REVIEW

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Assessing the Impact of Inclisiran on LDL-C and PCSK9 Reduction in Hypercholesterolemic Patients: A Meta-analysis of Cardiovascular Metabolic Prevention

Agung Cendekia Putra Nusantara[1], Ariella Diandihati Rapsanjani[1], Ikhwan Handirosiyanto[2], Tara Mandiricha[3], Aisyah Silvia Gaffar[1]

[1]University of Muhammadiyah Malang Faculty of Medicine, Malang, Indonesia
[2]Department of Cardiology and Vascular Medicine, University of Muhammadiyah Malang Faculty of Medicine, Malang, Indonesia
[3]Department of Pharmacology, University of Muhammadiyah Malang Faculty of Medicine, Malang, Indonesia

Abstract

Hypercholesterolemia, a major contributor to atherosclerotic cardiovascular disease, remains inadequately controlled despite widespread statin use, particularly in patients with familial hypercholesterolemia or statin intolerance. Inclisiran, a novel small interfering RNA therapeutic, targets hepatic proprotein convertase subtilisin/kexin type 9 (PCSK9) synthesis to provide sustained low-density lipoprotein cholesterol (LDL-C) reduction. This meta-analysis evaluated the efficacy of inclisiran 300 mg in lowering LDL-C and PCSK9 levels in patients with general hypercholesterolemia or heterozygous familial hypercholesterolemia (HeFH). A systematic search of PubMed, Cochrane, Wiley, and Scopus up to July 2025 identified 11 randomized controlled trials comparing inclisiran 300 mg with placebo. Pooled results showed significant LDL-C reductions of -31.89 mg/dL for general hypercholesterolemia and -61.47 mg/dL for HeFH; PCSK9 decreased by -65.96 ng/mL and -56.41 ng/mL, respectively, with no significant subgroup differences observed. Although the risk of bias was low, heterogeneity (I^2 >50%) and mild funnel plot asymmetry indicated potential variability and small-study effects. Overall, Inclisiran demonstrates consistent and substantial lipid-lowering efficacy across diverse hypercholesterolemic populations, supporting its use as an adjunct or alternative to statins. Its twice-yearly dosing may offer benefits for adherence and long-term lipid control; however, further studies are needed to confirm benefits on cardiovascular outcomes.

Keywords: Inclisiran, hypercholesterolemia, LDL-C, PCSK9

INTRODUCTION

Hypercholesterolemia is a major global health concern and a well-recognized contributor to atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease (CAD), stroke, and peripheral arterial disease.[1] Characterized by elevated levels of circulating low-density lipoprotein cholesterol (LDL-C), hypercholesterolemia accelerates the formation of lipid-rich atherosclerotic plaques, leading to vascular inflammation and luminal narrowing.[2,3] The condition may arise from genetic predispositions, such as familial hypercholesterolemia, or be acquired through lifestyle and metabolic factors, including obesity, type 2 diabetes mellitus, and dietary habits.[4,5]

Hypercholesterolemia affects an estimated 45% of the global population, with reported prevalence rates of approximately 30% in Southeast Asia and 35% in Indonesia.[6] Despite the widespread use of statins and other lipid-lowering agents, a significant proportion of hypercholesterolemic patients fail to achieve optimal LDL-C targets, particularly those with familial hypercholesterolemia or statin intolerance.[7,8]

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Address for Correspondence: Tara Mandiricha MD, Department of Pharmacology, University of Muhammadiyah Malang Faculty of Medicine, Malang, Indonesia
E-mail: tara@umm.ac.id
ORCID ID: orcid.org/0000-0003-0750-3332

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LDL-C levels in clinical practice often remain above recommended thresholds, posing a persistent challenge in cardiovascular risk reduction. International data indicate that over 83% of patients with established CAD do not reach the LDL-C goal of <1.4 mmol/L with this proportion rising to approximately 89% in Indonesian populations.[9] In line with these findings, a national multicenter study reported that only 8.5% of patients achieved LDL-C <55 mg/dL and 28.4% reached <70 mg/dL, while 71.6% remained above target and 20.6% had levels ≥ 6 mg/dL.[10,11] As a result, new therapeutic approaches that target distinct molecular pathways have been developed to improve lipid regulation and reduce the risk of cardiovascular disease. This disparity underscores the clinical need for more effective, longer-acting, and better-tolerated lipid-lowering interventions.

Inclisiran, a small interfering RNA (siRNA) agent, represents a novel class of lipid-lowering therapy that targets hepatic proprotein convertase subtilisin/kexin type 9 (PCSK9) synthesis.[11] By silencing the *PCSK9* gene at the messenger RNA (mRNA) level, inclisiran offers a sustained reduction in circulating PCSK9 and LDL-C with a convenient biannual dosing schedule.[12] Several randomized controlled trials (RCTs), notably the ORION trial program, have evaluated the safety and efficacy of inclisiran in various hypercholesterolemic populations.[13] However, a synthesis of the available evidence is needed to provide a comprehensive, quantitative assessment of inclisiran's lipid-lowering effects, particularly regarding PCSK9 suppression and LDL-C reduction.

This meta-analysis aims to comprehensively assess the impact of inclisiran on LDL-C and PCSK9 levels in patients with hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH). This study integrates data from recent RCTs to assess the impact of inclisiran across a broader range of patients, including patients with genetic conditions such as HeFH, in contrast to prior reviews that focused on individual trials or overall cholesterol outcomes.

METHODS

1. Study Methodology

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2. Eligibility Criteria

The following criteria, presented in Appendix 1, are considered eligible for this study: study population, intervention type, outcomes, study type, and reference standards.

