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Inclisiran in Atherosclerotic Cardiovascular Disease: A Systematic Review of Efficacy and Safety for Lipid Lowering and Risk Mitigation

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Abstract
Background:
Intensive lowering of low-density lipoprotein cholesterol reduces cardiovascular risk in patients with atherosclerotic cardiovascular disease. However, most patients do not achieve optimal LDL-C targets due to clinical inertia, side effects, and nonadherence. Inclisiran, a small interfering RNA targeting PCSK9 synthesis, offers a novel approach for lipid lowering.
Objectives:
To systematically review the efficacy and safety of Inclisiran for lipid management and cardiovascular risk reduction in patients with ASCVD.
Methods:
A comprehensive search of PubMed and Scopus was conducted for peer-reviewed articles published between January 1, 2019, and December 2024 that evaluated Inclisiran in ASCVD. Both prospective and retrospective observational studies and randomized controlled trials were included. Primary outcomes were changes in LDL-C and safety profile; secondary outcomes included rates of cardiovascular events and patient adherence.
Results:
Out of 314 identified articles, 20 studies met the inclusion criteria. Inclisiran consistently reduced LDL-C by 28–60% across diverse populations. The most common adverse event was mild injection-site reactions. While a significant 32% reduction in myocardial infarction incidence was reported in some studies, effects on stroke and major adverse cardiovascular events (MACE) did not reach statistical significance. Long-term data support durable LDL-C lowering with continued therapy.
Conclusions:
Inclisiran is a safe and effective lipid-lowering agent that significantly reduces LDL-C and is well tolerated, with mild injection-site reactions being the most common adverse effect. The convenient dosing schedule may improve adherence. While the reduction in myocardial infarction risk is promising, further long-term studies are needed to confirm broader cardiovascular benefits.

Keywords: Atherosclerosis, Inclisiran, LDL-C Reduction, Cardiovascular Disease, Safety, Efficac

1. INTRODUCTION

Despite intensive reductions in low-density lipoprotein cholesterol (LDL-C) being linked to substantially improved cardiovascular outcomes, nearly 80% of individuals with atherosclerotic cardiovascular disease fail to achieve guideline-recommended LDL-C targets. Contributing factors include clinical inertia, poor medication adherence, and adverse drug effects. (1) Although high-intensity statins have the potential to reduce LDL-C by approximately 50%, their use remains suboptimal, with fewer than half of high-risk patients continuing statin therapy or receiving optimal dosing beyond one year. Uptake of non-statin lipid-lowering therapies (LLTs) such as ezetimibe, bempedoic acid, and PCSK9 inhibitors also remains limited. (1)

PCSK9 plays a critical role in lipid metabolism by promoting LDL receptor degradation, thereby elevating circulating LDL-C. Genetic studies reveal that PCSK9 mutations are associated with lower LDL-C levels and reduced cardiovascular events, while gain-of-function mutations result in marked LDL-C elevation and increased risk. (1,2) Therefore, PCSK9 inhibition represents a promising therapeutic strategy. Nonetheless, many patients fail to attain adequate lipid control even with advances in PCSK9 monoclonal antibodies and statins, underlining the ongoing need for novel therapies. (1)

Inclisiran is a small interfering RNA (siRNA) agent that reduces hepatic PCSK9 synthesis, leading to sustained LDL-C lowering with only two injections per year administered by healthcare professionals. Phase 3 ORION trials and their extensions have confirmed the safety and efficacy of Inclisiran, highlighting a well-tolerated profile—most notably mild injection-site reactions—and LDL-C reductions approaching 50%. The biannual dosing schedule may significantly improve patient adherence compared with self-administered treatments. (2) In contrast, current PCSK9 monoclonal antibodies such as evolocumab and alirocumab require subcutaneous injections every two to four weeks and are approved for both primary and secondary prevention in familial hypercholesterolemia. For patients with ASCVD or heterozygous familial hypercholesterolemia who require further LDL-C reduction, Inclisiran offers an adjunct to maximally tolerated statin therapy and dietary measures, and may be an alternative for those intolerant to monoclonal antibodies or frequent injections. However, comprehensive cardiovascular endpoint data are still needed before Inclisiran can be widely recommended. (1,2)

This systematic review critically examines the mechanism of action, efficacy, and safety profile of Inclisiran as a lipid-lowering agent for cardiovascular disease prevention, summarizing the latest clinical evidence.

