponding table, as the pivotal trials for this drug (inclusiran) were not powered to demonstrate cardiovascular outcomes.

3.3 Synthesis Framework

Findings are presented in three complementary analytic frames that correspond to the tables and figures in Section 4: (i) a comparative pharmacology frame that summarizes the mechanism of action, efficacy and safety of each drug class (Table 1); (ii) a trial-evidence frame that summarizes design, population and outcome for each landmark trial (Table 2); and (iii) a real-world implementation frame that summarizes LDL-C goal attainment and the contributors across the registry level (Table 3). This structure follows the sequence of steps that a clinician or health-system planner takes when implementing trial evidence for population-level ASCVD prevention: mechanism to evidence to practice.

4. RESULTS AND DISCUSSION

4.1 Comparative Pharmacology of Lipid-Lowering Drug Classes

The 6 drug classes examined in this report work via mechanistically different but complementary pathways as shown in Table 1. Statins compete with HMG-CoA for binding to the rate-limiting enzyme in cholesterol synthesis, HMG-CoA reductase, resulting in a dose-dependent decrease in hepatic cholesterol levels of about 30–55%, which leads to increased expression of the LDL receptor and thus greater hepatic LDL clearance. Ezetimibe works by inhibiting the NPC1L1 transporter, which blocks the absorption of cholesterol from the intestine and bile independently of statins; the drug usually provides an additional 15-25% drop, in addition to the statin effect. PCSK9 monoclonal antibodies bind to a hepatic protein that normally directs degradation of LDL, which raises recycling of LDL receptor, and results in the greatest decreases of any approved class (usually 50–60% on top of statins + ezetimibe).

Inclisiran works similarly to PCSK9 inhibitors, but in a different way: It does not stop the PCSK9 protein from working in the bloodstream, it simply stops the translation of hepatocyte mRNA that leads to the production of new PCSK9. Pooled ORION-10/ORION-11 analyses confirmed these reductions, which remained approximately 51–52% after Day 510–540 and 87.6% of patients had LDL-C < 55 mg/dL [15], [16], [17] in a favorable clinical outcome for poor adherers with daily oral therapy. Similar to statins, Bempedoic acid works upstream of HMG-CoA reductase and, like statins, lacks a role in the skeletal muscle, therefore low muscle-related adverse events is logical for statin-intolerant patients. A new class of lipoprotein(a)-directed agents includes those that target a genetic, LDL-independent risk factor, such as pelacarsen, olpasiran, and lepodisiran, with early trials demonstrating a 80% or greater decrease in Lp(a) [5], [6], [7].

Table 1. Comparative Pharmacology of Lipid-Lowering and Residual-Risk-Reducing Drug Classes

Drug Class	Representative Agent(s)	Mechanism of Action	Typical Additional LDL-C Reduction	Principal Adverse Effects
Statins (HMG-CoA reductase inhibitors)	Atorvastatin, Rosuvastatin	Competitive inhibition of hepatic HMG-CoA reductase; up-regulates hepatic LDL-receptor expression, increasing LDL clearance	30–55% (dose- and agent-dependent)	Myalgia; rare myopathy/rhabdomyolysis; transaminase elevation; small increase in incident diabetes risk; majority of reported muscle symptoms are nocebo-mediated [11]

Cholesterol-absorption inhibitor	Ezetimibe	Inhibits NPC1L1-mediated intestinal cholesterol absorption; complementary, non-overlapping mechanism to statins	Additional 15–25% when added to a statin	Generally well tolerated; rare myalgia or hepatic enzyme elevation
PCSK9-directed therapy (monoclonal antibody)	Evolocumab, Alirocumab	Monoclonal antibody neutralization of PCSK9; increases hepatic LDL-receptor recycling	Additional 50–60% when added to statin ± ezetimibe	Injection-site reactions; generally well tolerated; no established renal/hepatic dose adjustment
PCSK9-directed therapy (siRNA)	Inclisiran	Hepatocyte-targeted small interfering RNA silencing of PCSK9 mRNA synthesis; twice-yearly dosing after loading regimen	Additional ~50% sustained to Day 510–540 [15], [16], [17]	Injection-site reactions (most common); favourable tolerability across pooled ORION analyses [18], [19]
ATP-citrate lyase inhibitor	Bempedoic acid	Inhibits ATP-citrate lyase upstream of HMG-CoA reductase in the cholesterol-synthesis pathway; prodrug not activated in skeletal muscle	Additional ~13–17% when added to statin, or as monotherapy in statin-intolerant patients [4]	Hyperuricaemia, gout; small increase in cholelithiasis and tendon rupture (rare); low incidence of muscle-related adverse events
Lipoprotein(a)-directed RNA therapeutics (investigational)	Pelacarsen (ASO), Olpasiran, Lepodisiran (siRNA)	Antisense or siRNA-mediated silencing of hepatic apolipoprotein(a) mRNA translation, reducing Lp(a) particle synthesis	Lp(a) reduction of 80–100%; minimal effect on LDL-C [5], [6], [7]	Injection-site reactions in early-phase trials; long-term cardiovascular outcome and safety data pending phase 3 completion