2.1. Populations of the Studies

Individuals diagnosed with elevated blood cholesterol levels, encompassing both general hypercholesterolemia or homozygous familial hypercholesterolemia (HoFH) and specific genetic forms such as HeFH.

2.2. Type of Intervention

The included studies compared the efficacy and safety of inclisiran with those of placebo or other lipid-lowering treatments. However, a limitation of these studies was that inclisiran was administered at a fixed dosage of 300 mg, thereby restricting the evaluation of different dosing strategies or dose-response relationships.

2.3. Outcomes

The primary outcomes assessed in these studies were reductions in LDL-C levels and changes in PCSK9 concentrations.

2.4. Type of Studies

Original research article using human study with RCT only design written in English we included in this study. Narrative review, systematic review, metaanalysis, non-comparative research, in silico studies, *in vivo* studies, technical reports, editor response, scientific poster, study protocol and conference abstracts we excluded. Unavailable full-text article, non-English, irrelevant topics were also excluded.

2.5. Reference Standards

The reference standard was experimental research conducted by qualified professionals to evaluate the effect of inclisiran compared with placebo on reductions in LDL-C and PCSK9 levels.

3. Data Source and Search

The literature search process was carried out using four electronic databases, i.e., PubMed, Cochrane, Wiley, and Scopus. The literature search was conducted through July 2025. The keywords used in electronic databases were combined using Boolean operators. The search strategy employed the following key terms: ("Inclisiran") AND ("siRNA therapy" OR "small interfering RNA") AND ("hypercholesterolemia" OR "high cholesterol"). In addition, the reference lists of the identified studies were reviewed to identify any additional relevant studies. The search strategy and keyword PICOs framework are shown in Appendix 1.

4. Study Selection

After removal of duplicate articles, the retrieved articles were screened by all authors (A.C.P.N., A.D.R., I.H., T.M.) based on

titles and abstracts. Potentially eligible full-text articles were thoroughly assessed using the eligibility criteria described above. Any emerging discrepancies were resolved by consensus among the authors. The entire study selection process was recorded in the PRISMA flow chart.

5. Data Extraction and Analysis

Included studies were extracted using Microsoft Excel 2019 (Microsoft Corporation, USA) and Rayyan.ai. The following data were recorded: author, year, country, study design, experimental intervention, control intervention, intervention duration, and outcome. All statistical tests for the meta-analysis were conducted using Review Manager v5.4 and Stata 19.0.

6. Risk of Bias in Individual Studies (Qualitative Synthesis)

The quality of each included study was assessed by three independent reviewers (A.C.P.N., A.D.R., I.H.); any disagreements were resolved by a fourth independent reviewer (T.M.) according to the Cochrane Risk of Bias (revised tool for risk of bias in randomized trials).

7. Quantitative Data Synthesis (Meta-analysis)

This meta-analysis reported data as mean and standard deviation (SD) with 95% confidence intervals (CIs). We used the heterogeneity level to determine which effect model to use, either a fixed-effect model or random-effect model. Furthermore, the Cochrane chi-squared test and inconsistency (I^2) examine the studies' heterogeneity. A $P < 0.05$ was considered significant; hence, heterogeneity was significant when $I^2 > 50\%$. Random-effects and fixed-effects models were used when heterogeneity was >50% and <50%, respectively. The pooled estimate was presented in our forest plot. Subgroup analysis will be used to assess any heterogeneity among the included studies.

RESULTS

1. Study Selection

The study selection process began with the identification of records from multiple electronic databases shown in Figure 1, including PubMed (n=117), Scopus (n=302), Cochrane (n=32), and Wiley (n=110), yielding a total of 561 records. Prior to screening, 242 duplicate records were removed, leaving 319 records for title and abstract screening. During the screening phase, 51 records were excluded based on titles and abstracts. A total of 268 full-text reports were sought for retrieval; however, 25 could not be retrieved. Subsequently, 243 full-text reports were assessed for eligibility. Of these, reports were excluded for the following reasons: inappropriate study design (n=22), inappropriate comparator (n=20), absence of hypercholesterolemic participants (n=15), and lack of relevant outcomes (n=175). Ultimately, 11 studies met the inclusion criteria and were included in the review.

Many records could not be retrieved due to paywall restrictions, unavailable full texts, duplicate database indexing, or non-English versions without accessible translations. These unretrieved records were documented but excluded from eligibility screening.

Despite the large number of unretrievable reports, none corresponded to RCTs evaluating inclisiran. The final sample of 11 RCTs likely reflects the entire body of currently available trial evidence.

2. Study Characteristics and Result of Individual Studies

A total of eleven RCTs were included in the qualitative synthesis.[14-24] These studies were published up to July 2025, and the majority were conducted at multiple centers. Moreover, there are two studies conducted in the USA and the UK, and one study each in China and Japan. Most studies enrolled patients diagnosed with general hypercholesterolemia or HeFH, in which inclisiran 300 mg was the intervention and placebo the comparator.

Participant ages ranged from 14 to 66 years, with a balanced distribution between male and female subjects. The total sample size across all included studies was approximately 5,365 individuals.

Regarding subject characteristics, a substantial portion of the population had established ASCVD or multiple cardiovascular risk factors. All studies reported outcomes as percentage changes from baseline and absolute mean differences from baseline in LDL-C and PCSK9 levels, which were used as the primary endpoints in the analysis. A detailed breakdown of each study's baseline characteristics and interventions is provided in Table 1.

3. Risk of Bias in Individual Studies (Qualitative Synthesis)

The risk-of-bias assessment of the eleven studies included in the qualitative synthesis indicates that most studies demonstrate a low risk of bias across most assessed domains. The evaluated domains include the randomization process (D1), deviations from intended interventions (D2), missing outcome data (D3), measurement of the outcome (D4), and selection of the reported result (D5). Most studies were rated as having low risk (green) in domains D1 through D4. However, several studies presented some concerns (yellow) and even high risk (red), particularly in the domains of D4 and D5. For instance, the study by Koenig et al.[16] showed high risk in D5, which may impact the reliability of its findings.