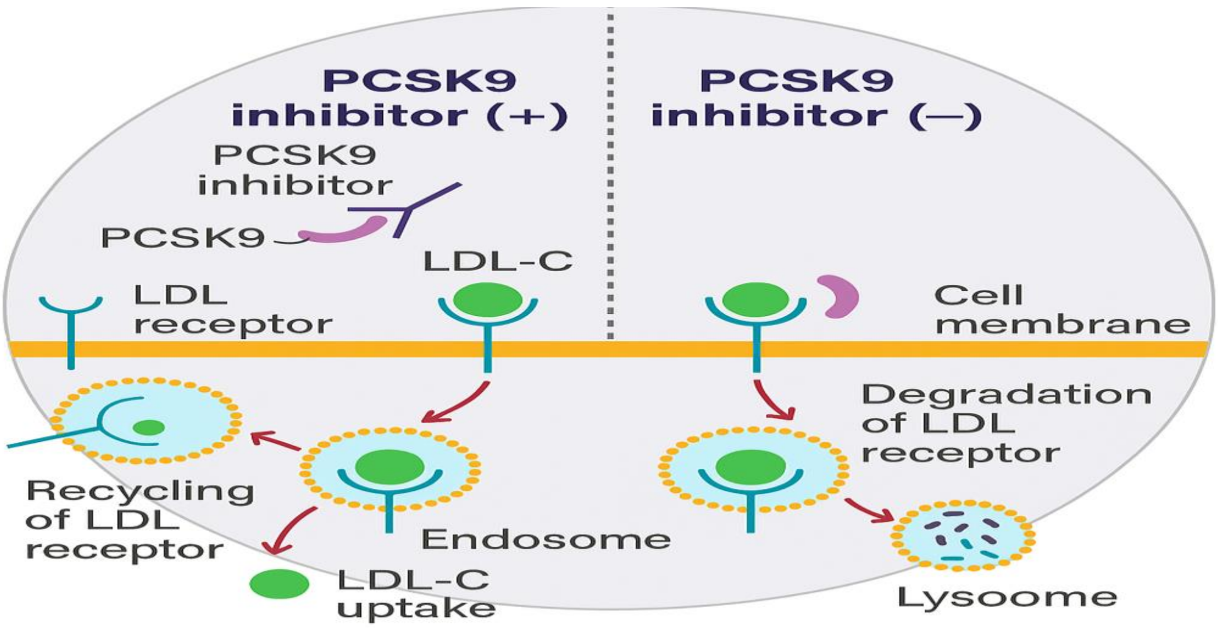

Figure 1: Role of PCSK9 Inhibitors in Modulating LDL Receptor Recycling and LDL-C Uptake

Evolocumab

Evolocumab is administered as either 420mg subcutaneously once monthly, or 140mg subcutaneously every two weeks. It is recommended for both the prevention of recurrent cardiovascular events and the management of primary hyperlipidaemia. For patients with homozygous familial hypercholesterolaemia (HoFH), the initial dose is 420mg subcutaneously once monthly in the United States and several other countries. If there is no clinically meaningful response after 12 weeks, the dosage may be increased to 420mg every two weeks. For HoFH patients on lipid apheresis, therapy can be initiated with 140mg every two weeks, administered immediately following apheresis. (3)

Alirocumab

For primary hyperlipidaemia or secondary prevention of cardiovascular events, alirocumab is typically dosed at either 150mg every two weeks or 300mg every four weeks to achieve maximal LDL-C reduction. An alternative starting dose of 75mg every two weeks is available; however, this regimen yields less pronounced LDL-C lowering. Plasma LDL-C levels should be evaluated 4–12 weeks after initiation or dose adjustment, and subsequently monitored every 3–12 months. For those receiving 300mg every four weeks, LDL-C levels should be measured just prior to the next scheduled dose. In patients with heterozygous familial hypercholesterolaemia, HoFH, or those at very high risk with persistently elevated LDL-C (greater than 50% above their treatment goal), alirocumab therapy is typically begun at 150mg every two weeks. Alirocumab administration does not require adjustment in relation to LDL apheresis timing. (3)

Inclisiran

Small interfering RNA (siRNA) therapies, such as Inclisiran, provide an alternative to monoclonal antibodies for PCSK9 inhibition by reducing both intracellular and extracellular PCSK9 levels with less frequent dosing. Inclisiran may be used in combination with maximally tolerated statin therapy and dietary modifications for individuals with heterozygous familial hypercholesterolaemia or atherosclerotic cardiovascular disease who require further reduction in LDL-C.

