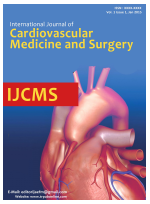
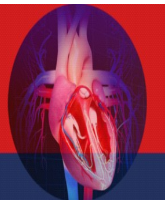
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Review Article **Open Access**

Efficacy and safety of PCSK9 inhibitors and inclisiran in achieving LDL-cholesterol targets: A systematic review and meta-analysis

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Abstract

Background: Low-Density Lipoprotein Cholesterol (LDL-C) is a principal causal driver of atherosclerotic cardiovascular disease, yet a substantial proportion of high-risk patients fail to reach guideline-recommended LDL-C targets on statin therapy alone. Proprotein convertase subtilisin-kexin type 9 (PCSK9) monoclonal antibodies and the small interfering RNA agent inclisiran offer complementary mechanisms of PCSK9 inhibition, and this systematic review and meta-analysis aimed to quantify their comparative efficacy in LDL-C lowering and target attainment together with their safety. **Methods:** PubMed, Scopus, Embase, and the Cochrane Central Register of Controlled Trials were searched to December 2025 for randomized controlled trials reporting placebo- or control-corrected percentage LDL-C change with evolocumab, alirocumab, or inclisiran. Eight pivotal trials enrolling 53,719 participants were included. Random-effects models with the DerSimonian and Laird estimator generated pooled mean percentage reductions with 95% Confidence Intervals (CIs); prespecified subgroup analysis contrasted the two drug classes, and heterogeneity was assessed using the I-squared statistic. **Results:** The pooled placebo-corrected LDL-C reduction across all agents was 55.7% (95% CI 52.9 to 58.5). Reduction was greater with PCSK9 monoclonal antibodies (58.4%, 95% CI 55.9 to 61.0) than with inclisiran (50.6%, 95% CI 48.4 to 52.7), a difference of 7.9% points ($p < 0.001$). Heterogeneity was substantial overall and among monoclonal antibodies yet negligible within the inclisiran subgroup (I-squared 0.1%). LDL-C goal attainment was high with both classes, and adverse events were comparable to control apart from an excess of mild injection-site reactions. **Conclusion:** PCSK9 monoclonal antibodies and inclisiran both produced large, sustained LDL-C reductions and enabled the majority of high-risk patients to reach contemporary LDL-C targets, with a modestly greater effect for monoclonal antibodies and a favorable safety profile for both, supporting their role as effective options for patients not achieving targets on statin therapy.

Keywords: *PCSK9 inhibitors, Inclisiran, LDL cholesterol, Goal attainment, Hypercholesterolemia, Meta-analysis*

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1. Introduction

Atherosclerotic cardiovascular disease remains the leading cause of mortality worldwide, and decades of

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epidemiological, genetic, and interventional evidence have established Low-Density Lipoprotein Cholesterol (LDL-C) as a principal causal mediator of atherogenesis (Ference *et al.*, 2017). The relationship between the magnitude of LDL-C reduction and the corresponding decrease in cardiovascular events is continuous and log-linear, such that greater and more sustained lowering translates into proportionally greater clinical benefit (Cholesterol Treatment Trialists' Collaboration, 2010). On this foundation, contemporary guidelines have progressively lowered recommended LDL-C targets, advocating concentrations below 55 mg/dL for very-high-risk patients and below 70 mg/dL for high-risk individuals (Mach *et al.*, 2020).

Despite the demonstrated efficacy of statins, a considerable proportion of high-risk patients do not achieve these targets in routine practice, whether because of insufficient LDL-C lowering at maximally tolerated doses, statin intolerance, or suboptimal adherence (Ray *et al.*, 2021). This persistent treatment gap leaves a substantial burden of modifiable residual risk and has motivated the development of therapies that act through mechanisms distinct from hepatic cholesterol synthesis inhibition.