Table 1. Study characteristics and results of individual studies

No	Author, year	Country	Study design	Age (year)		Sample size		Intervention			Main outcomes
				Inclisiran	Placebo	Inclisiran	Placebo	Drug (dosage)	Control (dosage)	Duration	
1	Yamashita et al.[14]	Japan	RCT double-blind, phase 2	63±10.7	63.8±11.1	96	56	Inclisiran SC 300 mg (single dose)	Placebo	360 days	Reduced LDL-C and PCSK9
2	Luo et al.[15]	China	RCT	59.5±7.45	57.3±9.59	15	10	Inclisiran SC 300 mg (single dose)	Placebo	90 days	Reduced LDL-C and PCSK9
3	Raal et al.[17]	Multicenter	RCT double-blind, phase 3	55.5±2.7	55.5±3.0	242	240	Inclisiran SC 300 mg (single dose)	Placebo	540 days	In adults with HeFH, inclisiran significantly reduced LDL cholesterol compared to placebo.
4	Leiter et al.[18]	USA	RCT	-	-	54	57	Inclisiran 300 mg (single dose)	Placebo	210 days	Reduced LDL-C
5	Fitzgerald et al.[19]	UK	RCT single-blind, phase 1	46±10	48±14	18	6	Inclisiran SC 300 mg (single dose)	Placebo	180 days	Reduced levels of PCSK9 and LDL cholesterol for at least 6 months
6	Ray et al.[20]	UK	RCT double-blind phase 2	63.9±12.8	62±11.4	60	64	Inclisiran SC 300 mg (single dose)	Placebo	360 days	Lower PCSK9 and LDL cholesterol levels among patients at high cardiovascular risk who had elevated LDL cholesterol levels.
7	Wright et al.[21]	USA	RCT double-blind phase 3	64.1±9.98	63.9±9.87	1833	1827	Inclisiran SC 300 mg (single dose)	Placebo	540 days	lowering PCSK9 and lower LDL-C in adults with heterozygous familial hypercholesterolemia
8	Ray et al.[22]	Multicenter	RCT double-blind phase 2	63.3±11.1	61.9±10.6	277	92	Inclisiran SC 300 mg (single dose)	Placebo	1440 days	reductions in LDL cholesterol and PCSK9 concentrations
9	Wiegman et al.[23]	Multicenter	RCT double-blind phase 2	14.6±1.5	15.1±2.7	9	4	Inclisiran SC 300 mg (single dose)	Placebo	330 days	Lowering PCSK9 and lower LDL-C in adolescents with HoFH
10	Ray et al.[24]	Multicenter	RCT double-blind phase 3	62.7±10.6	63.6±9.2	98	105	Inclisiran SC 300 mg (single dose)	Placebo	540 days	LDL-C reductions
11	Koenig et al.[16]	Multicenter	RCT double-blind phase 3	65.1±8.5	64.2±8.6	110	92	Inclisiran SC 300 mg (single dose)	Placebo	510 days	LDL-C reductions

RCT: Randomized controlled trial, LDL-C: Low-density lipoprotein cholesterol, PCSK9: Proprotein convertase subtilisin/kexin type 9, HeFH: Heterozygous familial hypercholesterolemia, HoFH: Homozygous familial hypercholesterolemia

The summary bar chart further illustrates that, while the the majority of data fall into the low-risk category, the presence of some concerns and high-risk ratings in key domains highlights the need for cautious interpretation of the overall evidence shown in Figure 2. The justification and comment for each question are displayed in Appendix 2.

4. Efficacy Outcomes

A total of 11 RCTs were included in the meta-analysis to assess the effect of inclisiran 300 mg compared to placebo on LDL-C levels in patients with hypercholesterolemia.[14-24]

4.1. Change in LDL-C Levels

A subgroup analysis, presented in Figure 3, was conducted to evaluate the efficacy of inclisiran 300 mg in lowering LDL-C and PCSK9 levels across two distinct patient populations: those with general hypercholesterolemia and those with HeFH. In terms of LDL-C reduction, inclisiran showed a statistically significant effect in both subgroups. Among patients with general hypercholesterolemia, the pooled mean difference was -31.89 mg/dL (95% CI: -41.61 to -22.17), while in the HeFH subgroup, the effect was more pronounced, with a mean difference of -61.47 mg/dL (95% CI: -99.10 to -23.85). Despite the larger effect size in the HeFH group, the test for subgroup differences did not reach statistical significance (Chi^2=2.23, P = 0.14), indicating that the difference in LDL-C reduction between the two subgroups may not be statistically significant.

The funnel plot in Figure 4, stratified by subgroup, revealed mild asymmetry, especially among studies involving general hypercholesterolemia, which may indicate publication bias or small-study effects. In contrast, the HeFH subgroup included fewer studies with larger standard errors, limiting the ability to draw firm conclusions about publication bias. Overall, inclisiran consistently reduced LDL-C levels across both populations, with a potentially greater effect in HeFH patients, although the difference between subgroups was not statistically significant.