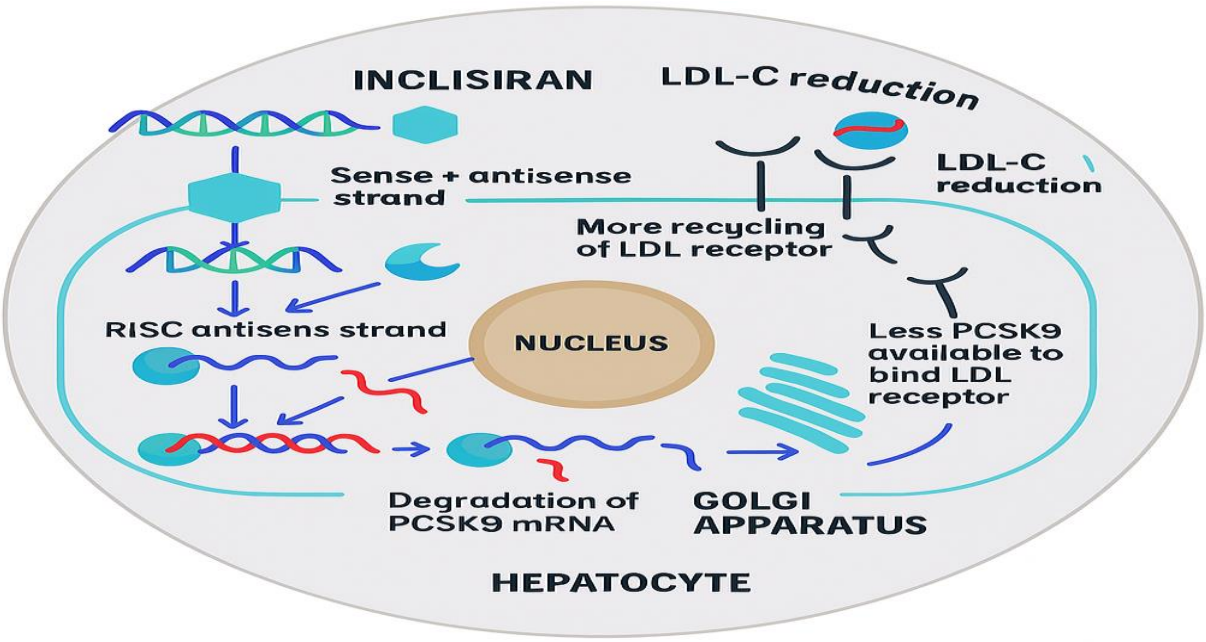

Figure 2: Action of Inclisiran in Hepatocytes: Enhancing LDL Receptor Recycling by Targeting PCSK9 mRNA.

Individuals exhibiting adverse reactions to both alirocumab and Evolocumab. Individuals with arthritis or diminished hand strength who experience difficulty operating a pen injector. It is a subcutaneous injection administered bi-monthly for the initial three months, followed by a semi-annual schedule thereafter. Before advocating for the extensive application of Inclisiran in patients with high-risk cardiovascular illness, we anticipate clinical endpoint data that evidences cardiovascular risk reduction. (3)

PRISMA FLOW CHART:

Following the screening process, 20 articles were included in the review chart out of the 314 records that were found.