4.2 Comparative LDL-C-Lowering Efficacy

The amount of LDL-C reduction that can be achieved varies significantly from regimen to regimen as shown in Figure 1. High-intensity statin monotherapy can lower cholesterol by 30-55% from baseline, ezetimibe can lower it by another 45-60% from baseline, and a PCSK9 monoclonal antibody or inclisiran can lower it even more, to 65-75%. The highest reductions (75-85%) occur in triple combination therapy (high intensity statin, PCSK9 monoclonal antibody and ezetimibe) which is usually used in familial hypercholesterolaemia and for those with high baseline LDL-C despite dual therapy. The efficacy of bempedoic acid, when used as a monotherapy or in combination with other agents, lies between that of the

other agents (40–53%), making it less potent than PCSK9-directed agents, but also offering a convenient oral formulation and a favourable muscle safety profile [4], [13].

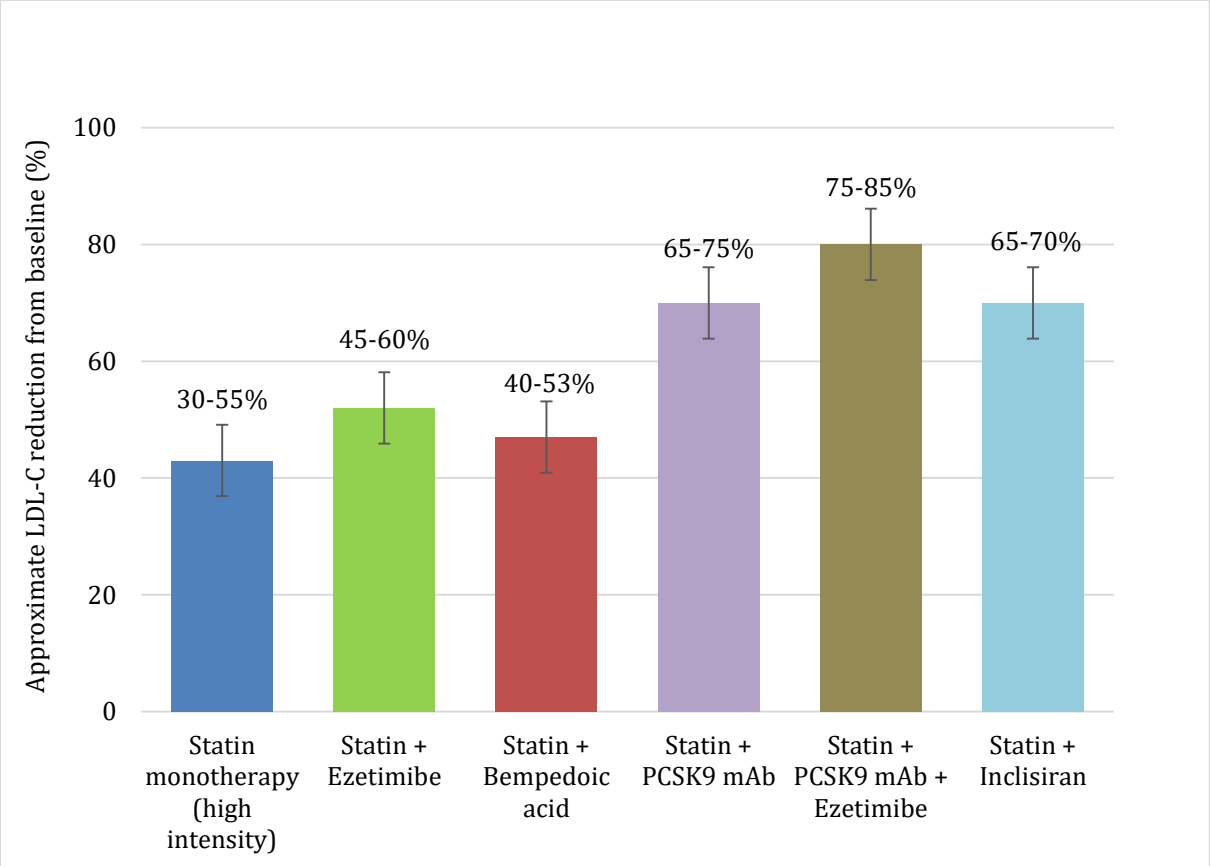

Figure 1. Comparative LDL-C-Lowering Efficacy of Statin-Based Combination Regimens

Bars represent the approximate additional percentage LDL-C reduction from baseline across trials of each regimen; error bars denote the reported range. Data synthesized from [4], [8], [15], [16], [17].

4.3 The Relationship between Achieved LDL-C Reduction and Cardiovascular Risk Reduction