Visual inspection of the funnel plot suggested mild asymmetry. However, Egger's regression test demonstrated no statistically

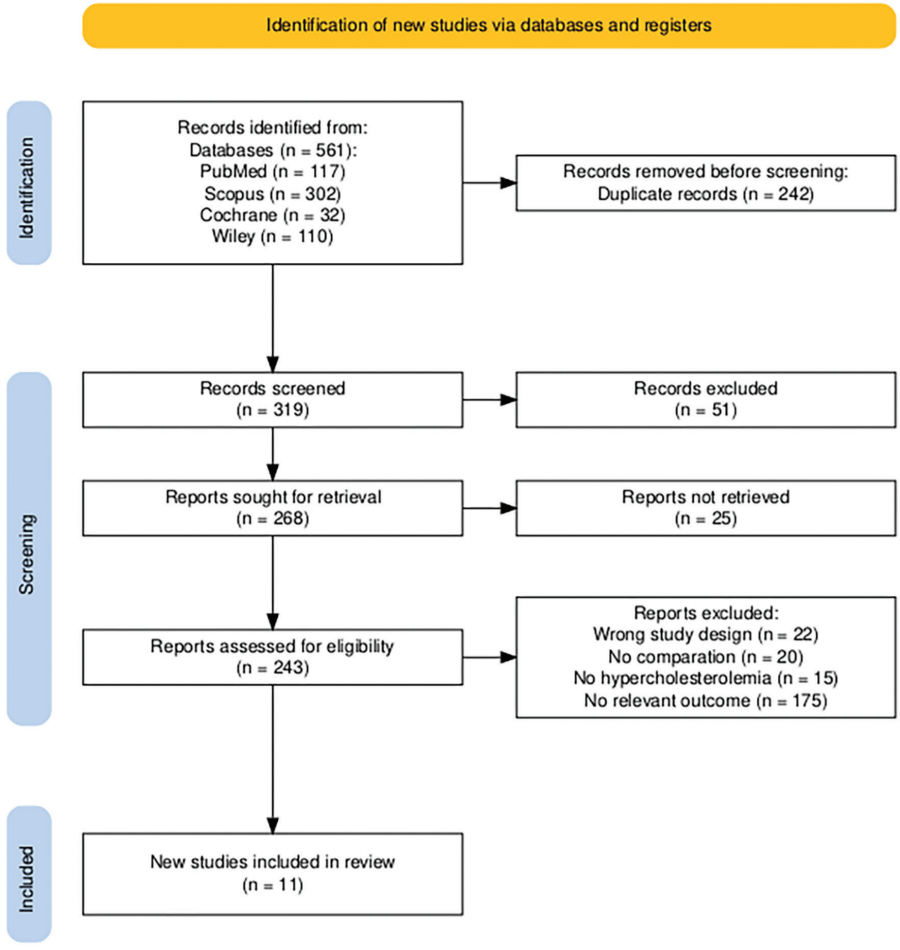

Figure 1. PRISMA flow diagram

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Figure 2. Risk of bias in individual studies (qualitative synthesis). (A) Risk of bias judgement for each included study based on five domains of assessment. (B) Summary bar chart showing the proportion of studies with low risk (green), some concerns (yellow), and high risk (red) for each domain and overall assessment

significant evidence of small-study effects (β=-0.46, standard error=17.60, z=-0.03, $P = 0.979$), as shown in Appendix 3.

An extended random-effects meta-regression was conducted using sample sizes for inclisiran and placebo, and follow-up duration as moderators. Although the overall meta-regression model was statistically significant (Wald χ^2 (3)=21.38, $P = 0.0001$), none of the individual moderators showed a significant association with effect size (all $P > 0.23$), as shown in Appendix 4.

Residual heterogeneity remained extremely high (τ^2=81.29; I^2=99.73%; Q_res $P < 0.0001$), indicating that these variables did not meaningfully explain between-study variance.

4.2. Change in PCSK9 Levels

PCSK9 levels after inclisiran treatment also showed consistent reductions (Figure 5). In the general hypercholesterolemia group, the mean difference was -65.96 ng/mL (95% CI: -85.14 to -46.79), while in the HeFH group, it was -56.41 ng/mL (95% CI: -73.46 to -39.37). Similarly, the test for subgroup differences was not statistically significant (Chi²=0.53, $P = 0.47$), suggesting that inclisiran's effect on PCSK9 reduction is comparable in both populations. Notably, heterogeneity was high in the general hypercholesterolemia group (I^2=100%) and moderate to high in the HeFH group (I^2=68-82%), possibly reflecting differences in study design or patient characteristics.

4.3. Sensitivity Analysis

A sensitivity analysis excluding the Koenig et al.[16] trial—rated as high risk in Domain 5 of the Risk of Bias 2 (RoB 2) assessment—was performed to evaluate its impact on the pooled estimate. Removal of this study resulted in only minimal changes in the effect size, and the CIs overlapped substantially with those of the main analysis. This indicates that the pooled results remain robust despite the presence of one trial at high risk of bias.