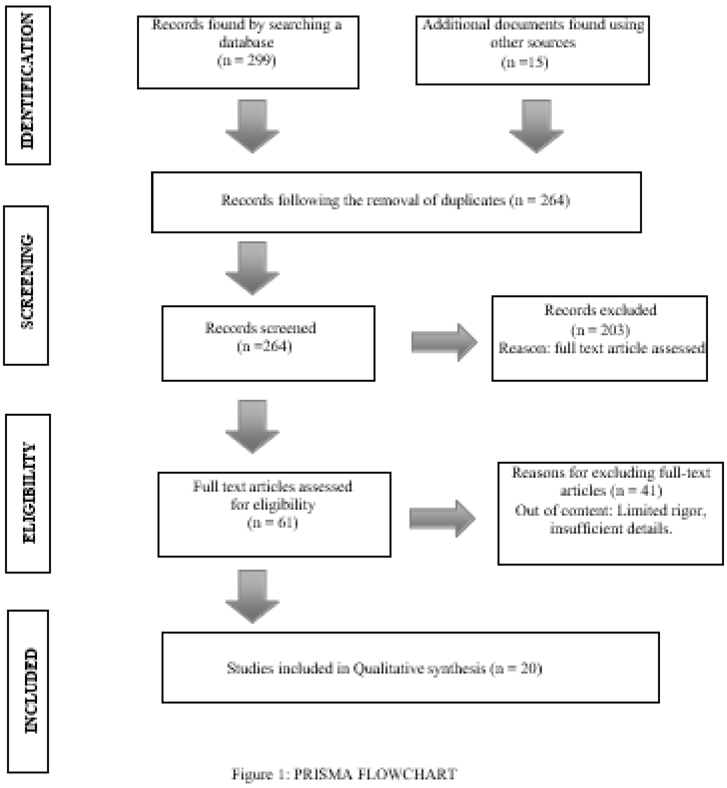

Figure 1: Prisma Flowchart

2. Methods

This systematic review was conducted in accordance with PRISMA guidelines, and the protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identifier CRD42024542572.

2.1 Search Strategy and Study Selection

A comprehensive literature search was performed to identify peer-reviewed publications assessing the efficacy and safety of Inclisiran for lipid management and cardiovascular risk reduction in patients with ASCVD. Key search terms included Inclisiran, PCSK9 inhibitors, LDL-C reduction, cardiovascular risk, atherosclerosis, lipid-lowering therapy, RNA interference, statin intolerance, and long-term cardiovascular outcomes. Boolean operators "AND" and "OR" were applied to enhance search sensitivity.

Eligible studies published from January 2020 to December 2024 were retrieved from PubMed (Medline), Scopus, and Europe PMC. The complete search methodology is detailed in Supplementary Table 1. Additional relevant articles were identified through screening reference lists of narrative reviews and selected studies. After removal of duplicates and preliminary relevance screening based on titles and abstracts, full texts of potentially eligible studies were reviewed. Any disagreements regarding study inclusion were resolved by discussion and consensus. Final eligibility required studies to provide extractable data on Inclisiran's impact on LDL-C reduction, cardiovascular event rates, and safety outcomes.

2.1 Inclusion criteria comprised:

Inclusion criteria were defined using the PECOS (Population, Exposure, Comparator, Outcome, and Study Design) framework. Studies were eligible if they: Included patients diagnosed with atherosclerotic cardiovascular disease (ASCVD) undergoing Inclisiran therapy, with or without control groups receiving conventional lipid-lowering treatments (e.g., statins, PCSK9 inhibitors). Reported outcomes on LDL-C reduction, cardiovascular event rates, and the overall safety profile of Inclisiran. Presented clear, extractable data in observational studies, randomized controlled trials (RCTs), or systematic reviews comparing Inclisiran against standard lipid-lowering therapies.

2.2 Exclusion criteria comprised:

Studies involving animals or cell models, case reports, case series, editorials, guidelines, opinion pieces, comments, hypotheses, book chapters, and interventional studies unrelated to Inclisiran. Articles written in languages other than English. Research focused on patients with lipid disorders other than ASCVD, or on cardiovascular conditions not treated with Inclisiran. Studies concerning lipid-lowering medications other than Inclisiran, or lacking accessible data on Inclisiran's safety and efficacy. Duplicate publications, in which case the most recent article was prioritized for data extraction.

2.3 Quality Evaluation

The methodological quality of the studies included in this review was evaluated independently through the use of validated critical appraisal tools. Case-control studies were examined using the Newcastle-Ottawa Scale (NOS), which assesses potential biases such as participant selection, comparability of study groups, and the determination of exposure or outcomes. The articles selected for this review were independently evaluated using the Newcastle-Ottawa Scale (NOS) for case-control studies and the Joanna Briggs Institute Critical Appraisal Tools for Analytical Cross-Sectional Studies. The Newcastle-Ottawa Scale (NOS) was specifically utilized in case-control studies to assess selection bias, comparability, and the evaluation of exposure/outcomes, thereby ensuring methodological rigor. Studies receiving a score of 7 or more were categorized as high quality, while those with scores of 4 or less were considered low quality. For cross-sectional studies, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist was employed. This tool assesses several methodological domains, including whether inclusion criteria were explicitly stated, whether exposure measurements were valid, how confounders were identified and managed, and the appropriateness of the statistical methods used. Studies fulfilling 70% or more of the checklist items were judged to have a low risk of bias, whereas those achieving less than 50% were assessed as having a high risk of bias. Applying these appraisal methods allowed us to include only studies that provided robust and reproducible findings, thereby increasing the confidence in our evaluation of Inclisiran's role in lipid regulation and cardiovascular risk reduction in patients with ASCVD. (5)