A key issue for clinicians is whether or not cardiovascular benefit from lowering LDL-C is related to the mechanism of action or whether it is related to the extent of LDL-C lowering, regardless of the mechanism of action. This was directly addressed in a recent meta-analysis of 51,425 major vascular events in 60 randomized trials including 408,959 participants, which found a pooled hazard ratio of 0.78 (95% CI 0.75–0.81) per 1.0 mmol/L LDL-C reduction—approximately a 22% relative risk reduction per 1.0 mmol/L lowering, broadly similar across mechanism and, in secondary prevention, across follow-up duration [23]. This is a reference relationship that serves as a useful guideline to interpret individual trial results.

In Table 2 and Figure 2, LDL-C reductions are plotted against relative risk reductions; there are deviations from this reference relationship. In spite of its relatively small LDL-C reduction (~0.5 mmol/L), CLEAR Outcomes demonstrated a 13% relative risk reduction, which is consistent with the reference relationship, thus suggesting that the benefits occur primarily through LDL-C reduction [4], [23]. Several trials of PCSK9 and statins are below the line, likely due to their shorter duration compared to the time required for full benefit to be seen, as benefit accrues over years, not immediately [3], [23]. The Figure 2 value is not observed but is a model-based projection as no completed outcome trial of inclisiran exists — ORION-10/11 were powered to reduce LDL-C, not events — (see Table 2 and legend of the figure).