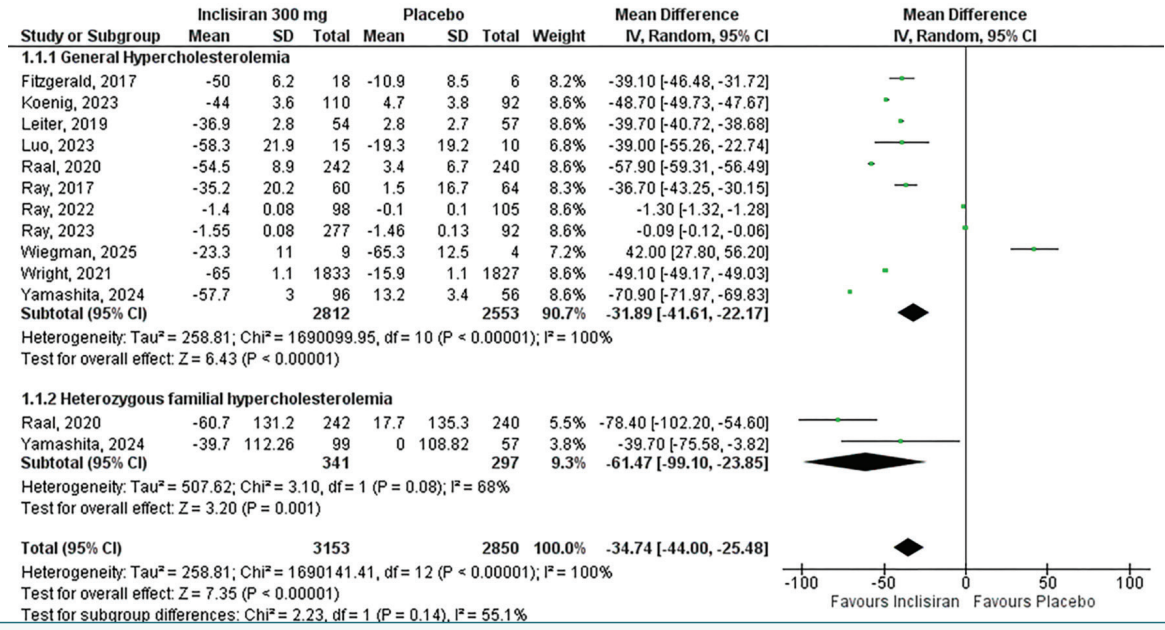

Figure 3. Forest plot of the effect of Inclisiran 300 mg on LDL-C levels in patients with hypercholesterolemia

LDL-C: Low-density lipoprotein cholesterol, CI: Confidence interval, SD: Standard deviation

DISCUSSION

We have systematically investigated 11 RCTs on the clinical efficacy of inclisiran 300 mg in reducing both LDL-C and PCSK9 concentrations in patients with hypercholesterolemia. The pooled results from RCTs demonstrated that inclisiran significantly reduced LDL-C and PCSK9 levels compared to placebo, highlighting its robust lipid-lowering potential. This effect remained statistically significant even when analyzed across different patient subgroups, including those with HeFH, a population known to be at higher cardiovascular risk and often less responsive to conventional therapies. Although the HeFH subgroup appeared to experience a greater reduction in LDL-C, the difference between the HeFH and non-HeFH groups was not statistically significant, suggesting a consistent therapeutic benefit across varying baseline risk profiles. Notably, the meta-analysis revealed a high degree of heterogeneity in both LDL-C and PCSK9 outcomes, which may reflect differences in study design, baseline lipid levels, or population characteristics across the included trials.

One included trial (Koenig et al.[16]) was rated as high risk in Domain 5 of the RoB 2 tool due to concerns related to selective reporting. While the sensitivity analysis demonstrated that excluding this study did not materially alter the findings, its presence may still contribute to uncertainty regarding the strength of the evidence. Therefore, the results should be interpreted with caution, especially regarding consistency across trials.

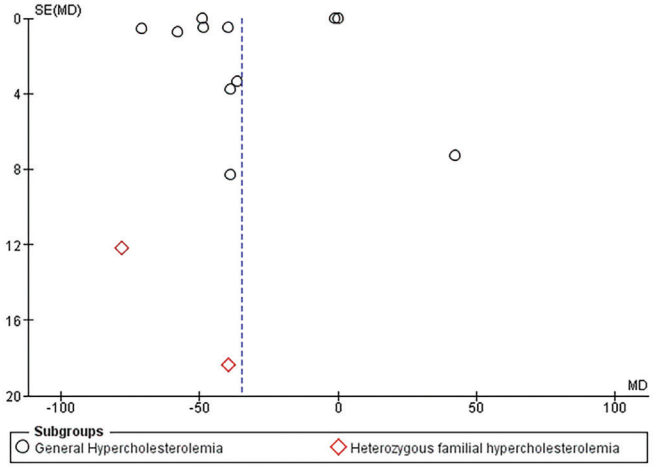

Figure 4. Funnel plot for publication bias by subgroup: LDL-C reduction in general vs. familial hypercholesterolemia

LDL-C: Low-density lipoprotein cholesterol

1. Consistency of Inclisiran Outcomes with Previous Studies and Standard Therapies

Comparable findings concerning the LDL-C-lowering capacity of inclisiran have been consistently observed in a range of RCTs and real-world clinical studies. The most compelling data originate from the ORION clinical trial series (ORION-9, ORION-10, ORION-11), which together confirm the drug's significant and sustained ability to reduce LDL-C levels across diverse patient populations. In particular, the ORION-10 and ORION-11 trials, which investigated individuals with pre-existing ASCVD or