2.4 Evaluation of Outcomes

This review synthesized available evidence on the efficacy and safety profile of Inclisiran in patients with atherosclerotic cardiovascular disease (ASCVD). Specific outcomes of interest included:

Efficacy outcomes: Reduction in low-density lipoprotein cholesterol levels and consistency of LDL-C lowering across different dosing regimens.

Safety outcomes: The Incidence and nature of adverse events, as well as overall tolerability.

The collective findings demonstrated that Inclisiran induces substantial and sustained LDL-C reduction while maintaining a favorable safety profile, supporting its potential as an effective therapeutic innovation in ASCVD management.

However, while the available evidence highlights its short- to mid-term benefits, this analysis underscores the necessity for long-term, event-driven clinical trials to establish the impact of Inclisiran on major cardiovascular outcomes, including myocardial infarction, stroke, and cardiovascular mortality. (7)

2.5 Extracting Information

Data were systematically extracted from each eligible study using a predefined standardized data extraction form. The following variables were collected: first author's last name, publication year, study design, country of study, participant characteristics, diagnostic criteria for atherosclerotic cardiovascular disease (ASCVD), methods of measuring cardiovascular outcomes and LDL-C, primary findings, and reported adverse events.

To ensure reliability, extraction was performed independently by two reviewers. Any discrepancies identified during this process were resolved through discussion and consensus. When required, the corresponding authors of the included studies were contacted via email to clarify incomplete information or obtain access to missing data and unavailable full texts.

3. RESULTS

A total of 314 records were identified through the comprehensive literature search. After removal of 12 duplicates, 302 unique studies remained. Screening of titles and abstracts led to the exclusion of 264 studies that were deemed irrelevant. The remaining 38 studies underwent full-text review, of which 16 were excluded for not meeting the pre-defined inclusion criteria.

Thus, 22 full-text articles were assessed in detail. Following this evaluation, an additional 6 articles were excluded due to ineligible design or insufficient data, resulting in a final inclusion of 20 studies (as outlined in the PRISMA flow diagram, Figure 1). Among these, 4 articles directly examined the efficacy and safety of Inclisiran specifically in patients with atherosclerotic cardiovascular disease (ASCVD).

3.1. Characteristics of Included Studies

The characteristics of the 20 studies included in this review are summarized in Table 1. The majority were conducted in Egypt (n = 3), United States (n = 3), United Kingdom (n = 2), and China (n = 2). Additional studies originated from Europe, the Netherlands, Indonesia, and the Middle East (one study each) (1,4,6,14–16). Regarding study design, the included literature comprised a mix of retrospective studies, prospective cohort studies, and randomized controlled trials (RCTs). Across most studies, the populations investigated had a mean age of ≤ 80 years (1–20). Of the twenty articles, four specifically evaluated Inclisiran in the management of atherosclerotic cardiovascular disease (ASCVD). These studies provided key evidence regarding the efficacy and safety of Inclisiran, with detailed reporting on the magnitude of LDL-C reduction, dosing regimens, and treatment-emergent adverse events. (Table 1)

Table 1: Qualities of the Included Research

Ref, no	**Author & Year**	**Country / Population**	**Study Design / Sample Size**	**Aim / Focus**	**Main Outcomes Reported**	**Key Findings**
[1]	Koren et al., 2024 [1]	USA (ASCVD)	RCT [450]	"Inclisiran -first" strategy after statin failure	% LDL-C change; goal attainment; statin discontinuation; safety	-60% LDL-C vs -7% usual care; 81.8% reached target; fewer statin discontinuations; mild ↑ injection-site reactions (ISRs)
2	Luo Z et al., 2023[2]	China (hypercholesterolemia)	Prospective [40]	Inclisiran PK/PD & efficacy in Chinese patients	LDL-C; plasma PCSK9; PK; safety	Significant LDL-C & PCSK9 drop; predictable PK; well tolerated
3	Ray KK et al. (ORION-1), 2019[3]	USA	Prospective [501]	1-year efficacy & safety; 1 vs 2 doses	Time-averaged LDL-C, PCSK9, AEs	LDL-C -30–46% (best with 2 × 300 mg); PCSK9 suppressed for 1 year; well tolerated
4	Ray KK et al., 2022[4]	Europe (Primary prevention)	RCT [2381]	High-risk patients without prior events	% and absolute LDL-C at day 510; non-HDL-C; apoB; safety	-43.7% LDL-C; non-HDL-C & apoB reduced; mild ISRs
5	Luo M et al., 2023[5]	Indonesia	SR/MA [3713]	Stroke & MACE prevention	Stroke, MI, MACE, safety	MI risk ↓32%; no significant effect on stroke or MACE; ISRs RR 6.6 (mild)
6	Ray KK et al., 2022[6]	Europe (pooled ORION 9-11)	Patient-level meta [3660]	MACE reduction	Composite MACE; MI; stroke; LDL-	MACE OR 0.74; no significant MI