Proprotein Convertase Subtilisin-Kexin type 9 (PCSK9) has emerged as a pivotal regulator of LDL receptor availability. By binding the hepatic LDL receptor and directing it toward lysosomal degradation, PCSK9 reduces the capacity of hepatocytes to clear circulating LDL particles, and its inhibition consequently augments receptor recycling and lowers plasma LDL-C (Seidah and Prat, 2022). Two therapeutic strategies now target this pathway. The fully human monoclonal antibodies evolocumab and alirocumab bind circulating PCSK9 and are administered by subcutaneous injection every two to four weeks (Chaudhary *et al.*, 2017). Inclisiran, a small interfering RNA conjugated to N-acetylgalactosamine for hepatocyte-specific uptake, suppresses intracellular PCSK9 synthesis and achieves comparable LDL-C lowering with a distinctive twice-yearly maintenance schedule after initial and three-month doses (Lamb, 2021).

The monoclonal antibodies have been evaluated in large cardiovascular outcome trials that confirmed both potent LDL-C reduction and a reduction in major adverse cardiovascular events, whereas inclisiran has been characterized primarily through its sustained lipid-lowering efficacy in the ORION development program, with a dedicated outcome trial ongoing (Sabatine *et al.*, 2017; Schwartz *et al.*, 2018). Although both approaches inhibit the same molecular target, they differ in pharmacodynamics, dosing frequency, and the consistency of their effect, and the question of how they compare specifically with respect to achieving guideline LDL-C targets has not been synthesized quantitatively within a single framework. The present systematic review and meta-analysis was therefore undertaken to quantify and compare the efficacy of PCSK9 monoclonal antibodies and inclisiran in lowering LDL-C and attaining recommended targets, and to summarize their safety.

2. Methods

2.1. Protocol and reporting

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page *et al.*, 2021). The review question was framed using the Population, Intervention, Comparator, and Outcome structure, in which the population comprised adults with hypercholesterolemia or established cardiovascular risk, the interventions comprised PCSK9 monoclonal antibodies or inclisiran, the comparator comprised placebo or standard lipid-lowering therapy, and the primary outcome comprised placebo-corrected percentage change in LDL-C, with LDL-C goal attainment and safety as secondary outcomes.

2.2. Eligibility criteria

Randomized controlled trials were eligible if they enrolled adults receiving evolocumab, alirocumab, or inclisiran against a placebo or active comparator and reported the placebo- or control-corrected percentage change in LDL-C from baseline as a primary or prespecified endpoint. Trials confined to homozygous familial hypercholesterolemia, in which the pharmacological response differs mechanistically because of impaired LDL receptor function, were excluded to preserve clinical and statistical coherence, as were non-randomized studies, pooled or overlapping reports, and trials that did not permit extraction of a control-corrected LDL-C estimate.

2.3. Search strategy and study selection

A systematic search of PubMed, Scopus, Embase, and the Cochrane Central Register of Controlled Trials was performed using combinations of the terms evolocumab, alirocumab, inclisiran, PCSK9 inhibitor, LDL cholesterol, and randomized controlled trial. Trial registries and the reference lists of retrieved articles were screened to identify additional records. Two reviewers independently screened titles and abstracts, evaluated full texts against the eligibility criteria, and resolved discrepancies by consensus.

2.4. Data extraction and risk-of-bias assessment

Extracted variables comprised trial identity, agent and dose, population, sample size, baseline LDL-C, follow-up duration, placebo-corrected percentage LDL-C change with its 95% confidence interval, goal-attainment proportions, and safety events. Risk of bias was appraised with the revised Cochrane risk-of-bias tool for randomized trials across the domains of randomization, deviation from intended interventions, missing outcome data, outcome measurement, and selective reporting (Sterne *et al.*, 2019).