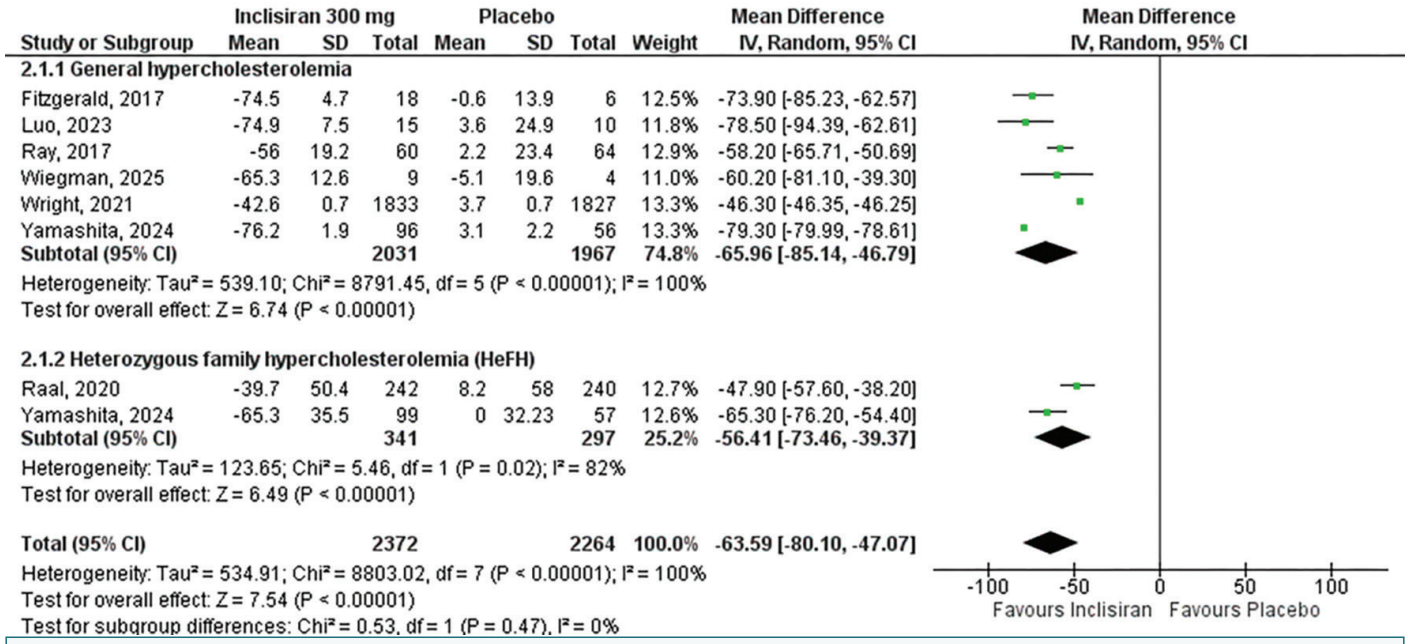

Figure 5. Forest plot of the effect of inclisiran 300 mg on PCSK9 levels in patients with hypercholesterolemia

PCSK9: Proprotein convertase subtilisin/kexin type 9, CI: Confidence interval, SD: Standard deviation

those considered at high cardiovascular risk, reported average reductions in LDL-C of 52.3% and 49.9%, respectively, by day 510.[25] Similarly, ORION-9, which focused on patients diagnosed with HeFH, demonstrated a significant LDL-C reduction of 47.9% compared to placebo.[17] Together, these studies offered the first compelling evidence that inclisiran is an effective long-term lipid-lowering agent, particularly when administered alongside the highest tolerated statin therapy.

Additional support for inclisiran's efficacy has been demonstrated in a retrospective cohort study conducted by Briani et al.[26] which observed a marked decrease in LDL-C concentrations, reaching an average of 58.5±42.8 mg/dL ($P <$ 0.001) as early as 32 days following single administration.[26] Notably, a considerable number of participants achieved the LDL-C thresholds outlined in the 2019 ESC/EAS guidelines, highlighting inclisiran's capacity to facilitate attainment of intensive lipid targets. The study further underscored the central role of statins as first-line therapy for lipid management and proposed inclisiran as a valuable adjunct or alternative, particularly for individuals with inadequate lipid control or statin intolerance.

Despite exploring several moderators, including the sample sizes of both treatment arms and the duration of follow-up, our meta-regression analysis did not identify any statistically significant predictors of effect size. Residual heterogeneity remained extremely high (I^2=99.73%), suggesting that substantial differences among studies persisted even after adjustment.

This indicates that heterogeneity is likely driven by multiple unmeasured clinical or methodological factors, such as variations in baseline LDL-C, background statin therapy, dosing intervals, and trial design across ORION and non-ORION studies.

These findings, together with consistent outcomes observed in both randomized trials and routine clinical use, consolidate the evidence base supporting inclisiran as a potent and dependable lipid-lowering intervention. Its reproducible efficacy across diverse patient profiles, rapid onset of action, and capacity to help patients meet recommended LDL-C goals suggest a meaningful role for inclisiran in comprehensive cardiovascular risk reduction strategies.

2. Implications of Inclisiran as an Adjunct or Alternative to Statin Therapy

Recent evidence drawn from real-world clinical experience increasingly supports the use of inclisiran both as an adjunctive and as an alternative approach in lipid-lowering strategies, particularly for individuals already on statins or for those who cannot tolerate them. The findings of this study support the role of statins as the primary therapy for lowering LDL-C levels. A study by Padam et al.[27] also demonstrated that the reduction in LDL-C was greater in patients who received statins in combinations with inclisiran compared to those who did not (56% vs. 44.9% within 2 months). This effect reflects a synergistic interaction in which statins increase the transcription of LDL receptor mRNA and PCSK9 mRNA, while inclisiran inhibits the translation of PCSK9 mRNA. This ultimately leads to an

increased number of LDL receptors on the cell surface and enhanced clearance of LDL-C from bloodstream.[28]

From safety standpoint, inclisiran classified as a siRNA therapy targeting PCSK9 mRNA-has consistently shown a favorable safety profile in both trial settings and clinical practice.[29] Moreover, inclisiran precise made of action minimizes systematic distribution, which contributes to its enhanced safety characteristics.[30] Inclisiran demonstrates both additive benefits when used alongside statins and independent utility in patients unable to tolerate standard therapies. As such, it fills a crucial therapeutic gap in current cardiovascular prevention strategies, supporting its growing role in long-term atherosclerotic disease management.