					C; safety	or stroke changes; LDL-C ↓50.6% at day 90; increased ISRs
7	Kosmas CE et al., 2020[7]	USA	Retrospective [501]	Mechanism, efficacy vs LLTs	LDL-C; adherence; safety	Biannual dosing ↑ adherence; LDL-C ↓ similar to PCSK9-mAbs; mild ISRs
8	Venugopal P et al., 2022[8]	USA	Retrospective [1542]	Long-term benefits (6 years)	LDL-C; safety; adherence	Sustained LDL-C reduction; safety preserved; better adherence
9	Leiter LA et al., 2019[9]	Global (Diabetes)	RCT[519]	Efficacy in diabetic and non-diabetic patients	LDL-C; PCSK9; apoB; non-HDL-C; glycaemia	LDL-C ↓28–55%; no glycaemic impact; balanced AEs
10	Hardy J et al., 2021[10]	USA	Cross-sectional [3700]	Efficacy & safety review	LDL-C; CV risk; safety	LDL-C ↓ ~50%; potential CV benefit; good tolerability
11	Agnello F et al., 2024[11]	Europe	Prospective [119]	Emerging LLTs overview	LDL-C; comparative efficacy	PCSK9 agents (incl. inclisiran) potent; personalized therapy emphasized
12	Iqbal S et al., 2023[12]	Middle East	Prospective [153]	Real-world inclisiran data	LDL-C, TG, goal attainment, safety	LDL-C ↓38–54%; 75% achieved goals; well tolerated

13	Fitzgerald K et al., 2016[13]	UK (Healthy Volunteers)	Phase I [69]	First-in-human dose-finding	PCSK9 & LDL-C change; safety	Single 300 mg ↓ PCSK9 by 74.5%, LDL-C by 50.6%; no serious AEs
14	Ray KK et al., 2023[14]	5 Countries	RCT [624]	4-year efficacy; switch from evolocumab	LDL-C trajectory; safety	Sustained LDL-C ↓; effective switch from evolocumab; no new safety issues
15	Raal F et al., 2024[15]	SA / Turkey (HoFH)	Prospective [56]	Inclisiran in HoFH	LDL-C; PCSK9; safety	PCSK9 ↓60%; no significant LDL-C change; tolerated but limited efficacy
16	Koenig W et al., 2022[16]	China (PVD subgroup)	RCT [3454]	Inclisiran in PVD subgroup	LDL-C; safety	LDL-C ↓49% in PVD vs ↓52% in non-PVD; mild ISRs
17	Koenig W et al., 2023[17]	USA (CeVD subgroup)	Prospective [202]	Inclisiran in CeVD subgroup (ORION 9-11)	LDL-C; MACE; safety	LDL-C ↓55%; MI risk ↓32%; stroke & MACE not significant; mild ISRs
18	Wright RS et al. (ORION-8), 2024[18]	Global	Open-label extension [3274]	Long-term durability of effect	LDL-C; goal attainment; safety	LDL-C ↓49.4%; 78% achieved target; safety maintained over 3.7 years
19	Ray KK et al., 2024[19]	USA	ORION-1 secondary analysis [501]	Atherogenic lipid impact	non-HDL-C, apoB, TG, Lp(a)	Significant reductions; further analysis pending
20	Elserafy A	Egypt	Prospective	Clinical	LDL-C;	Significant

	et al., 2022[20]		[3660]	perspectives & implications	safety; clinician view	LDL-C ↓; favourable safety; positive healthcare provider (HCP) acceptance

3.2 Risk of Bias Assessment

The methodological rigor of included studies was appraised using standardized checklists and rating systems. For the purpose of this review, studies were classified into three categories based on their proportion of "yes" responses in the critical appraisal tools: (Table 3)

High risk of bias (low quality): studies with a score of ≤49%

Moderate risk of bias (moderate quality): studies with a score between 50% and 69%

Low risk of bias (high quality): studies with a score of ≥70%

This stratification enabled a transparent evaluation of study quality, ensuring that higher-weighted conclusions were drawn primarily from robust, methodologically sound evidence.