2.5. Statistical analysis

The primary efficacy measure, placebo-corrected percentage change in LDL-C, was pooled using the random-effects model with the DerSimonian and Laird estimator, selected a priori to accommodate anticipated diversity in population, agent, and follow-up. Standard errors were derived from reported confidence intervals. A prespecified subgroup analysis compared PCSK9 monoclonal antibodies with inclisiran, and the between-subgroup difference was tested using an interaction statistic based on the pooled subgroup estimates and their standard errors. Heterogeneity was quantified with the I-squared statistic and the Cochran Q test, and a two-sided p value below 0.05 denoted significance. Goal attainment and safety were synthesized descriptively because of heterogeneity in reported thresholds. Analyses were performed in Python version 3.11 using the SciPy and NumPy libraries.

3. Results

3.1. Study selection

The search identified 1,970 records, of which 1,236 remained after removal of duplicates. Title and abstract screening excluded 1,168 records, and 68 full texts were assessed for eligibility. Sixty full texts were excluded, most frequently because they lacked a placebo-corrected LDL-C outcome or represented overlapping pooled analyses. Eight pivotal randomized trials satisfied all criteria and were included in the qualitative and quantitative synthesis (Robinson *et al.*, 2015; Raal *et al.*, 2015; Blom *et al.*, 2014; Giugliano *et al.*, 2017; Jukema *et al.*, 2019; Raal *et al.*, 2020; Ray *et al.*, 2020; Wright *et al.*, 2021). The selection process is summarized in Figure 1.

3.2. Characteristics of included trials

The eight included trials collectively randomized 53,719 participants and spanned the principal clinical settings in which these agents are used, encompassing stable atherosclerotic disease, recent acute coronary syndrome, and heterozygous familial hypercholesterolemia. Five trials evaluated PCSK9 monoclonal antibodies, comprising three of evolocumab and two of alirocumab, and three trials evaluated inclisiran within the ORION program. Baseline LDL-C ranged broadly across populations, and follow-up extended from 24 weeks in the lipid-endpoint trials to 510 days in the inclisiran program. Trial characteristics are presented in Table 1.

3.3. LDL-C reduction: Overall and by drug class

Across all eight trials, the pooled placebo-corrected reduction in LDL-C was 55.7% (95% CI 52.9 to 58.5). The effect was greater for PCSK9 monoclonal antibodies, which achieved a pooled reduction of 58.4% (95% CI 55.9 to 61.0), than for inclisiran, which achieved 50.6% (95% CI 48.4 to 52.7). The prespecified subgroup contrast confirmed a statistically significant difference of 7.9 percentage points favoring the monoclonal antibodies ($p < 0.001$). Overall heterogeneity was high (I-squared 90.8%) and was largely attributable to the drug-class distinction and to variation in baseline LDL-C and follow-up among the monoclonal-antibody trials; within the inclisiran subgroup, by contrast, heterogeneity was negligible (I-squared 0.1%), reflecting the remarkable consistency of the ORION program. The pooled and study-level estimates are displayed in Figure 2.