3. Benefits of Twice-yearly Dosing in Improving Patient Adherence

Extensive meta-analyses and systematic reviews consistently show that less frequent dosing significantly improves medication adherence in chronic diseases. Studies comparing once-daily regimens to twice-daily or more frequent dosing found adherence rates generally 13-26 % higher for once-daily therapy, with timing adherence (the strictest definition) showing even larger gaps.[31] Another analysis of cardiovascular medications reported regimen adherence lower by ~14 % and timing adherence by ~23% when switching from once- to twice-daily dosing.[32] These findings suggest that by further reducing dosing to every six months, adherence could improve even more, as patients face minimal regimen complexity.[17]

Inclisiran, an siRNA therapy for hypercholesterolemia, is administered only twice yearly after the initial loading doses. Its long-acting mechanism maintains LDL-C suppression for months with minimal follow-up visits. This extended dosing interval reduces cognitive load and "pill fatigue," especially in asymptomatic chronic conditions where motivation wanes over time.[33]

A recent retrospective claims-based study in the USA compared six-month adherence to inclisiran and anti-PCSK9 monoclonal antibodies. Patients on inclisiran achieved a mean proportion of days covered (PDC) of 0.85, which was significantly higher than the 0.70 observed with monoclonal antibodies. Approximately 70% of inclisiran patients achieved PDC ≥80%, compared to 48-51% for alternative injectable agents.[34] These early real-world results align with the expectation that a twice-yearly injectable has superior adherence compared with more frequent injectable or oral regimens.

In the ORION-3 open-label extension study (4-year duration), approximately 79% of patients completed follow-up while receiving inclisiran every six months, indicating strong treatment persistence. LDL-C reductions of 50% were sustained through 4 years, supporting both efficacy and real-world tolerability of infrequent dosing.[35]

4. Inclisiran 300 mg: The Optimal Therapeutic Dose

Phase 2 dose-ranging trials, particularly ORION-1, evaluated inclisiran at various single- and two-dose regimens: 100, 200, 300, and 500 mg. One-year follow-up revealed that the two-dose 300 mg regimen produced the strongest LDL-C reduction (about -52.6%) and had the highest persistence of response through day 360 (83% of participants maintained ≥80% of their baseline LDL-C reduction).[15,36-38] Although the 500 mg dose achieved a similar reduction, it did not materially outperform 300 mg in magnitude or durability, despite being higher in dose.[37]

Comparative meta-analysis further confirmed that 300 mg offered the best balance between efficacy and safety. Network meta-analyses demonstrated that while 100 mg and 200 mg doses produced some LDL-C lowering, the 300 mg dose yielded the greatest reduction, outperforming both lower and higher (500 mg) doses.[38,39] Importantly, adverse event rates remained similar across dose groups, meaning that increasing the dose above 300 mg did not confer meaningful safety advantages or additional therapeutic benefit.[39-41]

Pharmacodynamic data show that a single 300 mg dose suppresses PCSK9 levels by ~75% and LDL-C by ~50% for over 180 days.[37,42] Based on this sustained effect and the enhanced one-year persistence observed in the two-dose regimen, maintenance dosing every six months is feasible without retreatment. This creates a streamlined, efficacious, and convenient dosing schedule that aligns with both patient preference and long-term outcome frameworks.[37,41]

5. Mechanism of Action of Inclisiran siRNA Targeting of PCSK9 to Enhance LDL Receptor Recycling and Reduce LDL-C

Inclisiran is a sophisticated siRNA therapeutic that precisely binds to the mRNA of PCSK9 within hepatocytes. Through asialoglycoprotein receptor-mediated uptake, the GalNAc-conjugated siRNA enters the liver and becomes incorporated into the RNA-induced silencing complex (RISC). The RISC-siRNA complex then rapidly and catalytically cleaves PCSK9 mRNA, preventing its translation into protein.[11,15,43-46] This intracellular targeting contrasts with PCSK9 antibody therapies, which neutralize circulating PCSK9 rather than reduce its production.

By suppressing PCSK9 synthesis, inclisiran effectively halts the PCSK9-mediated lysosomal degradation of LDL receptors. Consequently, more LDLRs are available on the hepatocyte surface to remove circulating LDL-C from the bloodstream.[12,43,45,47,48] Increased receptor density leads to enhanced LDL-C clearance, driving cholesterol reduction.

Clinical pharmacodynamic studies illustrate that inclisiran maintains profound suppression of PCSK9—approximately 75%—and ~50% reduction in LDL-C for at least six months after a single 300 mg dose.[45] This prolonged effect supports its twice-yearly dosing schedule by maintaining plasma LDL-C at reduced levels over extended periods, without requiring frequent administration.

Phase III trials (ORION-10, -11, and -9) consistently showed ~50% LDL-C reduction over 18 months, confirming sustained pharmacodynamic and clinical efficacy.[11,45] These LDL-C reductions were achieved with biannual subcutaneous dosing after initial loading doses, consistent with a durable mechanism.

6. Assessment of Bias, Variability, and Subgroup Differences

Despite the overall low risk of bias across most included studies, a few trials exhibited a high risk of bias, specifically in domain D3 and domain D5. These risks may introduce reporting and attrition biases, which could undermine the internal validity and the reliability of the pooled results. For instance, missing data can distort treatment effects, particularly if loss to follow-up is related to treatment response or adverse events. Similarly, selective outcome reporting may exaggerate the perceived efficacy of inclisiran if only favorable results are disclosed. Although the overall evidence quality is robust, these methodological concerns necessitate cautious interpretation of specific study findings.

The substantial heterogeneity observed across studies (I^2 ranging from 68% to 100%) warrants careful interpretation. Although we performed subgroup analyses comparing general hypercholesterolemia and HeFH, the subgroup interaction was not statistically significant and did not meaningfully reduce heterogeneity. This suggests that the differences between these groups do not account for the variability in effect sizes.

A number of unmeasured or unreported factors likely contribute to the observed heterogeneity. These include substantial differences in baseline LDL-C levels, inconsistent background statin therapy, varying dosing schedules of inclisiran (the standard ORION regimen versus modified regimens), inclusion of both ASCVD and non-ASCVD populations, and heterogeneity in study design features, including follow-up duration, endpoint definitions, and assay methods for LDL-C measurement.