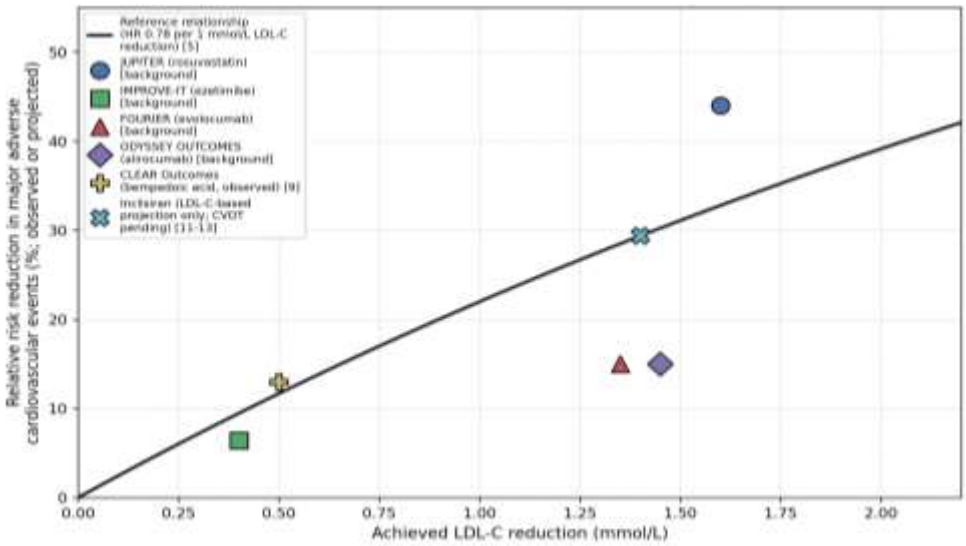

Figure 2. LDL-C Reduction vs. Cardiovascular Risk Reduction

The reference relationship (from a 60-trial meta-analysis [Hazard ratio 0.78 per 1.0 mmol/L LDL-C reduction]) is shown with the solid line. The trials are summarized by points marked "background," which represent historical trials grouped together as they are summarized in this meta-analysis. The inclisiran point is a model-based estimate rather than an actual outcome and there is a dedicated outcome trial on the horizon [15], [16], [17].

Table 2. Summary of Contemporary (2020–2025) Trial and Registry Evidence

Trial (Class)	Design / N	Population	Primary Endpoint Result	Reference
CLEAR Outcomes (bempedoic acid)	Double-blind RCT; N = 13,970	Statin-intolerant patients with, or at high risk for, ASCVD	4-component MACE: 11.7% vs 13.3%; HR 0.87 (95% CI 0.79–0.96); median follow-up 40.6 months	[4]
CLEAR Outcomes diabetes subgroup	Pre-specified subgroup analysis	Patients with and without diabetes within CLEAR Outcomes	Consistent MACE benefit across glycaemic strata; no increase in new-onset diabetes	[14]
ORION-10 / ORION-11 (inclisiran)	Pooled phase 3 RCTs; N = 3,660 (parent trials)	Patients with elevated LDL-C on maximally tolerated statin	Placebo-adjusted LDL-C reduction ≈ −51 to −52% sustained to Day 510–540; 87.6% reached LDL-C < 55 mg/dL	[15], [16], [17]
ORION pooled subgroup (diabetes/obesity)	Post hoc pooled analysis; N = 3 trials	Patients with diabetes or obesity	Consistent LDL-C reduction and favourable tolerability across metabolic subgroups	[18]
OCEAN(a)-DOSE (olpasiran)	Double-blind, dose-finding RCT; N = 281	Established ASCVD with Lp(a) > 150 nmol/L	Placebo-adjusted Lp(a) reduction up to	[5]

			−101.1% at 36 weeks (225 mg/12 weeks)	
DA VINCI (registry)	Cross-sectional observational; N = 5,888	Primary and secondary prevention patients on lipid-lowering therapy, 18 European countries	54% achieved 2016 ESC/EAS LDL-C goal; 33% achieved 2019 goal	[8]
SANTORINI (registry)	Prospective observational; N > 9,000	High/very-high-risk patients, 14 European countries, enrolled 2020–2021	Only ~20–33% achieved 2019 ESC/EAS LDL-C goal at baseline and 1-year follow-up	[9], [21]

4.4 Safety and Tolerability Considerations

Statins are still the most frequently discontinued treatment with muscle symptoms, but this has been influenced by the 0.90 nocebo ratio of statin-associated muscle symptoms (SAMSON) in which 90% of the burden of symptoms is also induced by placebo [11]. It does not mean that statin myopathy or rhabdomyolysis have not occurred at all – in practice, most cases of mild muscle symptoms are not directly attributed to the statin itself and informal stop–restart experiments lacking a placebo control may further strengthen a nonexistent causal link [11]. Before diagnosing intolerance, a statin should be tried at the lowest dose for a period of two statins, and only then will the National Lipid Association say that it is considered a statin intolerance statement, which recommends reducing, alternate-day and switching statins before non-statin monotherapy [12], [13].

In CLEAR Outcomes, Bempedoic acid had a low rate of muscle-related adverse events, as expected of a muscle-sparing drug, and a low rate of hyperuricaemia, gout and cholelithiasis compared with placebo [4]. In the case of PCSK9 monoclonal antibodies and inclisiran, renal and hepatic dose adjustment is not required and there is no evidence of contraindications or signals of concern in subgroups of patients with diabetes, obesity, chronic kidney disease and polyvascular disease in pooled analyses of ORION [16], [17], [18], [19]. Lipoprotein(a)-directed therapeutics are the earliest to be developed, and reactions at the site of injection have been most frequently observed during phase 2 trials, with long-term safety data to be determined once trials in phase 3 are completed [5], [6], [7].