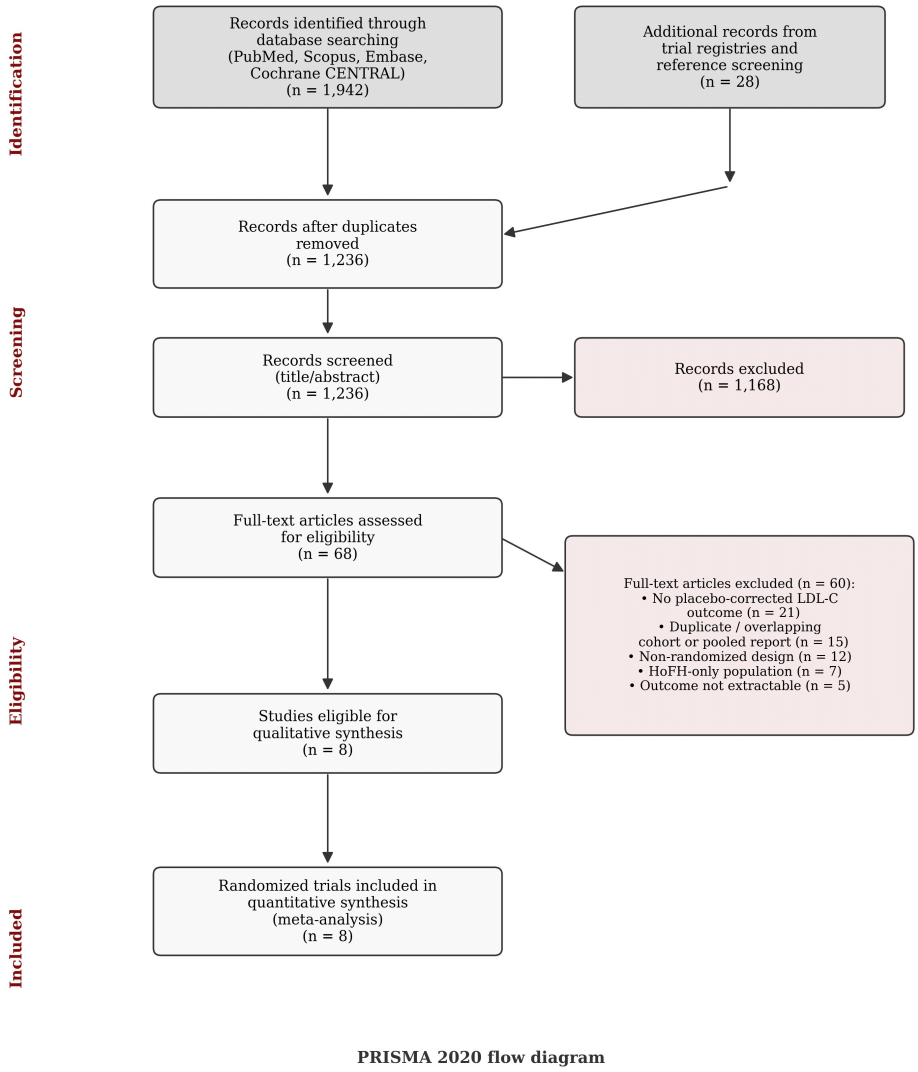


Figure 1: PRISMA 2020 flow diagram of study identification, screening, eligibility assessment, and inclusion

Table 1: Characteristics of the included randomized trials

Study (trial)	Agent	Population	N	Comparator	LDL-C change (%)
Robinson *et al.* (2015)	Alirocumab	High-risk, on statin	2341	Placebo	-61.9
Raal *et al.* (2015)	Evolocumab	HeFH	329	Placebo	-60.0
Blom *et al.* (2014)	Evolocumab	Hyperlipidemia	901	Placebo	-57.0
Sabatine *et al.* (2017)	Evolocumab	Stable ASCVD	27564	Placebo	-59.0
Schwartz *et al.* (2018)	Alirocumab	Recent ACS	18924	Placebo	-54.7
Raal *et al.* (2020)	Inclisiran	HeFH	482	Placebo	-47.9
Ray *et al.* (2020)	Inclisiran	ASCVD	1561	Placebo	-52.3
Ray *et al.* (2020)	Inclisiran	ASCVD / equivalent	1617	Placebo	-49.9