The persistence of high heterogeneity, even after meta-regression, indicates that no single study-level characteristic adequately explains the variability. Therefore, the pooled effect should be interpreted as an average estimate across highly diverse clinical contexts rather than a uniform effect applicable to all populations. Despite this, the directionality of inclisiran's LDL-C-lowering effect remained consistent, supporting the robustness of its pharmacologic action across different settings. Future trials would benefit from more standardized reporting, harmonization of baseline risk profiles, and adequately powered subgroup analyses to clarify which patient groups derive the greatest benefit.

The classification of the HoFH (Wiegman et al.[23]) into the general hypercholesterolemia category was based on the similarity of clinical parameters and treatment context with broader hypercholesterolemia trials.

Although the funnel plot displayed some asymmetry, our formal Egger regression test did not identify statistically significant small-study effects ($P = 0.979$). This suggests that publication bias is unlikely to be the primary explanation for the visual asymmetry. Instead, the extremely high heterogeneity (I^2>99%) across trials may account for the observed asymmetry in the plot. Nonetheless, publication bias cannot be entirely ruled out.

7. Strength and Limitation

This meta-analysis has several strengths. First, it systematically synthesizes evidence from RCTs, which represent the highest level of clinical evidence and minimize the risk of bias. The inclusion of both general hypercholesterolemic populations and a genetically high-risk subgroup—HeFH—allowed for a more nuanced evaluation of inclisiran's efficacy. The consistently significant reduction in both LDL-C and PCSK9 levels across studies highlights the biological plausibility and therapeutic potential of inclisiran, even in the presence of clinical heterogeneity.

Moreover, sensitivity and subgroup analyses were conducted to assess the robustness of the results and identify potential effect modifiers of the treatment, thereby strengthening the credibility of the findings.

Nevertheless, several limitations should be acknowledged in interpreting our results. The number of included studies, particularly those evaluating PCSK9 outcomes, was limited, reducing the statistical power to draw definitive conclusions regarding this biomarker. Additionally, most trials used a fixed dose of inclisiran (300 mg), preventing assessment of dose-response effects or optimization of alternative dosing strategies. The inclusion of studies with small sample sizes and outlier values—such as extreme SDs—may have inflated between-study heterogeneity (I^2=100%). Furthermore, the follow-up periods in most trials were relatively short, limiting our ability to assess long-term cardiovascular outcomes, safety profiles, and patient adherence.

A substantial proportion of records identified in the initial search (200 out of 268, approximately 75%) could not be

retrieved due to restricted access, institutional limitations, or lack of full-text availability. This introduces a potential non-retrieval (accessibility) bias, which may influence the completeness of the evidence base and the assessment of publication bias. Nevertheless, all available full-text RCTs evaluating inclisiran were retrieved, and the final 11 RCTs likely represent the complete set of eligible evidence currently available in English.

The meta-regression results revealed that heterogeneity remained very high (I^2>99%) even after adjusting for sample size and follow-up duration, suggesting that important moderators may be unmeasured or unreported. This limits our ability to fully account for between-study variability.

At least one included study was judged to have a high risk of bias, which may influence the certainty of the pooled estimates. Although sensitivity analyses showed that its exclusion did not significantly change the effect size, residual concerns about selective reporting should be acknowledged.

Future research should aim to address these gaps by conducting large-scale, long-term RCTs with diverse patient populations and endpoints capable of detecting statistically significant differences, such as major cardiovascular events, mortality, and quality of life. Specific attention should be paid to high-risk subgroups—such as elderly individuals, patients with diabetes mellitus, or patients with polyvascular disease—to determine whether therapeutic responses differ across populations. Cost-effectiveness analyses are warranted to inform policy decisions and to support equitable access to inclisiran, a next-generation lipid-lowering agent.

CONCLUSION

This meta-analysis demonstrates that inclisiran 300 mg produces significant and sustained reductions in LDL-C and PCSK9 levels in patients with hypercholesterolemia, including those with HeFH. The lipid-lowering effects were generally consistent across the studied populations; however, these findings should be interpreted within the context of the specific patient groups and trial designs included in the analysis.

The observed biochemical efficacy, together with the biannual dosing regimen, supports inclisiran as a potential adjunctive lipid-lowering therapy, particularly for patients with statin intolerance or inadequate lipid control despite standard treatment. Nevertheless, the current evidence base is largely derived from short-term randomized trials and relies on surrogate lipid endpoints rather than definitive cardiovascular outcomes.

Accordingly, inclisiran should not yet be considered a proven alternative to established lipid-lowering therapies. The impact of inclisiran on major adverse cardiovascular events remains uncertain in the absence of completed large-scale, event-driven outcome trials. Ongoing studies, including ORION-4, are essential for determining its long-term cardiovascular benefit, safety profile, and clinical positioning. Future research should also address cost-effectiveness and real-world adherence to better define the role of inclisiran in routine clinical practice.

Footnotes

Authorship Contributions

Concept: A.C.P.N., A.D.R., I.H., T.M., Design: A.C.P.N., A.D.R., I.H., T.M., Data Collection or Processing: A.C.P.N., A.D.R., I.H., T.M., A.S.G., Analysis or Interpretation: A.C.P.N., A.D.R., I.H., T.M., A.S.G., Literature Search: A.C.P.N., A.D.R., Writing: A.C.P.N., A.D.R., I.H., A.S.G.

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Appendix Tables: https://d2v96fxpocvxx.cloudfront.net/beb8919b-f013-4ea1-b1c8-40332e840fe1/content-images/47cdcf8e-894a-4357-9d00-86f04f7096a9.pdf