4.5 The Persistent Gap between Guideline Targets and Real-World Attainment

One potentially most important discovery is that of a discrepancy of implementation which is not the result of an efficacy gap. Although the ESC/EAS LDL-C targets are different from below 1.4 mmol/L for very-high-risk patients to <3.0 mmol/L for low-risk patients, registry data collected since the introduction of ezetimibe, PCSK9 inhibitors and inclisiran indicate that only a minority of eligible patients meet them. Only 33% of the patients (5,888/18 countries, DA VINCI) met the 2019 goal, even though they had already been treated [8]. Finally, SANTORINI reported only 20% (26.5% in the Spanish group, an equally low percentage in the Italian group) reached target, which indicates a similar trend across national groups [9], [21].

It can be partly blamed on complementary health-services research. The percentage of patients eligible for routine PCSK9-inhibitor use under guideline recommendations in secondary prevention in Spain was not identified and not treated with indicated combination therapy, suggesting that eligibility is under-recognized, patients remain clinically 'inert', and, in some healthcare systems, access is limited [22]. Together with the fact that most DA VINCI and SANTORINI participants continued statin monotherapy instead of conforming to the guidelines for combination therapy despite having persistently elevated LDL-C, this suggests under-titration, not underdoing of the drugs themselves, and underutilisation of already available combinations as the key contributor to the gap [8], [9], [21].

Table 3. Risk-Stratified LDL-C Targets (2021 ESC/EAS) and Corresponding Registry-Level Goal Attainment

ASCVD Risk Category	2021 ESC/EAS LDL-C Goal	DA VINCI Attainment (2019 goal) [8]	SANTORINI Attainment (2019 goal) [9], [21]
Very high risk (established ASCVD)	< 1.4 mmol/L (< 55 mg/dL) and ≥ 50% reduction from baseline	≈ 22% (secondary prevention subgroup)	≈ 19.9–20.3% (Italian subgroup, very-high-risk)
High risk	< 1.8 mmol/L (< 70 mg/dL) and ≥ 50% reduction from baseline	≈ 33% (overall cohort, mixed risk)	≈ 26.5–29% (Spanish subgroup)
Moderate risk	< 2.6 mmol/L (< 100 mg/dL)	Higher than high-/very-high-risk strata, but below guideline-implied optimum	Not separately reported in all national subgroups
Low risk	< 3.0 mmol/L (< 116 mg/dL)	Not a focus of DA VINCI (LLT-treated cohort only)	Not a focus of SANTORINI (LLT-treated, high/very-high-risk cohort only)

4.6 An Integrated Stepwise Treatment Algorithm

Reviewing the evidence above, it is possible to integrate this with a step-wise approach to recommend a pharmacotherapy algorithm for point-of-care use, as shown in Figure 3. It starts with Risk Stratification and LDL-C Goal setting according to the latest ESC/EAS SCORE2 [10] then moves on to high intensity statin therapy (HITS) as a first line approach followed by inclusion of Ezetimibe as a low cost, complementary second step for those above target. The third line should be a PCSK9-directed agent (either a monoclonal antibody or inclisiran, depending on preference and adherence) in patients with very high residual risk or if dual therapy is not effective, and the muscle sparing option of bempedoic acid for confirmed statin-intolerant patients [4], [12], [13], [15], [16], [17]. Residual triglyceride risk is the last step to be taken after LDL-C goal, as there is residual risk of modifiable lipoproteins in mixed dyslipidaemia which cannot be lowered by LDL-C lowering alone.