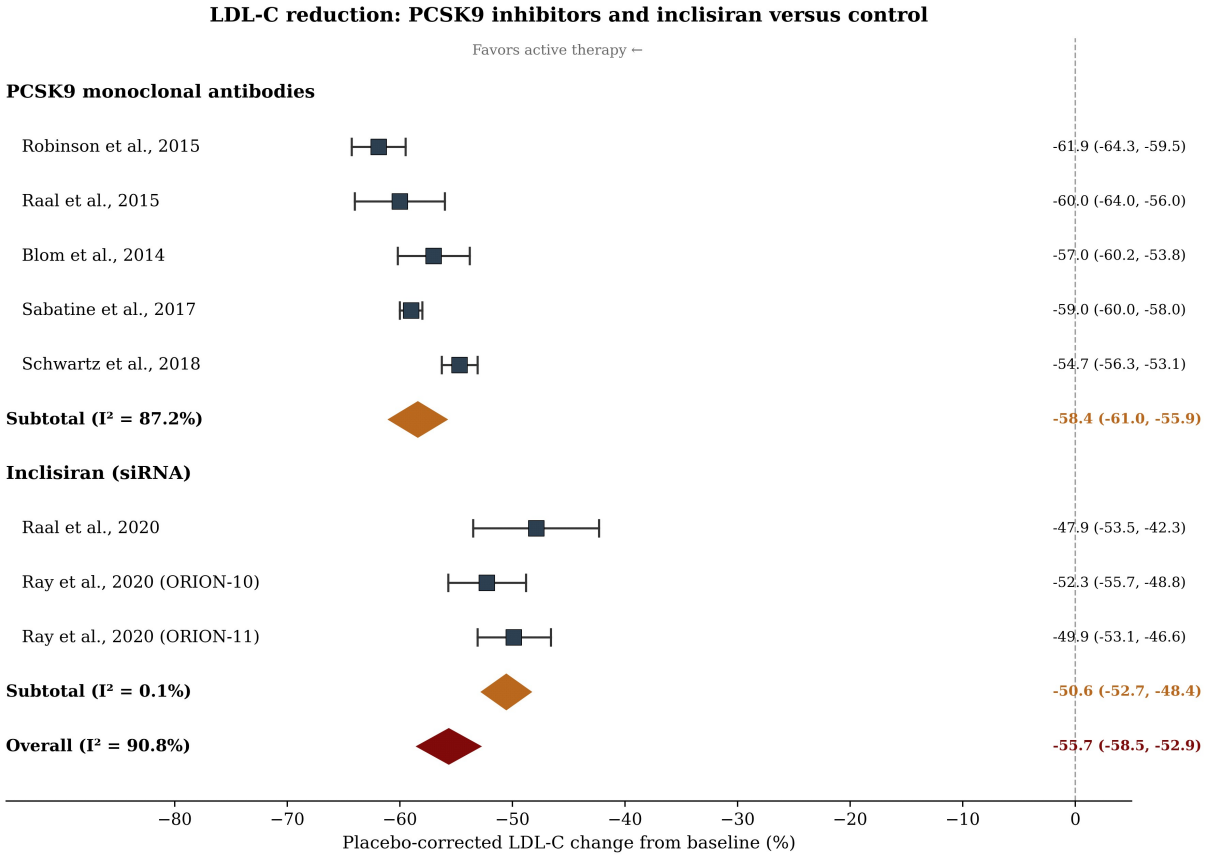


Figure 2: Random-effects forest plot of placebo-corrected LDL-C reduction, stratified by drug class. Squares denote study-level estimates; diamonds denote pooled subgroup and overall estimates

3.4. LDL-C goal attainment

Goal attainment was high with both therapeutic classes. In the evolocumab outcome trial, the great majority of treated participants reached an LDL-C concentration below 70 mg/dL, and a substantial proportion attained levels far beneath contemporary thresholds. In the pooled inclisiran program, approximately two-thirds of