Table 2: Methodological Quality Assessment (NOS for Case-Control Studies)

S. No	Author(s)	Selection Criteria	Comparability	Exposure / Outcome Assessment	Total Score	Quality Rating
1	Michael J. Koren et al. (1)	****	**	**	8	High
2	Zhu Luo et al. (2)	****	**	**	7	High
3	Kausik K. Ray et al. (3)	****	**	**	8	High
4	Min Luo et al. (5)	****	**	**	7	High

NOS scores of ≤4, ≥5, ≥6, and ≥7 were categorized as low, moderate, and high-quality studies, respectively.

Table 3: Evaluation of Methodological Quality (JBI for Cross-Sectional Studies)

JBI Appraisal Criteria	Michael J. Koren et al. (1)	Zhu Luo et al. (2)	Kausik K. Ray et al. (3)	Wolfgang Koenig et al. (17)
Inclusion criteria clearly defined	Yes	Yes	Yes	Yes
Detailed study settings and subjects	Yes	Yes	Yes	Yes
Exposure measured	Yes	Yes	Yes	Yes

reliably				
Standard criteria used for measurement	Yes	Yes	Yes	Yes
Confounding factors identified	Yes	Yes	Yes	Yes
Strategies for managing confounding stated	Yes	Yes	Yes	Yes
Outcomes are measured validly and reliably	Yes	Yes	Yes	Yes
Appropriate statistical analysis applied	Yes	Yes	Yes	Yes
Quality Rating (%)	**High (100)**	**High (100)**	**High (100)**	**High (100)**

4. Quality Assessment and Outcomes of Inclisiran

Evidence from the included studies consistently demonstrated that Inclisiran is effective in lowering LDL-C, with reductions ranging from 28% to 60% across different trial populations. In addition, treatment with Inclisiran was associated with a 32% reduction in the risk of myocardial infarction (RR = 0.68). However, no statistically significant reductions were observed in the rates of stroke or major adverse cardiovascular events (MACE) across the available studies. (Table 2)

Inclisiran was generally well tolerated, with the most frequently reported adverse effects being mild to moderate injection-site reactions. Serious treatment-related adverse events were rare. Notably, the available longitudinal evidence suggests that Inclisiran provides sustained LDL-C lowering efficacy for up to 6.8 years, without evidence of diminished therapeutic effect over time.

4.1. Clinical Significance and Personalized Medicine Approach:

Inclisiran represents a significant advancement in the management of atherosclerotic cardiovascular disease (ASCVD) by offering sustained LDL-C reduction through a convenient twice-yearly dosing regimen, which markedly improves patient adherence compared to daily lipid-lowering therapies. Its mechanism, based on RNA interference targeting PCSK9 production, enables durable LDL-C lowering with a low side effect profile, as demonstrated in both clinical trials and real-world studies, where sustained LDL-C reductions of approximately 50-60% have been observed over periods exceeding two years. This prolonged dosing interval not only enhances patient convenience but also reduces the burden on healthcare systems by facilitating simplified treatment delivery.

However, the effectiveness and safety of inclisiran may vary among individuals due to genetic differences affecting lipid metabolism and drug response. Understanding polymorphisms in key genes involved in cholesterol regulation and drug transport, such as PCSK9, SLCO1B1, ABCG2, and APOE, holds potential to guide personalized treatment strategies. Such pharmacogenomic insights can inform clinicians in optimizing therapy by tailoring dosing regimens, predicting therapeutic efficacy, and minimizing adverse effects, thereby advancing a precision medicine approach in ASCVD management. Overall, inclisiran's novel mode of action combined with the potential for genotype-guided therapy underscores its emerging role as a transformative option in personalized lipid management for patients at high cardiovascular risk.