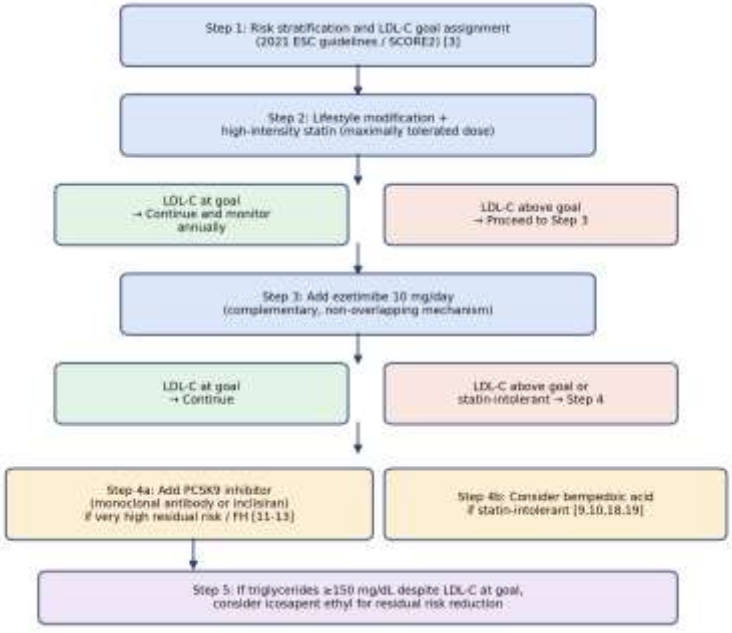

Figure 3. Stepwise LDL-C-Lowering Pharmacotherapy Algorithm

4.7 Limitations

There are certain limitations of the narration design in this review. First, the synthesis is not formal, systematic review protocol, and meta-analytic pooling, which renders it qualitative and interpretive, bearing the risk of selective emphasis. Second, limiting sources to 2020–2025 results in only a few trials being discussed indirectly, in recent meta-analyses, which can obscure the nuances of individual trials. Third, the projection of the inclisiran shown in Figure 2 and Table 2 is not necessarily the same as an outcome-trial result, and until the results of ORION-4 and VICTORION-2-PREVENT are available, definitive conclusions cannot be drawn. Lastly, the evidence found in the registry comes mainly from the European healthcare systems, and variations in attainment patterns can occur if there are variations in the financing of care, access to care, and implementation of guidelines.

5. CONCLUSION

ASCVD is the leading cause of death globally and the most well understood, causal and pharmacologically modifiable driver of ASCVD is LDL-C. The evidence presented here is overwhelming that statins are the cornerstone of ASCVD prevention and that the therapeutic options to complement statins are stronger than ever: ezetimibe is a low-cost, well tolerated second-line agent; the new class of monoclonal antibodies targeting PCSK9 can deliver LDL-C reductions of 50% or more, with excellent tolerability; and bempedoic acid offers an excellent muscle-safety profile for statin-intolerant individuals, while an emerging class of new RNA therapeutics targeting the genetically determined pathway responsible for the production of lipoprotein(a) has the potential to extend risk reduction to one of the most powerful pathways in the body. Despite this growing 'toolbox', the key take-home message of this review is that the primary challenge to reducing the global burden of ASCVD is not the availability of effective tools, but rather the lack of progress in achieving the targets set out in the guidelines in routine practice. Although there are regimens available that can reduce risk by 65% or more, registry data suggest that less than a third of those who are high and very-high risk reach their target. This represents a significant, low cost opportunity to lower cardiovascular morbidity and mortality at a population level by closing this gap, which can be achieved by: (1) increasing the scope of risk stratification; (2) implementing earlier treatment escalation; and (3) expanding access to non-statin combination therapy. Future studies should focus on conducting further outcome trials of inclisiran and lipoprotein(a) directed therapeutics, and implementation research to bridge the efficacy gap to real-world achievement.

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Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Makbul Hussain Choudhury	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓	✓

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed Consent

All participants were informed about the purpose of the study and their voluntary consent was obtained prior to data collection.

Ethical Approval

Not applicable.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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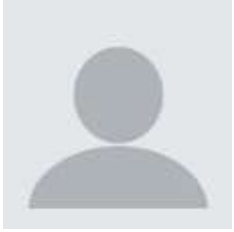
BIOGRAPHIE OF AUTHOR



Dr. Makbul Hussain Choudhury, serves as an Assistant Professor at the Rahman Institute of Pharmaceutical Sciences and Research in Guwahati, Assam, India. He is actively engaged in teaching and research within the field of pharmaceutical sciences, contributing to academic and scientific advancement in the domain. He remains dedicated to imparting quality pharmaceutical education to students. Email: makbulchy200@gmail.com