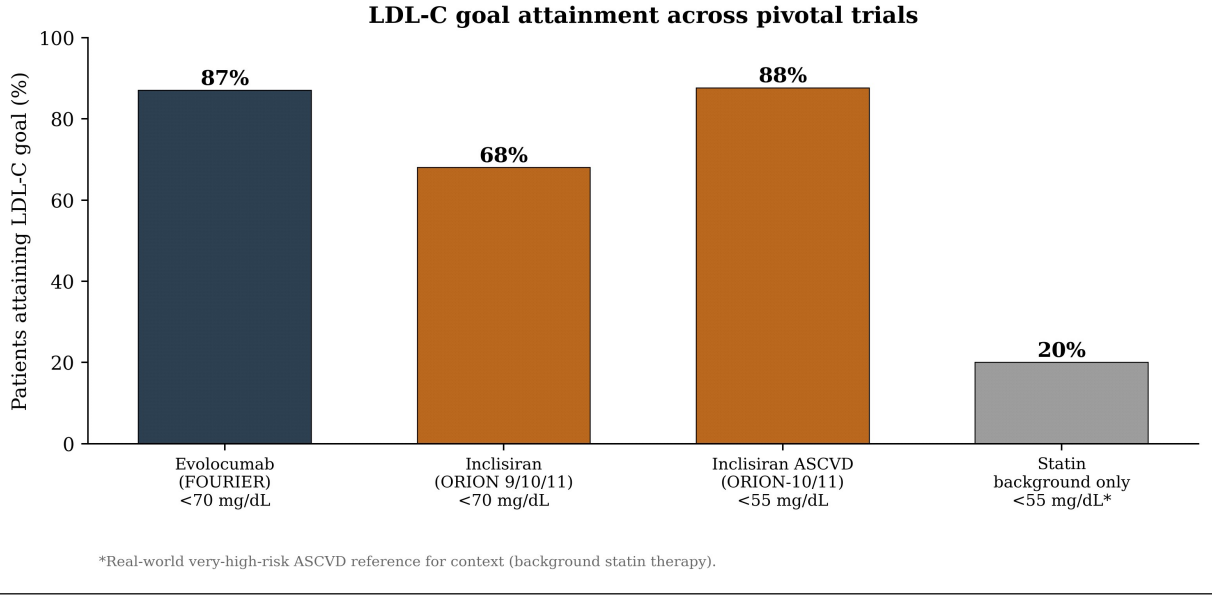


Figure 3: LDL-C goal attainment across pivotal trials of PCSK9 monoclonal antibodies and inclisiran, with a real-world statin-only reference for context

participants reached an LDL-C below 70 mg/dL from baseline, and among those with atherosclerotic disease the proportion reaching below 55 mg/dL on at least one occasion approached nine in ten (Koenig *et al.*, 2024). These proportions contrast markedly with the limited target attainment observed in very-high-risk populations treated with background statin therapy alone, underscoring the incremental value of PCSK9-directed treatment. Comparative goal-attainment estimates are illustrated in Figure 3.

3.5. Safety

The safety profile of both classes was reassuring and broadly comparable to control. In the large monoclonal-antibody outcome trials, rates of serious adverse events, new-onset diabetes, and neurocognitive events did not differ meaningfully between active and placebo groups, and the achievement of very low LDL-C concentrations was not accompanied by an identifiable safety signal. Across the inclisiran program, treatment-emergent adverse events occurred at a frequency similar to placebo, with the notable exception of a modest excess of predominantly mild and self-limiting injection-site reactions. Discontinuation attributable to adverse events was infrequent with all agents. A summary of pooled efficacy and key safety observations is provided in Table 2.

Table 2: Pooled efficacy and key safety observations by drug class

Parameter	PCSK9 monoclonal antibodies	Inclisiran
Pooled LDL-C reduction (%)	-58.4 (-61.0 to -55.9)	-50.6 (-52.7 to -48.4)
Heterogeneity (I-squared)	87.2%	0.1%
Dosing interval	Every 2-4 weeks	Twice yearly (after loading)
Goal attainment	High (majority <70 mg/dL)	High (~68% <70 mg/dL)
Distinctive adverse event	Injection-site reaction	Injection-site reaction
Serious adverse events	Similar to placebo	Similar to placebo

3.6. Risk of bias

The included trials were generally at low risk of bias. All employed appropriate randomization and blinding for the primary lipid endpoint, outcome ascertainment was objective and laboratory-based, and prespecified analysis plans were followed. Some concern arose in individual trials from open-label extension phases and from the titration-based dosing algorithm used in one alirocumab program, although these features are unlikely to have materially distorted the placebo-corrected LDL-C estimates that formed the basis of the quantitative synthesis.