4.2. Genetic Polymorphisms and Drug Response

Genetic variations significantly influence the pharmacokinetics and pharmacodynamics of Inclisiran, impacting its absorption, distribution, metabolism, and elimination. Notably, mutations in the PCSK9 gene alter LDL receptor (LDLR) expression by modulating the degradation of LDLRs on hepatocytes. Gain-of-function (GOF) mutations in PCSK9 lead to increased degradation of LDLRs, reducing LDL-C clearance and raising plasma LDL-C levels. In contrast, loss-of-function (LOF) mutations reduce PCSK9 activity, resulting in higher LDLR availability and lower LDL-C levels, thereby enhancing response to therapies like Inclisiran that target PCSK9 synthesis.

Variations in SLCO1B1 may affect the hepatic uptake and transport of Inclisiran, potentially modifying its effectiveness. Moreover, polymorphisms in ABCG2 can influence drug elimination pathways, contributing to interindividual variability in treatment response and the risk of adverse effects. Additionally, different APOE genotypes have been associated with distinct lipid metabolism profiles, further affecting therapeutic outcomes.

Identification and understanding of these genetic markers can enable clinicians to predict individual responses to Inclisiran therapy and optimize dosing strategies, thus advancing personalized medicine approaches in the treatment of atherosclerotic cardiovascular disease.

4.3. Future Research Directions

While the LDL-C lowering efficacy of Inclisiran and its potential to improve patient adherence through twice-yearly dosing are well established, further investigation is essential to comprehensively evaluate its broader cardiovascular effects. Future research priorities include:

Long-term cardiovascular outcomes: Rigorous trials focusing on the impact of Inclisiran on major adverse cardiovascular events such as myocardial infarction, stroke, and cardiovascular mortality are needed. Ongoing large-scale studies like ORION-4 and VICTORION trials are expected to provide definitive evidence on these endpoints.

Real-world effectiveness: Studies assessing Inclisiran's performance across diverse and high-risk patient populations—including individuals with diabetes and familial hypercholesterolemia—will help validate clinical trial outcomes in everyday clinical practice.

Pharmacogenomics integration: Incorporating genetic data to identify predictors of individual response will enable personalized prescribing strategies, improving both efficacy and safety.

Cost-effectiveness analyses: Evaluating the economic impact of Inclisiran in comparison to existing lipid-lowering therapies will be critical to support broader adoption in healthcare systems worldwide.

4.4. Challenges and Limitations

Despite the therapeutic potential of Inclisiran, several limitations must be acknowledged. Variability in study methodologies and populations complicates cross-study comparisons, limiting the ability to draw consistent conclusions across diverse patient groups. The current paucity of comprehensive meta-analyses and long-term data restricts the definitive assessment of genetic influences on treatment response. Publication bias remains a concern, potentially skewing reported efficacy and safety outcomes toward more favorable findings.

Furthermore, the relatively recent introduction of Inclisiran means that long-term safety data beyond several years are still emerging, necessitating cautious interpretation. While injection-site reactions are generally mild and serious adverse events rare, the extended duration of action may pose challenges in managing potential delayed adverse effects. Real-world data and larger, more diverse population studies are needed to confirm clinical trial results and evaluate effectiveness in broader settings.

Lastly, the high cost and limited accessibility of Inclisiran in some healthcare environments could impede widespread adoption, underscoring the importance of cost-effectiveness research and strategies to improve affordability and availability.

5. Conclusion

Inclisiran is a promising lipid-lowering agent for managing atherosclerotic cardiovascular disease (ASCVD), providing sustained reduction of low-density lipoprotein cholesterol through convenient biannual dosing that may enhance patient adherence. Clinical evidence shows LDL-C reductions ranging from approximately 28% to 60%, with mild injection-site reactions as the most common adverse event. Inclisiran demonstrates potential in reducing the risk of myocardial infarction by 32%, though its effects on stroke and overall major adverse cardiovascular events (MACE) remain inconclusive.
Further long-term studies are warranted to fully elucidate its cardiovascular benefits, pharmacogenomic influences on treatment response, and cost-effectiveness, which will be essential to establishing its optimal position in ASCVD therapy.

Ethical Approval

Not applicable.

Author Contributions

Lokesh Kumar Dhavanam Ramesh Babu: Conception of the idea, study design, methodology, data analysis, interpretation of results, manuscript writing, reviewing, and editing.
Leena Pavitha: Contribution to writing, reviewing, editing, data interpretation, and methodology.

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Conflict of Interest

The authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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