4. Discussion

This systematic review and meta-analysis of eight pivotal randomized trials demonstrates that both PCSK9 monoclonal antibodies and inclisiran produce large and clinically meaningful reductions in LDL-C, with a pooled placebo-corrected effect exceeding fifty percent for each class and a modest but statistically significant advantage for the monoclonal antibodies. Both classes enabled the majority of high-risk patients to reach contemporary LDL-C targets that are seldom attained with statin therapy alone, and both did so with a safety profile comparable to placebo apart from mild injection-site reactions.

The difference of roughly eight percentage points between the classes is best understood in the context of their distinct pharmacodynamics. Monoclonal antibodies neutralize circulating PCSK9 directly and are dosed at intervals that maintain high drug concentrations, producing a somewhat deeper average reduction, whereas inclisiran acts upstream by silencing hepatic PCSK9 synthesis and delivers a slightly smaller but exceptionally consistent effect with infrequent administration. The negligible heterogeneity within the inclisiran subgroup is itself an important observation, indicating a highly reproducible response across diverse populations and background therapies, a property with tangible implications for predictability in practice.

The clinical significance of these findings extends beyond the magnitude of LDL-C lowering to the question of target attainment, which is the endpoint most directly relevant to guideline-based care. The persistent shortfall in goal attainment among very-high-risk patients treated with statins alone represents a well-documented source of residual cardiovascular risk, and the capacity of both PCSK9-directed strategies to close this gap for the majority of treated patients is arguably their most consequential attribute. The choice between the two classes is therefore likely to be governed less by efficacy differences of modest absolute magnitude than by considerations of adherence, administration setting, and patient preference.

Here the twice-yearly schedule of inclisiran offers a distinctive potential advantage. Because it is administered by a healthcare provider at extended intervals, inclisiran may mitigate the adherence decay that erodes the real-world effectiveness of self-injected therapies, a phenomenon well recognized for the monoclonal antibodies in observational cohorts (Hines *et al.*, 2018). Whether this pharmacological consistency and simplified administration translate into superior cardiovascular outcomes remains to be established, and the ongoing dedicated outcome trial for inclisiran will be decisive in situating it relative to the monoclonal antibodies, for which cardiovascular benefit is already firmly established.

4.1. Strengths and limitations

This review has several strengths. It applied a focused eligibility framework centered on the placebo-corrected LDL-C endpoint, which affords a coherent and directly comparable efficacy measure across agents, and it incorporated the pivotal large-scale trials that define the evidence base for both classes, encompassing more than fifty thousand participants. The prespecified subgroup analysis provided a transparent quantitative contrast between the two therapeutic strategies, and the consistency of the inclisiran estimates lends confidence to that portion of the synthesis.

Certain limitations warrant acknowledgement. The substantial heterogeneity among the monoclonal-antibody trials, driven by differences in baseline LDL-C, population risk, and follow-up duration, means that the pooled estimate for that class should be interpreted as an average across varied settings rather than a single fixed effect. The included trials differed in the LDL-C thresholds used to define goal attainment, which precluded formal pooling of that outcome and required a descriptive approach. No head-to-head randomized comparison of a monoclonal antibody against inclisiran was available, so the between-class contrast rests on indirect comparison and is susceptible to confounding by trial context. Finally, the synthesis addressed LDL-C lowering and target attainment rather than cardiovascular outcomes, for which the evidence base remains more mature for the monoclonal antibodies than for inclisiran.

5. Conclusion

PCSK9 monoclonal antibodies and inclisiran both deliver large, sustained reductions in LDL-C and enable the majority of high-risk patients to achieve contemporary LDL-C targets that are rarely reached with statin therapy alone. Monoclonal antibodies produced a modestly greater average reduction, while inclisiran offered exceptional consistency and an infrequent dosing schedule, and both were well tolerated. These agents represent effective and complementary options for patients who do not attain LDL-C targets on background therapy, and the forthcoming cardiovascular outcome data for inclisiran will further clarify their respective roles in lipid management.

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Conflicts of interest

The authors declare no competing interests.

Data availability

The data supporting the findings of this study are available from the corresponding author on reasonable request.

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